An International Perspective on Topics in Sports Medicine and Sports Injury

Edited by Kenneth R. Zaslav

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Meet the editor

Born in New York City, Dr Zaslav completed medical school at the Albert Einstein College of Medicine in the Bronx, and Orthopedic Surgery Residency at SUNY Stony Brook, followed by a Sports Medicine Fellowship at the New York University. He has also served as a Shoulder Surgery Fellow at Lenox Hill Hospital of New York, before moving to Richmond, Virginia in 1990 to practice as a specialist in Sports Medicine and Shoulder Surgery at Advanced Orthopedic Centers. Dr Zaslav founded the Sports Medicine Center at AOC and The Cartilage Restoration Center and is currently The Group's President. Among many other duties, he lectures and writes on orthopedic topics, works as a Clinical Professor of Orthopedic Surgery at Virginia Commonwealth University, and is a Board Member of The International Cartilage Repair Society. Dr Zaslav serves on the Scientific Advisory Boards of several companies in the United States and Israel, and has held multiple sports medicine positions.

Contents

Preface

For the past two decades, Sports Medicine has been a burgeoning science in the USA and Western Europe. Great strides have been made in understanding the basic physiology of exercise, energy consumption and the mechanisms of sports injury. Additionally, through advances in minimally invasive surgical treatment and physical rehabilitation, athletes have been returning to sports quicker and at higher levels after injury. More recently, increasing contributions have been made by scientists and physicians on all five continents toward this important enterprise.

As this book will demonstrate, many researchers throughout the world are contributing greatly to our understanding of the kinetics of exercise, joint motion, and the epidemiology of sports-related injury. They are also providing strong evidence to support the benefits of exercise to avoid chronic disease.

This book contains new information from basic scientists on the physiology of exercise and sports performance, updates on medical diseases treated in athletes and excellent summaries of treatment options for common sports-related injuries to the skeletal system.

Our hope is that it will become an important compendium and resource for the physicians and surgeons who treat athletes, as well as professional coaches who are helping those athletes to train and maximize their performance. Additionally, we hope these reviews will act to stimulate researchers throughout the world to continue this important work and solve persistent clinical questions posed by these authors.

I would like to thank my family, specifically my wife Erica, and children Alexandra and Jake as well as my staff and Partners at Advanced Orthopedics who have supported me throughout the editing of this book and who allow me to continue with my teaching, writing and lecturing while maintaining an active clinical orthopedic practice.

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Part 1

Physiology of Sports Medicine

Measurement and Physiological Relevance of the Maximal Lipid Oxidation Rate During Exercise (LIPOXmax)

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1. Introduction

The intensity of exercise that elicits a maximal oxidation of lipids has been termed LIPOXmax, FATOXmax or FATmax. The three acronyms refer to three original protocols of exercise calorimetry which have been proposed almost simultaneously and it is thus interesting to maintain the three names in this review in order to avoid confusion. The difference among the three protocols is presented in table 1. Since our team has developed the technique called LIPOXmax (Perez-Martin et al., 2001; Brun et al., 2009b;) this acronym will be more employed in this chapter, keeping in mind that LIPOXmax, FATOXmax or FATmax represent obviously the same physiological concept.

As will be reviewed in this paper, the measurement of LIPOXmax by graded exercise calorimetry is a reproducible measurement, although modifiable by several physiological conditions (training, previous exercise or meal). Its measurement closely predicts what will be oxidized over 45-60 min of low to medium intensity training performed at the corresponding intensity. It might be a marker of metabolic fitness, and is tightly correlated to mitochondrial function. LIPOXmax is related to catecholamine status and the growth-hormone IGF-I axis, and occurs in athletes below the lactate and the ventilatory threshold (on the average around 40% VO_{2max}). Its changes are related to alterations in muscular levels of citrate synthase, and to the mitochondrial ability to oxidize fatty acids. A meta-analysis shows that training at this level is efficient in sedentary subjects for reducing fat mass, sparing fat-free mass, increasing the ability to oxidize lipids during exercise, reducing blood glucose and Hba_{1c} in type 2 diabetes, and decreasing circulating cholesterol. In athletes, various profiles are observed, with a high ability to oxidize lipids in endurance-trained athletes and in some samples of athletes trained for sprint or intermittent exercise a profile showing a predominant use of carbohydrates.

acronym	FATOXmax	FATmax	LIPOXmax	SIN model
initial publication	Dériaz et al., 2001	Achten et al., 2002, 2003, 2004; Jeukendrup, 2003; Venables et al., 2005	Perez-Martin et al., 2001; Brun et al., 2009b;	Chenevière et al., 2009b
Duration of steps	5-6 min (until steady state)	3 min	6 min	5 min
Calculation	Visual determination	Visual determination	Power intensity at which the derivative of the curve of lipid oxidation versus power is equal to zero (eg, top of the bell-shaped curve)	This model includes three independent variables (dilatation, symmetry, and translation). This SIN model has been reported to allow a more accurate calculation of Fatmin/LIPOXzero
Expression of results	% of maximal oxygen uptake ($\%VO_{2max}$ MFO in kJ.min-1	% of maximal oxygen uptake ($\%VO_{2max}$) MFO in g. min-1	usually % of theoretical maximal power; also % extrapolated maximal oxygen uptake ($\%VO_{2max}$ ACSM)] or % maximal oxygen uptake ($\%VO_{2max}$) determined by a previous test	Fatmax, MFO, dilatation, symmetry and translation

Table 1. Definition of LIPOXmax, FATOXmax or FATmax.

2. The physiological basis for measuring lipid oxidation during exercise

2.1 Balance of substrate oxidation during exercise: The "crossover concept"

Pioneering studies (Zuntz et al., 1901; Krogh et al., 1920; Christensen et al., 1939) have demonstrated that a mixture of carbohydrates and fat is used by the muscle as a fuel at rest and during exercise, and that the ratio between VCO_2 and VO_2 was a reflect of the relative proportion of lipids and CHO used for oxidation. It was clear already at this time that exercise intensity, exercise duration and prior diet modified this balance of substrates.

Recent studies have evidenced that quantitatively, the most important substrate oxidized at the level of the exercising muscle is glucose (Bergman et al., 1999; Friedlander et al., 2007). The maximal rate of CHO oxidation during exercise is about two fold higher than that of lipids (Sahlin et al., 2008). However, when substrate metabolism is assessed on the whole body, lipids remain a major source of fuel at rest and during exercise. At rest, lipids provide >50% of the energy requirements, and they remain an important source of energy during low to middle intensity exercise, while CHO become the main substrate at high intensity (>80% VO_2max) (Jeukendrup et al., 1998). As summarized in table 2, exercise may induce a significant amount of lipid oxidation by at least 4 mechanisms (Brun et al., 2011).

During the last quarter of the XXth century the literature became conflictual with several authors emphasizing the importance of carbohydrates and the others the importance of lipids. This controversy was actually clarified by the heuristic proposal of the "crossover concept" by George Brooks (Brooks et al., 1994). The "crossover concept" is an attempt to integrate the seemingly divergent effects of exercise intensity, nutritional status, gender, age and prior endurance training on the balance of carbohydrates and lipids used as a fuel during sustained exercise. It predicts that although an increase in exercise intensity results in a preferential use of CHO, endurance training shifts the balance of substrates during exercise toward a stronger reliance upon lipids (Fig.1).

The idea of developing a simple reliable exercise-test for assessing this balance of substrates thus emerged as a logical consequence of these fundamental studies (Perez-Martin et al.,

2001; Brun et al., 2007, 2011). Accordingly, several teams have developed this measurement and attempted to train patients at a level determined by this exploration, as reviewed below.

« CROSSOVER" CONCEPT
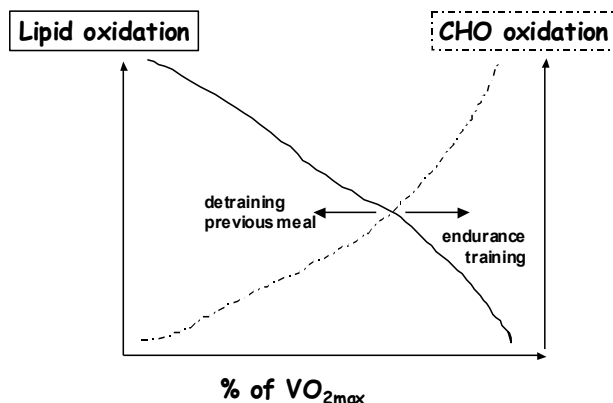
Fig. 1. The crossover concept: the balance of substrates at exercise is a function of exercise intensity, the proportion of lipids used for oxidation continuously decreasing when intensity increases, while CHO become the predominant fuel (>70%) above the "crossover point" (approximately 50% VO_{2max}, see text. This increase in CHO oxidation down-regulates lipid oxidation despite sustained lipolysis. Above the crossover point glycogen utilization scales exponentially. Endurance training, energy supply, overtraining, dietary manipulation and previous exercise modify this pattern. Most trained athletes exhibit a right-shift in this relationship.

a.	Muscular contractile activity by its own may use lipids as a source of energy.	During steady state exercise performed at low intensity, fat is oxidized at an almost constant rate (Bensimhon et al., 2006; Meyer et al., 2007), and there is an intensity of exercise that elicits the maximum oxidation of lipids termed *maximal fat oxidation rate* (MFO).
b.	Progressive rise in lipid oxidation with exercise duration	When exercise is heavy and prolonged enough to result in glycogen depletion, there is a shift toward lipids and their oxidation gradually increases (Ahlborg et al., 1974; Bergman et al., 1999; Watt et al.; 2003). This phenomenon is rather slow in mild to medium intensity exercise when the duration of this exercise does not exceed 1 hr.
c.	Compensatory rise in lipid oxidation after high intensity exercise	High intensity exercise oxidizes almost exclusively CHO but is frequently followed by a compensatory rise in lipid oxidation which compensates more or less for the lipids not oxidized during exercise (Folch et al., 2001; Melanson et al., 2002), but it is inconsistent and frequently quite low (Malatesta et al., 2009; Lazer et al., 2010), even more if exercise is discontinuous (Warren et al., 2009).
d.	Long term regular exercise may increase the ability to oxidize lipids at rest	Long term regular exercise may shift the balance of substrates oxidized over 24 hr toward oxidative use of higher quantities of lipids (Talanian et al., 2007). A training-induced increase in the ability to oxidize lipids over 24-hr is statistically a predictor of exercise-induced weight loss (Barwell et al., 2009).

Table 2. Effects of exercise on lipid oxidation: exercise may increase the oxidative use of lipids by at least 4 mechanisms (after Brun et al., 2011). According to Warren the most important and reliable of these mechanisms is the oxidation during exercise performed around the LIPOXmax or below. (Warren et al., 2009).

2.2 Mechanisms of substrate (fat vs CHO) selection during muscular activity

According to the data presented above, fat is the major energy supply for the muscle below 25% of VO_2max, since in this condition very few glycogen is employed as a source of energy (Romijn et al., 1993). Then, when exercise intensity increases, glycogen will rapidly become the predominant fuel. However, fat oxidation will still increase until the LIPOXmax/FATOXmax is reached. Above this level fat oxidation decreases. Interestingly, this decrease in fat oxidation coincides with lactate increase above baseline, as demonstrated in healthy adolescents during incremental cycling (Tolfrey et al., 2010).

The cellular mechanism of this decrease has been reviewed elsewhere (Sahlin et al., 2008) and is still incompletely understood. Theoretically, lipid supply by lipolysis, lipid entrance in muscle cell, lipid entrance in mitochondria, and mitochondrial fat processing may all be limiting steps. Experiments show that extracellular lipid supply is not limiting, since lipid oxidation decreases even if additional fat is provided to the cell. Limiting steps seem to be the entrance in mitochondria, governed by CPT-1, which can be inhibited by Malonyl-CoA and lactate (Starritt et al., 2000), and possibly downstream CPT-I other mitochondrial enzymes such as Acyl-CoA synthase and electron transport chain. All these steps are sensitive to the rate of CHO oxidation and thus a rise in CHO oxidation seems to depress lipid oxidation despite availability of fat and presence of all the enzymes of fat oxidation.

Experiments using intravenous infusion of labeled long-chain fatty acids in endurance-trained men cycling for 40 min at steady state at 50% of VO_2max clearly demonstrate that carbohydrate availability directly regulates fat oxidation during exercise. An increased glycolytic flux results in a direct inhibition of long-chain fatty acid oxidation (Coyle et al., 1997). Conversely, there is a wide body of evidence that glycogen depletion reverses this inhibition and thus increases fat oxidation, as observed during long duration glycogen-depleting exercise.

These processes are governed by cellular factors, that are under the influence of the central nervous system and circulating hormones (Ahlborg et al., 1974; Kiens & Richter, 1998; Kirvan et al., 1988; Thompson et al., 1998). Intracellular pathways have been reviewed elsewhere and this area of knowledge seems to be rapidly expanding. The activation of the AMPK (AMP-dependent kinase) pathway, together with a subsequent increase in the fatty acid oxidation, appear to constitute the main mechanism of action of these hormones in the regulation of lipid metabolism (Koulmann & Bigard, 2006). To summarize the main hormonal regulators of muscular lipid oxidation, epinephrine increases lipolysis (beta effect) and increases glucose oxidation in muscle (de Glisezinski et al., 2009). Norepinephrine increases lipid oxidation in muscle (Poehlman et al., 1994). Cortisol increases adipogenesis and lipolysis, and decreases non-insulin mediated glucose uptake. β-endorphin induces a lipolysis that can be blunted by naloxone (Richter et al., 1983, 1987). Growth hormone (GH) stimulates lipolysis and ketogenesis (Møller et al., 1990b). In the muscle and the liver, GH stimulates triglyceride uptake, by enhancing lipoprotein lipase expression, and its subsequent storage (Vijayakumar et al., 2010). GH also increases whole body lipid oxidation and nonoxidative glucose utilization and decreases glucose oxidation (Møller et al., 1990a). We have shown that GH-deficient individuals have a lower LIPOXmax and MFO that is restored after GH treatment (Brandou et al., 2006a). Dowstream GH, IGF-I that mediates many of the anabolic actions of growth hormone stimulates muscle protein synthesis, promotes glycogen storage and enhances lipolysis (Guha et al., 2009).

Interleukin-6 (IL-6) coming from the adipose tissue and the muscle acts as an energy sensor and thus activates AMP-activated kinase, resulting in enhanced glucose disposal, lipolysis and fat oxidation (Hoene et al., 2008). Adiponectin increases muscular lipid oxidation via phosphorylation of AMPK (Dick, 2009). Leptin increases muscle fat oxidation and decreases muscle fat uptake, thereby decreasing intramyocellular lipid stores (Dick, 2009).

Although the information on this issue remains limited, it is clear that the level of maximal oxidation of lipids is related to some of these hormonal regulators : norepinephrine, whose training induced changes are positively correlated to an improvement in LIPOXmax (Bordenave et al., 2008) and growth hormone, whose deficit decreases it, a defect that can be corrected by growth hormone replacement (Brandou et al., 2006a). Downstream GH, IGF-I has also been reported to be correlated to LIPOXmax in soccer players as shown on Fig 5 (Brun et al., 1999), reflecting either a parallel effect of training on muscle fuel partitioning or IGF-I release, or an action of IGF-I (or GH via IGF) on muscular lipid oxidation. Other endocrine axes are surely also involved but this issue is poorly known and remains to be studied.

3. Technical aspects of exercise graded calorimetry

3.1 Methodological aspects

As reminded above, the classic picture of Brooks and Mercier's "crossover concept" (Brooks & Mercier, 1994) has led to the development of an exercise-test suitable for routinely assessing this balance of substrates (Perez-Martin & Mercier, 2001; Brun et al., 2007). Based on our previous studies on calorimetry during long duration steady-state workloads (Manetta et al., 2002a, 2002b; Manetta et al., 2005) we developed a test (Perez-Martin et al., 2001) consisting of five 6-min submaximal steps, in which we assumed that a steady-state for gas exchanges was obtained during the 2 last minutes.

We proposed (Perez-Martin et al., 2001) a diagnostic test including four or five 6-minutes workloads, that may be followed by a series of fast increases in power intensity until the tolerable maximum under these conditions is reached. This final incremental part of the test can be avoided in very sedentary patients and the maximal level can be indirectly evaluated by the linear extrapolation according to the ACSM guidelines (VO_2max ACSM) (Aucouturier et al., 2009). The test is performed on an ergometric bicycle connected to an analyzer allowing the analysis of the gaseous exchange cycles by cycle. EKG monitoring and measurements of VO_2, VCO_2, and respiratory exchange ratio (RER) are performed during the test. After a period of 3 minutes at rest, and another period of initial warm-up at 20% of the predicted maximal power (PMP) for 3 minutes, the 6-min workloads set at approximately 30, 40, 50 and 60% of PMP are performed. The phase of recovery comprises two periods during which a monitoring of respiratory and cardiac parameters is maintained: active recovery at 20% of the PMP during 1 minute; passive recovery (ie, rest) during the 2 following minutes. At the end of each stage, during the fifth and sixth minutes, values of VO_2 and VCO_2 are recorded. These values are used the calculation of the respective rates of oxidation of carbohydrates and lipids by applying the classical stoichiometric equations of indirect calorimetry:

$$Carbohydrates\ (mg/min) = 4.585\ VCO_2 - 3.2255\ VO_2 \qquad (1)$$

$$Lipid\ Oxidation\ (mg/min) = -1.7012\ VCO_2 + 1.6946\ VO_2 \qquad (2)$$

These calculations are performed on values of the 5-6th minutes of each step, since at this CO_2 production from bicarbonate buffers compensating for the production of lactic acid becomes negligible. The increment in carbohydrate oxidation above basal values appears to be roughly a linear function of the developed power and the slope of this relation is calculated, providing the *glucidic cost of the watt* (Aloulou, 2002). The increase in lipid oxidation adopts the shape of a bell-shaped curve: after a peak, lipid oxidation decreases at the highest power intensities.

The exact mechanism of this reduction in the use of the lipids at the highest power intensities is actually imperfectly known: a reduction in lipolysis is likely to explain a part of it, together with a shift of metabolic pathways within the muscle fiber. The empirical formula of indirect calorimetry that gives the lipid oxidation rate is, as reminded above:

$$\text{Lipid oxidation (mg/min)} = -1.7\ VCO_2 + 1.7\ VO_2 \tag{3}$$

It is easy to deduce from this formula that the relation between power (P) and oxidation of lipids (Lox) displays a bell-shaped curve of the form:

$$\text{Lox} = \text{A.P (1-RER)} \tag{4}$$

The smoothing of this curve enables us to calculate the power intensity at which lipid oxidation becomes maximal, which is the point where the derivative of this curve becomes equal to zero. Therefore the LIPOXmax calculation is only an application of the classical empirical equation of lipid oxidation used in calorimetry.
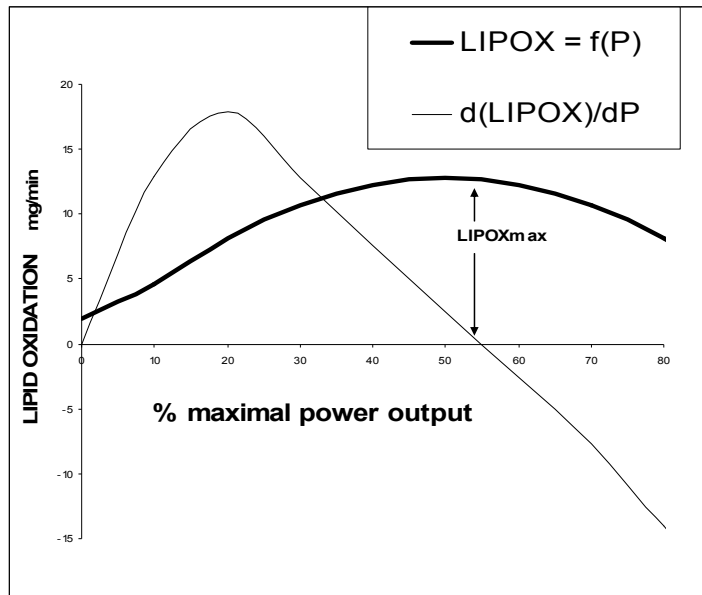
Fig. 2. Calculation of the LIPOXmax: The curve of lipid oxidation (mg/min) is given by the empirical formula of calorimetry Lipox = -1.7 VCO_2 + 1.7 VO_2. This curve Lipox = A.P (1-RER) (see text) can be derived and the point where its derivative equals zero is the top of the bell-shaped curve and thus represents the LIPOXmax. Actually in some subjects this is a broad zone and in others a narrow range of power intensities.

Recently a more sophisticated mathematical model (sine model, SIN) was proposed in order to describe fat oxidation kinetics as a function the relative exercise intensity [% of maximal oxygen uptake (%VO_{2max})] during graded exercise and to determine the exercise intensity elicits maximal fat oxidation and the intensity at which the fat oxidation becomes negligible. This model which will not be developed here includes three independent variables (dilatation, symmetry, and translation). This SIN model exhibits the same precision as other methods currently used in the determination of LIPOXmax and has been reported to allow a more accurate calculation of Fatmin/LIPOXzero (Chenevière et al., 2009b).

Actually, there is now a large body of literature to support the validity of such protocols of exercise calorimetry (Jeukendrup & Wallis, 2005). The theoretical concern was that, when exercise is performed above the lactate threshold, there is an extra CO_2 production which can be assumed to interfere with the calculations (MacRae et al., 1995). In fact, below 75% of the VO_{2max}, this increase in CO_2 has no measurable effect on calorimetric calculations (Romijn et al., 1992), so that these calculations predict closely oxidation rates measured by stable isotope labeling (Christmass et al., 1999). Clearly, even at high intensity exercise, respiratory gases are mostly the reflect of the balance of substrate oxidation.

A controversial issue appears to be: how to express the results. The crude power and/or heart rate at which lipid oxidation reaches its maximum is the most useful information if one aims at undertaking a targeted training procedure. The difficulty arises when units for reporting data in scientific studies are discussed. A percentage of the actual VO_{2max} is a logic solution, and was used by the team of A. Jeukendrup (Achten et al., 2002, 2003) but this requires to perform another exercise test designed for a precise measurement of VO_{2max}. Alternatively, in the initial protocol proposed by Perez-Martin (Perez-Martin & Mercier, 2001), after the four or five 6-min steps used for calorimetry, a rapid incremental protocol until the maximal level was proposed. However, after 24 or 30 min of exercise, subjects may be tired and unable to reach the actual maximum level which would thus be sometimes underestimated. In fact, in our team, we often express our results as a percentage of the theoretical maximal power calculated with Wasserman's equation. This method allows avoiding a maximal stress, which is sometimes perceived as very harmful by sedentary and obese individuals, and thus improves the acceptability of the test. Two French studies have challenged this approach. Aucouturier and coworkers (Aucouturier et al., 2009) report that a calculation of VO_{2max} according to the American College of Sports Medicine (ACSM) recommendations from submaximal VO_2 values provides a satisfactory evaluation of the actual VO_{2}max while theoretical VO_{2}max values given by Wasserman's equation are sometimes misleading in such subjects. These authors thus propose to express the LIPOXmax as a percentage of VO_{2}max ACSM. This approach was also employed by Lazzer (Lazzer et al., 2010). Michallet et al (Michallet et al., 2008) insisted on the fact that the theoretical design of the test with steps set at 20, 30, 40, 50 and 60% of theoretical maximal aerobic power can be inaccurate, and that a good protocol should include steps at a respiratory exchange ratio below and above 0.9, this value being that of the "crossover point". In a very recent study the team of E Bouhlel proposes an improvement that markedly increases the reproducibility and thus presumably the precision of the measurement : the authors propose a previous determination of the VO_{2}max with a maximal exercise test and then set the power intensity of the steps of the calorimetry according to this test (Gmada et al, 2011). This study has the interest to further demonstrate the precision and reproducibility of the method and to propose a protocol suitable for research purposes, but for the assessment of series of patients

or athletes it is clearly necessary to rely upon a single test, ie, calorimetry if we want to measure te balance of substrates.
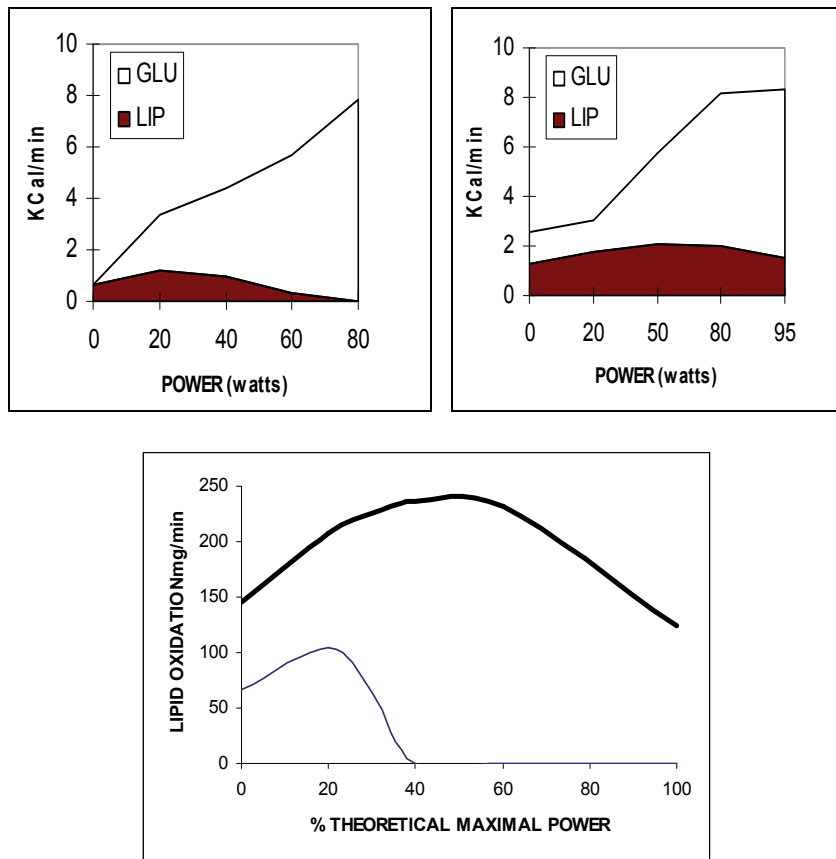
Fig. 3. Examples of individual exercise calorimetries: left; obese woman with "glucodependence" (ie, poor ability to oxidize lipids at exercise) with a peak of lipid oxidation at 135 mg/min located at a power intensity of 34 watts (40% % VO2max ACSM) ; right, overweight patient who oxidizes 235 mg/min of lipids at a LIPOXmax of 68 watts, (55% % VO2max ACSM.) In the last subject, the LIPOX zone is quite wide, indicating that lipids are oxidize over a wide range of exercise intensities. In the first subject it is restricted to a narrow area. The two curves of lipid oxidation are plotted together on the lower pannel, showing their difference in profile according to the theoretical maximal working capacity. Similar discrepancies can be found in athletes.

The maximal fat oxidation rate (MFO) has been expressed in mg/min (Perez-Martin & Mercier, 2001; Dumortier et al., 2002; Brandou et al., 2003, 2005, 2006a, 2006b), g/min (Achten et al., 2003; Achten & Jeukendrup, 2004; Jeukendrup, 2003), mg/min/kg body weight, mg/min/kg fat free mass, and more recently in mg/min/kg muscle mass (Lavault et al., 2011). Muscle can be evaluated from bioimpedance analysis with a validated equation (Janssen et al., 2000), and expression of MFO in mg/min/kg muscle offers at least two advantages: it helps to delineate the effects of training on muscle mass and on the ability of

each kg of muscle to burn lipids; it provides an index which has been shown to be predictive of the effects of exercise on weight loss (Lavault et al., 2011) as indicated below. A MFO lower than 5 mg.min^{-1}.kg^{-1} muscle mass predicts poor exercise induced weight loss while as a higher MFO value predicts more efficient exercise induced weight loss. MFO ranges on the average between 38 and 1073 mg/min and the boundary of the lowest quartile is 140 mg/min. The LIPOXmax occurs at a very variable level between 3.6 and 101.5% of P$_{maxth}$ so that the boundary of the lowest quartile is 22% (ie, it is at 64.01% ± 0.52% of FC$_{maxth}$ the boundary of the lowest quartile is 58%. Expressed in % of the reserve heart rate *ie* 44.5% of VO$_2$max. Thus targeting, on theoretical grounds, these values ±5 % would be actually set at the LIPOXmax in only 30-40% of subjects, ie 60-70% of patients would not be trained at the expected level. The crossover point occurs on average at 32% of W$_{maxth}$ so that the boundary of the lowest quartile is 23.4%. This corresponds to 45% of VO$_2$max (Brun et al., 2009b). Therefore, in an average French population, the LIPOXmax occurs around 30% of W$_{maxth}$ ie 45% of VO$_2$max. In sedentary obese and diabetic patients, there is now considerable evidence that this level is more or less lowered and is sometimes extremely low. The point where there are no longer lipids oxidized (LIPOXzero or FATmax) is at 80% of P$_{max}$ ie 85-90% of VO$_2$max (Brun et al, 2011c).

In addition as shown on Table 4, the LIPOXmax is shifted to lower intensities and the MFO is decreased in many situations referred as "glucodependence" (obesity, diabetes, sleep apnea… etc)

3.2 Physiological relevance of the balance of substrates at exercise as assessed with exercise calorimetry

During steady-state exercise at low intensity (LIPOXmax or below), lipid oxidation remains stable at the level predicted by exercise calorimetry over 45 min or more (Jean et al., 2007; Meyer et al., 2007).

When higher intensities are reached (60% VO$_2$max or more) there is a gradual increase in lipid oxidation when the duration of exercise increases. This enhanced fat oxidation results from a decrease in muscle glycogen content which diminishes the availability of CHO in the exercising muscle. For example, a 2hr exercise at 60% VO$_2$max induces a 77% reduction in muscle glycogen depletion (Thomson et al., 1979). The shift to lipids has been shown to occur when there is a reduction of 30-40% of glycogen stores (Kirwan et al, 1988).

Exercise calorimetry thus can be used as a basis for targeted training, as discussed below. On the other hand, the ability to oxidize lipids during exercise is likely to reflect a profile of "metabolic fitness" that is impaired in some diseases and improved by training, and which is correlated to muscle physiological status.

3.3 How short can be the steps of an exercise calorimetry?

The basic assumption that underlies exercise calorimetry is that blood lactate generation during exercise has minimal influence on RER after 3-4 minutes of exercise performed at a steady state. In this condition, the extra-CO$_2$ production from blood HCO$_3$- buffers can indeed be regarded as negligible. One can calculate that even the fastest increase (approximately 2 mmol^{-1}min^{-1}) in blood lactate produces an increase of VCO$_2$ by only 3%. Indeed, if we assume that the volume of distribution of lactate is proportional by a factor of 100 ml.kg^{-1} to body mass and thus represents approximately 8 L, this would mobilize 16 mmol HCO$_3$- and generate, over 6 min, roughly 1.8 CO$_2$ l.min^{-1}. Under these conditions,

VCO_2 would increase by less than 0.06 l.min^{-1}, *ie* roughly 3%. Thus, the increase in RER in these exercise conditions is almost completely explained by the balance between oxidized carbohydrates and lipids, independent of blood lactate. The validity of this calorimetric approach is further confirmed by a classical work of Romijn (Romijn et al., 1992) who showed in highly trained sportsmen that up to 80-85% VO_2max calorimetric calculations based on respiratory exchanges during exercise closely fit with much more sophisticated measurements using stable isotopes (MacRae et al., 1995). Concerning proteins, if one compares exercise bouts at 33 and 66% of VO_2max it can be demonstrated that their use for oxidation remains stable at the various levels of exercise, supporting the basal assumption that the balance of substrates may be interpreted in terms of respective percentage of oxidized fat and carbohydrates.

We have presented above our procedure based on 6-minutes workloads. However, other investigators (Achten et al., 2002) have simultaneously developed a procedure based on 3-minutes "ultra-short" workloads. This latter method has been validated by its promoters in athletes and healthy sedentary subjects (Achten et al., 2002, 2003). Actually, there was a paucity of data about its validity in very sedentary patients, in whom it usually takes more time to obtain a steady state of respiratory exchanges. We recently compared calorimetry data obtained with this procedure (2nd-3rd minutes) with the one presented above (5-6th minutes) and found that values measured during the 3 minutes steps are poorly correlated with values measured during the 6 minutes steps, due to an overestimation of steady state RER that can be as high as 0.35. This shift results in an average overestimation of carbohydrate oxidation of 15.8 mg/min (this difference can reach 1200 mg/min). Besides, lipid oxidations are poorly correlated between the two methods. Therefore, among very sedentary patients in whom these tests are used for targeting physical activity, 3-min steps appear too short to allow accurate calorimetric calculations. Our protocol based on 6-minutes workloads seems preferable (Bordenave et al., 2007).

As already developed above, Romijn (Romijn et al., 1992) compared, in highly trained endurance cyclists, calorimetric results and isotopic measurement during exercise tests up to 85% VO_2max and showed that at this level calorimetry is fully reliable. However, a look at the figures of this paper shows that the steady state of RER occurs after 4 min and is not obtained after 2 minutes. In addition, we recently showed that the estimate of lipid oxidation by this method during the 5th and 6th minutes of a 6 min step predicts fairly well the actual lipid oxidation rate that would be observed over 45 minutes performed at the same level (Fig.4). The mean difference between the predicted value and the measured value is only 4.51±8.7 mg/min (Jean et al., 2007). Meyer (Meyer et al., 2007) also reported that VO_2 used for fat oxidation after 6 min closely predicted fat oxidation measured between 30 and 40 min of a constant-load exercise performed at the same intensity. These two observations further support the use of the 6-min steps procedure rather than the 3-min steps procedure proposed by the team of Jeukendrup (Achten et al., 2002) that seems to be accurate mostly for sports medicine and exercise physiology but less reliable in sedentary subjects.

A recent study further addressed this issue in prepubertal children. Comparison of 10 min and 3 min steps showed that the 3 min procedure yielded a satisfactory assessment of the power intensity where the maximum was reached (55% VO_2peak) with 95% satisfactory limits of agreement ± 7% VO_2peak, but that the value of the lipid oxidation rate was less precisely assessed in this population with the 3 min procedure. The authors concluded that, in children, the 3 min procedure provides a valid estimation of the power intensity but was less precise for assessing the flow rate (Zakrzewski & Tolfrey, 2011).
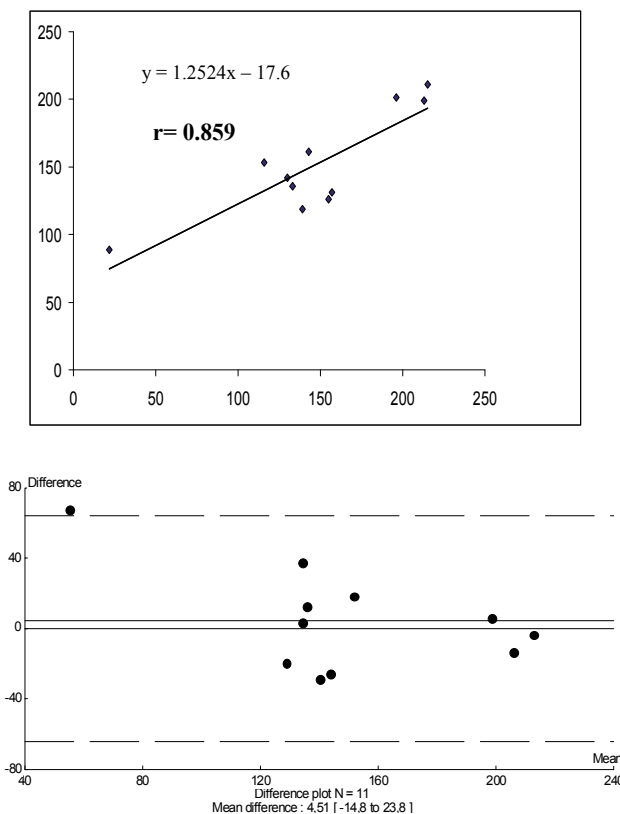
Fig. 4. Correlation and Bland-Altman plot showing the agreement between the measurement of MFO with LIPOXmax protocol and the average lipid oxidation rate maintained over 45 min during a steady state exercise set at this intensity level.

3.4 Factors of variation and reliability of LIPOXmax/FATmax

Initial studies on exercise calorimetry unanimously reported a fair reliability, which seems to be confirmed by daily clinical practice. The coefficient of variation (CV) for the LIPOXmax (at that time it was manually determined) was found to be 11.4% (Perez-Martin et al., 2001) and with Achten and Jeukendrup's procedure in 10 males tested three times it was 9.6% ie ±0.23 l/min (Achten et al., 2003). Similarly Michallet in 14 subjects aged 19-50 years found with the current LIPOXmax procedure a CV equal to 8.7%. The crossover point PCX appeared somewhat less reproducible with a CV of 17% (Michallet et al., 2006). However, Meyer investigating this methodology, reported variability as high as ±0.91 l/min that was supposed to be too wide (Meyer et al., 2009). Meyer's paper actually investigated the reproducibility in non-standardized conditions concerning recent exercise and food intake, two major modifiers of the balance of substrates, and therefore his conclusions are restricted to subjects tested in similarly non standardized conditions. More recently a careful methodological study proposing a more standardized approach based on prior determination of VO_{2max} by a maximal exercise test evidenced an even better reproducibility as low as 5.02% (Gmada et al, 2011). Therefore, on the whole, it is clear that the LIPOXmax is a fairly reproducible measurement, unless conditions of measure are not standardized for

the major factors of variation such as exercise or prior meal (see Table 3). This last remark is important because, like all physiological parameters, the LIPOXmax can be acutely modified by several factors (see Table 4).

Author (reference)	Parameters of reproducibility	remarks
(Perez-Martin et al., 2001)	CV= 11.4%	Early LIPOXmax protocol, visual determination
(Achten et al., 2003)	CV= 9.6% ie ±0.23 l/min	FATmax protocol
(Michallet et al., 2006)	CV = 8.7%	Current LIPOXmax protocol
(Meyer et al., 2009)	Variability ±0.91 l/min	Not standardized for prior exercise and feeding
(Gmada et al, 2011)	CV= 5.02%	Standardized determination after prior maximal test to determine VO_{2max} markedly increases reproducibility of the LIPOXmax protocol

Table 3. reproducibility studies of the LIPOXmax/FATmax: reproducibility is fair unless patients are not fasting and not standardized for recent previous exercise, and reproducibility is even greater if the protocol is more standardized

4. LIPOXmax/FATmax in sports medicine

As reviewed below, most literature on the LIPOXmax/Fatmax deals with alterations of this parameter in patients and its potential interest for exercise targeting. However, there are some reports suggesting that this parameter has some interest in athletes.

Modifying factor	Effect	references
previous meal taken less than 3 hr before	decreased MFO and shifted LIPOXmax to a slightly lower intensity	Bergman & Brooks, 1999; Jeukendrup, 2003; Friedlander et al., 2007
high-fat diets in which more than 60% of the energy is derived from fat	decreases fat oxidation during exercise, even if the diet is consumed for only 2 to 3 days, due to reduced muscle glycogen stores	(Coyle et al., 2001).
previous exercise performed just before the exercise calorimetry	MFO slightly increased	(Chenevière et al., 2009a)
puberty	LIPOXmax and MFO are higher in prepubertal children and gradually decrease throughout puberty to reach adult values at the end of puberty	(Brandou et al, 2006b; Riddell et al., 2008 ; (Zakrzewski & Tolfrey, 2011b).
type of exercise	Higher during running than cycling in adults and in pre- to early pubertal children	(Achten et al., 2003; Zakrzewski & Tolfrey, 2011a).

Modifying factor	Effect	references
gender	Women oxidize slightly more lipids and on average their LIPOXmax occurs at higher power intensity This difference is confirmed in all studies but is actually quite moderate and has probably little relevance On the opposite, fat oxidation is higher in pre- to early pubertal boys compared with girls at similar relative (but not absolute) intensities	(Friedlander et al., 1998a, 1998b; Chenevière et al., 2011 ; Brun et al., 2009a ; Zakrzewski & Tolfrey, 2011b).
temperature	Shift to preferential CHO oxidation during exercise in hot environments. Reversal after acclimation and training.	Febbraio et al, 1994; del Coso et al, 2010
highly trained athletes	Most of them exhibit a markedly high ability to oxidize lipids during exercise but in some sports like soccer, a preferential use of CHO is observed	(Bergman & Brooks, 1999; Achten et al., 2003; Venables et al., 2005; González-Haro et al., 2007; Varlet-Marie et al., 2006).
Obesity and diabetes	LIPOXmax values markedly shifted to lower power intensities and MFO lowered.	(Perez-Martin et al., 2001; Sardinoux et al., 2009)
Metformin	increases fat oxidation during exercise and decrease its postexercise rise	(Malin et al., 2010).
type 2 diabetes	Lower ability to oxidize lipids when compared to subjects matched for body mass index (difference not found by others)	(Ghanassia et al., 2006; Mogensen et al., 2009)
type 1 diabetes	Lower ability to oxidize lipids	(Brun et al., 2008).
sleep apnea syndrome	Lower ability to oxidize lipids at exercise. Training improves both apnea-index and lipid oxidation at exercise	(Desplan et al., 2010).

Table 4. Factors of variation of LIPOXmax/FATmax

4.1 Endurance training improves the ability to oxidize fat during exercise

Over the 60-70 the literature is full of papers showing that endurance training allows fat to become the predominant substrate for endurance exercise, while other leading authors in that time emphasized the importance of CHO-derived energy stores for exercise performance (see review in Brooks & Mercier, 1994). According to the initial formulation of the crossover concept, it could be expected that endurance athletes would exhibit a profile of "lipid oxidizers" proportional to their fitness and the efficacy of their training. Most of the exercise calorimetry studies in athletes confirm this early statement. They show that on the average endurance-trained athletes oxidize more lipids. Data from cross-sectional and longitudinal studies have supported the notion that training reduces the reliance on CHO as an energy source, thereby increasing fat oxidation during submaximal exercise (Achten et al., 2004). In pre- to early pubertal children, brisk walking or slow running promotes higher fat oxidation (Zakrzewski & Tolfrey, 2011). A specific study on the effects of endurance training in women shows that endurance-trained women had a higher fat oxidation rate, but their peak values occur at a very similar intensity (56±3% VO_2max) compared with the untrained women (53±2% VO_2max) (Stisen et al., 2006). González-Haro and coworkers have fairly evidenced in high competitive level triathletes and cyclists various profiles of high

lipid oxidation which differ among sports (González-Haro et al., 2007). However, the reason for the inter-individual variability of these parameters remains poorly understood (Achten & Jeukendrup, 2003, 2004; Brun et al., 2000; Jeukendrup & Wallis, 2005). Clearly, energetic pathways favorized by specific training programs may be markedly different among sports.

4.2 Endocrine correlates of this profile of high lipid oxidation

In soccer players relationships between the GH-IGF-I axis and the LIPOXmax were reported (Brun et al., 1999). These correlations are likely to reflect either a parallel effect of training on muscle fuel partitioning or IGF-I release, or an action of IGF-I (or GH via IGF) on muscular lipid oxidation (Fig. 5).
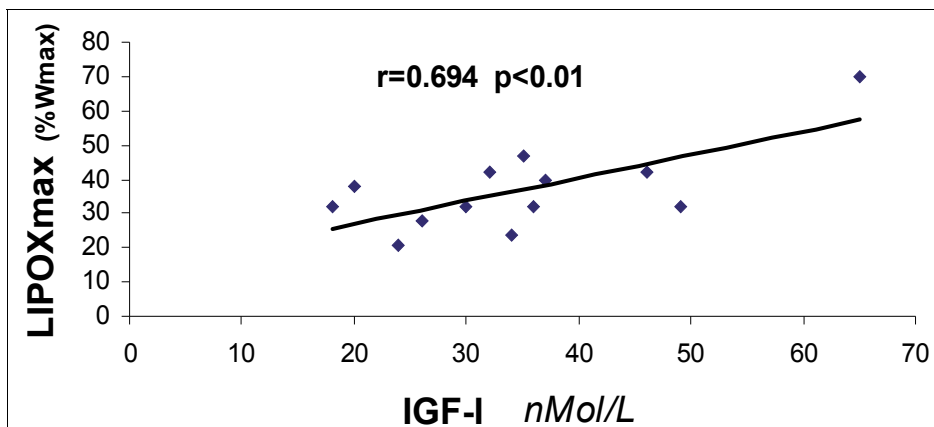
Fig. 5. Correlation between Insulin-like growth factor 1 (IGF-I) levels and the LIPOXmax in soccer players (Brun et al., 1999).

4.3 Are there 'glucodependent' sports

While low intensity training, as shown above, increases lipid oxidation, high intensity training has been reported to improve the ability to oxidize carbohydrates (Manetta et al., 2002a, 2002b).

Varlet-Marie et al (Varlet-Marie et al., 2006) described the profile of lipid oxidation in 90 trained athletes: 28 cyclists, 32 male soccer players, 19 male rugby players, 11 rugbywomen (national level in soccer and male rugby and regional level in cyclism and female rugby) and 41 healthy sedentary volunteers. All athletes had been involved in regular training for several years (>3 years), and trained 10.69 ± 0.9 hr/wk. The soccer team performed over the year a combination of endurance training under the form of interval training, strength training, speed training, skill and tactical training, in various proportions according to the period. Rugbymen and rugbywomen underwent an heavy training mostly based on strength training. The cyclists performed 14 hours of cycling (*ie*, about 450 km) per week during a nine-month training period. During the first month, training sessions were performed at low intensity with a specific target (below their ventilatory threshold: VT). During the other months, they added interval-training sessions to their endurance training, wherein they performed at high intensity with a specific target heart (above their VT).

When expressed as raw power values, the LIPOXmax and the crossover point ranked as follows: rugbymen > cyclists > male controls > rugbywomen > female controls > male soccer players (Figure 6).
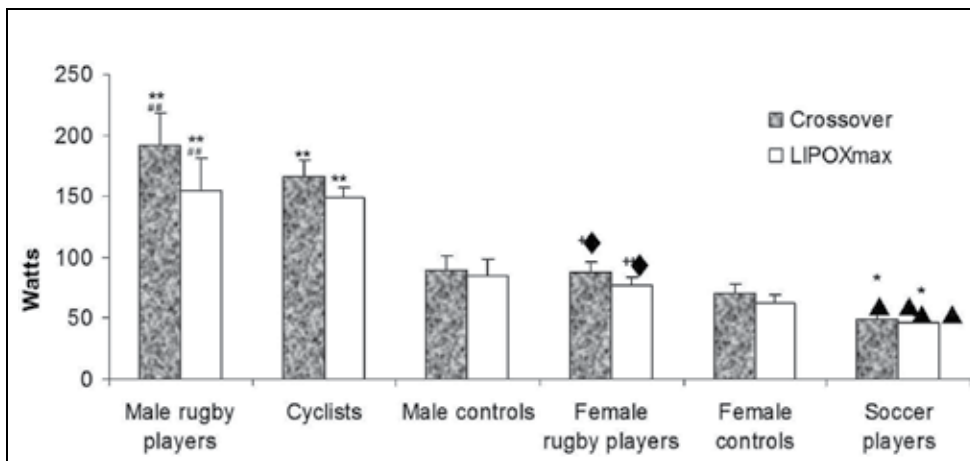
Fig. 6. Comparison of the power at which occur the crossover point and the LIPOXmax in control subjects and in various groups of athletes. *p<0.05; **p<0.0001 (male athletes vs. male control subjects); ##p<0.0001 (male rugby players vs. soccer players); ▲▲p<0.0001 (cyclists vs. soccer players); ◆p<0.05 (female rugby players vs. female control subjects); ++p<0.0001 (female rugby players vs. male rugby players)

When they were expressed as percentages of theoretical maximal power this ranking became: cyclists > rugbywomen > rugbymen > female controls > male controls > soccer players (Figure 7). Raw lipid oxidation rates at the level of the LIPOXmax ranked as follows (Figure 8): rugbymen > cyclists > rugbywomen > sedentary male controls > soccer. If lipid oxidation is expressed per kg of body weight this ranking becames: cyclists > rugbymen > rugbywomen > sedentary female controls > sedentary male controls > soccer players (Figure 9).
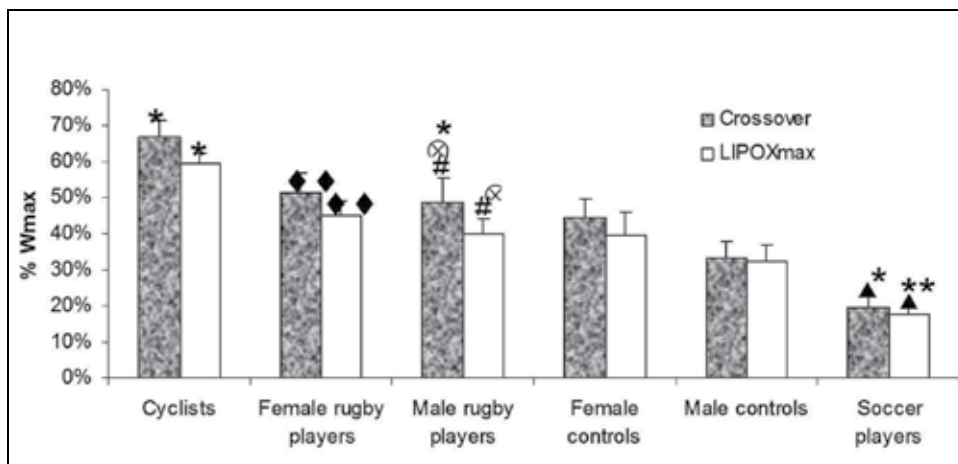
Fig. 7. Comparison of the crossover point and the LIPOXmax, expressed in % of Wmax, in control subjects and in various groups of athletes. *p<0.05; **p<0.0001 (male athletes vs. male control subjects); ##p<0.0001 (male rugby players vs. soccer players); ▲▲p<0.0001 (cyclists vs. soccer players); ◆◆p<0.0001 (female rugby players vs. female control subjects); ⊗p<0.05; ⊗⊗p<0.0001 (cyclists vs. male rugby players)

This study evidences markedly different patterns of balance of substrates among groups of athletes. Clearly, cycling and rugby are rather characterized by high rates of lipid oxidation which peaks at high exercise intensities, while in soccer there is an early predominance of CHO.

The finding of a high ability to oxidize lipids in athletes submitted to regular endurance training, like cyclists, is consistent with previous literature (Achten & Jeukendrup, 2003). By contrast, it is interesting to notice in soccer players, a pattern of "glucodependence" that implies a reduced reliance on lipids at exercise. Although in our study we can only present data on soccer, this pattern is likely to occur in several sports. Since exercise training at high intensity (Manetta et al., 2002a, 2002b) and intermittent exercise (Perez-Martin et al., 2000) both increase the ratio between CHO and fat used for oxidation during muscular activity, this pattern may reflect an adaptation of muscle metabolism to short repeated bouts of high intensity. Interestingly, such a "glucodependence" is also found in obesity (Perez-Martin et al., 2001) and type 2 diabetes (Blanc et al., 2000). In this case it can be rapidly reversed by a few weeks of targeted exercise training at the level of the LIPOXmax (Dumortier et al., 2002, 2003). Since physical inactivity rapidly shifts the balance of substrates at rest towards a lower ratio of lipid/CHO used for oxidation (Blanc et al., 2000) it can be assumed that sedentarity explains at least in part the glucodependence of these patients.
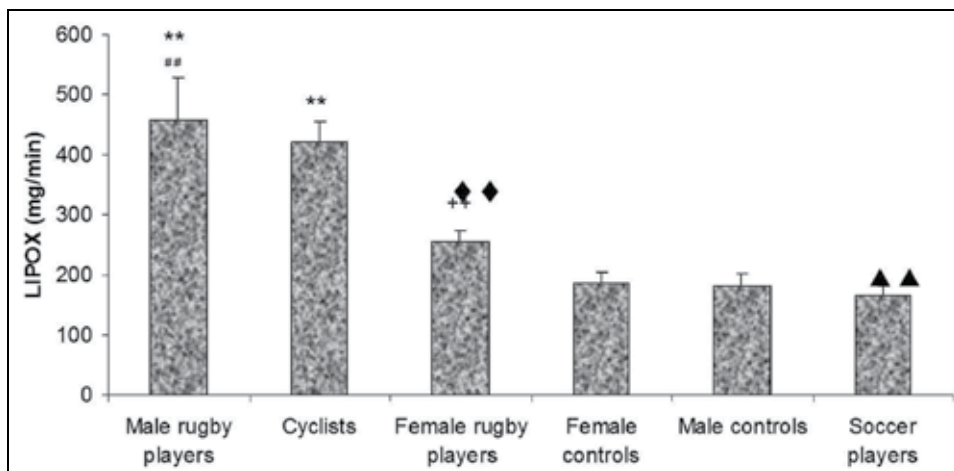
Fig. 8. Lipid oxidation rates in control subjects and in various groups of athletes, expressed in mg/min. **p<0.0001 (male athletes vs. male control subjects); ##p<0.0001 (male rugby players vs. soccer players); ▲▲p<0.0001 (cyclists vs. soccer players); ♦♦p<0.0001 (female rugby players vs. female control subjects); ++p<0.0001 (female rugby players vs. male rugby players)

4.4 Shifts in the balance of substrates during exercise with overtraining

According to the energy pathway mostly involved in a type of activity, training increases thus the ability to oxidize either lipids or CHO. This was clearly evidenced in a study conducted on competitive road cyclists in whom high intensity endurance training increased the ability to oxidize CHO above the ventilatory threshold, while at the end of the season most patients exhibited symptoms of overreaching associated with a reversal of this increase in CHO oxidation (Manetta et al., 2002a). By contrast overreaching in endurance athletes submitted to exercise calorimetry showed lowered ability to oxidize fat at low

intensities, leading to the concept that training effects on the balance of substrates at exercise are reversed by overtraining (Aloulou et al, 2003). This issue remains poorly documented and requires more investigation.
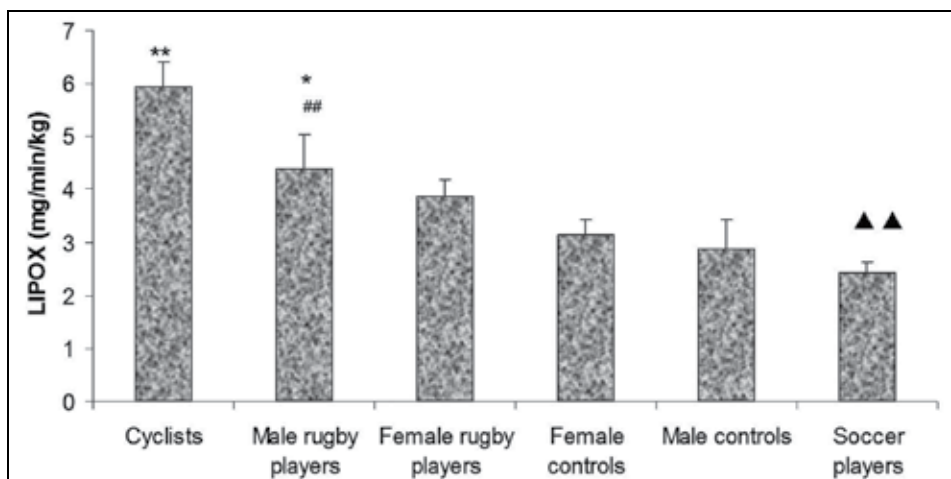
Fig. 9. Lipid oxidation rates in control subjects and in various groups of athletes, expressed in mg/min/kg of body weight.*$p<0.05$; **$p<0.0001$ (male athletes vs. male control subjects); ▲▲$p<0.0001$ (cyclists vs. soccer players); ##$p<0.0001$ (male rugby players vs. soccer players)

5. Interest of the LIPOXmax as a target for structured training in obesity and diabetes

5.1 Scientific background

It is now unanimously recognized that exercise is an efficient tool for : 1) preventing the onset of type 2 diabetes (Lindström et al., 2006; Kim et al., 2006); 2) improving blood glucose control (Marwick et al., 2009) and 3) preventing further weight regain in weight-reduced obese individuals (Bensimhon et al., 2006). Exercise is also beneficial for cardiovascular health, due to its positive effects on blood pressure (Pescatello et al., 2004; Pescatello, 2005), blood lipids (Kelley et al., 2006), inflammation (Fabre et al., 2002), blood viscosity (Brun et al., 2010b), mood (Krogh et al., 2010) and cognitive function (Fabre et al., 2002; Angevaren et al., 2008).

However the effects of exercise as a weight reducing procedure have been considered during many years as rather limited and almost negligible. It is beyond any doubt that regular exercise attenuates the metabolic drive to regain weight after long-term weight loss (MacLean et al, 2009). The interest of physical activity was thus mostly to prevent weight gain, to improve stabilization after slimming, and to reduce obesity-related co-morbidities but not to reduce weight by its own (Jakicic & Otto, 2005, 2006; Duclos et al., 2010).

This traditional view has been challenged by studies demonstrating that even without any change in diet, exercise alone may reduce body weight (Ross et al., 2000; Slentz et al., 2004). This has been further evidenced by a recent meta-analysis that concludes that exercise on its own improves the effects of a diet by on average 1.4 kg (Wu et al., 2009). It seems now well demonstrated that exercise considered alone can reduce body weight. The last American consensus (Donnelly et al., 2009) indicates that more than 250 min of weekly moderate-intensity physical activity is associated with clinically significant weight loss. Accordingly,

lower weekly amounts of moderate-intensity exercise (between 150 and 250 min per week) is effective to prevent weight gain, but can provide only modest weight loss by their own. They can result in significant weight loss if associated to moderate diet restriction but, interestingly, not severe diet restriction.

The picture is thus slightly modified. Exercise appears nowadays as an effective means to reverse overweight, but its effects are shown to be very variable, sometimes impressive, but often poor. A major explanation for this heterogeneity is that exercise may induce marked compensatory changes in energy intake (King et al, 2008). Therefore exercise should be combined with a dietary approach based on correction of compensatory behaviors and errors (Bouchard et al, 1990; Caudwell, 2009). This approach is surely more logic than the traditional restriction which has some short-term efficiency but almost always result in a subsequent weight gain due to homeostatic mechanisms of fat mass preservation (MacLean, 2011).

What is the most important: duration or frequency? Chambliss (Chambliss, 2005) examined the effect of duration and frequency of exercise on weight loss and cardiorespiratory fitness in 201 previously sedentary, overweight women (Chambliss, 2005) over 12 months. He found a mean weight loss after 1 year was 8.9, 8.2, 6.3 and 7.0 kg, for the vigorous intensity/high duration, moderate intensity/high duration, moderate intensity/moderate duration, and vigorous intensity/moderate duration groups, respectively, but there was no effect of exercise duration or exercise intensity on changes in body weight or in BMI. Duration of exercise (at least 150 min/week in walking) was more important than vigorous versus moderate intensity in achieving these goals.

Most of the studies make little or no reference to the substrate (lipid or CHO) that is oxidized during exercise. However, there is a rationale to do so, as largely described above. Multiple studies have show that fatty acid handling and oxidation is impaired in skeletal muscle of obese, impaired glucose-tolerant, and T2D individuals (Blaak, 2004; Corpeleijn et al., 2008, 2009; Kelley et al., 1999; Mensink et al., 2001). This defect leads to propose exercise protocols aiming at restoring muscular ability to oxidize lipids. For this reason, LI protocols designed for oxidizing more lipids during exercise sessions were described by several authors (Blaak & Saris, 2002; Blaak, 2004) and were shown to improve both the ability to oxidize lipids and body composition (Schrauwen et al., 2002).

As shown on the meta-analysis of 12 LIPOXmax training studies, 3 or 4 weekly sessions of 45 min cycling at the LIPOXmax result in a weight loss of -2.25 % [confidence range -3.53 to -0.97] which is at least as efficient as the various protocols studied in the literature (Romain et al., 2010). Therefore, LIPOXmax training is one of the strategies that can be proposed to reduce body weight in obese subjects. A comparison with other more classical protocols remains to be done.

The issue of the exercise protocol that should be recommended for weight maintenance remains incompletely studied. Cross sectional studies show that weight maintenance is improved with physical activity > 250 min per week. However, no evidence from well-designed randomized controlled trials exists to judge the effectiveness of physical activity for the prevention of weight regain after weight loss (Donnelly et al., 2009). According to this consensus document, resistance training does not enhance weight loss but may increase fat-free mass and increase loss of fat mass and is associated with reductions in health risk. Existing evidence indicates that endurance PA or resistance training without weight loss improves health risk. There is no evidence that PA prevents or attenuates obesity-related detrimental changes (Donnelly et al., 2009).

5.2 Standardized vs personalized targeting?

There is an important discussion that underlies all the controversies about exercise prescription in chronic diseases. This is: should we use standard or personalized exercise prescriptions. Some current rules of prescription emphasize the need for taking into account the personal characteristics of each patient, but they are by essence "standardized", ie, they do not take into account the specific physiologic profile of each subject. All is based on the assumption that the most important mechanism underlying the metabolic effect of exercise is to generate an energy deficit, regardless of the actual quantity of lipids or CHO that have been oxidized (Strasser et al, 2007).

Such a standardized approach was used in pneumology and cardiology, before it was challenged by a new paradigm: the "individualization concept". Personalized targeting of exercise has been promoted in respiratory and cardiac chronic diseases and was shown to provide better results (Vallet et al., 1997). The "Hippocratic" concept of superiority of the individualized approach is taken into account by a number of practitioners and appears in national guidelines (Guidelines, 2005). However, some guidelines do not mention it, considering that evidence for counseling is not sufficient (Rochester, 2003).

In metabolic diseases, such a discussion about the "individualization concept" has not yet been initiated. Usual French recommendations for exercise in diabetes (Gautier et al, 1998; Gautier, 2004) do not take into account the individual metabolic background. Authors only indicate a broad zone of % VO_2max or heart rates assumed to be the most accurate.

Extending the individualization concept to obesity and diabetes raises the question of a specific individual target, and obviously the LIPOXmax/FATOXmax appears as a logic candidate for this purpose. Accordingly, several teams have undertaken the study of the metabolic effects of exercise training targeted at this level.

5.3 Targeting endurance exercise close to the LIPOXmax vs higher intensity levels

A topic which has generated a lot of discussion over the last decade is the selection of the optimal exercise protocol that could be used for the management of obesity and diabetes. Initially, low intensity endurance training (LI), as it was know to be the variety of exercise that oxidized the highest quantity of lipids, was logically proposed (Thompson et al., 1998). However, later focus was given on other kinds of exercise such high intensity endurance training (HI), resistance training (RT) and interval training (IT). All of them were evidenced to exert beneficial effects when applied to obese (Jakicic & Otto, 2005, 2006) and diabetic (Praet & van Loon, 2007, 2009) patients. On the whole, LI remains the easiest and the most widely evaluated procedure. It is also the best demonstrated as shown by a recent meta-analysis on exercise and diabetes that selected 34 from 645 papers. This paper confirmed that endurance exercise alone improves Hba1c (-0.6%), blood pressure, (-6.08 mmHg) , and triglycerides (-0.3 mmol/L), while RT has no effects demonstrable by meta-analysis on these parameters (Chudyk & Petrella, 2011).

An overlook at the rapidly expanding body of knowledge in the field of molecular biology of muscle shows that either LI, HI, RT or IT are able to improve muscular function and to be helpful for the correction of metabolic disturbances (Burgomaster et al. 2008). It is however important to emphasize that RT and ET act on separate and antagonistic intracellular pathways (Koulmann & Bigard, 2006), hence they are independant tools that cannot be expected to provide equivalent effects on muscle cells.

At the cellular level (Koulmann & Bigard, 2006) endurance training induces a set of regulatory adaptations that improve mitochondrial function and protein synthesis and overall, the enzymes for both CHO and fat oxidation are increased. As a result of these cellular adaptations, exercise training improves whole body lipid metabolism and carbohydrate tolerance, thus consisting in a fully recognized tool for reducing both blood lipids and glucose (see below).

As reminded above, most exercise physiology papers describe exercise protocols applied at a given percentage of maximal aerobic capacity without reference to exercise calorimetry. When exercise is performed at 40% VO_{2max} or below, it is likely to be performed in the LIPOXmax zone, but, since LIPOXmax is frequently much lower in obese subjects, a significant percentage of subjects are likely to exercise above this zone, in the range where lipid oxidation is close to zero and CHO almost becomes the exclusive energy source.

Therefore, LIPOX training represents a better defined exercise protocol, whose effects on lipid oxidation are predictable. Exercise performed above this zone results in more CHO oxidation. This CHO oxidation may be followed by some degree of fat oxidation after exercise but may frequently fail to induce this lipid oxidation rise. Although the energetic balance is assumed to result in both cases in a negative fat balance, these two types of exercise do not involve the same energetic pathways.

At the date of redaction of this article, there are several studies (or abstracts) published in peer-reviewed journals reporting the results of LIPOX training (table 4). Therefore, these effects of LIPOX training can now be well described on the basis of a recent meta-analysis (Romain et al., 2010) that included 16 studies shown in table 1, *ie*, 247 participants belonging to 5 different populations: obese teenagers, metabolic syndrome, HIV patients with lipodistrophy, type-2 diabetics, and psychiatric patients treated by neuroleptics. Study length ranged between 2 to 12 months. Weekly frequency of sessions ranged between 2 and 4. Preliminary results showed that LIPOXmax was shifted to a higher power intensity by 4.93 watts (95% confidence interval (CI) 4.74-5.13; p<0.0001). Weight decreased by -2.9 kg (95%CI: -4.1; -1.7; p<0.0001). Fat mass decreased by 1.7% (95% CI 1.82 – 1.64; p<0.0001), and waist circumference decreased by -4.9 cm [95%CI: -6.6; -3.2] (p<0.0001).

We have not included in this meta-analysis an interesting study by the team of A. Sartorio (Lazzer et al, 2011) that compared over three weeks energy-matched programs of low intensity (40% VO2max) and high intensity (60% VO2max) endurance, and showed that the exercise in the LIPOX zone was twice more efficient for fat loss. This protocol was not exactly targeted on the LIPOXmax but designed to train the subjects in this zone, and its results are in agreement with those pooled in the meta-analysis.

The results of these studies demonstrate the efficiency of training targeted at the LIPOXmax on weight loss, even over a short time period. In diabetics, HIV-infected patients, and psychiatric patients under neuroleptics, the efficiency of this procedure seems to be lower than in obesity or metabolic syndrome. As expected, the association with a diet improves the efficiency of this training. However, two thirds of the studies were without added diet and thus most of the weight-lowering effects of LIPOX training are likely to be due to the effects of exercise alone on energy balance and eating behavior. Therefore, it is clear that LIPOX training alone decreases body fat, even if no specific diet is applied. This effect is clearly and constantly evidenced in training protocols containing as few as 2 or 3 sessions per week. In fact, the number of sessions per week seems to improve the results and a dose-relationship can be postulated. However, this issue remains to be specifically investigated.

A crucial issue is that the extent of fat loss in response to exercise training varies quite widely among individuals (Snyder et al., 1997; King et al., 2008; Byrne et al., 2006), even when differences in compliance to the exercise program and energy intake are accounted for. In other terms, exercise is very efficient to lose weight in some individuals while in others it fails to induce weight loss and even more may induce weight gain. Focus on the specific profile of responders and nonresponders helps to understand this variability. It appears to be explained by two variables: eating behavior and fat oxidation.

A role for fat oxidation is suggested by recent studies. In sedentary premenopausal women, a 7-week endurance-type exercise training program reaching progressively to 5 x 60 minutes per week at 65% -80% of predicted maximum heart rate resulted in a mean change in fat mass for the group was -0.97 kg (range +2.1 to -5.3 kg). The strongest correlate of change in fat mass was exercise energy expenditure, as expected. However, the change in fasting RER correlated significantly with the residual for change in fat mass after adjusting for the effects of both exercise energy expenditure and change in energy intake. This means that training-induced increase in fat oxidation explains 7% of the variance of exercise-induced weight loss. In multiple regression analysis, exercise energy expenditure and change in fasting RER were the only statistically significant predictors of change in fat mass, together explaining 40.2% of the variance. Thus, fat loss in response to exercise training depends not only on exercise energy expenditure but also on exercise training-induced changes in RER at rest. Whether it is also the case for RER during exercise is suggested by recent studies (Lavault et al, 2011). This suggests that development of strategies to maximize exercise-induced fat loss may be useful for optimizing exercise-induced slimming (Barwell et al., 2009).

Another important issue in these exercise-based strategies would be to control changes in eating behavior (Bouchard et al, 1990). Muscular activity may induce a temporary postexercise anorexia, which is dose-dependent on the intensity and duration of the exercise (King et al, 1994; Westerterp-Plantenga et al, 1997). On the long term, the effect of exercise on eating behavior are complex and variable and largely explain the variability of weight loss responses. In fact, recent studies show that the effects of regular exercise on appetite regulation involves at least 2 processes: an increase in the overall (orexigenic) drive to eat and a concomitant increase in the satiating efficiency of a fixed meal (King et al, 2009). The former may be related to glycogen deficiency, which increases appetite (Melanson et al, 1999), so that exercise protocols that spare glycogen may avoid this increase in orexigenic drive (Hopkins et al, 2011). Exercise targeted at the LIPOXmax, due to its greater reliance on fat, is likely to spare more glycogen and thus to be less orexigenic than acute exercise that oxidizes mostly carbohydrates.

Clearly, exercise may be an efficient and safe technique to lose fat as shown by the results obtained in responders. The study of non responders suggests that focus on the two parameters explaining the lower efficacy of exercise (fat oxidation and eating behavior) may help to improve the results. Targeting on lipid oxidation during exercise may be a way to better control these two parameters. More studies are needed to verify this concept (Hopkins et al, 2011).

5.4 LIPOX training improves mitochondrial respiration and enzymes of lipid oxidation

Bordenave (Bordenave et al., 2008) described the effects of ten weeks of mild exercise training targeted at the LIPOXmax (45 min of cycling, twice a week). This training was not sufficient to significantly decrease weight, but it exhibited marked effects on whole body

lipid oxidation and muscle oxidative capacities. Indeed, after training, the LIPOXmax was shifted to higher power intensity and the MFO was significantly increased compared with pre-training values (+51 mg.min^{-1}). This study included biopsies and evidenced LIPOX training-induced improvements in mitochondrial respiration and citrate synthase activity. Changes in whole body lipid oxidation were associated with changes in parameters of muscle oxidation. In another study the 3-Hydroxyacyl-CoA dehydrogenase (HAD), an important enzyme that functions in mitochondrial fatty acid beta-oxidation by catalyzing the oxidation of straight chain 3-hydroxyacyl-CoAs, was studied in trained and untrained women. It was shown that HAD activity and fat oxidation rates were highly correlated indicating that training-induced adaptation in muscle fat oxidative capacity is an important factor for enhanced fat oxidation (Stisen et al., 2006).

5.5 Does LIPOX training increase REE and resting fat oxidation?

There is no study on the effects of LIPOX training on resting fat oxidation. Endurance training at higher levels yields conflicting results and it is likely that this effect is not constant with endurance protocols. A study by Van Aggel-Leijssen (Van Aggel-Leijssen et al., 2001) using a low-intensity exercise training program (40% VO$_2$max, ie the LIPOXmax zone) three times per week for 12 weeks showed that this variety of training increased the contribution of fat oxidation to total energy expenditure during exercise but failed to do so at rest in obese women (Van Aggel-Leijssen et al., 2001). However, another study may suggest an effect of endurance training in the LIPOXmax zone or below on resting fat oxidation. A very mild exercise consisting in an increase of regular physical activity equivalent to 45 min of walking 3 days/week induces some improvements in lipid metabolism such as an increase in skeletal muscle protein expression of PPARdelta and UCP3 in type 2 diabetic patients (Fritz et al., 2006), and improves lipid oxidation without changes in mitochondrial function in type 2 diabetes (Trenell et al., 2008). This protocol of walking an extra 45 min per day over an 8-week period is an insufficient stimulus to induce detectable mitochondrial biogenesis but demonstrates physical activity-induced enhancement of resting lipid oxidation, independently of intramuscular lipid levels. A specific study on LIPOXmax training and lipid oxidation at rest in obese and nonobese people remains to be done.

5.6 Low intensity training targeted at the LIPOXmax training improves inflammatory status

Low-grade systemic inflammation is suggested to play a role in the development of a variety of chronic diseases including obesity, diabetes and cancer. A number of studies suggest that in these diseases regular exercise has anti-inflammatory effects therefore it may contribute to suppress systemic low-grade inflammation (Mattusch et al., 2000; Stewart et al., 2007; Goldhammer, et al., 2005). Overall, both endurance and resistance training decrease C-Reactive Protein (CRP) (Martins et al., 2010). In two studies, LIPOXmax training has been shown to decrease CRP (Ben Ounis et al., 2010; Brun et al, 2011b). In these studies, inflammatory parameters were also measured and changes in CRP were negatively related to those of lipid oxidation during exercise, suggesting that the improvement in the ability to oxidize lipids during exercise is associated with an anti-inflammatory effect. Further studies are needed.

5.7 LIPOXmax training maintains fat-free mass

All the aforementioned studies show that LIPOXmax training maintains fat-free mass, and in some of them an increase is found. This is a constant finding, while protocols using higher intensities in patients give less consistent result on fat-free mass (Brandou et al., 2005; Brun et al., 2010a). Obviously, it is well demonstrated that correctly performed resistance training is an efficient way to improve fat free mass (Schoenfeld et al., 2010), but low intensity exercise has also been demonstrated to protect lean mass and to prevent protein breakdown. A 45-min walk on a treadmill at 40% VO_2 peak induced short-term increases in muscle and plasma protein synthesis in both younger and older men (Sheffield-Moore et al., 2004).

In a study on dieting postmenopausal women with a total energy expenditure of 700 kcal/wk, *ie*, 8 kcal.kg body weight $^{-1}$wk^{-1} with LI being at 45-50% if heart rate reserve (HRR) and HI at 70-75% (vigourous-intensity) of HRR (Nicklas et al., 2009) found that with a similar amount of total weight loss, lean mass is preserved with either moderate- or vigorous-intensity aerobic exercise performed during caloric restriction and concluded that FFM is equally preserved with LI and HI. Both resistance (RE) and endurance (EE) exercise are able to stimulate mixed skeletal muscle protein synthesis, but the phenotypes induced by RE (myofibrillar protein accretion) and EE (mitochondrial expression) training are different and this is probably due to differential stimulation of myofibrillar and mitochondrial protein synthesis (Koulmann et al, 2006; Wilkinson et al., 2008; Harber et al., 2009). A mechanism that may play a role in this protective effect of LI is glycogen sparing. It has been shown that CHO availability influences the rates of skeletal muscle and whole body protein synthesis, degradation and net balance during prolonged exercise in humans (Howarth et al., 2010). On the whole, although more investigation is required, LIPOXmax training is an efficient way to maintain or even to improve fat-free mass by increasing the mass of metabolically active muscle. At the beginning of training protocols in very sedentary patients, it may be used for this purpose. For example, studies in undernutrition situations such as anorexia nervosa are in progress.

5.8 Comparison between high intensity (HI) and low intensity (LI) training

It is clear that during LI even more if it is targeted at the LIPOXmax quite important quantities of lipids are oxidized. By contrast, HI oxidizes mostly or exclusively CHO. HI is sometimes followed by a slight rise in oxidation of lipids, but this quantity of lipids oxidized postexercise remains low (Chenevière et al., 2009a; Warren et al., 2009) even more when HI is not continuous (interval training [INT]). Therefore, LI and HI or INT are not equivalent tools and have distinct properties.

This is clearly evidenced in a recent study comparing INT and LIPOX training in T2D (Brun et al., 2010a). 63 type-2 diabetics were compared over a period of 3 months without nutritional intervention: 39 were trained at the LIPOXmax determined with exercise calorimetry, 12 were submitted to a square wave endurance exercise-test (SWEET) protocol of training, and 12 untrained patients served as controls. After 3 months, both training procedures increased VO_{2max} (SWEET training +42% vs LIPOXmax training +14%) and this effect was stronger with SWEET than with LIPOXmax. SWEET training reduced resting systolic blood pressure (-12mmHg) and total cholesterol (-0.29 mmol/l), while LIPOXmax training did not. Both procedures decreased weight and BMI. As expected, the LIPOXmax training improved the ability to oxidize lipids (maximum lipid oxidation rate +53 mg/min) shifted to a higher power intensity (+21 watts), decreased fat mass (-1 kg), increased fat-free

Author	Journal	number	population	protocol	Duration (month)	Weight (Kg)	Waist circumference (cm)	Change in Fat Mass (Kg)	Change in total cholesterol (mmol/l)
Ben Ounis et al., 2008	Diabetes & metabolism	8	Obese adolescent	Training	2	-1,9	-1,8	-1,7	-0,21
Ben Ounis et al., 2008	Diabetes & metabolism	8	Obese adolescent	Training +diet	2	-11,5	-12,3	-11,2	-0,51
Brandou et al., 2003	Diabetes & metabolism	14	Obese adolescent	Training	2	-3,72	-3,73		0,04
Brandou et al., 2005	Diabetes & metabolism	7	Obese adolescent	Training +diet	3	-5,2		-5,07	
Dumortier et al. 2003	Diabetes & metabolism	28	Metabolic syndrome	Training	2	-2,6	-3,53	-1,4	
Fedou et al., 2008	Science et Sport	10	AIDS	Training	12	-0,92		-0,01	-0,28
Ben Ounis et al., 2009a	Science et Sport	18	Obese adolescent	Training	2	-2	-2,9	-2	
Ben Ounis et al., 2009a	Science et Sport	18	Obese adolescent	Training +diet	2	-6	-6,9	-7	
Dumortier et al., 2002	Clinical Hemorheology	21		Training	2				0
Bordenave et al., 2008	Diabetes & metabolism	11	T2D	Training	2			-3,13	
Ben Ounis et al., 2009b	Annales d'endocrinologie	9	Obese adolescent	Training	2	-1,2		-1,4	
Ben Ounis et al., 2009b	Annales d'endocrinologie	9	Obese adolescent	Training +diet	2	-9,5		-5,9	
Jean et al., 2006	Annales d'endocrinologie	28	T2D	Training	3	-1,3	-3,94	-0,66	-0,01
Romain et al., 2009	Science et Sport	17	Neuroleptic treated	Training	3	-2,9			
Venables & Jeukendrup, 2008	Med Sci Sports Exerc	8	Obese	training	2*4 wk	-0,2		-0,1	
Mogensen et al., 2009	diabetes, obesity and metabolism	12	T2D	training	2,5	0	-2,8	-1,5	
		7	Obese adolescent	training	2	-1,7			
Elloumi et al., 2009	Acta Paediatrica	7	Obese adolescent	Training +diet	2	-12,3	-10,5	-12,1	
Brun et al., 2010a	Diabetologia	39	T2D	Training	3	-2,23			

Table 5. Studies of training at the LIPOXmax/FATmax

mass (+1 kg), decreased waist circumference (-3.8 cm) and hip circumference (-2.2 cm) while SWEET training did not significantly modify any of those parameters. Over this short period, the effects of training on HbA1c were significant in the LIPOXmax group (-0.15%) but not in the SWEET group.

Roffey (Roffey, 2008) compared, in a randomized experiment, supervised cycling training at a constant-load FATmax intensity with high intensity interval training (HIIT) with intervals at 85% VO2max, both protocols being matched for total mechanical work volume (11250 kCal). Although both procedures reduced fat mass, the effect was twice more important in FATmax trained subjects than HIIT. A decrease in waist circumference and total cholesterol was evidenced with FATmax but not HIIT. Both procedures decreased systolic blood pressure and increased VO2max.

Put together, these studies show that interval training improves aerobic working capacity, blood pressure and lipid profile, while low intensity endurance training (LIPOXmax training) improves the ability to oxidize lipids during exercise, increases fat free mass, decreases fat mass and decreases HbA1c. The benefits of these two procedures are thus quite different and both are probably interesting to associate in the management of 2 type 2 diabetes.

The psychological tolerability of LIPOXmax training, and more generally low intensity endurance training, compared to high intensity training is poorly known. There is no specific study about the psychological tolerance of LIPOXmax training but some information exists about the effects of prescribing moderate vs higher levels of intensity and frequency on adherence to exercise prescriptions (Perri et al., 2002). In 376 sedentary adults randomly assigned to walk 30 min per day at a frequency of either 3-4 or 5-7 days per week, at an intensity of either 45-55% or 65-75% of maximum heart rate reserve, analyses of percentage of prescribed exercise completed showed greater adherence in the moderate intensity condition. The authors concluded that prescribing a lower frequency increased the accumulation of exercise without a decline in adherence, whereas prescribing a higher intensity decreased adherence and resulted in the completion of less exercise.

Interestingly, Roffey (Roffey, 2008) in his randomized work comparing FATmax training and HIIT, observed a number of clinically significant improvements in health-related quality of life in the FATmax but not the HIIT group.

5.9 Which exercise for diabetes?

Both endurance as well as resistance-type training have been shown to improve whole body insulin sensitivity and/or glucose tolerance and are of therapeutic use in diabetic and insulin-resistant subjects (Praet et al., 2007). Prolonged endurance-type exercise training has been shown to improve insulin sensitivity in both young, elderly and/or insulin-resistant subjects, due to the concomitant induction of weight loss, the upregulation of skeletal muscle glucose transporters GLUT4 expression, improved nitric oxide-mediated skeletal muscle blood flow, reduced hormonal stimulation of hepatic glucose production, and the normalization of blood lipid profiles.

Long-term resistance-type exercise interventions have also been reported to improve glucose tolerance and/or whole body insulin sensitivity. Other than the consecutive effects of each successive bout of exercise, resistance-type exercise training has been associated with a substantial gain in skeletal muscle mass, assumed improve whole body glucose-disposal capacity on the basis on the undemonstrated belief that the higher fat free mass, the higher insulin sensitivity.

While a recent meta-analysis concluded that the effects of both procedures on glucose homeostasis were similar, achieving a reduction in HbA1c by 0.6 to 0.8 (Snowling & Hopkins, 2006; Praet & Van Loon, 2009), a more recent one, after rigourous selection of papers for their methodology, concluded that endurance exercise alone improves Hba1c, blood pressure, and triglycerides, while RT has no demonstrable effects (Chudyk & Petrella, 2011). This issue remains thus controversial, and clearly the best demonstrated method remains endurance training.

When applying endurance-type exercise, energy expenditure should be equivalent to 1.7-2.1 MJ (400-500 kcal) per exercise bout on 3 but preferably 4-5 days/wk, since many of the benefits of exercise are temporary. More vigorous exercise in uncomplicated insulin-resistant states will further improve glycemic control and enhance cardiorespiratory fitness and microvascular function.

Endurance-type exercise combined with resistance (ie, intermittent intensity-type exercise) forms a lower cardiovascular challenge and improves functional performance capacity to a similar extent. Therefore, the combination of endurance- and resistance-type exercise is generally recommended, since its increases the diversity and, as such, the adherence to the exercise intervention program. This is in agreement with the above-reported study in which we compared INT and LIPOX training in T2D (Brun et al., 2010a) and which evidenced that SWEET training improves aerobic working capacity, blood pressure and lipid profile, while low intensity endurance training (LIPOXmax training) improves the ability to oxidize lipids at exercise, increases fat free mass, decreases fat mass and decreases HbA1c. This study shows that benefits of two procedures are rather different and both are probably interesting to associate in the management of type 2 diabetes. A study comparing LIPOX training to more traditional protocols is currently in progress.

Another important advance in this issue comes from a meta-analysis in diabetes (Umpierre et al, 2011) which shows that structured exercise is much more efficient for improving HbA1c than exercise advice alone, and that more than 150 minutes of endurance per week is twice more efficient than exercise performed less than 150 minutes per week.

6. Conclusions

LIPOXmax/Fatmax is a parameter that can be measured with validated protocols. It appears to be a reproducible measurement, although modifiable by several physiological conditions (training, previous exercise or meal). Its measurement closely predicts the amount of lipids that will be oxidized over a 45-60 min of low to medium intensity training performed at the corresponding intensity. It might be a marker of metabolic fitness, and reflects mitochondrial respiration. LIPOXmax is related to catecholamine status and the growth-hormone IGF-1 axis. Its changes are related to alterations in muscular levels of citrate synthase, and to the mitochondrial ability to oxidize lipids during exercise, reducing blood pressure and HbA1c in type 2 diabetes and decreasing circulating cholesterol. Whether the specific targeting on lipid oxidation during exercise has beneficial effects superior to those obtained by a similar energy deficit obtained by other protocols of exercise is suggested by recent studies but remains a current matter of research.

Little is known about the usefulness of these parameters in sports, but classification of athletes according to their metabolic profile during exercise may help to understand their ability to perform endurance sports or short term all of out exercise, and to detect overtraining-related alterations in metabolic adaptation to exercise.

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Glutamine and Glutamate Reference Intervals as a Clinical Tool to Detect Training Intolerance During Training and Overtraining

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1. Introduction

1.1 Training and overtraining

A training process consists of a sum of repeated exercise sessions with gradual overloads that are performed in a systematised and programmed way. The workload can be manipulated through variables such as weight load resistance, speed, duration, pauses between stimuli, muscular action, movement speed, amplitude, weekly frequency, number of sessions per day, number of exercises per session and the combination of different exercises in the same session.

Exercise triggers the synthesis of several enzymes and structural proteins that adapt tissues, organs and systems to changes in cellular homeostasis, in a task-oriented way and depending on the exercise stimulus. This set of chronic physiological and metabolic changes, currently termed supercompensation, allows for a more efficient and sustainable physiological environment during voluntary physical activity. Supercompensation supplies energy economy for habitual physical activities or enhances the energy supply during exercises of high metabolic demands. Recently, our group demonstrated, using proteomic analyses of rat muscle, that only one stimulus of exhaustive, incremental exercise (approximately 30 min) is enough to produce an acute, generalised, metabolic response in the muscular fibre (Gandra et al., 2010). This probably occurs to minimise the stress that will occur in a subsequent exercise session and, in the long term, the cumulative effects of exercise on gene expression lead to specific muscle phenotypic alterations, which is a major aspect of performance enhancement.

However, supercompensation is only achieved when the ratio between overload and recovery time is individually balanced. Damaged tissue structures resulting from the exercise stimulus are repaired during recovery, when rest and food intake are crucial for the energy supply that is required for the synthesis of new proteins and cellular components.

On the other hand, an excess of rest and a lack of exercise load may cause a loss of phenotypic adaptation, or performance stagnation. Therefore, athletes routinely use a continuous process of intense training to achieve maximal competitive performance (Bompa & Haff, 2009; Meeusen et al. 2006). The training load can be manipulated through substantial increases in duration, frequency, intensity or multiple variables simultaneously, along with a reduction of the regenerative period. However, a persistent imbalance between exercise load and recovery time can also lead to a state of chronic fatigue associated with previously acquired performance decrement, generally called overtraining (OT).

Throughout the years, different nomenclatures have been used to describe this loss of performance in previously well-adapted individuals, such as overtraining, overtraining syndrome (OTS), overreaching, non-functional overreaching (NFOR), staleness and chronic fatigue. Independent of the terminology, decreased performance seems to be the only critical feature of OT in human beings (Halson & Jeukendrup, 2004; Meeusen et al., 2006). Furthermore, OT may cause financial loss and emotional distress to trainers and athletes.

The European College of Sport Science proposed a change in terminology for OT (Meeusen et al., 2006). They defined OT as a continuous process of intense training that can generate different outcomes, depending on performance states. Upkeep, or a possible increase in performance after a brief recovery period (days to weeks), was named functional overreaching (FOR); meanwhile, a prolonged decay in performance, reversed only by a long regenerative period (weeks to months) was named non-functional overreaching (NFOR). Finally, the extreme state of the OT process was named OTS, where recovery may take years or may never happen.

The NFOR and OTS states can be associated with one or more symptoms, including accentuated catabolic state; physiological, immunological and biochemical alterations; increased incidence of injury; and mood alterations (Halson & Jeukendrup, 2004). Still, there is no set of conclusive characteristics that define the NFOR and OTS states. Diagnosis is only possible when a decrease in performance cannot be explained by other factors, such as high levels of muscle microtrauma (which is characterised by increased blood concentrations of muscle injury markers such as creatine kinase and lactate dehydrogenase), contusions, diseases, infections, allergies and abnormal cardiac symptoms (Meeusen et al., 2006). Elite athletes are susceptible to OT outcomes because they are constantly submitted to OT to maintain high physical performance during the training season. However, amateur sportsmen who do not respect the time for recovery between stimuli are also susceptible to undesirable OT outcomes.

There are many theories regarding the biological basis of the training–OT *continuum*, but the underlying mechanisms remain to be validated experimentally. Experimental difficulties that have impeded progress in this field include variability of research studies, the contradiction of applying a training program that aims to reduce functional physiological capacity and the lack of volunteer athletes willing to risk losing a season of training and competitions (Halson & Jeukendrup, 2004). These obstacles limit data collection to anecdotes from athletes who have been diagnosed as overtrained (Halson & Jeukendrup, 2004) due to the intensification of the training process (i.e., OT), which is routinely utilised by athletes who hope to improve their performance. Thus, physiological and psychological limits dictate a need for research that addresses the avoidance of the undesirable outcomes of OT, maximises recovery and successfully negotiates the fine line between high and excessive training loads (Kellmann, 2010).

1.2 Overtraining animal model

Experiments in humans must meet ethical requirements to protect the physical and emotional well-being of the volunteer subjects. Those subjects must also be aware of all possible benefits and disadvantages of the experimental protocol. Therefore, one must consider the risks of possible damage to the athlete's professional and social life when he or she is subjected to an OT induction protocol. Therefore, the study of OT in animal models is endorsed by The American Physiological Society (APS, 2006), which states that '...experimental protocols that use animal subjects are therefore developed when it would not be appropriate to use human subjects for studies of exercise's impact.'

Currently, animal models are used in all biological research areas. Claude Bernard (1865) advanced the principle of studying animal models and showed how findings in animal models could be translated to human physiology. A model is an imitation object that must have similar characteristics to the imitated object and the capacity to be manipulated without the limitations of the imitated object. Therefore, an OT animal model should display a set of similar alterations that would be expected in humans. In this vein, our group standardised an 11-week treadmill endurance training model using Wistar rats, where a gradual reduction in the recovery time between exercise sessions was introduced during the last three weeks (Hohl et al., 2009). Six incremental performance tests to exhaustion were performed during the training protocol, which is described in Table 1.

Experimental Weeks	Performance tests	Training Speed (m/min)	Training Time (min)	Number of Daily sessions	Recovery between training sessions (h)
	1	(--)	(--)	(--)	(--)
1st	no tests	15	20	1	24
2nd	no tests	20	30	1	24
3th	no tests	22.5	45	1	24
4th	2	25	60	1	24
5th to 7th	no tests	25	60	1	24
8th	3	25	60	1	24
9th	4	25	60	2	4
10th	5	25	60	3	3
11th	6	25	60	4	2

Table 1. Overtraining animal model protocol

This OT animal model was characterised by an adaptive training period (1st to 8th week) followed by a period of increased daily training sessions (9th, 10th and 11th weeks). This OT model is also unique because it allows for the comparison of two distinct groups of animals separated by performance *a posteriori*. One group show continuous performance improvement after 60 hours of complete rest, characterising the FOR state; and the other group show improvement followed by a sharp drop in performance that persists for two weeks, characterising the NFOR state (Fig. 1).

Analysis of performance during training was the parameter used both for selection criteria and to define the experimental FOR and NFOR groups. Thus, similar changes observed in the training groups (i.e., FOR and NFOR) as compared to a control group likely reflect the common response to OT, whereas differences that are unique to the NFOR group reflect the intolerance of some rats to OT. This generates a performance drop that is related to the effects of OT on the intrinsic characteristics of each animal. As observed in Fig. 1, although
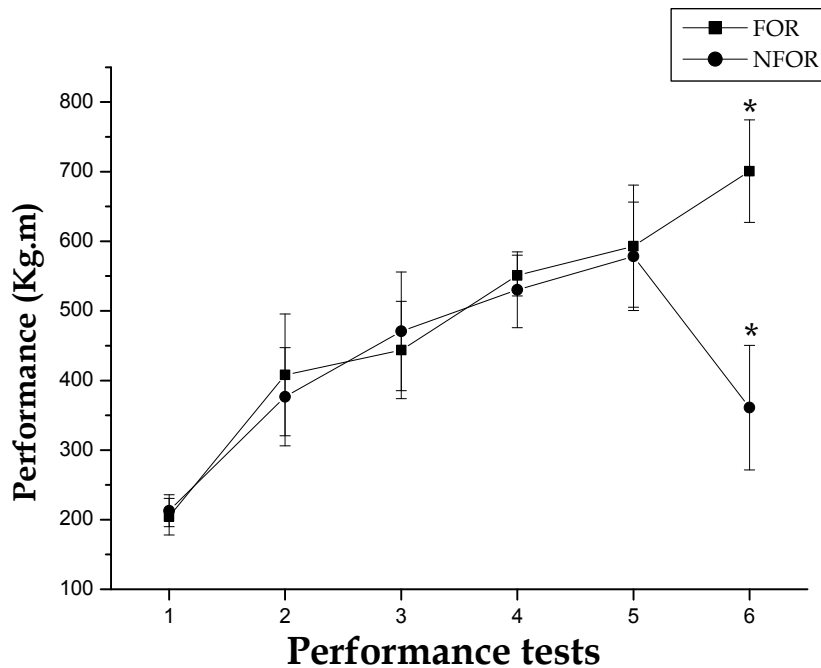
Fig. 1. Performance (mean ± sd) of the FOR (n = 11) and NFOR (n = 8) groups in the six performance tests performed during the 11-week training described in Table 1. * Significant difference between test 6 and test 5 in the paired *t* test analysis of FOR and NFOR groups (p < 0.01 for FOR and p < 0.001 for NFOR).

OT is necessary to maximise the increase in performance, it is also detrimental to the adaptive process for some animals. Lehmann et al. (1993) reported that inter-individual variability in recovery potential, exercise capacity and stress training tolerance explains the different vulnerabilities of athletes to OT under identical training stimuli. Therefore, OT is a process that deserves careful and individualised control of appropriate training loads and recovery times.

The animal model proposed by Hohl et al. (2009) has been a useful tool in seeking tissue and blood biomarkers for use in studying undesirable OT outcomes (i.e., NFOR/OTS) that are associated with an animal's tolerance or intolerance to the same OT protocol. This method can be used to compare the effects of OT in FOR and NFOR group of rats.

1.3 Glutamine and glutamate as potential biomarkers for training intolerance

Some blood biomarkers have been proposed to be associated with OT in humans (Petibois et al., 2002), but there is currently no consensus for all OT cases. One possible biomarker that could be used is the ratio of the concentration of glutamine to glutamate (Gm/Ga) in the blood. A decreased Gm/Ga ratio, due to a decrease in the glutamine blood concentration (Parry-Billings et al., 1992) and/or an increase in glutamate concentration (Coutts et al., 2007; Smith & Norris, 2000) after exercise, has been observed in overtrained humans (Coutts et al., 2007; Halson et al., 2003; Smith & Norris, 2000).

Keast et al. (1995) reported mean plasma glutamine decay from 630 μM to 328 μM in five highly trained male subjects who underwent intensive interval training sessions twice daily

for ten days. The authors concluded that 'reduced plasma glutamine concentrations may provide a good indication of severe exercise stress'. Smith and Norris (2000) reported a mean (± standard deviation (sd)) glutamine concentration of 522 ± 53 μM, glutamate concentration of 128 ± 19 μM and Gm/Ga ratio of 4.15 ± 0.57 'as the extreme values for athletes who have not met conditions of overtraining and are thus managing the training load imposed', and they also proposed that 'overreaching which can also lead to overtraining may occur when the Gm/Ga ratio is 3.58'. Additionally, Halson et al. (2003) reported a mean (± sd) glutamine concentration decrease from 631± 21 μM to 475 ± 40 μM, glutamate increase from 158 ± 18 μM to 235 ± 18 μM and Gm/Ga ratio decrease from 4.38 ± 0.49 μM to 2.13 ± 0.26 μM in 'overreached athletes' after two weeks of intense training loads. The terminologies and statements of 'severe exercise stress', 'who have not met conditions of overtraining' and 'overreaching' suggest that blood glutamine and/or glutamate levels change before the dangerous and undesirable outcomes of OT, here termed NFOR or OTS. We have also found the same pattern of plasma glutamine and glutamate responses in rats subjected to OT (Hohl et al., 2009). Hohl et al. (2009) showed a significantly higher glutamate blood concentration in the NFOR group compared to the FOR group. Moreover, blood glutamine level in the NFOR group suggested a trend to a lower plasma concentration than the FOR group. Therefore, the Gm/Ga ratio in the NFOR group was significantly lower than in the FOR group (3.1 ± 0.2 and 4.5 ± 0.9, respectively), confirming previous studies with humans. Together, these data suggest that changes in glutamine and glutamate levels may be early indicators of some critical aspects of metabolism related to the individual training intolerance.

1.4 Glutamine and glutamate changes due to metabolic maladaptation

Changes in glutamine and glutamate concentrations may not be the direct cause of OT outcomes (Keast et al., 1995), but those changes may be linked to many different aspects of metabolism, which may contribute, in different magnitudes, to the undesirable OT outcomes during the training program. Significant plasma glutamine and glutamate changes could be an indication of undesirable maladaptation in progress, in other words, that the training program is becoming more harmful than helpful to the subject.

In response to deleterious challenges, such as burn damage or surgery, plasma glutamine decreases, despite increased mobilisation from muscle (Lobley et al., 2001). This is probably due to increased metabolic usage by the immune system and the liver, due to immunological challenge. Of note, the skeletal muscle is the main glutamine exporter to the blood stream (Krebs, 1980), and glutamine is mainly metabolised by immune cells such as lymphocytes, macrophages and neutrophils, which all depend on glutaminolysis for cell proliferation (Krebs, 1980).

Smith (2000) proposed that OTS is a response to excessive muscle stress, which may induce a local acute inflammatory response that may evolve into chronic inflammation and can lead to systemic inflammation. Circulating monocytes are activated in response to muscle trauma, which may increase the demand for glutamine. In addition, the increases in pro-inflammatory cytokines IL-6 and Tumor necrosis factor (TNF-α) stimulate glutamine and alanine uptake in human hepatocytes (Fischer and Hasselgren, 1991). Increased glutamine uptake by the liver from blood also favours the synthesis of large quantities of inflammatory-related, acute-phase proteins, such as C-reactive protein and haptoglobin (Marks et al., 1996). Serum proteomic analyses have shown increases in other acute-phase

proteins in NFOR when compared to FOR rats (Lazarim et al., 2010), which may be linked to the decreased blood glutamine observed by Hohl et al. (2009).

Another complementary hypothesis to be considered for blood glutamine reduction is that a decrease in oxidative capacity is caused by muscle mitochondrial damage. The muscle glutamine synthetase (GS) requires α-oxoglutarate as co-substrate for glutamate synthesis that is actually used as GS substrate for glutamine synthesis with ATP and NH_3^+. It was speculated that mitochondrial injuries could limit the availability of α-oxoglutarate formed by the Krebs cycle, thereby diminishing glutamine production inside the muscle (Rowbottom et al., 1995).

This hypothesis is supported by the uncommon reduction in citrate synthase (CS) activity that we found in the NFOR group from the OT animal model protocol (Hohl et al., 2009). The unexpected chronic performance drop associated with lower oxidative capacity in the NFOR group could be related to the increased generation of reactive oxygen species (ROS, e.g., superoxide anion [$O_2^{\bullet-}$], hydrogen peroxide [H_2O_2] and hydroxyl radical [OH^-]). Ji et al. (1988) have shown that increased ROS production in muscles of rats during prolonged and exhaustive exercise causes an alteration in the intra-mitochondrial redox state. This occurs by the oxidation of thiol groups (-SH) of mitochondrial enzymes (e.g., CS, malate dehydrogenase and aminotransferase alanine), linking this alteration to the reductions in the activities of these enzymes for 48 hours after exercise. We observed oxidative stress in the NFOR rat group red gastrocnemius, along with decreased CS and mitochondrial Complex IV activities, 60 hours after the last training session (at 11th week in Table 1) (Hohl et al., 2010).

The increase in blood glutamate is less understood than the decrease in glutamine during OT. A possible explanation for the increase in blood glutamate in the NFOR/OTS states is that excessive skeletal muscle microtrauma causes a reduction in the electrochemical gradient in the muscle by increasing intracellular Na^+ (Hack et al., 1996).Glutamate is carried in the cell by Na^+-dependent transporters; therefore, increased intracellular Na^+ will result in decreased glutamate carried into the cell (McGivan & Pastor-Anglada, 1994). This problem was verified in hypercatabolism (cachexia) (Hack et al., 1996), which entails a great loss of body cell mass. In addition, excess tissue trauma may be associated with reduced food intake, causing gluconeogenesis to be up-regulated in order to maintain blood glucose level (Smith, 2000). Because alanine and glutamine are the main precursors for gluconeogenesis, glutamine will decrease in this case (Wagenmakers, 1998). Muscle microtrauma and up-regulation of liver gluconeogenesis could link the blood glutamate increase and glutamine decrease in a feedback loop.

Although measuring blood glutamine and glutamate may be useful to monitor the effects of exercise programs, they can only be used to individualise medical/nutritional programs or exercise training interventions if the blood values are increased or decreased in relation to a well-defined reference population. So far, there have been no reports describing the reference intervals for blood glutamine and glutamate that can be applied in the exercise/sport sciences.

1.5 Reference interval as a clinical tool

The results of laboratory tests are often used in the clinic to diagnose, monitor or prevent many different pathological states. The most commonly used interpretation task is to compare individual blood parameter values with reference intervals that have been obtained from a defined population. Reference intervals refer to the range of values for a laboratory test that are observed in a specific population, typically described by upper and lower reference limits.

The International Federation of Clinical Chemistry (IFCC) Expert Panel on Theory of Reference Values in 1986 established the terminology, analytical procedures and statistical analyses of reference intervals (Solberg, 1987a). A *reference individual* is an individual selected for comparison using defined criteria (Solberg, 1987a). For sport science studies, it is important to consider that physical training promotes significant alterations in blood cells, enzyme activities, and protein and metabolite concentrations (Lazarim et al., 2009; Nunes et al., 2010; Sawka 2000). The training characteristics, or sport modalities, can promote different adaptive responses that can be reflected in each analyte. For example, endurance athletes have lower haematocrit, haemoglobin and red blood cell count compared to individuals who perform strength training (Schumacher et al., 2002). In addition, biochemical and haematological biomarkers may be influenced by age, body mass, genotype, ethnicity, sex, diet, circadian rhythm (Ritchie & Palomaki, 2004) and biological variation (Nunes et al., 2010). Thus, the selection of a reference individual should include the training characteristics or sport modality.

The *reference population* consists of all possible *reference individuals* of a *reference sample group*. The IFCC recommend a minimum of 120 subjects to obtain reliable estimates and confidence intervals (Solberg, 1987a). This may be a problem when one decides to estimate reference intervals for team sports, such as soccer, volleyball or individual sports. One alternative is to obtain reference intervals in co-operation with laboratories that use the same methods for screening tests in athletes. Another important issue is the selection criteria for a reference sample group. It is important to consider the training level and adaptive state of each individual. In such a way, a performance test is important to characterise the subjects that will make up an exercised reference sample group. In addition, when the reference sample group is composed of professional athletes, it is important to consider possible variations of blood parameters during the training season and competition periods (Banfi et al., 2011).

The *reference values* are the values obtained in reference individuals for an individual analyte (the constituent that will be analysed) (Solberg, 1987a). The reference values are sensitive to pre-analytical and analytical variation; therefore, sample collection and handling techniques that are adopted should be standardised to minimise the sources of error (Fraser, 2001). Some techniques must be observed to obtain the reference samples: i) taking samples at the same time of day, considering possible circadian variations of the analyte; ii) ensuring that the reference individuals have been subjected to the same conditions (i.e., fasting for at least 10 hours and no consumption of alcohol or medication for at least 2 days before testing, particularly anti-inflammatory drugs); iii) the individual's training load or fitness level should be standardised; iv) taking blood samples with a standard phlebotomy technique (e.g., placing the samples into the same type of collection tubes and preferably having the subjects in a sitting position); and v) no training or exercise for at least 48 hours before the collection to avoid the acute haemodilution effects that can occur on the blood samples (Sawka, 2000). Also, the sample transport and handling should be carefully monitored to avoid haemolysis and to keep the analytes stable.

Analysis of reference samples sometimes requires many methodological steps. Therefore, applying the same equipment, reagents and calibrators is critical to ensure that the results are accurate. The analytical variation can be estimated by calculating the analytical coefficient of variation, obtained from the mean and standard deviation of the quality control analysis. The internal quality control should analyse a sample that simulates the reference values samples (e.g., serum, plasma, whole blood, urine or saliva).

After the reference sample assay, a histogram should be generated to inspect the distribution of the data (Fig. 2). We found that glutamine and glutamate show a Gaussian (Fig. 2A) and non-Gaussian distribution (Fig. 2B), respectively. In the visual histogram analysis, it is also possible to detect aberrant values (*outliers*) and to identify possible data errors. A number of statistical tests should also be performed to detect *outliers*. The IFCC do not recommend any particular method, but the Dixon test is commonly used, and it is relatively 'insensitive to moderate deviation from the Gaussian distribution' (Solberg, 1987b). However, this method often fails when several outliers are present. The *Horn's* algorithm (Horn et al., 2001) attempts to solve this problem by employing two stages. In the first stage, the data are transformed in a Gaussian distribution, and in the second stage, the extreme values are detected based on 50% of the transformed sample (Horn et al., 2001). The aberrant values, which are identified as *outliers*, should be removed following rational criteria: the pre-analytical process should be re-evaluated, the analytical process should be checked or samples re-assayed to discharge possible mistakes (Solberg, 1987b).
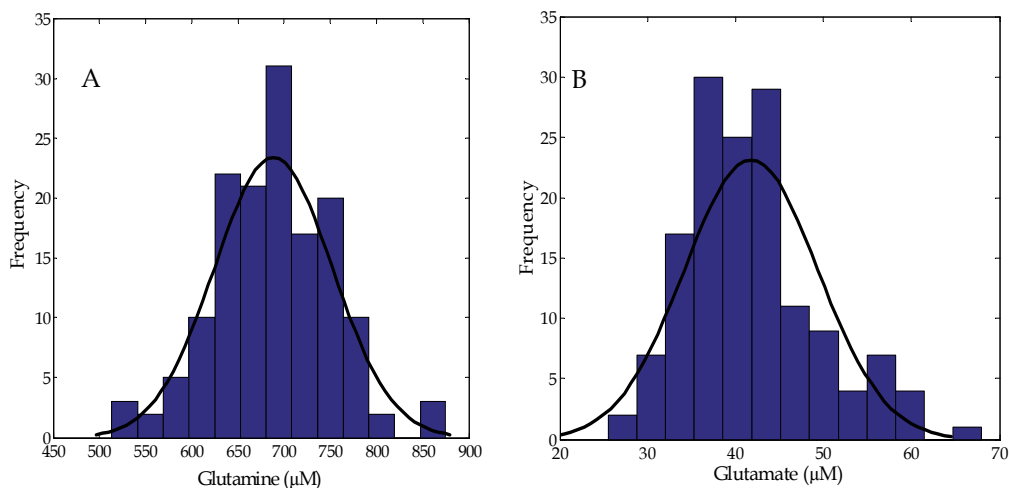
Fig. 2. Histograms representing the reference distributions of glutamine (A) and glutamate (B) in a physically active population (n = 146). The black line represents a normal fit.

Several types of reference intervals have been proposed in the literature: inter-percentile interval, tolerance interval and prediction interval. Most frequently, the reference intervals are estimated to be the lower and upper percentiles in the central 95% of the results (Solberg 1987b). This procedure is recommended because the reference intervals are easily estimated by parametric and non-parametric procedures. Other percentiles (e.g., 90%) can be adopted to narrow the intervals.

The percentiles may be estimated by parametric (Gaussian distribution) or by non-parametric methods (non-Gaussian distribution). There are several non-parametric methods for estimating reference intervals. The rank-based method is simple to apply manually or by using a computer, and it is also recommended by the IFCC and well described by Reed et al. (1971). As parametric estimates are more precise, we can transform the non-Gaussian distribution into a Gaussian distribution by applying statistical techniques (e.g., logarithms or square roots of the values) (Solberg, 1987b). To calculate reference intervals by parametric methods, we first need to test a Gaussian

distribution by applying a goodness-of-fit test, such as an Anderson-Darling or Kolmogorov-Smirnov test (Solberg, 1986). The calculation will use the mean - 1.96 x sd to estimate the 2.5th percentile and mean + 1.96 x sd for the 97.5th percentile of the reference intervals (Horn & Pesce, 2003). The RefVal program, developed by Solberg (2004), is a computer program that performs many statistical routines described above, including procedures and algorithms in accordance with the IFCC recommendations. It has a simple data input routine and intuitive interface.

One difficulty in assessing the effects of training on blood parameters is the lack of appropriate reference intervals obtained from a reference population that practices regular and systematised physical activity and following the IFCC rules. The aim of this study was to obtain glutamine, glutamate and Gm/Ga reference intervals, according to IFCC rules, using automated equipment that does not require extensive laboratory skills. The reference population consisted of a cohort of young men who had increased performance in a 3000-m time trial test after four months of periodic training, when compared with their performances at the beginning of training. Secondly, we present a suggestion for a practical method to follow training effects that combines routine performance analyses with glutamine level, glutamate level and Gm/Ga ratio.

2. Material and methods

2.1 Subjects

Male volunteers (n=526), with an average age of 18 ± 1 years, participated in this study. All volunteers were students in the first stage of physical and educational preparation for a career in the army. The participants responded to a questionnaire about their use of medication and their complaints of pain and injuries caused by training. Those who were using medications or were injured were not included in the study. Volunteer subjects were duly informed about the research and signed a free informed consent form. They participated for nine months (February to October) in a regular and strictly controlled exercise program, which consisted predominantly of aerobic activities (high volume and low intensity) for three hours daily. They trained five days per week, with two days of rest. This work was approved by the Human Research Ethics Committee of the Campinas State University (CAAE: 0200.0.146.000-08).

2.2 Performance test and subject selection for a reference population

All subjects performed four freely paced 3000-m time trial tests during the training period. The tests were performed in February, April, May and October, respectively, with all subjects performing them within the same one-week period. The time trial test is a feasible way to test the endurance capacity of the subjects, considering the large sample size. Each subject ran 3000 m with a numbered wristband. At the end of the 3000-m trial, the subjects placed their wristbands on a pole. A total of five poles were placed at the end line, and one evaluator stopped a memory stopwatch every time a wristband was placed on the pole. Later, the sequences on the wristbands were matched with the stopwatch times.

The students were highly motivated for the time trial test. The 3000-m time trial was graded by members of the army school, and students failed the year if they did not perform the 3000 m in at least 14' 59'' in the last test (October). A maximum grade (10) was obtained when the cadet performed below 11' 30'', and the grade dropped 0.5 per every additional 10''.

Software was developed to facilitate the visualisation, identification and selection of subjects from this large sample. It is based on the use of scatter plots and allows the user, in an interactive way, to observe trends and patterns of the group's results, providing the position of the individual within the group and showing the current results of the subjects compared to previous results (Reis et al., 2011).

The example shown in Fig. 3 illustrates the comparison between the time achieved for a 3000-m time trial performed in February and May. This type of comparison allowed for visualisation of the progress of the students during the training period between tests. By clicking on 'Identity Line', a straight line is drawn with a slope equal to 1 and an intercept equal to 0, which divides the graph diagonally. This line represents the set of identical results in both tests. The points below the identity line represent the students who responded well to the physical training program, as they performed the 3000-m time trial with a lower time in May than in February. There were also a few students positioned above the identity line who, for some reason, performed the test more slowly in May than in February.
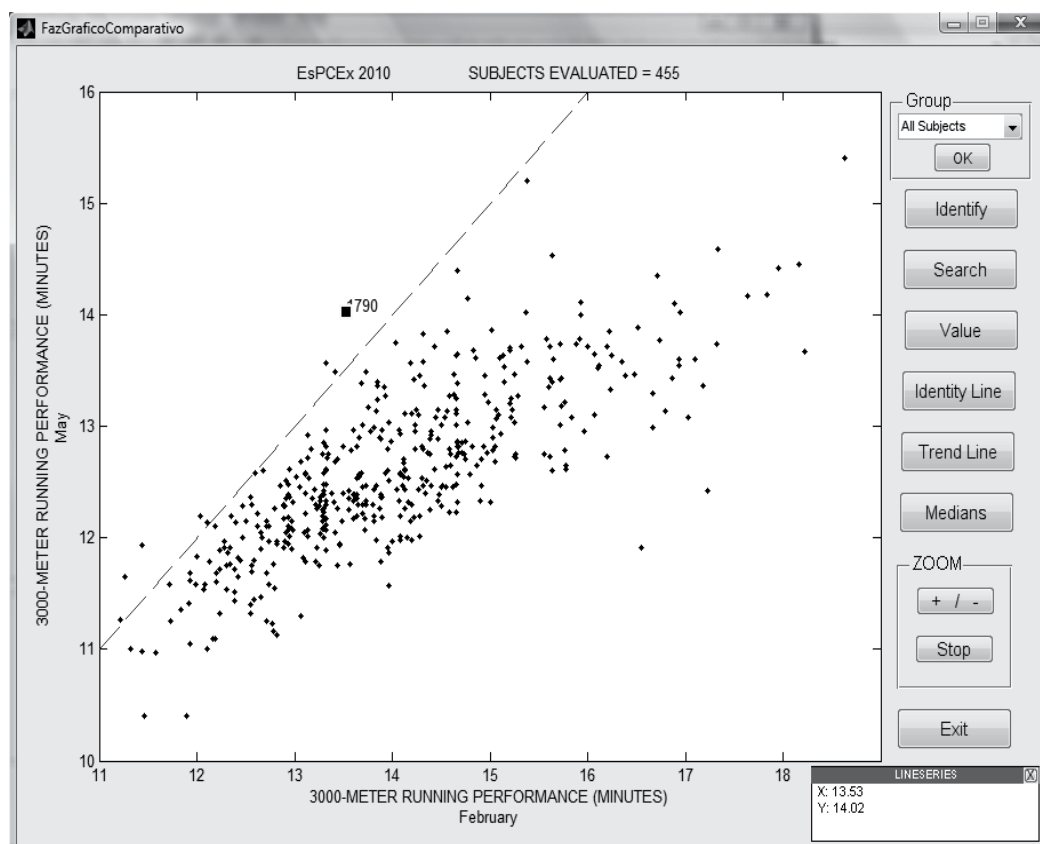
Fig. 3. Comparison between 3000-m time trials performed in February (*x*-axis) and May (*y*-axis). The dashed line represents the identity line. The text box indicates the exact value obtained by subject 1790 on both dates.

Figure 4 shows a zoom of a specific region of the graph and the selected students chosen to compose the reference population (points circled in gray). Thus, the glutamine and glutamate reference intervals presented here represent a population of young, physically active, healthy men who responded to 4 months of training.
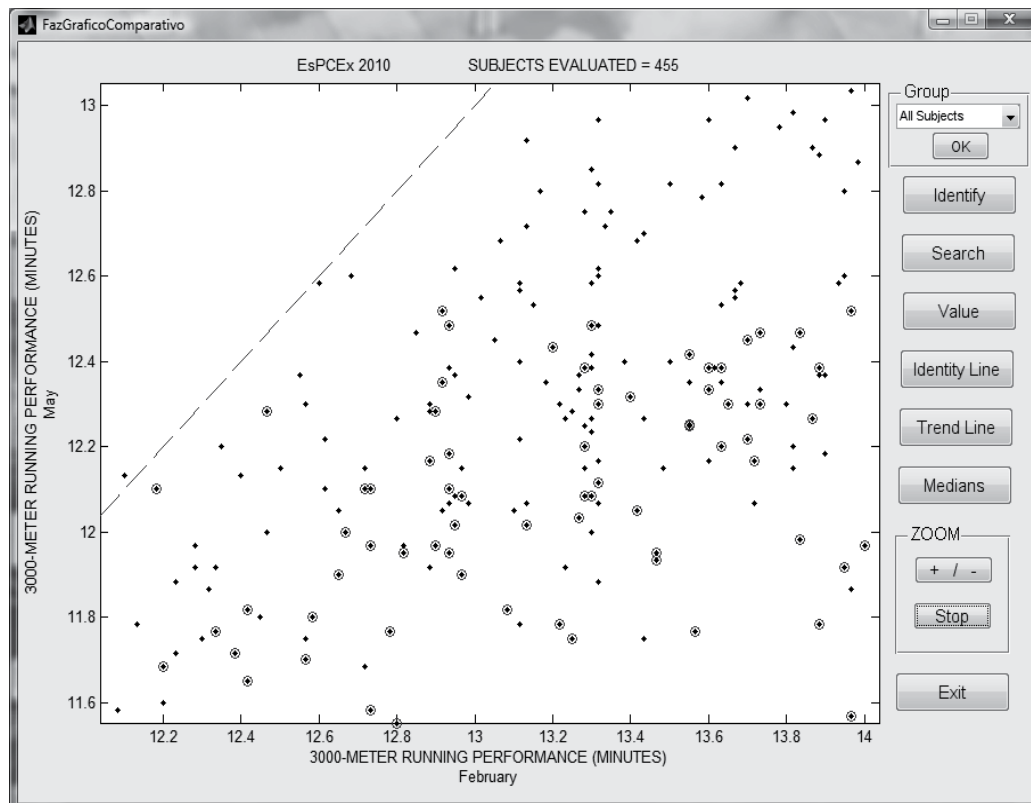
Fig. 4. Zoom applied on Fig.3. Comparison between 3000-m time trials performed in February (*x*-axis) and May (*y*-axis). The points circled in grey represent the individuals selected to establish the reference values for glutamine and glutamate. The dashed line represents the identity line.

The performances of the students in the 3000-m time trial tests between May and October were used to choose candidates to test the use of plasma glutamine level, glutamate level and Gm/Ga ratio as biomarkers of tolerance or intolerance to the same training protocol. Twenty-five subjects who were above the identity line were randomly selected as the non-responders to training (NRT), and an additional 25 subjects who fell below the identity line were randomly selected as responders to training (RT).

2.3 Collection of blood samples
All blood samples were collected after two days of rest to avoid the effects of hemodynamic variations and acute haemodilution that are induced by exercise. Blood samples were collected under standardised conditions. Eight millilitres of venous blood was collected in

heparin tubes with a Vacuette® (Greiner Bio-one) gel separator to obtain plasma for glutamine and glutamate assays. Blood samples were collected in the morning after 12 hours of fasting with subjects in a seated position, transported at 4°C to the laboratory within 30 min, centrifuged under refrigeration (4°C) at 1,800 x g for 10 minutes, and then immediately separated and protected from light. Plasma samples were finally stored at -80°C and analysed within 2 months.

2.4 Assays for glutamine and glutamate measurements

Glutamine and glutamate analyses were conducted with a dual-channel YSI 2700® Select Biochemistry automated analyser (Yellow Springs Instrument Co., Ohio, USA), according to the manufacturer's recommendations. This analyser uses a platinum electrode to measure the current generated by two enzyme-impregnated membranes. When a sample is injected into the sample chamber, the glutamine diffuses to the glutamine membrane, which contains glutaminase and glutamate oxidase. The glutamine is deaminated to glutamate and ammonia by glutaminase. In the presence of glutamate oxidase, glutamate is oxidised to hydrogen peroxide, α-ketoglutarate, and ammonia. The hydrogen peroxide is detected amperometrically at the platinum electrode surface. The current flow at the electrode is directly proportional to the hydrogen peroxide concentration and thus to the glutamate concentration. The glutamate in the sample is also oxidised at the glutamate and glutamine membranes by glutamate oxidase, producing hydrogen peroxide, α-ketoglutarate, and ammonia. Glutamine concentration is calculated as the concentration measured by the glutamine electrode minus that detected by the glutamate electrode.

We used 1 mM glutamine and 0.500 mM glutamate standards to calibrate the machine after every four measurements (sample size 65 µl). The standard solutions (5 mM) were provided by the manufacturer (Yellow Springs Instrument Co., Ohio, USA) and were diluted in Milli-Q water (Millipore Corporation, MA, USA).

The 146 samples used for the reference interval were analysed within two days, and the linearity of the enzyme membranes was evaluated every day before sample analysis. The 50 samples (RT, n = 25; NRT, n = 25) were analysed within the same day with other enzyme membranes and standard kits, after evaluation of membrane linearity. All plasma samples were measured in duplicate, and the mean of the duplicate runs was used in subsequent calculations. The linearity for glutamine and glutamate was calculated with diluted standards in three concentrations: 0.300 mM, 0.500 mM and 0.900 mM for glutamine and 0.05 mM, 0.100 mM and 0.200 mM for glutamate. In all linearity analyses, the correlation coefficient and the slope (r) were approximately 1.

We used one plasma pool to evaluate the within-day coefficient of variation (CVw) and four different plasma pools to evaluate the between-day coefficient of variation (CVb). The CVw of glutamine and glutamate were 0.60% and 1.20%, respectively (n = 20 using one plasma pool). The mean CVb, within three consecutive days, of glutamine and glutamate were 2.0% and 3.8%, respectively.

The accuracy of the YSI 2700D, when analysing the amino acids in non-deproteinated plasma, was evaluated by adding four different standard concentrations into four vials of the same plasma sample. Glutamine and glutamate standard concentrations that were diluted in plasma were thus calculated by subtracting the real glutamine and glutamate concentrations previously measured in plasma. We added 0.600 mM, 0.700 mM, 0.800 mM and 0.900 mM of glutamine standard into four different vials of one plasma sample, and the

standard concentrations detected were 0.620 mM, 0.692 mM, 0.812 mM and 0.892 mM, respectively. The same procedure was done for glutamate: the added standard concentrations were 0.020 mM, 0.030 mM, 0.040 mM and 0.050 mM, and the standard concentrations detected were 0.021 mM, 0.030 mM, 0.039 mM and 0.053 mM, respectively.

2.5 Statistical analysis

Initially, all data from the 3000-m time trial tests were organised using Microsoft Excel and were checked for consistency between the recorded values and their identities with the evaluated subjects. After this initial organisation, all data were imported into Matlab® 7.0, which is the platform on which the software that was designed for this study was developed. Despite having been developed in this environment, the software was compiled and can run on any computer using Microsoft Windows and does not require the installation of Matlab® 7.0. The software, Origin 6.0, was used to perform statistical analyses and to generate graphs. An unpaired t test was used to compare RT and NRT glutamine and glutamate measurements; $p < 0.05$ was considered significant. The *Horn's* algorithm was applied to detect and remove outliers (Horn et al., 2001). The RefVal program (Solberg 2004), including practical approaches and formulas recommended by the IFCC, was used to calculate the 97.5th and 2.5th percentiles of the subjects and their respective 0.90 confidence intervals. This was achieved by using parametric estimates of the glutamine levels, glutamate levels and Gm/Ga ratios that were obtained from plasma samples of the 146 volunteers after four months of daily, periodic physical activity.

3. Results

Table 2 shows the reference intervals (upper and lower limits) and the confidence intervals for healthy, physically active young men.

Analysis	Reference Interval	0.90 Confidence Interval		Subjects (n)	Outliers	Subjects Ref. Interval
	2.5th - 97.5th	2.5th	97.5th			(n)
Glutamine (µM)	566 - 798	546 - 586	782 - 813	146	514, 867, 875	143
Glutamate (µM)	31 - 59	30 - 32	55 - 62	146	26, 28, 68	143
Gm/Ga	12 - 23	12 - 12	22 - 24	146	10, 10, 26	143

Table 2. Reference intervals for glutamine level, glutamate level and Gm/Ga ratio for healthy, physically active young men.

Figure 5 presents the performance analyses of the test subjects for the 3000-m time trial, over the span of one training year. At the end of the training year (May x October, Fig. 4C) almost all subjects performed below 14' 59'' (cut off) and the 3000-m times were more homogenous than at the beginning of the year (February x April, Fig. 4A). However, the regression line in Fig. 4C approaches the line of identity due to the increase in the amount of time it took some the test subjects (n = 222) to complete the 3000-m trial in October compared to May.

3000-m running performance
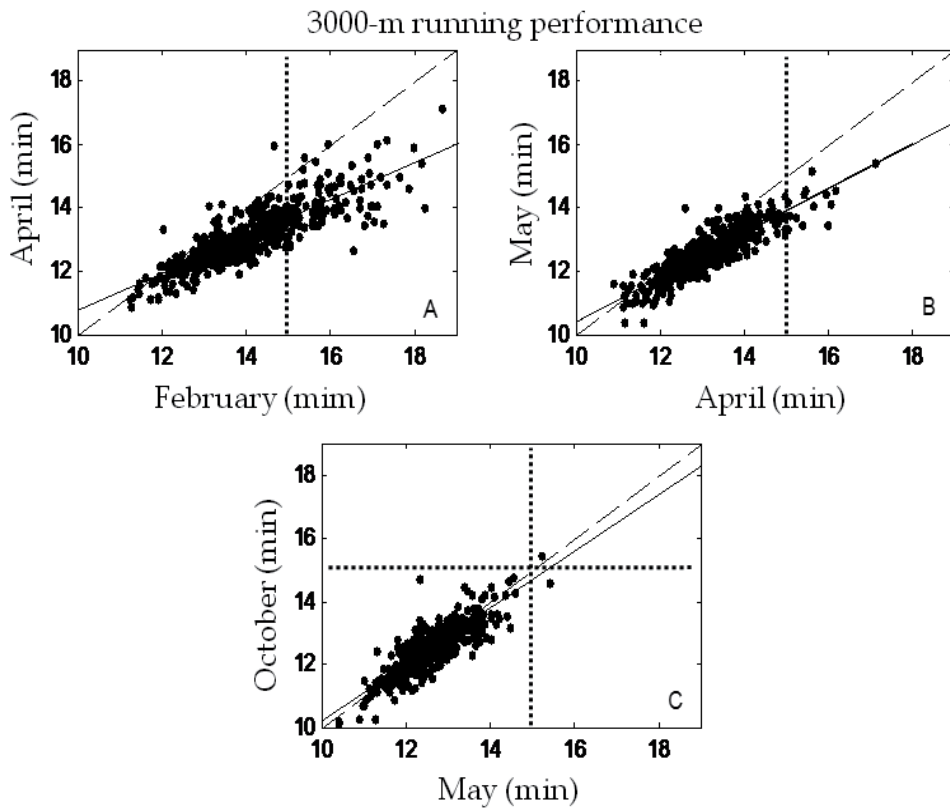
Fig. 5. Comparisons of 3000-m time trial tests over the training year. In these charts, the identity lines are dashed and the regression lines are solid. The identity line is the reference for time changes between the two tests. Subjects who fell below the identity line showed lower 3000-m times from one test to the next, so the performance was improved. The regression line shows the trend between the two 3000-m time trial tests over the year. Dotted lines show the Army School's cutting time in 14′59′′.

Table 3 shows the comparisons of glutamine, glutamate and Gm/Ga between the RT and NRT groups. We observed a tendency of lower glutamine, significantly higher glutamate and significantly lower Gm/Ga ratio in the NRT group compared to the RT group.

	RT	NRT
Glutamine (µM)	669 ± 49	645 ± 63
Glutamate (µM)	41 ± 5	46 ± 6 *
Gm/Ga	16 ± 2	14 ± 2 *

Table 3. Glutamine, glutamate and Gm/Ga ratio in the RT group vs. the NRT group. RT: Responders to training (n = 25). NRT: Non-responders to training (n = 25). * Unpaired t test: significant difference between groups (glutamate, $p = 0.002$ and Gm/Ga, $p = 0.0003$).

Figure 6 presents the blood glutamine and glutamate levels of responders and non-responders to training in relation to the 97.5th and 2.5th percentile reference interval. Only four NRT subjects had Gm/Ga ratios below the reference interval, and one of them also presented a glutamine concentration below the reference interval (subject "X").
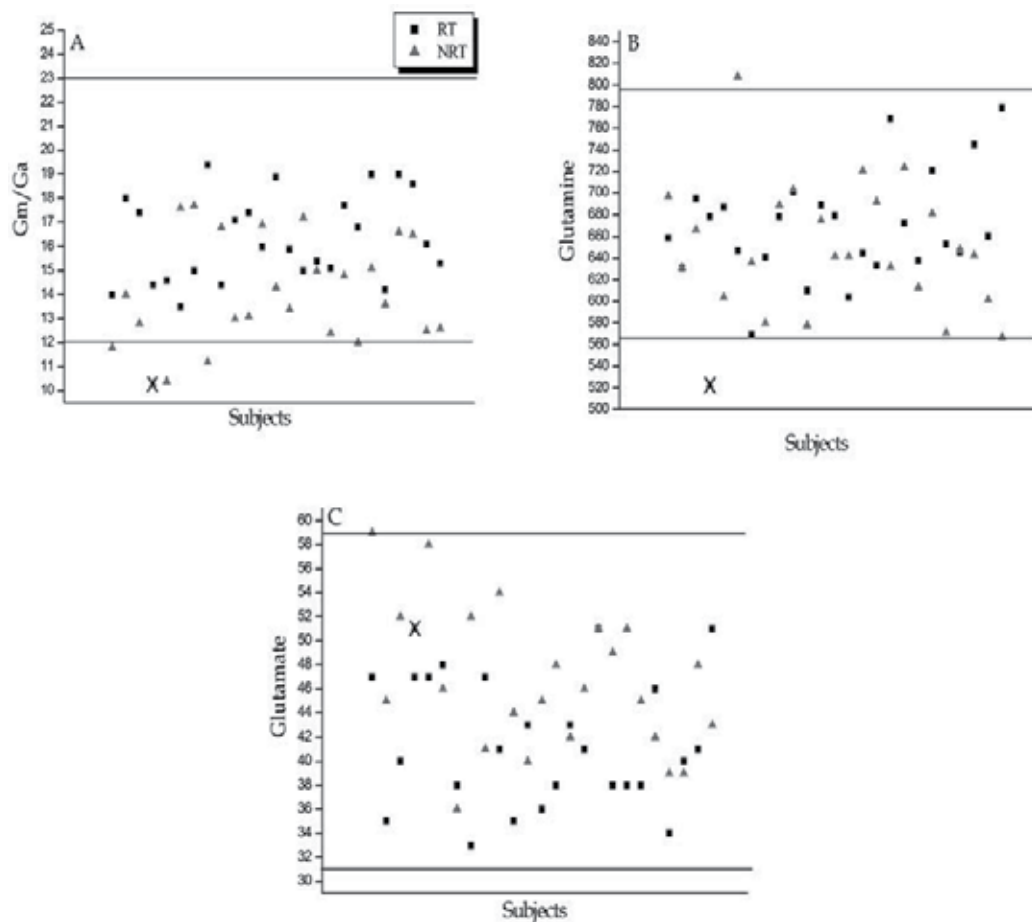
Fig. 6. Gm/Ga (A), glutamine (B) and glutamate (C) plasma levels (µM) of responders and non-responders to training (NRT; n = 25). Solid lines are the reference intervals. **X** identifies one subject with low Gm/Ga ratio and glutamine.

4. Discussion

This is the first study to establish reference intervals for glutamine, glutamate and Gm/Ga ratio in the plasma of test subjects, according to the IFCC recommendations. The reference intervals presented here are not comparable to other studies regarding the subject selection criteria or number (n= 143), sample preparation, sample storage or the equipment used for glutamine and glutamate measurements (i.e., YSI 2700).

4.1 Methodological aspects and confounding factors in measuring plasma glutamine and glutamate

To date, three different methods have been used to measure glutamine and glutamate concentrations: high-performance liquid chromatography (HPLC), the enzymatic method and a glutamine-dependent *Escherichia coli* bioassay (Hiscock & Pedersen, 2002). According to Hiscock and Pedersen (2002), the major difference amongst the three is in the concentrations of glutamine that is detected. When measured by the bioassay, the glutamine concentration is 40% higher than by HPLC. In addition, plasma glutamate measured by the enzymatic assay seems to be more than 200% higher than HPLC. The reason for disagreement amongst these methods is speculative. However, the discrepancies may be verified by noting the plasma glutamate values between 100 and 200 µM measured by the enzymatic assay (Halson et al., 2003; Keast et al., 1995; Smith & Norris, 2000) with values between 28 and 55 µM measured by HPLC (Abdulrazzaq & Ibrahim, 2001; de Jonge & Breuer, 1995; Van Eijk et al., 1994).

HPLC has been widely used in methodological studies that evaluate the stability of amino acids in non-deproteinated, deproteinated and neutralised samples at several storage temperatures (Abdulrazzaq & Ibrahim, 2001; de Jonge & Breuer, 1995; Van Eijk et al., 1994). Although HPLC is considered a reliable method for amino acid measurements, it also requires highly skilled laboratory personnel to guarantee reliability. According to the manufacturer (Yellow Springs Instrument Co., Ohio, USA), the YSI 2700 electrode method is highly correlated with HPLC glutamine measurements (slope 0.94 and r^2=0.99), with the advantage of being much more user-friendly than the HPLC method. The reliability tests performed in this study also showed outstanding accuracy in measuring glutamine and glutamate standards in plasma, good linearity and small within-day and between-day variability.

Blood plasma storage and deproteination add systematic errors that can influence inter-laboratorial comparisons of data (de Jonge & Breuer, 1996). Blood acid deproteination is frequently used to stop enzymatic activity; however, glutamine is particularly influenced by sample acid deproteination because a low storage pH accelerates the spontaneous degradation of glutamine in pyroglutamate (Khan et al., 1991). Nevertheless, the systematic error caused by deproteination is negligible when samples are stored below -70°C (Van Eijk et al., 1994). Glutamine and glutamate are stable for at least 6 months in non-deproteinated samples that are stored below -70°C (Van Eijk et al., 1994) but are not stable when stored at -20°C for more than 4 weeks (Abdulrazzaq & Ibrahim, 2001; de Jonge & Breuer, 1996). Therefore, based on those previous studies, non-deproteinated plasma stored at -80°C was used in this study.

Plasma glutamine and glutamate seem to not be affected by sex or age. Van Eijk et al. (1994) used deproteinated plasma and HPLC as their measurement technique. They showed mean glutamine levels between 663 and 693 µM and mean glutamate levels between 49 and 55 µM in healthy males 20–69 years old, with no significant differences in those amino acids between males and females. Planche et al. (2002) showed no differences in plasma glutamine and or glutamate between healthy children (12–71 months) and healthy adults (age not specified) using the YSI 2700. They observed a mean value (range min–max) of 532 (485–577) µM for glutamine and 32 (28–43) µM for glutamate. Both Planche et al. (2002) and Van Eijk et al. (1994) used only 8–12 subjects, which are insufficient numbers to consider those glutamine and glutamate values as references, according to the IFCC, who recommend a

minimum of 120 subjects (Solberg, 2004). However, those glutamine and glutamate values are slightly lower than the upper limits of the reference intervals found in this study (Table 2), probably due to the regular physical training effect. Particularly, glutamine may increase due to endurance training. Rowbottom et al. (1997) identified a positive correlation between the level of plasma glutamine and improved endurance performance. In addition, Kargotich et al. (2006) showed increased plasma Gm, VO$_2$max and time to exhaustion after 6 weeks of endurance training (3 to 6 × 90-minute sessions per week at 70% VO$_2$ max) in active, not well-trained subjects.

Plasma glutamine level is also influenced by acute exercise. The effect of acute exercise on plasma glutamine seems to depend on the intensity and duration of the exercise (Hiscock & Pedersen, 2002). For instance, intermittent, high-intensity bouts of activity decrease plasma glutamine (Walsh et al., 1998), but a single, short, high-intensity bout increases (Babij et al., 1983) or maintains glutamine (Sewell et al., 1994). Other studies have shown that blood glutamine decreases for 2–4 hours after acute exercise lasting more than 2 hours (Castell et al., 1997; Rohde et al., 1996). Therefore, to use the glutamine and glutamate reference intervals as a training monitoring tool, it is advised not to withdraw blood samples right after acute exercise of any type. Otherwise, the effect of acute exercise may overcome the chronic training effect on glutamine metabolism.

As well as being influenced by exercise, blood glutamine level may also change due carbohydrate (CHO) intake. Wagenmakers et al. (1991) showed that both plasma glutamine and glutamate decrease after glycogen depletion, compared to CHO loading during exercise. This change is probably due to increased deamination of amino acids. Blanchand et al. (2001) showed that resting mean plasma glutamine of test subjects was significantly higher after 14 days of rich CHO intake (70% of total energy; mean plasma glutamine of 857 μM) than in subjects with poor CHO intake (45% of total energy; mean plasma glutamine of 610 μM). In practice, athletes and coaches should carefully plan the CHO intake of the athlete because it can also negatively affect performance (Maughan et al., 1997). If performance decreases and glutamine falls below the reference interval, but CHO intake is sufficient for maintenance of liver and muscular glycogen levels during the training program, then intolerance to training may have occurred.

For the reasons expressed so far, the reference intervals for glutamine and glutamate presented here should be used whether the measurement conditions (i.e., storage, preparation and assay technique) are reproduced faithfully. Sufficient CHO energy intake for the maintenance of glycogen stores is recommended in order to avoid glutamine/glutamate changes associated with performance decay related to poor nutrition. Overnight fasting and 8 to 12 hours of recovery from a previous training session should be considered before blood sample withdrawal. Finally, it is advised, for endurance training monitoring, to use glutamine, glutamate and Gm/Ga reference intervals that have been established from endurance-trained subjects, as presented here.

4.2 Training monitoring using self-paced time trials and glutamine and glutamate reference intervals

To test the glutamine and glutamate reference intervals, 25 subjects were randomly selected as responders to training, due to their decreased times in the self-paced 3000-m time trial in October compared to May (subjects below identity line, Fig. 5C). The self-paced time trial is

influenced by an anticipatory component, which, in turn, is influenced by physiological inputs prior to exercise that are related to the fitness level, expected exercise distance/duration and previous experience of the test subject (Tucker, 2009). The army students were experienced in the 3000-m time trial because they had previously performed many trials throughout the year in addition to the four officially valid ones for the army school records. In addition, they were task-motivated, due to the internal competition amongst themselves and also to the army school grading. However, many students showed poorer performance in October compared to May (subjects above identity line, Fig. 5C), and therefore, an additional 25 subjects were randomly selected from this group to test the reference intervals. No additional symptoms, such as mood alterations or increased incidence of injuries, which would also be characteristic of NFOR/OTS, were observed (Meeusen et al., 2006); therefore, those subjects were considered non-responders to training.

The same exercise-training stimulus may be either efficient or insufficient in improving performance and physiological adaptation when applied to many different subjects. An insufficient training stimulus may cause unexpected stagnation or a mild decrease in performance in self-paced time trials of subjects who are not responding (i.e., adapting) to training. The pacing strategy also depends on external factors such as the environment, race situation and the influence of other competitors (Tucker, 2009). Therefore, decreased performance may not be caused only by physiological maladaptation, but may also be a result of stagnation and test variability. In this sense, the army training program does not aim for high performance levels, as in professional athletes; the goal, in this case, is to homogenise the fitness level of young cadets on their first step in an army career. To reduce the differences amongst the 3000-m time trials, all students were subjected to a similar training program and load.

Figures 5A to 5C show that the army training program was effective in improving the 3000-m time trial for those subjects with higher initial 3000-m times (above ~15 min). However, the training program was less effective in decreasing the 3000-m time trial for subjects who performed below 14 minutes. The scattered points behaviour suggest that the army endurance training program was an insufficient stimulus for students already performing the 3000-m time trial below ~14 min early in the season (Figs. 5A and B).

However, the self-pacing time trial is also the result of a complex, physiological, integrative model of exercise. It has been stated that 'pacing is controlled by the brain, which regulates exercise intensity and alters the adopted pacing strategy to ensure that potentially catastrophic derangements to homeostasis do not occur' (Noakes et al., 2005). This definition holds that during self-paced exercise, when one is able to select an exercise work rate, performance is regulated by a central governor (i.e., brain) to prevent changes in physiological systems that may be harmful during exercise (Noakes et al., 2005; Tucker, 2009). We hypothesize that glutamine and glutamate are related to many of the chronic and acute metabolic aspects related to exercise (topic 1.4 in this chapter) which could interfere with the central governor regulation. In this sense, glutamine and glutamate reference intervals may be used as additional tools for deciding between heavier training loads to avoid detraining/stagnation, or extended recovery to avoid maladaptation. In practice, when the performance decreases and the glutamine, glutamate or Gm/Ga ratio falls within the reference interval limits, then an adjustment in the training load should be considered.

On the other hand, when the performance decreases and the biomarker levels fall outside the reference interval limits, then extended recovery should be considered.

4.3 Practical use of glutamine, glutamate and Gm/Ga ratio reference intervals

Any blood biomarker that is measured during training monitoring would be useful when the detectable changes in blood happen before NFOR/OTS outcomes. In this sense, previous studies that have measured glutamine and glutamate before and after a period of intense training loads seem to agree that changes in these amino acids occur before the extreme OT outcomes, independent of the terminologies used to define them (Halson et al., 2003; Keast et al., 1995; Smith & Norris, 2000; Souza et al., 2005). Nevertheless, intense exercise is related to the context of biological individuality and fitness level.

The occurrence of mean lower glutamine, a significantly lower Gm/Ga ratio and higher glutamate in the NRT group compared to the RT group may indicate slight differences in glutamine and glutamate metabolism (Table 2). However, mean glutamine, glutamate and Gm/Ga ratio of the NRT group were all within the population reference interval. Therefore, glutamine and glutamate mean values may be indicative of higher training stress or lower endurance capacity within a group but are meaningless regarding individual intervention.

When the reference intervals were used, only four subjects from the NRT group showed Gm/Ga ratios below the reference interval, and one of them also showed low glutamine (Fig. 6). Of note, all 25 subjects in the RT group showed glutamine and glutamate levels, and Gm/Ga ratios within the reference intervals (Fig. 6).

These results suggest that only those four subjects, and particularly the subject with low glutamine concentration (X-mark in Fig. 6), should continue the training program with close daily or weekly monitoring of their mood profiles. The remaining 21 NRT subjects probably were not responsive to the training program in the last four months; therefore, the 3000-m time trial test probably reflects stagnation and the inherent variation of the test.

5. Conclusion

For most trainers and sportsmen, the main sign that an athlete has developed NFOR/OTS is sustained poor performance and fatigue. Poor performance and fatigue, however, can also be due to many other factors, such as inadequate training sessions and poor nutrition, respectively, as well as to extraneous factors such as loss of confidence, pressure outside of the sport, and sleep disturbances. The reference intervals of glutamine, glutamate and Gm/Ga ratio presented here may therefore be useful tools to monitor adaptation to training and to thereby identify those athletes who show early signs of OT before prolonged fatigue. In addition, glutamine and glutamate blood concentrations may identify those athletes who are intolerant to a training program versus those who are not responsive to the training program because of insufficient workload.

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7. References

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Physical Activity Measures in Children – Which Method to Use?

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1. Introduction

There is increasing evidence supporting the health benefits of physical activity in children both in the immediate term in terms of body composition and in the longer term in the prevention of risk factors for cardiovascular disease, type-2 diabetes osteoporosis and certain cancers (Lee at al, 2000; Mohan et al, 2005; Blair et al, 1999; Pan et al, 1997; Tuomilehto et al, 2001; Colditz et al, 2005; Samad et al, 2005).

Physical activity is defined as body movement produced by skeletal muscles which results in energy expenditure (Caspersen et al, 1985). It can be difficult to measure physical activity as it is a variable with many dimensions including type, frequency, duration and intensity. The context and location where activity takes place may also be of interest. As a behaviour physical activity is unstable, as habitual levels of activity vary during the day, throughout the week and at different times of the year. Children have less regular patterns of activity than adults and therefore a picture of overall activity may be more difficult to capture. Spontaneous un-planned activity is typical of children, particularly younger children, and may be due to opportunities that present within their environment such as play facilities and other children. Even in older children who do engage in regular planned sporting activities, there may be a degree of unplanned activity.

The "gold standard" method of measuring energy expenditure as a result of physical activity is by the use of doubly labelled water (DLW). The technique uses stable isotopes of hydrogen and oxygen i.e. deuterium (^{2}H) and oxygen (^{18}O) ingested as water. Oxygen uptake and therefore energy expenditure are then calculated from the rate at which these isotopes are eliminated from the body. The difference between these is the amount of CO_2 produced. DLW is not a technique that is generally suitable for use in field studies due to the resources required. Even if cost were not a consideration the information gained pertains to total energy expenditure over a time period e.g. a number of days/ weeks and does not permit the examination of acute patterns of physical activity such as time spent in specific activities or intensity of specific exercise sessions.

The methods that can be used in field and most clinical studies are generally divided into the following; subjective methods such as observation and questionnaires and objective methods such as heart rate monitoring and motion sensors. The advantages and limitations of these methods will be outlined below. Before discussing these methods a synopsis of energy expenditure in children will be presented.

2. Energy expenditure in children

The largest factor that determines total daily energy expenditure (TDEE) is the basal or resting metabolic rate. It refers to the energy expended during normal cellular and organ functioning during post-absorptive resting conditions and accounts for roughly 60-75% TDEE. The second factor is the thermic effect of feeding and it accounts for approximately 10% of TDEE. The third component is the energy expended during physical activity. This can occur as a result of volitional mechanical work, such as exercise and daily activities, and non-volitional activity, such as fidgeting, spontaneous muscle contractions, and maintaining posture. It is the most modifiable component of TDEE and accounts for 20-30% of TDEE. As the output of physical activity energy expenditure (PAEE) is the most modifiable component of total daily EE, it may elicit the greatest response to intervention and subsequently, produce a beneficial impact on health related issues.

A sum of the estimation of energy expended in activity can be calculated from the data provided in questionnaires. The concept of measuring energy expenditure as a multiple of an individual's basal metabolic rate is used and examples of many activities are presented in the form of tables and published in compendiums. The compendia express EE in METs which are multiples of the resting metabolic rate (RMR).

The concept of denoting energy expenditure as a multiple of an individual's basal metabolic rate (BMR) has been referred to as 1 MET. In 1955 Passmore and Durnin published a review of measurements of human energy expenditure of various activities made by indirect calorimetry. This enabled the calculation of an individual's daily energy expenditure by the total of the metabolic cost of each activity by its duration. Initial work in this area was performed using a human calorimeter where the heat produced by a subject's metabolism was directly related to the temperature change in a contained environment, but more recent studies have used indirect calorimetry where expired air is continuously sampled.

In adults the resting metabolic rate (RMR) is taken as 3.5 mL O_2/kg/min. However despite the widespread acceptance of the 1 MET = 3.5 mL O_2/kg/min studies that have made such measures in specific cohorts have found different mean values. Byrne et al (2005) found that average resting VO_2 was 2.56 +/- 0.4 ml/O_2/kg and in this case if the 1 MET of 3.5 was used the resting metabolic rate would have been overestimated by 35%.

The RMR is higher in children and teenagers due to a number of factors including growth and puberty. RMR has been found to be higher than the generic adult value for each age group of children and Tanner stage of pubertal development and significantly higher in younger children (Harrell et al, 2005). Boys have been found to have a higher RMR than girls (Goran et al, 1997). Variation in energy expenditure in typical activity in adolescent girls of approximately 20-25% has been found (Pfeiffer et al, 2006). While a number of studies have found higher RMR in overweight children, the differences are negated when corrected for Fat Mass/Fat Free Mass (Treuth et al, 1998; Molnar & Schutz, 1997; Dietz et al, 1994).

The actual energy cost of adult type activities may also be higher due to the smaller muscle mass in children. Generally it is believed that the adult MET values should be multiplied by the child's RMR for an estimation of EE. Clearly in light of the increasing prevalence of childhood obesity there is a need for further work into the actual energy expenditure due to physical activity in children.

3. Observation methods

Observation methods of determining physical activity are generally used only in documenting workplace activity or in young children who are confined to a physical area

e.g. a school playground. Observers are trained to note behavioural information about the types of activities, the time spent in each activity and the frequency of such. Short time periods may not be reflective of habitual physical activity but observing for longer periods can be tedious and may lead to inaccuracies in reporting information. Recording can also be done by video recording providing a permanent record. In order to obtain a complete picture of physical activity of children a number of time periods such as during school break times, lunch times and physical education classes may be required.

Information on the physical surroundings which may influence physical activity levels can be obtained in observational studies, and thus these studies can provide added data which may partly explain the reasons for particular findings e.g. environmental factors such as few public play areas which may explain low levels of activity (Johns & Ha, 1999). While accurate information on the intensity of activity cannot be captured by observation methods they may be useful where classification of activity is all that is required (Chen et al, 2002). Observation methods also allow data to be collected on inactivity as the length of intervals between activities can be determined. With the advent of lightweight activity monitors there may be less need for observation studies in children.

4. Questionnaires

Questionnaires and interviews are frequently the method of collecting data on physical activity in studies involving large numbers of subjects where simple, inexpensive methods are required. Questionnaires measuring activity in adults usually include questions on occupational, transport and leisure time activity. As data is collected after its occurrence the procedure does not influence performance. The validity of questionnaires measuring physical activity is difficult to establish due to the lack of a gold standard criterion against which to compare them and the problems with long term recall of activities and the likelihood of overestimation of time and intensity of activity.

The use of questionnaires in children requires specific considerations. Below the age of 10-12 years children can only give limited information about their activity patterns. Parents, teachers or other adults may give details of the child's physical activity but this information may be estimated especially for outside activities. Regular planned activity is relatively easy to remember in the short term but so much of childrens' activity is spontaneous, unplanned and of a stop start nature and therefore activity may be difficult to recall. Children can also have difficulties estimating the duration of activities and time frames may need to be provided for the child in terms of "*on the way to school, break time, way home from school, before dinner*" etc. Questions about participation in Physical Education (P.E.), method of transport to and from school and extra-curricular activities may be included to gain information on childrens' overall activity levels. Providing a list of activities can aid recall.

The Modifiable Activity Questionnaire for Adolescents (MAQA) assesses physical activity over the previous year (Aaron et al, 1993). It includes questions on the number of times in the previous 14 days the subject engaged in at least 20 minutes of hard and of light exercise. Hours per days spent watching television, videos, playing computer games each day and the number of competitive activities the adolescent participates in is assessed, as is the energy expended in regular physical activity each week.

5. Heart rate monitoring

Heart rate (HR) monitoring is an objective method of measuring physical activity. HR monitoring can provide details on the time, intensity and frequency of specific activities

based on the heart rate response to such activity. It is an indirect measure which is based on the linear relationship between heart rate and oxygen uptake, so the relative stress placed on the cardiopulmonary system due to physical activity is assessed. Advances in technology have made it possible to detect and store impulses over a number of weeks prior to being downloaded to a PC. While athletes commonly use heart rate recorders to determine and monitor exercise training zones these instruments can also be used in research and in clinical practice. Heart rates above a percentage of maximum can be identified and the data can be classified into time spent in specific zones for the time measured. Inactivity can be classified from heart rates close to baseline. However if heart rate is elevated for a period of time during inactivity (e.g. due to caffeine), on data analysis it can appear that this was related to activity. Heart rate can also be influenced by emotional stress, ambient temperature, humidity, and drugs and there may be some day to day variation. In addition resting heart rate and heart rate for any given workload is influenced by exercise tolerance. Fitter subjects have higher stroke volumes and hence lower the heart rates for any given workload.

The definition of resting heart rate and its' method of determination has an impact on the apparent level of activity (Logan et al, 2000). The interpretation of physical activity level depends on the threshold used and different thresholds will lead to different overall results. In terms of providing the most accurate results individual fitness testing would need to be performed prior to using heart rate monitoring so that data obtained can be correctly interpreted. Without individual data on exercise tolerance and/or the specifics of the activities being measured, lower heart rate data could be due to less activity in someone unfit or more intense activity for an individual who had a higher fitness level. In those who are less fit the return of heart rate to baseline after activity is slower than for those more fit but in the absence of this information it could appear that a less fit person is active for longer.

In summary heart rate monitoring is a useful method of measuring overall activity in children but interpretation of how active the child is depends on the fitness of the child and the definition of resting heart rate used. In addition heart rate may be influenced by other factors not related to physical activity.

6. Motion sensors

In recent years there has been a move away from other methods as described above to the use of instruments to detect body movement. The selection of motion sensors is ever increasing and ranges from simple pedometers to electronic accelerometers which reflect not only the occurrence of body movement but its intensity and in some instances its location. Pedometers record acceleration and deceleration of the waist in the vertical direction but do not record the intensity of movement. For large studies, where total activity is of interest, the pedometer may be useful and particularly in adults where Sequeia et al (1995) have demonstrated that the pedometer could differentiate between various levels of occupational activity (sitting, standing and moderate effort occupational categories). No differentiation could be made between heavy and moderate work, where heavy work involved much static work such as lifting but in assessing overall activity in large numbers this may not be that important. In adults and children much of the activity accumulated during the day is by walking which can be captured by pedometers.

These monitors have become more available and less expensive. Their use in epidemiological studies is helping to add significantly to our understanding of activity and

health status as has been demonstrated by Craig et al (2010) in CANPLAY (Canadian Physical Activity Levels Among Youth) where pedometer data on almost 20,000 children was measured. Validity, reliability and accuracy need to be determined for all pedometers used in research. The Walk4Life 2505 has been found to be within 5.3% of actual time across all speeds and was thus recommended for the quantification of physical activity in children (Beets et al, 2005). However in those with intellectual disability Pitetti et al (2009) found an underestimation of approximately 14% in registered steps and an overestimation of 8.7% in time spent in activity when the Walk4Life was compared to video-recorded activity. Outputs from different pedometers may not be comparable. In addition as stride lengths will vary considerably with different age groups of children data from similar instruments may not be comparable across age groups when distance is the variable of interest. While pedometers may be used in large scale studies due to relatively low cost it is only total ambulatory activity over the measured time period that can be captured. Data on intensity, duration or frequency of activity bouts within that period cannot be obtained.

The assessment of physical activity by accelerometry is based on the measurement of body movement or the dynamic component of activity and accelerometers may be uni-axial, bi-axial or tri-axial. Uni-axial accelerometers such as the Caltrac or the Computer Science Application (CSA) incorporate a single, vertical axis piezoelectric bender element which is displaced with movement, and this generates a signal which is proportional to the force of the movement that produced it (Puyau et al. 2002). A study examining the validity of the CSA in children walking and running on a treadmill found the activity counts were strongly correlated with energy expenditure by indirect calorimetry (Trost et al, 1998). In addition to walking and running other activities typical in children such as Nintendo, arts and crafts, aerobic warm up, and Tae Bo were measured by CSA and the Mini-Mitter Actiwatch (MM) (Puyau et al, 2002) and data was compared to by room respiration calorimetry, and heart rate measured by telemetry. Correlations of $r=0.78 \pm 0.06$ and $r=0.80\pm0.05$ were found for the MM and $r=0.66\pm 0.08$ and $r=0.73\pm 0.07$ for the CSA for the right and left hips respectively.

While uni-axial accelerometers can only measure movement in one plane most movements in the saggital and horizontal planes are accompanied by movement in the vertical plane and some would argue that a uni-dimensional (vertical axis) activity monitor may be just as valid as a three dimensional monitor. However as many activities in young children (such as crawling and climbing) may be captured better by tri-axial accelerometers. The Tritrac R3D is a three dimensional motion sensor which measures the acceleration in three planes and integrates values to a vector magnitude. Vector magnitude is calculated as the square root of the sum squared of activity counts in each vector.

Data from the Tritrac accelerometer has been compared to the energy expenditure measured by indirect calorimetry for treadmill walking and running in 60 young adults who walked and ran on a treadmill at speeds of 3.2, 6.4 and 9.7 $km.h^{-1}$ (Nichols et al, 1999). The mean differences between energy expenditure measured by indirect calorimetry and that measured by the Tritrac ranged from 0.0082 $kcal.kg^{-1}.min^{-1}$ at 3.2 $km.h^{-1}$ to 0.0320$kcal.kg^{1}.min^{1}$ at 9.7 $km.h^{1}$ with the Tritrac consistently overestimating EE during horizontal treadmill walking. Overall it was found that the Tritrac accurately distinguished between the various intensities of walking and running on level ground, was highly reliable from day to day and was sensitive to changes in speed of movement but not to incline.

The RT3 (Stayhealthy Inc, Monrovia, CA) has followed on from the Tritrac and although smaller it has a similar output to its predecessor. The validity of the RT3 in the assessment of physical activities which included walking on a treadmill, kicking a ball, playing hopscotch and sitting quietly was examined in 10 boys and 10 adult males (Rowlands et al, 2004). The RT3 vector magnitude correlated significantly with oxygen consumption in boys and in men. When compared to oxygen uptake excellent correlations with the RT3 have been found in 7-12 year olds (Hussey et al, 2009) and 12-14 year olds r-0,96, p< 001 (Sun et al, 2008). The measurements of inactivity, low activity, and moderate activity are very accurate with the RT3. The limits of agreement for vigorous activity are wider but this may not be highly important in measuring overall physical activity where short time periods are spent in vigorous activity each day and the classification of vigorous activity is needed but the absolute measure may not be required. Up to three weeks data can be acquired when the vector magnitude is sampled every minute. Data can be downloaded to a PC and saved in an excel files so data can be presented as required. The data can be manipulated in a number of ways depending on the needs of the project in question.

In our experience one of the most useful methods in the manipulation of the data has been to calculate the mean number of minutes per day spent in different classifications of activity e.g. inactivity, light activity, moderate activity, and vigorous activity. Alternatively the energy expended in activity may be used. However the intensity thresholds used need to be standardised if data is to be compared across groups. Where intensity is defined into categories on specific cut off points there will still be a wide variation in energy expended in subjects depending on where most of the activity within a wide range occurs. Two subjects may be classified as having spent the same amount of time in moderate/vigorous activity in a day yet one may have been at the lower range and the other at the higher and yet the data analysed will be the same. Thresholds for sedentary behaviour also need to be agreed as slight changes will have considerable impact on time spent sedentary per day as most of the day is spent either sedentary or in light activity. Reilly et al (2008) have demonstrated how using the cut off points provided by different researchers on the same data set can lead to significant differences in the time spent either sedentary or in moderate to vigorous activity. There is a real need for consensus on how data is analysed so data can be compared across studies. This needs to be done in children as well as adults and in children age may need to be a factor considered.

In the past decade there has been a substantial increase in the use of portable accelerometers and examples include the BioTrainer Pro and the SenseWear Armband. The former is a biaxial accelerometer that can sample data between 15 seconds and 5 minute intervals and can store up to 112 days of data. The SenseWear Armband is also a biaxial accelerometer with a heart rate receiver and thermocoupler which can measure heat production. The monitor is a wireless armband and is worn on the upper arm in contact with the skin surface. These newer monitors along with the CSA, the Tritrac R3D and the RT3 (King et al, 2004) were evaluated against indirect calorimetry for treadmill walking and running. No significant difference was found between the mean energy expenditure of the activity monitors at all speeds. The SenseWear Armband, Tritrac and RT3 had significant increases in mean EE as the speeds increased.

Another recent accelerometer is the IDEEA which provides an advantage over other acclerometers as it employs a more sophisticated motion-capture system using two dimensional accelerometers which are placed on the thighs, feet and sternum in conjunction with pattern recognition software which allows movement patterns to be detected (Zhang et

al, 2004). A particular attraction of the IDEEA is the data on the type of activity performed e.g. walking, running. The IDEEA is a portable device and consists of 5 sensors that are attached to the body and a small data collection device (or microcomputer). The basic working principle of the IDEEA is that the sensors are attached to the body in specific areas. One sensor is attached to the sternum (preferably just below the sternal angle that is supposedly perpendicular to the vertical axis of the upper body, its correct alignment is crucial for distinguishing between sitting, reclining and lying down), two sensors are placed on the anterior sides of the upper legs, halfway between the hip and the knee, and the other two sensors are placed on the inferior side of the feet. The IDEEA system monitors the body and limb motions constantly through these sensors and the different combinations of signals from the sensors represent different physical activities, which are coded for as different numbers. The monitor collects 32 samples/second while continuously distinguishing among different postures and gaits to identify the type of physical activity.

The ability of the IDEEA to correctly identify the type of activity and to quantify PA intensity allows for calculations of EE in free-living conditions. The IDEEA device has in-built equations that determine the EE in kcal.min^{-1} or kJ.min^{-1}. Recent work in our laboratory was performed with the objective of examining the validity of the IDEEA in the estimation of energy expenditure during rest, walking and running in 28 young adults against the criterion method of physiological energy expenditure by indirect calorimetry (Oxycon mobile VIASYS). Good correlations in rest and walking were detected ($r=0.73$, $p<0.0001$ at rest to $r=0.49$, $p< 001$ at 6 km/h). The IDEEA was able to differentiate between inactivity, light, moderate and vigorous activities and can provide a valid estimate of energy expenditure in rest and walking (Mc Creddin & Hussey, 2009). A particular beneficial feature of the IDEEA is identification of type of activity, gait analysis during walking and running and identifying most postures.

The multisensory monitors the IDEEA and the Sense Wear Pro Armband have also been evaluated in children along with the ActiReg. While it was found that all three needed further development, the IDEEA had the highest ability in assesses energy cost (Arvidsson et al, 2009). The Actireg contains two pairs of sensors worn over the sternum and right thigh. These sensors can determine body position and motion. Along with the data processor the body positions and motion captured are given an "Activity factor" based on a multiple of basal metabolic rate. All three monitors were comparable for resting and sitting but none accurately measured stationary cycling, jumping on a trampoline or playing basketball. The IDEEA was the only one to accurately measure stair walking. In walking and running activities the IDEEA showed a close estimate of EE where the Sense Wear accurately measured slow to normal walking but underestimated higher speeds. In health related research accurate measures of inactivity and light activity may be more important than differentiating between more vigorous activity.

Global positioning systems are potentially valuable in the assessment of physical activity. The technology permits the identification of location and such data is important in our understanding of physical activity behaviours in children. A Global Position System receiver position is calculated by measuring its distance from a number of GPS satellites. Once switched on the GPS device constantly receives signals from satellites and can calculate the distance from each. In addition to providing a profile of the child's activity patterns the GPS data can be combined with a GIS (Geographical Information Systems) database to provide information on where activity occurs and how the built environment/ transport options

may influence activity behaviours (Maddison & Ni Mhurchu, 2009). GPS systems may be combined with accelerometry or other methods to provide richer data. Ideally these should be incorporated into one monitor. A small pilot study that examined how well the combination of GPS and accelerometer data predicted activity modes. Using three variables 91% of observations were correctly classified by the combined methods (Troped et al, 2008) A feasibility study in combining heart rate and GPS data was performed on 39 children during a confined time period (Duncan et al, 2009) and the system was found it to be a promising method for measuring play related energy expenditure. In this instance location, distance, speed and HR data were captured every second using the F500 model.

A limitation to the use of GPS is that it can only be used out doors and even then high buildings and trees may effect the use. The location of the GPS system may effect sitting postures as typically it has been situated on the back in harness/backpack. Increased battery life for devices such as the Garmin is required in order to establish activity patterns in children where at least four days of monitoring is recommended (Trost et al, 2000).

In summary: accelerometers are designed to measure physical movement without impeding activity in free- living situations and can measure periods of inactivity as well as quantity and intensity of movement. The ability of newer accelerometers to store data over a number of weeks permits measurement of habitual activity. Motion sensors are for the most part small unobtrusive devices that have the capacity to store movement data for prolonged time periods. The development of wireless communication to the data collection device could reduce the inconvenience associated with wearing the multiple sensors.

7. Conclusion

Increased time spent inactive has been cited as one reason for the epidemic of childhood obesity and therefore it is important to be able to obtain valid measures. This review has concentrated on methods of measuring physical activity in both clinical and laboratory settings. Observational studies are time consuming, labour intensive and involve many observers who may require intense training. Their cost may be prohibitive in epidemiological or large scale studies where the use of questionnaires may be more appropriate. While assessing physical activity through the use of questionnaires has some limitations, it is the only feasible approach for epidemiologic investigations. Heart rate monitoring can distinguish between different intensities of activity in children and therefore can be used to determine light, moderate and vigorous activity. However as higher degrees of fitness are associated with lower resting heart rates, fitness may need to be individually assessed before measurement. This would be very difficult in large cohort studies. Accelerometers can measure habitual physical activity and inactivity, are easy to wear and do not interfere or influence movement. An additional benefit of accelerometry is the ability to measure intensity of activity. The ultimate choice of activity measure will depend on the question to be studied, the size of the cohort and the resources available.

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4

Applicability of the Reference Interval and Reference Change Value of Hematological and Biochemical Biomarkers to Sport Science

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1. Introduction

The training principle states that tissue adaptation depends upon overload applications. The cumulative effect of these programmed breaks in homeostasis through variations in the intensity, duration and frequency of the exercise is higher performance. However, it is important to point out that the positive adaptive response, which is reflected by increased performance, depends upon an adequate recovery time between each training session and during training sessions to result in phenotypic alterations (Hohl et al., 2009).

Training sessions and nutrition are highly interrelated. Repeated training sessions typically require a diet that can sustain muscle energy stores to execute the training proposed. The phenotypic alterations that lead to increased performance result from an intense process of protein synthesis that occurs during the recovery period and can last up to 24 h after the exercise session. This process is highly influenced by food ingestion, which offers energy and nutrients that are essential to the process and to the recovery of energy reserves (Hawley et al., 2006). Recent evidence shows that some nutrients can potentiate the protein synthesis pathways that are activated by exercise, influencing the adaptive process and performance (Hawley et al., 2011).

Professional athletes, for example, soccer players, are submitted to an annual training and competition routine with periods of recovery that are not always properly adjusted to the workload. The main problem is that the current championship schedule generally does not allow the teams to take the minimum time required for appropriate physical preparation because the different stages (competitions and physical, technical and tactical training) overlap. As a consequence, the athletes may suffer an imbalance between the effort put forth and the recovery time during the competitive season, which increases the likelihood that the workload will be excessive for some players.

Each overload stress results in different degrees of microtrauma in the muscle, connective tissue, and/or bones and joints, which trigger an inflammatory response promoting repair

and muscular regeneration. These microtraumas are therefore called adaptive microtrauma (AMT). An AMT may be regarded as an initial phase along an injury *continuum*. Conceivably, this injury might progress from the initial benign AMT stage to a subclinical injury in the athlete who is training strenuously and frequently (Smith, 2000). The main challenge for the better adjustment of physical training methodologies is therefore to program a sequence of exercise stimuli that has an ideal relationship between the amount of exercise and the time to recovery between sessions and that leads to increased performance with a lower energy cost.

The longitudinal evaluation of some blood analytes may reveal markers of previously altered situations, which could prevent the amplification of the response before the performance is affected. A variety of studies using different types of exercise protocols have already demonstrated that biomarkers, such as creatine kinase (muscular overload), urea (protein turnover), creatinine (muscular mass), uric acid (the major antioxidant in plasma) and hematological parameters, suffer some modulation by exercise (Sawka et al., 2000; Pattwell et al., 2004; Lac & Maso 2004; Finaud et al., 2006; Peake et al., 2007; Lippi et al., 2008; Lazarim et al., 2009). However, there is currently no consensus about the applicability of these biomarkers as markers of training effects that effectively contribute to reaching and maintaining a better performance.

1.1 Biomarkers of training effects
1.1.1 Muscular damage

The muscle tissue may be damaged both directly and indirectly. Direct damage may be due to crush injuries (Brancaccio et al., 2010; Cervellin et al., 2010), but the main force responsible for damage is the mechanical stress that occurs during training sessions (Fielding et al., 1993; Tidball, 2005a). Indirect damage can originate from several sources that reduce membrane permeability (e.g., drugs, toxins, electrolyte alterations, bacterial or viral infections and disorders in carbohydrate metabolism) (Brancaccio et al., 2010).

Muscle damage is related to a disorganization of the myofibrillar structure and a disruption of the Z line, extracellular matrix, basal lamina and sarcolemma, allowing some of the proteins present within the cell to be release into the bloodstream (Sayers & Clarkson, 2003). Among them are creatine kinase (CK), lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and myoglobin. These proteins are blood markers of muscle functional status, and an increase in their serum concentrations or activities may be an index for either muscle damage or muscular adaptation to training (Brancaccio et al., 2008; Lazarim et al., 2009).

The enzyme CK is a globular protein with a molecular mass of 43-45 kDa. It influences the availability of energy to the muscles through the exchange of high-energy phosphate from phosphocreatine (PCr) to ADP (adenosine diphosphate) for fast ATP (adenosine triphosphate) production, as follows:

$$PCr + ADP + H^+ \xrightarrow{\;CK\;} ATP + Cr$$
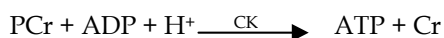
Five isoforms of the enzyme are present in the skeletal muscle, cardiac muscle and brain: three of them are found in the cytoplasm (CK-MM, CK-MB and CK-BB, respectively), and two isoforms are found in the mitochondria. Because of their differential tissue distribution, they provide different information about tissue damage: CK-MM is a marker for muscle damage, CK-MB is a marker for acute myocardial infarction and CK-BB is a marker for brain damage (Brancaccio et al., 2010).

Doubts about the application of CK analysis to the monitoring of the muscular workload in athletes are derived from studies suggesting that this analyte is an unreliable marker for histological muscle lesions (Malm, 2001). Another source of doubt is that the serum CK values measured in individuals exercising to a similar degree showed high variability and a non-Gaussian distribution (Clarkson & Ebbeling, 1988; Lazarim et al., 2009).

Studies of subjects performing specific exercises for short, defined periods have shown that the time of CK release into the bloodstream and its clearance from the plasma depends on the training level, type, and intensity as well as the duration of the exercise. Peak serum CK values of approximately twice the baseline levels occur eight hours after strength training (Serrão et al., 2003). After an acute bout of intense plyometric exercise, the serum CK levels reached peak values from 48 through 72 hours of recovery (Chatzinikolaou et al., 2010). Peak serum CK values of approximately sevenfold above the baseline were found 48 h after a soccer game (Fatouros et al., 2010). There are marked differences between the sexes, with lower basal CK values in females than in males. Estrogen levels may be one important factor in maintaining membrane stability post-exercise (Tiidus, 2000). Creatine kinase serum levels can also be influenced by muscle mass and ethnicity (Eliakim et al., 1995).

While these studies make important contributions to the understanding of acute responses, they do not provide enough information for longitudinal, seasonal application in actively competing athletes. An important point to be considered is that serum CK activity can arise in the absence of histological lesions as a consequence of changes in the muscle membrane permeability (Manfredi et al., 1991). Thus, monitoring the changes in serum CK may represent an indirect route for monitoring workload effects and a way to prevent sub-clinical damage due to muscle overload. However, to be a useful tool for individual adjustments in the stimulus/recovery ratio during a competitive season, it is necessary to compare individual blood values with population-based reference intervals. With this knowledge, it is possible to individualize training program interventions to adjust overloads or medical/nutritional programs only when necessary. Prevention thus leads to economy for all.

One difficulty in assessing the effects of training through blood biomarkers is the lack of appropriate reference intervals obtained from a reference population practicing regular and systematized physical activity or sports modality. To solve this problem, we have recently determined the reference interval for the plasma CK activity of blood samples obtained from 128 professional soccer players at different times during the Brazilian Championship (Lazarim et al., 2009). The upper limits of the 97.5th and 90th percentiles for the CK activity were determined according to the International Federation of Clinical Chemistry (IFCC) rules and were 1.338 U/L (CI = 1191−1639 U/L) and 975 U/L (CI = 810−1090 U/L), respectively. These percentile values were markedly higher than the values previously reported in the literature (< 207 U/L) (Rustad et al., 2004). Taking the upper limit of any percentile as the decision limit, the individual plasma CK activity above the upper reference limit may indicate the transition from adaptive microtrauma to a sub-clinical muscular injury, increasing the potential for histological damage.

In this study, we suggest the 90th percentile (975 U/L) as the upper plasma CK limit for the early detection of muscle overload in competing soccer players (Lazarim et al., 2009). We hypothesized that the same muscle membrane alterations that may increase plasma CK activity also affect the release of growth factors by muscle cells (McNeil & Khakee, 1992), explaining why changes in the plasma CK activity could also reflect muscular adaptation

when the values are lower than the upper limit values. To test this hypothesis, we evaluated a soccer team monthly throughout the Championship. During the five moments of analyses, we detected only six players with plasma CK values that were higher than 975 U/L. These players were asked to decrease their training for 1 week, after which they presented lower CK values. Only one player with a CK value higher than the decision limit (1800 U/L one day before a game) played on the field, and he was unfortunately injured during the game. The CK activity in all of the other players showed a significant decrease over the course of the Championship, and the values became more homogeneous toward the end.

Later, we showed that the 97.5th percentile for a young population with improved performance after four months of systematic endurance training was similar (< 1309 U/L, CI = 882 – 1464 U/L) to that found in soccer players (Nunes & Macedo, 2008). To us, this finding justified the use of blood samples from this physically active population to establish reference population intervals for analytes that respond to exercise stimulus, such as plasma glutamine and glutamate concentrations, which are discussed in another chapter of this book.

1.1.2 Inflammatory response

The response to AMT is a subsequent inflammation post-exercise, triggering tissue repair and remodeling. The activation of the inflammatory process is both local and systemic and is mediated by different cells and secreted compounds with pro- and anti-inflammatory activities. The objective is to reestablish organ homeostasis after a single bout of exercise or after several exercise sessions. The acute-phase response involves the combined actions of activated leukocytes, cytokines, acute-phase proteins, hormones, and other signaling molecules that control the response to an exercise session and guide the adaptations resulting from training (Gruys et al., 2005).

The leukocytes are the first cells of the immune system to respond to tissue damage (Smith, 2000), and the neutrophils are the first subpopulation to migrate to the damaged site (Tidball, 2005). Neutrophils are produced in the bone marrow and represent 50 to 60% of the total leukocytes in circulation (Toumi & Best, 2003; Tidball, 2005b). Cortisol stimulates their release (Pyne, 1994), and their main function is the removal, by phagocytosis, of undesirable elements that are related to injury. To accomplish this removal, they release proteases to degrade proteins and produce superoxide anions $[O_2^{\bullet-}]$ and subsequently other reactive oxygen species (ROS; hydrogen peroxide $[H_2O_2]$ and hydroxyl radical $[OH^{\cdot}]$) through a respiratory burst that is catalyzed by NADPH oxidase and myeloperoxidase (Pyne, 1994; Tidball, 2005b). This action is the starting point for the subsequent response of repair and tissue growth.

The monocytes are the second subpopulation of leukocytes that migrate to the damaged tissue. In the cells, they undergo differentiation and become macrophages (Tidball, 2005b). Recently, it was proposed that the macrophages that invade the lesion site earlier (between 24-48 h) have different functions than do those that appear later (between 48-96 h). The main function of the first group is the removal of damaged tissue, whereas the later group has a more active function in muscular repair and secrete remodeling molecules, such as insulin-like receptor, cytokines and TGF-α, that act in the recruitment and activation of fibroblasts and collagen secretion, contributing to tissue remodeling (Butterfield et al., 2006). Moreover, macrophages signal the activation, proliferation and differentiation of stem satellite cells, an important pathway for tissue remodeling (Pedersen et al., 1998).

The lymphocytes present a biphasic response to training. There is an increase during and immediately after the effort, especially of the Natural Killer (NK) cells, followed by a decrease

that can last for hours (mainly of T and NK cells). The latter effect can lead to a transitory immunosuppressive state that is related to a higher susceptibility for upper respiratory tract infections as an acute effect of exhausting, prolonged exercise (Glesson, 2007; Pedersen et al., 1998). This phenomenon is known as an open window, and it can lead to increased susceptibility for infections post-exercise (Rowbottom & Green, 2000; Glesson, 2007).

The literature related to exercise indicates distinct inflammatory responses to both acute and chronic exercise (Catanho da Silva & Macedo, 2011). In general, acute exercise induces a proinflammatory response that is characterized by transient leukocytosis (neutrophilia, monocytosis, and lymphocytosis), followed by a partial cellular immunosuppressive state. After a single bout of physical activity, there is an increase in the number of circulating leukocytes that is related to the intensity and duration of the exercise (Gleeson, 2007). Other substances related to leukocyte function, including inflammatory cytokines and inflammatory acute phase proteins are also increased. These values are generally normalized to basal concentrations within 3-24 hours (Gleeson, 2006). An increase in the serum concentrations of creatine kinase, C-reactive protein and cell adhesion molecules is also observed, in addition to an increase in the secretion of cortisol and cytokines (Pedersen & Hoffman-Goetz, 2000; Steensberg et al., 2000).

In contrast, chronic exercise (training) seems to result in a local and systemic imbalance in the anti-inflammatory status as compared to the pro-inflammatory status. This imbalance promotes tissue adaptation and protects the organism against the development of chronic inflammatory diseases and against the deleterious effects of overtraining, a condition in which a systemic and chronic proinflammatory and pro-oxidant state seems to prevail (Petersen & Pedersen, 2005; Catanho da Silva & Macedo, 2011). Some studies have shown an attenuation in the production and secretion of acute phase proteins, especially PCR (Kasapis & Thompson, 2005), greater production and secretion of anti-inflammatory proteins (IL-6) (Petersen & Pedersen, 2005) and improved antioxidant status (Petersen & Pedersen, 2005; Ji, 1999). A possible transient alteration in the production of IL-1β and TNF is dependent upon the exercise type, intensity and duration (Petersen & Pedersen, 2005). Adipose tissue also has been investigated in chronic protocols and has shown the same anti-inflammatory pattern (Lira et al., 2009).

In general, there is little evidence available to suggest clinical differences between the immune functions of sedentary and exercised subjects. Some studies have reported a lower frequency of upper respiratory tract infections in persons who are moderately active as compared to those with a sedentary lifestyle (Gleeson, 2007). Cross-sectional studies that have compared leukocyte numbers in sedentary control groups with athletes more than 24 hours after their last training session have generally found few differences (Gleeson, 2006).

We established reference intervals for hemogram in a large population (n = 357) after four months of systematized endurance training. We followed the criteria established by the International Federation of Clinical Chemistry (IFCC). The outliers were detected and removed before the estimation of the reference interval by Horn's algorithm (Horn et al., 2001). The RefVal program (Solberg, 2004), including practical approaches and formulas recommended by the IFCC, was used to calculate the non-parametric 2.5th and 97.5th percentiles, together with their 90% confidence intervals (CI), using a Bootstrap methodology. Table 1 shows the lower limit (2.5th percentile) and upper limit (97.5th percentile) of the reference intervals and their respective 90% confidence intervals for hematological parameters.

Analysis	Reference Interval	90% Confidence Interval		Subjects (n)	Outliers (n)	Total Subjects
	2.5th - 97.5th	2.5th	97.5th			
RBC (10^{12}/L)	4.4 - 5.6	4.3 - 4.5	5.6 - 5.7	357	5	352
Ht (%)	39.5 - 48.0	39.0 - 40.2	47.7 - 48.8	357	3	354
Hgb (g/dL)	13.0 - 16.1	12.8 - 13.2	15.9 - 16.3	357	2	352
MCV (fL)	80.9 - 94.9	80.0 - 82.3	94.3 - 95.4	357	6	351
MCH (pg)	26.1 - 31.6	25.7 - 26.5	31.4 - 31.7	357	9	348
RDW (%)	12.1 - 14.3	12.0 - 12.1	14.1 - 14.4	357	16	341
WBC (10^9/L)	4.5 - 10.1	4.2 - 4.7	9.7 - 10.4	357	12	345
Lym (10^9/L)	1.2 - 3.3	1.2 - 1.3	3.15 - 3.4	357	4	353
Neut (10^9/L)	1.8 - 6.7	1.7 - 2.0	6.5 - 7.0	353	10	343
PLT (10^9/L)	140 – 337	135 – 147	307 – 350	357	4	353

Table 1. Reference intervals, confidence intervals and outliers obtained from a hemogram of physically active individuals.

We found slightly higher values for counts of leukocytes ($4.5x10^9$ – 10.1 $x10^9$/L) and neutrophils (1.8 $x10^9$ – 6.7 $x10^9$cel/L) in our physically active population as compared to sedentary individuals ($3.5x10^9$ - $9.8x10^9$/L and 1.4 $x10^9$ – $6.6x10^9$/L, respectively) (Kjeldsberg, 1992). Our reference ranges are narrower than the traditional reference intervals for leukocyte counts, mainly due to the homogeneity of the reference population. The 2.5th and 97.5th percentile of the lymphocyte and platelet counts found were similar to those of healthy, non-exercised population values (Lym = 1.2 – 3.5 x 10^9/L) and (PLT = 145 – 348 x 10^9/L) (Kjeldsberg, 1992; Nordin et al., 2004), indicating no training effects on these parameters.

The erythrogram is a part of the hemogram that evaluates the red blood cell (RBC) number, volume and hemoglobin content. Erythrograms can be useful to diagnose sports anemia, which can impair the athlete's performance (Sottas et al., 2010, Schumacher et al., 2002). Exercise-induced hemolysis has been reported for more than 50 years (Gilligan et al., 1943). This phenomenon is associated with the destruction of red blood cells (RBC), with higher RBC turnovers in runners as compared to non-trained subjects, although it is commonly observed in other modalities (e.g., swimming, weight lifting, rowing) (Telford et al., 2003). A persistent decrease in the hemoglobin concentration, decreases in indices such as the mean corpuscular volume and the hemoglobin corpuscular volume and an increase in red distribution width (RDW) can also indicate iron deficiency (Zoller & Vogel, 2004). Three subjects presented higher RBC values and lower MCV values, characteristics of thalassemia, while four subjects were detected to have microcytosis (MCV < 80.0 fL and RDW>15%) and hypochromia (HCM=26.0 pg), suggestive of an iron deficiency: these subjects were classified as outliers and were excluded from the calculations of the reference intervals.

The data presented in Table 1 show a more narrow reference interval for RBC, hematocrit and hemoglobin in our population as compared to a sedentary subject's values (RBC = 4.4 – 5.9 x 10^{12}/L; hematocrit = 40 – 50% and hemoglobin 13 – 18 g/dL) (Kjeldsberg, 1992). The mean erythrocyte lifespan in athletes and physically active subjects may be shorter than that in non-exercised subjects, mainly due to the exercise-induced hemolysis that is inherent to

endurance training (Weight et al., 1991). This lifespan may lead to the narrow values observed in the red blood cell parameters in our study. The accelerated turnover and increased rate of RBC production in endurance trained subjects can lead to a steady state of a population of younger RBCs, which are more efficient at oxygen transportation due partly to higher 2,3-diphosphoglycerate concentrations (Smith, 1995).

1.1.3 Nitrogen compounds

A prolonged, uncontrolled local neutrophil action can damage other cells near the inflammatory site due to increases in ROS production, which compromises the integrity of the muscle cells, contributing to systemic inflammation (Tidball, 2005b). A series of enzymatic and non-enzymatic antioxidants (Ji, 1999) limit the biological activity of ROS. Uric acid is one of the most important non-enzymatic antioxidants in plasma and tissues (Lippi et al., 2008). In addition, the plasma antioxidant system is also composed of other molecules and enzymes, such as ascorbic acid, proteins, vitamin E, bilirubin and peroxidases (Finaud et al., 2006).

Athletes and physically active subjects displayed an enhanced antioxidant capacity (Carlsohn et al., 2008) with increased serum concentrations of uric acid (Finaud et al., 2006). It was suggested that urate quantification could be useful for monitoring athletes in training (Youssef et al., 2008). We have found (Nunes et al., 2010) a slightly higher serum uric acid reference interval in athletes (0.24 – 0.49 mmol/L) than in sedentary subjects (0.23 – 0.47 mmol/L) (Rustad et al., 2004). This difference can be explained by the intensity of the subject's training (Finaud et al., 2006).

Biomarkers, such as serum creatinine and urea, are also used to monitor the effects of training. The urea is an end product of the degradation of nitrogenous compounds from proteins; it is synthesized in the liver and is excreted by kidneys. The main factors influencing the higher urea serum levels found during the training period may be the increased consumption and protein turnover, the reduced water intake and the incomplete replenishment of glycogen after exercise (Hartmann & Mester, 2000). The serum concentrations of urea have been used as a marker of protein catabolism and were found to stimulate gluconeogenesis during higher training loads. It was proposed that monitoring the serum urea concentrations and the CK activity may indicate an acute impairment in exercise tolerance (Urhausen & Kindermann, 2002; Lehmann et al., 1998). The serum urea level seems to respond to exercise training, and the upper limit of the reference interval observed by Nunes & Macedo (2008) (3.0 – 8.51 mmol/L) in physically active subjects at a well-trained stage is higher compared than that of a non-exercised healthy population (3.20 – 8.20 mmol/L) (Rustad et al., 2004).

Serum creatinine concentrations have long been the most widely used and commonly accepted biomarker of renal function in clinical medicine (Perrone et al., 1992). Their concentrations can be modified by age, sex, ethnicity, muscle mass and exercise (Banfi et al., 2009). The serum creatinine concentrations found in professional athletes can vary according to their modality, the training load, their aerobic/anaerobic metabolism, the frequency of their competitions, the lengths of their competition and the annual training period (Banfi et al., 2009). The creatinine reference intervals commonly used for sedentary people are 62.0 – 115.0 µmol/L. In physically active individuals, we observed higher values (77.8 – 132.6 µmol/L) (Nunes & Macedo, 2008), which are typically influenced by the higher muscle mass that is found in exercised populations, as observed by Banfi & Del Fabro (2006).

Our data have shown that the reference intervals were significantly higher in trained subjects than in a non-exercised population, suggesting a training effect on blood analytes,

such as the hemogram, which were slightly different from those values reported in the literature for a healthy, non-exercised population (Kjeldsberg, 1992; Nordin et al., 2004). In the biochemical parameters, the main differences found were as follows: urea (3.0 – 8.51 mmol/L), creatinine (77.8 – 132.6 μmol/L), uric acid (0.24 – 0.49 mmol/L), creatine kinase (<1309 U/L), aspartate aminotransferase (<62 U/L) and C-reactive protein (<19.8 mg/L), all of which had higher reference intervals in trained subjects as compared to a non-exercised population (Nunes & Macedo, 2008). Now that the lower and upper reference values for the blood analytes of an exercised population are known, it will be possible to use these biomarkers to differentiate between the adaptation and maladaptation states that are induced by training.

1.2 Biological variation and reference change values

A comparison of individual blood parameter values with the reference intervals obtained from a defined, physically active population has certain limitations, one of which is that the laboratory test results may be influenced by natural fluctuations that are particular to a given analyte: this phenomenon is called biological variation (Fraser, 2004). This biological variation should be assessed in longitudinal studies with serial blood analyses of the same subjects. For example, a determined analyte concentration can change over time within an individual, reflecting the random temporal variation of an analyte in homeostasis that can occur during steady state conditions (Ricos et al., 2004).

The point of biological homeostasis (estimated by the arithmetic mean value, μ) is different for each person, and it is assumed to be constant for a certain period (e.g., months, years). The biological within-subject variation is described by the standard deviation (σ), which is obtained from measurements around the mean value (Petersen, 2005). To facilitate the comparison between individuals and analytes, the coefficient of intra-individual variation (CV_I%) is calculated from the following equation:

$$CV_I = σ/μ \times 100 \tag{1}$$

The Table 2 shows an example of the biological variation in the serum CK activity from samples that were collected monthly during the training/competition season of six soccer players.

Athletes	1st result	2nd result	3rd result	4th result	5th result	Individual mean (μ)	Standard deviation (σ)	CV_I (%)
1	1232	911	1239	1232	1380	1232	173	14
2	424	455	327	347	324	347	60	17
3	218	218	147	247	189	218	38	17
4	1214	1055	667	557	560	667	304	46
5	205	111	230	116	137	137	54	40
6	427	173	200	181	273	200	67	33

Table 2. Coefficient of intra-individual variation (CV_I) related to serum CK activity (U/L) of six male soccer players.

These data show that each athlete has a different point of homeostasis for CK activity (represented here as the individual mean), and this is also true for any other analyte. These individual values span different parts of the reference interval for CK activity (Lazarim et al., 2009).

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Another component of biological variation is the coefficient of variation between subjects (CV_G), which is obtained via the mean and standard deviation between different subjects. For example, if ten soccer players exhibited mean serum CK values of 390 U/L with a standard deviation of 266 U/L from blood samples collected after one month of training, the calculated CV_G for these soccer players is 68%.

Both CV_I and CV_G are influenced by age, sex, weight, diet, circadian rhythm, pathologies and physical activity (Ricós et al. 2004), and it is possible to estimate them using data banks that are available in the literature for many analytes in healthy, non-exercised subjects (Ricos et al., 1999). In addition to the biological variation, pre-analytical and analytical variation can also influence the laboratory test results. The pre-analytical variation can be minimized through the adoption of standardized instructions for the patients before sample collection, handling and transportation (Banfi & Dolci, 2003). All analytical measurement techniques (manual or automatic) have some intrinsic sources of variability. This variability cannot be completely eliminated, but it can be minimized by quality laboratory practices and the choice of sound equipment, reagents and methodologies (Fraser, 2001). We can usually identify two types of analytical variation: random (precision) and systematic (bias).

The precision of one methodology or piece of equipment is measured by replicate analysis of the same sample (a control sample). The precision will be influenced by the analytical conditions. If we use the same equipment, technician, reagent lots and calibration, we will generate smaller variations than if we take replicate results over a long period, varying these components (Fraser, 2001). The precision has a Gaussian distribution, and we can calculate the coefficient of analytical variation (CV_A%) from the mean and standard deviation of control sample replicates. The International Organization for Standardization (ISO) defines bias as *the difference between the expectation of the measurement results and the true value of the measured quantity*. In practice, bias is the difference between the results that we obtain and some estimate of the true value (Fraser, 2001).

The analytical variation can be monitored by an internal quality control (IQC) program. The protocol of IQC should include control samples that simulate the matrix of the sample analysis (Westgard, 2004). The statistical analysis of the quality control can be performed through the Levey-Jennings flow chart for each analyte and the correct applications of the Westgard control rules (Westgard, 2004). In addition, the level of performance must be established. The most widely applied term is *quality specifications.* Other terms include *quality goals, quality standards, desirable standards, analytical goals,* and *analytical performance goals* (Fraser, 2001). Considering that all analytes suffer from the influence of biological variation (intra- and inter-individual), one useful quality specification is based on biology (Fraser & Petersen, 1999). In this model, the quality specification has 3 levels for judging imprecision: *desirable performance* is defined as $CV_A < 0.5 \times CV_I$; *optimum performance* is defined as $CV_A < 0.25 \times CV_I$ and the *minimum performance* is defined as $CV_A < 0.75 \times CV_I$ (Fraser & Petersen, 1999).

The analysis of consecutive samples by comparison with values from a reference population is useful mainly when $CV_I > CV_G$ (Fraser 2004). However, the majority of analytes that are quantified in the clinical laboratory have $CV_I < CV_G$. In this case, the comparison of an individual result with a population-based reference interval might not be useful in monitoring slight effects because some individuals may show significant changes in serial testing that are within the normal limits of a reference population (Petersen et al., 1999).

A proposed alternative tool to verify a significant and biologically relevant difference between two consecutive analyses is the reference change value (RCV) or critical difference calculation

(Harris & Yasaka, 1983; Ricos et al., 2004). The RCV defines the percentage of change that must be exceeded given the inherent biological and analytical variation in the test. This tool can increase the sensitivity of serial analyses due to the exclusion of false positive results.

1.3 Calculating reference change values

The total variation associated with a laboratory test result is the sum of the component variations (pre-analytical, analytical and intra-individual biological variation). The pre-analytical variation can be minimized if we standardize the conditions of patient preparation and the procedures for collecting and handling the samples. Therefore, we must consider only the biological and analytical variation when calculating the total variation (CV_T) according equation 2 (Fraser & Harris, 1989).

$$CV_T = (CV_A^2 + CV_I^2)^{\frac{1}{2}} \qquad (2)$$

The coefficient of analytical variation (CV_A) can easily be obtained from the mean and standard deviation of the control sample analytes, and the CV_I is available in the data bank for most of the analytes from healthy subjects (Ricos et al., 1999) or physically active subjects (Nunes et al., 2010).

The term RCV was introduced by Harris & Yasaka (1983) and can be calculated by the following equation (3):

$$RCV = 2^{\frac{1}{2}} \times Zp \times (CV_A^2 + CV_I^2)^{\frac{1}{2}} \qquad (3)$$

Where $2^{1/2}$ denotes the probability of bidirectional change, and Zp denotes the standard deviation corresponding to the level of statistical significance for the bidirectional change (1.96=95% and 2.58=99%) (Harris & Yasaka; 1983; Fraser & Harris, 1989).

Recently, we have established the respective $RCV_{95\%}$ for hemograms and for certain biochemical parameters from individuals who had undergone 4 months of regular and planned physical activity (Nunes el al., 2010). We showed that the RCV values for leukocytes and for all biochemical analytes were elevated as compared to the literature values of sedentary subjects, clearly indicating a training effect on these blood analytes. However, the RCV values for the red blood cell count were slightly lower in physically active than in sedentary individuals (Nunes el al., 2010).

Soccer is the most widely played sport worldwide, and it also has many different cultural, social and economic aspects. The elite soccer player must have good, but not exceptional, all-around physical strength and must be able to effectively respond to the diverse demands of the game. Several studies have determined the pattern of activities performed and the individual distance covered during a game: these values have been used as an indication of the total work performed. It is well accepted that outfield players cover 8-12 km during a game that involves many different activities, with a rapid change in the type or level of activity each 4-6 seconds (Reilly, 1997; Bangsboo, 1994). While the majority of the exercise associated with competitive soccer is at sub-maximal intensities, the intermittent efforts with higher energy demands should not be slighted during a match, and often their successful execution determines the results of a game (Bangsbo et al., 2006).

The trade of elite soccer players produces large sums of money and affects the emotional state of soccer fans all around the world. Great savings can therefore be obtained by elite

soccer players and their clubs with the physical protection of athletes. Our aim in this study was to verify the applicability of the reference interval described here and the previously determined RCVs (Nunes et al., 2010) for monitoring, through hematological and biochemical analyses, the effects of training/competition on soccer players during five months of the competitive season.

2. Material and methods

2.1 Subjects

Fifty-six male soccer players (17-19 years old) participated in this study. The athletes were evaluated during four months that included both training (pre-season) and competitive periods (regional soccer championship for players under 20). The volunteers responded to a questionnaire about their use of medications and complaints of pain and injuries caused by training or competition. Those who were using medications or who were injured were not included in the study. Volunteer subjects were duly informed about the research and signed an informed consent form. This research was approved by the Human Research Ethics Committee of the University (CAAE: 0200.0.146.000-08).

2.2 Collection of blood samples

The subjects were longitudinally evaluated through five blood samples that were collected monthly [C1 = pre-competitive period of training; C2 = after 1 month (training); C3 = after 2 months (training and beginning of competitions); C4 = after 3 months (training and competitions); and C5 = after 4 months (mainly competitions)]. The blood samples were collected under standardized conditions: 2.0 mL of total venous blood was collected in vacuum tubes containing EDTA/K3 to determine the hematological parameters, and 8.0 mL of venous blood was collected in tubes with a Vacuette® (Greiner Bio-one) gel separator to obtain serum for the biochemical measurements. The blood samples were collected in the morning after 12 hours of fasting, in a seated position, and they were transported at 4ºC to the laboratory within 30 minutes, centrifuged under refrigeration at 1,800 x g for 10 minutes, were immediately separated, and were protected from light. All blood samples were collected after two days of rest to avoid the effects of hemodynamic variations and the acute hemodilution that is induced by exercise (Sawka et al., 2000).

2.3 Hematological and biochemical analysis

The hematological parameters were measured with a KX-21N Sysmex® analyzer, and the biochemical analyses (CK activity, uric acid, urea and creatinine concentration) were run in an Autolab analyzer (Boehringer) using commercial kits (Wiener Lab, Rosario, Argentina). All analyses were run in parallel with commercial serum and blood controls. To minimize analytical variations, all samples were tested by the same technician without changing reagent lots, standards, or control materials.

2.4 Statistical analysis

The percent differences between the serial results were calculated for each subject using Microsoft Excel® and were compared with $RCV_{95\%}$ to detect significant changes. As the activity of CK had a value distribution that was slightly skewed to the right, we opted to transform the data using natural logarithms (Wu et al., 2009). The Matlab 7.0 software was used to generate graphs.

3. Results

Figure 1 presents, as an example, the CK values analyzed in comparison to both the upper reference limit and the RCV established from a physically active population (Nunes & Macedo, 2008; Nunes et al., 2010). Thus, Figure 1A presents the CK values (mean, minimum and maximum) for each soccer player at five time points in comparison with the reference upper limit (97.5th percentile - <1.309 U/L), and Figure 1B presents the percentage change between successive pairs of serial results of the five time points in comparison to the RCV (119.8%).

A.

B.
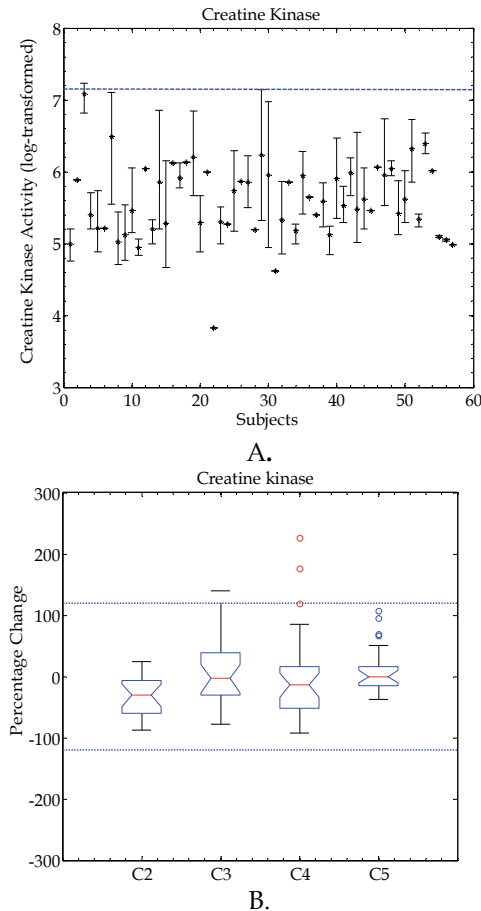
Fig. 1. (A.) CK values (mean, minimum and maximum) for each soccer player at five time points. The dotted horizontal lines indicate the reference interval (97.5% upper limit = 1309 U/L) from a physically active population. (B.) CK percentage change between successive pairs of serial results of the soccer players during the training/competition season. The dotted horizontal lines indicate the RCV 95% for CK = 119.3%.

We can observe that the five consecutive results for all individuals were within the reference upper values (Figure 1A). However, the comparison of the serial analytes to the RCV showed a significant increase of 119.8% in three players (Figure 1B), even though the serial results were within the upper reference limit.

It is important to point out that the behavior observed in Figure 1A and 1B was the same for all other analytes monitored. Thus, we will show only those athletes who presented at any time point a significant change, based on the RCV values, as compared to the previous analysis. The results are presented in Table 3.

Analyte	Time point	Players	Measured values current - previous (Δ)	Percentage change (%)
CK (U/L) $RCV_{95\%}$ = 119.3% RI = 1309 U/L	C3	35	535 – 223 (312)	+139.9
	C4	14	951 – 345 (606)	+175.7
		19	942 – 289 (653)	+226.0
Urea (mmol/L) $RCV_{95\%}$ = 42.5% RI = 3 – 8.5 mmol/L	C2	8	6.2– 3.7 (2.5)	+68.2
		14	4.7 – 3.2 (1.5)	+47.4
		19	7.7 – 5.0 (2.7)	+53.3
		23	4.4 – 2.7 (1.7)	+62.5
		25	3.8 – 2.6 (1.2)	+43.8
		27	5.3 – 3.5 (1.8)	+52.4
		29	4.9 – 3.4 (1.5)	+45
		32	6.4 – 3.7 (2.7)	+72.7
	C3	9	4.2 – 4.34 (1.3)	+47.1
	C4	3	4.9 – 2.9 (2)	+70.6
		32	3.3 – 6.3 (- 3)	-47.4
		38	5.8 – 4.0 (1.8)	+45.8
		42	3.8 – 2.6 (1.2)	+43.8
Creatinine (μmol/L) $RCV_{95\%}$ = 26.8% RI = 77.8 – 132.6 μmol/L	C3	4	113 – 87. 6 (25.4)	+29.3
		7	95.4 - 74.2 (21.2)	+28.6
		15	93.7 – 70.7 (23)	+32.5
		42	95.4 – 73.4 (22)	+30.1
		44	121.0 – 88.0 (33)	+37

RI= reference interval for physically active subjects; RCV = reference change value for physically active subjects; Δ = absolute difference between 2 consecutive analyses.

Table 3. Soccer players and their biochemical analytes with significant change based on RCV values.

One player at C3 and two at C4 presented CK values above 119.3%. The serum urea concentrations were significantly increased in eight subjects after the first month of training (C2). Five athletes showed creatinine values that were significantly increased at C3. Note that all of the altered analytes were inside of the reference intervals for the physically active population.

The Table 4 presents the results of the hematological parameters of those athletes that showed significant changes, based on the RCV values, as compared to the previous analysis.

Analyte	Time point	Players	Measured values current - previous (Δ)	Percentage change (%)
WBC (10^9/L) RCV$_{95\%}$ = 43.9% RI = 4.5 – 10.1 10^9/L	C2	1	7.8 – 4.5 (3.3)	+73.3
		4	6.2 – 4.0 (2.2)	+55
	C3	14	9.6 – 6.5 (3.1)	+47.7
		15	7.2 – 4.9 (2.3)	+46.9
		44	9.3 – 5.3 (4.0)	+75.5
	C4	19	10.1 – 5.4 (4.7)	+105.6
	C5	20	9.8 – 6.6 (3.2)	+48.5
		47	8.1 – 4.8 (3.3)	+68.8
		53	7.1 – 4.5 (2.6)	+57.8
Neutrophils (10^9/L) RCV$_{95\%}$ = 65.3% RI = 1.8 – 6.7 10^9/L	C2	1	5.1 – 2.3 (2.8)	+119.5
		4	4.5 – 2.4 (2.1)	+84.9
		23	4.0 – 2.4 (1.6)	+69.7
	C3	14	6.9 – 3.7 (3.2)	+86.4
		15	4.8 – 2.5 (2.3)	+92.9
		44	6.4 – 3.0 (3.4)	+113.8
	C4	19	8.6 – 3.0 (5.6)	+182.7
		42	3.9 – 2.2 (1.7)	+79.6
	C5	20	7.9 – 3.7 (4.2)	+112.2
		47	4.8 – 1.9 (2.9)	+150.8
		53	4.9 – 2.4 (2.5)	+104.6
Hemoglobin (g/dL) RCV$_{95\%}$ = 8% RI = 13 – 16 g/dL	C2	23	13.2 – 14.4 (-1.2)	-8.3
	C3	7	15.2 – 14.0 (1.2)	+8.6
		15	15.7 – 14.5 (1.2)	+8.3
		17	15.3 – 13.3 (2.0)	+15
		23	14.8 – 13.2 (1.6)	+12.1
		39	16.5 – 14.7 (1.8)	+12.2
		42	13.8 – 12.5 (1.3)	+10.4
		43	15.6 – 13.7 (1.9)	+13.9
	C4	23	13.6 – 14.8 (-1.2)	-8.1
RBC (10^{12}/L) RCV$_{95\%}$ = 8.3% RI = 4.4 – 5.6 10^{12}/L	C3	7	5.3 – 4.8 (0.5)	+10
		17	5 – 4.3 (0.7)	+15.9
		20	4.3 – 4.8 (-0.5)	-9.8
		23	5.1 – 4.6 (-0.5)	+10.3
		39	5.4 – 4.9 (0.5)	+10.4
		42	5.1 – 4.6 (0.5)	+10.4
		43	5.3 – 4.7 (0.6)	+14.1
	C4	20	5.0 – 4.3 (0.7)	+10.3

RI= reference interval for physically active subjects; RCV = reference change value; Δ = absolute difference between 2 consecutive analyses.

Table 4. Soccer players and their hematological parameters with significant changes based on RCV values.

Nine athletes were found to have elevated leukocyte counts, mainly neutrophils, at one or more time points. We found seven athletes with hemoglobin values that were significantly increased at C3. It is important to point out that all variations in these hematological parameters were within the reference intervals shown here (Table 1). The exception for this rule was the serum uric acid concentrations, as shown in Figure 2.
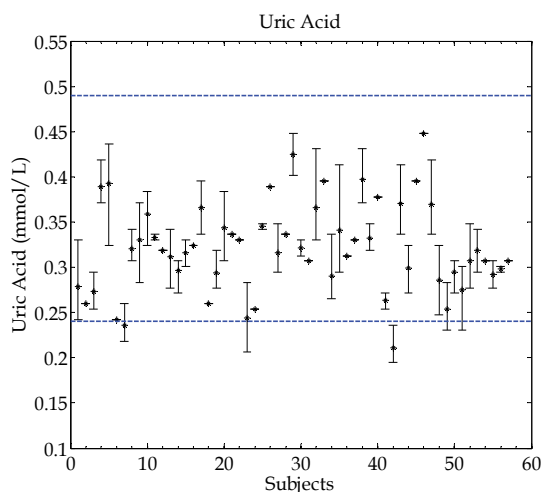
A.
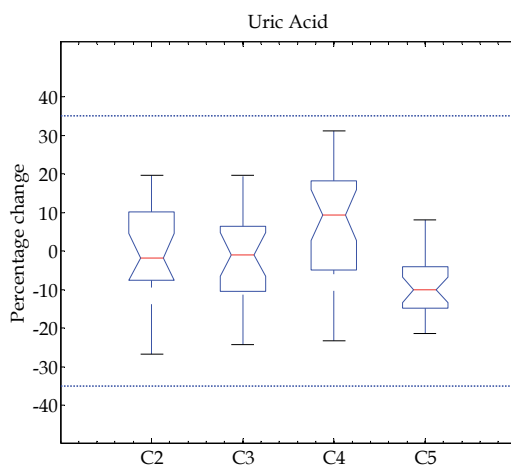
B.

Fig. 2. (A.) Uric acid concentration (mean, minimum and maximum) for each soccer player at five time points. The dotted horizontal lines indicate the reference interval (2.5% lower limit = 0.24 mmol/L and 97.5% upper limit = 0.49 mmol/L) from a physically active population. (B.) Uric acid percentage change between successive pairs of serial results for the soccer players during a season of training/competition. The dotted horizontal lines indicate the RCV95% for uric acid = 35.0%

While there were no significant changes in the serial results during the season (Figure 2B), three players were determined to be below the lower reference interval (Figure 2A).

4. Discussion

This study is the first to test the applicability of reference intervals and the RCV values obtained from physically active individuals (Nunes & Macedo, 2008; Nunes et al., 2010) in longitudinally monitoring the effects of training/competition on soccer players.

The players analyzed in this study were from the under-20 category. During the competition season (14 weeks), the games occurred on Saturday mornings. All players, including the outfield players, were submitted to a daily game-based training, where modified games are played on reduced pitch areas, often using adapted rules and involving a smaller number of players than in traditional soccer games. Different small-sided game designs were used during the season to improve specific physical capacities (e.g., sprint, speed, aerobic) (Hill-Haas et al., 2011). An important observation emerging from our data is that all of the soccer players supported this type of training very well for the entire season, including the competitions schedule, as the majority of the alterations shown here were within the reference interval for all of the analytes.

On the other hand, the comparison of serial analyses with RCV values increased the sensitivity and specificity of some analytes as biomarkers of individual training effects. From 56 players, only 17 and 15 exhibited significant alterations in a biochemical analyte or hemogram parameter, respectively, at any time point (Table 3 and 4). Knowledge of the RCV values permits an individual response to those subjects who exceed the percentage of alteration at one or more blood analyses as compared to previous analyses; these subjects can undergo a closer follow up daily or weekly, contributing to the individual adjustment of the training intensity, improvement of nutritional interventions and prevention of stress overload.

For example, the athletes 14 and 19 (Table 3 and 4) were submitted to the same training load and competitions and showed significant increases in the levels of their CK, leukocytes and neutrophils after three months. Although only the neutrophils showed changes that were above the reference interval, this set of changes may be related to a higher inflammatory response and muscle damage after this period of training and competitions, which can lead to an acute deterioration in performance (Ispirlidis et al., 2008). Note that athlete 35 at C3 also exhibited a ΔCK that was higher than the RCV (119.8%), but no other parameters were altered. Additionally, the absolute value was lower than that for athletes 14 and 19. It is likely that the higher ΔCK for this player merely indicated a higher participation in the training schedule. This information can therefore be useful to help the coach plan for adequate recovery time for just those athletes, especially if they are competing players. This information can also be useful to the nutritionist in individually adjusting some nutrients to improve the recovery rate between training sections and games, preserving these athletes.

An interesting point observed here is that after the first month of training, 8 athletes showed significant changes in their serum urea when compared to RCV values. This result may indicate a continuous catabolic state at the beginning of competitions (Hartmann & Mester, 2000). It is not unusual that soccer players present with an inadequate ingestion of carbohydrates because of a low energy intake or a high fat and protein intake (Garrido et al., 2007). As this macronutrient is important in preserving muscle mass, an inadequate ingestion can lead some athletes to a catabolic state that can impair their performance if not corrected. Thus, these 8 athletes could undergo a specific nutritional intervention.

The time point (C3) showed a higher number of positive training adaptations in the majority of the players. The serum creatinine values were significantly higher than the RCV values for five players, which could indicate a muscular mass gain in these subjects at the

beginning of the competitions. In addition to creatinine, the hemoglobin concentrations increased significantly at C3, mainly in the athletes with levels near the lower limit of the population-based reference interval, indicating a positive training adaptation that is related to O_2 transport, such as increasing the plasma volume and the erythrocyte number (Sawka et al., 2000; Convertino, 2007). Only athlete 23 must be followed more carefully after C4 due to a significant decrease in the Hb concentration as compared to C3. This decrease can also be influenced by nutritional status, such as an inadequate intake of minerals like iron, zinc, copper, folic acid and complex B vitamins (Lukaski, 2004).

In this study we have also shown the need for a comparison of results with reference intervals that were established from a physically active population. For example, all of the players exhibited serum urate concentrations that were within the RCV values (Figure 2B), but three athletes exhibited values below the 2.5% percentile (Figure 2A). As uric acid is one of the most important plasma antioxidants (Lippi et al., 2008) this result could indicate a lower capacity of defense against ROS. The nutritionist could individually improve the antioxidant content of the diet, offering to these athletes more vegetables and fruits rich in this nutrient. This simple intervention may increase plasma antioxidant levels (Brevik et al., 2004).

5. Conclusions

The data presented here point to the Reference Interval and the RCV as important tools for the correct interpretation of the results proceeding from blood analyses related to the monitoring of athletes' training. Advances in analytical technology, such as proteomic analysis, may present new information concerning the athlete's protein and metabolic profile. These methods must also have their reference intervals and RCVs determined for effective for sport science application, providing coaches and interdisciplinary teams with the ability to make individual, punctual interventions that could make a difference in the continuous adaptive processes of all athletes throughout the season.

6. Acknowledgments

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Body Mass Bias in Exercise Physiology

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1. Introduction

Body mass bias in the field of exercise physiology has been the subject of increased focus over the past twenty years. This is based primarily on the fact that key widely held assumptions about the relationships between body mass and human performance have been challenged by theory and empirical data. The result for how we express certain variables of physical fitness has been generally two-fold: a systematic and meaningful body mass bias against larger, not fatter, individuals and spurious attribution of the effect of body mass on key dependent variables.

Physical educators, the military services, law enforcement agencies, and conditioning coaches have readily used fitness tests comprised of events that involve body mass as the primary resistance. Common tests include pushups, situps, and timed distance runs. Virtually none of these tests takes into account one's body mass in scoring because a common assumption has been that larger people have more muscle to move the heavier mass. In short, these factors are assumed to "wash out" any body mass bias. Empirical research has shown, however, that these types of tests impose a substantial and predictable bias against larger, not just fatter, body mass (Crowder & Yunker, 1996; Harman & Frykman, 1992; Jaric et al., 2005; Markovic & Jaric, 2004; Vanderburgh et al., 1995). Similarly, because maximal oxygen consumption (VO_{2max}, in L/min) and maximal strength increase with body mass, a common convention to compare individuals is to divide VO_{2max} or strength measures by body mass. Expressing these human performance indices as simple ratios this way has been scrutinized given that the numerator does not change at the same rate as the denominator (Astrand & Rodahl, 1986; Heil, 1997). Again, the result is not only a body mass bias against larger individuals but, in the case of inferential research, improper accounting for the effects of body mass on outcome variables.

In certain physically demanding occupations, especially the military, body mass bias has substantive implications. Work physiologists have determined that despite body mass bias in the common military physical fitness tests, the larger service members were often better performers of the physically demanding occupational tasks (Bilzon et al., 2002; Lyons et al., 2005; Rayson et al., 2000). That is, they could carry more, more easily evacuate casualties, and better engage in heavy materiel handling. Yet, the smaller personnel were achieving better scores on the physical fitness tests, the results of which have significant promotion and advancement implications (Vanderburgh & Mahar , 1995; Crowder & Yunker, 1996).

This chapter chronicles the fundamentals and applications of body mass bias in fitness and exercise physiology, to include the theory and empirical data used to evaluate it. It also

explains the real world implications of body mass bias in the military services, and how to mitigate its undesirable or unintended effects.

2. Body mass bias and biological scaling

Body mass bias is simply the notion that larger individuals have an unfair advantage over smaller, or vice-versa, in measures of exercise performance. It is more formally defined as the correlation between a raw score (e.g., maximal weight lifted, pushups repetitions, oxygen uptake) and body mass. A non-zero correlation indicates the presence of bias; a correlation not different from zero indicates the absence of such bias. Some biases are rather intuitive. Maximal grip strength, bench press or absolute work rate on a cycle ergometer are measures that would give larger individuals an advantage since each is largely dependent on muscle yet body mass is not the source of the resistance. As a result, a sport like powerlifting employs body weight classes and maximal power is often expressed relative to body mass. Less intuitive, perhaps, are measures that advantage smaller individuals. These include those that measure the capacity to move one's body mass in exercises such as pushups or distance running. The less-than-intuitive quality is based on the common assumption that larger individuals have more muscle to move body mass so there should be no particular advantage to the smaller. A closer look, however, at laws of biological scaling and their application to military physical fitness data make a compelling case that the common fitness test events of pushups, situps and distance running, and even VO_{2max} expressed per unit of body mass, impose a bias against larger, not just fatter, personnel (Vanderburgh, 2007, 2008).

Perhaps an easy way to think of this is through the analogy of a 2 x 2 x 4 solid rectangular block (Fig. 1) of constant density. Its cross-sectional area (CSA) would be 2 x 2 or 4 sq ft and, with a density of 1.0, its weight would be 16 lbs. Imagine that the block (PRE) turned into an identical scale-model block of the same density, but with sides 25%, or 1.25 times longer (the POST block). Simple geometric principles dictate, then, that CSA would be 2.5 x 2.5, or 5.25 sq ft. This represents a 56.25% increase in CSA. Similarly, the new weight of 31.25 lbs (2.5 x 2.5 x 5 = 31.25 lbs) is a 95.3% increase.
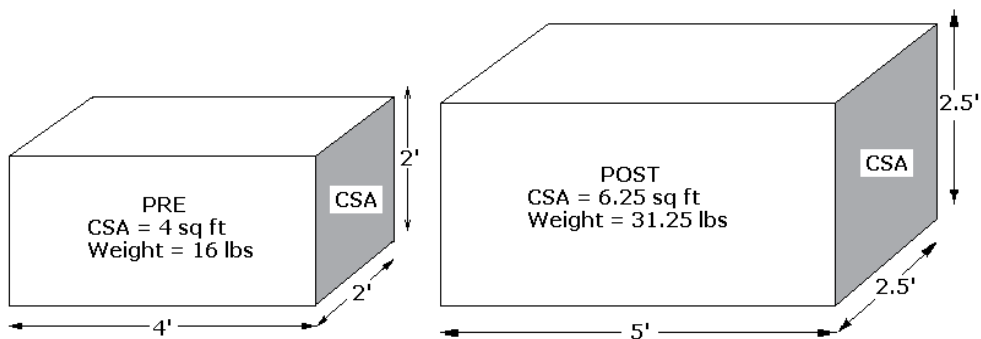
Fig. 1. Comparison of change in length, cross-sectional area (CSA) and weight

Scaling theory helps us understand why these dimensions change at different rates and biological scaling principles elucidate the relevance to human performance. As shown in

Table 1, if length increases by 1.25 (a 25% change), then CSA changes by 1.25^2 and weight changes by 1.25^3. This is because length is considered a one-dimensional variable, area is two-dimensional, and weight (just like volume) is three-dimensional. In terms of biological significance, one can think of the human body just like the block in the present example. It has its own body mass and its CSA is considered to be muscle cross sectional area, one of the prime determinants of strength. Therefore, the 95% increase in weight shown in Table 1 is accompanied by only a 56.25% increase in strength. This human performance scaling concept is critically important because it challenges the common assumption that an X% larger person should be X% stronger. Empirical evidence supports the fallacy of this assumption. Also of critical importance is the notion that "larger" assumes an exact scale model, not larger because he/she is fatter or taller.

	PRE	POST	Multiplier / % Increase	Calculation
Length	4′	5′	1.25 / 25%	$(1.25)^1 = 1.25$
CSA	4 ft²	6.25 ft²	1.5625 / 56.25%	$(1.25)^2 = 1.5625$
Weight	16 lbs	31.25 lbs	1.9531 / 95.31%	$(1.25)^3 = 1.9531$

Table 1. Calculations of Fig. 1 changes in dimensions due to scale model increase in size

3. Allometric scaling in fitness tests

Allometry, a term often associated with biological scaling, is the relationship between the size of an organism and the size of any of its parts, such as muscle or blood vessel CSA, limb length, eyeball radius, etc. Allometry provides the theoretical bases upon which empirical findings can be compared. In the case of Fig. 1 and its analogous application to the human body, strength (S) does not change proportionally to body mass (M). If it did, it would also increase by 95.3%. Instead, its 56.25% increase can be explained by the allometric relationship:

$$S \; \alpha \; M^{2/3} \tag{1}$$

This is derived from the fact that weight is a three-dimensional and CSA a two-dimensional variable (Astrand & Rodahl, 1986; Jaric, 2002). From Eq. 1 we can substitute the delta, or change on both sides such that:

$$\Delta S \; \alpha \; \Delta M^{2/3} \tag{2}$$

Indeed, 1.5625 (the change in CSA, or strength) = $1.9531^{2/3}$ (the change in mass). This exponent of 2/3, often called an allometric exponent, tells us that the proper way to express muscle strength to allow for comparisons between individuals of different body mass is: $S/M^{2/3}$. This is because both sides change at the same rate – a necessary condition for expressing ratios in physiology (Astrand & Rodahl, 1986; Vanderburgh, 1998). Though unconventional, this index should show zero correlation with body mass in a large sample of subjects. It is also very useful in understanding how other variables, such as fitness test scores, or maximal oxygen uptake, change with body size changes.

Since blood vessel CSA is also a two-dimensional variable, and oxygen delivery is associated with blood flow, then maximal oxygen uptake, VO_{2max}, would be subject to a similar relationship:

$$VO_{2max} \; \alpha \; \Delta M^{2/3} \tag{3}$$

and the following index: $VO_{2max}/M^{2/3}$. Once again, this is an unconventional index but allows for comparisons of maximal aerobic capacity between individuals of different body mass such that body mass bias is zero. This index has been validated this index in a large sample of 230 women and 210 men (Heil, 1997).

The effects of body mass changes on strength and VO_{2max} can be used to derive appropriate scaling indices for events like distance runs (DR) and maximal pushups (PU) or situps (SU) repetitions. One explanation (Jaric et al., 2002b) for its derivation is that the ability to move one's body mass is directly proportional to strength (which is directly proportional to $M^{2/3}$) and indirectly proportional to body mass (M^1). Therefore, since PU or SU α $M^{2/3}/M^1$, then:

$$\text{PU or SU } \alpha \text{ } M^{-1/3} \tag{4}$$

Interestingly, the ratio scaling that results, $PU/M^{-1/3}$, is equivalent to $PU^{.}M^{1/3}$ (same for SU). For the distance run (DR), the scaling index is derived as follows (Vanderburgh & Mahar, Vanderburgh & Crowder, 2006; Vanderburgh & Laubach, 2007): Since distance run time is indirectly proportional to VO_{2max}, expressed per unit of body mass (Nevill et al., 1992), and VO_{2max} in L/min (i.e., no adjustment for body mass) is directly proportional to $M^{2/3}$ (Eq. 3), then DR α $M^1/M^{2/3}$, or

$$\text{DR } \alpha \text{ } M^{1/3} \tag{5}$$

This means that DR time goes up as M goes up. Since low score wins in run time, the DR expression would be $DR/M^{1/3}$. This index has been empirically validated as well (Crecilius et al., 2008; Crowder & Yunker, 1996; Vanderburgh et al., in press).

4. Empirical validation of allometric modeling in fitness tests

"Empirically validated" in these cases indicates that researchers have tested the hypotheses of Eqns. 1,3-5 in reasonably large samples to determine the actual body mass exponent and compared it with the theoretical. For purposes of illustration, this can be done using real data from the sport of competitive powerlifting and the methods described in more detail by Vanderburgh (1998). Powerlifting, comprised of maximal one-repetition lifts in the squat (SQ), bench press (BP), deadlift (DL), and total (TOT) of all three, is a good choice for examining body mass exponents for several reasons. First, it is a sport of primarily muscular strength, not power, hand-eye coordination, or even complex cognition, all of which could be confounders in examining the relationship between performance and body mass. Second, at the elite level (not counting the super heavyweight division, which has no weight limit), all competitors are very lean, thus eliminating body fat as a confounder. Third, the two primary determinants of performance are strength and body mass. Therefore, a sample of powerlifting world record holders would be heterogeneous in body mass and weight lifted – almost nothing else.

The determination of the empirical exponent is done using linear regression, but on the logarithmic transformations of M and SQ, BP, DL and TOT. The procedure starts with Eq. 1, S α M^b, but with SQ, BP, DL and TOT replacing S. Scatterplots of current male world record holders (as of May, 2011, http://records.powerlifting.org/world) for these four events are shown in Fig. 2. Note that the exponent is the unknown, as the purpose of empirical testing is to determine the actual M exponent for that sample. For purposes of illustrations, TOT will be chosen: TOT α M^b. This really means that the best-fit curve of a scatterplot of TOT vs. M will conform to the following equation:

$$\text{TOT} = aM^b \tag{6}$$

where a and b are constants. This is an allometric, not linear relationship. For linear regression, the terms must be in the form of y = mx + b. A log transformation of both sides, then, yields the following:

$$lnTOT = (b)lnM + ln(a) \tag{7}$$

Squat

Bench Press

Deadlift

Total
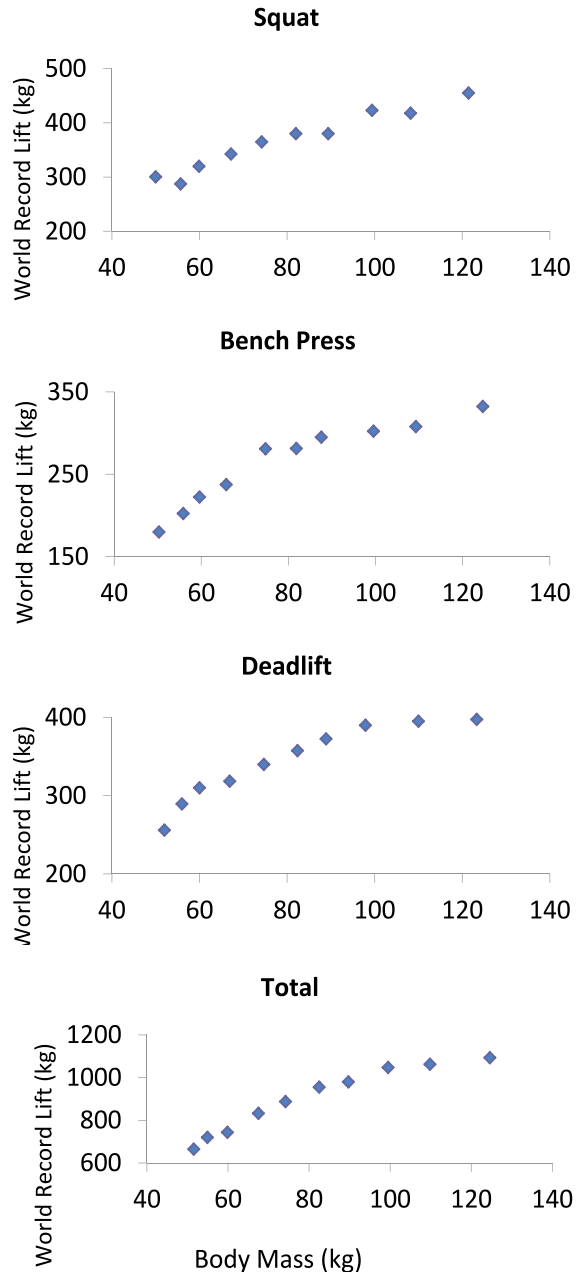
Fig. 2. World powerlifting records by body mass (as of May, 2011, http://records.powerlifting.org/world)

Now, lnTOT becomes "y," b becomes "m," and ln(a) becomes "b" in the linear equation. Regressing lnTOT on lnM will yield not only the value of b but its confidence interval (CI) as well. This is quite important since scatterplots of human performance always deviate from the best-fit curve and CIs give an indication of probability that the population's true exponent lies within it. Linear regression of the log-transformed terms for the TOT event yields an exponent of 0.58 with a 95% confidence interval of 0.48 to 0.67. Within this confidence interval (CI), an M exponent would yield zero body mass bias for TOT. Note that 2/3, or 0.667, is within (but barely) the CI. Table 2 shows the actual body mass exponents for the four different powerlifting events, along with the 95% CI ranges.

	SQ	BP	DL	TOT
Exponent	0.50	0.65	0.48	0.58
95% CI	0.42 – 0.59	0.49 – 0.80	0.37 – 0.60	0.48 – 0.67

Table 2. Body mass exponents for world record powerlifting performances (Fig.2)

This table illustrates a number of key points in evaluating empirical data for allometric scaling. First, among the world's elite, a small number of subjects (N = 10 in this case) can show the characteristic curvilinear allometric relationship between body mass and performance. Each event indicates, as body mass increases, the expected smaller and smaller increase in performance. Said differently, the relationships are clearly not linear. Second, since neither is in the CI ranges, the exponents of 0 or 1 impose a body mass bias. While an exponent of 0 yielding such bias is expected since that would be analogous to no weight classes, the exponent of 1 doing the same might be surprising. These data show that, in any of the events, dividing the performance by body mass (e.g., SQ/M^1) would also yield body mass bias. This actually conforms to the laws of biological scaling since the exponent of 1 is too large. In other words, the index SQ/M makes too much of an adjustment for M, thus penalizing larger competitors.

Third, and perhaps surprisingly, not all the exponents' CIs contain the expected value of 2/3. There are many reasons why this can, and often does happen in allometry research. With a small sample size, one case can influence the magnitude of the exponent. In the TOT, for example, removing the heaviest competitor changes the exponent from 0.58 to 0.63, the latter for which the 2/3 exponent easily fits within the 95% CI range, not barely as with all the competitors. In the case of world record holders, as others have conjectured for world class powerlifting events (Dooman & Vanderburgh, 2000; Vanderburgh & Batterham, 1999; Vanderburgh & Dooman, 2000), there are more competitors worldwide in the middle weight classes and fewer at the extremes. This would suggest that, adjusted for body mass differences, the world's best in the middle weight classes would be better than the best from the lightest and heaviest classes, thus "bumping" up the middle of the curve. This would affect goodness-of-fit with an allometric model and alter the exponent value away from the theoretical. One other worthwhile explanation in the present data is that both the squat and deadlift exercises, unlike the bench press, lift not only the barbells but a substantial percentage of the body mass as well. Since moving body mass is disadvantageous for larger individuals, this would lessen the slope of the best-fit curve for the scatterplots such as those in Fig. 2, the result would be a smaller exponent. Indeed, Table 2 indicates that the smallest exponents are for squat and deadlift. In large samples of non-world-class subjects, there are many other confounders such as body composition, effort, biomechanics, etc. Often, when deviation from theoretical is

found, researchers are faced with offering reasonable explanations without the statistical control to back such claims. The best research samples, then, are those in which the subjects are heterogeneous in the dependent variable (performance score) and body mass but homogeneous in the potential confounders such as effort and body composition.

Some studies have indicated deviation from theoretical for the body mass exponent for expressing VO_{2max}. Batterham et al. (1999) found that, in a sample of 1314 adult men, although the body mass exponent was 0.65, the fat-free mass exponent was not different from 1.0. Since body fat is essentially metabolically inert, and fat-free mass is the body compartment largely responsible for generating oxygen consumption, then body composition was a confounder in leading to the spurious conclusion that the 0.65 body mass exponent matched the theoretically expected value of 2/3. Similarly, Vanderburgh et al. (1996a), in a sample of 94 adult women, determined that while ratio scaling of VO_{2max} penalized heavier women, the penalty was due to the body fatness.

Another interesting but quite common dilemma is assuming validity when the empirically derived exponent matches the theoretical, as is the case with the BP and TOT events. Indeed, these findings could be the result of confounding effects on the exponent such that the primary reason it "made the 95% CI" is that certain confounders, such as those listed above, happened to push the exponent value into the theoretical range. In other words, one can never be quite sure how the empirical did or did not match the theoretical.

As is the case with inferential statistics, however, one should always consider the totality of research evidence from multiple samples from different populations using appropriate statistical control to evaluate the overall trend for allometry's effects on human performance. Based on two extensive reviews (Jaric et al., 2005; Vanderburgh, 2008), one can make a compelling case that use of the exponents as described in Table 3 is appropriate for fitness testing, especially for adult men.

	PU (max reps)	SU (max reps)	BP (1RM)	DR (time)
Exponent	$PU \cdot M^{1/3}$	$SU \cdot M^{1/3}$	$BP / M^{2/3}$	$DR / M^{1/3}$
References	Crowder & Yunker, 2000 Markovic & Jaric, 2004 Vanderburgh et al., in press	Markovic & Jaric, 2004	Dooman & Vanderburgh, 2000 Markovic & Jaric, 2004 Vanderburgh & Dooman, 2000	Crowder & Yunker, 2000 Nevill et al., 1992 Vanderburgh & Mahar, 1995 Vanderburgh et al., in press

PU = Pushups, SU = Situps, DR = Distance run time

Table 3. Allometric indices for common fitness tests

5. The utility of allometry in fitness testing

These indices can be used to compare individual fitness scores among people of varying body weights. The results of some hypothetical examples can be illuminating. Consider two individuals, Ellen and June, with the fitness scores as shown in Table 4. Scaled scores are calculated using the indices from Table 3, maintaining the appropriate units. Clearly, body mass influences scoring with the allometric indices, which make a proper adjustment for its

influence. One can interpret allometric comparisons as follows, using a Table 4 example: "Without consideration of the influence of body mass on pushups, Ellen performed 11.8% more repetitions. Considering the influence of body mass, however, June scored 4.6% better." In the case of the bench press, June's performance was 47.7% better than Ellen's for raw score but only 8.0% better when making a proper adjustment for body mass.

On a more significant scale, the effect of body mass bias among military personnel has been quantified (Vanderburgh & Crowder, 2006). For example, a 90 kg man performing at the same physiological level as a 60 kg man who achieved a maximum score on the U.S.

		Ellen	June	Comparison
Body Mass	--	50 kg	80 kg	--
Pushups	Raw	38 reps	34 reps	Ellen by 11.8%
	Scaled	140.0 reps·$M^{1/3}$	146.5 reps·$M^{1/3}$	June by 4.6%
Bench Press	Raw	44 kg	65 kg	June by 47.7%
	Scaled	3.24 kg·$M^{-0.67}$	3.50 kg·$M^{-0.67}$	June by 8.0%
2-Mile Run	Raw	13:24	15:00	Ellen by 10.7%
	Scaled	3.64 min·$M^{-1/3}$	3.48 min·$M^{-1/3}$	June by 4.4 %

Table 4. Hypothetical example of the effects of allometry in fitness testing

Army Physical Fitness Test of pushups, situps, and two-mile run, would actually receive a 15% lower score (256 vs. 300 points). In this case, "same physiological level" is the expected performance of a 90 kg man who is an exact scale model of the 60 kg man. Similarly, for a 45 kg vs. 75 kg woman, the U.S. Navy's test levies a 20% penalty. In the case of the Armed Services, there are actually two very real undesirable consequences for the larger service members. First, advancement and promotion is influenced by the fitness test scores. For the two women above, the heavier who scored physiologically equivalent 240 points compared to the lighter's 300 max points, is at a substantial promotion disadvantage, all other factors being equal. Second, occupational physiology findings suggest that larger military personnel tend to be better performers of physically demanding military tasks (Bilzon et al., 2001; Bilzon et al., 2002, Harman & Frykman, 1992; Harman et al., 2008; Lyons et al., 2005; Rayson et al., 2000). These include: heavy materiel handling, load carriage, and casualty evacuation - tasks that involve not only moving one's own weight but additional external weight. As a result, and because physical fitness test performance is linked with promotions and advancement within the services, the current physical fitness tests of the U.S. Army, Air Force, and Navy penalize the very populations that perform physically demanding military tasks better.

Body mass bias also occurs in competitive sports, most notably distance running which attracts over two million competitors in race distances of five kilometers or greater each year in the United States. The implications can be substantial. For example, a 68 kg woman's 50:00 10 km race time would be physiologically equivalent to a 50 kg woman's 45:07 10 km time. Accordingly, body weight handicap models for distance runs have been developed and validated to account for body weight differences in determining race performance (Vanderburgh & Laubach, 2007). Despite the additional credit for larger body mass, these models have also been determined to be disadvantageous for those whose larger mass is due to excess fat mass, an important health-related finding (Vanderburgh et al., in press).

In some sports, such as wrestling and power lifting, weight classes are the main method of accounting for body weight differences. One of the challenges of such a convention is that there are often few competitors in the extremes of weight and many in the middle weights. This imposes a body weight bias against the middle weight competitors who must compete against many more athletes to win or place. Recent empirical evidence suggests that allometric scaling is a technique that can be used to eliminate all weight classes for each gender and determine the best overall lifter when properly adjusting for body weight differences (Vanderburgh & Batterham, 1999). In competitive rowing, there are typically only two weight classes for each gender, light and heavy. Vanderburgh et al. (1996) developed and validated an allometric index that allows all rowers of any size within each gender, to be compared to each other while properly factoring out the influence of body mass and age. Their results suggest that rowing time multiplied by stature (or $M^{1/3}$) was the optimal index to remove body mass bias among these competitive rowers.

6. Body fatness and allometry in fitness testing

One of the main critiques of using allometric scaling in fitness testing is that giving credit for weight in the scoring is to also give credit for excess body fat. In other words, some perceive that such scoring gives advantages for being fatter. Indeed, one's denominator of $M^{1/3}$ for the distance run score computed from the $DR/M^{1/3}$ calculation would be larger for a fatter individual, thus leading to a lower (and better score, since low score wins). What is not often considered, however, is the effect of the excess fatness on the numerator – in this case, the distance run time. Vanderburgh and colleagues have modeled the effects of adding additional fat weight on the resultant distance run time for the 5 km and 2-mile runs and have shown that, in all cases, adding fat weight leads to a worse scaled score (Crecilius et al., 2008; Vanderburgh & Laubach, 2007). Recently, they tested this empirically, by adding external weight to the DR and PU events for college-age men. Results indicated that the addition of 16 kg of external weight led to 38% worse scaled PU scores and 12% worse two-mile run scaled scores (Vanderburgh et al., in press).

7. Practical techniques for using allometry in fitness testing

As shown in Table 4, allometrically scaled scores yield strange units and currency. That is, one may find the interpretation of a scaled score for a 65 kg bench press, 3.50 $kg \cdot M^{-0.67}$, quite difficult to interpret. This is likely due to the units, $kg \cdot M^{-0.67}$, being unlike those encountered elsewhere and the magnitude of 3.50 not being as readily evaluated as 65 kg would be. Another problem with these scores is that they require a calculator to compute. In short, though arguably proper and fair, allometrically scaled scores are not practical.

Other solutions have been proposed. The first, correction factors, are dimensionless numbers based on body weight, which are multiplied by the raw score to produce an adjusted in the same units and more easily interpretable (Vanderburgh, 2007). For example, from Table 4, Ellen's and June's correction factors would, for PU, be: 1.0 and 1.17, respectively. This is calculated based on a body mass standard - a baseline from which all ratios are computed, the individual's body mass, and the particular event. For a standard weight of 50 kg, for example, and June's body mass of 80 kg, and the PU, her correction factor would be (80 kg/50 kg)$^{1/3}$, or 1.170″ (in both cases). Multiplying her raw score of 34 pushups by 1.211 yields an adjusted score of 39.78 pushups. Using the same methodology,

Ellen's adjusted score would be 38 x 1.0 = 39.4 pushups and June's adjusted performance is exactly the same 4.6% better than Ellen using the correction factors.

Simple tables can be constructed to determine correction factors without calculators and the multiplication of raw score by correction factor can be done with pencil-and-paper. Table 5 illustrates an example from Vanderburgh (2007), applied to the distance run events of United States armed forces fitness tests. In this case, the weight standards were selected as 120 lbs. and 150 lbs. for women and men, respectively. These values were specifically chosen to allow no credit below these body weights. Though the selection of the standard is arbitrary, it must be used consistently once chosen. Also, correction factors can be less than one as well. Nonetheless, correction factors still impose a logistical challenge in developing tables for each event and their use is not intuitively obvious to users with very little exercise science background.

Women	120	130	140	150	160	170	180	190	200
0	1.00	0.99	0.96	0.94	0.92	0.90	0.89	0.87	0.85
1	1.00	0.98	0.96	0.94	0.92	0.90	0.88	0.87	0.85
2	1.00	0.98	0.96	0.94	0.92	0.90	0.88	0.87	0.85
3	1.00	0.98	0.96	0.93	0.92	0.90	0.88	0.87	0.85
4	1.00	0.98	0.95	0.93	0.91	0.90	0.88	0.86	0.85
5	1.00	0.97	0.95	0.93	0.91	0.89	0.88	0.86	0.85
6	1.00	0.97	0.95	0.93	0.91	0.89	0.88	0.86	0.85
7	0.99	0.97	0.95	0.93	0.91	0.89	0.87	0.86	0.85
8	0.99	0.97	0.95	0.92	0.91	0.89	0.87	0.86	0.84
9	0.99	0.97	0.94	0.92	0.90	0.89	0.87	0.86	0.84

Men	150	160	170	180	190	200	210	220	230	240	250
0	1.00	0.98	0.96	0.94	0.92	0.91	0.89	0.88	0.87	0.85	0.84
1	1.00	0.98	0.96	0.94	0.92	0.91	0.89	0.88	0.87	0.85	0.84
2	1.00	0.97	0.96	0.94	0.92	0.91	0.89	0.88	0.86	0.85	0.84
3	0.99	0.97	0.95	0.94	0.92	0.90	0.89	0.88	0.86	0.85	0.84
4	0.99	0.97	0.95	0.93	0.92	0.90	0.89	0.87	0.86	0.85	0.84
5	0.99	0.97	0.95	0.93	0.92	0.90	0.89	0.87	0.86	0.85	0.84
6	0.99	0.97	0.95	0.93	0.91	0.90	0.89	0.87	0.86	0.85	0.84
7	0.98	0.96	0.95	0.93	0.91	0.90	0.88	0.87	0.86	0.85	0.84
8	0.98	0.96	0.94	0.93	0.91	0.90	0.88	0.87	0.86	0.85	0.83
9	0.98	0.96	0.94	0.93	0.91	0.90	0.88	0.87	0.86	0.84	0.83

Table 5. Correction Factors for Distance Runs, Pushups, or Situps Tests. A 186 lb man with an actual score two-mile run time of 15:05, for example, would go to the "180" column and down to the row corresponding to "6" to yield the correction factor of 0.93. Since low score wins, this number would be multiplied by the actual time of 905 sec to yield an adjusted score of 841.7 sec or 14:02. For a 172 lb woman with 32 pushups, and high score wins, one would divide her raw score by the 0.90 correction factor to yield an adjusted score of 35.6 pushups (from Vanderburgh, 2007).

A third solution is the use of a balanced fitness test – one that imposes no body mass advantage. They can be single or multi-event. A backpack run is an example of a single-event balanced test, in which neither larger nor smaller personnel are disadvantaged. This test, which would require all military personnel to run a given distance with a standard-weight backpack, has been mathematically modeled and shown to eliminate body mass bias in men (Vanderburgh & Flanagan, 2000). This has occupational relevance since the standard backpack load for service members is typically the same, regardless of one's body mass. He/she must carry that load often over some considerable distance in arduous terrain. The advantage to the larger body mass of the standard weight for everyone is counterbalanced by the disadvantage of moving one's body mass. This backpack run test, along with a backpack pushups test, using the same standard weight of 16 kg, has been validated for college-age men as being free of body mass bias (Vanderburgh, in press). These types of tests, then, require no special calculations and produce raw scores that are fair and occupationally relevant. They do, however, pose a mass testing challenge in terms of the extra equipment needed.

One multi-event test that purports to be balanced is the popular "Pump & Run,"which entails a distance run and bench press event. One's final score is equal to the distance run time (in sec) minus 30 sec times each repetition of the bench press. The weight lifted, however, is based on a percentage of one's body mass. As Vanderburgh & Laubach (2008) determined empirically for 74 female and 343 male competitors of one event, the body mass bias against larger competitors was substantial, largely because both events imposed the penalty. The bench press was actually analogous to the pushup exercise which also lifts a percentage of one's weight. The researchers proposed a correction factor table but also recommended the study of a standard weight lifted for all competitors, not one based on body mass. This case study is probably the best single example of the non-intuitive nature of body mass bias; race officials were trying to level the playing field with the two events but the result had just as much body mass bias as the distance run alone.

8. Conclusion

Body mass bias is a real phenomenon in fitness testing which is based on the fundamental notion that the ability to move one's weight is not directly proportional to one's body mass. This bias, especially in large-scale testing such as the military, leads to not only an advantage for smaller service members, but a disadvantage against those who perform the physically demanding occupational tasks of the military better – the larger service members. Allometric scaling and its derivative technique of correction factors can be used to erase such biases but, while these are mathematically appropriate and valid, they impose logistical and non-intuitive challenges. Such scoring is also useful in determining the best overall performer in sports such as distance running, powerlifting, and even indoor rowing. Evidence suggests that, although allometric scaling grants a credit for being heavier, if the increased body mass is fat mass, then the resulting scaled score is worse. This is because the detriment in raw score performance is of greater magnitude than the credit granted. Balanced fitness tests like the backpack run and pushups tests, which impose no body mass bias, have been shown to be intuitive, useful and occupationally relevant but are not without their mass testing challenges with regard to equipment needed. Most importantly, exercise scientists who can exercise some level of fluency in the principles of biological scaling and allometry as they apply to fitness testing

will be able to best interpret human performance scores not only sport, but in occupational fitness and health-related fitness as well.

9. Acknowledgment

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Eccentric Exercise, Muscle Damage and Oxidative Stress

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1. Introduction

Participation in exercise has been linked with positive results on the cardiovascular system, metabolism, musculature etc. Some of these benefits are linked with reductions in blood pressure, increases in resting energy expenditure, changes in lipid profile, reductions in fat mass, increases in fat free mass etc. (Evans, 1999). There are different types of exercise that someone can participate in, i.e. walking, running, lifting weights, participating in organized sports which involve different muscular contractions. Isometric, concentric and eccentric muscle actions are the main muscular contractions involved in all exercise activities. Eccentric muscular contraction is this type of contraction where the length of the muscle is increased while tension is developed. Unaccustomed eccentric exercise has been linked with greater muscle damage compared to isometric or concentric muscular contractions. However this phenomenon is temporary and perturbations in functional and biochemical indices are back to normal within a week from the initiation of the trauma. Furthermore, the damage works as a protective mechanism since data indicates that the muscle damage is attenuated when a subsequent exercise bout of the same intensity is performed even a few months later. Eventhough eccentric exercise leads to greater muscle damage, recent data indicates that eccentrically induced muscle damage is related with positive changes in lipid profile that are evident for a few days following the initial event. Furthermore, the limited data from eccentric training studies indicate that this type of exercise is linked with positive changes in strength as well as in the metabolic profile of the exercise participant.

Oxidative stress indicates a condition where the cellular production of pro-oxidant molecules exceeds the ability of the antioxidant system to reduce reactive oxygen or nitrogen species (RONS). There are several studies that indicate that oxidative stress is evident following muscle damaging exercise. Its role has been related to cleaning the debris from the damaged tissue and providing the means for biochemical adaptations that lead to a stronger and more resistant to muscle damage muscular tissue. This phenomenon is transient and existing evidence suggests that oxidative stress indices are attenuated when a

subsequent exercise bout is performed a few weeks after the initial damaging protocol. Finally, eccentric exercise has been linked with health benefits that are evident either after an acute bout of exercise or following a training protocol.

This review highlights muscle damage and oxidative stress adaptations as well as the health benefits associated with acute and chronic eccentric exercise.

2. Benefits from exercise

Numerous experimental and epidemiological studies have documented a large number of health benefits derived from systematic engagement with cardiovascular exercise training such as enhanced physiologic, metabolic, and psychologic adaptations, as well as reduced risk for development of many chronic diseases and premature mortality (USA, 1996; Kesaniemi et al., 2001). It is well-established that physical activity and/or chronic exercise prevent the occurrence of adverse cardiac events, decreases the incidence of hypertension, atherosclerosis, stroke, osteoporosis, obesity, insulin resistance, type 2 diabetes, cancer, and depression, causes body weight and fat loss, and delays mortality (USA, 1996; Kesaniemi et al., 2001; ACSM, 2006; Feskanich et al., 2002; Leitzmann et al., 1999; Sahi et al., 1998; Rockville, 1995). Large-scale studies have also demonstrated that systematic exercise or switching from being sedentary to a more physically active life-style reduces disease rates and premature mortality (Hein et al., 1994; Paffenbarger et al., 1993; Blair et al., 1995; Erikssen et al., 1998). In fact, exercise-induced health benefits occur even at old ages (Paffenbarger et al., 1993).

Resistance exercise training (a form of which is eccentric training) also induces substantial health benefits, especially to older individuals. Strength training increases not only muscular strength and power but also improves bone mineral density as well as cardiovascular and psychological function (Ay and Yurtkuran, 2005; Takeshima et al., 2002; Wang et al., 2007). Although, the response to resistance exercise training is individualized, there is a consensus that a properly designed and supervised program should improve not only muscular fitness parameters (strength, muscular endurance, power, balance, speed) but the quality of life as well (Evans, 1999). These adaptations are particularly evident in the elderly. Resistance exercise training has been repeatedly shown to increase muscular strength and muscle mass which in turn improve the functional status (coordination, balance etc.) and limit sarcopenia in the aged (Evans, 1999; Fatouros et al., 2006; Fiatarone et al., 1993; Frontera et al., 1991; ACSM, 1998).

3. Eccentric exercise

Daily movement involves different muscular contractions. Concentric type of contractions occurs when a muscle is activated and shortens. In contrast, eccentric contraction occurs when a skeletal muscle lengthens while it produces force. Both types of contractions occur during the day and the best example to differentiate between the two types of contraction is the ascending or descending the stairs. During the ascending of stairs leg muscles are working concentrically while during the descending of the stairs leg muscles are working eccentrically.

Eccentric exercise has been used as a means to develop muscle strength and size (Dudley et al. 1991). However, eccentric exercise training has been used lately as a novel rehabilitation modality in order to improve several conditions, i.e. tendinopathy, following anterior cruciate ligament reconstruction e.t.c. (Gerber et al. 2009) The health benefits derived from eccentric exercise training on metabolism will be discussed in a subsequent section.

4. Eccentric exercise and muscle damage

During eccentric exercise, force is generated when muscle fibers are lengthened. It is well documented that intense, unaccustomed eccentric exercise is associated with muscle damage (Clarkson et al. 1992). Evidence of damage includes morphological changes with ultrastructural damage to muscle fibers usually seen with microscopy Friden 1984), decrements in muscle force and the involved joint's range of motion (ROM) (Nosaka & Newton 2002), deterioration of running economy (Paschalis et al. 2005; 2008; Chen et al. 2007; 2009), alterations in position sense and reaction angle (Paschalis et al. 2007; 2010) elevated plasma proteins such as creatine kinase (CK) and myoglobin (Nosaka & Clarkson 1995; Jamurtas et al. 2000), elevation in inflammatory by products (Fatouros et al. 2010; McIntyre et al. 2001), connective tissue damage (Tofas et al. 2008), large increases in blood and muscle oxidative stress (Paschalis et al. 2007; Theodorou et al. 2010; 2011) and delayed onset of muscle soreness (Cheung et al. 2003). Eccentric exercises have been shown to produce the greatest amount of delayed onset muscle soreness (DOMS) and larger elevations of plasma CK compared to concentric or isometric exercises (Ebbeling & Clarkson 1989; Jamurtas et al. 2000).

Eccentric exercise results in greater muscle damage because fewer muscle fibers are recruited to exert a given amount of force as compared to concentric contractions. Since the force–velocity relationship indicates that each individual muscle fiber can exert a larger force while being stretched than it can while being shortened (Hill, 1938) and fewer fibers are activated during eccentric contractions, larger forces per muscle fiber are developed during eccentric actions thereby resulting in greater damage. Furthermore, during an eccentric contraction, some sarcomeres in muscle fibers are more resistant to stretching than others forcing weaker sarcomeres to absorb more stretch. With repeated eccentric contractions, the weaker sarcomeres first and then the stronger sarcomeres are overstretched. If the latter fail to withstand the stretching force during the relaxation phase, damage may occur. If the damage spreads to adjacent fibers, disruption of the membrane of the sarcoplasmic reticulum or sarcolemma may be seen. In that case intracellular Ca^{++} concentration increases leading to additional degradation of muscle fibers due to activation of calcium dependent proteolytic enzymes, such as the calpain mediated proteases, resulting in neutrophil infiltration to the injured site (Raj et al. 1998; Proske & Allen 2005).

Histological changes are evident following an intense bout of eccentric exercise and data indicates that approximately one third of the muscle fibers obtained from individuals who performed 300 maximal voluntary eccentric contractions of the knee extensors show intense myofibrillar disruptions, myofillament disorganization and loss of Z line integrity (Raastad et al. 2010). Changes in functional measurements are considered to be the best tool for quantifying muscle damage and monitoring exercise-induced muscle damage (Warren et al. 1999). Following eccentrically induced muscle damage, functional measurements (Maximal Voluntary Contractions, eccentric peak torque, jumping performance) demonstrate a marked deterioration reaching their lowest values approximately 72 hours post exercise and return to normal values within 7 days of recovery (Miyama & Nosaka 2004; Nikolaidis et al. 2008).

Following eccentrically induced muscle damage, changes in running economy appear to depend on the intensity of exercise used to asses this parameter. Reports indicate no changes in running economy following eccentric exercise when a moderate intensity exercise is used to assess running economy (Paschalis et al. 2005; 2008; Chen et al. 2009) whereas others report significant perturbations when higher intensities are used (Braun & Dutto 2003; Chen

et al. 2007; 2009). For example, Chen et al. reported significant changes in running economy during level running when the intensity of exercise was set at 80% and 90% of VO2max but not at 70% VO_{2max} (Chen et al. 2009). When submaximal intensities (55% and 75% of VO2max) were used to assess changes in running economy following eccentrically induced muscle damage it was found that running economy indicators remained unaffected throughout recovery (24-96 hours post exercise) (Paschalis et al. 2005; 2008). Perhaps there is an impairment in the fast twitch fibers, which are the ones that are mainly affected by intense eccentric exercise thereby leading to changes in running economy and kinematic measures (Paschalis et al. 2007; Tsatalas et al. 2010).

As it was indicated earlier, eccentric exercise may cause a disruption to the plasma membrane of a muscle fiber. Disruption of the sarcolemma results in the release of intracellular proteins (CK, myoglobin) into circulation. The time frame of entry of various muscle proteins into the circulation following sarcolemma damage may depend on the size of the protein. For instance, there is a difference in the peak between CK and myoglobin (Nosaka, 2011). Small proteins such as myoglobin (the molecular weight of myoglobin is 18 kD) enter the circulation through capillaries whereas large proteins such as CK (the molecular weight of CK is 80 kD) enter the circulation via the lymph (Lindena et al. 1979).

One of the main characteristics of the unaccustomed eccentric exercise is the development of muscle soreness. Muscle soreness needs to be differentiated between the temporary soreness and DOMS. Temporary soreness is usually felt during the final stages of fatiguing exercise and is a product of metabolic waste accumulation (Friden J 1984). DOMS is characterized by a sensation of dull, aching pain that is usually felt during movement or palpation of the affected muscle (Clarkson et al. 1992). DOMS appears 24 hours after exercise and peaks 48-72 hours post-exercise. DOMS subsides and dissipates slowly and does not fully disappear until 7-10 days after exercise. The delayed response of DOMS seems to be related to an initial insult to the muscle due to mechanical reasons and this insult sets off a chain of events that leads to more damage while regeneration processes are also activated. Inflammatory responses to eccentric exercise play a role in the degeneration and regeneration of the damaged muscle (Peake et al. 2005). Following the initial insult, neutrophils are released into the circulation and enter the damaged muscle tissue within several hours (Beaton et al. 2002). Natural killer cells and lymphocytes are also released into the circulation during and after eccentric exercise. Macrophages and proinflammatory cytokines are produced in the muscle within 24 hours and can be present for several days following exercise. These responses are important for the acute phase response of the immune system and the removal of the damaged muscle tissue. Reactive oxygen and nitrogen species (RONS), such as superoxide produced by neutrophils and nitric oxide generated by macrophages, contribute to muscle damage (Close et al. 2005). The role of RONS on muscle damage will be discussed in a following section.

5. Oxidative stress

Oxidative stress may be defined as a condition in which cellular production of prooxidants exceeds the physiological ability of the system to quench reactive species. It is an imbalance between the production of reactive oxygen and nitrogen (RONS) species and antioxidant defense mechanisms. When the imbalance is in favor of RONS it can lead to biomolecular damage (Sies, 1991). RONS include several molecules such as superoxide ($O_2^{\cdot-}$), hydroxyl radical ($\cdot OH$) and nonradical derivatives of oxygen such as hydrogen peroxide (H_2O_2), nitric

oxide (NO·) and nonradical derivatives of NO· such as peroxynitrite (ONOO·). These molecules have a singlet electron in the outer membrane and often are called free radicals. RONS occur as a consequence of normal cellular metabolism and have an effect on important biological processes such as gene expression (Pendyala & Natarajan 2010), signal transduction (Santos et al. 2011) and posttranslational modifications (Radak et al. 2011). Therefore, it appears that low levels of RONS are important for normal physiological function and homeostasis. RONS seem to be increased under conditions of psychological and physical stress (Sen et al. 1994). Evidence also indicates that enhanced production of RONS can lead to cardiovascular diseases and cancer due to chronic inflammation (Halliwell B, 1993).

Due to short half-life of RONS an indication of their presence is monitored by the measurement of by-products resulting from damage of various macromolecules such as proteins, lipids and nucleic acids. Oxidative damage to proteins involves the oxidation of amino acids and the most often utilized index of protein oxidation is protein carbonyls (Vincent & Taylor 2006). Lipid peroxidation markers include lipid hydroperoxides, conjugated dienes, malondialdehyde (MDA), thiobarbituric acid reactive substances (TBARS), and isoprostanes, with the level of F_2-isoprostanes in blood or urine to be widely regarded as the reference marker for the assessment of oxidative stress (Nikolaidis et al. 2011). Significant alterations to normal physiological function can be induced due to elevated lipid peroxidation and loss of membrane fluidity and cytosolic membranes are examples of this modification. Strand breaks and single base modifications of DNA are examples of RONS associated DNA damage. 8-hydroxy-2'-deoxyguanosine (8-OHdG) represents the most frequently marker used to assess DNA damage (Vincent & Taylor 2006).

RONS are quenched through molecules that are called antioxidants. The main purpose of these molecules is to delay or prevent oxidative stress and damage. Antioxidants donate one of their electrons in order to reduce the formed oxidizing agent. Antioxidants are separated into the ones that have enzymatic activity and those with non-enzymatic activity. The main enzymatic antioxidants include superoxide dismutase, glutathione peroxidase and catalase. Non enzymatic compounds include vitamins (e.g. vitamin C, vitamin E), proteins (e.g. ferritin, transferrin, ceruloplasmin) or peptides (e.g. glutathione).

6. Eccentric exercise, oxidative stress and muscle damage

It was stated in a previous section that eccentric exercise leads to DOMS. At the same time numerous evidence suggests that eccentrically induced muscle damage appears concurrently with changes in oxidative stress. Paschalis et al. had 10 healthy females with no previous history of eccentric training perform five sets of 15 eccentric maximal voluntary contractions of the knee extensors and assessed indices of muscle function and muscle damage (isokinetic peak torque, ROM, CK) as well as indices of oxidative stress and the antioxidant system (glutathione, TBARS, protein carbonyls, catalase, uric acid, total antioxidant capacity) (Paschalis et al. 2007). The results showed that eccentric exercise resulted in significant loss of torque, decreases in ROM and elevation in CK concentration for several days following the exercise bout. These changes coincided with marked elevations of selected oxidative stress indices manifested in a uniform and prolonged pattern. Oxidative stress indices peaked at 48 hours of recovery and remained significantly elevated for 72 hours post exercise (Paschalis et al. 2007). The authors also report a moderate relationship between muscle damage and oxidative stress indices that may indicate a link between muscle damage and oxidative stress.

Nikolaidis et al. assessed also oxidative stress following eccentric exercise in healthy females and found significant perturbations in all assessed indices (Nikolaidis et al. 2007). Subjects had to perform five sets of 15 eccentric maximal voluntary contractions of the knee flexors and indices of muscle function and muscle damage (isokinetic peak torque, ROM, CK) and indices of oxidative stress and the antioxidant system (glutathione, TBARS, protein carbonyls, catalase, uric acid, total antioxidant capacity) were assessed before the exercise session and 1, 2, 3, 4 and 7 days post exercise. Eccentric exercise caused muscle damage and uniformly modified the levels of the selected oxidative stress indices in the blood. Oxidative stress indices peaked at 72 hours and returned toward baseline after 7 days post exercise (Nikolaidis et al. 2008).

Results from another study from our laboratory (Theodorou et al. 2010) performed in healthy males provided similar results with the aforementioned studies. In Thedorou et al. study, nine healthy males performed five sets of 15 eccentric maximal voluntary contractions of the knee extensors and indices of muscle function and muscle damage and oxidative stress were also assessed. Indices of oxidative stress in this study were assessed in plasma and erythrocyte lysate before, as well as 1, 2, 3, 4, and 5 days post-exercise in order to determine whether there was a different response between the two blood compartments (plasma and red blood cells) as well. The results showed that eccentric exercise markedly increased muscle damage, oxidative stress and hemolysis indices that peaked at 2 and 3 days post exercise (Theodorou et al. 2010).

Silva et al. reported significant elevation in lipid peroxidation (TBARS) and protein carbonylation indices following eccentric exercise (Silva et al. 2010). Subjects performed three sets of eccentric exercise of the elbow flexors at an intensity of 80% of maximum repetition until exhaustion. A point of interest is the significant elevated TBARS and protein carbonyls for 7 days after the eccentric exercise which is in contrast with previous reports indicating a return of oxidative stress indices at baseline levels within five to seven days post exercise (Nikolaidis et al. 2007; Theodorou et al. 2010). Goldfarb et al. reported significant elevations in protein carbonyls and MDA up to 72 hours post exercise in subjects that performed four sets of 12 maximal repetitions of eccentric actions at an angular velocity of $20^{o} \cdot s^{-1}$, with 60 s of rest between sets using their nondominant arm elbow flexors (Goldfarb et al. 2011). Eccentric exercise resulted also in significant changes in force and muscle damage indices. Other reports also indicate significant elevations in indices of oxidative stress (i.e. protein carbonyls) following eccentric resistance exercise (arm elbow flexors) performed by humans (Goldfarb et al. 2005; Lee et al. 2002) or downhill running (Close et al. 2004; 2005; 2006).

Eventhough the previously reported studies suggest that eccentrically induced muscle damage is accompanied with changes in oxidative stress indices for some days after exercise there are reports indicating no changes in oxidative stress following eccentric exercise. Kerksick et al. showed no changes in lipid peroxidation (F2-isoprostanes) and superoxide dismutase following eccentric exercise (10 sets of 10 repetitions at an isokinetic eccentric speed of $60^{o} \cdot s^{-1}$ on an isokinetic dynamometer) that caused muscle damage (Kerksick et al. 2010). In Goldfarb et al. study no changes in lipid hydroperoxides and glutathione levels were observed (Goldfarb et al. 2011). Saxton et al. also did not find significant changes in oxidative stress measures immediately post and two days following exercise of the forearm flexors (Saxton et al. 1994).

Taken collectively, the results from the aforementioned studies suggest that muscle damaging exercise seems to increase lipid peroxidation and protein oxidation in blood of humans. These results also indicate that disturbances in indices of blood oxidative stress may persist for several days following muscle-damaging exercise. This response is different compared to non-

muscle damaging exercise where the disturbances in oxidative stress indices are not uniform and return towards baseline within hours after the end of exercise (Michailidis et al. 2007).

Direct comparisons of different studies are difficult. It has to be stated here that only human studies were presented in this section. A point of consideration relates to the mode of exercise used to cause muscle damage and the muscle groups used to perform the exercise. Eccentric exercise on an isokinetic device and downhill running are primarily the two main modes of exercise used to induce muscle damage following which oxidative stress markers were assessed. These two modes differ considerably since eccentric exercise on an isokinetic device isolates the muscle group used to perform the exercise whereas downhill running integrates the action of multiple muscle groups besides quadriceps in order to perform the exercise. In addition, the aerobic component of downhill running might be an additional confounding factor in causing oxidative stress (through electron leakage from mitochondrial respiration and other mechanisms).

Another point of consideration that relates to eccentrically induced muscle damage is the cause of the enhanced appearance of RONS following eccentric exercise. Muscle mitochondria (through electron leakage in the electron transport chain) could be one source of RONS during or shortly after muscle damaging exercise. However, that mild elevation of RONS production is unlikely to contribute to the delayed increased oxidative stress response that appears hours or days following exercise. Ischemia-reperfusion could be another cause of RONS elevation during exercise. It is well-known from cardiac physiology that reperfusion in cardiac tissue following angioplasty operations leads to elevated myocardium damage that is partly attributed to elevated RONS production (Zhao et al. 2000). Blood flow redistribution during exercise is a well-known adaptation in exercise physiology and describes the vasodilation of the vascular system of the active muscle and the vasoconstriction of the vasculature of the non-active muscle tissue. The hypoxic non-active tissue receives a greater quantity of blood after exercise and enhanced formation of RONS is possible due to the xanthine oxidase mechanism (Finaud et al. 2006; Veskoukis et al. 2008). This mechanism of RONS production seems also unlikely to account for the increased oxidative stress that appears days following eccentrically-induced muscle damage. Oxidation of hemoglobin and myoglobin during exercise can also cause RONS formation (Finaud et al. 2006) but this mechanism is also unlikely to be responsible for the delayed response of oxidative stress when muscle damage is present.

Inflammatory responses to eccentric exercise play a major role in the degeneration and regeneration of the damaged muscle (Peake et al. 2005). Following the initial insult neutrophils are released into the circulation and enter the damaged muscle tissue within several hours (Beaton et al. 2002). Therefore, infiltrating white blood cells into skeletal muscle may be another source of RONS production following the insult caused to skeletal muscle due to eccentric exercise. Indeed activated neutrophils and other phagocytic cells are a major cause of RONS production leading to tissue damage and if remain unchecked can destroy adjacent healthy tissue (Close et al. 2005). Therefore, RONS can assist in repairing damaged tissue via phagocytosis and white blood cell respiratory burst activity. Production of RONS when muscle damage is present may serve a secondary role which is not other than the induction of the antioxidant activity of the damaged tissue in order to prevent harm when a subsequent exercise session is performed. Figure 1 illustrates a simplistic approach to the events that takes place following an eccentrically induced muscle damage exercise session. In brief, eccentric exercise due to mechanical stress causes injury to the sarcolemma and muscle damage is induced. The inflammatory

processes that take place lead to enhanced production of RONS which serve a dual purpose: first, they clean the debris and repair the damaged tissue and secondly upregulate several transcription factors that lead to increased antioxidant activity of the remaining healthy muscle fibers that become more resistant to muscle damage when a bout of similar exercise is performed.

Eccentric exercise $\Rightarrow$ ↑ Muscle damage $\Rightarrow$ ↑ Inflammation $\Rightarrow$ ↑ RONS

Repair of muscle tissue

Upregulation of antioxidant activity & resistance to muscle damage

7. Eccentric exercise, oxidative stress and the repeated bout effect

As it has been mentioned earlier unaccustomed eccentric exercise results in muscle damage. Furthermore, it was eluded that the initial injury to muscle tissue leads to changes in its structure that make it more resistant to a subsequent bout of exercise. This process is referred in the literature as the "repeated bout effect". Numerous studies have shown an attenuation of indices related to muscle damage due to the repeated bout effect (Chen et al. 2007; McHugh et al. 2003). In regards to oxidative stress similar changes (i.e. attenuation) to indices of muscle damage have been observed. Nikolaidis et al. had 12 females perform two sessions of eccentric exercise, separated by three weeks, and assessed muscle damage and oxidative stress indices prior to exercise and 1, 2, 3, 4, and 7 days after exercise (Nikolaidis et al. 2007). The two exercise sessions were identical in intensity and duration and consisted of five sets of 15 maximum eccentric voluntary contractions of the knee flexors. The first exercise bout changed significantly all muscle damage and oxidative stress indices indicating that severe muscle damage and increased oxidative stress had occur. Nevertheless, the second exercise bout resulted in significant attenuation in the perturbations of muscle damage and oxidative stress indices. Assessment of the increase or decrease area under the curve for the oxidative stress indices revealed a 1.8-6.1-fold less change in oxidative stress compared to the changes induced by the first bout (Nikolaidis et al. 2007). One possible explanation for the reduced oxidative stress following the second bout of exercise relates to the less muscle damage and less invasion of white blood cells in the damaged tissue. Data from animal work supports this idea since no significant changes in the concentration of ED1^{+} and ED2^{+} macrophages were found after a second bout of lengthening contractions (Lapointe et al. 2002) and treatment with diclofenac, a widely used non-steroidal anti-inflammatory drug (NSAID), affected in parallel the concentration of macrophage subpopulations and the adaptive response after the second bout of exercise (Lapointe et al. 2002). Therefore, inflammation plays a significant role in repair or strengthening of the muscle and might

be the basis for the repeated bout effect. Results from human data are needed in order to substantiate the results obtained from the animal studies.

8. Health benefits from eccentric exercise

Participation in exercise has been linked with positive results on the cardiovascular system, metabolism, musculature etc. Some of these benefits are linked with reductions in blood pressure, increases in resting energy expenditure, changes in lipid profile, reductions in fat mass, increases in fat free mass etc. The majority of the studies that examined the positive effects of exercise have used either endurance exercise or resistance exercise with both types of exercise showing beneficial effects on health (Booth et al. 2000).

It has been mentioned previously that pure eccentric contractions lead to increased muscle damage and soreness levels. This phenomenon is transient, lasts a few days and can make the muscle more resistant to further damage when a repeated bout is performed. However, due to appearance of muscle soreness and the associated changes in muscle function eccentric exercise was viewed as the "bad guy" in the exercise physiology area. Besides the negative effects on muscular function eccentrically induced muscle damage was associated with impaired insulin action (Kirwan et al. 1992) and impaired muscle glycogen resynthesis (O'reilly et al. 1987). The transient augmented insulin responses to hyperglycaemia resulting from muscle damaging exercise seems to serve a dual purpose, i.e. to maintain glucose homeostasis and provide an anabolic environment for the damaged muscle, at least in muscles predominately composed of fast twitch fibres (Flucke et al. 2001).

Eccentric exercise has been used as means of training for several pathological conditions showing positive results in patients with Parkinson disease (Dibble et al. 2006), older cancer survivors (LaStayo et al. 2010), patients undergone anterior cruciate ligament reconstruction (Gerber et al. 2007) etc. Lately there has been an attempt to elucidate the acute and chronic effects of eccentric exercise on metabolism. Eventhough previous reports have attempted to examine the acute effects of muscle damaging exercise on blood lipids only total cholesterol was used as an index of blood lipid profile in these studies (Smith et al. 1994; Shahbazpour et al. 2004). In a study that was performed in our laboratory, the acute effects of muscle damaging exercise on time-course changes of blood lipid profile and the effect of the repeated bout on blood lipids were assessed (Nikolaidis et al. 2007). Twelve healthy females participated in this study. They performed two isokinetic eccentric exercise sessions (five sets of 15 eccentric maximal voluntary contractions at an angular velocity of $60^{o}\cdot s^{-1}$) during the luteal phase. The two exercise sessions were separated by 24-30 days, depending on the duration of their menstrual cycle. Markers of the lipid profile and muscle damage indices were assessed before, immediately, 1, 2, 3, 4, and 7 days after exercise. The results revealed that eccentric exercise uniformly modified the levels of the lipids and lipoproteins (triglycerides, total cholesterol, HDL and LDL). The repeated bout effect affected the assessed variables in a way that the response of lipids and lipoproteins were higher after the first session of exercise compared to those induced by the second identical session performed 4 weeks later. Those changes in the blood peaked at 2 to 4 days post exercise (Nikolaidis et al. 2007). Beneficial changes in lipid profile after eccentric exercise in overweight and lean women were observed in another study performed in our laboratory (Paschalis et al.

2010b). Subjects performed again five sets of 15 maximal voluntary contractions and energy expenditure, respiratory quotient (RQ), muscle damage and lipid and lipoprotein (triglycerides, total cholesterol, HDL and LDL) changes were assessed prior to, immediately after, 12, 24, 48 and 72 hours post exercise. The results revealed increased energy expenditure at all time-points following exercise, lower RQ at 24 hours post exercise andsignificant changes in muscle damage indices and lipids and lipoproteins at 24, 48 and 72 hours post exercise. These changes were exacerbated in the overweight group probably due to the higher muscle damage that was induced by the eccentric exercise protocol in this group of participants (Paschalis et al. 2010b). Similar results with the aforementioned studies were obtained from another study where significant lower triacylglycerol total area under the curve by approximately 12% and significantly elevated insulin incremental area under the curve, indicating transient insulin resistance, were also found 16 hours and 40 hours following an acute bout of eccentric exercise (Pafili et al. 2009).

Eccentric training seems also to improve muscle performance and diminishes the reductions in muscle performance, the elevation in muscle damage indices and the oxidative stress responses (Theodorou et al. 2011). The chronic effects of eccentric training on metabolism have been examined and show promising results in regards to this type of training. Drexel et al. had two groups of subjects hiking either upwards or downwards, three times a week, and assessed metabolic and inflammatory indices (Drexel et al. 2008). The results showed a reduction in total cholesterol (4.1%), LDL (8.4%), apolipoprotein B/apolipoprotein A1 ratio (10·9%), homeostasis model assessment of insulin resistance (26·2%) and C-reactive protein (30.0%) in the eccentric group. These results indicate favorable metabolic and anti-inflammatory results following this type of exercise. Paschalis et al. examined also the effects of a weekly bout of eccentric versus concentric exercise on health parameters of healthy women (Paschalis et al. 2011). Subjects performed an isokinetic eccentric or concentric exercise protocol once per week for eight weeks. Subjects had to complete five sets of 15 concentric or eccentric maximum voluntary contractions in each of their lower limbs with a 2-min rest between sets. The results showed that eccentric training improved the resting levels of blood lipid profile. More specifically, triglygerides, total cholesterol (TC), LDL and TC/HDL ratio decreased by 12.8%, 8.8%, 16.4% and 17%, respectively whereas HDL levels increased by 9.3%. No changes in apolipoprotein A1, apolipoprotein B and lipoprotein (α) were seen. Eccentric training resulted also in significant reductions in glucose, insulin, HOMA and glycosylated hemoglobin levels (Paschalis et al. 2011). However, Marcus et al. did not find any significant changes in insulin sensitivity in overweight or obese postmenopausal women with impaired glucose tolerance (Marcus et al. 2009). Subjects performed three exercise sessions per week for 12 weeks. The exercise was performed on a high-force eccentric ergometer and ranged from 5 minutes in the beginning to 30 minutes at the end of training. Eventhough the eccentric training resulted in significant positive changes on body composition, strength, and physical function no significant changes were found in insulin sensitivity following a hyperinsulinemic-euglycemic clamp test. The different modes of exercise (isolated isokinetic eccentric exercise vs. aerobic type eccentric exercise on an ergometer) might account for the difference in the results obtained in the latter study compared to the former studies.

9. Eccentric exercise programming

Latest research indicates that systematic eccentric exercise can lead to positive changes in physical capabilities, improved rehabilitation and health outcome measures. It has been also reported that unaccustomed eccentric exercise produces greater muscle damage and pain which subsides in a few days. Therefore, it is of great importance to develop exercise programs that incorporate eccentric actions that minimize muscle damage and the associated pain discomfort. Initial low intensity, short duration and progression are key elements in designing eccentric exercise programs. Rate of perceived exertion (RPE) is an important element that could be used in the exercise program. An example of how the aforementioned elements could be appropriately used is presented in an elegant study by Lastayo where older cancer survivors participated in an eccentric exercise intervention study (Lastayo et al. 2011). Subjects begun the intervention program participating in an exercise regimen of low intensity (7, very very light on an RPE scale) and short duration exercise (3-5 minutes per session) that progressed to a higher intensity (11-13, fairly light to somewhat hard on an RPE scale) and longer duration (16-20 minutes) after 12 weeks which was the duration of the exercise program. The program proved to be efficacious since increases in muscle size, strength and power along with improved mobility were noted. Another area where eccentric training could be applied is rehabilitation. Program designing in this area should also follow the same principles as the ones outlined previously. Lorenz & Reiman have outlined the role of eccentric training in various injuries in the athletic field and the reader is encouraged to read their review (Lorenz & Reiman 2011). In conclusion, eccentric training could be an effective means of increasing performance and lead to better health. Incorporation of basic principles in exercise program development (load, volume, intensity, frequency and progression) is essential in order to avoid unwanted outcomes (i.e. muscle damage).

10. Conclusion

Unaccustomed eccentric exercise can cause muscle damage that is evident by morphological changes of the muscle fiber, reductions in physical performance, elevation in inflammatory products and muscle soreness. These responses are significantly attenuated when a second exercise bout of the same intensity is implemented, a phenomenon known as the repeated bout effect. Oxidative stress indices follow the same pattern of response as the one previously mentioned. Significant perturbations in oxidative stress are evident following an eccentrically induced muscle damage exercise protocol that are attenuated due to the repeated bout effect. Elevation in oxidative stress seems to be related with cleaning the debris from damaged muscle fibers and upregulating the antioxidant activity of healthy fibers making them more resistant to muscle damage. Finally, strong evidence indicates that eccentric training can induce health-promoting effects.

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Aging in Women Athletes

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1. Introduction

Since instating Title IX of the Education Amendments of 1972, there has been a significant increase in sports participation and athletic opportunities among women (1). While it is still more common for younger than older women to engage in athletic competition, the participation of older women is growing, with over 50 countries sponsoring master athletes events (2). While aging is associated with a decrease in metabolic and physiologic function, competitive athletic women may experience more gradual declines. These declines can be slowed further, by combining adequate dietary intake with proper exercise training. Therefore, this chapter will 1) discuss how aging influences physiologic and metabolic adaptations of highly trained women athletes and 2) explore how nutrition recommendations may change with exercise and the possible benefit of supplementation of micronutrients to improve athletic performance.

2. Aging and physiological adaptations of women athletes

2.1 Endurance performance

Many master athletes are capable of performances equal to those of non-elite young athletes (3). Nevertheless, age-related alteration to functional and physiological capacities are inescapable and as a result these age-related alteration lead to a decline in performances. It is widely accepted that aerobic capacity decreases with age. The rate of decline in maximal oxygen consumption (VO_2max) varies between 5-9% per decade starting at the age of ~35 years in healthy sedentary adults (4, 5, 6). Several studies report a greater rate of decline with age in endurance-trained men and women (7, 8). Running performances decrease in a curvilinear fashion with the greatest decline after 60 years of age with women demonstrating a threefold greater decrease in performance compared to men (8, 9). Marcell et al. (10) provided evidence that a decline in VO_2max is the best predictor of age-related changes in endurance performances in female athletes. Elite endurance performances are attributed to three primary determinants: aerobic capacity, lactate threshold, and exercise economy.

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2.2 Aerobic capacity

A high VO_2max is an identifiable marker for a successful endurance athlete. Observed VO_2max in elite male endurance athletes can measure between 75 and 85 ml/kg/min; whereas; VO_2max is approximately 10% lower in elite women athletes (11). VO_2max is higher in athletes at any age than sedentary women (8, 7, 11). Endurance performance and aerobic capacity are strongly related across varying age groups of competitive athletes (9). Aerobic capacity, as measured by VO_2max is determined by cardiac output and arteriole-venous oxygen difference (12). Both cardiac output and arteriole-venous oxygen difference decrease with age in endurance athletes (5). Cardiac output is the product of heart rate and stroke volume and accounts for approximately 50% of oxygen consumption during exercise (12). Heart rate is the primary factor for increases in cardiac output during exercise; whereas stroke volume peaks at ~50% of max exercise then levels off or slightly decreases (12). The age-related loss in maximal heart rate is between 0.5-1 beat per year (13). Several studies have exhibited that habitual exercise status has no effect on the age-associated reductions in maximal heart rate (7, 14, 4). With maximal heart rates similar between athletes and non-athletes, the principle difference in cardiac output is stroke volume (11). Ogawa et al. (5) observed a greater rate of decline in stroke volume in female athletes compared to that observed in sedentary controls. The decrease in maximal heart rate, stroke volume, and arteriole-venous oxygen difference contributes to the decline in master athletes' endurance performances.

2.3 Lactate threshold

Lactate threshold is the fraction of VO_2max where there is a significant increase in blood lactate accumulation (12). Lactate threshold is a primary factor in determining endurance performances of both men and women (11). In sedentary subjects there is typically a rise in blood lactate concentration to ~60% VO_2max. In trained athletes this value can be 75–90% of VO_2max (14). A study by Evans et al. (7), showed that lactate threshold as a percentage of VO_2max did not change with age in female distance runners. This evidence coupled with similar findings in male distance runners (15) suggests that a reduction in VO_2max rather than a reduction in lactate threshold contribute the most to the decline in performance with age.

2.4 Exercise economy

Exercise economy is the oxygen cost of an endurance performance at a given velocity and can vary up to ~ 30-40% among individuals (11). Exercise economy is a predictor of performance in a population with similar VO_2max (11). Results in male runners suggest that exercise economy does not change with age in highly trained endurance runners (15). Older female runners have demonstrated a slight change in economy at submax speeds and yet displayed no relationship between age and economy at a 10K race pace (7). Therefore, exercise economy is unlikely to contribute to the age-related decline in endurance performances.

2.5 Physiological and training mechanisms for aging declines in VO_2 max

Both central (cardiac output and blood volume) and peripheral (muscle mass and oxygen delivery/utilization) factors contribute to the high VO_2max demonstrated in elite athletes (11). At present, it is still unclear as to the exact cause(s) of the age-related decrease in VO_2max in master athletes compared to young athletes. Stroke volume is responsible for the higher cardiac output in athletes versus healthy sedentary individuals (11). Determinates of

stroke volume are cardiac preload, left-ventricular end-diastolic volume, and myocardial contractility. Blood volume plays an important role in stroke volume and decreases with normal aging in healthy sedentary females. However, total blood volume is maintained in older endurance trained female athletes (16). Master athletes demonstrate a larger left ventricular mass and left ventricular end-diastolic volume compared to healthy sedentary adults (17). Given the benefits of habitual endurance training, it is uncertain how advanced age alters stroke volume which would consequently result in a similar decrease in VO_2max in aging athletes compared to sedentary women. Peripheral adaptations with aging have also been suggested to contribute to reductions in VO_2max through changes in both oxygen delivery and utilization to active skeletal muscles (9). Arteriole-venous oxygen difference decreases slightly with age in trained athletes (5). It has been observed that enzyme activity and capillarization (expressed per muscle fiber) of skeletal muscle are preserved in older male athletes (18). Though muscle characteristics have not been examined in older female athletes, the reduced VO_2max per kilogram muscle in female athletes is similar to male athletes (19). Therefore, it is likely that the age-associated reductions in VO_2max are a result of oxygen delivery and/or muscle mass.

Changes in body weight/composition may be a second mechanism for the decline in performance with age in athletes. Regardless of age, a decrease in lean body mass and an increase in percent body fat may contribute to a decrease in VO_2max (6, 19). Endurance trained women did not demonstrate the expected relationship between changes in body composition and age-related changes in VO_2max (4). Male endurance runners who maintained their lean body mass also maintained their relative VO_2max, whereas the female runners who maintained their relative VO_2max had the greatest decrease in lean body mass (4). This finding suggests that other factors, including the maintenance of training and/or estrogen rather than body composition have a greater affect on the female age-related decline of VO_2max (4).

The training stimulus may also play a role in the performance decline with age. With advanced age there seems to be a reduction in overall exercise "stimulus" (i.e. intensity, duration, and frequency) (5, 9, 14). VO_2max is positively associated with training volume and as such, the age-related decrease in VO_2max is associated with a reduction in training volume (14). However, female endurance athletes between the ages 34-78 years who maintained or increased their training volume with age, exhibited a similar change in VO_2max compared to healthy sedentary adults (14). Training stimulus appears to be a key determinant in the decline in aerobic capacity with age. Whether the decline in training is a result of the aging-process, injury, time, or motivation, has yet to be determined.

Despite the health benefits achieved through a lifetime of participating in physical activity, it seems that diminished performances are an inevitable aspect of aging. The exact mechanism(s) for the reduction in performance with age has yet to be determined. The finding that women demonstrate a greater rate of decline in performances compared to men could be a result of fewer women participating in competitive events as they age (3). However, given that more women have been encouraged to participate in sporting events since the induction of Title IX, it will be interesting to see whether the gender difference is maintained in the future.

3. Aging and metabolic adaptations in women athletes

3.1 Body composition

Normal aging results in significant changes in body composition with increases in abdominal fat and losses of muscle mass. The increase in obesity alters the risks for type 2

diabetes, cardiovascular disease, and hypertension, whereas the decline in fat-free mass (FFM) may alter energy expenditure and resting metabolic rate. It is interesting to question whether the increase in visceral fat and decrease in FFM can be prevented in women athletes. Our study of highly trained competitive women athletes aged 18 – 69 years indicates that percent body fat by DXA (dual energy x-ray absorptiometry) was lowest in 30 – 39 year old women athletes (~16% body fat) but was not different in 18 – 69 yr, 40 – 49 yr, and >50 yr old athletes (20). Total body fat was low and averaged 21 – 23% in these groups and considerably lower than normal BMI age-matched controls who were approximately 30 - 36% fat. To address whether central fat was different with age in women athletes, we measured visceral fat and subcutaneous fat by CT (computed tomography) scans. Visceral fat was significantly lower in the youngest athletes (18 – 29 yrs vs. 30 – 39 yrs) and significantly lower in the middle-aged than older athletes (Figure 1). Thus, despite the finding that athletes prevented gains in total body fat with aging, visceral fat increased with age in women athletes. However, putting the central obesity in context, it is remarkable that the oldest athletes have similar visceral fat and lower subcutaneous abdominal fat than normal BMI control women who were one-third their age. Lastly, FFM was not significantly different among the women athlete groups suggesting that muscle mass was maintained with aging and may be, in part, explained by the competitive training of these women.
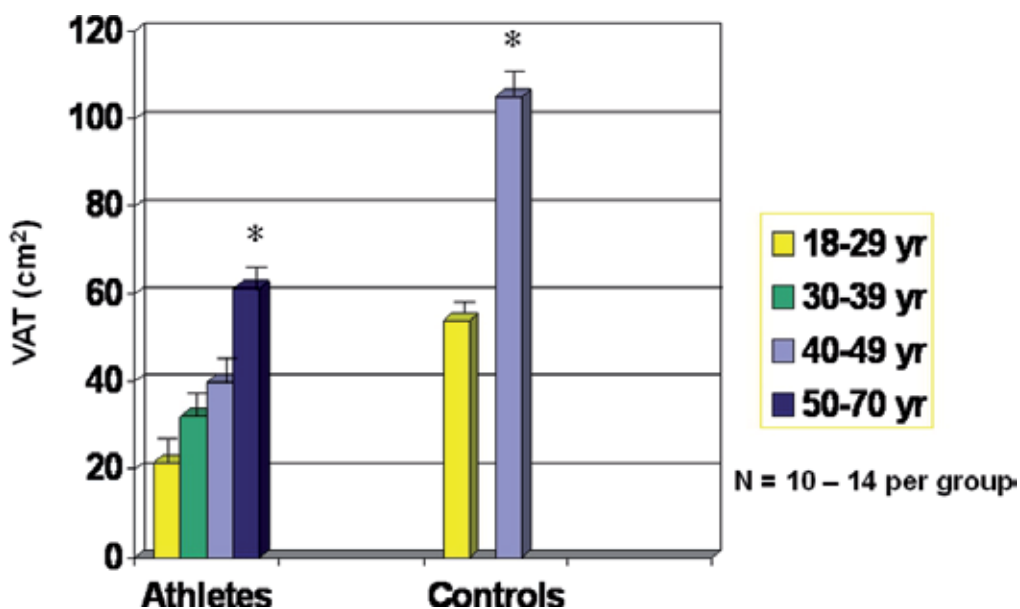
Fig. 1. Visceral adipose tissue (VAT) of women athletes and controls. Values are means ± SE. * P< 0.01

There are only a few other studies besides our own that have examined body composition in older women athletes. In agreement with our study, FFM did not differ between pre- and post-menopausal women runners (21). However, in contrast to our results, postmenopausal women athletes had higher % body fat and fat mass than the premenopausal athletes (21) but these differences were modest. More specifically, the difference was less than half that of the comparison between the healthy sedentary premenopausal and postmenopausal

women. In comparison to sedentary controls, the athletes had lower % body fat, fat mass, waist circumference and trunk fat. Their results suggest that women who engage in vigorous exercise have a much smaller increase in total adiposity with advancing age (21). Two more studies (7, 22) provide some contrast as to whether age-related changes in body fat occur in women athletes. When female runners are divided into three age groups (e.g. 23-35, 37-47, 49-56 years), percent body fat by hydrostatic weighing did not differ by age and averaged 15, 14, and 18%, respectively (7). Across a continuum of age (40-77 years), body fat measured by hydrostatic weighing increased with age in women athletes, the majority of whom (90%) competed in running events (22). Thus, athletes have less total and central body fat than sedentary women (21, 23) and the vigorous training of master athletes may prevent an increase in total adiposity (7, 21).

Menstrual dysfunction in athletes could potentially alter body composition in young women. Young rowers with menstrual disorders have less subcutaneous and visceral fat by MRI compared to young controls (23). We are unaware of any studies in women athletes in the perimenopausal state. Further investigation is necessary to investigate whether the changes in hormonal status as women athletes age and go through menopause, influence body composition.

3.2 Glucose metabolism

There are two studies examining glucose metabolism in women athletes (24, 25) with one in older women athletes. We utilized a sequential clamp procedure which allowed the assessment of both ß-cell sensitivity to glucose and peripheral tissue sensitivity to insulin in a single session in young, middle-aged and older female athletes (25). Plasma insulin responses during the hyperglycemic clamp were reduced in older athletes vs. older controls and ß-cell sensitivity was maintained across the age span. First and second phase insulin response was positively correlated with body fat and negatively with VO$_2$max suggesting that high levels of training and low body fat in women athletes across the age span predict insulin action. Rates of utilization (Rd) of glucose during the euglycemic portion of the clamp were significantly higher in athletes than controls and were not different across the age groups of athletes (Figure 2). Although some studies show a difference in insulin clearance rate with age (26), we showed that insulin clearance rate was similar across the age of 18 to 70 years in women athletes. Thus, older sedentary women had a 70% greater first-phase and 103% greater second-phase insulin response during hyperglycemia than the athletes. Moreover, older athletes utilized on average 31% more glucose than similarly aged sedentary women, suggesting an increase in insulin sensitivity due to the effects of training. Investigators have examined the relationships between insulin sensitivity, body composition, fitness, and muscle and metabolic predictors. In younger women athletes (age 29 yrs), insulin sensitivity determined by the frequently sampled intravenous glucose tolerance test (FSIGT) was weakly correlated with VO$_2$max and proportion of type 1 muscle fibers but not with percent body fat, fasting respiratory exchange ratio (RER) or RER during exercise, energy intake, macronutrient composition, and muscle triglyceride and glycogen content (24). In women athletes aged 18-69 years, we showed that percent body fat is associated with first-phase insulin release, whereas visceral fat and total body percent fat predict second-phase insulin release during hyperglycemic clamps (25). In addition, glucose uptake during the last hour of a hyperinsulinemic-euglycemic clamp was positively associated with FFM and VO$_2$max, negatively associated with total fat mass, visceral fat, and subcutaneous abdominal

fat (25). Thus, greater physical fitness and muscle mass and lower total and abdominal fat contribute to the enhanced tissue sensitivity observed in female athletes.
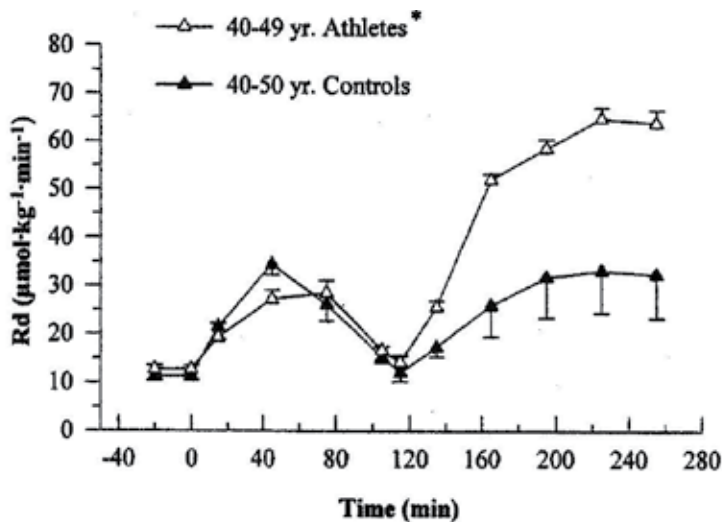
Fig. 2. Rate of utilization (Rd) of glucose during the 3-step clamp in 40- to 50 yr-old athletes and controls. Values are means ± SE. * P< 0.005

3.3 Cardiovascular risk factors

Lipid profiles are generally better in endurance trained athletes than sedentary individuals (27, 28). What occurs with aging in athletes with respect to lipid levels? We showed that total cholesterol, LDL-C (low density lipoprotein cholesterol) and triglyceride levels increased with age in women athletes (27). These relationships persisted even after adjusting for age-related declines in VO$_2$max and increases in visceral fat. HDL-C (high density lipoprotein cholesterol) was higher in athletes than controls and LDL-C was lower in athletes than sedentary women. Regarding the lipoprotein subfractions, we also demonstrated that LDL3-C (larger LDL-C subfraction) was lower in athletes than untrained women and there was a tendency for a higher HDL5-C (the largest HDL-C subfraction) which would suggest a protective effect. Middle-aged women (n =147) who were grouped into active ex-athletes, sedentary ex-athletes, recreational exercisers, and non-exercisers did not differ in TG (triglycerides) and HDL-C (29). In another study, HDL-C was higher in master athletes than older sedentary women but LDL-C did not differ (28). These lipid differences suggest that women athletes would have a lower risk of coronary heart disease.

Intensity or the level of exercise may influence lipoprotein lipid levels. Williams (30) utilized a national survey of ~1800 female recreational runners to examine the dose-response relationship between exercise levels and HDL-C and CVD risk factors. The women were divided into groups based on weekly running mileage and were on average 40 years of age. Lipid levels were obtained from medical records. The results of the survey indicated that women who ran more than 64 km/week had significantly higher HDL-C levels than women who ran less than 48 km/week. Further analysis revealed that plasma HDL-C was 0.133 mg/dl higher for every additional kilometer run per week. The results suggest that women

who exercise at greater levels have significantly greater increases in HDL-C which in turn reduced their risk for CVD (30).

Other cardiovascular risk and metabolic parameters have been examined in older athletes. Women athletes (n=94) between 13 and 77 years of age showed some cardiovascular risk factors, including hypertension that were prevalent in athletes over the age of 35 (31). In a small sample of women master athletes (n=6), coronary artery calcium which is linked to endothelial dysfunction (32) was not significantly different than age-matched sedentary women (28). In another study that also contained only six females, older endurance trained athletes with pre-hypertension had lower arterial stiffness than sedentary controls and longer travel time of pressure waves (33). In addition, the greater augmented pressure in the athletes which disappeared after controlling for resting heart rate may have contributed to the lack of difference in carotid SBP (systolic blood pressure) and carotid intima-media thickness. The authors suggest that the vascular stiffening with pre-hypertension can be modified by chronic exercise training but that chronic training is unable to compensate for age-associated increases in pressure from wave reflections (33).

4. Nutrition recommendations in women athletes

4.1 Energy and macronutrients

Most athletes strive to achieve energy balance where energy intake = energy expenditure during exercise training. Energy expenditure (EE) consists of 3 components: basal metabolic rate, thermic effect of activity, and the thermic effect of food. These generally account for 60-70%, 25-35%, and 5-10%, respectively, of total daily energy expenditure, but can be greatly altered by the type, intensity, and duration of exercise.

Typically, energy requirements decline with age; however, debate exists whether these declines are due only to decreases in physical activity patterns or if there is also an accompanying decline in basal metabolic rate. This information is difficult to obtain because environmental factors, such as work schedules and family obligations, often make maintaining vigorous intensity training difficult for older athletes. However, in older adults, matched for exercise volume, compared to younger adults, RMR is not different (34). This one study would suggest that the decline in RMR does not occur in older adults who maintain their exercise volume. Lean mass is the greatest determinant of basal metabolic rate, accounting for up to 75-80% of energy expenditure. In our study of women athletes, age and FFM were independent predictors of the decline in RMR where the oldest athletes expended approximated 965 kJ/day less than the youngest athletes (20). In middle aged women with similar BMI and fat-free mass, habitual exercisers (9 hours per week of physical activity for 10 or more years) have greater RMR than their sedentary counterparts (35).

In women athletes, decreased energy intake can result in declines in body weight, muscle mass and bone density, as well as increased menstrual dysfunction, fatigue, injury and illness. Maintaining or gaining body weight is often difficult for athletes performing large volumes of physical activity. A popular trend is for athletes to consume only extra protein which may promote greater WL, (weight loss) by increasing EE through thermogenesis (36). Ideally, extra energy should come from a combination of all three macronutrients. Caloric intake recommendations are often based upon prediction equations, which multiply a predicted resting metabolic rate by a physical activity factor, and the athlete's goal to maintain, gain, or lose weight.

While numerous studies exist examining the macronutrient requirement of athletes, a variety of variables (i.e. sport type, training status) affect nutritional requirements, resulting in broad recommendations. Current recommendations for a trained women include 45-65% (5-7 g/kg/d for general training, 7-10 g/kg/d for endurance athletes, and 11+g/kg/d for ultraendurance athletes) of energy from carbohydrates, 20-35% (~1 g/d) from fat, for general training, and 10-35% (1.2-1.4 g/kg/d for endurance trained and 1.6-1.7 g/kg/d for strength trained athletes) from protein (37). For all athletes, carbohydrates are recommended to make up the majority of energy intake, with an emphasis on whole grains, fruits, and vegetables. A diet high in carbohydrates typically results in adequate total protein intake, but may be lacking some of the essential amino acids, as well as intake of essential fatty acids and fat soluble vitamins and minerals.

Meal timing and nutrient composition recommendations surrounding athletic competition recommendations are based upon substrate utilization. Exercise intensity and duration drive these recommendations. For lower intensity activities (performed at ~25% of VO_{2max}), circulating fat provides the majority of energy during exercise. At moderate intensity (performed at ~65% VO_{2max}), fat oxidation contributes less and energy is mainly supplied from intramuscular stores of fat and glycogen. During high intensity exercise (performed at ~85% VO_{2max}), glycogen is the major energy source. At lower intensities where fat oxidation is providing the dominate source of energy, exercise can be sustained for up to a few hours; however, as intensity increases and requirements switch to glycogen, the ability to perform physical activities decline without carbohydrate repletion. Few studies have examined how macronutrient needs of women are altered by age; therefore, current macronutrient recommendations are similar between older and younger women athletes. During endurance based activities, depletion of plasma and muscle glycogen results in reduced exercise performance and fatigue. Prior to endurance exercise, it is recommended that 1 g/kg of carbohydrates be consumed for each hour prior to exercise (i.e. 1 g/kg if 1 hour prior and 4 g/kg if 4 hours prior) (37). Also, the meal should be low in fat and fiber and moderate in protein to facilitate gastric emptying and minimize gastrointestinal distress. During exercise, 30-60 g should be consumed every hour. If longer than 90 minutes, 6-20 g of protein should also be consumed during exercise and 1.5 g/kg carbohydrates with a small amount of protein immediately following exercise, with an additional 1.5 g/kg of carbohydrates consumed 2 hours later (37). Ensuring adequate fat intake during aerobic training is important since fat oxidation results in sparing of glycogen. Very low fat diets reduce intramuscular fat stores, impeding endurance. For strength based activities, protein intake has been suggested to maximize muscle synthesis by enhance amino acid uptake into skeletal muscle, providing substrate for hypertrophy if consumed immediate after the strength training bout. However, protein intake greater than 1.7-1.8 g/kg/d results in oxidation of the excess amino acids and is not incorporation into greater muscle mass, even when coupled with vigorous resistance training (38).

4.2 Micronutrients

Exercise and micronutrient activity work synergistically to ensure maximal performance of the body; therefore, if micronutrient deficiencies exist, there is a subsequent risk for declines in metabolic and physical function. Studies of dietary intake in women endurance athletes shown low intakes of calcium, vitamin D, vitamin E and zinc (39, 40). However, numerous other nutrients should be monitored for insufficient intake in women master athletes,

including B_{12}, folate, riboflavin, pyridoxine, and magnesium (41). Additionally, the Dietary Reference Intakes (DRIs) acknowledge a decreased need for iron in older women (http://www.iom.edu/Activities/Nutrition/ SummaryDRIs.pdf). Because specific recommendation regarding micronutrient intake for older women have not been established, women athletes should consume at least the recommended dietary allowance (RDA) for all micronutrients to avoid nutrient deficiencies. In female master athletes partaking in nutritional supplementation, the supplemented group had significantly greater intakes of calcium, magnesium, vitamin C, and vitamin E than non supplemented women, indicating that female master athletes may rely on supplements to assist achieving micronutrient intake goals (40). If women consume a variety of foods in their diets and meet caloric requirements, vitamin and mineral supplementation typically is not necessary. Women greater than 60 years of age may want to consider a synthetic form of vitamin D and B_{12} because of altered absorption and nutrient action occurring with age. If a nutrient-balanced diet is not consumed, athletes should consider taking a multivitamin and mineral supplement. Too little data exists to recommend micronutrient supplementation above the RDA to improve athletic performance.

Free radicals produce oxidative damage during aging, as well as following strenuous exercise. During an intense endurance competition, master athletes experience elevations in reactive oxygen metabolites and biological antioxidant potentials, which continue at least 48 hours after completion of competition (43). Antioxidant supplementation may improve athletic performance, recovery time, and overall health by reducing oxidative damage. In endurance trained master athletes supplemented with antioxidants 21 days prior to intense cycling, antioxidant supplementation resulted in improved cycling efficiency (44). Unfortunately, most over the counter antioxidant supplements are not regulated by the FDA, and are not subject to thorough safety and effectiveness tests. One should heed caution not to consume vitamin intakes beyond the recommended upper limit (i.e. 2,000 mg for vitamin C and 1,000 mg for vitamin E).

The injury rate for master athletes is higher than younger athletes, making a balanced dietary intake especially important to support tissue healing (45). Ensuring adequate protein intake is important during all phases of tissue repair. Insufficient protein intake can inhibit wound healing and increase inflammation (46). It appears that several amino acids, including leucine, arginine, and glutamine, play a role in tissue repair mainly through amelioration of muscle atrophy (47) and/or stimulation of collagen formation (48). Current recommendations do not include supplementing with a specific amino acid as limited research exists research exists. While it is possible to consume all essential amino acids from plant based sources, it is easier to consume the essential amino acids from animal based protein sources. Omega-3 fatty acids modulate inflammation, resulting in reduced wound healing time (49). Unless the athlete encounters excessive inflammation following an injury, supplementation is not necessary. A diet high in omega-3 rich foods, such as salmon, walnuts, and flaxseeds would be effective. Several micronutrients also act to enhance tissue healing. For example, vitamin A is required for epithelial and bone formation, cellular differentiation, and immune function, vitamin C for collagen formation, proper immune function, and as a tissue antioxidant. Vitamin E is the major lipid-soluble antioxidant in the skin (50). Although not enough information exists to warrant supplementation to promote wound healing above RDA recommendations, nutritional intake should be assessed to ensure recommended dietary intake of all micronutrients.

4.3 Fluid

Dehydration can have serious health consequences to all athletes, but older athletes are more susceptible than younger ones. During periods of heat stress, older individuals typically respond with attenuated sweat gland output, decreased skin blood flow, reduced cardiac outputs, and smaller distribution of blood flow from the splanchnic and renal circulation (51). Kenney et al. (52) compared the effects of fluid restriction while exercising under different environmental stimuli in older versus younger women. They found that the percent decrease in sweat rate and plasma volume is greater in older versus younger women, indicating that older women have a greater propensity to develop dehydration associated with lack of fluid replacement. Additionally, older individuals are more likely to have altered thirst and kidney function placing them at increased risk for consequences of dehydration. However, if older women athletes are well conditioned and acclimatized to exercising in warm environments, a tolerance to heat stress can be developed. Athletes should drink 16 oz of fluid 30-40 minutes prior to exercise to ensure enough time to optimize hydration status and excrete excess fluid (37). During exercise, athletes should attempt to match their sweat rate with fluids following the guideline to consume 6-12 fl oz every 15-20 minutes (37). Sports drinks containing 6% to 8% carbohydrates and electrolytes are recommended for events lasting greater than 1 hour (41). One needs to compare post exercise weight to pre exercise weight and replace 16-24 fl oz of a fluid for every 0.5 kg of weight lost during exercise. This should supply ample fluid for rehydration following exercise (41). Additionally, consuming foods with high water content will aid rehydration following exercise.

Prior to and during exercise, nutrition intake should be aimed at maintaining hydration, while providing carbohydrates to maintain blood glucose concentrations during exercise. After exercise, meals should provide adequate fluids, electrolytes, energy, protein, and carbohydrates to replace nutrients lost during exercise and promote recovery. More research is needed before nutritional supplementation to improve performance, promote tissue healing, and optimize aging are recommended to women master athletes. However, encouraging a varied diet with balanced energy intake will help to ensure adequate macro- and micronutrient intakes.

5. Summary

Competitive athletic women may experience successful aging. Older trained women athletes can have a 30-50% higher VO_2max than sedentary women but may have a greater age-related decline per decade than the normal population. Factors such as a decrease in cardiac output due to a decrease in maximal heart rate and stroke volume, altered pulmonary function, changes in arteriole compliance, and a decrease and change in skeletal muscle fibers may play a role in the age associated decrease in aerobic capacity in the normal population as well as in athletes. Women athletes also confer a favorable body composition coincident with enhanced glucose and lipid metabolism. Highly trained women athletes maintain a low percentage of total and central body fat compared to healthy sedentary women. The reduced body fat and maintenance of muscle mass may contribute to enhanced glucose uptake and insulin action observed in highly trained women athletes. Proper nutrition is essential for maximizing athletic performance and general health in older women athletes. Specific needs are highly individualized and depend upon the athlete's

mode of exercise, stage of training, and recovery time, as well as the intensity, duration, and frequency of each exercise session. Athletes may want to consider taking a multivitamin and mineral supplement, pay attention to fluid requirements and consume a nutrient-balanced diet.

6. Acknowledgements

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Exercise and the Immune System – Focusing on the Effect of Exercise on Neutrophil Functions

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1. Introduction

A relationship between intense exercise, leukocytosis and susceptibility to illness was already reported at the beginning of the past century (1-3). Today there is a consensus among researchers and clinicians that exercise have effects on various aspects of the immune function (4). The complexity of the underlying mechanisms and the clinical implications and directions need continuous evaluation. Investigators face challenges associated with immune measures and the interpretation of their changes. They should bear in mind that there is inter-individual variability of the exercise capacity, recovery, stress tolerance and immunocompetence. Short exposure to exercise could promote beneficial and apropriate physiological response of the immune system, while heavy exertion could be detrimental to health. In recent years, the development of advanced laboratory techniques contributed to enrich our knowledge and deepened the understanding of the mechanisms underlying the immune system in sports medicine. The development of fluorescent antibodies techniques allow identifying cell sub-types and receptors. Molecular technology and new cytokine methods of identification have permitted the detection of humoral factors present in the body at low concentrations, for short periods of time and to study the effect of exercise on gene expression profiles (5,6).

Studies on recreational and elite athletes should be systematic and well controlled in order to formulate evidence-based guidelines to preserve a balanced immune function.

2. The immune system

The immune response can be divided into innate, natural-non-adaptive immunity and acquired-adaptive immunity. Innate immunity is the first response to physical or chemical foreign agents and it occurs naturally and immediately, providing the first line of defense in early stages of the infection. The innate immunity is comprised of phagocyte cells, natural killer cells, soluble factors as the complement and acute phase proteins, as well as the mucosal immune responses. The acquired immunity occurs after an adaptive, specific response to a pathogen and involves the antigen-antibody response. It includes B and T lymphocytes and the immunoglobulines (7).

In the innate immunity phagocytes can recognize and act immediately against the foreign agent without prior exposure, while the adaptive immunity is characterized by a specific response to the infectious agent, becoming fully activated after a lag period. The innate mucosal defenses are the first line of defense against pathogens present at the mucosal surfaces. The 'Common Mucosal Immune System' is a network of organized structures that protect the oral cavity, the respiratory, thegastrointestinal and the urogenital systems. The major effector function of this system is the secretory IgA (8,9)**.**

The adaptive immunity involves the action of specialized immune cells, as are the lymphocytes, which generate antibodies against specific microorganisms, killing them directly or activating other cells through the secretion of cytokines. This adaptive response generates memory which is the basis of the preventive immunization. Both systems of immunity, the innate and the acquired, work synergistically and are essential for an optimal function of the immune response. Phagocytes play an important role in the initiation of the adaptive response by presenting antigens and secreting cytokines that stimulate cells of the adaptive system.

Neutrophils (55-65% of blood leukocytes) and monocytes (5-10%) play an important role in innate immunity and provide a major defense system against microorganisms. They act as the first line of defense against infectious agents and are involve in the muscle tissue inflammatory response to exercise-induced injury (10). The multi-step phagocytic process is activated in response to invasion of foreign microorganisms and includes the rolling and adherence of neutrophils to the blood vessel endothelium, the diapedesis and chemotaxis towards the invading organism, the ingestion, degranulation and the oxidative burst, ending with killing of the pathogen (11). Experienced and well equipped laboratories in this specific field, have established the normal range values, based on a large number of subjects examined, in health and disease. Today it is possible to assess the different steps of the phagocytic process and to detect dysfunctions at each level (11-13).

3. Exercise and the immune response – Clinical implications

The potential influence of exercise on the immune system could be beneficial, detrimental or neutral. The immune response depends on the type of the particular exercise, its intensity, volume and duration. While mild or moderate exercise was shown to be beneficial, acute intense or prolonged exercise elicits depression of several aspects of the immune response. The fitness level of the performers could also exert influence in their immunological response. It seems that there is a combination of physiological and psychological factors, known to exert their influences on the immune system. Appropriate interpretation of the immune response is vital for determining the clinical directions and the integral training program for each athlete.

The physical activity could affect one or all three arms of the immune system, the humoral, the phagocytic and the cellular arm. Eventually, dysfunction of one or more arms of the immune system could lead to the outburst of an infection. In general, the etiology of infections is usually of bacterial origin when the humoral or phagocytic arm is affected, while viral–parasitic infections are usually originated when the cellular arm is involved. Excessive, prolonged training and major competitions have been long considered factors affecting the susceptibility to infections in athletes (14-16), however, in shorter and less

competitive events infections are less common (7). Frequent illness has been associated with the overtraining syndrome in athletes (17-19). During heavy exertion could be an immune suppression that creates an 'open window' of decreased host protection. Bacteria or viruses may gain a foothold, increasing the risk of subclinical and clinical infections (17, 20). In team sports or in other sports where participants are in close physical contact before, during or after the sporting event, both the infected individual and the fellow sportsmen may become infected. Some infections may appear in clusters in the sports setting, such as gastroenteritis, herpes simplex, meningitis, viral hepatitis, skin infections, tonsillo-pharyngitis (21,22). A large number of viruses and bacteria can give rise of myocarditis that can be aggravated by physical exertion (15).

There is consistent data suggesting that male endurance athletes may develop after 1 to 2-wk period increased rates of Upper Respiratory Tract Infection (URTI), following marathon or ultramarathon race events (16,23,24). URTI appears to be the most common minor viral infection in athletes. The current consensus is that the cause of URTI in athletes is uncertain (4). There is today disagreement whether 'sore throats', frequently reported by athletes, are caused by infections or are a reflexion of other inflammatory stimuli mimicking URTI (25,26). Cytokines play an important role in modulating the immune function, inducing changes that increase the risk of infection or the appearance of inflammatory symptoms (27). The physician diagnosis of URTI is based on clinical symptoms and signs, rather than by determining the infectious etiology. In few studies the pathogen was identified as the usual respiratory pathogens associated with URTI in the general population **(4).** The salivary IgA concentrations and secretion rates have been shown to be significantly decreased in athletes with prolong high intensity exercise (28,29). We could hypothesize that their immunity is reduced with an increase tendency to develop URTI. Other markers of infection as antimicrobial proteins in saliva (α-amylase, lactoferrin, and lysozyme) have been identified (26,30). Further, viral infections as URTI may lead to a debilitating state and an unexplained deterioration in athletic performance. Viral infections could run a protracted course of easy fatigability, myalgia and lethargy for weeks or even months (31). Additionally, it seems that athletes are more susceptible to develop Infectious Mononucleosis (32).

Infections of non-viral origin, as bacterial pneumonia, mycoplasma and Chlamydia myocarditis, sinusitis, etc., although uncommonly reported in athletes, could also develop following intense exercise (2,15,33). Athletes could aggravate the course of the disease during incubation periods of infections (34,35).

Neutrophils comprise the majority of circulating leukocytes and represent the early body's response in the battle against bacterial and fungal infections. Multi-factorial elements could be involved in the neutrophil behavior and in the immune responses to exercise, as neuro-endocrine mediators (36), corticosteroid release, interleukin production (37) and oxy-reduction processes associated with free radical production (38). Most studies show that of all subsets of circulating leukocytes, mainly neutrophils and lymphocytes, increase dramatically during exercise (39,40). The magnitude is related to the exercise intensity and duration, being more persistent with intense, prolonged exercise (40, 41). Neutrophil count may exhibit a biphasic response, characterized by an initial small increase, followed by a decline to resting values 30-60 minutes after the cessation of exercise. A delayed larger increase in neutrophil numbers could be observed

2 to 4 hours post-exercise (42). This leukocyte trafficking reflect recruitment into the circulation of neutrophils and could be related to hemodynamic changes as increased cardiac output, hyperthermia or could reflect changes in circulating stress hormones, particularly epinephrine and cortisol, released during exercise (42). Resting leukocyte number is generally normal in athletes, although long periods of high-volume training may be associated with long lasting suppression of circulating cell numbers, which may persist low over weeks (43). This may be attributed to migration of leukocytes out of the circulation to possible damaged skeletal muscle (44).

Disproportionate changes in lymphocyte subsets occur during exercise. Usually, during prolonged exercise the NK and CD8 T- cells increase far more than B cells and CD4 T- cells counts (40). Significant decline in the CD4:CD8 ratio was reported after 60 min of treadmill running. Although neutrophil counts may remain elevated for several hours after exercise cessation, lymphocyte number may decline bellow baseline values for up to 6 hours post exercise (7). Following vigorous exercise it was reported a transient fall of circulating natural killer (NK) cell count (45).

In summary, exercise increases neutrophil numbers and may reflect an appropriate response to exercise-induced stress rather than an impaired immunocompromised state. In contrast, the post-exercise decrease in the absolute lymphocyte counts, the NK decrease and the inversion of the CD4 to CD8 ratio, could indicate immunosuppresion.

It is remarkable that no significant changes were reported in B-cell circulating lymphocytes and only local salivary IgA reduction was shown following intense, prolonged exercise. The relationship between the leukocyte dynamics and the clinical implications is still unclear.

4. Immunological studies – Our experience

Scant information exists on exercise-induced changes in the immune system among children. We investigated the effect of aerobic exercise on several aspects of cellular and humoral functions among 10-12 year-old highly trained female gymnasts and untrained girls (46). All girls were pre-pubertal. Venous blood samples were drawn before, immediately after and 24 h following 20 min of treadmill running (heart rate 170-180 beats.min-1). White blood cells' number rose significantly following exercise and remained elevated for 24 h. The increase in leukocyte number was due to an increase in granulocytes as well as an increase in lymphocytes and monocytes. While neutrophil count returned to basal values after 24 h, lymphocytes and monocytes number remained elevated 24 h following exercise. Exercise resulted in a significant elevation of T cell lymphocytes, T helpers, T suppressors and natural killer cells. All values returned to normal after 24 h. There were no changes in B cell lymphocytes following exercise (Table 1). Exercise had no effect on serum immunoglobulin's and sub-types of IgG {IgG1, IgG2, IgG3 and IgG4} (Table 2). No differences were observed between gymnasts and untrained girls (46). The changes observed were similar to those found in adults (40).

Our laboratory for leukocyte functions focused within the last 30 years on granulocyte functions and dysfunctions in healthy subjects and in patients suffering from recurrent, severe, opportunistic infections. For the last 15 years, our group focused on neutrophil functions following a single bout of submaximal aerobic exercise (47-50). Neutrophil

functions as chemotaxis, oxidative burst, and bactericidal activity were unaffected immediately post-exercise, however neutrophil chemotactic activity was found significantly decreased 24 h after the cessation of the exercise (Table 3) (47).

		Pre exercise		Immediately after exercise		24 h following exercise	
		X	SD	X	SD	X	SD
WBC	gymnasts	5561	596	*7046	1306	*6505	436
	untrained	6340	1043	*8263	1225	*6738	1150
Neutrophils	gymnasts	2710	349	*3554	692	3126	498
	untrained	3570	1000	*4658	1184	3490	805
Lymphocytes	gymnasts	1930	235	*2690	360	*2365	524
	untrained	2106	544	*2671	834	*2464	401
T cell	gymnasts	1590	493	*1860	682	723	340
	untrained	1413	219	*1953	357	1677	458
Th cells	gymnasts	943	251	*1030	248	1003	155
	untrained	792	197	*1059	303	992	334
Ts cells	gymnasts	663	278	* 851	410	776	205
	untrained	550	98	* 784	193	669	173
B cells	gymnasts	306	101	320	96	344	93
	untrained	295	56	329	92	350	103
Natural killer cells	gymnasts	161	132	* 256	119	231	124
	untrained	124	47	* 267	85	139	43
Monocytes	gymnasts	293	61	* 391	127	# 424	72
	untrained	373	82	* 462	125	375	18

* significantly different from pre-exercise value in both groups
# significantly different from pre-exercise value in the gymnasts group only

Table 1. Changes in the cellular components of the immune system. WBC and lymphocyte subpopulations (cells/µl) following exercise in gymnasts and untrained girls (46).

	IgM (mg/dl)		IgA (mg/dl)		IgE (unit/ml)		IgG (mg/dl)		IgG-1 (mg/dl)		IgG-2 (mg/dl)		IgG-3 (mg/dl)		IgG-4 (mg/dl)	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
pre exercise	207.0	83.3	120.6	26.1	81.6	53.2	1194.0	138.2	673.7	108.0	235.3	63.7	69.7	35.5	61.2	24.1
post exercise	199.3	67.6	120.4	21.6	81.1	49.8	1180.7	151.2	705.9	132.6	242.1	66.8	59.1	18.5	63.4	25.1
24 h post exercise	179.4	73.2	116.4	36.4	83.1	56.5	1181.4	147.3	669.9	144.3	232.4	69.0	63.6	22.1	61.4	24.2

Table 2. Immunoglobulin levels pre-exercise, immediately post-exercise among gymnasts (46).

		Pre-exercise (Basal)	Post-exercise	24 h post-exercise
Neutrophils (cells/μl)	trained	2710 ± 349	3554 ± 692	3126 ± 498
	untrained	3570 ± 1000	4658 ± 1184	3490 ± 805
Chemotaxis (cells /field)	trained	58 ± 11	55 ± 13	36 ± 11 *
	untrained	47 ± 7	52 ± 15	42 ± 8 *
Killing (log decrease of colonies) with autologous serum	trained	0.8 ± 0.3 #	0.8 ± 0.2 #	0.8 ± 0.1 #
	untrained	1.1 ± 0.1	1.1 ± 0.1	1.0 ± 0.2
Killing (log decrease of colonies) with homologous serum	trained	0.7 ± 0.2 #	0.8 ± 0.1 #	0.8 ± 0.2
	untrained	1.0 ± 0.1	1.0 ± 0.02	0.9 ± 0.2
Superoxide production (nmol $0_2^-/10^6$ PMNs/min) with PMA stimulation	trained	5.7 ± 0.4	4.4 ± 1.0 *	4.8 ± 1.0 *
	untrained	5.1 ± 0.7	4.7 ± 1.3	4.9 ± 1.2
Superoxide production (nmol $0_2^-/10^6$ PMNs/min) with fMLP stimulation	trained	3.4 ± 1.9	3.2 ± 1.3	2.6 ± 1.3
	untrained	4.1 ± 1.3	3.3 ± 0.5	3.7 ± 0.6

*⟩<0.05 compared with basal values (before vs. following exercise).
#⟩<0.05 compared with control group (trained vs. untrained).

Table 3. Effect of exercise on neutrophil count and neutrophil functions (mean+SD), Pre-exercise (basal), immediate post-exercise and 24 h post-exercise (47).

A consistent decrease of neutrophil migration was detected 24 h post-exercise in trained and untrained subjects, children and adults, male and female (47-50). The following studies focused on the recovery time of the impaired neutrophil chemotaxis, using various chemoattractans. We also aimed to learn about the possible mechanisms involved in the post exercise-associated chemotactic defect. We found that the transient impairment shown in the chemotactic activity 24 h post-exercise, returned to normal after 48 h (Figure 1) (49).
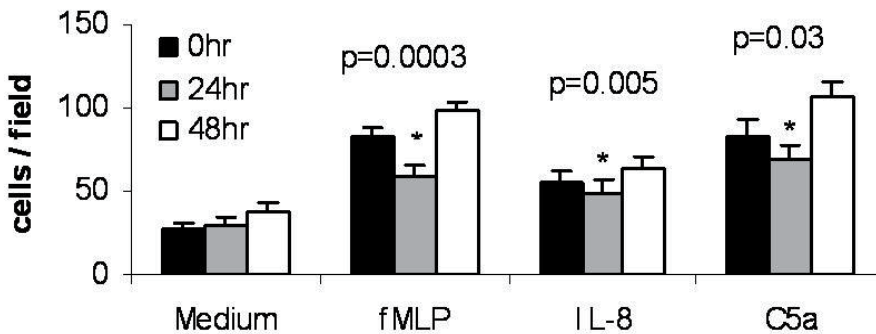
Fig. 1. Kinetics of the neutrophil chemotactic activity in 16 athletes; Pre-exercise, immediately post-exercise and 24 h post-exercise. The chemotaxis was induced by the chemoattractant: fMLP (1 μM), IL-8 (10 nM), or C5a (10 nM). Random migration was conducted in the presence of medium M199. The results were expressed as the number of migrating cells per field (mean±SE) (49).

Looking at the response of the neutrophil specific membrane receptors to the different chemoattractants, we repeatedly found reduction of the chemotaxis following intense exercise, regardless of the chemoattractant used, including Formylated peptides (fMLP), the

chemokine IL-8, and the activated complement component(C5a) (49). These chemokines attach to their specific receptors, fMLP-R (N- formyl-Met-Leu-Phe), IL-8-R (CXCR1 and CXCR2), and C5aR, which belong to the seven-transmembrane helix surface receptor family ("serpentine receptors") that transduces signals downstream the cytoskeleton by coupling to heterotrimeric G-proteins (51). Once the signal has been triggered, rapid cytoskeletal rearrangement and chemotaxis take place. "Target" chemoattractants (fMLP, C5a) function primarily through a common signal-transduction pathway by stimulating p38 MAPK, whereas "host" intermediary chemoattractants (IL-8, LTB4) primarily function via the PI3K/Akt pathway (52). The surface density of the chemotactic receptor (C5aR), which serves as a representative model of receptor availability, was not affected 24 h after exercise. Moreover, the integrin CD11b/CD18, which represent one of the main receptors for neutrophil adhesiveness and crucial for normal chemotaxis, was also unaffected by exercise. Therefore, the chemotactic defect is not dependent on the specific receptor of activation, or on its specific pathway of transduction. We could speculate that the chemotactic impairment was related to a common defect at the membrane level, leading to decreased receptor availability or to other factors yet to be elucidated. For achieving appropriate chemotactic responses, an intact cytoskeleton structures are necessary (53,54). Continuous reorganization of the cytoskeleton is required for efficient F-actin polymerization and polarization. Both are important steps in the skeletal rearrangement during migration (55). Consequently, we studied the neutrophil F-actin neutrophil polarization and polymerization (49). Following fMLP stimulation, the cell undergoes sequential morphological changes from round to elongated geometrical forms (figure 2A). These changes reflect the cell activation and the ability to migrate against the chemotactic gradients toward the target (49,53). Using the green phalloidin test we found no correlation between the chemotactic defect and the ability to polymerize F-actin, indicating that the reduction in chemotaxis following exercise was not a result of the F-actin dysfunction. Despite the fact that positive correlation between chemotaxis and F-actin polymerization usually occurs, a lack of correlation in certain conditions has been reported (55).

To elucidate other cell skeletal responses to aerobic exercise, we studied the neutrophil polarization, known to be in tight correlation with the chemotactic activity.

Indeed, the neutrophil polarization was significantly decreased 24 h following aerobic exercise. This change also correlated with the decrease in chemotactic activity (r= 0.945; P= 0.001) (figure 2B) (49,50).

Since the neutrophil bactericidal activity and the oxidative burst were found to be normal, it seems that the signal transduction pathways are not affected following 30 min of intense aerobic exercise. Rather, it seems that aerobic exercise causes a skeletal impairment, and this eventually could leads to a reduction of the chemotactic activity. Most probably the impaired chemotaxis event, following a short bout of submaximal exercise, occurred at the effectors' machinery level, rather than at the level of the neutrophil membrane receptors. Others found no change in chemotaxis 24 h after a graded exercise to exhaustion (56). Giraldo et. al. reported increased chemotaxis immediately after moderate (45 min of 55% VO2max) and intense (1 hr of 70% VO2max) aerobic exercise that returned to basal values after 24 h (57). These discrepancies are probably related to differences in the type, intensity, and duration of exercise, timing of blood sampling, or use of different laboratory assays.
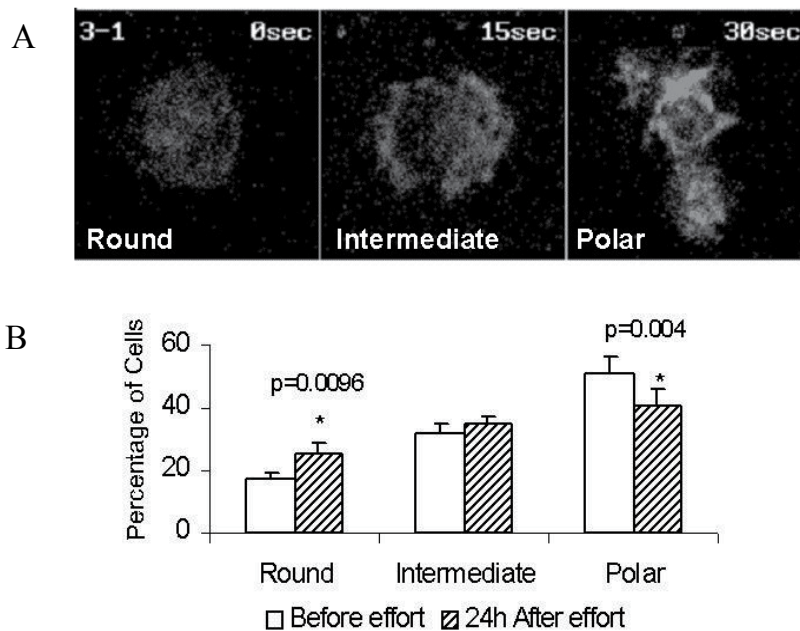
Fig. 2. Neutrophil polarization. A. The cell shape changes that occur following fMLP-stimulation. Three different cell shapes were recorded: non-activated - round cells (R), partially activated - intermediate cells (I), and fully activated - polarized cells (P).
B. Analysis of the cells' morphological changes following fMLP-stimulation, in 11 athletes, before and after effort (mean±SE) (49).

5. Therapeutic approach to exercise-induced immune suppression

Dietary and drug intervention have been reported to boost performance in athletes (58). They could block the transient immune changes, to prevent the oxidative stress and the inflammation induced by prolonged, intense exercise or excessive training. Some supplements as flavonoids were reported to benefit the immune system (59). In endurance events, iron and mineral supplements, together with antioxidant vitamins, help to prevent muscle damage (60). Carbohydrates enhance muscle glycogen stores. Glutamine and aminoacid supplementation did not prove to be beneficial (61).

Vitamin E (VE) and vitamin C, as antioxidants, play an important role in protecting the cells and muscles from damage (62-65). It is well-established that exercise exerts imbalance on the oxidative state by increasing Reactive Oxygen Species (ROS) and decreasing the level of antioxidants (63). As previously shown, intense or prolonged exercise can adversely affect the function of the immune system. It was found that submaximal aerobic activity (1h swim at 75-80% of VO2max) could produce oxidative damage within the neutrophils (64), which lose the appropriate antioxidant defense mechanisms, leading to a defective chemotactic ability (65). This impairment could rise from the increased levels of ROS and lipid peroxidation; both potentially could damage neutrophil function. The enhanced production of ROS, mainly by mitochondria, is associated with excessive oxidation of lipids, proteins, and nucleic acids, causing damage to cell membranes and to the physiological function of proteins and DNA (66-68). To defend themselves from ROS induced damage, cells contain

complex antioxidant mechanisms including enzymatic (e.g. superoxide dismutase, glutathione peroxidase, catalase) and non-enzymatic antioxidants (e.g., vitamin E (VE), vitamin C, beta-carotene). VE is the most important lipid-soluble antioxidant due to its abundance in cell and mitochondrial membranes and its ability to act directly on ROS and stop lipid peroxidation. This antioxidant is known to decrease the exercise-induced oxidative stress (69-71) and has been shown to protect against exercise-induced muscle damage (70). Neutrophils play a dual role in exercise-induced oxidative damage. On the one hand, they contribute to ROS formation during intense or prolonged exercise; on the other hand, intense exercise can produce oxidative damage within neutrophils. VE has an important role as anti-oxidant and an important role in maintaining normal neutrophil function. Chemotaxis, adherence, and phagocytic capacities of neutrophils were shown to be reduced in VE deficiency, improving after antioxidant treatment (65,72,73).

Our research focused on the phagocytic immune response to exercise, showing prevention of the impairments by vitamin E supplementation. The results of chemotaxis and polarization are shown in Figure 3, representing the mean +/- SEM of 7 trained men pre- and post-exercise, before and after 28 days of daily VE supplementation (74). We can see that daily supplementation of 800 IU d-alpha tocopheryl succinate, indeed corrected the defective neutrophil chemotaxis and polarization observed 24 hr post-exercise.

A relatively small number of studies have dealt with the effect of VE on neutrophil functions following exercise. To the best of our knowledge, there are no studies addressing the effect of VE on exercise-induced impaired chemotaxis. However, a beneficial effect of VE on chemotaxis was shown in other populations, such as healthy elderly men and women and elderly women with coronary heart disease or major depressive disorder (72,73). Improvement in chemotactic ability after VE supplementation was also found in rats with VE deficiency and in periparturient dairy cows (75,76).
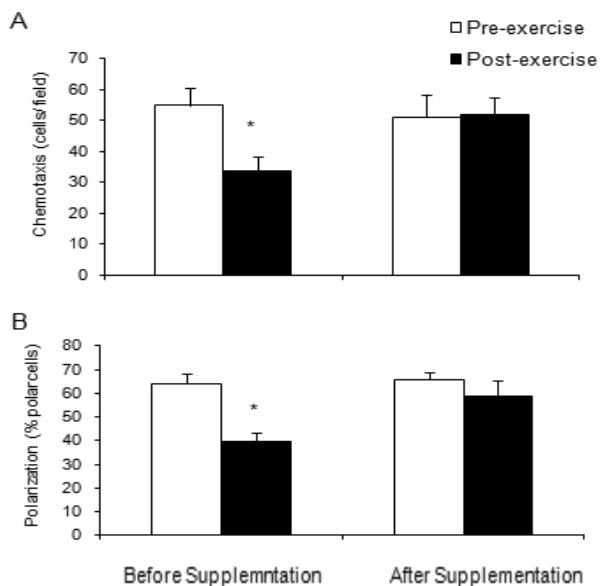
Fig. 3. A. Correction of the defective neutrophil chemotactic activity (observed 24 h post-exercise) by vitamin E supplementation. B. Correction of the defective neutrophil polarization (observed 24 h post-exercise) by vitamin E supplementation (74).

Of note is that recent reports have emphasized that ROS production, through the reversible oxidation of thiol groups, has also important physiological influences on gene transcription and protein synthesis, as part of the adaptive processes that occurs after exercise. High dose antioxidant supplementation may interfere with these processes. Cooper's Group reported gene reorganization after intense exercise (77, 78).

In recent years, it has been reported that regular physical activity can have beneficial role in cancer's prevention and therapy (79,80). There is evidence of a protective effect of physical activity on colon and postmenopausal breast cancer (81). Further, it is also mounting that physical activity reduces risks of lung tumor metastases (82). It has been reported that exercise prevent the loss of muscle mass and functional capacity in chronic deteriorating conditions, beyond the beneficial psychological effects, which certainly improve the quality of life (83-85).

Athletes are not immunocompromised by clinical definition, but could suffer from transitory, persistent immunosuppression, eventually leading to subclinical or clinical diseases. Recovery time is imperative in elite athletes involved in intense training and competitions. The temporary, sometimes multiple, mild impairments of the immune system could change into a chronic more severe immune dysfunction.

The approach should be multidisciplinary, including all care givers as sport medicine physicians, physiologists, immunologists, physiotherapists, nutritionists, psychologists and coaches. To achieve the main goals, an integrated model with programmed activities and clear guidelines for any specific type of sport is imperative. Recommendations should be directed to elite athletes and recreational sports, for sedentary individuals, for moderate and well trained subjects. The target is to maintain the balance of the immune system for the health of the athlete and his optimal performance.

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Physical Activity, Physical Fitness and Metabolic Syndrome

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1. Introduction

The metabolic syndrome is recognized as one of the leading worldwide health problems, which is a constellation of metabolic risk factors that is associated with increased risk for developing cardiovascular disease, type 2 diabetes mellitus and myocardial infarction. Clustered metabolic risk factors include abdominal obesity, dyslipidemia, elevated blood pressure, glucose intolerance, and insulin resistance, as standardized by the international criteria [1]. Evidence from observational epidemiological studies indicates that the metabolic risk factors begin early in life [2,3]. Childhood overweight and obesity are closely associated with insulin resistance, in which result the development of metabolic syndrome. The overall prevalence of metabolic syndrome can be identified in children and adolescents. Obesity and insulin resistance may develop the metabolic syndrome during the early years of life and throughout in adulthood. In Finland, the prevalence of metabolic syndrome has increased dramatically over the past decades [4,5].

The benefits of physical activity and physical fitness on the health of the general population have been attested beyond dispute [6]. There is overwhelming evidence that participation in regular, moderate-intensity physical activity may be a preventive intervention of the metabolic syndrome and that activity of greater intensity may provide even greater benefit [7]. Remarkably, supervised exercise training in either aerobic exercise or resistance training may be an effective adjunctive treatment and produce significant functional benefits for individuals with the metabolic syndrome [8]. Physical activity and exercise are thus uniquely positioned to improve physical and psychosocial health and function by reducing the clustered metabolic risk and, in turn, by delaying or avoiding the onset of diabetes and cardiovascular diseases. However, most of the studies have been cross-sectional, but a few have been longitudinal.

The aim of this chapter is to outline physical activity and fitness to prevent or reduce the prevalence or incidence of metabolic syndrome among youth and adults. I start with the definition of physical activity, cardiorespiratory fitness and muscular strength and proceed to a discussion of the role of physical activity and fitness on the metabolic syndrome. I will discuss the importance of physical activity and fitness as their primary sources of health information that affect the metabolic syndrome in both youth and adults. Special emphasis is given to the use of long-term physical activity as a possible means of effectively reducing the prevalence of metabolic syndrome.

2. Rationale of physical activity and fitness in the prevention of metabolic syndrome

2.1 Definitions

The terms 'physical activity', 'exercise' and 'physical fitness' have been described in detail by Caspersen et al. [9]. Although these terms are related and have similar meanings, they aren't identical in meaning. Physical activity is defined as any bodily movement produced by skeletal muscles that result in energy expenditure. Exercise is a subset of physical activity that is planned, structured, and repetitive and has as a final or an intermediate objective the improvement or maintenance of physical fitness. Physical fitness is a set of attributes that are either health-related (i.e. cardiorespiratory endurance, muscular strength and endurance, body composition, and flexibility) or skill-related (i.e. agility, balance, coordination, speed, power, and reaction time). Physical fitness is also referred to almost exclusively as cardiorespiratory fitness (also called cardiovascular fitness or maximal aerobic power), which relates very closely to maximal capacity for oxygen consumption. An important distinction between physical activity and fitness is the intraindividual day-to-day variability; physical activity will undoubtedly vary on a daily basis, whereas cardiorespiratory fitness will remain relatively static, taking time to change. This variability will impact on the ability to measure these two quantities and consequently will influence the ability to demonstrate their relationship with metabolic outcomes. In this chapter physical activity will be used as a generic term, whereas cardiorespiratory fitness and muscular strength will be used in their specific meanings. Based on previous studies of assessments of physical activity and physical fitness, the main methods of these standard measures have been summarized and presented in Table 1.

The term 'metabolic syndrome' is generally defined as the clustering risk factors associated with medical disorders that increase the risk of developing atherosclerotic and insulin resistance, i.e. elevated levels of central adiposity, hypertension, dyslipidemia, impaired glucose metabolism, and a low level of high-density lipoprotein cholesterol [10]. Table 2 summarizes five international criteria in the following: World Health Organization [11], European Group for the Study of Insulin Resistance [12], American College of Endocrinology/American Association of Clinical Endocrinologists [13], International Diabetes Federation [14], and National Cholesterol Education Program Adult Treatment Panel III [10].

The World Health Organization criteria requires the presence of impaired glucose tolerance, impaired fasting glucose, type 2 diabetes, and insulin resistance in top quartile of non-diabetic population and at least two of the following: waist:hip ratio > 0.9 in men and > 0.85 in women, serum triglycerides ≥ 1.7 mmol/L, systolic/diastolic blood pressure ≥ 140/90 mmHg or medication, high-density lipoprotein cholesterol ≤ 0.9 mmol/L in men and ≤ 1.0 mmol/L in women, and microalbuminuria: urinary albumin excretion ratio ≥ 20 μg/min or albumin:creatinine ratio ≥ 30 mg/g. The European Group for the Study of Insulin Resistance criteria includes the presence of hyperinsulinemia (defined as nondiabetic subjects having fasting insulin level in the highest quartile) and at least two of the following abnormalities: fasting plasma glucose ≥ 6.1 mmol/L (110 mg/dL), triglycerides > 2.0 mmol/L, high-density lipoprotein cholesterol < 1.0 mmol/L or medication, systolic/diastolic blood pressure ≥ 140/90 mmHg or current use of antihypertensive medication, and waist circumference ≥ 94 cm in men and ≥ 80 cm in women. The American College of Endocrinology/American

Physical activity	Children and adolescents	Adults
Questionnaire	Physical activity at school Organized sport Non-organized sport Commuting to school Leisure activities Time spent sitting	Sports Occupation Household/Caregiving Transportation Conditioning Leisure/Recreation activities Time spent sitting
Interview	Face to face	Face to fact Telephone
Instrument	Heart rate monitoring Pedometer Accelerometer	Heart rate monitoring Pedometer Accelerometer
Physical fitness	Laboratory	Epidemiologic
Cardiorespiratory	Maximum oxygen uptake on treadmill or cycle ergometer	12-minutes run 1-mile walk Bench (30 cm high) step
Body composition	Underwater weighing Near infrared Bioelectrical impedance analysis	Waist girth / waist-to-hip ratio Body mass index (kg/m^2) Skinfolds (biceps, triceps, abdomen, suprailium, subscapula and thigh)
Muscular strength and endurance	Dynomometer Cable tensiometer Load cells Strain gauges	Handgrip Chin ups Push ups Sit / Curl ups
Flexibility	Leighton flexometer	Sit-and-reach flexometer

Table 1. Main assessment of physical activity and physical fitness

Association of Clinical Endocrinologists criteria requires the presence of abdominal obesity (waist circumference ≥ 102 cm in men and ≥ 88 cm in women) and at least two of the following abnormalities: fasting plasma glucose ≥ 5.6 mmol/L (100mg/dL), systolic/diastolic blood pressure ≥130/85mmHg or medication, triglycerides ≥1.7 mmol/L (150 mg/dL) or medication. The International Diabetes Federation criteria includes the presence of abdominal obesity (waist circumference ≥ 94 cm in men and ≥ 80 cm in women) and ≥ 2 of the following four indicators: fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL), triglycerides ≥ 1.7 mmol/L (150 mg/dL), high-density lipoprotein cholesterol < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.29 mmol/L) in women, and systolic/diastolic blood pressure ≥130/85 mmHg or treatment for hypertension. The National Cholesterol Education Program Adult Treatment Panel III criteria includes the presence of at least three of the following: waist circumference ≥ 102 cm in men and ≥ 88 cm in women, triglycerides ≥ 150 mg/dL, high-density lipoprotein cholesterol < 40 mg/dL in men and < 50 mg/dL in women, systolic/diastolic blood pressure ≥130/85 mm Hg or use of medication for hypertension, and fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL) or medication.

	WHO (1999)	EGIR (1999)	ACE/AACE (2003)	IDF (2006)	NCEP-ATP III (2005)
Required criteria	IGT, IFG, T2D, insulin resistance in top quartile of non-diabetic population	Insulin resistance in top quartile of non-diabetic population	High risk[1]), WC > 102 cm (M) or > 88 cm (F)	WC ≥ 94 cm (M) or ≥ 80 cm (F), and WC with ethnicity specific values, or BMI > 30 kg/m²	
Other criteria	plus ≥ 2 of the following:				
Waist circumference (WC)	WHR > 0.9(M), or >0.85 (F); or BMI > 30 kg/m²	≥ 94 cm (M) or ≥ 80 cm (F)			≥102 cm (M) or ≥ 88 cm (F)
Triglyceride	≥ 1.7 mmol/L	≥ 2.0 mmol/L	≥ 1.7 mmol/L (150 mg/dL)	≥ 1.7 mmol/l (150 mg/dL) or medication	≥ 150 mg/dL
High-density lipoprotein cholesterol	≤ 0.9 mmol/L (M) or ≤ 1.0 mmol/L (F) or medication	< 1.0 mmol/L or medication	< 40 mg/dL (M) or < 50 mg/dL (F)	< 40 mg/dL (1.03 mmol/L) (M) or < 50 mg/dL (1.29 mmol/L) (F)	<40 mg/dL (M) or <50 mg/dL (F)
Blood pressure	≥ 140/90 mmHg or medication	≥ 140/90 mmHg or medication	≥ 130/85 mmHg or medication	≥ 130/85 mmHg or medication	≥130/85 mmHg or medication
Glucose		≥ 6.1 mmol/L (110 mg/dL)	≥ 5.6 mmol/L (100 mg/dL)	≥ 5.6 mmol/L (100 mg/dL)	≥5.6 mmol/L (100 mg/dL) or medication
Other	Microalbuminuria; UAER ≥ 20 µg/min or ACR ≥ 30 mg/g				

WHO, World Health Organization, EGIR, European Group for the Study of Insulin Resistance; ACE/AACE, American College of Endocrinology/American Association of Clinical Endocrinologists; IDF, International Diabetes Federation; NCEP-ATP III, National Cholesterol Education Program- Adult Treatment Panel III; IGT, impaired glucose tolerance; IFG, impaired fasting glucose, T2D, type 2 diabetes; WHR, waist:hip ratio; BMI, body mass index; UAER, urinary albumin excretion ratio; ACR, albumin:creatinine ratio.
[1])High risk: family history of type 2 or gestational diabetes, known cardiovascular disease, polycystic ovary syndrome, physically inactive lifestyle, >40 years of age, and ethnic populations at high risk for type 2 diabetes. M = male, F = female.

Table 2. Metabolic syndrome definitions and diagnosis issued by international criteria

It has been noted that these definitions overlap but differ in the points of emphasis of the components. Using the above definitions of the metabolic syndrome, there are quantitatively significant differences in sample sizes, age groups and rates of healthy participants as well. For example, the International Diabetes Federation definition identifies a high degree of overlap among the participants with the metabolic syndrome using the

National Cholesterol Education Program Adult Treatment Panel III criteria. The two definitions similarly classified approximately 93% in 3601 American adults aged ≥ 20 years [15], 85% in 2182 Finnish young adults aged 24–39 years [4], and only about 16% in 5047 Swedish adults aged 46–68 years [16].

2.2 Systemic mechanisms

In general, leisure-time physical activity and aerobic exercise may provide an advantage in helping reducing the metabolic syndrome in middle-aged and elderly population. The potential mechanisms are often proposed by which physical activity and fitness can reduce the risk of the metabolic syndrome in response to insulin resistance and abdominal obesity. From a psychosocial standpoint, physical activity and fitness have a beneficial effect that can improve psychosocial well-being, leading to better mood, higher self-efficacy and stronger social motives for exercise [17,18]. Participation in regular physical activity or aerobic exercise is an effective way to establish lifelong habits for reducing the increased risk of insulin resistance and obesity. Individuals who want to maintain physical abilities may have better awareness of other health-related habits such as diet, smoking and sedentary lifestyle, all of which have been found to be related to the risk for the metabolic syndrome [19,20]. Increased physical activity and fitness may also lead to enhanced overall cardiovascular function and muscular endurance which, in turn, delay the onset or help prevent the development of metabolic syndrome. These psychosocial effects may then interact with biological processes that may result in reduction of subclinical inflammation involving cytokines derived from adipose tissue and modulation of various adipocytokines that lead to reduce the prevalence of metabolic syndrome [21]. The benefit of increased and maintained physical activity and physical fitness may be directly or indirectly associated with reduced incidence of the metabolic syndrome.

However, the relationship between physical activity or physical fitness and the metabolic syndrome may also be bidirectional. The prevalence of metabolic syndrome may lead to declining levels of physical activity and fitness as symptoms of metabolic syndrome may increase sedentary lifestyle, unhealthy diet, low energy level and lack of exercise and physical activity. Therefore, the precise mechanisms underlying the effect of physical activity and fitness on the metabolic syndrome still need further clarification.

3. Effect of physical activity and fitness on metabolic syndrome in adults

A number of cross-sectional epidemiological studies have been conducted to examine the effect of leisure-time physical activity and cardiorespiratory fitness on the metabolic syndrome in adult population over the last decade. Several studies have only focused on the association in men. An English cohort of 711 employed middle-aged men demonstrated a dose-relationship between both leisure-time physical activity and cardiorespiratory fitness and the clustering of the metabolic syndrome including fasting glucose, triglycerides, high-density lipoprotein cholesterol, blood pressure, and body mass index [22]. Men with higher physical activity, as defined by a physical activity index, were found to be less likely to have the metabolic syndrome when compared with the inactive ones. The age-adjusted odds ratios and their 95% confidence intervals for having the clustering of metabolic syndrome were 0.56 (0.33-0.96) for occasional/light physical activity, 0.37 (0.19-0.71) for moderate/moderately vigorous physical activity, and 0.12 (0.03-0.50) for vigorous physical activity. Men with moderate to high levels of the fitness were also found to be less likely to

develop the metabolic syndrome when compared with those with unfit. The corresponding age-adjusted odds ratios and 95% confidence intervals were 0.27 (0.15-0.46) in the moderate fitness category and 0.18 (0.09-0.33) in the high fitness category compared to the unfit group. A similar study design and analysis was performed in a Finnish study of 1 069 middle-aged men [23]. Leisure-time physical activity, as measured by metabolic equivalent hours per week (MET h·wk^{-1}), was divided into three levels of intensity: low, moderate and high. The each level was grouped again into three categories from low to high. Men who engaged in moderate-intensity physical activity (<1.0 h·wk^{-1}) were 60% more likely to have the metabolic syndrome than those engaging in physical activity (≥ 3.0 h·wk^{-1}). Men with low fitness (VO$_{2max}$ ≤ 29.1 ml·kg^{-1}·min^{-1}) were approximately seven times more likely to have the metabolic syndrome than those with high fitness (VO$_{2max}$ ≥35.5 ml·kg^{-1}·min^{-1}). The relationships remained significant after adjustment for confounders.

In the Whitehall II study, which assessed a dose-response relationship between leisure-time physical activity and metabolic syndrome in 5 153 Caucasian civil servants (ages 45-68 years) from 20 departments in the London offices, showed that the odds ratios and their 95% confidence intervals for having the metabolic syndrome were 0.52 (0.40–0.67) in vigorous (≥12.5 MET h/wk) activity and 0.78 (0.63–0.96) in moderate (≥24 MET h/wk) activity than in low activity, when controlling for confounders, e.g., age, smoking, alcohol intake, socioeconomic status, and other activity [24]. Katzmarzyk et al. [25] carried out a cohort study of 19 223 men (ages 20–83 years), who were selected randomly from a general population in Canada. Cardiorespiratory fitness was used to classify each subject into two fitness exposure categories. Men with the metabolic syndrome had 1.29-fold higher all-cause mortality and 1.89-fold higher cardiovascular disease (CVD) mortality compared with healthy men. However, the associations were no longer significant after accounting for cardiorespiratory fitness. The relative risks comparing unfit vs. fit men for all-cause mortality was similar in healthy men and men with the metabolic syndrome (2.18 vs. 2.01), whereas the relative risks for CVD mortality for unfit vs. fit men were 3.21 in healthy men and 2.25 in men with the metabolic syndrome. Also, a significant dose-response relationship between cardiorespiratory fitness and mortality was observed in men with the metabolic syndrome. It was concluded that exercise provided a protective effect against the risk of all-cause and CVD mortality in healthy men and men with the metabolic syndrome.

Although there is a consistent inverse association between leisure-time physical activity and metabolic syndrome and its components in men, the association is not as consistent in women. For example, results from the Quebec family study (158 men and 198 women aged 20-60 years) found that cardiorespiratory fitness was independently related to the metabolic syndrome among both men and women. Cardiorespiratory fitness was inversely related to plasma insulin only for men, while cardiorespiratory fitness was only positively related to high-density lipoprotein cholesterol for women. However, cardiorespiratory fitness was not independently related to the components of metabolic syndrome in both sexes after accounting for total and abdominal adiposity [26]. As in another Canadian population-based study (6 406 men and 6 475 women aged 18-64 years) [27], the odds ratios and their 95% confidence intervals for having the metabolic syndrome in physically active men was 0.45 (0.29-0.69) than their physically inactive counterparts, after consideration of covariates including age, smoking, alcohol consumption, and income adequacy. The association disappeared in women after adjusting for the covariates. Sex differences were also found for the association of the metabolic syndrome with leisure-time physical activity in the Fels Longitudinal Study [28], investigating a sample of US young adults (249 women and 237

men aged 18–40 years). Among men, the odds ratios for having the metabolic syndrome risk were independently reduced with increases in both total physical activity (OR = 0.65, 95% CI = 0.47–0.90) and sport activity (OR = 0.40, 95% CI = 0.23–0.70). The components of metabolic syndrome such as abdominal circumference, triglycerides and high-density lipoprotein cholesterol also improved with total and sport physical activity. Among women, the associations of types of physical activity, i.e., leisure, sport, work, and total with the metabolic syndrome were marginal. Only high-density lipoprotein cholesterol was increased by both total physical activity (OR = 0.79, 95% CI = 0.63–0.98) and sport physical activity (OR = 0.54, 95% CI = 0.35–0.84) after controlling for age, smoking and body mass index. These differences may be partly explained by race, age and sex hormone differences, varying patterns of fat distribution, and differences in types and intensity of physical activity.

Two studies have reported an inverse association between leisure-time physical activity and metabolic syndrome in women. A cohort study [29] of a tri-ethnic sample of women (49 African-American, 46 Native-American, and 51 white) aged 40–83 years in the USA demonstrated that the odds ratios and their 95% confidence intervals for having the metabolic syndrome were 0.18 (0.03–0.90) for women in the highest category of moderate-intensity physical activity (≥491 MET min/d) compared with those in the lowest category (<216 MET min/d). The odds ratios for having the metabolic syndrome was 0.07 (0.02–0.35) for women in the highest quartile of maximal treadmill duration (>16 minutes) compared with women in the lowest quartile (≤10 minutes). Although the study population is relatively small, the increased physical activity has important implications in the prevention of metabolic syndrome independently of potential confounding variables. Similar results were found in another study [30] of 7 104 US women, which showed that prevalence of the metabolic syndrome was significantly lower across cardiorespiratory fitness quintiles, with the prevalence ranging from 19.0% in the lowest fit quintile to 2.3% in the highest fit quintile. Also, the prevalence of metabolic syndrome in the different age groups for women who achieved a maximal MET level of 11 or higher was one-third to one-fourth that of women who achieved lower maximal MET levels.

Most studies found that physical activity and fitness was related to the metabolic syndrome in both sexes. An early cohort study [31] of 15 537 men and 3 899 women in the adult US population found that the least-fit men had 3.0- and 10.1-fold higher risk factors for the metabolic clusters (elevated systolic blood pressure, serum triglycerides, fasting blood glucose, and central adiposity) compared with moderately-fit and the most-fit men, respectively. Similarly, the least-fit women had 2.7- and 4.9-fold higher risk factors for the metabolic clusters compared with moderately-fit and the most-fit women, respectively. Data from a cohort of 874 healthy Caucasian participants from the Medical Research Council Ely Study indicated that there was a strong and significant inverse association between physical activity energy expenditure and the metabolic syndrome, while the association between cardiorespiratory fitness and the metabolic syndrome was attenuated after adjusting for age, sex, physical activity, and measurement error. However, cardiorespiratory fitness modified the relationship between physical activity and metabolic syndrome [32]. Thus, prevention of the metabolic syndrome may be most effective in the subset of unfit inactive people.

An Australian study by Dunstan et al. [33] examined the associations of television viewing and physical activity with the metabolic syndrome in 6 241 adults aged ≥ 35 years. They found that the adjusted odds ratios and their 95% confidence intervals for having the metabolic syndrome were 2.07 (1.49-2.88) in women and 1.48 (0.95-2.31) in men who watched TV for >14 hrs/wk compared with those who watched ≤ 7.0 hrs/wk. Compared

with those who were less active (<2.5 hrs/wk), the odds ratios for having the metabolic syndrome were 0.72 (0.58-0.90) in men and 0.53 (0.38-0.74) in women who were active (≥2.5 hrs/wk). Additionally, increased TV viewing time or physical activity was also associated with individual components of the metabolic risk in both sexes. Recently, a Swedish study by Halldin et al. [34] included 3 864 60-year-old men and women in the Stockholm region. The results showed that, compared with the low physical activity group, the odds ratios for having the metabolic syndrome in the high physical activity groups (i.e. intensive regular activity more than 2 times/week, at least 30 min each time) was 0.33 (0.22-0.51) after adjustment for covariates.

Based on a nationally representative population-based sample of US adults aged 20 years and older from the National Health and Nutrition Examination Survey (NHANES), several studies have utilized the NHANES to explore the relationship between leisure-time physical activity and metabolic syndrome. However, the results are inconsistent. Park et al. [35] used a physical activity intensity score to examine the association between physical activity and metabolic syndrome. The score was calculated as a dichotomized variable based on the frequency and intensity of leisure-time physical activity. Participants with the total density rating score > 3.5 were active and those with a total density rating score of ≤ 3.5 were inactive. When compared to the active group, the odds ratios for having the metabolic syndrome were significantly higher (OR = 1.4, 95% CI = 1.0–2.0) among inactive men, but not among inactive women. Similar findings have been reported by Zhu et al. [20], although these participants were grouped into 3 categories: active (score > 15.0), moderately activity (score > 3.6 to 14.9) and inactive (≤ 3.5). Men with the active group were found to be 42% less likely (OR = 0.58, 95% CI = 0.39–0.85) to have the metabolic syndrome compared to those with the inactive group, even after controlling for age, race, education, income levels, and other modifiable factors. In women, the association disappeared after adjusting for the confounders. These finding were also supported by a study reported by DuBose et al. [36]. Leisure-time physical activity was classified as regularly active (≥ 5 d/wk moderate- and/or ≥ 3 d/wk vigorous-intensity physical activity), irregularly active (some physical activity), and inactive (no physical activity). Regularly active represented that the participants met the recommendations of the Centres for Disease Control and Prevention and the American College of Sports Medicine [37]. The results indicated that the odd ratios for having the metabolic syndrome were only higher in men with the irregular activity (OR = 1.52, 95% CI = 1.11–1.23) and inactivity (OR = 1.60, 95% CI = 1.18–1.98) groups than those with the regularly active group after adjustment for age, race, smoking status, and educational attainment.

However, to continue to expand this field, the duration of physical activity, in addition to the frequency and intensity of physical activity, is required to examine a more precise measure of physical activity dose. In the study of examining the interaction between time spent in physical activity and sedentary behaviour on the metabolic syndrome [38], participants were asked about their moderate/vigorous intensity physical activity patterns and moderate intensity household activity, designating these activities in minutes per week (min/wk^{-1}) based on frequency, duration, and intensity of each activity. These participants were then grouped into three categories: 0, < 150, and ≥150 min/wk^{-1} of moderate/vigorous physical activity. However, after adjustment for covariates, the cross-sectional association between physical activity and metabolic syndrome was attenuated for both sexes. In a recent study [39], leisure-time physical activity was measured in two ways: (1) a six-level measure based upon participants reporting no physical activity and quintiles of physical activity (0, >

0 to ≤156.24, >156.24 to ≤393.10, >393.10 to ≤736.55, >736.55 to ≤1360.15, and >1360.15 MET·min·wk-1) based on the compendium of physical activities for adults [40,41] and (2) a three level categorical measure (inactive, insufficiently active, and met physical activity recommendation) based on the recent physical activity public health recommendation of the American College of Sports Medicine/American Heart Association (ACSM/AHA) [42]. When compared to the no physical activity group, adults with physical activity between 736 and 1360 MET·min·wk-1 were found to be 35% less likely (OR= 0.65, 95% CI = 0.48–0.88) to have the metabolic syndrome using the National Cholesterol education Program-Adult Treatment Panel III criteria, while adults with physical activity between 393–737 MET·min·wk-1 were found to be 30% less likely (OR = 0.70, 95% CI = 0.51–0.96) to have the metabolic syndrome using the World Health Organization criteria. Additionally, adults with physical activity met the ACSM/AHA guidelines were found to be 45% (OR = 0.54, 95% CI = 0.44–0.66 for the World Health Organization criteria) and 39% (OR = 0.61, 95% CI = 0.48–0.77 for the American College of Endocrinology/American Association of Clinical Endocrinologists criteria) less likely to have the metabolic syndrome compared with those who were inactive. In addition, cardiorespiratory fitness was first measured by using a submaximal treadmill test in both healthy men (n = 692) and women (n = 608) aged 18–49 years in the 1999-2002 NHANES [43]. Participants were divided into low, moderate, and high fitness tertiles based on the age-adjusted VO_{2max} values. It was showed that the odds ratios for having the metabolic syndrome in men but not women were significantly lower in moderate and high fitness categories compared with the low fitness category, after controlling for confounding variables such as age, ethnicity, poverty-income ratio, alcohol consumption, smoking and fat consumption. These inconsistent findings may be caused by different assessments of physical activity and fitness and different criteria of metabolic syndrome in different age and samples. Also, it remains unknown whether menopausal or hormonal status in women contributes to this observation.

Only two studies have addressed the relationship between muscle strength and metabolic syndrome in adult men. An American study followed 8 570 men aged 20–75 years from 1981 to 1989 [44]. Muscular strength score was computed by combining body weight-adjusted one-repetition maximal measures for leg and bench presses and then divided into strength quartile (Q) from Q1 (low strength) to Q4 (high strength). Men with high levels of muscular strength were found to be less likely to have the metabolic syndrome than those with low strength after adjusting for age and smoking. Similar results were found in an average of 6.7 years follow-up study by Jurca et al. [45]. They stated that men with more muscular strength were also less likely to develop the metabolic syndrome, even after adjusting for smoking, alcohol intake, number of baseline metabolic syndrome risk factors, family history of diabetes, hypertension, and premature coronary disease. However, these associations were partially explained by cardiorespiratory fitness. To our knowledge, only one study has explored the combined effects of muscular strength and aerobic fitness on the metabolic syndrome in both Flemish adult men (n =571) and women (n = 448) aged 18–75 years [46]. Muscular strength was evaluated by measuring isometric knee extension and flexion peak torque, using a Biodex System Pro 3 dynamometer. The relationship between muscular strength, aerobic fitness and the metabolic syndrome score was analyzed as continuous variables using a multiple linear regression. The risk of metabolic syndrome was inversely associated with muscular strength, independently of aerobic fitness and other confounding factors in women, whereas the association was attenuated when controlling for aerobic

fitness in men. Thus, strength training in addition to aerobic exercise may provide additional effects in reducing the prevalence of metabolic syndrome, particularly for women. These findings are inconsistent that may be partially explained by socio-cultural differences of the samples and the methodological issues including different measures, methods of analysis and sample size.

In summary, these findings imply that leisure-time physical activity, cardiorespiratory fitness and muscular strength may be an important determinant of the overall prevalence of metabolic syndrome independent of several other confounding factors. Accumulating evidence suggests that regular physical activity which increases aerobic capacity and cardiovascular fitness and maintain muscular strength has a beneficial effect on the metabolic syndrome. However, the relationship between physical activity and metabolic syndrome is still somewhat controversial, particularly for women. Such studies have varied in assessments of physical activity (subjective vs. objective), cardiorespiratory fitness (ergometer cycle vs. treadmill tests) and muscular strength (1-repetition maximum vs. isometric dynamometry), as well as criteria or risks to define the metabolic syndrome. In addition, the cross-sectional nature of most of these studies does not allow inference of causality. Further studies examining sex differences in the relation between physical activity and metabolic syndrome that address confounding factors such as menopausal status and concurrent medical conditions are needed. A longitudinal study design is also needed to examine the causal relationship between physical activity and metabolic syndrome.

4. Effect of physical activity and fitness on metabolic syndrome in children and adolescents

The beneficial effect of leisure-time physical activity on the metabolic syndrome in children and adolescents has been assessed within the contemporary reviews [47–50]. Froberg and Andersen [47] have authored a review on the linking physical inactivity and low fitness to metabolic disorders including CVD risk factors and obesity in European children. The authors concluded that there was only weak evidence of the association between physical activity or physical fitness and CVD risk factors in children when risk factors were analyzed isolated, but the clustering of risk factors was strongly associated with low physical activity or physical fitness among children. They also stated that participation in regular physical activity was one of the key determinants of lifestyle-related health. Furthermore, the relationship between aerobic fitness, fatness and the metabolic syndrome in children and adolescents was reviewed [48]. It was concluded that the relationship between fatness and the metabolic syndrome remained significant after controlling for fitness, whereas the relationship between fitness and metabolic syndrome disappeared after controlling for fatness. The author also reviewed four studies [51–54] of the combined influence of fatness and fitness on the metabolic syndrome and concluded that fitness attenuated the metabolic syndrome score among fat children and adolescents when they were cross-tabulated into categories (fat-fit, etc.), it might be possible to involve genetics, adipocytokines and mitochondrial function.

A recent review by Steele et al. [49], outlined the evidence from 6 studies [55–60] on objectively measured physical activity (i.e. accelerometer) and 11 studies [51–54, 59–65] on cardiorespiratory fitness, identifying the influence of physical activity and fitness on the clustered metabolic risk in youth. They concluded that physical activity and fitness were separately and independently related to metabolic risk factors in children and adolescents,

possibly through different causal pathways. Among more recent studies, findings have been mixed. In a population-based sample of 3 193 10- and 15-year-old youth from three European countries (Estonia, Denmark, and Portugal), Ekelund et al. [66] further found that both cardiorespiratory fitness (OR = 0.33, 95% CI = 0.15–0.75) and objectively measured physical activity (OR = 0.40, 95% CI = 0.18–0.88) were significantly and independently associated with being categorized as having the metabolic syndrome. Relatively small increases in physical activity might significantly reduce the risk of metabolic syndrome in healthy youth. Conversely, Martínez-Gómez et al. [67] did not find the same association between physical activity and metabolic syndrome in 202 adolescents (99 girls) aged 13-17 years after controlling for age, sex and maturation status, and suggested that cardiorespiratory fitness appeared to have a pivotal role in the metabolic syndrome and in the association of physical activity with the metabolic risk.

There were only few studies have reported on the effect of diet and physical activity on prevention of the metabolic syndrome in adolescents. For example, Pan and Pratt [68] investigated a sample of 4 450 US adolescents aged 12 to 19 years from the National Health and Nutrition Examination Survey 1999-2002. They reported that although there was not significant relationship between physical activity and the overall prevalence of metabolic syndrome, the differences in some metabolic syndrome components among groups were statistically significant. Adolescents with low physical activity had higher levels of triglycerides and blood pressure than those with moderate or high physical activity. In addition, the prevalence of metabolic syndrome was a 16-fold higher in overweight adolescents (BMI ≥ 95th percentile) compared with their normal weight peers (BMI ≤ 85th percentile). Higher overall healthy eating index and fruit scores were also associated with lower risk of the metabolic syndrome. The authors concluded that unhealthy lifestyle behaviours might be the major underlying cause for the metabolic syndrome in adolescents. The primary means for preventing the metabolic syndrome was needed to engage adolescents in regular physical activity and healthful dietary practices to prevent excessive weight gain.

However, these studies have not addressed issues specific to population subgroups or intervention-delivery modalities. In a very recent review of the literature on the relationship between physical activity and metabolic syndrome in youth, Brambilla et al. [50] provided an overview of 11 studies [69–79] on physical activity intervention, focusing on a subsample of obese youth and intervention modalities and concluded that the different physical activity programs, relatively short duration and small sample size of these studies likely contributed to the inconsistent results. Although there were some controversies regarding the risk of insulin resistance, fat mass and body mass index for certain subgroups of children and adolescents with obesity, regular vigorous intensity physical activity on blood pressure and lipid levels did much to alleviate concerns that physical activity programs could have positive effect in these metabolic risk parameters. Furthermore, the authors suggested that the effect of low-intensity physical activity (e.g., playing at home, walking to school, dancing, and downstairs) on the metabolic risk in a large sample of overweight and obese children and adolescents should be taken into consideration in future study.

To summarize, several studies have shown that metabolic risk factors are readily detectable in children and adolescents because obesity is closely associated with insulin resistance in youth. It seems that physical activity intervention strategies may be most effective in childhood and adolescence before the development of metabolic syndrome. The main question to be asked is whether the positive effects of physical activity seen in adults will

occur in children and adolescents. Most studies have found that objectively measured physical activity and cardiorespiratory fitness are inversely associated with clustered metabolic risk score in children and adolescents, while some have shown that physical activity in adolescents does not result in significantly reduce the prevalence of metabolic syndrome when cardiorespiratory fitness is adjusted for in the analysis. A question which remains unanswered, however, is how much physical activity is needed to prevent the metabolic syndrome and the diseases with which it is associated. Also, the clustered metabolic risk score has been applied in these studies, but no clear definition of the metabolic syndrome has been formally established for either children or adolescents. Attention to these questions with further research is needed.

5. Early physical activity and fitness as a predictor of metabolic syndrome in adulthood

The mechanism behind the relationship between physical activity in childhood and adolescence and adult risk for the metabolic syndrome has been explored. Referring to the model including three possible paths from childhood physical activity to adulthood health presented by Blair et al. [80], one of the hypothetical paths is a direct connection from physical activity or physical fitness in youth to cardiovascular and metabolic health in adult life. In the Cardiovascular Risk in Young Finns Study [19], 961 participants aged 12-18 years from five cities of Finland were included and followed from 1980 to 1983 and 1986. Physical activity was assessed with a standardized questionnaire and then summed a physical activity index from its intensity, frequency and duration. The results showed that the change in physical activity over 6 years was inversely associated with changes in insulin and triglycerides among boys. Among girls, the change in physical activity did not make any independent contribution to the models for serum lipoproteins. It was concluded that participation in regular leisure-time physical activity should be encouraged among adolescents in order to improve coronary risk profiles. Similar observations have been reported in other European studies. In the Amsterdam Growth and Health Study [81], 181 13-year-old Dutch adolescents were followed over a 15 years. The daily physical activity and fitness (both cardiopulmonary and neuromotor fitness) have been measured with six repeated times during the period. They found that daily physical activity was positively related to high-density lipoprotein cholesterol, and inversely to the total cholesterol/high-density lipoprotein ratio and to the sum of four skinfolds. Additionally, cardiopulmonary fitness was inversely associated with the total cholesterol. Neuromotor fitness was inversely associated with the sum of four skinfolds, and positively to systolic blood pressure. The authors stated that during adolescence and young adulthood both daily physical activity and fitness were related to a healthy coronary heart disease risk profile.

There are two recent studies for extending the Cardiovascular Risk in Young Finns Study. Yang et al. [82] followed 1 319 boys and girls (ages 9–18 years) from five Finnish university towns and their rural surroundings from 1980 to 2001. Leisure-time physical activity was assessed by a short self-report questionnaire. The results indicated that youth physical activity predicted adult physical activity in men (R^2 = 0.10) and women (R^2 = 0.03), which, in turn, predicted waist circumference in adulthood. Youth body mass index was directly related to waist circumference in adulthood in both sexes. The models were significant explaining 19% of variance of abdominal obesity in men and 13% in women. Also, youth physical activity was indirectly associated with waist circumference in adulthood through

both the maintenance of physical activity in adulthood and reducing body weight in youth. The path from youth physical activity to adult obesity through youth obesity seemed to be stronger than the path through adult physical activity. However, the level of youth physical activity did not predict adult abdominal obesity in either men or women (Figure 1). The authors concluded that the prevalence of abdominal obesity as defined by waist circumference during adulthood was directly related to adult physical activity and youth overall obesity in both sexes. Youth physical activity had an indirect effect on abdominal obesity through both the maintenance of physical activity in adulthood and reduction in body weight in youth. Participation in and maintaining physical activity from youth into adulthood might play an important role in reducing obesity in adulthood.

R² = 0.10 (0.03)

Youth physical activity → 0.32 (0.18) → Adult physical activity

Youth physical activity → -0.13 (-0.15) → Adult body mass index

Adult physical activity → -0.13 (-0.12) → Adult waist circumference

Adult body mass index → 0.40 (0.34) → Adult waist circumference

R² = 0.02 (0.02)   R² = 0.19 (0.13)
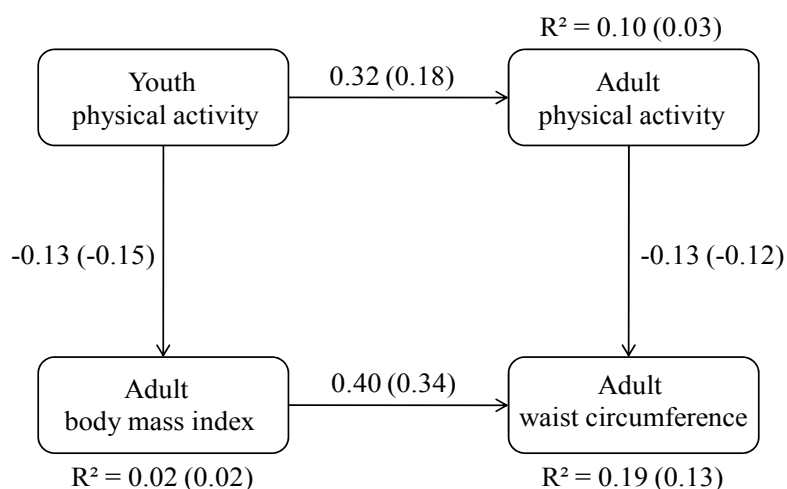
Fig. 1. Estimadtd parameters (stan dardized solution) in structural equation for males (females)

In another study by Yang et al. [83], 1 493 Finnish children and adolescents aged 3 to 18 years were followed over a 21-year period. Participation in sport-club training and competitions were assessed by use of a self-report physical activity questionnaire. Participants were divided into athletes and non-athletes at each measurement point (1980 and 1983), and then classified into four groups: persistent athlete, starter, leaver and non-athlete. A mean score of youth sport was assessed by calculating the average of four consecutive measurements (1980-1989). The metabolic syndrome in adulthood was defined as a categorical variable based on the guidelines of the European Group for the Study of Insulin resistance and as a continuous metabolic syndrome risk score by summing the z-scores of individual metabolic variables. The results indicated that the mean score of youth sport across the four time points and covariate variables were simultaneously entered as predictors for the adult metabolic syndrome risk score. Mean youth sport level emerged as a significant predictor of the metabolic syndrome in men (β = -0.149, P = 0.001) and women (β = -0.118, P = 0.005). Furthermore, non-athletic males and females had a significantly higher prevalence of the metabolic syndrome in adulthood than persistent athletes (Table 3). The relationships remained significant after adjustment for age and baseline clustered metabolic risk scores. The adds ratios and 95% confidence intervals for non-athletic males and females were 2.94 (1.01–8.99) and 4.04 (1.18–13.85), respectively. After additional adjustment for adult leisure-time physical activity, the trend of the associations was the same but

significant difference between persistent athletic and non-athletic males disappeared. Those males who dropped out from organized sport during the 3 years had higher prevalence of the metabolic syndrome compared with persistently athletic counterparts. The difference remained significant after adjustment for age, baseline clustered metabolic risk scores and adult leisure-time physical activity (OR = 4.52, 95% CI = 1.29–15.84).

The mechanisms explaining the relationship between sport participation in youth and the prevalence of metabolic syndrome in adulthood are not well understood. One of the more obvious explanations can be that youth sport may reduce the risk of metabolic syndrome in youth, which then tracks into adulthood. However, the explanation is not clear because adjustment for youth clustered metabolic risk does not change the result. In addition, sustained youth sport seems to predict low prevalence of the metabolic syndrome in adulthood 21 years later independently of adult physical activity. It is possible that participation in organized youth sport may establish lifelong habits for good health that in turn reduces risk for the metabolic syndrome. Participation in sustained youth sport may also lead to improved cardiovascular function and physical fitness that carries over into adulthood. Furthermore, children and adolescents who want to maintain their athletic abilities may have better awareness of other health related habits such as diet, smoking and sedentary lifestyle, all of which have been found to be related to risk for the metabolic syndrome. Finally, self-selection and genetic factors shall be taken into account as possible explanations for the direct relationship between youth sport and adult health. Thus, intensive and sustained participation in youth sport may benefit adult cardiovascular health and prevent the development of metabolic syndrome. Organizers of youth sport may have a significant impact on public health by paying attention to the factors that increase adherence in youth sport.

Group	Unadjusted OR (CI)		Adjusted OR (CI) [2]		Adjusted OR (CI) [3]	
Boys						
Persistent athlete	1.00		1.00		1.00	
Starter	1.62	0.45 – 5.80	1.49	0.39 – 5.71	1.55	0.41 – 5.85
Leaver	4.55	1.39 – 14.87*	4.70	1.31 – 16.91*	4.52	1.29 – 15.84*
Non-athlete	3.06	1.08 – 8.64*	2.94	1.01 – 8.99*	2.72	0.90 – 8.17
Girls						
Persistent athlete	1.00		1.00		1.00	
Starter	1.67	0.38 – 7.27	1.63	0.35 – 7.64	1.66	0.36 – 7.69
Leaver	2.24	0.60 – 8.35	1.98	0.47 – 8.30	1.57	0.38 – 6.44
Non-athlete	3.54	1.08 – 11.55*	4.04	1.18 – 13.85*	3.46	1.03 – 11.66*

[1] 3-year follow-up youth sport: persistently athlete (did between 1980 and 1983); starter (did not in 1980 but did in 1983); leaver (did in 1980 but did not in 1983); and non-athlete (did in neither 1980 nor 1983).
[2] Adjusted for baseline age, smoking, total caloric intake and baseline-clustered risk for metabolic syndrome.
[3] Additionally adjusted for adult leisure-time physical activity. * $p < 0.05$.

Table 3. Odds ratios for the prevalence of metabolic syndrome (European Group for the Study of Insulin Resistance) according to organized youth sport [1] over 3 years in boys and girls

Contrary to the expected beneficial effect, no association between the level of physical activity and the risk of metabolic syndrome was found. In the Leuven Longitudinal Study on Lifestyle, Fitness and Health [84], 166 Belgian adolescent boys aged 13–18 years were

followed over a 28-year period. Physical activity was assessed by means of a sports participation inventory in youth and the Tecumseh community health study questionnaire in adulthood. The results found that sports participation during adolescence was not related to levels of cardiovascular risk factors at 40 years of age. In the Danish Youth and Sport Study [85], 101 adolescents aged 15–19 years were followed over an 8-year period. Physical activity was assessed by a questionnaire including the number of hours per week of sports participation and physical education lessons. Physical fitness in terms of aerobic fitness was calculated as VO_{2max} relative to body weight (ml/min/kg). It was showed that the relationships between the absolute levels of physical fitness and activity in adolescence and the subsequent level of CVD risk factors were generally weak. However, the changes in physical fitness and physical activity were related to the absolute levels of CVD risk factors in young adulthood, especially in men. A subsequent study conducted by the same investigators [86] reported similar results when a physical activity index was constructed from the intensity and duration of the organized and unorganized sports activities. The results showed that the youth sports activities and fitness were not associated with clustered risk in adulthood. The lack of significant associations could be due to methodological limitations such as small samples and assessment of physical activity based on self-reported minutes spent on sports activities rather than objective measure to physical activity.

Moreover, future study is indicated in distinguishing between active and inactive on the adulthood risk of developing the metabolic syndrome. Future research is also need to develop and evaluate objective measures of physical activity (e.g., pedometers, accelerometers) in youth, define and measure the criteria of metabolic syndrome and clarify whether long-lasting changes in physical activity decrease the metabolic risk for different lifespan.

6. Effect of change in physical activity and fitness on metabolic syndrome in adulthood

According to the model [80], the most probable path is from childhood physical activity to adult physical activity and further to adult metabolic health. This supported by the studies on tracking of physical activity [87–90], and also studies on the relationship between physical activity and metabolic syndrome in either youth or adults as has just been mentioned above. Another potential path is physical activity in youth through youth clustered metabolic risk to adult metabolic syndrome. This path is supported by the finding that physical activity and physical fitness correlate negatively with the metabolic risk in youth [49]. Further, metabolic risk variables, especially obesity, likely track rather well from childhood to adulthood [82,91]. Only a few prospective population-based studies have reported long-term physical activity in predicting the prevalence of metabolic syndrome over time and especially of changes in physical activity in association with adulthood metabolic syndrome.

Laaksonen et al. [92] followed a cohort of 612 middle-aged men in the Kuopio Ischemic Heart Disease Risk Factor Study over a 4-year follow-up period. Leisure-time physical activity was measured by a questionnaire with the dose calculated as MET-minutes per week. Physical activity was then grouped into three levels: low-intensity (< 4.5 METs-min/wk), moderate- and high intensity (≥ 4.5 METs-min/wk) and high-intensity physical activity (≥ 7.5 METs-min/wk). Cardiorespiratory fitness (VO_{2max}, ml·kg^{-1}·min^{-1}) was divided into three levels: low (≤ 28.9), moderate (29.0–35.6) and high (≥ 35.7). Men with moderate and vigorous physical activity were significant lower prevalence of the metabolic syndrome than those with low physical activity. The odds ratios were 0.60 (0.37–0.99) for physical activity ≥ 4.5 METs (>3 h/wk vs. ≤60 min/wk) and 0.48 (0.29–0.77) for physical activity ≥ 7.5

METs after adjustment for major confounding variables (age, body mass index, smoking, alcohol, and socioeconomic status) or potentially mediating variables (insulin, glucose, lipids, and blood pressure), especially in high-risk men. Vigorous physical activity had an even stronger inverse association, particularly in unfit men. Men in the highest tertile of cardiorespiratory fitness were 75% less likely to develop the metabolic syndrome than men in the lowest tertile of cardiorespiratory fitness after adjustment for major confounders, but the association was attenuated after adjustment for possible mediating variables. it was included that physical activity and cardiorespiratory fitness predicted directly or indirectly the development of metabolic syndrome.

A randomized controlled trial was used to investigate the effectiveness of supervised aerobic exercise training in 105 participants with the metabolic syndrome before and after 20 weeks [93]. 30.5% (32 participants) of the participants were no longer classified as having the metabolic syndrome following exposure to a standardized 20-week exercise program. It was suggested that aerobic exercise training showed prolonged vigorous exercise programs and reduced substantially in those with the metabolic syndrome. Although limited by lack of a control group, this study supported that the effectiveness of aerobic exercise training could be useful as a treatment strategy in prevention of the metabolic syndrome. In their further study of the impact of cardiorespiratory fitness on the risk of metabolic syndrome, obesity and mortality among 19 173 American men aged 20–83 years, Katzmarzyk et al. [94] reported that the odds ratios and their 95% confidence intervals for having risks of all-cause mortality were 1.11 (0.75-1.17) in normal weight, 1.09 (0.82-1.47) in overweight, and 1.55 (1.14-2.11) in obese men with the metabolic syndrome, compared with normal weight healthy men. The corresponding risks for cardiovascular disease mortality were 2.06 (0.92-4.63) in normal weight, 1.80 (1.10-2.97) in overweight, and 2.83 (1.70-4.72) in obese men with the metabolic syndrome, compared with normal weight healthy men. However, the risks of all-cause mortality associated with obesity and metabolic syndrome were no longer significant after adjustment for cardiorespiratory fitness, which suggested that these risks were largely explained by overall physical fitness levels.

In the Medical Research Council Ely Study [95], 605 (249 males) middle-aged adults in England were followed over the past 5.6 years. Physical activity energy expenditure was measured objectively by individually calibrated heart rate against energy expenditure and was then divided into quartiles: < 44 kJ/kgFFM/d, 44-70 kJ/kgFFM/d, 71-100 kJ/kgFFM/d, and > 100 kJ/kgFFM/d. Aerobic fitness was predicted from a submaximal exercise stress test. Physical activity energy expenditure predicted progression toward the metabolic syndrome after adjusting for sex, baseline age, smoking, socioeconomic status, follow-up time, and baseline phenotypes. The associations remained significant after additional adjustment for aerobic fitness. While the relationship between aerobic fitness and metabolic syndrome was attenuated after adjusting for physical activity. In a cohort of the Oslo study, Holme et al. [96] followed 6 410 Norwegian middle-aged men from 1972/3 to 2000 in the city of Oslo. Leisure-time physical activity was measured by a questionnaire to classify men into four groups as follows: sedentary/light (usually reading, watching television or other sedentary occupations at leisure), moderate (walking, bicycling or other forms of physical activity including walking or bicycling to and from the place of work and a Sunday walk totalling at least four hours a week), moderately vigorous (exercise, sports, heavy gardening and similar activities totalling at least 4 hours a week), and vigorous (hard training or competition sports regularly several times a week). Physical activity was a significant predictor of the prevalence of metabolic syndrome (OR = 0.65, 95%CI = 0.54–0.80)

and diabetes (OR = 0.68, 95%CI = 0.52–0.91) over 28 years when adjusted for age and educational attendance. However, these associations were markedly attenuated when additional adjusted for baseline clustered metabolic risks.

Yang et al. [97] followed six cohorts of 2 060 (961 males) young adults aged 24–39 years in the Young Finns Study. Leisure-time physical activity was assessed using a self-report questionnaire completed in connection with a medical examination at two consecutive measurements in 1992 and 2001. By summing the physical activity items, a physical activity index was formed for both measurement points according to which the participants were divided into tracking groups: persistently active, increasingly active, decreasingly active, and persistently inactive. The prevalence of the metabolic syndrome on all three definitions was significantly lower in men and women who were persistently active during the 9 yr of follow-up compared with persistently inactive ones. In men, the odds ratios and their 95% confidence intervals were 0.23 (0.11–0.49) for the European Group for the Study of Insulin Resistance (EGIR) criteria, 0.54 (0.31–0.93) for the National Cholesterol Education Program-Adult Treatment Panel III (NCEP) criteria, and 0.49 (0.29–0.83) for the International Diabetes Federation (IDF) criteria. In women, the odds ratios were 0.33 (0.12–0.94) for EGIR, 0.21 (0.06–0.67) for NCEP, and 0.27 (0.11–0.63) for IDF. Also, women who were increasingly active were less likely on all definitions to have the metabolic syndrome than their persistently inactive counterparts. The associations remained significant for EGIR (OR = 0.28, 95% CI = 0.09–0.92), NCEP (OR = 0.22, 95% CI = 0.07–0.73), and IDF (OR = 0.42, 95% CI = 0.19–0.94). All of these associations remained significant after adjustment for potential confounders such as age, smoking and education (Table 4). The authors concluded that

Group	EGIR Adjusted OR (CI) [2]		NCEP-ATP III Adjusted OR (CI)		IDF Adjusted OR (CI)	
Men						
Persistently inactive	1.00		1.00		1.00	
Decreasingly active	0.69	0.41 – 1.15	0.99	0.62 – 1.57	1.07	0.69 – 1.65
Increasingly active	0.73	0.30 – 1.79	0.58	0.22 – 1.52	0.48	0.19 – 1.27
Persistently active	0.23	0.11 – 0.49***	0.54	0.31 – 0.93*	0.49	0.29 – 0.83**
Women						
Persistently inactive	1.00		1.00		1.00	
Decreasingly active	0.68	0.35 – 1.34	0.65	0.35 – 1.21	0.59	0.33 – 1.05
Increasingly active	0.28	0.09 – 0.92*	0.22	0.07 – 0.73*	0.42	0.19 – 0.94*
Persistently active	0.33	0.12 – 0.94*	0.21	0.06 – 0.67**	0.27	0.11 – 0.63**

EGIR, European Group for the Study of Insulin Resistance; NCEP-ATP III, National Cholesterol education Program-Adult Treatment Panel III; IDF, International Diabetes Federation.
[1]Physical activity groups: persistently inactive (inactive both in 1992 and 2001); decreasingly active (change 1992-2001 from active to inactive); increasingly active (change 1992-2001 from inactive to active); and persistently active (active both 1992 and 2001).
[2] Adjusted for age, smoking and education. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

Table 4. Adjusted odds ratios for three definitions of metabolic syndrome according to change in physical activity groups [1] over a 9-yr period

maintaining a high level of physical activity across the life span might decrease the prevalence of the metabolic syndrome not only in the short term but also in the long term. Individuals should be encouraged to participate in regular physical activity as early as possible to prevent the risk of developing the metabolic syndrome and related adult-onset diabetes and cardiovascular diseases.

7. Conclusion

Outlined in this chapter is a brief overview of leisure-time physical activity, cardiorespiratory fitness and muscular strength which focus is on prevention and intervention of the prevalence of the metabolic syndrome in youth and adulthood. In addition, there is a brief summarizes on maintaining regular physical activity and aerobic exercise over time focused on the metabolic syndrome in adulthood.

It is worth highlighting that regular leisure-time physical activity, endurance training, and strength training are critically important for prevention of the metabolic syndrome and its components in both early life and later life. Evidence is beginning to accumulate in the epidemiological literature which suggests that participation in regular aerobic and strength exercises, particularly when combined with moderate- or vigorous-intensity activity may alter all metabolic risk factors. Leisure-time physical activity is an effective intervention or modulation to improve cardiovascular functional capacity and prevent or delay the development of metabolic syndrome, which in turn maintains health status and reduces the incidence of diabetes and cardiovascular diseases. According to the recommendations of the American College of Sports medicine and the American Heart Association, all adults shall participate in accumulated moderate-intensity physical activity during leisure time for a minimum of 30 minutes or more on 5 days per week or vigorous intensity activity for a minimum of 20 minutes on 3 days per week [42]. It may be that the combination of reductions in energy intake and increases in energy expenditure, through structured exercise and other forms of physical activity, is one of the most effective way to prevent or delay the development of metabolic syndrome over time. This chapter focuses mainly on physical activity and aerobic exercise during leisure time related the prevalence of metabolic syndrome, however there is limited literature relating to specific sport activities, work-related physical activity, commuting physical activity and household physical activity. Emphasis will be placed on the impact of these activities in the future.

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9. References

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Part 2

Medical Issues in Sports Medicine

Effects of Exercise on the Airways

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1. Introduction

In the last ten years, the effects of exercise on bronchial epithelial cells and inflammatory cells in the airways have been studied in detail, and such new information has been combined with previous knowledge on bronchial reactivity and asthma evoked by exercise in asthmatic patients and athletes. The resulting picture is very complex, and the potential clinical consequences are often contradictory, suggesting the opportunity to define different phenotypes of exercise-associated airway changes (Lee & Anderson, 1985; Haahtela et al., 2008; Moreira et al., 2011a).

Studies in asthmatic athletes in the 90' had began to explore the possibility that airway inflammation might be involved in exercise-associated respiratory symptoms. However, studies in non-asthmatic athletes also found increased number of inflammatory cells not only at rest, but also after strenuous endurance exercise (Bonsignore et al., 2001). It was therefore hypothesized that endurance exercise may physiologically cause influx of inflammatory cells into the airways, associated with low or absent inflammatory activation (Bonsignore et al., 2003a). Subsequent studies in athletes and animal models have extended these finding, but the mechanisms of inflammatory cell recruitment into the airways and the tight control of inflammatory activation physiologically associated with exercise remain poorly understood.

Exercise is a known cause of bronchoconstriction in asthmatic patients (Cabral et al., 1999) and athletes (Parsons & Mastronarde, 2005). A large number of asthmatic elite athletes participate to international top-level competitions, and guidelines regarding management of asthmatic athletes (Fitch et al., 2008) and rules on the use of anti-asthmatic drugs have been issued (World Anti-Doping Agency, WADA, Oct. 18 2010 report). However, exercise is a powerful physiologic stimulus for bronchodilatation, and some reports underlined that exercise training may actually downmodulate bronchial reactivity in normal subjects (Scichilone et al., 2005, 2010), asthmatic children (Bonsignore et al., 2008) and animal models of asthma (Hewitt et al., 2010).

This chapter will summarize the changes induced by acute exercise and training in bronchial reactivity and airway cells in both humans and animal models. It will also discuss the changing paradigm regarding the impact of physical activity in patients with bronchial asthma, and the new perspectives of exercise-based rehabilitation in patients with respiratory diseases such as chronic obstructive pulmonary disease (COPD).

2. Exercise-induced bronchoconstriction

In patients with bronchial asthma, occurrence of bronchoconstriction and symptoms after exercise is common and has been known for a long time (Lee & Anderson, 1985; Cabral et al., 1999). Exercise-induced bronchoconstriction (EIB) is characterized by respiratory symptoms, such as wheezing and chest tightness, secondary to an acute, transient airway narrowing that typically occurs in the first 15-20 min after cessation of exercise. In some instances, a late-phase response also occurs 3 to 13 h after completing exercise (Freed, 1995; Speelberg et al., 1989). In asthmatic patients, exercise-induced symptoms are considered as clinically important indicators of insufficient asthma control, and suggest the opportunity to increase or change the medication regimen.

In the laboratory, EIB is defined as a decrease in forced expiratory volume of 1s (FEV_1) $\geq$ 10% from the baseline value after appropriate exercise provocation (Kyle et al., 1992). Exercise is the most common trigger of bronchospasm in those who are known to be asthmatic, and 50% to 90% of asthmatic individuals have airways that are hyperreactive to exercise (Rundell et al., 2002).

EIB also occurs in up to 10% of subjects who are not known to be atopic or asthmatic (Gotshall et al., 2002). Prevalence of EIB or exercise-induced symptoms in elite athletes is high (Parsons & Mastronarde, 2005; Turcotte et al., 2003), and asthma in athletes may develop according to different phenotypes, likely influenced by environmental exposures during exercise (Haahtela et al., 2008). Prevalence of asthma is high in athletes of winter sports and endurance sports such as swimming or running (Helenius & Haahtela, 2000; Karjalainen et al., 2000; Lumme et al., 2003; Langdeau et al., 2004; Durand et al., 2005; Vergès et al., 2005, Lund et al., 2009), even in subjects who do not report symptoms during childhood, atopy or a family history of asthma (Langdeau et al., 2004). On the other hand, exercise-induced symptoms are poor predictors of EIB (Parsons, 2009) since they are variably associated with objectively documented bronchial hyperreactivity to exercise (Sue-Chu et al., 1996; Rundell et al., 2001; Langdeau et al., 2000, 2004; Bougault et al., 2010). Finally, a gender effect has been recently underlined, with female athletes reporting more exercise-associated symptoms and showing a higher prevalence of bronchial hyperreactivity at rest compared to male athletes (Langdeau et al., 2009). Unfortunately, data on prevalence of EIB according to gender are not available, and more studies are necessary to ascertain whether exercise-associated bronchoconstriction is more common in women than in men, and the mechanism(s) responsible for such an effect.

2.1 Pathophysiology of EIB: Main theories

While bronchial asthma is known to be associated with a complex inflammatory picture at the airway level usually triggered by exposure to allergens or exercise, EIB in otherwise healthy subjects is difficult to explain. To this aim, two theories have been proposed, based

on the possibility of post-exercise engorgement of bronchial vessels with decreased bronchial luminal area (the vasomotor hypothesis) and the hypothesis of insufficient conditioning of inspired air (the hyperosmolar theory).

The vasomotor hypothesis proposed that cooling of the airways followed by rapid re-warming may cause vasocostriction followed by reactive hyperemia of the bronchial microcirculation, together with edema of the airway wall (McFadden, 1990). Nevertheless, neither airway cooling or re-warming appear necessary for EIB to occur (Lee & Anderson, 1985; Anderson & Daviskas, 1992; Anderson & Daviskas, 2000; Anderson & Kippelen, 2008).

The main theory on EIB pathophysiology is that exercise hyperventilation causes drying of the airways, thus increasing osmolarity of the airway surface lining fluid (Anderson et al., 1989; Boulet & Turcotte, 1991; Anderson & Daviskas, 1992, 2000; Freed, 1995; Anderson & Kippelen, 2008). As water evaporates, the airway surface liquid becomes hyperosmolar and provides an osmotic stimulus for water to move from any cell nearby, resulting in cell volume loss. Therefore, the change in regulatory volume after cell shrinkage is believed to be the key event, which results in release of inflammatory mediators that cause airway smooth muscle to contract and the airways to narrow (Anderson & Daviskas, 2000). It has been calculated that severe hyperosmolarity can occur in the airways during intense exercise (Anderson & Daviskas, 1992), and clinical tests based on hyperosmolar stimulation, such as eucapnic voluntary hyperventilation (EVH) (Anderson et al., 2001) or mannitol inhalation (Holzer et al., 2003; Anderson et al., 2009), are widely used, instead of exercise provocation tests, to assess the predisposition to develop EIB in the laboratory.

Both hyperosmolarity and vasomotor changes might be involved in the pathogenesis of EIB in asthmatic patients (Kanazawa et al., 2002). Bronchial epithelial cells *in vitro* release IL-8 upon stimulation with either hyperosmolar solutions or cooling-rewarming, indicating that the proposed mechanisms are capable of activating the bronchial epithelium (Hashimoto et al., 1999). In addition, corticosteroids have been shown to inhibit the activation of bronchial epithelial cells caused by hyperosmolar exposure (Hashimoto et al., 2000).

2.2 EIB in athletes of different sports

In athletes involved in winter sports, EIB is especially frequent (Durand et al, 1995; Provost-Craig et al., 1996, Lumme et al., 2003) and a specific clinical picture has been described in cross-country skiers ("ski asthma"). Similar to other athletes, elite cross-country skiers show a high prevalence of exercise-induced respiratory symptoms, which however resulted poorly correlated with the degree of bronchial hyperresponsiveness (Durand et al., 2005; Stenfors, 2010). Ski asthma shows some peculiar features, such as evidence of airway remodelling and inflammation (Sue-Chu et al., 1999; Karjalainen et al, 2000), lymphoid aggregates in endobronchial biopsies (Sue-Chu et al., 1998), and lack of clinically significant response to corticosteroids (Sue-Chu et al., 2000).

Summer sports can also be associated with asthma and EIB, possibly because of increased allergen exposure during outdoor activities (Helenius & Haahtela, 2000). Asthma and EIB show the highest frequency among adult elite swimmers, possibly due to the prolonged exposure to the irritant effects of chlorine in indoor swimming pools (Helenius et al, 1998a; Langdeau et al, 2000). A role of swimming on bronchial reactivity and airway inflammation

is confirmed by reversibility of such changes upon cessation of intense training in adult athletes (Helenius et al., 2002; Bougault et al., 2011). In young swimmers, the relevance of exposure to chlorine-derived products in causing pathological airway changes has been recently questioned (Pedersen et al., 2008; Font-Ribera et al., 2011; Piacentini et al., 2011). Nevertheless, the increasing popularity of swimming suggests the opportunity to further assess the potential detrimental effect of exposure to chlorine associated with swimming, especially at young age (Bernard et al., 2008, 2009, 2011; Voisin et al., 2010).

2.3 Do acute exercise and training decrease bronchial reactivity?

Exercise is a very powerful bronchodilator stimulus, in both normal subjects and asthmatic patients. Even symptomatic patients with insufficiently controlled mild or moderate asthma showed bronchodilatation during acute incremental exercise, with preserved maximal ventilation and oxygen consumption (Crimi et al., 2002). The effects of acute incremental exercise were about 60% of the maximal bronchodilatation obtained after inhalation of albuterol (Milanese et al., 2009). The response to bronchoconstrictor agents in asthmatic patients was also lower during submaximal exercise compared to resting conditions (Stirling et al., 1983; Inman et al., 1990). The effects of constant-load submaximal exercise are somewhat controversial, since some studies reported persistent bronchodilatation in asthmatics (Mansfield et al., 1979; Inman et al, 1990), while others found that initial bronchodilation was followed by progressive bronchoconstriction during exercise in adult asthmatic patients (Milanese et al., 2009). Finally, eucapnic voluntary hyperventilation, mimicking the ventilation profile observed during exercise in asthmatic patients, was associated with bronchodilatation (Stirling et al., 1983; Gelb et al., 1985), while sympathoadrenal activation did not appear to play a major role (Gilbert et al., 1988; Hulks et al, 1991). Therefore, during acute exercise, the behaviour of airways appears quite similar in asthmatic patients and normal subjects.

Recent data indicate that intensive physical training may profoundly affect the airways and could decrease airways responsiveness (Scichilone et al., 2005). The intricate mechanisms underlying the pathophysiology of increased airway responses to inhaled broncoconstrictors, and the impact of physical activity on the occurrence and/or worsening of bronchial hyperreactivity, imply that research should first focus on interventions in healthy, non-asthmatic subjects. Therefore, we tested whether bronchial reactivity at rest differed between trained non-asthmatic amateur athletes and sedentary non-asthmatic controls, and found that the airway response to a spasmogen was lower in amateur runners than in sedentary individuals (Scichilone et al., 2005). Moreover, the "airway hyporesponsiveness" state of the athletes became more pronounced immediately after a competitive marathon.

This phenomenon can be explained by airway smooth muscle alterations induced by habitual heavy exercise. We speculated that the increased frequency of airway stretch that occurs with exercise hyperpnea could change the plasticity of airway smooth muscle cytoskeleton (Gunst & Tang, 2000; Gunst & Wu, 2001) or the myosin-actin interactions (Fredberg et al., 1996; Fredberg et al., 1997), enabling the smooth muscle fibers to become more resistant to spasmogens. Reorganization of the contractile apparatus of the airway smooth muscle may take place with habitual endurance exercise, thus enabling the smooth muscle fibers to adapt to changes in cell shape. Although we favour the mechanical explanation, other mechanisms, such as changes in the neural and/or biochemical control of the airways induced by physical training, may also contribute (Moreira et al., 2011a).
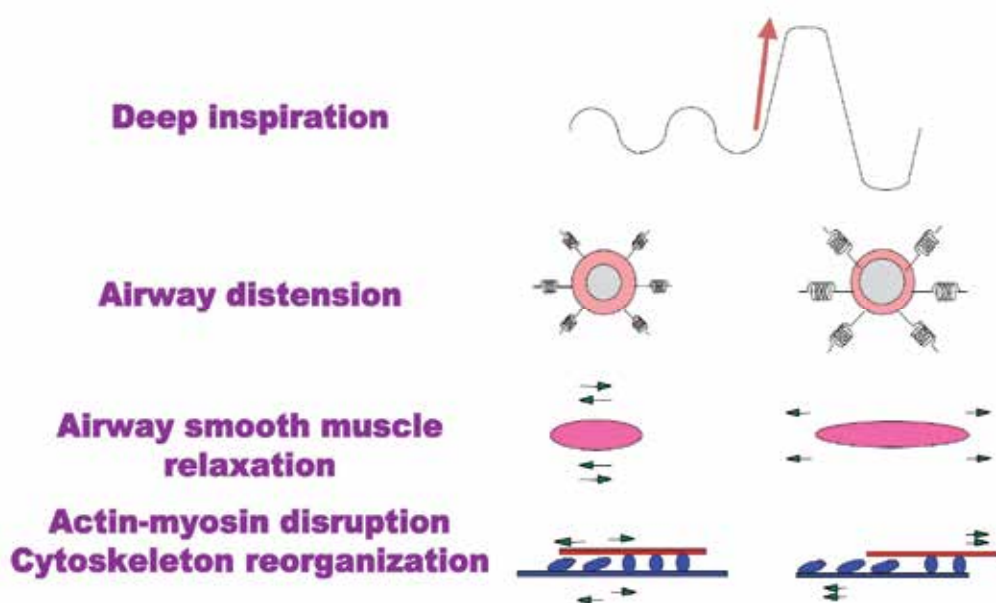
Fig. 1. Cascade of events that likely contribute to reduce airway smooth muscle contractility during lung inflation

In this scenario, development of asthma in atopic individuals could be in part secondary to lack of exercise and a sedentary lifestyle. In the European Community Respiratory Health Survey (ECRHS) II study, both frequency and duration of physical activity, as assessed by questionnaires, were inversely related to bronchial reactivity in a large population cohort independent of other variables (Shaaban et al., 2007). In a cohort of 411 Danish children born to mothers with asthma and closely monitored for occurrence of symptoms suggestive of asthma, the amount of habitual physical activity correlated inversely with occurrence of bronchial reactivity (Brasholt et al., 2010). These epidemiological data suggest that increased prevalence of asthma could be a consequence of changes in lifestyle related to physical activity and dietary habits, as confirmed by the increased prevalence of obesity worldwide, also at young age. In addition, a large longitudinal study recently found a decreased risk of asthma exacerbations associated with regular physical activity in older women (Garcia-Aymerich et al., 2009), suggesting that exercise may positively affect asthma control.

2.3.1 Results of methacholine tests in the absence of deep breaths in sedentary subjects and nonasthmatic athletes

Altered airway responsiveness in asthmatics has been primarily attributed to enhanced shortening ability of the airway smooth muscle. However, a wealth of evidence has accumulated to support the concept that factors other than smooth muscle reactivity are implicated in the overall response to a spasmogen. Indeed, changes in breathing pattern can modulate the response to bronchoconstrictor stimulation in healthy subjects, since the response to methacholine becomes almost indistinguishable from that of asthmatics when only shallow breaths are allowed (Skloot et al., 1995). Thus, excessive airway narrowing

likely results from an imbalance of opposing factors: on one hand, the forces generated by airway smooth muscle contraction; on the other hand, the effects of increased lung volumes, which may mechanically counteract smooth muscle shortening (Macklem, 1989).

Deep inspirations have been demonstrated to play a central role in opposing to airway narrowing, in that they are able to prevent bronchoconstriction in nonasthmatic subjects (Kapsali et al., 2000). Interestingly, such physiological function of lung inflation fails to occur in subjects who have airways hyperresponsiveness. In addition, deep inspirations can also reverse bronchoconstriction in both healthy subjects and patients with mild asthma (Scichilone et al., 2001); this phenomenon tends to decrease with increasing severity of asthma (Scichilone et al., 2007). Taken together, these observations imply that at least three factors are involved in the hyperreactive phenotype: the smooth muscle contractile properties and the bronchoprotective and bronchodilatory effects of deep inspirations.

We reasoned that by avoiding any effect of deep inspiratory maneuver thoroughout a bronchoprovocation protocol, the "true" smooth muscle reactivity could be assessed. Our group applied a single dose methacholine bronchoprovocation test to specifically study the response to spasmogen in the absence of large lung inflations (Scichilone et al., 2001). This modified bronchoprovocation challenge is more sensitive than the conventional challenge with incremental methacholine doses, as it causes substantial bronchoconstriction even in healthy individuals. In such protocol, the response to methacholine can be evaluated based on the dose of spasmogen inhaled, and the degree of bronchoconstriction obtained.

Nonasthmatic amateur runners responded less to methacholine in the absence of deep inspirations (higher amount of methacholine and lower degree of bronchial obstruction) than age-matched sedentary subjects (Scichilone et al., 2005). These findings suggest that smooth muscle of the athletes underwent exercise-induced structural changes, thus becoming more resistant to the effect of a bronchial spasmogen (bronchoprotective effect). The decreased reactivity in the athletes did not appear to depend on higher lung volumes at baseline compared to sedentary subjects (Scichilone et al., 2005). Deep inspiration may also exert a stronger bronchodilatory effect in athletes compared to the sedentary controls, but this hypothesis has not been tested yet.

Following this cross-sectional study, we longitudinally tested the effects of training in a group of healthy sedentary subjects undergoing intensive rowing training for 3 months. A significant reduction in the degree of bronchial reactivity in the absence of deep breaths was recorded during and at the end of the study (Scichilone et al., 2010). This observation shed new light in the field of bronchial hyperreactivity, since it indicates a significant effect of regular intensive exercise. Interestingly, Hewitt and colleagues recently reported that repeated bouts of moderate-intensity aerobic exercise (Hewitt et al., 2010), but not acute exercise (Hewitt et al., 2009), improved bronchial reactivity in OVA-treated mice. In amateur endurance athletes training in the Mediterranean area, no evidence was found for increased prevalence of EIB, suggesting that moderate intensity training does not worsen respiratory health (Kippelen et al., 2004). Therefore, moderate physical training could become a new, still relatively unexplored, management tool in asthma. In addition, given the potential to affect the progression of asymptomatic bronchial reactivity to asthma, we could conclude as stated in the editorial from Chapman and colleagues in 2010: "*the next time a physician hands an asthmatic patient a prescription and exclaims "take two at a time", the response may be – "do you mean pills or stairs?"* (Chapman et al., 2010).

2.3.2 Experimental data on the effects of deep inspirations on airway smooth muscle

Airway smooth muscle is subjected to mechanical strain associated with tidal breathing, and more so when deep inspirations take place. In 1995, it was shown that the active force generated by the airway smooth muscle decreases with increasing the amplitude of stretch (Pratusevich et al., 1995). In another *in vitro* study (Gump et al., 2001), a 3% increase of muscle length reduced force generation by 50%, which was comparable to the effect of isoproterenol treatment. *In vitro* experiments also showed that the magnitude of force generation of the airway smooth muscle decreases in parallel with increasing amplitude and duration of length oscillations applied to the relaxed muscle.

After a deep inspiration, the smooth muscle is believed to increase its length by 12% from its baseline value, and greater values can be reached during exercise (Fredberg et al., 1997). Bridge dynamic disruption (Fredberg et al., 1996, Fredberg et al., 1997) and plastic reorganization of the cytoskeleton (Gunst & Wu, 2001) both of which can lead to a state of lower airway smooth muscle contractility, have been advocated to explain the effect of lung inflation on airways. Kuo and colleagues showed that the density of thick myosin filaments decreases with varying the length of the airway smooth muscle (Kuo et al., 2001).

Prolonged changes in the contractile function of airway smooth muscle have been shown after long-term alterations in smooth muscle resting length. Chest strapping to maintain low end-expiratory lung volume in sheep increased airway smooth muscle contractility (McClean et al., 2003), while prolonged application of continuous positive airway pressure, which increased end-expiratory volume, decreased airway smooth muscle contractility in ferrets (Xue et al., 2008).

In summary, there is growing evidence indicating a major effect of deep inspiration in modulating airway smooth muscle cell reactivity. Habitual exercise training, with repeated intense hyperpnea, may be an important factor in regulation of bronchial reactivity in healthy and asthmatic subjects. More studies, however, are needed to extend the available results and identify optimal frequency and intensity of training to evoke positive changes in bronchial reactivity in humans.

3. Exercise-induced changes in airway cells

Exercise–induced changes in airways cells were initially studied in relation to occurrence of EIB. It was hypothesized that, similar to bronchial asthma, subjects developing EIB after intense exercise might also show a background of inflammatory activation in their airways.

In asthmatic patients, occurrence of EIB was found to be associated with intense eosinophilic inflammation (Yoshikawa et al., 1998). Asthmatic patients with EIB showed increased bronchial epithelial cells and eosinophil counts, as well as increased histamine, cysteinyl-leukotrienes and tryptase, and decreased prostaglandin E2 (PGE2) and thromboxane B2 in induced sputum after exercise challenge (Hallstrand et al., 2005a, 2005b). Leukotrienes are believed to be major players in EIB and asthma (Hallstrand et al., 2010), and increased leukotriene concentrations have been reported in exhaled breath condensate in asthmatic children with EIB (Carraro et al., 2005). A role for oxidative stress was also suggested by increased 8-isoprostane levels in exhaled breath condensate collected in asthmatic children developing EIB (Barreto et al., 2009). For further information, the reader is referred to a comprehensive review on EIB in asthmatic patients (Brannan & Turton, 2010). Finally, recent data suggest a relationship between neutrophilic inflammation and airway dehydration in asthmatics (Loughlin et al., 2010), indicating that asthma and EIB may share the common

pathophysiological mechanism of airway drying and hyperosmolarity. However, more studies are needed to confirm this hypothesis.

Studies in athletes found that changes in airways cells are common and occur independent of exercise-associated symptoms or spirometric changes. Increasing evidence suggest that habitual training is associated with airway inflammation in athletes of different endurance sports performed in cold or temperate environments (Bonsignore et al 2001, 2003b; Karjalainen et al., 2000; Sue-Chu et al., 1999; Lumme et al. 2003; Morici et al., 2004). However, the degree and type of airway inflammation under resting conditions is variable in athletes who perform different sports, and the role of inflammatory cells in the airways is currently unclear. Furthermore, airway inflammation in endurance athletes shows some peculiarities, since it may not be associated with bronchial hyperreactivity, post-exercise respiratory symptoms (Karjalainen et al., 2000; Bonsignore et al., 2001) or clear evidence of cell activation after acute exercise in humans or mice (Bonsignore 2001, 2003b; Morici et al., 2004; Hewitt et al., 2008) or after training in animal models (Chimenti et al. 2007, 2009; Silva et al., 2010; Vieira et al., 2007, 2011).

3.1 Studies in human athletes

Airway inflammation has been well characterized in athletes who exercise in a very cold environment (e.g skaters, ice hockey players, cross-country skiers) (Provost-Craig et al., 1996 ; Karjalainen et al., 2000, Lumme et al., 2003; Bougault et al., 2009). In cross-country skiers studied at rest, lymphocytes were increased in bronchoalveolar lavage fluid (Karjalainen et al., 2000), and endobronchial biopsies of proximal airways showed increased lymphocytes, but also neutrophils and eosinophils and evidence of airway remodelling, i.e. increased tenascin expression in the basement membrane (Sue-Chu et al., 1999). Skiers showed neutrophil infiltration, and relatively mild infiltration with eosinophils, mast cells, and macrophages. These results suggested that the inflammatory process in these athletes is different from classic asthma. Moreover, bronchial biopsy findings did not correlate with bronchial reactivity, atopy, or symptoms of asthma (Sue-Chu et al., 1999). Ice hockey players also showed increased neutrophil and eosinophil counts in induced sputum (Lumme et al., 2003). All these data were obtained in athletes under resting conditions, and the effects of acute exercise on airway cells in skiers have not been assessed, at least in part because of the objective environmental difficulties in collecting samples in these athletes.

Airway inflammation has been found in endurance athletes who perform sports in a temperate climate. In non-asthmatic amateur runners, neutrophil counts in induced sputum were increased after a marathon race compared to baseline level (Bonsignore et al, 2001); under resting conditions, the percentage of neutrophils in induced sputum of runners was higher than in sedentary controls, suggesting a chronic increase in neutrophils in the airways possibly related to habitual training (Bonsignore et al, 2001; Kippelen et al., 2004; Denguezli et al., 2008; Bougault et al., 2009). More recently, increased bronchial epithelial cell counts and interleukin-8 concentration, and apoptosis of bronchial epithelial cells, were found in induced sputum collected in nonasthmatic runners shortly after a half-marathon race, while neutrophil absolute counts were unchanged (Chimenti et al., 2010). Induced sputum samples collected the morning after a half-marathon race showed a slight increase in neutrophils compared to resting conditions (Chimenti et al., 2009). Increased bronchial

epithelial cell counts were also reported in induced sputum of elite swimmers collected at rest (Bougault et al. 2009).

These data suggest that neutrophil influx into the airways might be secondary to mild bronchial epithelial damage caused by intense exercise, but requires some time to occur. Similar to runners, well-trained young competitive rowers with normal bronchial reactivity to methacholine showed predominance of neutrophils in induced sputum both at rest and after exercise, and increased bronchial epithelial cell counts in induced sputum collected after a short bout of very intense exercise (Morici et al., 2004; Bonsignore et al, unpublished observations). Therefore, studies on the effects of exercise should take into account both the duration and the intensity of exercise; in addition, the time course of airway cell changes is likely to be complex, explaining some discrepancies between results of different studies.

The inflammatory pattern found in swimmers is very complex, as recently underlined (Haahtela et al., 2008), and different phenotypes of asthma in swimmers likely exist. On one hand, swimming is traditionally considered as a good type of physical activity for asthmatic patients, since it is associated with low allergen exposure. On the other hand, data in elite swimmers do suggest an important pro-inflammatory role played by environmental exposure to chlorine-derived compounds. Some time, however, might be required for airway cell changes to develop, as suggested by the negative results recently found in adolescent elite swimmers (Pedersen et al., 2008). Adult elite swimmers at rest, about half of them hyperreactive to methacholine, showed more eosinophils and neutrophils in induced sputum than sedentary subjects, with some evidence of inflammatory activation (Helenius et al., 1998a). Airway inflammation increased at 5-year follow-up in swimmers who continued training, but decreased in swimmers who had stopped competitive activity (Helenius et al., 2002). In adult non-asthmatic swimmers habitually training in an outdoor pool, airway neutrophil differential counts at baseline were higher than in sedentary controls but cell counts did not change significantly after a 5-km trial (Bonsignore et al., 2003b). After a 5-km competition in the sea, a condition of potential hypertonic airway exposure during exercise, the same swimmers showed slightly increased eosinophil and lymphocyte differential counts in induced sputum (Bonsignore et al., 2003b). These results suggested that the effects of chlorine exposure might be limited in athletes training in outdoor swimming pools; however, a study in adolescents swimmers attending outdoor pools confirmed an elevated risk of asthma also in this population (Bernard et al., 2008). More recently, asthmatic and nonasthmatic swimmers showed increased neutrophil counts in induced sputum, which correlated with increased airway vascular permeability assessed as the ratio of albumin in sputum and serum (Moreira et al., 2011b). Conversely, other studies found increased airway neutrophils only in swimmers who were hyperreactive to methacholine (Boulet et al., 2005; Belda et al., 2008, Bougault et al., 2009). Finally, a mixed type of inflammation, with increased eosinophil and neutrophil counts in induced sputum at rest, was reported in elite swimmers who showed hyperreactivity to methacholine (Moreira et al., 2008).

To our knowledge, only one study assessed airway cells in non-asthmatic athletes experiencing EIB (Parsons et al., 2008). The study shows some methodological limitations, such as EIB assessment only as response to eucapnic voluntary hyperventilation, and lack of baseline induced sputum samples. This study reported increased inflammatory mediators in

EIB+ athletes. However, airway cell counts were similar in EIB+ and EIB- athletes and did not correlate with concentration of mediators in sputum supernatants (Parsons et al., 2008). Our study on the effects of training in non-asthmatic subjects found that changes in airway cells and in the response to methacholine in the absence of deep inhalations showed different time courses (Scichilone et al., 2010). The picture can be further complicated by interactions between airway epithelial cells and smooth muscle cells, as suggested by a study showing that hyperosmotic stimuli induce epithelial dependent relaxation in the guinea pig trachea *in vitro* (Munakata et al., 1988). Therefore, further studies are needed to better characterize the role of airway epithelium in airway inflammation and its relationship with occurrence of EIB.

3.2 Studies in animal models and cultured bronchial epithelial cells

The functional and cellular events triggered by exercise hyperventilation have been studied in animal models, confirming that bronchial epithelial cells likely play an important role in exercise-induced airway changes. Besides functioning as a barrier against environmental toxins and injury, bronchial epithelial cells may modulate the immune response. In addition, in the long term, epithelial damage may favour sensitization to allergens, at least partly explaining the high prevalence of asthma in elite athletes (Helenius et al, 1998b).

In anesthetized dogs challenged with high flows of air into a lung segment during bronchoscopy, hyperventilation with dry air caused hyperosmolarity of airway surface lining (Freed & Davis, 1999) and bronchoconstriction (Freed et al., 1985). Repeated dry air challenges (DACs) in the same model, mimicking chronic exposure such as during training, caused epithelial damage with eosinophil and neutrophil influx, and increased peptidoleukotriene concentrations in bronchoalveolar lavage fluid (BALF) (Davis et al., 2001). Bronchial epithelial damage also occurred in horses after exercise while breathing cold air (Davis et al., 2002). In cultured human bronchial epithelial cells, exposure to a hyperosmolar medium or cooling-rewarming increased the expression of IL-8 and RANTES partly through the activation of p38 MAP Kinase (Hashimoto et al., 1999, 2000). Therefore, both hyperventilation and airway hyperosmolarity appear capable to cause bronchoconstriction and inflammatory response.

Data obtained in a normal mouse model of endurance training support the interpretation that exercise causes limited inflammation in small airways but may damage bronchial epithelium. Increased leukocyte infiltrate was observed in bronchiolar walls and lumen of endurance-trained mice undergoing mild-intensity training for 45 days (Chimenti et al., 2007). Bronchiolar epithelium showed progressive changes during training. In mice trained for 45 days, the number of ciliated epithelial cells was significantly lower compared to sedentary mice, and apoptosis of bronchiolar epithelial cells increased. Epithelial thickness was increased in trained compared to sedentary mice. Bronchiolar epithelium of trained mice showed an increased number of proliferating cells, suggesting that habitual exercise may increase epithelial turnover in the airways (Chimenti et al., 2007).

Bronchial epithelial cells play a crucial role in the asthma pathophysiology. A number of studies have demonstrated the beneficial effects of aerobic exercise in chronic allergic airway inflammation (Table 1).

Author, yr	Animal model	Aerobic training intensity	Aerobic training duration	Airway inflammation	BHR	Other post-training data
Pastva et al., 2004	OVA-sensitized mice	Moderate	4 wk	Trained mice showed ↓ inflammation when OVA-tested	Not tested	↓ NFkB expression
Davis et al., 2003	Sled dogs	High	2-4 mo	Not tested	=, but increased pre-training compared to control dogs	-
Chimenti et al., 2007	Normal mice	Low-moderate	45 d	↑inflammatory cells, ↓ NFkB expression in small airways	Not tested	-
Vieira et al, 2007	OVA-sensitized mice	Low-moderate	30 d	Trained OVA+ mice showed ↓ inflammation	Not tested	↓ remodeling
Vieira et al, 2008	OVA-sensitized mice	Low-moderate	30 d	Trained OVA+ mice showed ↓ vascular and parenchymal inflammation	Not tested	
Hewitt et al, 2009	OVA-sensitized mice	Moderate	4 wk	Not tested	↓	B2AR involved in BHR response
Silva et al., 2010	OVA-sensitized mice	Moderate	4 wk	Trained OVA+ mice showed ↓ inflammation		↓ remodeling
Lowder et al., 2010	OVA-sensitized mice	Moderate	4 wk	trained OVA+ mice showed ↓ inflammation associated with ↑ Treg cell response	Not tested	-
Vieira et al., 2011	OVA-sensitized mice	Moderate	4 wk	Trained OVA+ mice showed ↓ inflammation	Not tested	↓ remodeling; ↑ IL-10 in bronchial epithelium in OVA+ and OVA- trained mice

Table 1. Effects of training on airway inflammation and bronchial reactivity in animal models. Abbreviations: BHR: bronchial hyperreactivity; OVA: ovalbumin; B2AR: beta2-adrenergic receptor; NFkB: nuclear factor k B; = unchanged; ↑: increased; ↓ decreased; IL-10: interleukin-10

Regular aerobic exercise performed at low or moderate intensity decreased eosinophilic and lymphocytic inflammation and Th-2 immune response in a murine model of allergic asthma (Pastva et al., 2004; Vieira et al., 2007, 2008, 2011; Hewitt et al., 2009, 2010; Lowder et al., 2010). These studies showed that the effects of exercise training were mediated by reduced activation and expression of NF-kB, insulin like growth factor 1 (IGF-1), RANTES (CCL2) and glucocorticoid receptors. Exercise training increased the expression of interleukin 10 (IL-10) and of the receptor antagonist of IL-1 (IL-1ra) suggesting an immune-regulatory role of habitual exercise on airway epithelium.

3.2.1 Markers of airway inflammation

To assess whether the increased inflammatory cells in the airways were activated, markers of inflammation were analysed in endurance athletes or animal models. According to some studies, the increased number of airway inflammatory cells was not associated with major signs of inflammatory activation in BALF or induced sputum in cross-country skiers at rest (Sue-Chu et al., 2000), or in induced sputum of runners studied at rest and after a marathon race (Bonsignore at al., 2001). In amateur swimmers who trained outdoor throughout the year, there was no evidence of inflammatory cell activation at rest or after exercise in outdoor pool or sea as suggested by low levels of neutrophil elastase and decreased expression of L-selectin by airway cells (Bonsignore et al., 2003b). However, in runners IL-8 concentration in induced sputum supernatants doubled after a half-marathon and was positively correlated with absolute bronchial epithelial cell counts (Chimenti et al., 2010). We speculate that the increase in neutrophils found in large airways of athletes after prolonged exercise (Bonsignore et al., 2001) or the morning post-race (Chimenti et al., 2009) might be at least partly secondary to release of chemotactic factors, such as IL-8, by bronchial epithelial cells during exercise. On the other hand, IL-8 concentration in sputum supernatants collected on the morning after a half-marathon race was low (Chimenti et al., 2009), suggesting that exercise-induced inflammatory activation is transient. In runners, increased IL-8 in induced sputum at rest was found during a competitive period, but did not correlate with sputum cells counts (Denguezli et al., 2008).

Data on lung-derived proteins measured in serum or urine, suggest that pulmonary epithelial permeability may increase after intense exercise (Hermans et al., 1999; Chimenti et al., 2010, Romberg et al., 2011) or after eucapnic hyperventilation, independent of training status or occurrence of EIB (Bolger et al., 2011). In amateur runners, CC-16 levels did not correlate with air pollutants levels, and were normal in samples collected the morning after a half-marathon race (Chimenti et al., 2009). Thus, intense exercise appears to transiently increase epithelial permeability.

Data obtained in a murine model of allergic asthma suggest that inflammatory activation in the airways may actually be inhibited by exercise training (Table 1). In ovalbumin-sensitized mice, nuclear translocation of nuclear-factor-κB (NF-κB) in airway cells was lower in trained compared to sedentary animals (Pastva et al., 2004). More recently, exercise training in ovalbumin-sensitized mice decreased epithelial expression of IL-4, IL-5, IL-13, CCL11, CCL5, adhesion molecules ICAM-1 and VCAM-1, iNOS and NF-kB, while the expression of the anti-inflammatory cytokine IL-10 increased, suggesting a positive effect of training on control of inflammation in asthmatic airways (Vieira et al., 2011). In small airways of endurance-trained nonasthmatic mice, NF-κB translocation and inhibitor-alpha of NF-κB (IκBα) phosphorylation were not affected, and goblet cells in bronchioles were negative at

Alcian-PAS staining, indicating that training did not cause excess mucus production (Chimenti et al., 2007).

Other studies found increased airway inflammatory markers in athletes. Increased concentrations of eosinophil peroxidase and neutrophil lipocalin in induced sputum were observed in elite swimmers of the Finnish National team (Helenius et al., 1998). In young athletes, concentration of cysteinil-leukotrienes, prostaglandin E2 (PGE-2), histamine, thromboxane B2 (TXB2), and leukotriene B4 (LTB4) in induced sputum after a eucapnic voluntary hyperventilation challenge were higher in subjects with than without EIB (Parsons et al., 2008).

In summary, data from athletes or animal models are somewhat controversial, as some studies did not show any clear evidence of significant inflammatory activation in the airways, while others reported increased inflammatory mediators. These studies did not assess exercise-induced changes but only examined airway cells and mediators under resting conditions. The few data available on the effects of acute exercise suggest that changes in inflammatory markers, if any, might be transient. The relationship between EIB and inflammation is still unclear, and its assessment is often complicated by the concomitant occurrence of asthma and bronchial hyperreactivity in athletes.

4. Could exercise training be useful in patients with respiratory disease?

The possibility that habitual exercise may affect inflammatory processes in the airways opens the way to a new perspective regarding exercise-based rehabilitation. Until recently, exercise training in patients with respiratory diseases, such as asthma or chronic obstructive pulmonary disease (COPD), was based on the assumption that the main effect of rehabilitation was to improve muscle function and decrease ventilatory requirements. While this holds true, especially in physically deconditioned patients, the possibility that exercise training may also modulate airway cell biology is being increasingly considered. The following paragraphs report a summary of recent findings suggesting that this could well be the case in patients with asthma or COPD, respectively.

4.1 Asthma

In subjects with asthma, the level of activity is restricted mainly because bronchoconstriction occurs after exercise. On the other hand, physical training increases the capacity for physical work (Freedman, 1992; Arborelius & Svenonius, 1984), and the anaerobic threshold (i.e., the level at which lactic acid production, and the associated increase in ventilation, occur). Consequently, hyperpnea, one of the major stimuli for EIB, is delayed and exercise tolerance improves after aerobic training. Ventilatory muscle training might also improve the capacity for sustaining physical activity, or, at least, minimize muscle fatigue (Leith & Bradley, 1976).

In asthmatic patients, an exercise-based training program improved asthma symptoms (Arborelius & Svenonius, 1984; Haas et al., 1987), even though baseline lung function remained unchanged. None of these studies tested whether airway responsiveness was affected by exercise training.

Table 2 summarizes the studies on the effects of physical training in normal subjects and patients with asthma. Some studies examined the effects of training on inflammation, other studies tested bronchial reactivity before and after training, and some did analyze other aspects such as quality of life and asthma control.

Author, yr	n	Training type	Training duration	Airway inflammation	BHR	Other post-training data
Matsumoto et al., 1999	8 children with mild-moderate asthma	swimming	6 wk	Not tested	=	Lac Thr ↑
Neder et al., 1999	42 children with mild-moderate asthma	aerobic	2 mo	Not tested	=	↓ use of B2A
Hallstrand et al., 2000	5 pts with mild asthma, 5 controls	aerobic	10 wk	Not tested	Not tested	Less HV during exercise
Kippelen et al., 2005	13 healthy subjects	aerobic	1 yr	Not tested	Not tested	Lung function=
Fanelli et al, 2007	Moderate-severe persistent asthma (21 T, 17 C children)	mixed	16 wk	Not tested	↓ EIB in trained group	↑ QoL
Bonsignore et al., 2008	Mild asthma (25 placebo, 25 montelukast, M, children)	aerobic	12 wk	=	↓ Mch PC20 in both groups	↓ FEV1 slope and exacerbations in M group
Moreira et al., 2008	34 asthmatic children (17 T, 17 C)	aerobic	12 wk	Not worsened by training, possible ↓ in IgE	Not tested	-
Dengzueli et al., 2008	10 endurance runners	aerobic	1 yr	↑ in precompetitive period	Not tested	Lung function =
Mendes et al., 2010	Moderate-severe persistent asthma (51 C, 50 T)	aerobic	3 mo	Not tested	Not tested	↑ asthma control and QoL
Scichilone et al., 2010	10 sedentary healthy subjects	rowing	10 wk	↑IL-8 in induced sputum supernatants at 10 wk	↓ response to Mch in the absence of deep inspiration at wk 5 and 10	-
Dogra et al., 2011	Incompletely controlled asthma (15 C, 21 T adults)	Mostly aerobic	24 wks	Not tested	Not tested	↑ asthma control and QoL
Mendes et al., 2011	Moderate-severe persistent asthma (24 C, 27 T adults)	Aerobic	3 mo	↓ only in trained group	Not tested	↑ asthma control

Table 2. Effects of training on airway inflammation and reactivity in normal and asthmatic subjects. Abbreviations: BHR: bronchial hyperreactivity; Lac Thr: lactate threshold; T: trained; C: control; B2A: beta2-agonist; FEV1: forced expiratory volume in 1 second; HV: hyperventilation; Mch: methacholine; PC20: provocative concentration causing 20% fall in FEV1; QoL: quality of life; NFkB: nuclear factor k B; = unchanged; ↑: increased; ↓ decreased; IL-8: interleukin-8.

Overall, the data in humans show no worsening or improvement of asthma after exercise training. The studies in animal models (Table 1) are much more refined in term of assessment of mediators and potential mechanisms involved. Therefore, additional work is required to improve our understanding of the effects of exercise training in human patients with asthma. The asthmatic athlete, on the other hand, might be considered a "special case", given the high intensity/frequency of training and the role of environmental exposures.

4.2 Chronic obstructive pulmonary disease

The literature on the physiological effects of pulmonary rehabilitation in COPD is large, but the majority of studies have examined the effects of training on skeletal muscles and markers of systemic inflammation, while changes in airway cells occurring during exercise or physical training in COPD patients remain largely unknown. The most recent studies have focused their attention on the amount, intensity, and pattern of daily physical activity in COPD patients, rather than the degree of physical fitness examined by traditional exercise stress tests, since the former is a better indicator of the impact of the disease on the quality of life of the patients. These studies are made easier today by the availability of accelerometers, which are very useful tools to objectively assess daily physical activity in and elderly population such as COPD patients. At least two meta-analyses have shown that daily physical activity in COPD patients is lower than in controls (Bossenbroek et al., 2011; Vorrink et al., 2011), but the involved mechanism are far from being clarified.

Interestingly, similar to studies on asthmatic patients, some epidemiological studies highlighted the prognostic importance of maintaining a good level of daily physical activity in COPD. Patients maintaining a regular level of physical activity underwent less hospital admission for COPD exacerbations (Garcia-Aymerich et al., 2006; Benzo et al. 2010). Moreover, in a population-based cohort the decline in lung function and the risk to develop COPD were found to be lower in smokers with an active lifestyle compared to smokers with a sedentary lifestyle (Garcia-Aymerich et al., 2007). Finally, an active lifestyle was associated with a more favorable clinical and functional status in a large sample of COPD patients (Garcia-Aymerich et al., 2009). An inverse association between life-long physical activity and the risk of COPD has also been recently reported by a case-control study conducted in Japan (Hirayama et al., 2010). Therefore, increasing evidence suggests a protective effect of an active life against the development of COPD and disease severity.

No study is available yet in humans on training-associated changes in airway responses in COPD patients. In a mouse model of COPD, favourable effects of 24-week exercise training in animals chronically exposed to cigarette smoke compared to the sedentary group have been reported (Toledo et al., 2011). Regular aerobic physical training of moderate intensity reduced oxidative stress and the development of emphysema in mice (Toledo et al., 2011). Therefore, it can be expected that studies in the near future will increasingly examine the protective effects of exercise training in the lung of COPD patients.

5. Conclusions

The effects of acute exercise and training on bronchial reactivity and airway inflammation are still a puzzle with many missing elements, but the general picture is appearing with an increasing number of details. In elite athletes, the combination of high exercise intensity,

environmental exposure and genetic background is likely responsible for the varying airway involvement described for different sports. However, it is likely that the levels of exercise commonly observed in the active population are associated with positive effects on bronchial reactivity and tight control of airway inflammation.

The majority of studies in patients with asthma similarly suggest a beneficial effect of training on the control of airway inflammation, although little evidence is currently available on the potentially beneficial effects of habitual exercise on bronchial reactivity. Instead, the only evidence in favour of physical activity in COPD patients comes from epidemiological observations and limited experimental results. A better understanding of the pathophysiology of exercise training in patients with asthma and COPD will be the first step towards a rational, evidence-based development of specific recommendations targeted to improve the quality of life and possibly the prognosis of these patients.

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7. References

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Comparison of Seminal Superoxide Dismutase (SOD) Activity Between Elite Athletes, Active and Non Active Men

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1. Introduction

It is increasingly recognized that reactive oxygen species (ROS) originating from the spermatozoa as well as from the leukocytes are of significant pathophysiological importance in the etiology of male infertility (Iwasaki and Gagnon, 1992; Zini *et al.*, 1993; Ochsendorf *et al.*, 1994; Shekarriz *et al.*, 1995; Smith *et al.*, 1996; Agarwal *et al.*, 2006; Tremellen, 2008). ROS, defined as including oxygen ions, free radicals and peroxides, may cause infertility by two principal mechanisms. First, ROS damage the sperm membrane which in turn reduces the sperm's motility and ability to fuse with the oocyte. Secondly, ROS directly damage sperm DNA, compromising the paternal genomic contribution to the embryo (Tremellen, 2008). Due to their high content of polyunsaturated fatty acids and their capacity to generate ROS, human spermatozoa are very sensitive to oxidative stress (Aitken and Clarkson, 1987; Aitken *et al.*, 1989; Smith *et al.*, 1996). To protect spermatozoa from oxidative damage, seminal plasma is endowed with numerous enzymatic antioxidants (AOs) such as superoxide dismutase (SOD), catalase and glutathione peroxidase (Fujii *et al.*, 2003; Garrido *et al.*, 2004; Murawski *et al.*, 2007). It has recently been reported, that superoxide anion (O_2) may be involved in fatty-acid peroxidation (Niess and Simon, 2007). Superoxide dismutase (SOD) and catalase inactivate the superoxide anion (O_2) and peroxide (H_2O_2) radicals by converting them into water and oxygen. SOD as an important element of seminal plasma superoxide anion scavenging capacity plays an essential role in maintaining the balance between ROS generation and degradation. Decrease of its capacity can result in abnormal sperm motility determined as sperm hyperactivation, and hence infertility (De Lamirande and Gagnon, 1993). The addition of SOD to sperm in culture has been confirmed to protect

them from oxidative attack (Kobayashi *et al.*, 1991). Although some investigators have shown no association between SOD activity and male fertility (Miesel *et al.*, 1997; Zini *et al.*, 2000; Hsieh *et al.*, 2002), others have reported a reduction in seminal plasma SOD activity in infertile males (Alkan *et al.*, 1997; Sanocka *et al.*, 1997; Siciliano *et al.*, 2001). Recently Murawski et al. (2007) reported a significantly lower semen SOD activity in infertile males, as compared with normospermic men. They showed a positive correlation between SOD activity in seminal plasma and semen quality parameters - sperm concentration and overall motility, which are regarded as most important for normal fertilizing ability of the spermatozoa (Murawski *et al.*, 2007).

Physical exercise has been shown to increase ROS and oxidative stress causing disruptions of homeostasis. Given that generation of oxidative stress is a natural part of physically active people may be susceptible to ROS-induced damage in sperm motility and male infertility, depending on the exercise mode, intensity, and duration as well as antioxidant capacity. Exercise training, on the other hand, has been shown to have modifying effects on oxidative stress, depending on training load, training specificity and the basal level of training. Growing evidence suggests that aerobic exercise training can result in an augmented SOD activity and a reduction in lipid peroxidation (Mena *et al.*, 1991; Ortenblad *et al.*, 1997; Ji, 1998; Suzuki and Ohno, 2000; Niess *et al.*, 2007). It is well documented that due to intensive training programs, trained and athletic people have developed total antioxidant capacity, and in particular high levels of SOD, in several tissues (Banfi *et al.*, 2006; Dekany *et al.*, 2006; Tayler *et al.*, 2006). However, our knowledge about antioxidant capacity in seminal plasma of athletic and trained men is less than meager, and it was up to now unclear if and under which conditions exercise training may influence seminal antioxidant capacity. Nonetheless, the amounts of enzymatic antioxidants in human semen have been well measured in normal and infertile men (Nissen and Kreysel, 1983; Jeuilin *et al.*, 1989; Kobayashi *et al.*, 1991; Alkan *et al.*, 1997; Miesel *et al.*, 1997; Sanocka *et al.*, 1997; Zini *et al.*, 1993).

Taken together, considering the probable positive correlation and beneficial impact of SOD activity on human semen quality parameters and male fertility on the one hand, and the fact that the SOD and antioxidant capacity of various tissues are highly different between individuals with different level of physical fitness on the other hand, we wanted to find an answer to the question if the SOD activity of seminal plasma is different in individuals with different levels of physical activity. Thus, the purpose of this study was to evaluate the SOD activity in elite athletes, recreationally active and non active men.

2. Materials and methods

2.1 Subjects

A total of 40 semen samples were obtained from investigated groups in this study (*Table1*). Of these, 15 samples were obtained from competitive elite athletes (e.g. including wrestlers, runners, football players, and swimmers) who were regularly training 4-5 days per week (Elite group). Thirteen samples were provided by non-obese and physically active males (active group) who participated in educational or recreational physical activities for 4-5 h per week. And 12 samples were obtained from healthy males who had a sedentary lifestyle without practicing in any sport for at least 6 months prior to study (control group). Physical activity of subjects was assessed by a questionnaire and subjects were matched based on training status and training quantity.

To be eligible to participate in the study, subjects were required to meet the following criteria: 1) unmarried men 18–28 year of age; 2) in good health, as determined by a normal physical examination and routine laboratory tests within the previous year; 3) no history of chronic disease, including reproductive disorders; 4) no history of use of medications that could alter the H-P-G axis, such as anabolic steroids; 5) regular eating patterns and no history of depressive illness; 6) normal physical and sexual development; 7) not working in professions where the activity might influence reproductive capacity; 8) no relevance previous surgery (eg, vasectomy reversal or varicocele removal) ; and 9) appropriate history of physical activity for the different groups described above (Lucía *et al.*, 1996; Di Luigi *et al.,* 2001). Informed consent was obtained from each subject. Before the initiation of the study protocol, each of them was introduced to the methods of this investigation. The Human Subject Internal Review Board committee of the Urmia University of IRAN approved the study (approval number 03/686).

Variable	Group	Elite	Active	Control	Sig*
Age (*year*)		23.1±1.3	23.4±0.9	22.0 ±2.0	0.053
Height (*cm*)		176.6±6.3	175.8±6.3	175.5±6.3	0.884
Weight (*kg*)		74.1±12.3	72.1±6.6	75.8±10.9	0.515
BMI (*kg/m²*)		20.9±2.5	22.1±1.4	24.3±2.6	*0.001
Fat (%)		8.5±3.7	11.2±3.1	15.5±5.1	*0.014

BMI = Body Mass Index.
*: P<0.05, significant difference between groups.

Table 1. Individual physical characteristics of subjects.

All subjects were given clear instructions on how to collect their semen at site. Each subject collected one semen sample by masturbation into a sterile container after at least 3-4 days of abstinence from ejaculations (Chia *et al.*, 1998; Nikoobakht *et al.*, 2005; Kao *et al.*, 2008). The majorities of samples were provided on site or were delivered to the laboratory within 30 min of collection. Each subject also completed a questionnaire concerning the duration (days) of the abstinence before collecting each sample (Jeuilin *et al.*, 1989).

2.2 Seminal SOD activity measurement
Semen analyses were performed according to WHO guidelines (Caballero *et al.*, 1992; Nikoobakht *et al.*, 2005). Semen evaluations were performed on each sample by the same experienced technician throughout the study, for the assessment of SOD activity. All of the semen samples were then cryopreserved using the Test Yolk Buffer with Glycerol as a freezing medium, according to the protocol described in WHO guidelines (4-th edition, 1999).
SOD activity was measured by colorimetric assay (Zini *et al.*, 2000 and 2002). The commercially available colorimetric method was used (Randox Laboratories Ltd, UK). This method employs xanthine and xanthine oxidase to generate superoxide radicals which react with 2-(4-iodophenyl)-3-(4-nitrophenol) - 5-phenyltetrazoliumchloride (I.N.T) to form red formazan dye. The SOD activity is then measured by the degree of inhibition of this reaction. One unit of SOD inhibits reduction of INT by 50% under the conditions of the assay. After thawing, the seminal plasma was diluted 30-fold with 10 mM phosphate buffer, pH 7.0. The assay was performed at 37°C. Phosphate buffer was used as blank. Mixed

substrate and xanthine oxidase were added into standards and sample tubes and vortexed well. With spectrophotometer adjusted at a wavelength of 505 nm, the initial absorbance (A1) was read. Final absorbance (A2) was read exactly after 3 minutes, and percentages of inhibition of standards and samples were calculated. The SOD activity was measured using calibration curve of percentage inhibition for each standard against Log10 of standards and SOD activity was expressed as IU/ml.

2.3 Statistical analysis

Data are expressed as means ± SD. Differences among groups were determined by analysis of variance (ANOVA) for continuous variables. If the *F*-ratio was significant, differences among groups were subsequently identified using a Bonferroni *post-hoc* analysis. The statistical software program SPSS for windows, version 17.0 was used for all data analyses. All statistical tests were performed at a significance level of 0.05.

3. Results

Semen parameters (mean ± SD) were compared between study groups and the results are shown in *Table 2*. No significant differences were observed between groups in semen parameters (P > 0.05) except of normal morphology (P ≤ 0.05). The result of Bonferroni test showed that the observed difference is more pronounced between elite group with active and control groups. However, there was no significant difference between active and control groups.

At this study the seminal SOD activity (IU/ml) of 3 groups was investigated. One-way ANOVA analysis showed that there is a significant difference between three groups (*Table 2*). The result of Bonferroni analysis revealed significantly higher SOD activity in seminal plasma of elite group than those of active and control groups (P ≤ 0.05). However, no statistically significant difference was observed between active and control groups (P > 0.05).

Variable	Group	Elite	Active	Control	Sig*
Total sperm count (*millions*)		89.6±55.1	86.2±52.9	87.4±54.5	0.089
Volume (*ml*)		3.3±1.4	2.7±1.2	2.3±1.3	0.071
Concentration ($\times 10^6$/*ml*)		56.6±2.9	51.7±2.6	53.5±2.8	0.123
Motility (%)		72.8±15.6	66.2±16.1	69.7±14.9	0.068
Viability (%)		80.5±13.5	77.9±12.9	74.7±13.8	0.059
Normal morphology (%)		31.4±10.6	19.1±11.4	23.7±10.1	* 0.034
SOD (*IU/ml*)		34.3±9.4	17.9±5.6	24.2±6.6	* 0.001

*: P<0.05, significant difference between groups.

Table 2. Comparison of Semen parameters and SOD activity between elite athletes, recreationally active and sedentary men.

4. Discussion

The results emerging from this study show that semen from elite athletes have higher SOD content than those of the active and sedentary (control) men. However, no significant difference was observed between samples of active and control groups. Therefore, these results represent that elite athletic men have developed seminal antioxidant capacity at least

in the case of SOD, suggesting that spermatozoa from elite athletes may be less susceptible to ROS-induced peroxidative damage, and hence, infertility. ROS have been shown to cause infertility by directly damaging the sperm DNA (Tremellen, 2008). Spermatozoa are susceptible to oxidative damage because their plasma membranes are rich in polyunsaturated fatty acids and have low concentrations of scavenging enzymes. SOD as one of the important elements of seminal plasma superoxide anion scavenging capacity plays an essential role in maintaining the balance between ROS generation and degradation through preventing increases in ROS concentration. Due to the protective effects against peroxidative damage and oxidative stress, seminal SOD has been shown to preserve sperm motility and viability. Sperm motility has been found to associate with men fertility (Jones *et al.*, 1979; Smith *et al.*, 1996; Murawski *et al.*, 2007; Agarwal *et al.*, 2008). The essential role of SOD as antioxidative defense enzyme is inferred from the observation that complete loss of motility of a sperm sample is directly proportional to the SOD activity of that sample (Storey, 1997). In particular, low SOD activity has been shown to be responsible for male infertility (Alkan *et al.*, 1997). Several investigators have reported reductions in SOD activity in semen of infertile men (Alkan *et al.*, 1997; Sanocka *et al.*, 1997; Siciliano *et al.*, 2001), although some have not (Zini *et al.*, 1993; Miesel *et al.*, 1997; Hsieh *et al.*, 2002). Recently Murawski et al. (2007) reported a significantly lower semen SOD activity in infertile men, as compared with normospermic men. They showed a positive correlation between SOD activity in seminal plasma and semen quality parameters - sperm concentration and overall motility, which are regarded as the most important for normal fertilizing ability of the spermatozoa (Murawski *et al.*, 2007).

Although the protective effect of seminal plasma has been well recognized, no study has investigated its antioxidative properties in individuals with different fitness level, in particular in athletic men. To the best of our knowledge, the present study provides the first evidence that elite athletes have an augmented SOD capacity than recreationally active and sedentary control men. Although there is no definitive explanation for this discrepancy, but the notion that high maximal oxygen uptake (VO_{2max}), which is a consequence of systemic endurance training (Tanaka and Swensen, 1998), are correlated to elevated antioxidant enzyme activity in other tissues (Jenkins *et al.,* 1984), can explain some of the disparities in our study. These observations suggest that the fitness level of subject as well as the type and amount of exercise training could be taken into consideration when comparing antioxidant capacity of active people. As the active group in our study were exercising just 4-5h per week, it seems possible that this amount of exercise is not enough to enhance antioxidant capacity. Dekany et al. (2006) have also referred to fitness level of athletes and type of exercise as important factors determining the blood level of antioxidant enzymes (Dekany *et al.*, 2006). In the review by Clarkson (1995) it has been documented that the ``weekend athlete`` may not have the augmented antioxidant defense system produced through continued training (Clarkson, 1995). This may make them more susceptible to oxidative stress.

The fact that rigorous exercise training programs may be required to promote antioxidant enzyme activity in skeletal muscle (Powers and Leeuwenburgh, 1999), can support our results. Intensive endurance training has been postulated as a potential muscle`s antioxidant defense system up-regulator (Fatouros *et al.*, 2004). Powers et al. (1994) experimentally analyzed the relationship between the magnitude of the training stimulus (i.e., exercise intensity and daily duration) and the activity of SOD in locomotor skeletal muscles. Nine groups of rats ran at three different daily durations (i.e., 30, 60, 90 min.d) and three different exercise intensities (i.e., 55, 65, and 75% of VO_{2max}) (**Powers** *et al.*, 1994). Furthermore, previous studies have reported

that high-intensity running training can elevate antioxidant enzyme activities in erythrocytes and decrease neutrophil superoxide anion production both at rest and in response to exhaustive acute exercise (Miyazaki *et al.*, 2001). These data clearly show that high intensity long-term exercise training is superior to recreationally exercise in the up-regulation of seminal plasma SOD activity, representing adaptation to regular training. In fact, the training-stressed cells provide high antioxidant enzyme content. It has been generally believed that training induction of antioxidant enzymes is a cellular adaptation to oxidative stress caused by free radical generation during heavy exercises (Jenkins, 1988; Ji, 1998).

Prior to this work, numerous studies have been published focusing on the adaptation of different tissue's antioxidant capacity to exercise training (Mena *et al.*, 1991; Ortenblad *et al.*, 1997; Ji, 1998; Suzuki *et al.*, 2000; Banfi *et al.*, 2006; Dekany *et al.*, 2006; Tayler *et al.*, 2006; Garcia-Lopez *et al.*, 2007; Niess *et al.*, 2007). Recently Garcia Lopez et al. (2007) showed an increase in MnSOD mRNA levels of peripheral mononuclear cell (PBMC) in response to endurance training in middle-aged men (Garcia-Lopez *et al.*, 2007). Tauler et al. (2006) reported an increase in erythrocyte superoxide dismutase activity after the training/competition period for amateur trained male athletes (Tayler *et al.*, 2006). Banfi et al. (2006) showed a significantly higher plasma Glutathione reductase (GR) activity in trained elite soccer players, as compared with sedentary controls (Banfi *et al.*, 2006). Investigating antioxidant status of interval-trained athletes, Dekany et al. (2006) reported high level of blood enzymatic antioxidants in highly trained athletes (Dekany *et al.*, 2006). Ravi et al. (2004) showed a significantly increase in myocardium superoxide dismutase after 4 weeks low-intensity swim training in rats (Ravi *et al.*, 2004). Also, Yamamoto et al. (2002) reported higher superoxide dismutase activity and antioxidant capacity for physically active rats in compared to sedentary rats (Yamamoto *et al.*, 2002). However, both in treadmill-trained rats (Leeuwenburgh *et al.*, 1994) and running trained humans (Tiidus *et al.*, 1996) endurance training did not affect antioxidant defense.

Some limitations of the present study should be taken into consideration. First, we measured the SOD activity just in seminal plasma and did not measure in spermatozoa. Secondly, five subjects (active group n=2, and control group n=3) could not provide the semen sample in time and were excluded from the study. This might influence the compared results. Thirdly, this study comprised a relatively small sample thus limiting statistical power to detect differential effects. However, this is, to our knowledge, the first study analyzed the seminal antioxidant activity in individuals with different level of physical fitness.

In conclusion, the results of present study demonstrate that in compared to recreationally active and sedentary men, the elite athletes have developed SOD capacity. The mechanisms responsible for this increase are unknown and remain an active area of research. However, this raises the question that does the training-induced increase in seminal plasma SOD capacity provide increased protection against ROS-induced sperm dysfunction and infertility in high level athletes? If it does, we are able to provide novel insights into athletic health and male fertility. Further studies are warranted to deal the antioxidant capacity of seminal plasma and spermatozoa of individuals with different level of physical fitness as well as the effect of various exercise programs on seminal antioxidant capacity.

5. Acknowledgment

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Aquatic Sports Dermatoses:
Clinical Presentation and Treatment Guidelines

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1. Introduction

Aquatic sport dermatoses include a variety of skin conditions that occur in athletes who participate in sporting activities in or on the water. Chemicals and microbes inhabiting the aquatic environment are often responsible for the development of these cutaneous conditions. We review common water sports dermatoses and divide them based on activities that occur in saltwater, freshwater and activities outside the water. Some of the water sports represented in the review include swimming, diving, scuba diving, snorkeling and water polo which are mainly based in the water, as well as sailing, rowing, fishing, surfing, whitewater rafting and water-skiing which are based on the water and outside the water. Aquatic sports dermatoses are presented according to their etiology including infectious and organism-related, contact dermatitis and miscellaneous causes. We also describe conditions specifically associated with water sports including sailing, rowing, fishing and surfing. This comprehensive review focuses on the key recognizable clinical features and principles of management of aquatic sports dermatoses. Our aim is to help sports medicine physicians, dermatologists and other health care providers recognize and treat water sport dermatoses in athletes.

2. Freshwater

2.1 Infectious and organism-related
2.1.1 Swimming pool granuloma

Swimming pool granuloma, also known as fish tank granuloma or fish fancier's granuloma is caused by infection with atypical mycobacteria, including *Mycobacterium marinum* and *Mycobacterium scrofulaceum.* Swimmers may be infected from exposure to freshwater or saltwater. Fish, dolphins, snails and water fleas are proposed vectors of disease transmission (Huminer *et al.,* 1986).

Clinical presentation. Individuals present with verrucous nodules or plaques that occasionally ulcerate approximately 6 weeks after inoculation. The lesions commonly manifest in the upper extremities, particularly the fingers, and may spread linearly demonstrating a sporotrichoid pattern along the route of lymphatics (Ang *et al.,* 2000; Gluckman, 1995). Diagnosis is best made with biopsy of skin lesions for histopathologic examination and culture. Rare and severe infection may occur from direct extension from the skin to the bones and joints resulting in osteomyelitis, arthritis and tenosynovitis

(Clark *et al.*, 1990; Collins *et al.*, 1988). Disseminated infection typically occurs in immunosuppressed hosts and may be fatal (Tchornobay *et al.*, 1992; King *et al.*, 1983).
Management. The first-line treatment includes oral clarithromycin 500 mg twice daily for 6 weeks. Oral minocycline 100 mg twice daily may also be used, but mycobacterial resistance to minocycline has been reported (Adams, 2006).

2.1.2 Hot tub folliculitis

Hot tub folliculitis, also known as *Pseudomonas aeruginosa* folliculitis and "splash rash" is an infection caused by *Pseudomonas aeruginosa* after exposure to contaminated water. Swimming pools, showers, baths, hot tubs, saunas and water slides are associated with this condition (Chandrasekar *et al.*, 1984; Fox & Hambrick, 1984; Zichini *et al.*, 2000).
Clinical presentation. Individuals present with follicular-based macules and papulopustules that typically manifest 8–48 hours after exposure with contaminated water (Fox & Hambrick, 1984; Highsmith *et al.*, 1985). The lesions usually heal without scaring, although post-inflammatory hyperpigmentation and desquamation of the skin may occur less commonly. Systemic symptoms occasionally occur and include fever, malaise, sore throat, otalgia, lymphadenopathy, nausea and diarrhea. Rare complications which typically occur in immunosuppressed individuals include abscess formation, ecythma gangrenosum, subcutaneous nodules and cellulitis (Berger *et al.*,1995; El Baze *et al.*, 1985). Use of a Wood's lamp may help detect hot tub folliculitis in the early stages by visualizing a pale green fluorescence (Amichai *et al.*, 1994).
Management. In immunocompetent individuals treatment is not required and infection typically resolves spontaneously in less than 2 weeks. Supportive treatment includes acetic acid 5% compresses used for 20 minutes 2-4 times daily for symptomatic relief (Tlougan *et al.*, 2010a). Only in severe cases should the use of antibiotics be considered.

2.1.3 Diving suit dermatitis

Diving suit dermatitis is an infection caused by *Pseudomonas aeruginosa* serotypes O:10 and O:6, which are different from the serotypes associated with hot tub folliculitis.
Clinical presentation. Individuals present with erythematous papules that are diffusely scattered on the trunk and extremities. Rarely, systemic symptoms may manifest including fever, headache and malaise (Tlougan *et al.*, 2010a).
Management. First-line treatment consists of oral antibiotics such as ciprofloxacin 500 mg twice daily. Preventive methods include cleaning diving suits with 0.45% lactic acid after each use and showering immediately after diving (Tlougan *et al.*, 2010a).

2.1.4 Pitted keratolysis

Pitted keratolysis is an infection caused by *Corynebacterium* or *Kytococcus sedentarius.* This condition is usually seen in individuals who walk barefoot and is associated with excessive sweating (Shelley & Shelley, 1982; Zaias, 1982).
Clinical presentation. Individuals present with superficial pinpoint or ringed erosions with multiple shallow and sharply punched-out (1-3 mm) pits. The lesions have a "dirty" appearance and a foul odor (Tlougan *et al.*, 2010a)
Management. The infection generally responds well to topical or oral erythromycin, topical clindamycin or topical 5% benzoyl peroxide (Pharis *et al.*, 1997). Pitted keratolysis may clear on its own with elimination of excess moisture.

Fig. 1. Pitted keratolysis. Multiple shallow punched-out pits on anterior sole of foot (Tlougan *et al.*, 2010a). Reproduced with permission from *International Journal of Dermatology*.

2.1.5 Bikini bottom

Bikini bottom is a deep bacterial folliculitis typically caused by *Streptococcus* or *Staphylococcus aureus.* It usually occurs in swimmers who wear tight-fitted wet swimwear for prolonged periods of time (Saltzer *et al.*, 1997).

Clinical presentation. Individuals present with firm nodules that manifest along the inferior gluteal crease (Basler *et al.*, 1998).

Management. First-line treatment includes a course of oral antibiotics for 10 days, such as Cephalexin (Basler *et al.*, 1998). Prevention of this condition includes prompt removal of wet swimwear.

2.1.6 Swimmer's Itch

Swimmer's itch, also known as Schistosome dermatitis, clam-digger's itch or cercarial dermatitis, is caused by infection with larvae from the fluke family Schistosomatidae. The condition typically occurs in swimmers exposed to freshwater, but may also occur in saltwater (Mulvihill & Burnett 1990). Rodents and birds are the primary hosts that release ova containing the immature larvae which mature in snails (Wolf *et al.*, 1995). The larvae infect humans through penetration of the skin and eventually die causing an immunologic reaction and sensitization two weeks after initial contact. Further exposures result in lesions within hours (Wolf *et al.*, 1995).

Clinical presentation. Individuals present with multiple erythematous pruritic papules (3-5 mm) with occasional urticarial plaques (Adams, 2006; Hicks, 1977). Systemic symptoms occur rarely and include fever, chills and lymphadenopathy (Cort, 1950; Wall, 1976).

Management. Lesions typically resolve spontaneously within 3 to 7 days, but topical corticosteroids and antihistamines may help relieve pruritus. Only severe cases require systemic corticosteroids (Adams, 2006).

Fig. 2. Swimmer's itch. Scattered erythematous papules on thigh of a swimmer (Tlougan et al., 2010a). Reproduced with permission from *International Journal of Dermatology*.

2.1.7 Molluscum contagiosum

Molluscum contagiosum, also known as "water warts" is a cutaneous viral infection caused by the poxvirus *Molluscum contagiosum* (Gottlieb & Myskowski, 1994). Various studies have documented an association between this infection and water exposure (Niizeki *et al.,* 1984; Weismann *et al.,* 1973).

Clinical presentation. Individuals present with pearly-white or skin-colored papules and nodules that may demonstrate a central dimple or umbilication (Tlougan *et al.,* 2010a).

Fig. 3. Molluscum contagiosum. Several 1-2 mm pearly dome-shaped papules with central umbilication (Tlougan *et al.,* 2010a). Reproduced with permission from *International Journal of Dermatology*.

Management. Lesions usually resolve spontaneously without scarring within one year but may persist longer. Therapeutic options to facilitate the resolution of lesions include curettage, liquid nitrogen, trichloroacetic acid and cantharidin. Other off-label options include topical 5-FU or imiquimod (Tlougan *et al.,* 2010a).

2.1.8 Warts

Verrucae or warts are caused by human papillomavirus (HPV) and are common in swimmers and individuals that use communal showers (Gentles & Evans, 1973; Johnson, 1995; Penso-Assathiany *et al.*, 1999).

Clinical presentation. Individuals present with well-defined, papillomatous or verrucous papules with a roughened surface. Plantar warts appear as endophytic papules or plaques of the soles with black specs at the center (Tlougan *et al.*, 2010a).

Management. Therapeutic options include mechanical destruction with liquid nitrogen, laser and curettage. Methods of chemical destruction include salicylic acid, cantharidin and trichloroacetic acid. Athletes may apply imiquimod, 5-FU, squaric acid (SADBE) and diphenylcyclopropenone (DPCP) for self-management of these lesions. (Tlougan *et al.*, 2010a). Recalcitrant warts may be treated with injected *Candida antigen*, mumps antigen or bleomycin. (Tlougan *et al.*, 2010a). Oral cimetidine has been shown to be effective in some studies, although its clinical utility remains debated (Orlow & Paller, 1993; Tlougan et al, 2010a).

Fig. 4. Verrucae. Plantar wart with roughened surface and black specs at the center (Tlougan et al, 2010a). Reproduced with permission from *International Journal of Dermatology*.

2.1.9 Athlete's foot

Athlete's foot, also known as tinea pedis, is a common cutaneous fungal infection caused by dermatophytes. Infection may be transmitted through swimming pools, pool decks and shower floors (Bolanos, 1991; Kamihama *et al.*, 1997).

Clinical presentation. Individuals typically present with the interdigital subtype that manifests as erythema and scaling with or without pruritus. Other clinical forms include the moccasin subtype with plantar erythema, scaling and hyperkeratosis and the inflammatory subtype with painful bullae or pruritic vesicles (Tlougan et al., 2010a).

Management. First-line therapy includes topical antifungal agents used twice daily to affected areas for one to several months. Systemic antifungal agents such as terbinafine 250 mg daily or itraconazole 200 mg daily for 2 weeks may be required for more extensive or refractory lesions. Infection may be prevented by wearing protective sandals in public

showers or pool decks. Athletes may prophylactically apply topical antifungal agents twice weekly to prevent reinfection (Adams, 2006).

Fig. 5. Athlete's foot. Interdigital subtype of tinea pedis with erythema and scaling between digits (Tlougan *et al.*, 2010a). Reproduced with permission from *International Journal of Dermatology*.

2.2 Contact dermatoses

Contact	Dermatosis	Offending Agent
Allergic	Swim goggles dermatitis	dibutylthiourea (rubber accelerator)
	Nose clip & ear plug dermatitis	rubber accelerator compounds
	Diving mask dermatitis	isopropylparaphenylenediamine (IPPD)
	Wet suit dermatitis	diethylthiourea dibutylthiourea diphenylthiourea ethyl butylthiourea para-tertiary-butylphenol-formaldehyde resin
	Swim fin dermatitis	dibutylthiourea diethylthiourea IPPD
	Swim cap dermatitis	mercaptobenzothiazole
	Pool water dermatitis	bromine chlorine potassium peroxymonosulfate (PPMS)
Irritant	Pool dermatitis	bromine chlorine

Table 1. Freshwater contact dermatoses

2.2.1 Swimming gear

Athletes may develop contact dermatitis to a variety of components found in swimming gear. Swim goggles, nose clips and ear plugs may result in dermatitis from exposure to rubber accelerators with dibutylthiourea (Azurdia & King, 1998; Cronin & Rubber, 1980; Goette, 1984; Romaguiera *et al.*, 1988). Diving mask dermatitis, also known as scuba diver facial dermatitis, may result from exposure to isopropylparaphenylenediamine (IPPD), a rubber antioxidant in face masks (Maibach, 1975; Maibach, 1975; Tuyp, 1983). Swim fin dermatitis may also occur from contact sensitivity to IPPD, in addition to other components including dibutylthiourea and diethylthiourea (Balestrero *et al.*, 1999; Fisher, 1999). Swim cap dermatitis may result from contact sensitivity to mercaptobenzothiazole (Cronin & Rubber, 1980). Other components of swim gear that may elicit a contact allergy include diphenylthiourea, para-tertiary-butylphenol-formaldehyde resin and ethyl butylthiourea found in swim suits, as well as Tego103G, a disinfectant of wet suits (Boehncke *et al.*, 1997; Munro *et al.*, 1989; Nagashima *et al.*, 2003; Reid *et al.*, 1993).

Clinical presentation. Individuals with swim goggles dermatitis present with pruritic, periorbital erythema with vesicles, and yellow exudative lesions in severe cases (Tlougan *et al.*, 2010a). Diving mask dermatitis presents with redness and pruritus over areas of direct contact (Fisher, 1980; Maibach, 1975; Tuyp, 1983). Individuals with contact dermatitis to swim caps, ear plugs and nose clips present with well-defined, erythematous, scaling plaques and occasionally vesicles over areas in direct contact with the offending agent. Wet suit dermatitis manifests as a pruritic, vesicular or eczematous eruption on the neck, trunk and extremities (Tlougan *et al.*, 2010a).

Management. Mainstay treatment for swim goggle dermatitis includes the use of medium-potency topical corticosteroids, while systemic steroids may be required in severe cases. Topical immunomodulators may also be effective in mild and chronic conditions (Tlougan *et al.*, 2010a). For contact allergies to other types of swim gear described above, avoidance of the offending allergen and use of silicone based gear is recommended (Fisher, 1980; Goette, 1984; Taylor & Rubber, 1986).

2.2.2 Pool and pool water dermatitis

Pool dermatitis is an irritant dermatitis to chemicals in swimming pools, particularly chlorine and bromine.

Fig. 6. Pool dermatitis. Eczematous plaques in uncovered areas in a swimmer (Tlougan *et al.*, 2010a). Reproduced with permission from *International Journal of Dermatology*.

One study found that swimmers developed more severe cutaneous eruptions after swimming in brominated pools compared to chlorinated pools (Penny, 1991). In contrast to pool dermatitis, pool water dermatitis is an allergic contact dermatitis to chlorinated or brominated compounds in the water. Potassium peroxymonosulfate (PPMS) which is another decontaminant used in pools and hot tubs may also cause pool water dermatitis (Gilligan *et al.,* 2010).

Clinical presentation. Individuals with pool dermatitis present with pruritic, urticarial or eczematous plaques in uncovered areas of skin (Penny, 1991; Rycroft & Penny, 1983). Individuals with pool water dermatitis present with pruritic, erythematous, scaling plaques in uncovered areas of the skin (Fitzgerald *et al.,* 1995; Sasseville *et al.,* 1999).

Management. Avoidance of the offending irritant and halogenated water is recommended for sensitized athletes (Penny, 1991). Diligent use of emollients is also imperative.

2.3 Miscellaneous
2.3.1 Purpura gogglorum

Purpura gogglorum or periocular purpura induced by goggles is thought to be caused by collision forces, suction trauma or pressure of the goggles on the periocular soft tissue (Jonasson, 1997; Jowett & Jowett, 1997; Metzer & Berlob, 1992).

Clinical presentation. Individuals present with purpura around the eyes.

Management. These lesions usually heal spontaneously. In severe cases with vision changes and extensive swelling and facial tenderness, referral to the emergency department to evaluate for possible fracture of facial bones is warranted (Tlougan *et al.,* 2010a).

2.3.2 Platform purpura

Platform purpura is a skin condition that occurs during a missed dive in which the forces upon entering the pool are transmitted to the skin of the thighs (Tlougan *et al.,* 2010a).

Clinical presentation. Individuals present with symmetrical, erythematous plaques on the thighs that may be painful (Tlougan *et al.,* 2010a).

Management. Supportive care includes nonsteroidal anti-inflammatory drugs and application of warm compresses for 5–10 minutes two or three times daily for pain relief. The lesions typically resolve within a few days (Tlougan *et al.,* 2010a).

2.3.3 Aquagenic pruritus

Aquagenic pruritus occurs after brief exposure to water at any temperature and is associated with mast cell degranulation, elevated blood levels of histamine and local release of acetylcholine in the skin (Greaves, 1992).

Clinical presentation. Individuals present with pruritus or a tingling, burning or stinging sensation after exposure to water without any apparent skin changes. The symptoms last between 10 minutes and a couple of hours (Steinman & Greaves, 1985).

Management. Phototherapy, particularly PUVA and narrow-band UVB may help relieve pruritus, while some patients may respond to antihistamines (Greaves, 1992; Xifra *et al.,* 2005).

2.3.4 Aquagenic, cold and cholinergic urticaria

Aquagenic urticaria is a rare type of physical urticaria that occurs upon contact with any form of water at any temperature (Hide *et al.,* 2000; Shelley & Rawnsley, 1964). In contrast,

cold urticaria occurs in athletes exposed to cold water and is also associated with winter sports (Sarnaik *et al.*, 1986). While essential acquired cold urticaria is the most common type of cold urticaria, secondary causes include cryoglobulinemia and connective tissue disorders (Sarnaik *et al.*, 1986). Familial cold autoinflammatory syndrome is another condition that manifests with cold urticaria in addition to periodic fever and joint pain (Hoffman *et al.,* 2001). Cholinergic urticaria is the most common subtype of physical urticaria found in athletes, and is typically induced by physical exertion, exposure to heat or emotional stress (Jorizzo, 1987).

Clinical presentation. Individuals with aquagenic urticaria present with urticarial wheals on any submerged skin surface shortly after contact with water. Occasionally, only a focal urticarial eruption may occur (Shelley & Rawnsley, 1964). Systemic symptoms occur rarely and include headache and respiratory distress (Baptist & Baldwin, 2005; Luong & Nguyen, 1998). Cold urticaria presents with erythematous, edematous papules along cold-exposed skin surfaces that are very pruritic. Individuals may also present with systemic symptoms including anaphylaxis and loss of consciousness which may result in drowning (Sarnaik *et al.*, 1986).Cold urticaria may be differentiated from aquagenic urticaria by placement of an ice cube on the forearm for several minutes, with resulting development of a square urticarial plaque during rewarming of the skin (Blanco *et al.*, 2000). Individuals with cholinergic urticaria typically present initially with itching or burning, with subsequent development of flushing and hives minutes after the onset of physical activity (Jorizzo, 1987). The diagnosis is supported by exercise testing, sauna test or hot bath challenge with a resulting urticarial eruption (Jorizzo, 1987).

Fig. 7. Cold urticaria. Square urticarial plaque develops after placement of an ice cube on the forearm skin during rewarming of the skin (Tlougan *et al.,* 2010a). Reproduced with permission from *International Journal of Dermatology*.

Management. Individuals with aquagenic urticaria may respond to antihistamines and anticholinergic agents. Other alternative treatment options include PUVA and UVB (Juhlin & Malmros-Enander, 1986; Parker *et al.*, 1992). Individuals with cold urticaria generally respond well to antihistamines (Juhlin, 2004; Zuberbier *et al.*, 2006). Health care providers

should also consider secondary causes of cold urticaria including cryoglobulinemia and connective tissue disorders and treat the underlying conditions (Sarnaik *et al.*, 1986). It is recommended that affected athletes wear protective clothing when exposed to cold environments. Traditional therapy for cholinergic urticaria includes antihistamines and leukotriene inhibitors (Otto & Calabria, 2009).

2.3.5 Green hair

Green hair occurs in swimmers with blonde, gray or white hair after exposure to copper in pool water. Frequent hot air drying, brushing, sun exposure, peroxide bleaching and use of alkaline or tar shampoos increases the likelihood of developing green hair (Carson, 1977; Holmes & Goldsmith, 1974).

Clinical presentation. Individuals present with green-colored hair after swimming (Goette, 1978).

Management. Effective treatment options for green hair include 3-5% hydrogen peroxide and copper chelating shampoos (Adams, 2001).

2.3.6 Swimmer's shoulder

Swimmer's shoulder typically occurs during the crawl stroke in which the athlete's chin rubs against the shoulder while turning the head to breathe, with the development of irritation dermatitis (Koehn, 1991).

Clinical presentation. Individuals present with erythematous and slightly roughened plaques on the anterior aspect of the shoulder after swimming (Tlougan *et al.*, 2010a).

Management. Lesions typically heal without treatment, while application of petroleum jelly or polysporin ointment may provide additional relief (Tlougan *et al.*, 2010a).

2.3.7 Pool palms

Pool palms describe a type of frictional dermatitis resulting from repetitive rubbing of the skin surfaces against rough surfaces in the pool (Blauvelt *et al.,* 1992; Wong & Rogers, 2007).

Clinical presentation. Individuals present with symmetric erythematous plaques on the convexities of the palmar hands and fingers (Lacour, 1995).

Management. This condition usually resolves spontaneously after cessation of the irritating activity (Tlougan *et al.,* 2010a).

3. Saltwater

3.1 Infectious and organism-related
3.1.1 Cnidarial dermatoses

Cnidarial dermatoses result from contact with marine invertebrates of the phylum *Cnidaria*. These organisms contain nematocysts on their tentacles which may pierce the skin and release toxins that may result in cutaneous as well as systemic reactions. Several organisms known to affect water athletes and swimmers include Portuguese man-of-war, jelly fish, sea anemones, fire corals and red sea corals.

Clinical presentation. Individuals stung by Portuguese man-of-war present with pain after the initial sting, followed by development of a pruritic, erythematous, urticarial eruption that subsides after a few days. Violaceous lesions and vesicles occasionally occur, while

systemic symptoms including anaphylaxis are rare (Adams, 2006). Similarly, jellyfish stings present with initial stinging sensation followed by urticarial or papulovesicular lesions in a linear distribution (Burnett, 1992; Currie & Jacups, 2005).Delayed reactions including hyperpigmentation, lipodystrophy, keloid-like scars and erythema nodosum may result, while severe reactions including respiratory distress and cardiac arrest rarely occur (Burnett et al., 1986; Manowitz & Rosenthal, 1979; Tamanaha & Izumi, 1996; Veraldi & Carrera, 2000).

Individuals stung by sea anemones present with an initial stinging or burning sensation with erythema, edema, petechial hemorrhages and ecchymoses. Eventually, an erythematous, papulovesicular eruption develops and local necrosis, ulceration and desquamation may occur (Halstead, 1988). Bathing or showering exacerbates the stinging or burning sensation. Severe side effects include acute renal failure and fulminant hepatic failure (Garcia et al., 1994; Mizuno et al., 2000). Seabather's eruption results from contact with larvae of the adult sea anemone and the thimble jellyfish and presents similarly with systemic symptoms occurring in up to 10% of cases. (Freudenthal & Joseph, 1993; MacSween & Williams, 1996; Sams, 1949; Tomchik et al., 1993).

Fig. 8. Jellyfish sting. Linear erythematous plaques, which may be vesicular or urticarial (Tlougan et al., 2010b). Reproduced with permission from *International Journal of Dermatology.*

Individuals stung by the fire coral present with erythematous, burning lesions caused by formic acid on the coral's outer shell. Individuals stung by the red soft coral present with urticarial eruption of the hands and arms with vesicular-bullous lesions, in addition to conjunctivitis, rhinitis and asthma from release of a toxin (Addy, 1991; Canarasa et al., 1993; Fisher, 1999; Miracco et al., 2001; Onizuka et al., 2001).

Management. Supportive care for Cnidarial dermatoses includes application of warm compresses, topical corticosteroids and antihistamines for symptomatic relief. Some authors recommend applying sand to the affected areas to facilitate removal of the nematocysts. Severe anaphylactic reactions require epinephrine. Clinicians should consider pain management and tetanus prophylaxis as well (Tlougan et al., 2010b).

For jellyfish stings, application of vinegar may provide relief. Some authors recommend prompt placement of meat tenderizer to help inactive toxins (Freiman *et al.*, 2004). It is important to note that swimmers should not immerse themselves in freshwater after being stung by saltwater Cnidaria because this may activate nematocysts (Tlougan *et al.*, 2010b).

Treatment of fire coral dermatitis includes application of ammonium to neutralize formic acid (Tlougan *et al.*, 2010b).

3.1.2 Echinodermata dermatoses

Echinodermata dermatoses result from contact with marine invertebrates from the phylum *Echinodermata*. Organisms which may result in injury to aquatic athletes and swimmers include sea stars, sea urchins and sea cucumbers.

Clinical presentation. Individuals in contact with the spines of seastars may present with puncture wounds and a burning sensation which may persist for one month (Auerbach, 1991). Contact with sea urchin spines may result in a painful puncture wound with surrounding erythema and edema, while broken spines may remain lodged in the skin. Rarely, tenosynovitis and systemic reactions including nausea, syncope and respiratory distress may occur (Baden, 1987). Contact with sea cucumbers may present as a burning irritant dermatitis. The sea cucumber toxin holothurin, a potent cardiac glycoside, may cause a chemical conjunctivitis and even blindness, while ingestion may result in death (Tlougan *et al.*, 2010b).

Fig. 9. Sea urchin spine. Spine punctured through the skin with resulting pain, redness and swelling (Tlougan *et al.*, 2010b). Reproduced with permission from *International Journal of Dermatology*.

Management. Symptomatic relief for individuals affected by seastars and sea urchins includes warm compresses, topical corticosteroids and antihistamines. Anaphylaxis should be promptly treated with epinephrine. Athletes affected by sea cucumbers should immediately irrigate the wound with warm water, soap, vinegar or isopropyl alcohol to rinse off the holothurin toxin. Healthcare providers should treat eye injury with topical anesthesia, irrigation and consultation with an ophthalmologist (Tlougan *et al.*, 2010b).

3.1.3 Sponge dermatitis

Marine sponge dermatitis results from contact with marine invertebrates of the phylum *Porifera*. Marine sponges with sharp spicules can cause minor abrasions upon contact with swimmers. In addition, marine sponges may cause an irritant dermatitis as well as local and systemic reactions from the production of crinitoxins by some species (Brown & Shepherd, 1992; Sims & Irei, 1979).

Clinical presentation. Individuals present with a stinging sensation followed by pain, pruritus, and swelling shortly after contact with the organism. Severe effects may result from the crinitoxins with cutaneous manifestations including vesiculations, bullae, desquamation, in addition to delayed allergic contact reactions, erythema multiforme and rarely anaphylaxis (Brown & Shepherd, 1992).

Management. Similar to Cnidarial dermatoses, management includes symptomatic relief as described above and epinephrine for anaphylactic reactions (Tlougan *et al.*, 2010b).

3.2 Contact dermatitis
3.2.1 Seaweed dermatitis

Seaweed dermatitis is a type of contact dermatitis that results from irritants produced from *Lyngbya majuscula*, a blue-green alga that is prevalent in the Pacific, Indian, and Caribbean oceans (Chu, 1959; Osborne e*t al.*, 2001).

Clinical presentation. Individuals present with blisters and desquamation with associated stinging, burning, or pruritic sensation within 24 hours after contact (Gauer & Arnold, 1961; Izumi & Moore, 1987). The lesions progress to an erythematous dermatitis that commonly surrounds the perineal and perianal areas lasting for about one week. Ingestion or inhalation of the irritants may result in burning of the upper gastrointestinal tract and respiratory irritation (Anderson e*t al.*, 1988; Marshall & Vogt, 1994).

Management. Supportive therapy includes symptomatic relief with cool compresses, treatment with topical corticosteroids, antihistamines and analgesics (Izumi & Moore, 1987).

4. On the water

4.1 Sailing/rowing
4.1.1 Pulling boat hands

Pulling boat hands is due to a combination of mechanical injury and exposure to cold, and is usually seen in sailors, rowers and crew team members (Toback *et al.*, 1985). There is a strong association between this condition and Raynaud's phenomenon, which causes pallor and numbness of the distal digits with resulting color changes from white to blue to red (Toback *et al.*, 1985).

Clinical presentation. Individuals present with erythematous papules, macules, nodules and blisters that may be painful and pruritic. The lesions typically manifest over the distal dorsal aspect of the hands and proximal phalanges, with sparing of the skin over the metacarpophalangeal (MCP) joints and fingertips (Tlougan *et al.*, 2010c).

Management. The mainstay treatment includes topical corticosteroids, while supportive care includes use of moisturizers, gloves and freshwater soaks (Tlougan *et al.*, 2010c).

4.1.2 Sailor's marks

Sailor's marks are associated with repetitive contact and friction between the rope and hands of sailors, with resulting thickening of the skin (Unal *et al.*, 2005).

Clinical presentation. Individuals present with hyperkeratotic thickening of the superficial skin, with band-shaped calluses that manifest bilaterally on the dorsolateral and palmar regions of the first MCP joint and the mediopalmar site of the fifth MCP joint (Tlougan *et al.*, 2010c).

Management. Prevention of the condition includes wearing protective gloves while sailing (Tlougan *et al.,* 2010c).

4.1.3 Rowing blisters

Rowing blisters result from friction between rower's hands and the oar handles (Rumball *et al.*, 2005).

Clinical presentation. Individuals present with painful blisters that typically manifest on the anterior surfaces of the fingers and palms (Tlougan *et al*., 2010c).

Management. Treatment consists of supportive care of the blisters by draining the lesions without disruption of the roof of the blister up to three times in the first day, and application of petroleum jelly and occlusive dressing (Tlougan *et al.,* 2010c).

4.2 Fishing
4.2.1 Fishing rod dermatitis

Fishing rod dermatitis is a contact dermatitis that results from exposure to isopropylparaphenylenediamine (IPPD) or other closely related components of carbon-fiber fishing rods (Minciullo *et al.*, 2004).

Clinical presentation. Individuals present with unilateral erythematous, scaly hand plaques (Tlougan *et al.,* 2010c).

Fig. 10. Fishing rod dermatitis. Erythematous, scaly plaques on the hand (Tlougan *et al.,* 2010c). Reproduced with permission from *International Journal of Dermatology*.

Management. Treatment consists of topical corticosteroids and oral antihistamines. Preventive methods include using a protective cover and insulating tape over the fishing handles and avoidance of IPPD fishing rods (Tlougan *et al.,* 2010c).

4.2.2 Live fish bait allergy

Live fish bait allergy occurs from exposure to the insects and worms used as fish bait. Contact dermatitis may result from exposure to various species of worms such as *Lumbrinereis latreilli, Nereis versicolor* and *Chironomus thummi thummi,* as well as larvae of the maggot *Calliphora*

vomitoria (Camarasa & Serra-Baldrich, 1993; De Jaegher & Goossens, 1999; Janssens *et al.,* 1995; Usamentiaga *et al.,* 2005; Virgili *et al.,* 2001). Additionally, fisherman may develop allergic contact dermatitis to azo compounds used to dye maggots (Warren & Marren, 1997).

Clinical presentation. Individuals typically present with bilateral pruritus and edema of the hands, and occasionally with hyperkeratotic lesions of the thumbs and index fingers (Virgili *et al.,* 2001). Fish bait allergy may cause an urticarial eruption, respiratory reactivity or rhinoconjunctivitis (Bernstein *et al.,* 1983; Siracusa *et al.,* 1994).

Management. Individuals gradually improve with avoidance of the offending allergens (Tlougan *et al.,* 2010c).

4.2.3 Erysipeloid

Erysipeloid, also known as "fish poison", "shrimp poison", "crab poison" and "scallop poison" is a bacterial infection of traumatized skin by *Erysipelothrix rhusiopathiae,* mostly seen in fisherman (Burke *et al.,* 2006; Reboli & Farrar, 1989). Infection most commonly results in localized cutaneous disease, while disseminated cutaneous disease and generalized systemic infections may occur as well (Barnett *et al.,* 1983).

 Clinical presentation. Patients typically present with well-circumscribed, violaceous, edematous plaques on the fingers and hands that are painful and tender to palpation. The lesions generally display central clearing over time and vesicles may develop as well (Gorby & Peacock, 1998; Reboli & Farrar, 1989). Systemic infection may manifest with constitutional symptoms such as fever and malaise, as well as septicemia, arthritis, empyemas, endocarditis and cerebral abscesses (Gorby & Peacock, 1998; Reboli & Farrar, 1989).

Management. Mainstay treatment of localized cutaneous and diffuse cutaneous forms of disease includes a one week course of penicillin (Varella & Nico, 2005). Severe systemic reations require larger doses of penicillin G (Reboli & Farrar, 1989). Erythromycin may be used in individuals with penicillin allergy.

4.2.4 Rubber boot dermatitis

Rubber boot dermatitis is an allergic contact dermatitis that fisherman develop after exposure to rubber fishing boots (Ross, 1969).

Clinical presentation. Individuals present with a diffuse eczematous eruption throughout the leg. If the lesions progress without treatment, a pompholyx-like eruption may manifest on the palms and soles with scaling, thickening, fissures and exfoliation of the skin (Tlougan *et al.,* 2010c).

Management. Topical corticosteroids and antihistamines are the mainstay treatment. Oral steroids may be required for severe infections. Prevention includes avoidance of rubber boots in sensitized fisherman (Tlougan *et al,* 2010c).

4.3 Surfing
4.3.1 Surfer's nodules

Surfer's nodules are a type of athlete's nodules and occur from repetitive contact and pressure between the surfboard and surfer's bony prominences such as the knees and ankles (Basler., 1989; Erickson & Von Gemmingen, 1967). Some authors also propose that this condition may represent a foreign body reaction to sand or other foreign material (Pharis *et al.,* 1997).

Clinical presentation. Individuals usually present with nontender, fibrotic nodules on the pretibial surface of the leg or the mid-dorsum of the foot (Cohen *et al.,* 1990).

Management. Treatment consists of topical keratolytics such as salicylic acid and lactic acid. Other therapeutic modalities include intralesional corticosteroids, topical corticosteroids and excision of the lesions (Adams *et al.,* 2006). Prevention of this condition includes the use of protective padding on the knees and ankles (Cohen *et al.,* 1990).

4.3.2 Surf rider's dermatitis

Surf rider's dermatitis is a type of irritant contact dermatitis that is generally seen in surfers and users of belly boards, boogie boards and body boards. Friction, shearing forces and pressure between the athlete's body and the surfing board contribute to the development of the eruption (Bischof, 1995). Allergic reactions to surfing board polymers and wax may also occur (Tennstedt *et al.,* 1981).

Clinical presentation. Individuals present with painful erythematous and edematous lesions on the nipples. Surfers may also present with small abrasions and fissures (Tlougan *et al.,* 2010c).

Management. The lesions resolve spontaneously without treatment. Supportive care includes analgesics for pain relief as well as protective dressings and soft clothing (Tlougan *et al.,* 2010c).

5. Conclusion

Aquatic sports dermatoses consist of a variety of cutaneous conditions that occur in athletes who participate in activities on or in the water. Certain conditions are specifically associated with freshwater or saltwater, while others may occur in both settings. Furthermore, participation in particular sporting activities predisposes athletes to certain dermatoses. The approach to athletes with water-related dermatoses consists of taking an appropriate history to recognize the type of water sport, nature of the water exposure with regards to duration in or on the water, saltwater versus freshwater, and any related equipment or contact with organisms. The etiologies of water-related dermatoses are usually infectious and organism-related or result from contact dermatitis. Our review highlights the key physical findings that are most consistent with particular aquatic sports dermatoses. We discuss first-line treatment guidelines and preventive measures that should help guide healthcare providers in the management of athletes with water-related skin conditions.

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Evaluation of Neural Networks to Identify Types of Activity Among Children Using Accelerometers, Global Positioning Systems and Heart Rate Monitors

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1. Introduction

There is a growing awareness of the health benefits of physical activity during childhood and adolescence. However, there is still much to be learned about the nature of children's physical activity patterns and the mechanisms underlying these benefits (Rowland, 2007; Twisk, 2001). The physical activity pattern of children is very different from that of adults. Children's physical activity pattern is characterized by frequent spasmodic bursts of short duration (Baquet et al., 2007). They participate in intermittent and unstructured activities and the type of activities children engage in changes as they develop, going from informal active play during early childhood to activities that begin to mirror those of adults during adolescence (Salmon & Timperio, 2007). The understanding of children's physical activity pattern has been hampered by the lack of satisfactory instruments for measuring it.

Children's physical activity has traditionally been measured with self-reports. Self-reports are easily administered, low-cost measurements. However, they do not capture the sporadic short-burst nature of children's physical activity very well (Baquet et al., 2007). Furthermore, self-reports are influenced by recall bias or social desirability. Accelerometers have therefore, in recent times, become the method of choice in physical activity research. These lightweight, unobtrusive devices provide objective information about the frequency, intensity, and duration of physical activity. In most studies, the raw acceleration signal is converted into activity counts. Total or mean activity counts per day and minutes per day spent above a certain intensity threshold are reported. Activity counts are linearly related to energy expenditure. This does not value the richness of accelerometer data (Esliger et al., 2005) because this approach is unable to correctly distinguish between different types of activities with different levels of energy expenditure but that produce similar mean activity counts over time. A solution for this problem is to use not only the mean counts over a certain time period, but also more information about the distribution of these counts (i.e. standard deviation, percentiles) over time.

Recently, statistical models have been developed to identify specific types of physical activities based on a new methodology for processing accelerometer data. The most common classification algorithms have been developed by using the pattern-recognition or

"machine-learning" approach. These algorithms are decision trees (Bonomi et al., 2009a, Bonomi et al., 2009b), neural networks (Staudenmayer et al., 2009; De Vries et al., 2011a), and hidden Markov models (Pober et al., 2006), and they use several descriptive statistics calculated over non overlapping segments of accelerometer data as input variables of the models to classify a set of previously registered physical activities. Pattern-recognition approaches have shown to be successful in classifying a number of controlled physical activities among adults and elderly but not many studies apply these approaches to accelerometer data from children.

Our research group has developed several neural network algorithms to classify a number of controlled physical activities among children (De Vries et al., 2011b). The study population was a group of 58 healthy children between the age of 9 and 12 years. The physical activities observed were sitting, standing still, walking, running, rope skipping, playing soccer, and cycling. The children were wearing uni-axial and three-axial accelerometers on the hip and on the ankle. Our results showed that algorithms based on data from three-axial accelerometers worn on the hip performed better (77%) than models based on uni-axial accelerometers (72%), and models based on accelerometers worn on the ankle (57% and 68% for the uni-axial and the three-axial model respectively). However, the developed algorithms could not discriminate between two self-paced speeds of cycling, and there were misclassification errors when classifying the activities playing soccer and cycling. Discriminating between activities performed with different intensity is important to accurately estimate energy expenditure.

The classification performance of pattern-recognition models to discriminate between activities performed with different intensity may be improved by including information about the intensity of physical activities assessed with other sensors than accelerometers such as global positioning systems (GPS) and heart rate monitors. GPS not only provides information about the geographic location of physical activity, but also provides a precise time reference, which can be used in combination with location information to assess velocity. Until now, GPS measurements have only been combined with accelerometer data to provide insight into the location of the physical activity. Maddison and Mhurchu (2009) describe several studies in which accelerometer data are integrated with location GPS data to map participant's neighborhood to identify where physical activity took place, to describe physical activity pattern, and to discriminate between active and inactive transportation. Velocity measurements assessed by GPS can be included in a pattern-recognition model to discriminate between physical activities performed at different speeds (for example, regular walking or cycling versus brisk walking or cycling).

Another objective assessment methods that may be valuable in relation to accelerometer based pattern-recognition models are heart rate monitors. Heart rate monitors do not register physical activity directly; their assessment of physical activity is based on the linear relationship between oxygen uptake and heart rate. When the intensity of an activity increases, the heart rate increases. Eston et al. (1998) showed that models that combine three-axial accelerometer data and heart rate data assessed a better prediction of energy expenditure than models based on three-axial accelerometers alone. Recent evidence suggests that the Actiheart, an integrated accelerometer and heart rate unit, provides a more accurate prediction of children's energy expenditure than either heart rate or accelerometry alone. However, there are no studies combining accelerometer and heart rate data to improve the classification performance of pattern-recognition models. Therefore, the purpose of this study was to examine whether the accuracy of the previously developed

ANN models based on three-axial accelerometer data from the hip might be improved by including more information about the intensity of activities by means of heart rate data or by adding information about the velocity of activities fromGPS.

2. Methods

2.1 Subjects and data collection

Children between the age of 9 and 12 years were recruited from three elementary schools in the Netherlands by sending written information about the purpose and nature of the study to their parents. Finally 58 healthy children (31 boys, 27 girls) were permitted by one of their parents to participate in the study. Data from 52 children (27 boys, 25 girls) had measurements from all devices (accelerometer, GPS and heart rate monitors), and could be used for the analyses. The characteristics of these children are shown in Table 1. Each child was observed by a research assistant while performing a fixed sequence of 20 minutes comprising the following activities: sitting during a writing task, standing, walking, running, rope skipping, playing soccer (i.e., kicking the ball back and forth to the research assistant), regular cycling and brisk cycling. The research assistant recorded the starting and the finishing time of each activity with a stopwatch. In order to imitate real-life, all activities were performed at a self-paced speed. With the exception of sitting, all activities were conducted outdoors in the direct vicinity of the subject's school in similar weather conditions (i.e., no rain, mild wind). For cycling, the subjects used their own bicycle. All subjects wore various measurement instruments: a heart rate receiver unit (Polar Electro S610i, Finland) on the wrist with the transmitter (Polar T61 Coded Transmitter, Finland) worn on the chest, a three-axial ActiGraph accelerometer (ActiGraph GT3X, Pensicola, FL) and a GPS (QSTARZ travel recorder V4.3, Taipei, Taiwan) on the right hip. The ActiGraph is the most validated and widely used accelerometer. It has good reproducibility, validity, and feasibility when used to assess physical activity in children (De Vries et al., 2009). The axes senses of the three-axial accelerometer are vertical, medio-lateral and anterior-poterior direction. Accelerometer data (counts) were collected for each axis in one second epochs. The default sample-rate frequency setting of the GPS (kilometer per hour) is also 1 Hz and the Polar heart rate monitor (beats per minute) sampled at 0.2 Hz (once in every 5 seconds). Children's body height and body weight were measured with a portable stadiometer (Seca 225, Vogel & Halke GmbH & Co, Germany) and a digital scale (Soehnle 62882, Leifheit AG, Germany).

	Boys (n = 27)	Girls (n = 25)	Total (n = 52)
Age (years)	10.9 (0.8)	11.1 (0.7)	11.0 (0.7)
Height (cm)	151.6 (5.7)	148.0 (5.5)	149.9 (5.8)
Weight (kg)	43.5 (9.2)	41.1 (5.4)	42.3 (7.7)
BMI (kg/m²)	18.8 (3.2)	18.8 (2.5)	18.8 (2.9)

Table 1. Children's characteristics (mean and standard deviation).

2.2 Data processing

When the data collection was complete, the accelerometer data were downloaded to a personal computer and processed using the ActiLifeGT3X software program. GPS data were

also downloaded to the computer and processed using Qstarz Travel Recorder PC Utility V4 software. Polar Precision Performance software was used to read the Polar Electro S610i receiver. Next, the data was labeled to one of the eight physical activities according to the starting and the finishing time of each activity. Data from the physical activity sitting were eliminated because this activity was performed inside of the school and the GPS monitors cannot receive an accurate signal inside of buildings. For each of the seven remaining activities the first and the last four seconds of the signals were deleted to eliminate any noise in the data of the transition period between activities. This time buffer was determined by visually inspecting the data set. If the activity (e.g., standing) was carried out several times, the signal was cleaned for each period. The cleared data for the physical activities were then used for further analyses.

2.3 Statistical analysis

First, descriptive statistics were used to characterize the sample and to study signal differences between activity types. Second, correlations between accelerometer counts (3-axes) and GPS data and between accelerometer counts (3-axes) and heart rate data were computed to study the relationship between these variables. Third, differences in the mean accelerometer counts from different axes, GPS speed, and heart rate per child between activities types were tested with an ANOVA. Finally, post hoc tests comparing all pairs of physical activity were performed. Values were considered statistically significant when the two-sided P value was lower than 0.05.

To classify the activity type, four artificial neural networks (ANN) models were developed; a model based on: three-axial accelerometer data (Model 1), three-axial accelerometer data and GPS data (Model 2), three-axial accelerometer data and heart rate data (Model 3), and three-axial accelerometer data, GPS data and heart rate data (Model 4).

ANNs provide a flexible non-linear extension of multiple regression. Feed-forward neural network models were used for the analyses (Ripley, 1996). They consist of a function with a set of predictors or input variables that represent characteristics or statistical summaries describing the signals, a single hidden layer with several hidden units, and one discrete dependent or output variable with several categories that represent physical activity types. Figure 1 presents an illustration of a feed-forward ANN model with five hidden units. The mathematical equations of the model are also provided. If x_i denotes an input variable, y_k an output variable with k categories and f_j and f_k denote the transformation functions, then this model can be written as

$$y_k = f_k \left(\alpha_k + \sum_{j \to k} w_{jk} f_j \left(\alpha_j + \sum_{i \to j} w_{ij} x_i \right) \right) \qquad (1)$$

The transformation functions f_j and f_k are taken to be the logistic function

$$f(x) = \frac{\exp(x)}{1 + \exp(x)} \qquad (2)$$

since this transformation performed better than other alternative functions. Alternative transformation functions are described in Ripley (1996). The parameters w_{ij} and w_{jk} are known as weights, and they are linear combinations of the inputs or the hidden units. Finally, the intercepts α_j and α_k are known as biases.
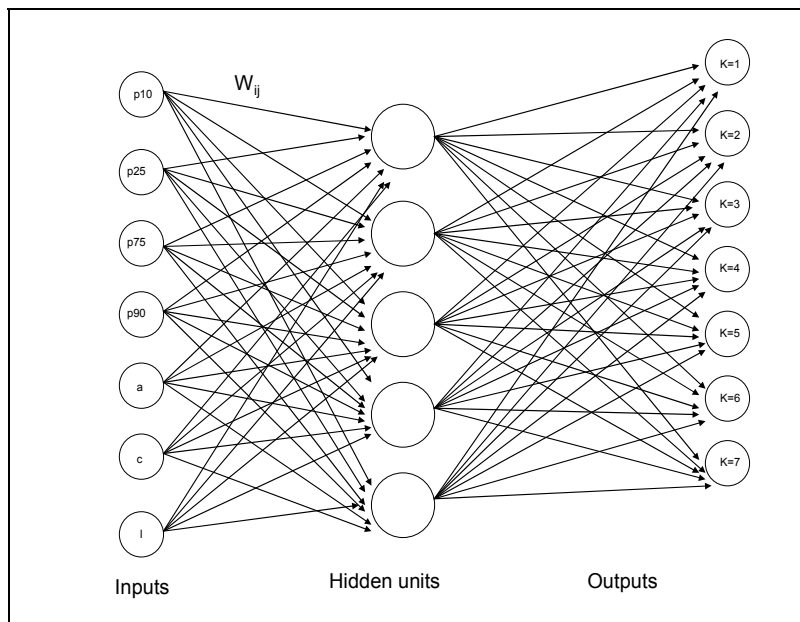
Note: The input variables represent the characteristics of the acceleration signal: p10 = 10th percentile; p25 = 25th percentile; p75 = 75th percentile; p90 = 90th percentile; a = absolute deviation; c = coefficient of variability; and l = lag-one autocorrelation; the hidden units are weighted combinations of the input variables; in the output, each k represents a physical activity.

Fig. 1. Feed-forward neural network model for k=7 activities

Before estimating the ANN models, all signals were segmented into non overlapping intervals of 10 seconds. For heart rate the intervals only contained two data points because the sampling interval was 5 seconds. Next, several signal characteristics or statistical summaries were computed for each 10 second segment. The statistical summaries used in this study were selected from the set of characteristics used by Rothney et al. (2007), Bonomi et al. (2009), and Staudenmayer et al. (2009). For the accelerometer data, we used the following signal characteristics: 10th, 25th, 75th, and 90th percentiles, absolute deviation (i.e., the sum of the absolute difference between each element of the interval and the mean), coefficient of variability (i.e., the ratio of the standard deviation and the mean), and lag-one autocorrelation (i.e., the correlation between consecutive elements within intervals). These statistics were computed for each axis independently. For the GPS signal, the features mean and absolute deviation were included as input variables for the two models with GPS data. For the heart rate signal, only the mean was computed because of the reduced number of data points per interval.

The accuracy of the four models was evaluated by leave-one-subject-out cross-validation (Venables & Ripley, 2002). In this method a set of n-1 subjects was used as a training set and the subject left out was used as a test set. This process was repeated for all n subjects. Feed-forward ANN models with a single hidden layer, five hidden units, and a weight decay[1] equal to 0.006 showed the highest classification accuracy. Next, contingency tables were built to evaluate the classification errors of the models in more detail.

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[1] In order to use a weight decay as penalty, the input variables were rescaled to range between 0 and 1.

All statistical analyses were performed using the software package R version 2.8.0 (R Development Core Team, 2008). The classification models were developed with the function nnet (Venables & Ripley, 2002). Both R and nnet are freely available.

3. Results

3.1 Descriptive results

Figure 2a-c shows the main output per measurement instrument. Figure 2a reports accelerometer mean counts per second and standard deviations for the x-, y- and z-axes. The figure shows that the differences in mean counts between physical activities are larger for the x-axis than for the other two axes. Furthermore, it can be seen that the standard deviations are larger for the activity rope skipping than for the other activities. The differences in mean counts per second between standing and all other activities are significant for each axis (x-axis: $F_{(6,330)}=401.03$, $p<.001$; y-axis: $F_{(6,330)}=207.7$, $p<.001$; z-axis; $F_{(6,330)}=72.01$, $p<.001$).

Figure 2b represents bar-charts of mean heart rate output and standard deviations in beats per minute (bpm) across children per physical activity. The mean heart rate is higher for standing (129.5 bpm) than for walking (114.9 bpm). This unexpected result most likely occurred because the recovery time of the heart rate returning to resting status between physical activities is larger than the eliminated data of the time buffer of 4 seconds. The activity standing was performed for short intervals of 1 minute after each activity. Because heart rate values for standing are very high, the differences in heart rate between standing and walking and between standing and regular cycling (136.7 bmp) are not significant. The global test was ($F_{(6,248)}=54.02$ $p<.001$).

Figure 2c reports the mean speed in kilometers per hour (km/h) and standard deviation across children for each activity ($F_{(6,323)}=742.4$, $p<.001$). Mean speed is higher for cycling than for all other activities and there is a significant difference between regular cycling (10.3
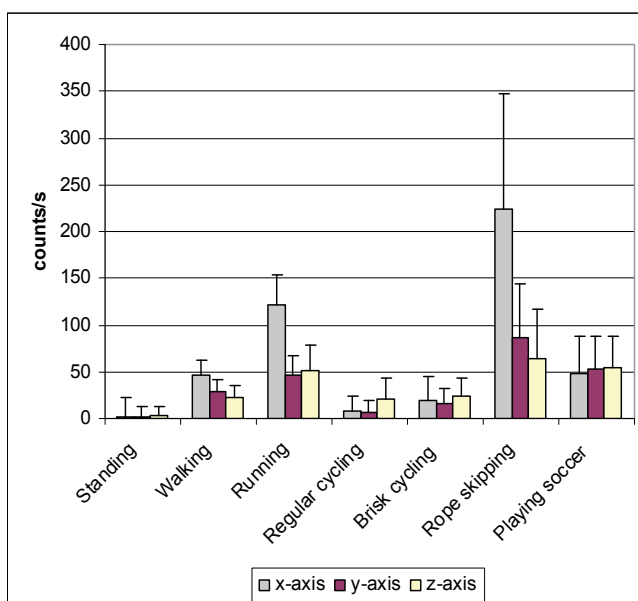
Fig. 2a. Three-axial accelerometer data in counts per second for seven physical activities (mean and standard deviation)
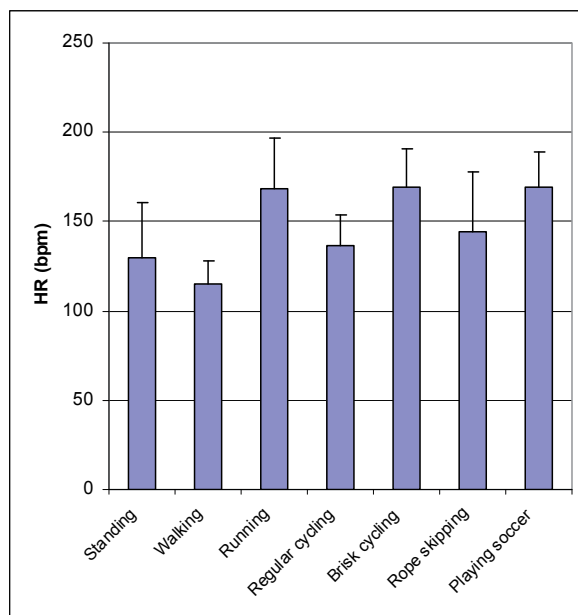
Fig. 2b. Heart rate in beats per minute for seven physical activities (mean and standard deviation)
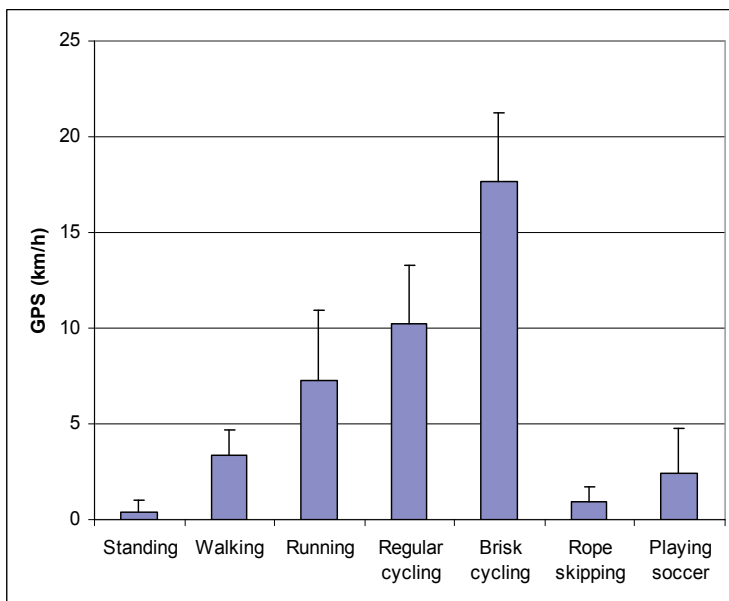
Fig. 2c. GPS velocity in kilometer per hour for seven physical activities (mean and standard deviation)

km/h) and brisk cycling (17.7 km/h). There is also a significant difference between walking (3.4 km/h) and running (7.3 km/h). The mean speed for playing soccer (2.4 km/h) is lower than the mean speed for walking. This unexpected result may be due to differences in

intensity that children play soccer (i.e., long periods of standing still and short bursts of movement). The standard deviation for playing soccer (2.3) is also larger than the standard deviation for walking (1.3).

From Figure 2a-c it can be seen that the mean counts for regular cycling and brisk cycling are very similar while the differences in mean speed and mean heart rate suggest that the intensity of brisk cycling is higher than the intensity of regular cycling. This illustrates the additional value of these monitors to discriminate between two activities with similar means counts.

3.2 Activity classification

Table 2 reports the percentage of correctly classified activities of the cross-validated results for the four developed ANN models. In general all models performed well (>80%) in classifying the activities walking, standing still, rope skipping, running and playing soccer. Cycling was best classified by models including GPS data. Overall, the model based on accelerometer data (Model 1) correctly classified 82% of the activity types. When adding GPS data (Model 2), the overall percentage of correctly classified activities improved to 89%. The improvement was lower (from 82% to 84%) when heart rate data were added to the model (Model 3). Finally, the overall percentage of correctly classified activities with the complete model including accelerometer, GPS and heart rate data (Model 4) was 90%. This is 1% higher than the percentage of correctly classified activities achieved by Model 2.

	Model 1	Model 2	Model 3	Model 4
Standing	87	94	89	95
Walking	92	94	94	95
Running	89	84	87	85
Regular cycling	67	87	70	89
Brisk cycling	33	80	56	72
Rope skipping	91	91	90	90
Playing soccer	87	86	87	89
Total	82	89	84	90

Table 2. Percentage of correctly classified activity types for the fitted ANN models: Model 1 (accelerometer), Model 2 (accelerometer + GPS), Model 3 (accelerometer + heart rate), and Model 4 (accelerometer + GPS + heart rate).

In order to evaluate the classification errors of the four models in more detail, a contingency table was built for each model representing the relationship between the observed and the predicted physical activities. Table 3 shows that the highest percentage of misclassification errors occurred for allocation to the activities brisk and regular cycling. The percentages of misclassification were higher for brisk cycling than for regular cycling. Model 1 achieved the highest misclassification error for both cycling activities (53.6%) followed by Model 3 (31.2%). Furthermore, Model 1 and Model 3 could not discriminate between the activities regular cycling and standing very well. Model 2 achieved the highest misclassification errors between the activities standing and rope skipping.

4. Discussion

The purpose of this study was to investigate whether the accuracy of the previously developed ANN models from De Vries et al. (2011b) could be improved by the inclusion of

data on the intensity of activities by means of heart rate data and/or inclusion of data on the speed of activities from GPS. The results have shown that the performance of the previously developed accelerometer based ANN model, which classified 82% of the activities correctly, improves by 2-8% when including other sensor data. The largest improvement was found when adding GPS data. Including GPS data seemed especially valuable for distinguishing between regular and brisk cycling. The percentages improved from 67% to 87% for regular

Observerd activities	Predicted activities						
	Standing	**Walking**	**Running**	**Regular cycling**	**Brisk cycling**	**Rope skipping**	**Playing soccer**
Standing							
Model 1	**87.5**	0.7	0.4	8.2	0.0	0.8	2.4
Model 2	**94.4**	0.7	0.0	1.0	0.4	1.1	2.5
Model 3	**88.6**	0.3	0.3	6.6	1.4	1.0	1.6
Model 4	**94.8**	0.5	0.3	1.0	0.5	0.9	1.9
Walking							
Model 1	0.7	**92.3**	0.9	1.0	2.6	0.0	2.6
Model 2	1.8	**94.0**	0.3	1.0	1.1	0.2	1.5
Model 3	0.7	**94.0**	0.0	3.5	0.6	0.0	1.2
Model 4	1.2	**95.3**	0.0	2.3	0.1	0.1	0.9
Running							
Model 1	1.0	2.5	**89.2**	1.2	0.6	1.5	3.9
Model 2	2.3	3.4	**84.2**	0.9	0.9	3.2	5.1
Model 3	0.5	2.4	**86.9**	1.6	1.6	2.4	4.6
Model 4	1.3	1.3	**85.5**	0.8	1.9	3.8	5.4
Regular cycling							
Model 1	13.7	2.6	1.1	**67.4**	10.8	0.5	4.0
Model 2	0.3	2.5	0.8	**86.9**	6.3	0.0	3.3
Model 3	13.9	2.7	1.6	**70.3**	8.0	0.6	2.9
Model 4	0.6	2.0	1.4	**88.8**	5.5	0.0	1.8
Brisk cycling							
Model 1	3.1	8.8	3.6	42.5	**33.4**	0.0	8.5
Model 2	0.0	3.2	1.9	13.8	**80.4**	0.0	0.8
Model 3	2.8	3.1	5.2	25.8	**55.7**	0.0	7.3
Model 4	0.0	3.8	4.5	16.4	**72.5**	0.0	2.8
Rope skipping							
Model 1	2.9	0.0	1.4	2.0	0.4	**91.2**	2.2
Model 2	4.9	0.0	0.6	0.3	0.0	**91.2**	3.0
Model 3	2.6	0.2	2.3	2.4	0.5	**89.5**	2.6
Model 4	4.5	0.5	0.8	0.5	0.0	**90.4**	3.4
Playing soccer							
Model 1	1.5	3.9	3.0	2.8	1.1	0.9	**86.8**
Model 2	3.0	4.0	3.4	1.3	0.9	1.0	**86.4**
Model 3	1.4	2.1	2.4	2.6	4.1	0.5	**86.9**
Model 4	2.6	2.4	2.7	0.6	1.8	1.1	**88.7**

Table 3. Cross-validation results for the classification of seven physical activities of Model 1 (accelerometer), Model 2 (accelerometer + GPS), Model 3 (accelerometer + heart rate), and Model 4 (accelerometer + GPS + heart rate) in percentages.

cycling, and from 33% to 80% for brisk cycling. Though the model based on data from all sensors (Model 4) produced the best overall classification, the gain in the percentage of activities correctly classified was only 1% higher that the improvement achieved by the model based on accelerometer and GPS data (Model 2), and the differences in performance per activity were very small (<=3%). Compared to Model 4, Model 2 could discriminate better between regular and brisk cycling, and it was simpler because it used less input variables. Therefore, the addition of GPS data to the model based on three-axial accelerometer data is sufficient to discriminate between activities performed with different intensity.

It is difficult to compare our results with those of previous studies because all the studies differ in the age groups studied, the type of accelerometer monitor the participants worn, the type of patter-recognition model used, the type of signal analyzed (raw data or counts), and also the type of physical activities classified (see Bonomi et al., 2009a, Khan et al., 2008; Liu & Chang, 2009; Staudenmayer et al., 2009). Staudenmayer et al. (2009) achieved a high percentage of correctly classified activities (89%) with an ANN model with a sample of adults. Bonomi et al. (2009) also achieved a high percentage of correctly classified activities (93%) with a decision tree model for a sample of adults. An advantage of the models proposed by Khan et al. (2008) and Liu & Chang (2009) could be that they used combined characteristics of the three-axial accelerometer signal as input variables in the models. However, our classification results did not improve when we performed additional analyses including combined characteristics of the three-axial accelerometer data.

To our knowledge, this is the first study that used ANN models with data from multiple sensors to classify children's physical activity type. We can only compare our results to the single sensor model proposed in De Vries et al. (2011b). Though the performance of the model based on three-axial accelerometer data presented in this paper (82%) is better than the performance of the equivalent model proposed in De Vries et al. (2011b) for children (77%), the differences in performance can be mainly explained by the differences in the type of activities classified. De Vries et al. (2011b) did not distinguish between regular and brisk cycling, and they included data from the activity sitting. In their model a high misclassification error was found between the activities sitting and standing. In this study, data from the activity sitting were not included because this activity was performed inside of the schools and accurate GPS data cannot be registered inside of buildings.

In previous studies, the output of multiple sensors has been combined to increase the prediction of energy expenditure. There are several monitors available that combine multiple sensors. For example, the Actiheart is an integrated accelerometer and heart rate unit and it provides a more accurate prediction of children's energy expenditure than either heart rate or accelerometry alone (Rowlands and Eston, 2007). Another device is the Intelligent Device for Energy Expenditure and Activity (IDEEA) which consists of five mini-accelerometers attached to the chest, to both thighs and under both feet (Rothney et al., 2007). However, these monitors cannot be used in large epidemiological studies because they are either very expensive or difficult to place. Heart rate monitors perform better in combination with other sensors than alone when classifying physical activity because their assessment of physical activity is based on the linear relationship between oxygen uptake and heart rate. If the intensity of an activity increases, the heart rate increases. Moreover, there are large inter-individual differences in the heart rate recovery time, and in rest heart rate levels. Therefore, heart rate data must be calibrated before including them in a pattern recognition model.

Beside heart rate units, GPS monitors have already been combined with accelerometer data in previous studies to assess physical activity. Mostly location GPS data were combined with accelerometer data to assess physical activity (Maddison & Mhurchu, 2009). Our study has showed that speed GPS data may help to discriminate between physical activities performed with different intensity, such as regular cycling and brisk cycling, better than heart rate data because GPS data do not need to be calibrated. Furthermore, other factors such as emotional stress can change the heart rate. A drawback of GPS monitors is that the GPS signal strength is not always sufficient, for example, when the monitors are worn inside of buildings.

This study had some weaknesses. First, it is known that children's activity pattern is different from the adults' activity pattern. In children's physical activity, there is more variance in intensity within and between activities. In addition they more often change of type of activity. In this study, all signals were segmented in non overlapping intervals of 10 seconds, and signal features were calculated for each interval. However, 10 seconds may be a too long time period when there are several transitions between activities within a few seconds. Therefore, it must be studied whether the classification performance of the models may increase when shorter time intervals are used.

Furthermore, future studies should determine whether the accuracy of the ANN models based on accelerometers and heart rate data could be further improved by increasing the measurement frequency of heart rate, by calibrating the heart rate signal or by computing other signal features. Alternative features could be the maximum peak per interval or the maximum deviation from the baseline heart rate.

5. Acknowledgment

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The Application of Medical Infrared Thermography in Sports Medicine

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1. Introduction

Medical Infrared Thermography (MIT) is a non-radiating and contact-free technology to monitor physiological functions related to skin temperature control. The efficiency, safety and low cost of MIT make it a useful auxiliary tool for detecting and locating thermal abnormalities characterized by increases or decreases in skin surface temperature. It has been successfully utilized in the field of veterinary medicine to detect locomotion injuries in racehorses and to monitor their health status. However, research on human athletes with modern infrared sensor technology is more rare. Athletes are exposed to physical stress in training and during competition season. Overuse reactions and so-called "minor traumas" are very frequent; therefore, early detection is critical to avoid injuries. Research suggests that the most beneficial application of MIT is the screening of individuals for overuse injuries. In the following chapters, the use of MIT in clinical practice is presented with special focus on sports injuries and exercise-induced physiological functions. Case studies illustrate the clinical applicability.

2. MIT – Quo Vadis?

2.1 History and development

The association between changes in temperature and disease is almost as old as medicine itself. Hippocrates stated, "should one part of the body be hotter or colder than the rest, then disease is present in that part". The first application of thermal imaging was in the early 19th century and did not have any commercial purpose. Following the 2nd World War, infrared imaging systems were used to monitor changes in skin temperature in relation to certain diseases (Ring, 2007). Poor quality imaging systems and a lack of methodological standards in the past has limited quality, resulting in non-acceptance of the technique (Elliot & Head, 1999). Technological advances in infrared cameras within the last few years have promoted MIT as a powerful measurement tool. A new generation of high-resolution cameras,

appropriate software and standardized protocols have been developed for medical imaging, resulting in improved diagnostic capability and reliability (Plassmann et al., 2006; Diakides & Bronzino, 2008). In 1987, the American Medical Association recognized MIT as a feasible diagnostic tool. The following worldwide Thermographic organizations promote the proper application of medical thermal imaging.

- International Academy of Clinical Thermology
- International Thermographic Society
- American Academy of Medical Infrared Imaging
- European Association of Thermology
- Northern Norwegian Centre for Medical Thermography
- German Society of Thermography and Regulation Medicine

2.2 Technical principles

Most of the diagnostic imaging modalities in medicine utilize portions of the electromagnetic spectrum (Hildebrandt et al., 2010) (Figure 1). However, in contrast to other medical devices, MIT uses non-ionising radiation, thus allowing an unconstrained and
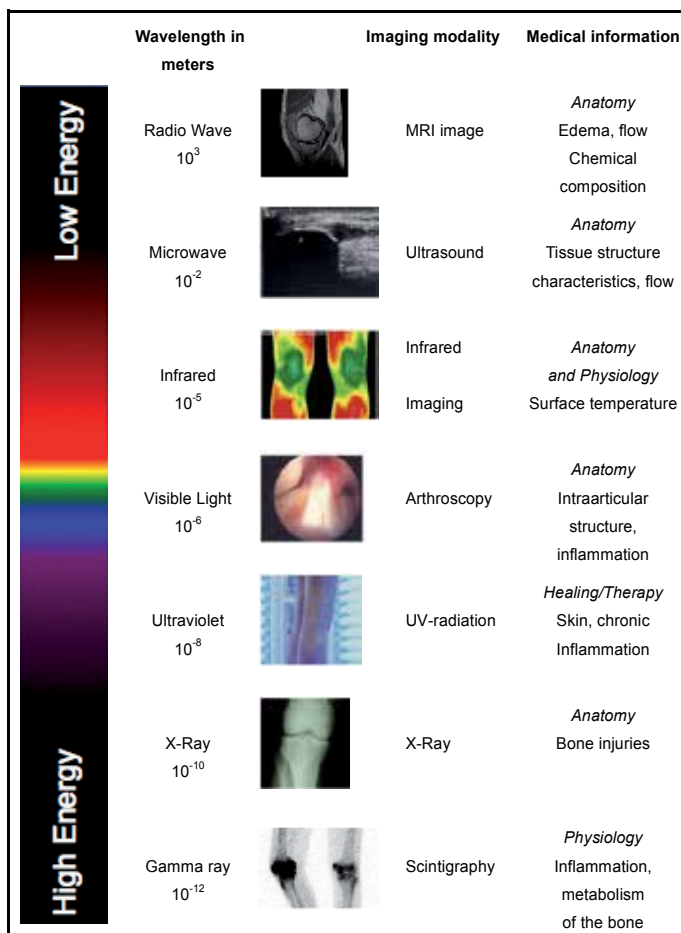

Fig. 1. Medical imaging modalities within the electromagnetic spectrum

harmless application in patients. Using infrared radiation, infrared cameras generate thermal images based on the amount of heat dissipated at the surface. Roughly 80% of the emitted infrared radiation of human skin is in the wavelength range of 8-15μm (Steketee, 1973). The technology operates in the long-wave infrared region and is a sophisticated way of receiving electromagnetic radiation and converting it into electrical signals. These signals are finally displayed and matched to colors on the screen for calculations. Modern focal plane array detectors ensure a stable image with high thermal resolution. Sensitivity and resolution are important parameters for medical devices (Plassmann et al., 2006). High-resolution cameras with focal plane arrays of 320×240 pixels, a thermal sensitivity less than 50mK and a spatial resolution of 25-50μm ensure useful thermal and spatial details (Ring & Ammer, 2000). The resulting information can be used to provide instant feedback on the patient or athlete. Unlike other medical imaging modalities, MIT is not related to morphology. However, to study cutaneous circulation, the non-contact method of MIT was compared with other medical imaging modalities. Merla et al. (2007) calculated blood flow by using MIT and laser Doppler imaging (LDI) and showed that cutaneous blood perfusion values obtained from MIT correlate with those obtained by means of LDI and have the advantage of a better time resolution.

2.3 Biological principles

Human skin, with an emissivity (an object's ability to emit radiation) of 0.98, is almost equal to a black body radiator (Steketee, 1973). The physics of heat radiation and the physiology of thermoregulation in the human body make the reliable and valid interpretation of thermal images difficult. Skin temperature regulation is a complex system that depends on blood-flow rate, local structures of subcutaneous tissues and the activity of the sympathetic nervous system (Kellog & Pergola, 2000). However, there is evidence that the sympathetic nervous system is the primary regulator of blood circulation in the skin and is, therefore, the primary regulator of thermal emission (Charkoudian, 2003). Vasoconstriction and vasodilation of the blood vessels function to regulate blood flow in the skin. Thermoreceptors in the skin, also known as Ruffini corpuscles, recognize the ambient temperature. An increased temperature results in vasodilation, leading to increased blood flow to the skin, whereas vasoconstriction occurs by a decrease in temperature and results in reduced blood flow to the skin (Wallin, 1990). These physiological processes combine with heat transfer and thermoregulation in convection, conduction, radiation and sweat evaporation. Heat transfer by radiation is of great value in medicine (Blatteis, 1998). To date, the mechanism of thermoregulatory adaption to exercise is complex and not entirely understood.

3. MIT – What is its place in medicine?

3.1 Human medicine

MIT is used in a variety of medical applications in the fields of neurology, oncology, orthopedics, and dermatology (Diakides & Bronzino, 2007). The technique has gained widespread use in breast cancer research (Arora et al., 2008; Ng, 2009; Kontos et al., 2011). Tumors are characterized by increased angiogenesis and, therefore, increased metabolic activity, leading to higher temperature gradients compared to surrounding tissue. In addition, MIT is well accepted in surgery. In aortic-coronary bypass surgery, it is possible to monitor the restart of blood flow through the coronary blood vessels (Wild et al., 2003). In

plastic surgery, an infrared camera can evaluate the reperfusion of perforator flaps (de Weerd, 2006). For all medical areas, it should be noted that MIT, as an outcome measure, provides a visual map of the skin temperature distribution but cannot quantify absolute temperature values. In addition, MIT alone should not be used as a diagnostic tool; clinical examinations must be included for interpreting thermograms. Several global medical institutions are concerned about scientific work, and the practical application of MIT in medicine has lead to an increased number of publications in peer-reviewed journals. Figure 2 illustrates medical applications including relevant and recent studies.
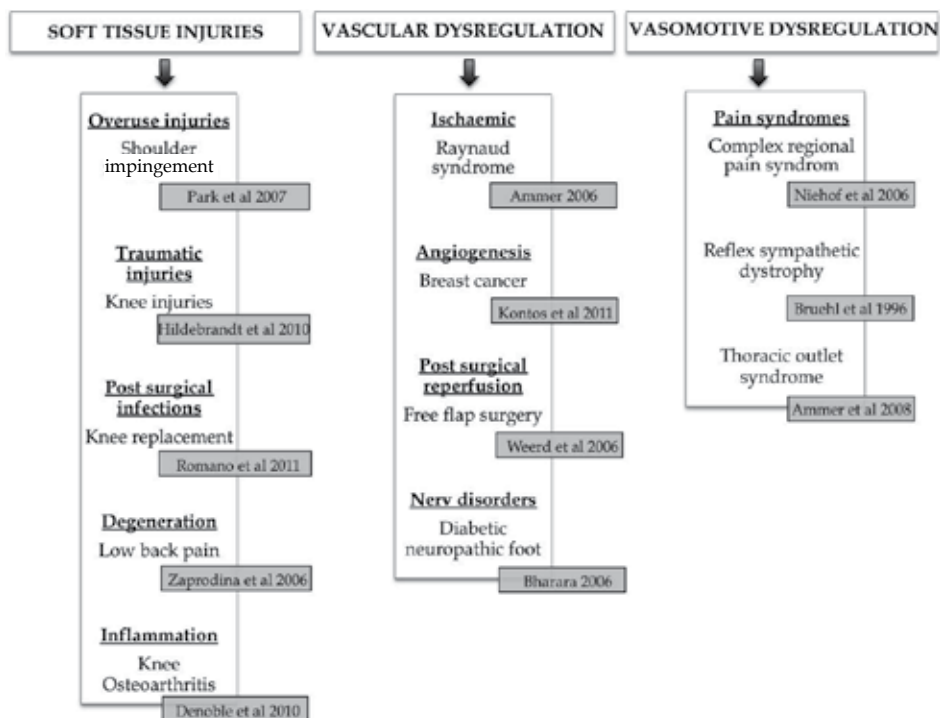
Fig. 2. Recent medical applications of MIT

3.2 Sports medicine

MIT has been successfully utilized in the field of veterinary medicine to detect locomotion injuries in racehorses and to monitor their health status (Turner, 2000; Eddy et al., 2001). By using an infrared camera, Turner et al. (2000) examined tendonitis in race horses and detected hot spots before clinical evidence of swelling and lameness. However, research on human athletes is more rare. Sports medicine must provide high-quality care for athletes, and a modern approach for identifying risk factors and injury prevention should be of primary importance (Bruckner & Khan, 2006). Athletes are exposed to great physical stress in training and during competition. Overuse reactions are frequent; therefore, their early detection is important. Furthermore, early detection and localization of inflammation is a critical step in determining the appropriate treatment. Inflammation will usually cause a localized increase in skin temperature, thereby disturbing the "normal" symmetry. Nerve damage or disturbances to the autonomic nervous system may also cause a change and may

lead to a localized cooling of the affected area. Because this is a remote sensing technique, it is possible to monitor body surface temperature during and after movement and thereby detect changes in skin temperature caused by the exercise or therapy (Ring & Ammer, 1998, Hardaker et al., 2007). Within the field of sports medicine, long-time sport specific changes in physiology and therefore thermoregulatory processes, as well as changes in anatomy such as muscle structures, needs to be considered.

3.3 Standardization methods

Modern state-of-the-art technology has made MIT a reliable measurement tool (Jiang et al., 2005). When used as an outcome measure it must satisfy the basic criteria of measurement. The quality of thermal imaging depends on the technical equipment and the experience of the examiner (Plassmann et al., 2006, Ring & Ammer, 2000). Proper care must be taken with standardization of the imaging procedure to avoid misinterpretation of the thermograms. Thermography societies provide protocols including examination recommendations and technical guidelines. The following aspects are considered:

- Control of Examination Room Conditions
- Patient Preparation
- Number of Studies and Views
- Equipment
- Patient Identification
- Thermogram Analysis

A thermogram represents the human skin temperature profile illustrated by a color spectrum. However, false colors do not necessarily represent a particular temperature. To standardize the analyses of medical thermograms used for fever detection, the International Standards Organization (ISO) recommended the use of the "rainbow" temperature scale (Figure 3a) that represents high temperatures with red colors and low temperature with blue colors. To visualize differences within similar tissues or structures, the "rainbow strong-contrast" scale can also be used (Figure 3b). When focusing on the vascular system, a gray color scale is preferred (Figure 3c).
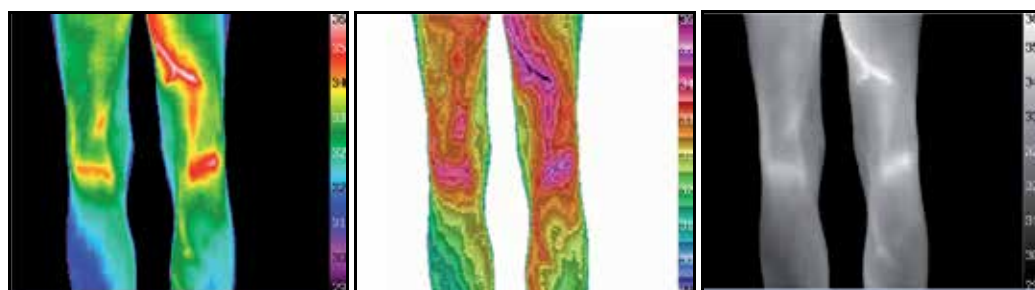
a. "rainbow"   **b.** "rainbow strong-contrast"   **c.** "gray color"

Fig. 3. Temperature scales of thermograms

Image fusion (Figure 4a-c), merging the infrared image and a digital image, is another important step for reliable analyses. This technique allows better mapping of anatomical landmarks and therefore provides a precise definition of the region of interest (ROI).

Additional labeling of anatomical landmarks within the ROI provides consistency for repeated measurements.

To provide a standard for size, shape and placement of the ROI, a research group from the University of Glamorgan has proposed a protocol based on anatomical landmarks (Plassmann & Murawski, 2003; Ammer, 2008).

a. digital image   **b.** merged image   **c.** infrared image
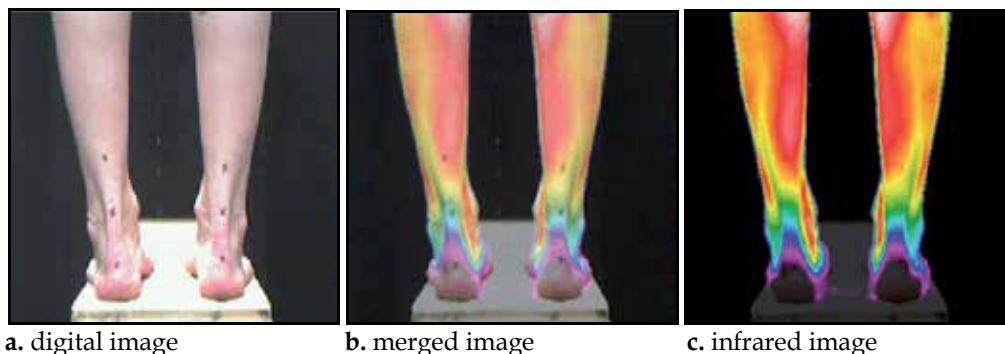
Fig. 4. Process of image fusion

4. Applicability of MIT in clinical and athletic use

Peripheral circulation plays an important role in tissue healing and thermoregulation. To interpret skin temperature changes following injuries (non-thermal stimuli) and exercise (internal stress stimuli), we need to understand the different physiological responses in the structures involved.

4.1 Non-thermal stimuli / sport-specific case studies of injuries

The following chapter focuses on case reports of specific sport injuries. Thermal images were taken with a modern infrared camera. Further technical details can be found in the article from Hildebrandt et al. (2010). Normal findings in human body skin temperature are a symmetrical distribution (Vardasca 2008; Selfe et al., 2008), and injury can affect this thermal symmetry. Figure 5 represents an example of a symmetrical temperature distribution of the knees from a healthy subject. On the anterior view (Figure 5a), the patella appears as a cold shield due to bony structure. The muscles of the upper and lower leg represent hot areas due to high metabolic activity in the muscles. The posterior aspect of the knee (Figure 5b) shows high temperature in the popliteal fossa because of the popliteal arteries and veins. From a qualitative point of view, side-to-side comparison shows a very symmetrical pattern. To define whether a thermogram is normal, a current project at the University of Glamorgan aimed to create a database of thermal images from different parts of the body from healthy subjects. Previous literature has shown that a difference of more than one degree centigrade between sides of the body may indicate a pathophysiological process (Selfe et al., 2008). However, long-time, observational data from injured and non-injured athletes needs to be investigated to define sports specific thermogrammes. An injury causes blood flow variations that then affect skin temperature. Many medical conditions are associated with regional vasodilation and constriction, hyperperfusion, hypervascularization and hypermetabolism that cause higher temperature profiles of the skin surface. Physicians need a deeper understanding of the biological nature of thermal signals and consistent thermal

alterations of sport specific injuries for early intervention and correct treatment. In addition, the natural healing process of traumatic and overuse injuries can be easily monitored by using thermal imaging. However, this requires the comparison of baseline images prior to and following an injury.

a. anterior aspect   **b.** posterior aspect
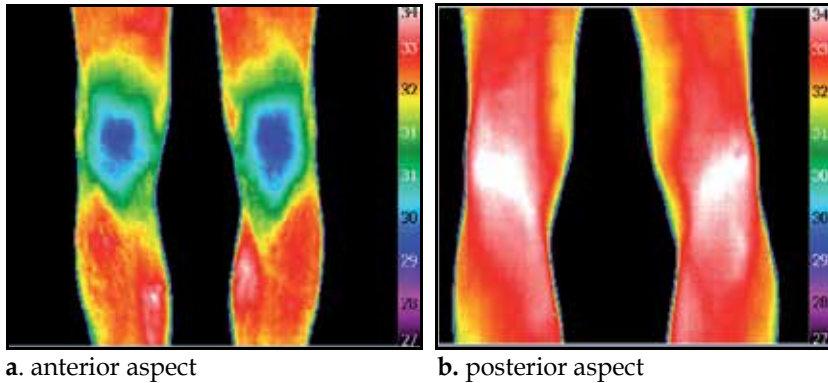
Fig. 5. Infrared image of healthy knee

4.1.1 Overuse injuries

FOOTBALL

High-intensity training combined with frequent competition pushes the locomotor system to its anatomical and physiological limits. Woods et al. (2002) stated that young football players are at a greater risk of minor injuries, overuse injuries, lower leg injuries and muscle strains during the preseason period. We conducted preseason measurements of 25 football players (mean age 17.6± 3.9 years, height 176.1± 8.1 cm, mass 67.8±9.1 kg) from a Football Academy. Fifty two percent of the athletes reported no injuries, 28% had an overuse injury and 20% sustained a traumatic injury within the previous 6 months. The following example shows a non-acute overuse injury of a 17-year old football player. He was diagnosed with recurrent medial shin splint on his left leg and was asymptomatic when the baseline images were taken (Figure 6a). However, the area of referred pain on the left leg matches the area of

a. pre-exercise   **b.** post-exercise
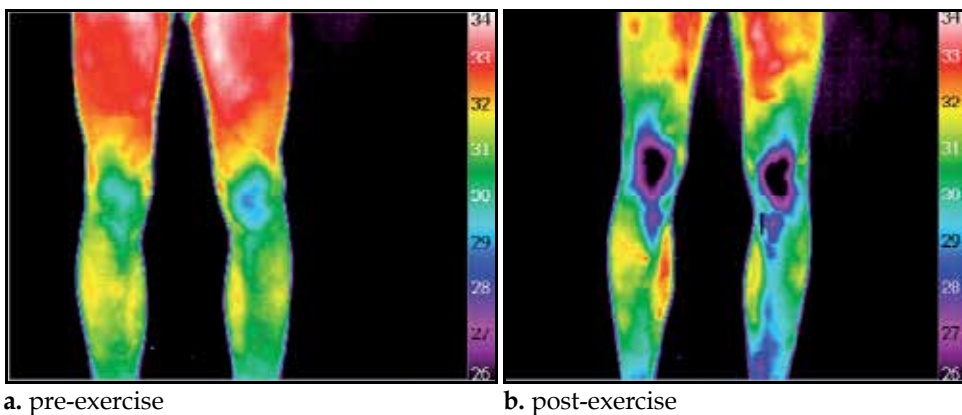
Fig. 6. Infrared image of the anterior aspect of the knee

cooler skin along the tibiae. This problem became even more visible following a sport-specific warm up program, indicating a low metabolic activity around the affected structures (Figure 6b). In addition, the athlete had a history of osteochondrosis at the tibial tuberosity of both knees. Especially following exercise, the tibial tuberosity on both knees appeared as a cold area.

The following example of a 25-year old professional football player represents an incidental finding. Images were taken within the scope of a team screening. On the injury questionnaire, no acute problems were reported. Upon enquiry no signs of venous disease were reported. However, the subject´s right greater saphenous vein appeared very clearly as an area of increased warmth on the thermogram that may indicate a vascular dilatation with beginning venous insufficiency (Figure 7). Further observational research will determine if this abnormality predict future problems prior to the onset of symptoms.
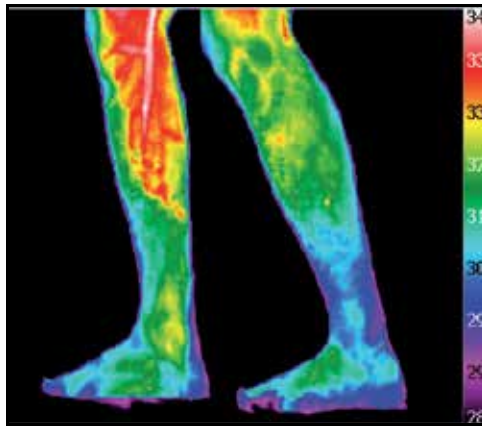
Fig. 7. Infrared image of the medial aspect of the right leg

The thermogram of a 26-year old professional football player represents a problem in the Achilles region (Figure 8). This athlete reported a feeling of morning stiffness on the musculotendinosus junction on his left leg. The thermograms showed a side-to-side difference in the affected area of 1.7° C.
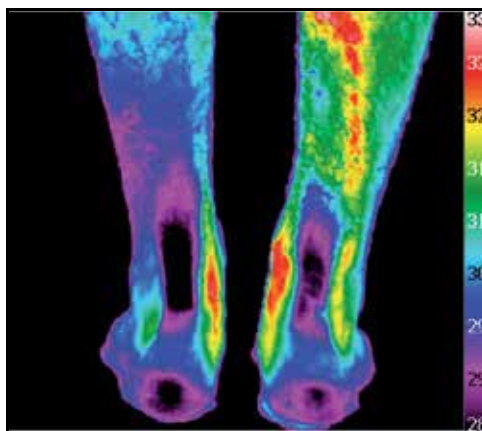
Fig. 8. Infrared image from the dorsal view of the lower leg

RUNNING

Epidemiological studies have shown an alarmingly high incidence of knee, foot, ankle and lower leg injuries in recreational and competitive runners. Most of these injuries were overuse injuries including stress fractures, shin splints, patellar tendinitis and, most prevalently Achilles tendinitis (Hreljac, 2005). The following thermograms were taken of a 22-year old competitive middle distance runner who runs 40-100km a week (Figure 9). He reported pain in his right Achilles tendon that occurs gradually, especially during exercise. The athlete was diagnosed with midportion Achilles tendinopathy with mild morphological abnormalities. At the time the images were taken, there was a small but noticeable pain at rest and no swelling. The average temperature of the ROI on the right side was 1.6° C lower compared to the non-affected side. The lower temperature may indicate lower metabolic activity due to affected tissue with a loss of normal fiber structure.
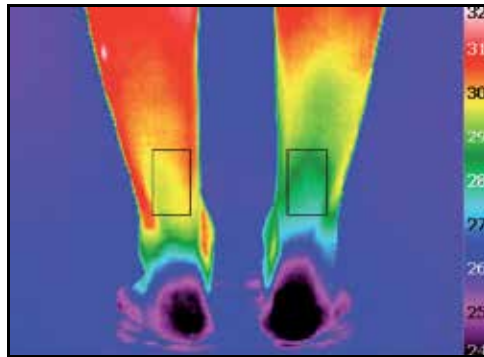
Fig. 9. Infrared image from the dorsal view of the lower legs with ROI

Following a treatment period of 8.5 weeks, including electro-physical and physiotherapeutic treatment, thermograms were taken again under resting conditions (Figure 10a) and following a 45-minute run of low intensity (Figure 10b). The side-to-side temperature difference dropped to 0.6°C before exercise, indicating better metabolic activity of the affected side. Following exercise, the right Achilles tendon junction was colder compared to the left one, with a temperature difference of 1.0°C. The athlete reported no pain at rest or following exercise. The regular treatment seemed to improve the Achilles tendon metabolism. However, the impaired metabolic activity following the sport-specific exercise needs to be further addressed with continuing therapy to prevent recurrent problems.

a. pre-exercise   b. post-exercise
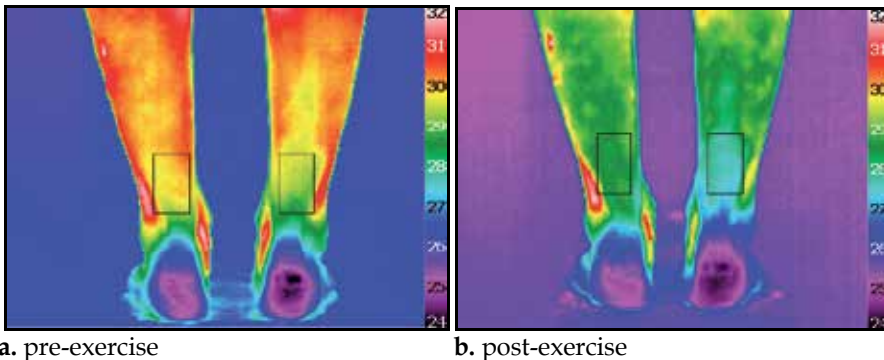
Fig. 10. Infrared image of the lower legs with ROI

SWIMMING

A study, by Sein and co-workers in 2008, investigated shoulder pain in elite swimmers and found that 91% of the swimmers reported shoulder pain; moreover, 84% of the athletes demonstrated a positive impingement sign. The following thermal image was taken of a 27-year-old elite female swimmer under resting conditions (Figure 11). Following a high-volume swimming program, she reported pain and stiffness in both shoulders. With her right arm, she had difficulty reaching behind her back. The clinical examination confirmed overloading of the supraspinatus tendon and general stiffness of the shoulder muscles on both sides. The thermal image shows a hot area above the right deltoid muscle and a hot spot on both shoulders in the region of the humeral head, near the insertion of the supraspinatus muscle. Based on healthy baseline thermal images, MIT should be used to further monitor pathophysiological thermal changes during high-volume swim training prior to the onset of symptoms.

a. right shoulder   **b.** left shoulder
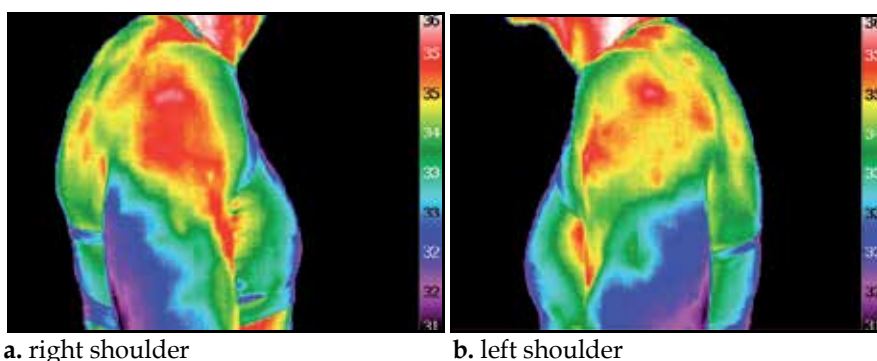
Fig. 11. Infrared image from the lateral view of the shoulder

YOUTH SPORTS

A common problem, predominantly in young, male athletes is the occurrence of enthesopathy of the ligamentum patellae (Gholve et al., 2007). This insertion tendinitis, caused by repetitive mechanical strain of the patella tendon, is characterized by pain, swelling and tenderness above the tibial tuberosity (Brukner & Khan, 2006). Thermal images clearly show a hyperthermic area above the tibial tuberosity (Figure 12). Long term evaluation of affected athletes from alpine skiing (n= 7), football (n=3), running (n=2) and tennis (n=1), who showed acute symptoms in one leg, revealed a side-to-side temperature difference of 1.1°C (± 0.71 °C). The technique provides a quick screening tool and should be used as a first-line detection tool prior to ultrasound or conventional X-rays.
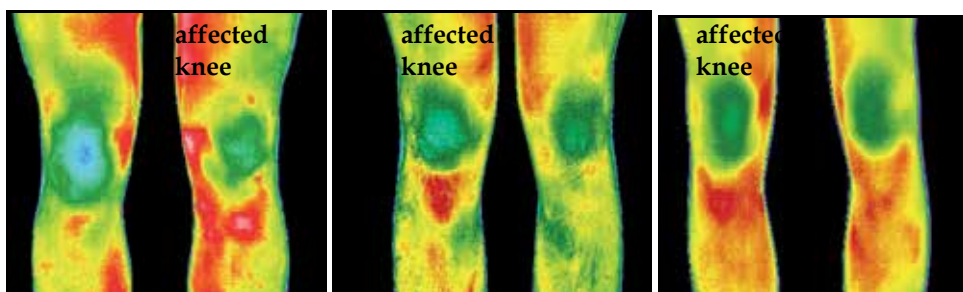
Fig. 12. Infrared images from athletes with enthesopathy of the ligamentum patellae

4.1.2 Traumatic injuries

Traumatic injuries usually involve a long, costly rehabilitation period, and they are challenging for the athlete. An injured athlete is under pressure to return to competition as soon as possible. High-quality treatment can reduce the duration and negative impact of the rehabilitation period. It is well known that richly vascularized areas heal faster compared to poorly vascularized areas (Singer et al., 1999). MIT may give information about the state of vascularization and the on-going healing process to ensure the most effective treatment and provide recovery information to decrease the likelihood of re-injury by returning to the sport too quickly.

ALPINE SKIING

Knee injuries, especially ruptures of the anterior cruciate ligament (ACL), represent a significant problem in professional alpine skiing (Flørenes et al., 2009) as illustrated by the case of a 21-year-old skier. At 16 years the skier ruptured his left anterior cruciate ligament, medial collateral ligament and the medial meniscus. Since that time, he has suffered from periodic pain, predominantly around the patellae. At age 20 years he was diagnosed with articular cartilage, damage grade three. According to the International Cartilage Repair Society, grade three indicates that the lesion affects more than 50% of the cartilage layer. The average temperature difference of the left patellae was found to be 1.6°C lower compared to the right side (Figure 13). The temperature difference from the area above the upper kneecap showed a side difference of 1.2°C, indicating poor metabolic activity of the lower quadriceps muscle under resting conditions.
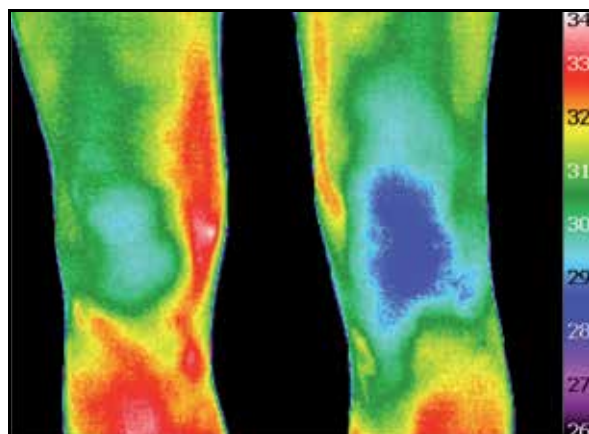
Fig. 13. Infrared image from the anterior view of the knees

TRIATHLON

The incidence of tendon ruptures has increased in recreational sport activities, with the highest incidence in older age groups (Clayton et al., 2008). However, Rettig et al. (2005) stated that the potential risk of re-rupture is highest in athletes younger than 30 years of age. The infrared images below were taken of a 26-year old triathlete, 6 months following a complete rupture and direct operation of his right Achilles tendon (Figure 14). When the images were taken, he was reffered with mild pain that was exercise dependent and a feeling of numbness in the outer toes. The ongoing healing process did not seem to be sufficiently complete. The temperature difference of an area from the upper Achilles tendon

to the muscle belly of the musculus triceps surae was found to be 1.6°C, suggesting delayed healing with impaired circulation. In particular the cooler area of the musculotendinous junction should be considered further within physiotherapeutic treatment.
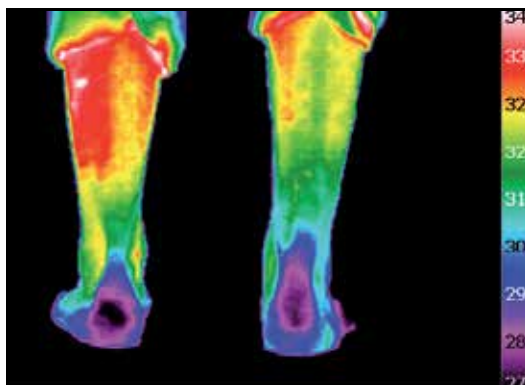
Fig. 14. Infrared image posterior view of lower leg

The area of numbness becomes visible through a clear hypothermia on the affected toes and must be a target of further rehabilitation (Figure 15a,b). Future research will determine if tissue remodeling is still on-going after symptoms disappear.

a. left foot   **b.** right foot
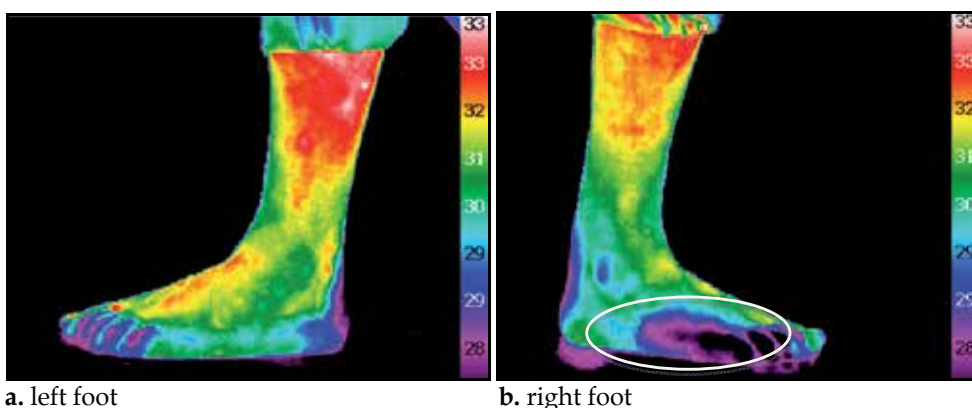
Fig. 15. Infrared image of the lateral view of the foot

4.1.3 Static versus dynamic measurements

Baseline recordings, following a sport-specific strain, should be conducted to visualize thermal regulatory processes. Regarding infrared images of overuse injuries, repeated measurements following sport-specific exercise will clarify if symptom-free asymmetrical temperature distributions are predictive for presymptomatic identification of initiating overuse reactions. The following example of an 18-year old football player indicates a presymptomatic thermal abnormality during pre-season measurement. The thermogram at rest demonstrated symmetrical patterns (Figure 16a). Following sport-specific exercise, local side differences on the knee were visible (Figure 16b). The athlete reported no pain at that time.

However, during the season, he reported a feeling of load-dependent, diffuse knee pain in his left leg. The medical examination confirmed a low threshold for pressure on the medial aspect of the knee. No clear diagnosis could be confirmed, indicating a local overuse reaction. Excessive stress should be administered with caution.

a. pre-exercise   **b.** post-exercise
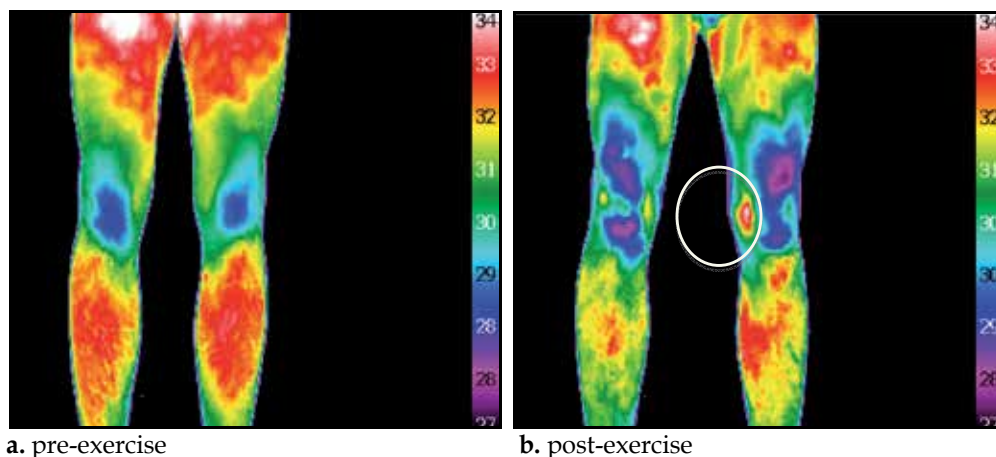
Fig. 16. Infrared image of the anterior view of the legs

4.2 Thermal stimuli- time sequential images following different exercise

Physical exercise and repetitive strain is a challenge to thermal homeostasis. During exercise, the thermoregulatory control of blood flow in the skin is important to maintain normal body temperature and leads to changes in hemodynamics, and, therefore, thermal signals (Kenney & Johnson, 1991). Using state-of-the art infrared sensor technology, cutaneous temperature changes during exercise can be evaluated. Skin blood flow is predominantly regulated by neural regulation (Thomas & Segal, 2004). By taking time-sequential images of exercise, the immediate response of the sympathetic nervous system via the somatocutaneous reflex can be visualized. The investigation of infrared images taken before and after sport-specific exercise may further determine the applicability of MIT to investigate the physiology of biological tissue. Furthermore systemic cutaneous blood flow regulation can be monitored as a function of exercise type, duration and intensity.

AEROBIC VERSUS ANAEROBIC EXERCISE

The mechanism of homeostasis during exercise is guaranteed through multiple functions, such as cardiac processes, peripheral circulatory control, blood pressure regulation and temperature control (Berne & Levy, 2000). A better understanding of the cutaneous circulation, and, therefore, the control of blood flow during exercise is a challenge in integrative physiology (Kellog & Pérgola, 2000). We investigated thermal characteristics of aerobic and anaerobic bicycle exercise to predict evidence of altered perfusion. Twelve athletic males (mean age 26.0 ± 2.7 years, height 177.2cm ± 4.3 cm, mass 71.1 ± 8.4 kg) performed both, anaerobic exercise (5 minutes, 80rpm, 90%HRmax) and aerobic exercise (45 minutes, 80rpm, 60%HRmax) under thermo-neutral conditions.

Images were taken prior to (Figure 17a) and immediately following aerobic (Figure 17b) and anaerobic exercise (Figure 17c). The ROI was defined above the middle portion of the M. quadriceps. The temperature above the exercising muscle increased following aerobic

exercise (0.7°C, p=0.215) and decreased following anaerobic exercise (-1.5°C, p=0.094). In addition hot colored dots over the thigh occurred after aerobic exercise. To meet the increased metabolic demand of active muscles, short- term, intense exercise leads to a redistribution of blood flow away from inactive tissues such as the skin, to exercising muscles through the vasoconstrictor system (Kenney & Johnson, 1991). This process explained the marginal skin temperature decrease following anaerobic exercise. From a clinical point of view, this observation becomes interesting for patients with compromised cardiac function. As previously reported, these patients showed a higher magnitude of vasoconstriction compared to a healthy group, suggesting that the initial reflex vasoconstriction may be linked to cardiovascular functional capacity (Zelis et al., 1969). With continuing exercise, the body core temperature begins to rise. When internal temperature increases toward a threshold, a regulating system starts to stimulate thermo- sensitive neurons in the central nervous system. This triggering of cutaneous vasodilation ensures the transfer of metabolic heat from the core to the skin (Charkoudian, 2003). The present study showed that the competing system of thermoregulatory drive for cutaneous vasodilation and the non-thermoregulatory drive for cutaneous vasoconstriction could be visualized by using MIT. As previously reported, the interactive control system, as a normal function of dynamic muscular exercise, seems to dependent upon the intensity and duration. The multiple hot spots seen on the thigh (Figure 17b) illustrate the so-called perforating blood vessels that originate in deeper lying tissue. The vasoconstrictor mechanism at the beginning of the exercise is mainly in the skin blood vessels, whereas the perforator vessels are less affected. As exercise duration increases, they contribute to the rewarming of the skin (Merla et al., 2010). The identification of a skin thermographic map of perforator vessels that includes their perfusion area can be important to define individual anatomy of certain tissues (Salmon et al., 1988). Further research should examine the time-course of thermal changes by taking multiple images during and following an exercise. In addition, the relationship between thermal changes, aerobic capacity and performance may further determine different functional states of the body dependent on intensity and duration.

a. pre-exercise   **b.** post aerobic exercise   **c.** post anaerobic exercise
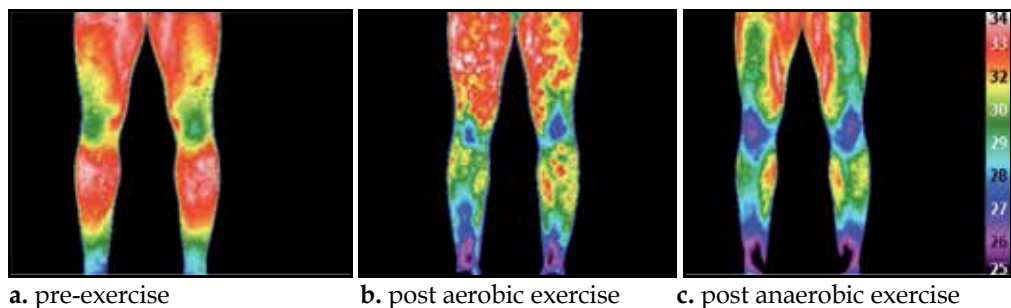
Fig. 17. Infrared images of the anterior aspect of lower legs

5. Conclusion

High-quality scientific work with modern 21st-century technology coupled with a better understanding of the regulation of skin blood flow has improved the capability of MIT in medical use. Our research findings suggest that the most beneficial output of MIT seems to be in the screening of athletes for overuse injuries. We suggest combining baseline images with images taken following sport-specific exercise to provoke sufficient thermal alterations

in the tissues. A main challenge is to combine the anatomical and physiological information demonstrated by the thermal pattern of the skin. The biological nature of thermal signals and consistent thermal alterations of different sport-specific injuries should be further addressed. Thermal screening of injured and non-injured athletes is the first step to create a sport-specific database with individual thermograms. Repeated follow-up measurements during the sport season will further clarify the link between asymmetrical temperature distributions, pathophysiological changes on the skin surface and the extent of injury. The long-term aim is to create a knowledge-based database of thermograms of overuse and traumatic injuries. However, it should be considered that within a certain time span, different pathologies could alter their patterns of temperature. A deeper understanding of the different time courses of injuries is important to clarify the benefit of MIT in injury management and to define whether a thermogram is "normal" or not. In terms of quantification of side-to side differences within a defined ROI, it is important to use the medical analysis function of image fusion. The main advantage of MIT is its safety, however, the disadvantage of MIT results from its physical limitations. The non-radiating, two-dimensional technique provides information about surface structures. A conclusion of processes in deeper tissues needs to be further investigated by combining different medical imaging modalities. In addition, it must be clearly stated that the aim of MIT use in sports medicine is not to be a substitute for clinical examination, but to enhance and support it. It can be concluded that MIT is a reliable, low-cost detection tool that should be applied for pre-scanning athletes.

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The Involvement of Brain Monoamines in the Onset of Hyperthermic Central Fatigue

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1. Introduction

The fatigue that results from physical exercise is a multifactorial phenomenon that is comprised of complex interactions between physiological and psychological factors. Fatigue is assumed to be an inability to maintain the required force or power or an increasing difficulty to continue the work rate at a given exercise intensity. Taking into account that homeostasis disturbances may be harmful, fatigue should be considered a defense mechanism that prevents tissue damage by reducing the intensity of or even interrupting physical activity.

Fatigue is known to have peripheral and/or central origins. Although most studies focus peripheral factors, which include circulatory, metabolic, muscular, nutritional and thermoregulatory disorders, exercise-induced cerebral metabolism and neurohumoral or neurotransmitter turnover are also implicated in fatigue genesis. "Central fatigue" refers to these central nervous system alterations that may prevent muscular and neural damage by failing to drive the muscles appropriately.

Most authors consider central fatigue during prolonged exercise to be a consequence of the accumulation or depletion of neurotransmitters, serotonin in particular. Although the role of serotonergic neural trafficking on exercise performance has been well documented, dopamine and noradrenaline neurotransmissions also contribute to central fatigue. In addition to having their activity modified by exercise, all of these brain monoamines exhibit relevant thermoregulatory effects. These amines play an important role in the function of thermoregulatory centers, such as the preoptic area and the anterior hypothalamus, and it is hypothesized that changes in their turnover are associated with the development of fatigue as a consequence of heat imbalances.

The brain is especially endangered by hyperthermia. For this reason, the exacerbation of exercise-induced hyperthermia appears to diminish the central nervous system drive to the working muscles; this protects the brain from thermal damage while causing a detriment to physical endurance. This effect is more pronounced when hyperthermia occurs simultaneously with inhibitory signals from the central nervous system, as in the case of altered neurotransmitter metabolisms. Even though it has been stated that central fatigue

coincides with critical high core body and brain temperatures, as well as increased heat storage, evidence indicates that complex and dynamic mechanisms are reliable regulators of exercise performance. In this way, the heat storage and the body heating rates associated with changes in neurotransmitter content in thermoregulatory centers emerge as important factors in determining fatigue.

The main focus of this section is to link serotonin, dopamine and noradrenaline brain levels and exercise-induced hyperthermia with the onset of central fatigue. It is improbable that central fatigue is caused by a unique pathway; therefore the interaction between these systems may play an important role in establishing hyperthermia-induced central fatigue. From a health perspective, fatigue should be considered a warning sign that prevents the organism from the harmful consequences of sports activities.

2. Fatigue as a defense mechanism during exercise

Fatigue can disturb performance in many occupations, including firefighting, the military, construction and laboring, and it can limit participation in most recreational activities and sports (McKenna & Hargreaves, 2008). Understanding fatigue has implications far from those circumscribed to sports performance. In ill patients, fatigue and, thus, exercise limitations can drastically restrict daily activities and lead to a poor quality of life. Therefore, it is not surprising that exercise-induced fatigue has gained so much attention among researchers in the fields of exercise science and medicine.

Exercise-induced fatigue has been traditionally defined as an elevation in the perception of effort to develop a desired force or power and also as an eventual inability to produce this force (Davis & Bailey, 1997; Enoka & Stuart, 1992). Many different models have been proposed in an attempt to understand the underlying mechanisms of fatigue. Since the early works by Fletcher and Hopkins (1907) and Hill et al. (1924), lactic acid production, cardiovascular system inefficiency, metabolic substrate depletion and waste product accumulation have been recognized as the main signs of fatigue. Until recently, most studies have dealt with exercise-induced fatigue under a failure perspective, which means that any limitation arising from exercising muscles would lead to an interruption in the motor task. In such an approach, the failure to maintain force depends on "peripheral" fatigue that occurs distal to the point of nerve stimulation and on "central" fatigue that results from a failure to voluntarily activate the muscle (Gandevia, 2001). However, it is important to emphasize that fatigue during exercise can occur without any signs of muscle dysfunction, substrate inadequacy within the exercised muscles or cardiovascular system overload; it may thus be under the influence of psychological factors such as arousal, mood and external motivation (Foley & Fleshner, 2008).

A more recent approach differs from the failure perspective and points to a more integrative scenario where fatigue should be seen as a defense mechanism. Thus, exercise is ended or its intensity is turned down to protect the individual from tissue damage (Marino, 2004). In 1996, Ulmer proposed the concept of teleoanticipation, where a feedback control system would exist for the optimal adjustment of the metabolic rate during exercise and would include a programmer that would take a finishing point into consideration. In this way, a marathon runner would consciously choose to run at a pace that would not pose a threat to himself. This assumption was further developed as the "Central Governor Model" that considers fatigue to be a sensation that results from a complex neural integration between afferent information and the brain (Noakes et al., 2005; Noakes & St Clair Gibson, 2004).

Peripheral information, such as substrate depletion and waste product accumulation, would act as a modulator of the cerebral control process in a dynamic, non-linear and integrated manner; this would cause an oscillatory behavior of the physiological responses and power output during exercise. This integrative model of fatigue proposes that a continuous interrelated control of feed-forward and feed-back mechanisms would exist and would be responsible for a secure system of homeostasis control during exercise (Noakes et al., 2005; Tucker, 2009; Tucker et al., 2006). This integration could be consciously and verbally manifested through the perception of effort, as measured by Borg's scale (1982) (St Clair Gibson et al., 2006; Tucker, 2009). Moreover, the teleoanticipatory central nervous system would be molded by previous exercise experiences and training (Noakes et al., 2005). Thus, fatigue may provide the cognitive system with a signal that encourages the organism to lower present goals and/or seek lower effort alternative strategies (Perrey et al., 2010).

In spite of being accepted by some research groups (Marino, 2010; Baron et al., 2009; Flouris & Cheung, 2009; Castle et al., 2006), this model has been criticized by others (Ament & Verkerke, 2009; Shephard, 2009). As discussed later in this chapter, our group has been working with a conception of fatigue that goes in this direction. We have shown that before any harm can occur, afferent information from different physiological systems must be centrally integrated, and exercise must be voluntarily interrupted (Balthazar et al., 2009, Leite et al., 2010; A. G. Rodrigues et al., 2004, 2009; Soares et al., 2004, 2007).

3. Central fatigue hypothesis

Although most studies have focused on the peripheral factors of fatigue, including circulatory, metabolic, muscular, nutritional, and thermoregulatory disorders (Bassett & Howley, 2000; Coyle et al., 1986; Coyle & González-Alonso, 2001; Febbraio, 2000; Hargreaves & Febbraio, 1998; Kreider et al., 1993; Noakes, 2000), exercise-induced cerebral metabolism and neurohumoral or neurotransmitter alterations are also implicated in the genesis of fatigue (Foley & Fleshner, 2008; Nybo & Secher, 2004; Roelands & Meeusen, 2010). This participation of central nervous system factors in the reduction of the voluntary activation of skeletal muscles during physical effort has been termed "central fatigue" (Foley & Fleshner, 2008; Gandevia, 2001). In this section, a focused discussion on the possible role of serotonin neurotransmission on exercise-induced central fatigue will be presented.

As first suggested by Newsholme et al. (1992), fatigue during prolonged exercise may be influenced by the activity of the brain serotonergic system; this has been commonly referred to as the "central fatigue hypothesis." Its major premise is that elevated central tryptophan availability increases serotonin activity during prolonged exercise, which may cause fatigue by increasing lethargy and loss of central drive/motivation (Newsholme et al., 1992). During resting periods, most tryptophan, the amino acid precursor of serotonin, circulates in the blood bound to albumin, the same transporter of free fatty acids. During prolonged exercise and as a response to metabolic demands, there is an increase in the plasma concentration of free fatty acids. This displaces tryptophan from the biding sites on albumin and causes an elevation in the free portion of this amino acid. As a consequence, tryptophan is readily available to cross the blood-brain barrier. Concomitantly, during prolonged exercise, the plasma concentrations of branched-chain amino acids either fall or do not change. Because these amino acids and tryptophan in its free form share the same transporter across the blood-brain barrier, a reduction in plasma concentrations of branched-chain amino acids during exercise could increase the uptake of tryptophan into

the central nervous system and lead to an increase in serotonin synthesis during exercise. Thus, these two interrelated mechanisms underlie the "central fatigue hypothesis". Tryptophan increases induced by exercise have been described as occurring simultaneously with a significant rise in the concentration of 5-hydroxyindoleacetic acid, which is the main serotonin metabolite; these data indicate that exercise increases serotonin synthesis and turnover. Tryptophan alters serotonin within the brain, and there is a positive relationship between endogenous serotonin content and the activity of tryptophan transport mechanisms in hypothalamic brain slices or synaptosomal preparations. Electrolytic lesions of raphe nuclei or intracerebroventricular injections of 5,7-dihydroxytryptamine lead to a decrease in synaptosomal tryptophan accumulation with reduced nerve terminals (Denizeau & Sourkes,1977). In addition, both spontaneous and electrically evoked serotonin release from hypothalamic slices have been shown to be dependent on precursor availability, which causes parallel changes in brain serotonin levels and serotonin release (Schaechter & Wurtman, 1990).

Central serotonin activity can affect many physiological responses, such as pain tolerance (Prieto-Gomez et al., 1989), motor activity (Gerin & Privat, 1998), thermoregulation (Imeri et al., 2000; Lin et al., 1998; Myers, 1981, Soares et al., 2007) and hypothalamo–pituitary–adrenal axis activity (Chaouloff, 2000; Korte et al., 1991). Thus, alterations in one or more of the physiological responses mediated by the serotonergic system may decrease work capacity during exercise.

It has been shown that an increased availability of tryptophan, in the central nervous system reduces the mechanical efficiency and running time to fatigue, which are both related to serotonin content in the preoptic area (Soares et al., 2003, 2007). Moreover, serotonin content in the preoptic area is also associated with increased heat production and storage during exercise (Soares et al., 2007). Recently, it has been shown that alterations in the serotonin levels in the preoptic area and in the hypothalamus are also modulated by central angiotensinergic and cholinergic pathways (Leite et al., 2010; A. G. Rodrigues et al., 2009). For more details see section 7.

Serotonergic neurons have many important functions in the central nervous system, including motor activity control. However, the role of serotonin in the regulation of motor control is complex. There is widespread evidence that serotonin in the hippocampus is involved in locomotion (Meeusen et al., 1996; Takahashi et al., 2000). According to Soares et al. (2007), at fatigue, the hippocampal serotonin content was directly correlated with the exercise time of rats but not correlated with the heat storage rate. Data from A. G. Rodrigues et al. (2009) also showed that, at fatigue, the hippocampal serotonin content was not directly correlated with heat storage. Together, these results suggest that hippocampal serotonergic activity might also participate in fatigue during exercise through a mechanism other than thermoregulation. This is in agreement with reports that serotonergic neurons in the median raphe nuclei that project to the hippocampus are related to motor activity (Hillegaart & Hjorth, 1989; Jacobs et al., 1975).

Although the involvement of serotonin in central fatigue has been well documented, it has become evident that other neurotransmitters participate in the mechanisms of exercise-induced fatigue (Lacerda et al., 2006; A. G. Rodrigues et al., 2009). These data indicate that central fatigue is a more complex phenomenon than previously thought and that it involves the balance of at least two central aminergic neurotransmitter systems, as indicated by the serotonin/dopamine ratio (Balthazar et al., 2010; Foley & Fleshner 2008; Meeusen, 2006).

4. Proposed central mechanisms of fatigue

Fatigue should be seen as a multifaceted phenomenon influenced by both central and peripheral factors (Meeusen et al., 2006; Nybo & Secher, 2004). There is no doubt that alterations within the muscle contribute to exercise-induced fatigue; however, it is unlikely that alterations in muscle function are the sole mechanism of fatigue. In fact, the contribution of either central factors or factors upstream of the neuromuscular junction has been, for the most part, ignored in the literature (Foley & Fleshner, 2008).

At least three factors have been proposed to contribute to the delay in establishing the role of "central" factors in human muscle fatigue. First, it has simply been more convenient to assume that the muscle limits to produce force that have been established in reduced preparations of muscle that are devoid of effective neural input also apply to a conscious human subject. Second, the existing methods to gauge the central drive to muscles have not always been technically rigorous, and findings obtained with these methods have been easily criticized or ignored. Third, although changes in the central nervous system during exercise can be measured, it has been more demanding to show that they cause a deficit in force production (Gandevia, 2001).

Because muscle contractions are under the control of the central nervous system, it is likely that any significant alteration in the brain or the spinal cord would alter the neural drive to the neuromuscular junction, thus initiating fatigue (Taylor & Gandevia, 2008). In order to identify the adjustments that occur within the nervous system during fatiguing contractions, most studies have investigated the influence of afferent feedback, descending inputs, and spinal circuitry on the output of the motor neuron pool (Hunter et al., 2004). For example, the metabolites that accumulate in muscles during a prolonged exercise excite afferent fibers; these fibers enhance the central drive to maintain muscle perfusion by increasing the mean arterial pressure and modulating the motor neuron discharge rate (Gandevia, 2001). Such observations indicate that the decrement in force during a fatiguing contraction usually involves multiple neural mechanisms (Hunter et al., 2004).

During maximal voluntary isometric tasks, voluntary activation usually diminishes, and motor unit firing rates decline (Gandevia, 2001). However, it is not possible to clearly specify all of the putative sites within the central nervous system at which contributions to voluntary activation, central fatigue, and supraspinal fatigue occur. The traditional model indicates that there is a "chain", from higher levels within the central nervous system to the motoneuron via descending paths, and then through motor axons to the neuromuscular junction, the sarcolemma, T tubules, and, ultimately, to actin and myosin (Taylor & Gandevia, 2008).

Thus, central fatigue can be considered to be an impaired muscular performance that arises from decreased efferent signaling from the central nervous system. There are two general ways to study central fatigue. The first one seems to be a fairly direct way, and consists of using a technique where "added force" is determined. This occurs by overlaying a supramaximal electrical stimulus of a muscle onto a maximal voluntary contraction for that muscle. Any "added force" that may be generated that is in addition to that produced by the maximal voluntary contraction is indicative of an impairment from the central nervous system down to the level proximal to the neuromuscular junction. The second way to study central fatigue is to use an exogenous substance that is believed to induce central fatigue, and observe its effects on exercise capacity. However, unlike the first alternative, this method is indirect, because it cannot be exactly known if the substance had peripheral and/or central effects (Evans & Lambert, 2007).

4.1 Central nervous system biochemical changes and central fatigue

Given that intense exercise challenges the cardiovascular, respiratory, endocrine, and peripheral and central motor systems, changes in many central nervous system transmitter systems would be expected to accompany exercise and task failure or fatigue (Gandevia, 2001). All types of physical or psychological constraints lead to the activation of noradrenergic, dopaminergic and serotonergic systems at the brainstem level. These systems are particularly important for the global regulation of behavior, and they participate in the formulation of an adapted response of the central nervous system to an external stimulus (Sesboue & Guincestre, 2006).

The widespread central actions of many of these systems make it unlikely that any one is uniquely responsible for central fatigue. For example, there are serotonergic projections from the brain stem raphe nuclei to the cortex, hippocampus, hypothalamus, medulla, and spinal cord. There are noradrenergic projections from the locus coeruleus. Arousal, motivation, attention, tolerance to discomfort, and sensitivity to stress can all alter voluntary drive, at least subjectively, which suggests that many neural systems can modify central fatigue (Gandevia, 2001).

There is evidence of the roles of these neuromodulators on fatigue that will be minutely covered later in this chapter. However, it is important to first elucidate some aspects of the interrelatedness of central neuromodulators and fatigue. We have already discussed some aspects of serotonergic neurotransmission and its implication on the central fatigue during exercise.

Central noradrenergic neurons modulate humor and motivation, and when their activity is low, motivation decreases. This decrease leads to a diminishment of motor cortex activation and a subsequent decline in the stimulation of the descending path chain to the motoneurons (Sesboue & Guincestre, 2006). On the other hand, the response of cerebral dopamine to, for example, a physical constraint is biphasic. It has been shown that there is a small elevation in the levels of this neurotransmitter at the beginning of muscle work, which is followed by a reduction in its concentration as the intensity and duration of the effort increases; this reduction is most prominent at fatigue (Foley & Fleshner, 2008).

There are several other transmitters and their subtypes that need to be examined for their role in central fatigue. For example, it is already known that brain gamma-aminobutyric-acid (GABA) levels diminish with exercise (Gandevia, 2001) and that baclofen, a GABAergic agonist that acts on GABA B receptors, can postpone fatigue (Abdelmalki et al., 1997). Other humoral signals that must be considered to be involved in central fatigue are glutamine and ammonia, which are diminished and increased, respectively, after exercise (Gandevia, 2001).

Another important proposed mechanism of central fatigue is related to hyperthermia during exercise. It is well known that hyperthermia reduces the central nervous system drive for exercise performance (Nielsen et al., 1993; Walters et al., 2000) and precipitates feelings of fatigue during exercise. However, this essential aspect of central fatigue will be discussed in detail in the next section.

5. Fatigue induced by exercise hyperthermia

It has been shown that hyperthermia reduces physical performance in many mammalian species (Bruck & Olschewski, 1987; Fuller et al., 1998; González-Alonso et al., 1999; Nielsen et al., 1993; Walters et al., 2000), reduces central nervous system drive for exercise performance (Nielsen et al., 1993; Walters et al., 2000) and precipitates feelings of fatigue at a

sublethal threshold by establishing a safety level against heat stroke, thus protecting the brain, among other tissues, from thermal damage (Caputa et al., 1986; Marino,2004). The reduction in exercise performance as a consequence of hyperthermic stress has been described in isometric tasks (Nybo & Nielsen, 2001; Thomas et al., 2006; Todd et al., 2005), in dynamic exercises with fixed intensity, i.e., a constant workload (Nybo & Nielsen, 2001), and in self-paced prolonged exercises (Ely et al., 2010; Tatterson, 2000). Recently, from an evolutionary perspective, it has been suggested that physiological and (or) psychological safeguards should protect individuals by voluntarily reducing exercise and metabolic heat production before catastrophic hyperthermia (Cheung, 2007). In fact, various animals will cease exercise when their core temperatures exceed safe limits, and there must be a similar behavioral response in humans to reduce metabolic heat production and ultimately to protect the physiological integrity (Cheung & Sleivert, 2004).

5.1 Body temperature and thermoregulation

Humans possess efficient physiological and behavioral mechanisms for maintaining their internal temperature within narrow limits; these mechanisms allow survival even in diversified thermal environments such as tropical forests, deserts and very cold regions. Our body temperatures are carefully regulated at 37°C ± 1°C. However, our thermal physiology is "asymmetrical", which means that body temperature is placed very closely, within just a few degrees Celsius, to the upper existence limit (possibly related to the denaturation of regulatory proteins) but somewhat far, a few tens of degrees, from the lower survival limit (probably defined by the freezing temperature of water) (Romanovsky,2007).

The lowest values for body temperature occur in the morning, between 04:00 and 06:00 a.m., and the highest are observed between 17:00 and 20:00 h (Waterhouse et al., 2005). It should be noted that the temperature is not the same throughout the human body. There is a temperature gradient between the core (visceral) and body surface (cutaneous). With an elevation in body temperature to values over 42°C, there is an eminent risk of protein denaturating with subsequent cellular death. However, despite being more tolerant to hypothermia than to hyperthermia (see above) when the former is severe, i.e., when body temperature falls below 32°C, there are critical risks for life maintenance that include the loss of motor coordination, cardiac arrhythmias and even death by cardiac arrest (Kanosue, 2010).

Body temperature is the net result of the heat produced by metabolic actions and the heat dissipated to the environment. If the heat dissipation is smaller than heat production, excessive heat is stored and body temperature increases.

Metabolism generates heat from exergonic oxidative reactions that use adenosine triphosphate (ATP) as fuel. Basal metabolism is around 50% efficient, and the remaining energy is lost as heat. Exercising muscles are even less efficient, at no more than 25%. For example, given that the mean value for the specific heat of body tissue is 0.83 kcal.kg^{-1}.^{o} C^{-1}, a male adult weighting 70 kg with a body temperature of 37°C has around 2,150 Kcal of total heat stored in his body.

The basal metabolism produces 1 Kcal. kg^{-1}.h^{-1}, even in a thermoneutral environment, where temperature regulation is achieved only by means of sensible heat loss, i.e., without regulatory changes in metabolic heat production or evaporative heat loss. Because human tissues only need 0.83 kcal.kg^{-1} to increase the internal (core) temperature by 1°C, core temperatures would be elevated by 1°C.h^{-1}, even during rest periods, if no heat loss mechanisms are activated. Thus, losing heat to the environment is essential for survival. If there were no effective means by which body could lose heat, hyperthermia would be achieved very rapidly.

Thermoregulation is a typical example of an integrative hypothalamic function that generates autonomic, endocrine, motor and behavioral patterns as a response to an external challenge. Thermoregulation systems are composed of multiple independent neural pathways that have both feedback and feedforward mechanisms; these mechanism are activated by afferent information from peripheral temperature sensors and modulate the relationship between ambient and skin temperatures (Mekjavic & Eiken, 2006; Webb, 1995).

The endothermic/homoeothermic animals are relatively independent from environmental conditions because they are able to regulate their body temperature through an association of autonomic and behavioral mechanisms (Mekjavic & Eiken, 2006; Schlader et al., 2009, 2010). The autonomic processes consist of involuntary thermoeffector responses, either to heat or cold, which modify heat production and dissipation rates, and include sweating, shivering and vasomotor alterations at the body surface (IUPS, 2001). However, as pointed out by some authors (Schalader et al, 2010; Romanovsky, 2007), those autonomic responses have a limited capacity to regulate body temperature. In contrast, behavioral mechanisms of thermoregulation are intended to establish a thermal environment that represents a preferred condition for heat exchange (heat gain, heat loss, or heat balance) between the organism and its environment. The responses involved in such regulation include moves to a different thermal ambiance, changes in posture, wetting of body surfaces, changes in microclimate by nest building, parental behavior (huddling), and, in humans, voluntary exercise and cultural achievements (e.g. clothing, housing, and air-conditioning) (IUPS, 2001).The association of behavioral and autonomic responses allows humans to survive in different and extreme environments (Mekjavi & Eiken, 2006).

Vasomotion and evaporation are the main mechanisms of heat defense. However, sweating (or panting) usually starts at a higher threshold temperature than skin vasodilation. Thus, sweating functions as a second line of defense for situations where an increase in skin blood flow alone is not sufficient to prevent a serious increase in body temperature. Cold defense processes operate in a parallel manner such that non-shivering thermogenesis is activated before shivering (Kanosue et al., 2010).

5.2 Exercise hyperthermia and fatigue

Because the mechanical efficiency of active muscles is around 25%, most of the remaining energy produced during exercise should be dissipated to the environment; otherwise, exercise may impose thermal stress to the organism. This dissipation can be hard if exercise takes place in a warm environment where heat dissipation mechanisms, such as conduction and radiation, are impaired. Dissipation can be even worse if it is associated with high humidity because heat lost by sweat evaporation would be severely compromised. In these environmental conditions, keeping up the same intensity effort during physical exercise could lead to a harmful situation in which the heat dissipation would be insufficient to compensate for the heat production. As a result, the body temperature would continuously increase, and a thermal equilibrium would not be reached.

To avoid serious injuries induced by excessive body heat storage and subsequent hyperthermia, it is imperative that the related activation of both the autonomic and behavioral responses, along with the different physiological systems, results in a decrease of exercise intensity or even in a termination of the activity (Cheung, 2007).

An elevation in internal body temperature and an increase in heat storage have been proposed as limiting factors to physical performance. Recent data support the hypothesis

that both the heat storage rate and the internal body temperature seem to be the important determinants of fatigue during exercise (Balthazar et al., 2010; Coelho et al., 2010; Garcia et al., 2006; Lacerda et al., 2005; Leite et al., 2006; Magalhães et al., 2010; Nassif et al., 2008; A. G. Rodrigues et al., 2008; Soares et al., 2004, 2007). Thus, dissipation of heat from the body is thought to be more important than the control of heat production in the regulation of body temperature during exercise (Cheung & Sleivert, 2004).

Temperature regulation during exercise can be divided into two phases. During the first minutes of exercise, in what has been called the dynamic phase, there is a imbalance between heat production, which depends mainly on exercise intensity, and heat dissipation; this imbalance results in an abrupt increase in body (internal) temperature. Rapid peripheral vasoconstriction, mediated by the noradrenergic sympathetic system and observed at this earlier phase, impairs heat dissipation during this stage of exercise and leads to hyperthermia. Venous blood that drains exercising muscles brings excessive heat to the body core. Hypothalamic thermosensors detect the increase in blood temperature, and the thermal integrative center of the hypothalamus activates efferent heat loss mechanisms. The second phase of exercise, known as the steady phase of thermal balance, begins as thermal thresholds for heat dissipation mechanisms (vasodilation and sweating) are attained (Lacerda et al., 2006). From this point on, there is an increase in skin blood flow, mediated by the vasodilator cholinergic sympathetic system, which parallels the increase in the sweating rate. These autonomic actions increase the body heat dissipation and minimize the body temperature elevation. When heat storage reaches a critical limit, protective fatigue occurs independently of body energy stores. This excessive stored heat reduces the motivation for voluntary exercise before the individual integrity is compromised.

Neuromuscular control and hyperthermia have been widely investigated, and it has been consistently shown that hyperthermia diminishes neuromuscular activation (Morrison et al., 2004; Nybo & Nielsen, 2001; Todd et al., 2005). A model has been proposed that suggests that this impairment causes systemic failures in order to protect the organism from severe heat injuries (Cheung, 2007). A reduction in the central drive to the motor neuron pool during hyperthermia is thought to result from at least two possibilities. One considers that there is a reduction in the descending message from the higher brain impulses to the motor neurons. The other indicates that inhibition occurs subcortically, at the site of the motor neurons, where afferent feedback may decrease the excitability of those motor neurons (Cheung & Sleivert, 2004). The reduction in central drive may also result from both of these possibilities.

Brain function may also be altered during hyperthermia. Changes in behavior seen with overheating, such as confusion, a loss of coordination, syncope, and, in extreme hyperthermia, a loss of consciousness or seizures, have been consistently observed (Fuller et al., 1998; Schlader et al., 2010; Walters et al., 2000). These data indirectly suggest a change in central nervous system function with hyperthermia (Cheung & Sleivert, 2004; Nybo, 2008). Brain activity, specifically the ratio of low frequency (α: 8–13 Hz) and high frequency (β: 13–30 Hz) brainwaves, is an indicator of arousal during hyperthermia. Exercise has been investigated in subjects cycling at 60% aerobic power in both a hot ($\cong 40°C$) and cool ($\cong 19°C$) environment (Nielsen et al., 2001). There was a reduction in β waves in the hot exercise condition such that the ratio of α to β waves increased, which indicates a reduced state of arousal in hyperthermic subjects. Moreover, the magnitude of the increase in the α to β wave ratio was correlated to elevated core temperatures. In the same study, subjects continually rated their perception of effort to be higher during hyperthermic condition (Nielsen et al., 2001).

Another important aspect regarding fatigue induced by exercise hyperthermia is cardiovascular function. It has been suggested that cardiovascular strain accompanying hyperthermia could indeed be one of the main factors underlying fatigue (Cheung & Sleivert, 2004). When heat production during exercise surpasses the capacity for heat dissipation to the environment and hyperthermia consequently develops, the ability to maintain cardiac output is jeopardized because stroke volume declines as the core temperature increases (Nybo, 2008). The competition between metabolic and thermoregulatory demands for blood flow during exercise may also accelerate the onset of fatigue through localized ischemia in specific tissues such as the brain or the gastrointestinal tract. Reduced blood flow to the gastrointestinal tract during exercise in heat may compromise the integrity of the intestinal walls (Sakurada & Hales 1998). As a result, the eventual leakage of lipopolysaccharides (endotoxins) into the circulation, a well-documented response to severe exercise-induced hyperthermia, can occur. It is important to point out that an occurrence of endotoxemia can trigger a cascade of detrimental physiological responses mediated by cytokines, which can induce a fever-like situation and can accelerate heat storage and heat stroke.

Neurohumoral factors, primarily disturbances in cerebral neurotransmitter levels, are part of the diverse mechanisms underlying fatigue induced by exercise hyperthermia. It is clear that several neurotransmitter systems are activated during exercise and that several of these systems affect the preoptic area and the anterior hypothalamus, which is of major importance for thermoregulation (Nybo, 2008). Therefore, it is important to highlight studies that correlate high heat storage and heating rates with elevated levels of serotonin in centers essential for thermoregulation (Leite et al., 2010; A. G. Rodrigues et al., 2009; Soares et al., 2007). However, there are only a few that have examined whether hyperthermia alters monoamines and other neurotransmitter levels in the brain during exercise. Although this subject will be discussed in detail in subsequent topics in this chapter, it is essential to first call attention to some aspects.

Among the monoamines, serotonin is of particular interest because it influences arousal levels. If serotonin levels increase, this could contribute to an increase in perceived effort and a reduction in work rate, actions that have often been observed during hyperthermia (Cheung & Sleivert, 2004). In contrast, because dopamine and noradrenaline have been associated with arousal, motivation, reinforcement and reward, control of motor behavior and mechanisms of addiction, some authors have investigated the role of these neurotransmitters on fatigue induced by exercise hyperthermia (Meeusen et al., 2006). Recently, it has been demonstrated that an alteration in dopamine transmission induced by the central blockade of dopamine D1 and D2 receptors impaired running performance in rats by decreasing the tolerance to heat storage. Furthermore, this blockade also impaired both the dissipation of exercise-induced heat and the recovery of the metabolic rate during the post-exercise period. These data provide evidence that the central activation of either dopamine D1 or D2 receptors may be essential for heat balance and exercise performance (Balthazar et al., 2010).

6. Ergogenic and ergolytic amines

Most theories consider central fatigue during prolonged exercise to be a consequence of changes in neurotransmitter turnover, particularly in the serotonergic system (Foley & Fleshner, 2008; Hasegawa et al., 2008; Nybo & Secher, 2004; Roelands & Meeusen, 2010).

Although the role of serotonergic neural traffic on exercise performance has been well-documented, evidence demonstrates that dopaminergic and noradrenergic neurotransmissions contribute to central fatigue as well (Foley & Fleshner, 2008; Hasegawa et al., 2008; Nybo & Secher, 2004; Roelands & Meeusen, 2010). Interestingly, all of these brain monoamines, in addition to having their activity modified by exercise, exhibit relevant thermoregulatory effects (Balthazar et al., 2009; Foley & Fleshner, 2008; Hasegawa et al., 2008; Roelands & Meeusen, 2010; Soares et al., 2004, 2007). It has been proposed that shifts in the turnover of these amines, which play an important role in the centers responsible for body temperature control, like the preoptic area and the anterior hypothalamus, may be associated with the development of fatigue coupled with heat imbalance.

6.1 Serotonin

Many authors have provided convincing evidence of the involvement of serotonin on the development of central fatigue (Blomstrand et al., 1989; Chaouloff, 1997; Fernstrom & Fernstrom, 2006; Gomez-Merino et al., 2001, Soares et al., 2007). The major premise is that increased brain serotonergic activity contributes to the onset of fatigue, possibly through its influence on many behavioral functions, such as elevated feelings of lethargy, tiredness and a loss of drive (Blomstrand, 2006; Meeusen et al., 2006; Roelands & Meeusen, 2010; Soares et al 2004, 2007). In contrast, low serotonin brain levels would favor improved exercise performance through the maintenance of motivation and arousal.

One the first studies that associated physical activity with elevated levels of serotonin in the central nervous system is Barchas & Freedman (1963), who reported high brain serotonin activity in rats who swam until exhaustion. Since then, many findings have confirmed that serotonin levels in the central nervous system increase during exercise and peak at the fatigue point (Blomstrand et al., 1989; Chaouloff, 1997; Fernstrom & Fernstrom, 2006; Gomez-Merino et al., 2001, Soares et al., 2007). Exercising until fatigue has been shown to cause an increase in the levels of both serotonin and its metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the brain stem and hypothalamus and an additional increase in the level of 5-HIAA in the hippocampus and striatum. The authors concluded that because there was an increase in the turnover of serotonin in some parts of the brain, these may play a role in physical performance (Blomstrand et al., 1989). Gomez-Merino et al. (2001) examined the impact of acute intensive treadmill running on serotonin levels in the hippocampus and the frontal cortex and observed high levels of the monoamine in both regions after 90 minutes of exercise. In these same regions, as well as in the hippocampus, Soares et al. (2007) and A. G. Rodrigues et al. (2009) reported elevated concentrations of serotonin after running until fatigue. More recently, Caperuto et al. (2009) reported that although swimming training induced similar hypothalamic serotonin concentrations as sedentarism, its concentration in this brain region increased after an exhaustive training program with an insufficient recovery period. The data led to the hypothesis that elevated serotonin content may contribute to poor exercise performance during periods of excessive training.

A special focus has been given to the pharmacological manipulations used to elucidate the relationship between increased serotonergic activity and the early onset of fatigue (Bailey et al., 1993; Roelands et al., 2009). A study by Bailey et al. (1993) demonstrated that exercise performance benefitted from the use of a serotonin antagonist, while treatment with a serotonin agonist led to a detriment in exercise performance. Similarly, increased brain serotonin availability during exercise results in poor physical performance (Soares et al.,

2004, 2007). Reduced exercise performance related to higher serotonin content in the preoptic area and the hypothalamus was also verified after a central blockade of angiotensinergic synapses (Leite et al., 2010). Serotonin reuptake inhibitors have also been widely used, with the purpose of investigating the relationship between the neurotransmitter and central fatigue (Meeusen et al., 2001; Pannier et al., 1995; Parise et al., 2001; Struder et al., 1998; W. M. Wilson et al., 1992). However, the results are contradictory and inconclusive. Although data have demonstrated no effect of different serotonin reuptake inhibitors (pizotifen, fluoxetine, citalopam) on exercise performance in humans (Meeusen et al., 2001; Pannier et al., 1995; Parise et al., 2001; Roelands et al., 2009; Strachan et al., 2004), findings from Struder et al. (1998) and W. M. Wilson et al. (1992) indicate that fatigue occurs sooner with pharmacological augmentation of the brain's serotonergic activity by serotonin re-uptake inhibitor (paroxetine) supplements. These different outcomes might be explained by divergent exercise protocols, pharmacological manipulations, drug receptor specificity and drug dosages.

Recent evidence indicates that serotonin neurotransmission also contributes to the development of central fatigue through its interference with thermoregulation. Particularly in the preoptic area/anterior hypothalamus, increased serotonin availability has been associated with hyperthermia that was brought about by an increase in metabolic heat production and a decrease in heat loss (Lin et al., 1998; Soares et al., 2004, 2007).The central treatment with tryptophan during exercise results in the precipitation of fatigue due to a disruption of the thermal balance, which accelerates the increase in exercise-induced hyperthermia (Soares et al., 2004, 2007). This finding indicates an important role of serotonin in thermoregulation during exercise and agrees with the observation that the rate of body heating reduces the central nervous system drive for exercise performance (Soares et al., 2004, 2007). In fact, the data show that tryptophan-induced central fatigue due to hyperthermia and increased heat storage was intimately related to enhanced serotonin content in the preoptic area. In other words, increased serotonergic tonus in the preoptic area contributed to the aggravation of hyperthermia during exercise and the earlier settlement of central fatigue (Soares et al., 2007). This assumption is also true after the central manipulation of angiotensinergic transmissions (Leite et al., 2010). The central fatigue due to intense hyperthermia that was induced by central angiotensinergic inhibition was related to higher serotonin content in the preoptic area and the hypothalamus. In contrast, central cholinergic stimulation was associated with a decreased elevation in body temperature during exercise by abolishing the exercise-induced increase in serotonin content in the preoptic area (A. G. Rodrigues et al., 2009). These data emphasize that the onset of hyperthermic central fatigue seems to depend greatly on serotonin trafficking in thermoregulatory centers.

6.2 Dopamine

Although the role of serotonin in central fatigue has been well-documented, there is data that shows that dopamine also influences central fatigue (Balthazar et al., 2009, 2010; Foley & Fleshner, 2008; Hasegawa et al., 2008). Dopamine neurotransmission is associated with many physiological functions that could modify running performance, such as arousal, motivation, reinforcement, reward, motor behavior control and mechanisms of addiction (Balthazar et al., 2009, 2010; Foley & Fleshner, 2008; Hasegawa et al., 2008; Meeusen et al., 2007).

Central dopamine metabolism has been shown to increase in several brain regions during exercise (Balthazar et al., 2009; Foley & Fleshner, 2008; Hasegawa et al., 2008; Meeusen et al., 2007). Meeusen et al. (1997) showed that 60 min of exercise significantly increased dopamine content in the striatum. The same increase in dopamine concentration was seen in the midbrain, hypothalamus and hippocampus during exercise (Balthazar et al., 2009, 2010; Chaouloff et al., 1987). On the other hand, Bailey et al. (1993) reported reduced cerebral dopamine levels after prolonged running, which indicates that low dopamine levels during intense exercise may contribute to the reduction in physical capacity through an interference with motivation, arousal and the motor drive. It is important to point out that recent studies reveal that the variation in the brain dopamine content during exercise exhibits a dynamic profile; the levels increase between exercises and return to basal levels at the point of fatigue, which is the same time that serotonin content is at its peak (Bailey et al., 2003; Balthazar et al., 2009; Foley & Fleshner, 2008; Struder & Weicker, 2001a,b). Therefore, it seems that exercise continuation is favored by the increase in dopamine brain levels in between exercises, while central fatigue is a consequence of the reduced central dopamine concentrations along with other factors, such as the increased brain serotonin concentrations.

Findings that elevations in brain dopamine levels are associated with a delay in fatigue come primarily from pharmacological manipulations (Hasegawa et al., 2005; Watson et al., 2005). The administration of amphetamine, a potent dopamine releaser (Chandler & Blair, 1980), has been shown to significantly increase running time until exhaustion (Gerald, 1978). Acute inhibition of dopamine reuptake with bupropion has also been shown to result in exercise performance improvements (Hasegawa et al. 2008; Watson et al., 2005). Similarly, central dopamine activation prior to running until fatigue has also been shown to increase exercise time (Balthazar et al., 2009). In contrast, the blockade of brain dopaminergic receptors markedly reduces exercise tolerance (Balthazar et al., 2010). Interestingly, all of these changes in physical capacity were followed by an elevation in body temperature. In fact, various studies provide evidence that central dopamine activation plays an important role in thermoregulatory mechanisms; this leads to heat loss and body temperature reduction by inducing central temperature set-point adjustments and increasing heat dissipation through skin vasodilation (Balthazar et al., 2010; Barros et al., 2004; Chaperon et al., 2003; Nunes et al., 1991; Varty & Higgins, 1998). Nevertheless, there is evidence that an increase in dopamine levels in the preoptic area/anterior hypothalamus is followed by hyperthermic responses during exercise (Balthazar et al., 2009, 2010; Hasegawa et al. 2005, 2008; Watson et al., 2005). Watson et al. (2005) reported that bupropion, despite enabling subjects to maintain a greater time-trial power output while in the heat, led to a higher body temperature. Hasegawa et al. (2008) showed further evidence that the improved physical performance that was a result of bupropion treatment was accompanied by increased brain and body temperatures and related to an increase in the concentration of dopamine in the preoptic area/anterior hypothalamus. The central activation of dopaminergic transmissions also induces a longer time of running until fatigue, despite a higher heat storage and body temperature at the fatigue point (Balthazar et al., 2009). In contrast, a central blockade of D1 or D2 dopaminergic receptors impairs the dissipation of the exercise-induced heat stored during running, and results in persistent hyperthermia and markedly reduced exercise tolerance (Balthazar et al., 2010). Because the ergogenic response is affected by thermoregulation, the preoptic area/anterior hypothalamus seem to be the brain areas in

which dopamine exerts its thermoregulatory actions; dopamine modulates heat production and dissipation during exercise, thus affecting running performance (Balthazar et al., 2009; Hasegawa et al. 2008; Watson et al., 2005). Another possible locus for the effects of central dopaminergic stimulation seems to be the dopaminergic reward circuits (Koob & Moal, 2008). Dopamine, acting on the mesolimbic reward system, could overrule the inhibitory signals arising from the central nervous system that normally compromise running performance (Balthazar et al., 2009; Hasegawa et al. 2008; Watson et al., 2005). The results of the interaction between thermoregulatory and reward adjustments that are induced by central dopamine may be an increase in the drive and motivation to continue exercise; this increased drive could dampen or override the inhibitory signals that arise from the central nervous system that end exercise due to hyperthermia. Therefore, it seems that the interference of central dopamine with the development of hyperthermic central fatigue depends mainly on the activation of reward circuitries that could overrule the hyperthermic inhibitory pathways (Balthazar et al., 2009; Hasegawa et al. 2008; Watson et al., 2005).

6.3 Noradrenaline

Little data has been reported on the contribution of noradrenaline in central fatigue. Although noradrenaline is associated with arousal, consciousness and reward mechanisms in the brain (Roelands & Meeusen, 2010), researchers have shown that elevated brain levels of this catecholamine has a negative effect on exercise performance (Piacentini et al., 2002; Roelands et al., 2008; Roelands & Meeusen, 2010). The administration of reboxetine, a noradrenaline reuptake inhibitor, led to a trend towards a decrease in exercise performance in well-trained endurance athletes (Piacentini et al., 2002). This response was later confirmed by Roelands et al. (2008), who suggested that an increase in the concentration of noradrenaline could be unfavorable for exercise performance because treatment with the noradrenaline reuptake inhibitor decreased physical capacity in both normal and high ambient temperatures. The inhibitory effect exerted by noradrenaline on physical performance, even though it was not accompanied by a significant change in body temperature, induced a tendency for hypothermia. This inclination was further corroborated by thermal stress scale scores that indicated a cold sense by the subjects after noradrenaline reuptake inhibition (Roelands et al., 2008).

Studies have provided conflicting data about the role of noradrenaline in thermoregulation. The literature points out that the divergent thermal effects of noradrenaline depend on the type of receptor that is being stimulated. Therefore, it seems that α-1 noradrenergic receptors mediate a rise in body temperature, while α-2 noradrenergic receptors are involved in a fall in body temperature (Feleder et al., 2004; Imbery et al., 2008; Quan et al., 1991, 1992). Noradrenaline administered in the preoptic area induces a hypothermic response because of a reduction in the metabolic rate (Quan et al., 1991). This response has been shown to be mediated by α-2 receptors, as demonstrated by the fact that an α-2 agonist evoked a dose-dependent decrease in body temperature that was abolished by an α-2 antagonist (Quan et al., 1992). Similar results were found after noradrenaline activation in the anterior hypothalamus during rest and exercise (Feleder et al., 2004; Gisolfi & Christman, 1980). On the other hand, Myers et al. (1987) suggested that both α-1 and α-2 noradrenergic receptors in the hypothalamus are required to evoke hypothermia. Moreover, it has been shown that α-1 activation of hypothalamic neurons results in a rapid

hyperthermia (Feleder et al., 2004) and that α-1 agonists infused into the preoptic area evoke a quick rise in body temperature (Imbery et al., 2008).

The involvement of brain noradrenergic transmission in the onset of hyperthermic central fatigue is still uncertain. A study from Hasegawa et al. (2008) showed the most convincing evidence of the role of noradrenaline on the development of fatigue due to hyperthermia. The administration of a dopamine/noradrenaline reuptake inhibitor (bupropion) in the heat, prior to exercise until exhaustion, induced an increase in brain and body temperature; both were associated with a decreased heat loss response and a better physical capacity (Hasegawa et al., 2008). These responses were followed by similar level of increases in the concentrations of dopamine and noradrenaline in the preoptic area/anterior hypothalamus. Therefore, although bupropion has a higher potency for dopamine than noradrenaline (Holm & Spencer, 2000), the results demonstrate that the drug acts in the brain by enhancing the concentration of both dopamine and noradrenaline in a nucleus of major importance for thermoregulation. The interaction of dopamine and noradrenaline in the preoptic area/anterior hypothalamus likely extends the safe limits of hyperthermia. Nonetheless, the brain noradrenergic contribution to hyperthermic central fatigue needs to be investigated further. Special attention should be given to the interaction between noradrenaline and dopamine, in addition to serotonin, on the onset of central fatigue related to hyperthermia.

7. Brain monoamines and other neurotransmitters on the development of central fatigue: Balance between serotonin and dopamine?

It would be simplistic to assume that central fatigue is a result of the altered metabolism of a single neurotransmitter. On the contrary, data indicate that the phenomenon is much more complex and includes the interaction between many neurotransmitters that interfere with exercise performance, together with thermoregulation, through the modulation of brain monoamine concentrations (Bhattacharya & Sen, 1992, Foley & Fleshner, 2008; Leite et al., 2010; Meeusen et al., 2006, A. G. Rodrigues et al., 2004, 2009). In light of the facts that central fatigue is coincident with high body temperature and/or high rates of body heating and heat storage and that serotonergic, dopaminergic and noradrenergic transmissions are in command of fatigue, the interaction between such systems and with other neurotransmitters implicated in thermoregulation seems to affect physical capacity by influencing heat balance in important thermoregulatory centers.

The most commonly described interaction is between serotonin and dopamine (Davis & Bailey, 1997; Foley & Fleshner, 2008; Leite et al., 2010; Meeusen et al., 2006). The precursor of dopamine, tyrosine, competes with other amino acids, including tryptophan, for entry into the brain (Blomstrand, 2006; Fernstrom & Fernstrom, 2006; Foley & Fleshner, 2008; Meeusen et al., 2006). The interaction between serotonin and dopamine may be an important factor affecting the central component of fatigue (Foley & Fleshner, 2008; Leite et al., 2010; Meeusen et al., 2006). Both serotonin and dopamine transmissions increase in the central nervous system due to exercise; however, while serotonin concentration peaks at the fatigue point, dopaminergic activity increases in between exercises and returns to resting levels at fatigue (Bailey et al., 1993; Balthazar et al., 2009; Foley & Fleshner, 2008; Struder & Weicker, 2001a,b). On the basis of this data, the "central fatigue hypothesis" postulates that a high serotonin/dopamine ratio is associated with poor exercise performance, being the converse also true i.e. improvement of exercise performance (Foley & Fleshner, 2008; Leite et al., 2010;

Meeusen et al., 2006). In the first case, the increase in the brain activity of serotonin during physical activity seems to contribute to fatigue through an inhibition of the central dopaminergic system (Foley & Fleshner, 2008; Leite et al., 2010; Meeusen et al., 2006). To support such an assumption, it has been demonstrated that the administration of a serotonin agonist blocked the exercise-induced increase in brain dopamine concentrations; it has also been shown that treatment with a serotonin antagonist prevented a decrease in central dopamine levels at exhaustion (Bailey et al., 1993). Therefore, a decline in exercise performance seems to depend primarily on a serotonin level increase that could override the ergogenic effect of dopamine. Taking into account these data and data that show that both dopamine and serotonin mediate thermoregulation, it has been demonstrated that another factor that contributes to premature central fatigue is the association of high serotonin/dopamine ratio in the hypothalamus with intense hyperthermia (Leite et al., 2010).

Many studies have focused on analyzing the effects of the relationships between brain catecholamines on the development of hyperthermic central fatigue, particularly in regards to dopamine and noradrenaline (Hasegawa et al., 2005, 2008; Watson et al., 2005). Both neurotransmitters have been implicated in thermoregulation, and both have their activity elevated during exercise, likely as a function of the increased sympathetic tonus (Balthazar et al., 2009; Davies & Bailey, 1997; Hasegawa et al., 2008). The administration of bupropion has been the most commonly used drug to investigate such catecholaminergic interactions (Hasegawa et al., 2005, 2008; Watson et al., 2005). The acute administration of bupropion during rest has been shown to increase dopamine and noradrenaline levels in the hippocampus and in the preoptic area/anterior hypothalamus, and this effect was followed by hyperthermic responses (Hasegawa et al., 2005; Piacentini et al., 2003). During exercise, the acute ingestion of the drug in humans has been shown to improve time-trial exercise performance in a warm environment, despite higher body temperatures (Watson et al., 2005). In contrast to acute bupropion administration, the chronic ingestion of the drug does not influence time-trial exercise performance under the same environmental conditions, aside from inducing lower body temperature values than the temperatures observed during the acute bupropion study (Roelands et al., 2009; Watson et al., 2005). The mechanism for these observed discrepancies in bupropion administration seems to be the possible adaptation of central neurotransmitter homeostases during the treatment (Roelands et al., 2009). Hasegawa et al. (2008) showed further evidence that acute bupropion treatment prior to exercise until exhaustion in the heat induces increased brain and body temperatures and better physical capacity; these effects are both accompanied by similar increases in the concentrations of dopamine and noradrenaline in the preoptic area/anterior hypothalamus throughout exercise. Therefore, although bupropion has a higher affinity for dopamine than noradrenaline (Holm & Spencer, 2000), these results demonstrate that the drug acts in the brain by increasing the concentrations of both dopamine and noradrenaline in nuclei of major importance for thermoregulation; their interaction probably extends the safe limits of hyperthermia. The communication between these catecholamines seems to potentiate motivation, arousal and reward, thus enabling subjects to continue to sustain a high power output, despite approaching critical levels of body temperatures that could contribute to central fatigue development (Balthazar et al., 2009; Hasegawa et al., 2008; Watson et al., 2005). Nevertheless, the nature of such interplay between dopamine and noradrenaline is still uncertain.

Brain serotonergic activity has been demonstrated to be affected by cholinergic neurotransmission (Bhattacharya & Sen, 1992). The administration of muscarinic receptor

agonists induces a dose-related decrease in the brain concentrations of serotonin. In contrast, the muscarinic receptor antagonist, pirenzepine, increases the central levels of this monoamine. These results indicate that an inverse relationship exists between the cholinergic and serotonergic neurotransmitter systems in the brain (Bhattacharya & Sen, 1992). More recent reports show evidence that central cholinergic activation also influences central fatigue through interactions with the serotonergic system (A. G. Rodrigues et al., 2004, 2009). Studies have shown that the stimulation of heat dissipation mechanisms is related to cholinergic activation and produces hypothermia when cholinoceptor agonists are injected centrally (Lin et al., 1980, Pires et al., 2007; Prímola-Gomes et al., 2007; A. G. Rodrigues et al., 2004, 2009). This effect was seen during exercise after central activation of the cholinergic system with physostigmine (an acetylcholinesterase inhibitor). The treatment decreased body heating rate and heat storage due to improved heat loss (A. G. Rodrigues et al., 2004, 2009). As a consequence, body temperature increases attenuated, which enabled fatigue to be established at a lower body temperature without exercise performance improvement. In such a situation, the cardiovascular overload was the main inductor of fatigue, prevailing over the hypothermic excitatory signals from the central nervous system that could ultimately favor physical work performance (Pires et al., 2007). It is important to note that the lower heat storage, as a product of central physostigmine treatment, was closely associated with decreased serotonin levels in the preoptic area at the moment of fatigue (A. G. Rodrigues et al., 2009). These data indicate that cholinergic stimulation abolishes the exercise-induced increase in serotonin content in the main thermoregulatory site. Moreover, these data support the idea that central cholinergic stimulation promotes decreases in heat storage during exercise by altering the activation of the brain serotonergic system.

Adding to the hypothesis that central fatigue is determined by interactions between neuronal signal substances, it has been demonstrated that a central angiotensinergic blockade during exercise affects serotonin concentration in the preoptic area and hypothalamus, in association with excessive hyperthermia and premature central fatigue (Leite et al., 2010). Acting centrally, angiotensin II exerts thermoregulatory effects that are characterized by hypothermia (Fregly & Rowland, 1996; K. M. Wilson & Fregly, 1985).Central treatment with losartan (angiotensin II AT_1 receptor antagonist) worsens hyperthermia and increases the body heating rate and heat storage rate that are indirectly related to the time to fatigue. This hyperthermic response is due to a heat imbalance that is characterized by higher heat production and lower peripheral heat loss (Leite et al., 2006, 2007). These effects of angiotensin II on heat balance during exercise were shown to be linked to serotonergic pathways (Leite et al., 2010). These findings provide evidence that the inhibition of the central angiotensinergic system during exercise causes an increase in serotonin content in the preoptic area and hypothalamus that is directly associated with hyperthermia and a higher body heating rate and that is indirectly related to the time to fatigue. In addition, although losartan did not alter the concentration of dopamine in the analyzed brain areas, it did lead to a high hypothalamic serotonin/dopamine ratio, which was directly correlated with the body heating rate and inversely correlated with the time to fatigue. Thus, serotonin and dopamine interaction in these regions contributes to hyperthermia and premature central fatigue when central angiotensinergic pathways are inhibited. Taken together, the data indicate that central angiotensinergic transmission has important effects on serotonin levels in the brain during exercise and interacts with dopamine-affected central fatigue through a modulation of body temperature control.

There is also the possibility that serotonin interacts with noradrenaline in the establishment of central fatigue, despite results from Piacentini et al. (2002), where the administration of a

serotonin/noradrenaline reuptake inhibitor (venlafaxine) had no effect on exercise performance. Evidence indicates that the dorsal raphe serotonin neurons receive noradrenergic projections from the locus coeruleus (Szabo & Blier, 2001, 2002). Conversely, noradrenaline neurons of the locus coeruleus receive dense serotonergic projections mainly from the dorsal raphe (Szabo & Blier, 2001, 2002). These pathways suggest the possible existence of modulation between the activity of serotonin and noradrenaline in the brain nuclei that are responsible for thermoregulation, which could interfere with thermal balance and exercise performance.

A question remains regarding the participation of other neurotransmitters that also influence thermal control, such as GABA and glutamate (Ishiwata et al., 2005; Nikolov & Yakimova, 2011), which could interact with central monoamines in the development of hyperthermic central fatigue. Thus, knowledge of the mechanisms of central fatigue is still limited and presupposes a complex interplay of different neurotransmitter systems that affect thermoregulation and exercise performance; serotonin, dopamine and noradrenaline likely play the most important roles.

8. Predictors of fatigue: Static and dynamic perspectives

The combination of exercise with excessive hyperthermia appears to diminish the central nervous system drive to the working muscles, protecting the brain from thermal damage in detriment of exercise performance (Kay & Marino, 2000; Nielsen & Nybo, 2003; Noakes, 1998). The thermoregulatory-sensed variables that initiate these central inhibitory signals of exercise performance in order to avoid heat stroke are still the subject of debate. Even though it has been stated that central fatigue coincides with the attainment of fixed high body and brain temperatures (Fuller et al., 1998; Gonzalez-Alonso et al., 1999; Nielsen et al., 1993; Walters et al., 2000), there is evidence that dynamic mechanisms are consistent regulators of feelings of fatigue. In support of this hypothesis, the rates of heat storage and body heating that are associated with changes in neurotransmitter content in thermoregulatory centers emerge as important factors in determining fatigue (Cheuvront et al., 2010; Hasegawa et al., 2008; Lacerda et al., 2005, 2006; Leite et al., 2006, 2010, L. O. Rodrigues et al., 2003; A. G. Rodrigues et al., 2004, 2009; Soares et al., 2004, 2007; Wanner et al., 2007).

Reaching critically high and predetermined body and brain temperatures, very close to the level of heat stroke, has been proposed as an ultimate warning sign that causes a reduction in the mental drive for exercise performance (Fuller et al., 1998; Gonzalez-Alonso et al., 1999; Nielsen et al., 1993; Walters et al., 2000). In this light, fatigue would be anticipated by such a static thermal indicator, which would establish a hyperthermic threshold to prevent homeostasis failure. There are a number of reports that have linked the attainment of a decisive high body temperature to the settlement of fatigue in humans and in animals. This was the conclusion of Nielsen et al. (1993), who reported that endurance-trained individuals always stopped exercising until exhaustion (~60% of VO_2 max) when esophageal temperatures reached 39.5°C. In addition, these subjects exhibited a prolonged endurance time after 9-12 consecutive days of exercising at an ambient temperature of 40°C, which was associated with a decreased body temperature rise rate; these changes suggest that the body heating rate could interfere with the physical capacity. To hold Nielsen's hypothesis, results from Fuller et al. (1998) indicate that exercise (~60% of VO2 max) trials that differed in ambient temperature (33.0 and 38.0°C) and initial body temperature (23 and 38°C) promoted fatigue at the same abdominal (~39.9°C) and brain temperatures (~40.2°C). It is important to

point out that the exercises were executed under a higher thermal load that induced fatigue earlier, which leaves open the possibility that the rates of body heating and heat storage might have been higher in this circumstance to enable fatigue to be reached at equal abdominal and brain temperatures. This possibility was seen in the case of trained subjects cycling in the heat (60% VO2, 40°C), whose time to fatigue was directly related to the body temperature increase rate, which was controlled at 0.10 or 0.05°C/min-1, and inversely related to the initial level of esophageal temperature (35.9 ± 0.2, 37.4 ± 0.1, or 38.2 ± 0.1) (Gonzalez-Alonso et al., 1999). In both experimental conditions, all subjects reached exhaustion at similar esophageal (40.1–40.2°C) and muscle temperatures (40.7–40.9°C) (Gonzalez-Alonso et al., 1999). However, the manipulation of the body temperature increase rate was restricted to a very narrow range and was possibly not large enough to induce noticeable changes in body temperature. Moreover, individual body temperatures respond differently to heat stimuli and depend on many factors, such as dehydration, nutrition, fitness and motivation, as well as exercise intensity and thermal environmental stress (Kay & Marino, 2000; L. O. Rodrigues et al., 2003). Therefore, in absolute terms, the thermal load imposed would be expected to vary between subjects. Also contributing to the concept that a critical body temperature limits exercise, Walters et al. (2000) demonstrated that running (~60% of VO2max) at an ambient temperature of 35°C establishes both hypothalamic and rectal temperatures at exhaustion of 42.1°C and 42.4°C, respectively, regardless of a manipulation in the initial hypothalamic temperature (41.5°C, 42.5°C or 43.5°C). The hypothalamic and rectal temperatures before exercise correlate negatively with the run-time until exhaustion, which means that the run-time to exhaustion was significantly reduced after preheating. Interestingly, the rectal temperatures at the fatigue point that were observed by the authors were considerably higher than previously seen with exercise at approximately the same intensity (Fuller et al., 1998). Furthermore, the body temperature values at fatigue from the studies mentioned above (Fuller et al., 1998; Walters et al., 2001) also differed from the data from Soares et al. (2004), who demonstrated that increased central serotonin availability with tryptophan treatment before exercise (~66% of VO2max) resulted in the same intraperitoneal temperature at fatigue as in the control group (38.32°C tryptophan vs. 38.03°C saline). It is important to point out that the tryptophan administration elevated the body heating rate and the heat storage rate, and both were negatively correlated with the time to fatigue. Therefore, central serotonergic-activation-induced higher body temperature variations are associated with increased body heating and heat storage rates, which anticipated fatigue (Soares et al., 2004). This detail allows for the possibility that reaching a critically high body temperature by itself may not be the main factor in predicting fatigue. In fact, this result is in agreement with the concept that dynamic variables strongly contribute to the reduction of physical performance (Cheuvront et al., 2010; Hasegawa et al., 2008; Lacerda et al., 2005, 2006; Leite et al., 2006, 2010, L. O. Rodrigues et al., 2003; A. G. Rodrigues et al., 2004, 2009; Soares et al., 2004, 2007; Wanner et al., 2007).

There are many findings that differ from the hypothesis that fatigue is predicted by a defined high body temperature (Cheuvront et al., 2010; Hasegawa et al., 2008; Lacerda et al., 2005, 2006; Leite et al., 2006, 2010, L. O. Rodrigues et al., 2003; A. G. Rodrigues et al., 2004, 2009; Soares et al., 2004, 2007; Wanner et al., 2007). These findings show that the rates of body heating and heat storage play an important role in signaling fatigue development to the brain. Both parameters are characterized by the variation of body temperature as a function of time; the heat storage rate is further corrected for body weight (Lacerda et al.,

2005, 2006; Leite et al., 2006, 2010, L. O. Rodrigues et al., 2003; A. G. Rodrigues et al., 2004, 2009, Soares et al., 2004, 2007; Wanner et al., 2007). Recently, it has been proposed that skin temperature also provides important sensory input to the central nervous system during exercise in the heat and has a negative effect on performance that worsens as the cutaneous temperature progressively increases (Cheuvront et al., 2010).

Considering this dynamic hypothesis, L. O. Rodrigues et al. (2003) demonstrated that exhaustion was inversely correlated with the heat storage rate during running at a speeds of 21 or 24 m/min, without an incline in the treadmill, at three different ambient temperatures (18.0, 23.1 or 29.4°C). The exercise under the higher intensity and thermal load resulted in precipitation of fatigue. More importantly, the intraperitoneal body temperature at the fatigue point was different between the groups and higher after running in the heat. This profile was also seen by Hasegawa et al. (2008), whose data demonstrated that both intraperitoneal and brain temperatures at the point of exhaustion were significantly lower after exercise in a cool condition (18.0°C) compared to a warm environment (30 °C). Therefore, in these two examples, the body temperature at the point of exhaustion in the cool condition did not reach the critical level. Brain manipulations of neurotransmitters/neuromodulators during exercise also give strong evidence of the involvement of dynamic variables on the reduction in exercise time. Central nitric oxide blockade with L-NAME (N-nitro-l-arginine methyl ester, a nitric oxide synthase inhibitor) results in higher intraperitoneal body temperatures at fatigue and lower exercise performances (Lacerda et al., 2005). Due to the increased heat production associated with decreased heat loss, this treatment results in a higher body heating rate that rapidly produces hyperthermia (Lacerda et at., 2005, 2006). It is important to point out that the reduced exercise performance observed after a blockade of nitric oxide pathways is closely associated with the higher body heating rate (Lacerda et al., 2005). This relationship is absent after a stimulation of the central cholinergic transmissions during exercise (~66% of VO_2max). Although this treatment attenuated colonic temperature increases, the time to fatigue was not affected, which was the same as that of controls (A. G. Rodrigues et al., 2004). This evidence emphasizes that even though both groups reached fatigue at the same moment, the body temperature at fatigue was different between groups; that is, body temperatures were lower after central cholinergic stimulation, which is attributable to the activation of heat loss mechanisms (A. G. Rodrigues et al., 2004, 2009). Additionally, this treatment promoted a decrease in the body heating rate (A. G. Rodrigues et al., 2004). On the other hand, a direct relationship between the heat storage rate and the time to fatigue was present when cholinergic transmissions where blocked by a central administration of methylatropine (a muscarinic receptor antagonist) (Wanner et al., 2007). A central cholinergic blockade during running (~80% of VO_2max) increases the heat storage rate, leading to greater exercise-induced hyperthermia and a higher intraperitoneal temperature at fatigue, which is followed by exercise performance impairments. Therefore, the increased heat storage rate, as a consequence of a higher metabolic cost and decreased heat dissipation, contributes significantly to the interruption of exercise (Wanner et al., 2007, 2011). Adding to the hypothesis that fatigue is determined by active variables, Leite et al. (2006) verified that a close correlation between the elevated body heating rate and the reduced time to fatigue (~66% of VO_2max) is seen after central angiotensinergic blockade with losartan. This treatment increases intraperitoneal temperatures at the fatigue point because of an enhanced heat production that is not compensated by a proportional heat loss

(Leite et al., 2006, 2007). Thus, an infusion of losartan induces a significant increase in the body heating rate, and also the heat storage rate, that rapidly produces aggravation of hyperthermia and reduces exercise performance (Leite et al., 2010). In view of the fact that dissimilar values of body temperatures at the fatigue point were seen between groups assessed with distinct approaches, the authors postulated that as the elevated rates of body heating and heat storage progressively exacerbate the exercise-induced hyperthermia, the central nervous system becomes sensitive to such a dynamic event and induces fatigue as a safety mechanism to prevent a dangerously high body temperature that could jeopardize physical integrity.

Recent findings have also associated elevated rates of body heating and heat storage with high levels of serotonin in centers responsible for thermoregulation (Leite et al., 2010; A. G. Rodrigues et al., 2009; Soares et al., 2007). In the case of central angiotensinergic blockade, the augmented body heating rate and reduced exercise performance were directly associated with high levels of serotonin at fatigue in thermoregulatory centers like the preoptic area and hypothalamus (Leite et al., 2010). An elevation of serotonin content in the preoptic area is also related to increased body temperature variations and a reduced time to fatigue shown by central serotonin activation (Soares et al., 2007). In contrast, lower heat storage, which attenuates the exercise-induced hyperthermia as a result of stimulation of the central cholinergic system, is closely associated with decreased serotonin levels in the preoptic area at the moment of fatigue (A. G. Rodrigues et al., 2009). Central dopamine metabolism is also enhanced during exercise (Balthazar et al., 2009; Foley & Fleshner, 2008; Hasegawa et al., 2005), and its interaction with serotonin has been linked with high rates of body heating and precipitation of fatigue (Foley & Fleshner, 2008; Meeusen et al., 2007). A combination of effects is induced by central angiotensinergic blockade, which leads to a higher serotonin/dopamine ratio within the hypothalamus at fatigue that correlates directly with the body heating rate and indirectly with the exercise time to fatigue (Leite et al., 2010). This observation asserts that the high concentrations of serotonin achieved during exercise, in addition to their interactions with dopamine in nuclei responsible for thermoregulation, contribute to the increases in body heating and heat storage rates, thereby adding to exercise-induced hyperthermia and decreasing running performance. Changes in neurotransmitter content in thermoregulatory centers, which are associated with afferent feedback arising from variations in the body heating and heat storage rates during exercise, provide new insights into possible mechanisms by which individuals may terminate exercise.

9. Conclusions

The mechanisms underlying hyperthermic central fatigue include decreased efferent signaling from the central nervous system that protects the brain from thermal damage. There is strong evidence that these mechanisms depend greatly on monoamine traffic, mainly the serotonin/dopamine ratio, in thermoregulatory centers. Hyperthermic central fatigue during exercise should be seen essentially as a defense mechanism. Reaching a critically high body temperature, by itself, may not be the main factor in predicting fatigue. In fact, this is in agreement with the concept that dynamic variables determine physical performance more than static ones.

10. Acknowledgments

11. References

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Part 3

Epidemiology of Sports Medicine Injury and Disease

Community Options for Outdoor Recreation as an Alternative to Maintain Population Health and Wellness

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1. Introduction

Among professional, elite amateur and recreational athletes, having a sports injury can cause physical, social and psychological concern. Individuals with a sports injury may experience a significant challenge due to the reduced ability to participate in regular training. The injury may result in changes to their daily routine, and require time to heal. Regardless of etiology or prognosis, the loss presents a serious challenge to the athlete's health. In order to promote recovery, it is important for the injured person to adopt alternative approaches to remaining active. The injured athlete can engage in a variety of challenging and satisfying activities which will provide assistance in overcoming physical psychological and social concerns associated with being inactive. Outdoor recreation allows injured athletes the opportunity to modify their training activity in order to rest the injured body part, and provide a variety of physical activity opportunities to maintain health and wellness.

2. Health and wellbeing

The health benefits of outdoor recreational physical activity can be attributed to many different dimensions beyond physiological. Researchers have studied the relationship between outdoor recreational physical activity and psychological health and have found improved ratings of quality of life, decreased stress reduction, improved feelings of self-competence, and positive changes in mood and emotions. Thus, the health benefits of outdoor recreational activity are extensive, and outdoor recreation is a viable community alternative for places to participate in sport, exercise and physical activities. The outdoor environment provides an opportunity for people to recover from daily stress and fatigue, and on any given day, ¼ or about 54 million U.S. adults participate in a sport, exercise, or recreational activity. The benefit of many community outdoor recreational locations is that they provide an easily accessible place to maintain an active lifestyle. Community options surround everyone and to name a few, may consist of forests, beaches, parks, and sports fields. There is growing recognition for the value of outdoor recreation in promoting activity options to recover from sports-related injuries.

3. Physical health

Prolonged inactivity is detrimental to recovering from a sports injury. Research has shown that regular physical activity reduces people's risk for heart attack, colon cancer, diabetes, and high blood pressure and may reduce risk of stroke (USDHHS, 2008). Evidence compiled from many decades of research investigating the frequency, intensity and duration of physical activity show that regular physical activity assists in increasing and maintaining muscle strength, balance, and neuromuscular control. Evidence also suggests that moderate physical activity may in part offer some protection against injuries and may mediate tissue repair, the formation of new blood vessels, tissue remodeling and scar tissue healing. Movement also helps to provide a continued supply of nutrients and ensures that the muscles do not atrophy. Current guidelines for physical activity suggest that to prevent repetitive strain on the initial injury site, early movement is important for tissue to repair. The U.S. Department of Human Health and Human Services recommends that all adults should set the goal to accumulate at least 150 minutes per week or more of moderate-intensity physical activity (e.g., brisk walking) to reduce the risk of disease (USDHHS, 2008; USDHHS, 1996). In addition, these guidelines suggest that benefits can also be obtained with 75 minutes per week of vigorous-intensity physical activity (e.g., biking). Those with acute injuries may consider beginning a new activity plan with small amount of moderate- to vigorous-intensity physical activity such as 10 minutes, and gradually build up to the 150 minutes per week goal overtime. To strengthen muscle and bones, this minimal standard may be derived by intermittent or short bouts of activity (such as brisk walking, cycling, swimming and yard work) of at least 10 minutes in duration. The impact of an inactive lifestyle has severe consequences, thus injured athletes are encouraged to engage in a variety of their preferred type of activity. People who perform more formal exercise (e.g., structured exercise program) can accumulate this daily total through a variety of recreational or sports activities. Community outdoor recreation environments provide numerous opportunities such as participation in low impact sports, walking or hiking groups and can accommodate most individual preferences.

Public park settings provide opportunities for a variety of physical activities such as walking, biking, playing sports and games, etc. and oftentimes offer places to engage in hobbies such as boating, gardening, and picnicking. Participation in hobbies of the recreational kind may assist in providing opportunities for more gentle movement of the injured area. Encouraging participation in low-impact sports and recreation activity in the community provides alternative activity options that can help prevent re-injury and recovery from the sports injury. Recreational fitness facilities are also sought out places.

4. Psychological health

Little is known about the mechanism by which physical activity plays in treating mental illness. The most common mental illness is depression. Evidence of reduced depression in populations defined as being clinically depressed, have been noted within 4 to 8 weeks and results have persisted for up to one year. Moreover, studies show that physical activity provides an equally beneficial anti-depressant effect to that of standard psychotherapeutic treatments. One possible explanation is that physical activity reduces anxiety and improves mood. Exercise helps to improve psychological health through the release of neurotransmitters and endorphins. The release of the 'feel-good' brain chemicals may help

ease the feelings of depression. Also, physical activity helps to improve the immune system and increase the body temperature, all which have calming effects on the body.

It is also plausible that the environment in which people are active in has an effect on their psychological health. Studies have examined the amount of green space in people's direct living environment and the amount of time they spend walking or bicycling. In the Netherlands, where bicycling for leisure or transportation is very popular, children under age 12 who reported living in a lush green neighborhood had lower levels of anxiety or depression. Researchers found that the environment influences positive mental health (Maas et al., 2008). Physical activity in the outdoors can provide emotional benefits as well. By being active in the outdoors may provide a healthy distraction from negative thoughts, and help individuals take their mind off of their worries. Some adults may choose to 'walk away their worries' as a coping mechanism.

Whether the changing of the environment or being active in a new environment influences psychological health, it is important to do something positive to manage symptoms of distress. Regardless of the outdoor setting, the natural environment has long been thought of as an ideal environment for rest, reflection, and positive mental health. The relationship between an individual's home, work and play life as well as their feelings of mental health, security and calmness will continue to be the subject of much discussion in future years.

A green environment has also been found to reduce stress (Pretty et. al., 2005). In some cities, planting of flowers and trees in the median of the roadways can to reduce accidents as the creation of these aesthetically pleasing surroundings narrows the roads causing drivers to reduce their speed and slow down. The use of aesthetically pleasing road designs such as buried utility cables, improved storm water management (e.g. raising curbs, improving storm water drainage) and pedestrian friendly sidewalks have also helped to reduce accidents among pedestrians and bicyclists. Another successful advancement in urban centers is the expansion of multi-use trails (those that connect residential areas with green spaces), the creation of pocket parks, planting of street trees (those planted along streetscapes) which help to establish green spaces and absorb heat. People who live in environments without viable green spaces may be forced to seek community options for places to participate in sports, exercise and physical activities.

5. Social health

The benefits of recreational physical activity also support social health. Being active outdoors gives people the chance to meet or socialize with others. Just exchanging a friendly smile or a greeting with others can help raise one's mood. The action of strolling around the block by foot or by rollerblade is an activity that can also boost self-confidence and familiarity with the environment and with those who reside in the surrounding area. Research has found that social support from both family and friends are positively associated with wellbeing (Warr et. al., 2009). Being active with a partner or in a group provides social cohesion or support, and this can enhance psychological health as well. Recently it has been found that people who lack a strong network of friends and family are at greatest risk of developing and dying from heart disease. Therefore, a lack of companionship can be a detriment to health.

The social environment can encourage physical activity, which does not need to be strenuous to be beneficial. The outdoor environment allows people to encounter others to make new friends or become acquainted with others who enjoy engaging in the same

activity (e.g., biking on a trail). Being part of a team-based activity (e.g., playing softball) can help one develop social skills as team activities require commitment to participating in a weekly practice schedule. Interacting on a team can encourage physical activity among people who tend to be socially isolated. Also selecting activities that require refined skill such as pool, shooting, archery, and so on, can enhance focus and attention. The challenge of these types of activies can increase self-confidence. Successfully developing new skills and builds self-esteem and mastery.

Neighborhood parks provide opportunities for social cohesion within a community. Neighborhood corner parks also provide viable outdoor recreational options to walk or bike to and are great places where people can gather. Access to parks via multi-use trails provide socially responsible communities opportunities to volunteer to assist with trail maintenance. Natural environments also allow local residents to have places to read, relax or view birds or animals. The provision of parks and connective trails in non-urban areas has been found to improve wellbeing for local residents and increase overall physical activity levels (Sugiyama et al., 2008).

6. Physical activity and weight loss and weight maintenance

Research has shown that physical activity helps to control weight, contributes to healthy bones, muscles and joints. The negative consequences of an inactive lifestyle and being obese have resulted in over 300,000 premature deaths a year. Increasing physical activity is one of the cornerstones of a long-term healthy weight management program (USDDHHS, 2008). Physical activity has been effective at helping people to keep from gaining weight and in losing weight when combined with a decrease in caloric intake. Injured athletes may find themselves inactive for the first time after an injury, and as a result, start to gain weight.

Physical activity should be an integral part of a weight control treatment plan since an inactive lifestyle is an important contributor to gradual weight gain and can lead to obesity. Sometimes the reason for being inactive in the first place is because of an acute or re-occurring sports injury. An athlete in this predicament may need to look closely at their activity pattern and select an activity that they can participate in fully without being re-injured. More research on patterns of physical activity among persons trying to lose weight or trying to maintain their weight may provide injured athletes with direction as to how to increase their physical activity levels beyond their preferred form of sport.

The inter-relationship between physical activity and weight maintenance is complex. Research has found that aerobic physical activity alone only produces a modest weight loss of 1-2kg compared to that seen with combined physical activity and diet interventions (USDDHHS, 2008). Research has found that sedentary habits may lead to obesity. In the general population, those trying to lose weight or maintain their weight, compared to those not trying to control their weight are three times more likely to be regularly active than inactive (Kruger et. al., 2008). Pooled data from the 1999-2002 National Health and Nutrition Examination Survey (NHANES) showed that the most common physical activities reported by those trying to control their weight were: yard work, biking, running and weight lifting (Table 1). Walking was the most common activity reported across all weight control categories, although the prevalence of walking was greater among those trying to maintain (45.3%) compared to those trying to lose (38.3%) or not lose/maintain (24.0%).

	Lose weight		Maintain weight only		Not lose/maintain	
Activity	%*	95%CI**	%*	95%CI**	%*	95%CI**
Walk	38.3	(36.1, 40.7)	45.3	(41.1, 49.6)	24.0	(21.4, 26.8)
Yard work	14.5	(11.5, 18.1)	15.9	(11.8, 21.1)	11.9	(9.5, 14.8)
Biking	12.5	(10.9, 14.4)	15.4	(11.8, 19.9)	8.3	(6.9, 9.9)
Run	11.6	(10.3, 13.0)	12.6	(8.6, 18.1)	8.7	(7.1, 10.6)
Weight lifting	10.0	(8.5, 11.7)	11.1	(8.4, 14.5)	6.2	(5.0, 7.6)
Dancing	9.8	(8.5, 11.3)	9.7	(7.7, 12.2)	6.4	(5.5, 7.5)
Aerobics	9.0	(7.6, 10.6)	6.2	(4.7, 8.0)	2.9	(2.3, 3.6)
Basketball	5.2	(4.0, 6.7)	7.3	(5.6, 9.4)	5.2	(4.3, 6.1)

* Percent is weighted.; ** Confidence interval.

Table 1. Prevalence of most common physical activities reported among all adults (≥18 years), stratified by trying to lose weight, maintain weight only or not lose/maintain – National Health and Nutrition Examination Survey, 1999-2002.

Studies have also shown that increases in physical activity can result in reductions in abdominal adiposity (LaMonte et al., 2009) and an increased dose of physical activity can improving overall health. Research shows that increasing the amount of energy expended can result in more calories being burned. Thus persons trying to lose weight or keep from gaining weight should be active at a minimum level of ≥150 minutes on most days through moderate- or vigorous intensity physical activity.

7. Sports injury prevention

Because injury results in days lost from work or training, it is important to promote safe alternatives to protecting joints and muscles while maintaining a physically active lifestyle. Murphy's Law states that "If anything is used to its full potential, something will break". This saying sums up the etiology of overuse injuries. Recovery from a sports injury requires time for the area to heal. Pain often accompanies injury and may occur when starting to be active after a period of rest. That is why it is important set activity goals that are pain-free, promote range of motion and gradual increase in intensity and duration when the area is restored back to normal function. Injury incidence may differ by physical activity level because of the differences in the amount of potential overuse of a specific body part due to repetitive activities. Outdoor recreation is a healthy option for injured athletes to consider because low intensity recreational physical activities can be modified easily in regard to frequency, intensity and duration.

Because recovery requires a change in usual activities (from the original activity which caused the initial injury to occur), community options offer viable solutions to maintaining an active lifestyle. Walking has been shown to produce lower rates of injury than other activities such as running. Walking is also the most common form of physical activity and can be performed in any environment such as an inside or outside track, park, beach or neighbourhood. In general, walking can be performed by most people at varying speed. It has been estimated that' in front of 50% of athletes

50% of athletes who participate in team sports have reported one or more injuries over a season of activity. This is much higher than estimates in the general public (non-athletes)

where 5% those who participate in sport activities report an injury. One reason that injuries are not as common in the general public is because they engage in sports less frequently (they are only occasionally active). Second they may be active at a lower intensity level instead high-intensity activities of sprinting or.

Table 2 reports the distribution of sports injuries by the specific region or site of the injury. Data from the Aerobics Center Longitudinal Study showed the most frequently injured site of the body for both men and women (Hootman et al., 2002). In general for both sexes, the three most common sites of the body are the knee (23.3% men, 22.3% women), the foot (12.9% men, 15.7% women), and the back (10.6% men, 10.3% women). Interestingly, less than one percent of women reported eye injury compared to 12.9% of men.
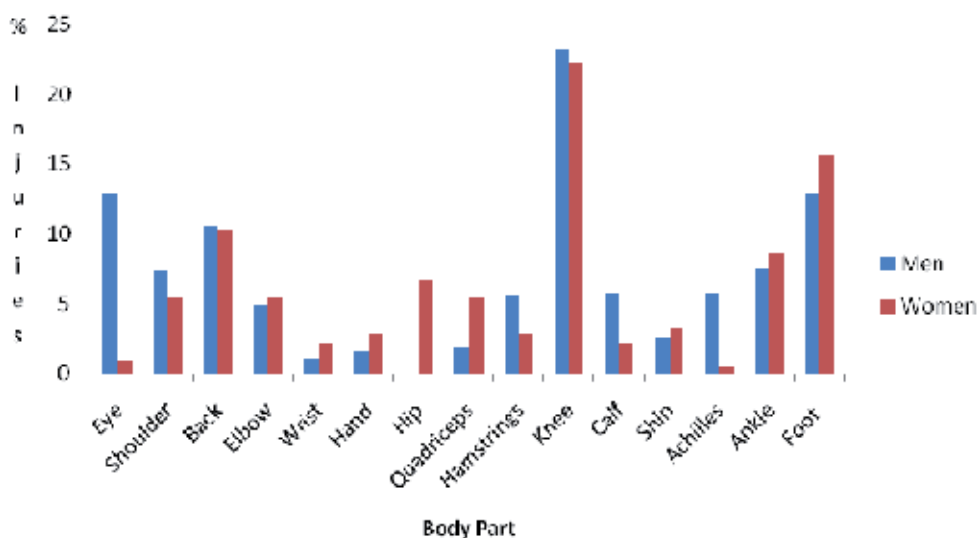
Fig. 1. Distribution (percentage) of injuries by body part for men and women—Aerobics Center Longitudinal Study, 1970-1886.

8. Classification of sprains, strains and other injuries

Injuries can be classified by the body part affected, or the site of the injury. Table 2 is a simple classification overview of the anatomical site (includes the area, tissue and anatomical structures affected) and resultant injury (what is wrong with the area). Depending on the nature of the problem and its severity, rest or modified activity may be recommended. The type of injury reported may depend on the sport.

Regardless of the cause of sports injury, general management include restoring function, enhancing the healing of the injury and being comfortable while engaging in activities of daily living. Sprains and strains are the most common form of sports injury. A sprain is defined as damage to a ligament or its attachment due to overstress. A strain is defined as damage to a muscle or tendon due to overstress (acute strain) or over use (chronic strain).

Sprains, when acute require the traditional RICE approach which consists of Rest, Ice, Compression, Elevation, and encouraged movement. The principle is to prevent increased injury by controlling swelling and promoting recovery of function. Rest may require a tensor bandage, and adhesive strap, splint or plaster cast. Sprains can become chronic

depending on the severity of the initial injury, and re-occurrence due to additional injuries. Principles for treating chronic sprains require encouraging the individual to get back to regular physical activity as much as possible, localized muscle strengthening activities, pain management to relieve distress, prevention of further ligament lengthening problems (e.g., use of orthotic brace or straps) and in some situations surgery. Self-treatment modes used by injured athletes for musculoskeletal injuries also include the use of bandages, orthotics or change in the model or brands of the shoes they currently wear. Studies have shown that with these adaptations, injured athlete have been able to continue participating in moderate-intensity physical activity for >30 minutes a day.

Acute muscle strains often result from an accidental injury. A single event will cause sudden pain usually due to tears at the muscle-tendon junction. This types of this sports injury often results in localized tenderness at the muscle or tendon due to the violent force acting against great opposition. Chronic muscle strain often results from too much strain overtime on the muscle-tendon junction. In some cases, muscle strain begins as a minor injury (that is often neglected and becomes chronic), or as a poorly treated acute injury. Overtime, micro tears may occur at the muscle-tendon junction or muscle-bone junction, resulting in common problems such as shin-splints, jumper's knee, and Achilles tendonitis.

Anatomical site	Result of injury
Soft tissue	Cut
	Abrasion
	Laceration
	Contusion/hematoma
	Muscle strain
	Ligament sprain
	Tendonitis/bursitis
Bone injury	Bruise
	Fracture: stable, unstable
Joint injury	Dislocation
	Cartilage: contusion/fracture
	Cartilage: bone/ligament sprains
Special areas: head injury	Fracture, concussion, hematoma
Special areas: chest injury	Rib cage, lungs, heart
Special areas: abdominal injury	Various internal organs

Table 2. Classification of Injuries

9. Common sports injuries

The human skin provides a protective cover for the internal body structure and organs. The skin is the largest body organ of the body and accounts for between 15-18% of total body weight. The skin has average thickness of 0.00394 mm and it is the most injured human organ. Injured athletes often sustain abrasions, cuts and lacerations to the skin. The layer of skin that envelopes the body is comprised of three separate components, namely the epidermis

(outer shell), the dermis (middle layer) and the sub cutis (lower layer). In general, abrasions and cuts are less serious and affect the more superficial outer shell. A common cause of an abrasion is the friction produced between an athlete's unprotected skin and another surface (e.g., such as gravel or pavement). This type of injury generally heals within a few days after the initial incident. A cut is a penetration of the epidermis and generally results in damage to the circulatory system with blood being drawn to the opening. Contact with a sharp object such as a hockey puck or hockey stick can require stitches to close the opening and a bandage to prevent foreign objects from entering the skin. Generally, once the cut is bandaged and protected, athletic performance is usually not impaired. Lacerations are often regarded a more serious wound and often impact the deeper layers of skin, the fatty tissues or underlying muscles. A laceration is often associated with significant blood loss from a large opening. Repair often requires medical treatment to repair the jagged edges of the skin and may require suturing of the skin. Restricted movement may be required to allow the wound to heal (often 10-14 days).

Sports injuries often do not result in immediate death but may require hospitalization. In Table 3, U.S. data from 2009 are shown. These data provide an overview of the frequency of sports injury. Based on the number of injuries reported, the ten most popular sports injuries are: bicycling, basketball, football, exercise equipment, baseball/softball, playground equipment, soccer, swimming, skateboards and skiing/snowboarding. Of course popularity of these sports will influence the frequency in which these sports injuries are reported.

Estimated Number of Injuries	Sport	Type of Injury
544,470	Bicycling	Feet caught in spokes, head injury, collision
501,251	Basketball	Cut hands, sprained ankles, broken leg, eye and forehead injury
451,961	Football	Fractured wrists, chipped teeth, neck strain, head laceration, dislocated hips, jammed fingers
349,543	Exercise, Exercise Equipment	Twisted ankles and cut chins from tripping on treadmill. Head injury from falling backwards, ankle sprains
286,708	Baseball, Softball	Head injury from bats and balls. Ankle injuries from running or sliding on bases
237,184	Playground Equipment	Fractures from climbers, slides, swings, falls to the surface below playground equipment
208,214	Soccer	Twisted ankles or knees after falls, fractured arms during game
160,542	Swimming	Head injuries from hitting the bottom of pools, leg injuries from accidental falls
144,416	Skateboards	Fractures and cuts from falls
100,359	Skiing, Snowboarding	Head injuries from falling, cut legs and faces, sprained knees or shoulders

Table 3. Estimated Number of Sports Injuries in the 2009 National Electronic Injury Surveillance System.

Sports injuries are very common and can be examined using data from the U.S. Consumer Product Safety Commission's National Electronic Injury Surveillance System (NEISS). Data describing the number of injuries by sport type have been collected during hospital emergency department visits. Although fitness status (e.g., whether one is an athlete or not) is not determined with these data, estimates on the incidence of injury during sport and non-sport activities for the general population are provided. One limitation of these data is that adults who are physically active in general, have a lower incidence of injury compared to those who are inactive. However, data that make up the NEISS surveillance system are obtained from a national probability sample of hospitals of differing sizes and locations.

Unintentional injuries (falling) may happen during performance of a skilled sport such as skiing, which can give rise to a number of injuries such as cuts, sprains, strains or fractures. As the body ages, it takes longer for the body to heal. For example the skin (epidermis) of a 60 year old is 30-80% thinner than that of a 20 year old. Both acute and overuse injuries will take significantly longer for the older athlete to heal.

The growing increase in the number of baby boomers (those born between 1946 and 1964) and the desire of this cohort to remain active in recreation and competitive sports has resulted in an increase in the number of reported sports injuries over time. According to the U.S. Consumer Product Safety Commission, sports injuries among baby boomers (age $\geq$65) increased slightly from 2007 to 2009 (see Figure 2).
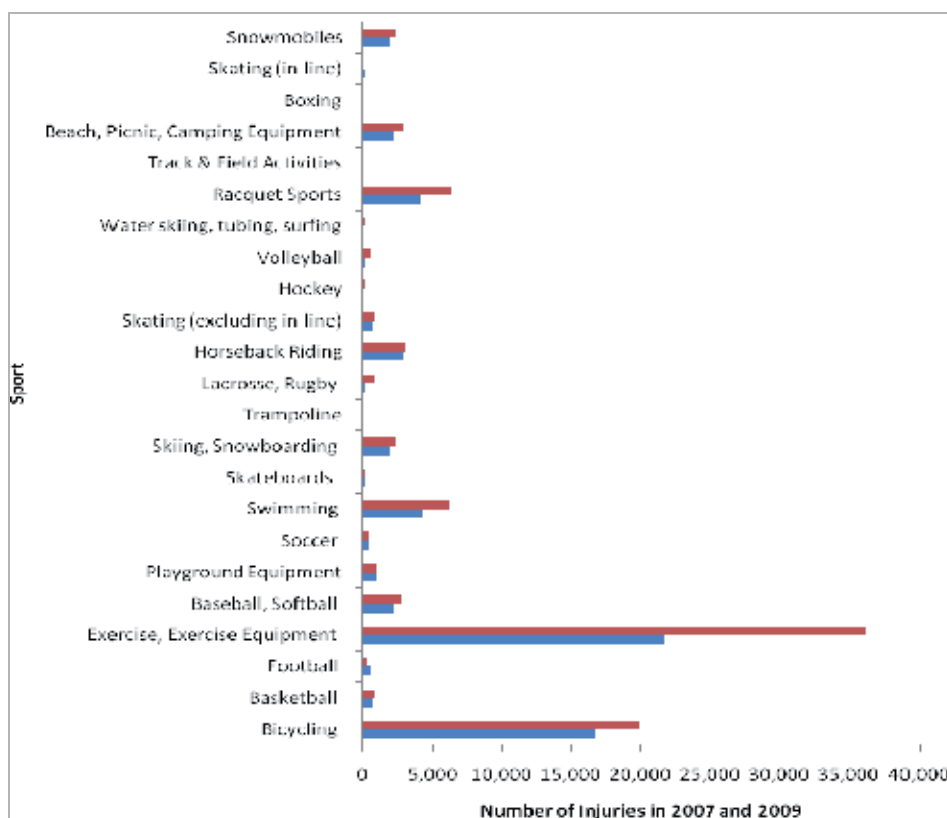

Fig. 2. Estimated Number of Emergency Room Treated Sports Injuries among Persons $\geq$65 Years of Age—National Electronic Injury Surveillance System, 2007 and 2009.

Figure 2 shows the number of injuries reported for 23 popular sports categories. The number of injuries associated with bicycling, basketball and football continue to rise. Although major advances have been made through the promotion of protective equipment, these data show that exercise equipment are the most popular category responsible for emergency room treated sports injuries among those $\geq$65 years of age. Educational efforts to assist older athletes to begin low-intensity activity programs and progress gradually to more intense activity levels are needed.

By 2050 the percentage of the population 65 years or older will be 21% (US Census Bureau, 2010). Research shows that baby boomers may appear to be aging actively. Data suggests sports-related injuries among baby boomer have been reported to cost almost $20 billion dollars a year. Therefore, prevention of injuries through education on rehabilitation after injury, early recognition of symptoms of overuse and training principles in addition to the promotion of recreational physical activity is needed.

The rise in chronic disease rates among adults at large requires injured athletes to consider ways to prevent and manage their injuries as they grow older. The growing increase in the baby boomers as a whole will require promotion of sustainable recreational physical activities that encourage lifelong activity patterns. Although medical advances continue to improve recovery from sports injuries, the use of sports protective equipment such as helmets, mouth guards, skin pads and knee pads have been shown to be effective in reducing injury. To date, laws have been developed require the use of protective equipment to protect to protect athletes from injury. These laws require the use of select equipment such as face masks among hockey players, and helmets among bicyclists, have been shown to help reduce head injuries.

10. Implications and future research

Community options for outdoor recreation allow individuals to experience the physical, psychological and social benefits of nature directly as a preventative measure to maintain health and wellness. Participation in outdoor recreational activities offers viable alternative to sports, gyms and community centers and can be a fun way to be physically active. Within this chapter, an overview of activities and sport injuries observed in national surveys has been highlighted.

It is clear from an extensive body of evidence that movement is important for everyone. Given the acceptability of walking among people with and without sports injuries, and the fact that brisk (e.g., fast walking) can improve fitness, walking should be considered a community options for outdoor recreation. Elimination of sedentary behavior is a public health priority and most people can meet the 150 minute/week recommendation by engaging in intermittent walks throughout the day (e.g., such as three 10-minute bouts). This is especially important to athletes with a sports injury who may be unable to sustain prolonged activity.

As adults age, they begin to experience re-occurring aches and pains often as a result of a repetitive unintentional injury. Maintaining or increasing involvement in physical activity with or without a chronic disease has significant implications for health in terms of maintaining balance, muscular control prevention of falls, and offers mental stress relief. Because age-related injuries are common among high impact sports, some athletes will tend to switch to more moderate-intensity types of physical activity over time. Research suggests that participation in several types of recreational leisure activities can meet the functional needs of injured athletes.

Alternative options in the community allow individuals to engage in an active lifestyle by using local parks or nearby places as places to be physically active. As one ages, priorities change and participation in sports declines, community based approaches to obtaining physical activity may play a bigger role. Community engagement through physical activity can provide internal satisfaction for athletes. Outdoor recreational activity can be a forum for developing or maintaining a social support system different from the sports teams previously held.

11. Conclusion

The health benefits of outdoor recreational activity are extensive, and outdoor recreation is a viable community alternative for places to participate in sports, exercise and recreational physical activities. Among professional, elite amateur and recreational athletes, having a sports injury can cause psychological concern. Injuries require time to heal and considerations to adopt a modified training plan may be required. Community options for outdoor recreation can assist injured athletes to overcome functional decline, social isolation and depression. Outdoor recreation allows individuals with a sports injury to modify their activity in order to rest the injured part, and provides social opportunity to maintain health and wellness.

12. Acknowledgement

13. References

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The Physical Demands of Batting and Fast Bowling in Cricket

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1. Introduction

Even though cricket is one of the oldest organized sports, there are very few studies on the physical demands of the game (Woolmer & Noakes, 2008; Christie & King, 2008; Christie et al., 2008). Batting and bowling are intermittent in nature with the demands placed on the players being dictated by the type of match being played. Due to this stop-start nature of cricket, accurate assessments are often difficult and as such, research is sparse (Bartlett, 2003) and as a consequence, there are few scientifically sound training programmes for cricketers. In fact, the idea that cricketers need to be well trained is a relatively new one (Woolmer & Noakes, 2008). Historically cricket players never trained as hard as other sportsmen in team based sports such as rugby and soccer and in fact, many were overweight which dispelled any reason to be trained for their sport (Woolmer & Noakes, 2008). It wasn't until the Australians (cricket) and New Zealanders (rugby) demonstrated that, by focusing on physical training, performance benefits would be derived, that this started to change. This was a direct consequence of more scientifically based physical training programmes prior to their Cricket and Rugby World Cup wins in 1991 and 1987 respectively.

Further, the increased demands being placed on many cricketers now provide further need for them to be in peak physical condition not only for performance, but also for prevention of injury. International cricketers are now exposed to greater demands reflected by more five-and one day matches per season, longer seasons and more frequent touring (Noakes & Durandt, 2000). For example, during the 1998/1999 cricket season, the South African cricket team played eight five-day Test matches, 17 one-day international games and were eligible to play in eight four-day and ten one-day provincial (county) cricket matches – 99 days of playing (Woolmer & Noakes, 2008). In 1970, in contrast, players were asked to play 35 days of cricket (Woolmer & Noakes, 2008). Woolmer & Noakes (2008) therefore argue that only the best physically prepared cricketers will perform better, more consistently and with fewer injuries and, in turn, will enjoy longer and more illustrious careers. Thus, understanding the physiological demands placed on players and in particular batsmen and bowlers is imperative. Having said that, it is important to acknowledge the skills and mental aptitude needed to succeed in the game of cricket and that being physically trained cannot, on its own, fully compensate (Noakes & Durandt, 2000). However, being physically well

conditioned will differentiate between two players of equal skill and, as such, enhancing our understanding of the physical requirements of the game can assist in bringing the game forward. Despite the limited data on cricket, teams that have embraced the concept that research in the sport contributes to improved performance, have excelled over the last few decades (Mansigh, 2006). Science and cricket is a fairly new marriage and only now do many of the international teams realize the gap between those who incorporate science and those who rely solely on talent (Mansigh, 2006).

2. Physical characteristics of cricketers

As a generalization, it has been found that batsmen tend to be smaller and lighter than bowlers (Stretch, 1987; Noakes & Durandt, 2000; Bartlett, 2003) but that they have similar morphological profiles with both batsmen and bowlers averaging approximately 12-14% body fat (Figure 2) (Noakes & Durandt, 2000; Bartlett, 2003). Batsmen also have higher predicted maximal oxygen uptake values and faster running (simulated three runs protocol) with quicker turn times than bowlers but have similar strength and 35 m sprint performances (Noakes & Durandt, 2000). When compared to rugby players, cricketers demonstrate similar performance characteristics (Figure 2). This is despite the fact that rugby is typically viewed as more physically demanding requiring players to be well trained. Cricket, in contrast, has tended to be viewed as less physically demanding requiring less training (Fletcher, 1955). Data on South African international rugby and cricket players clearly shows differences in morphology as well as performance with cricketers reaching higher levels on the typical shuttle run test (Figure 1). Further, there are no reported differences in strength measures between the two groups (Figure 2) which is interesting, as rugby players are also viewed as stronger possibly due to the larger size (Figure 2).
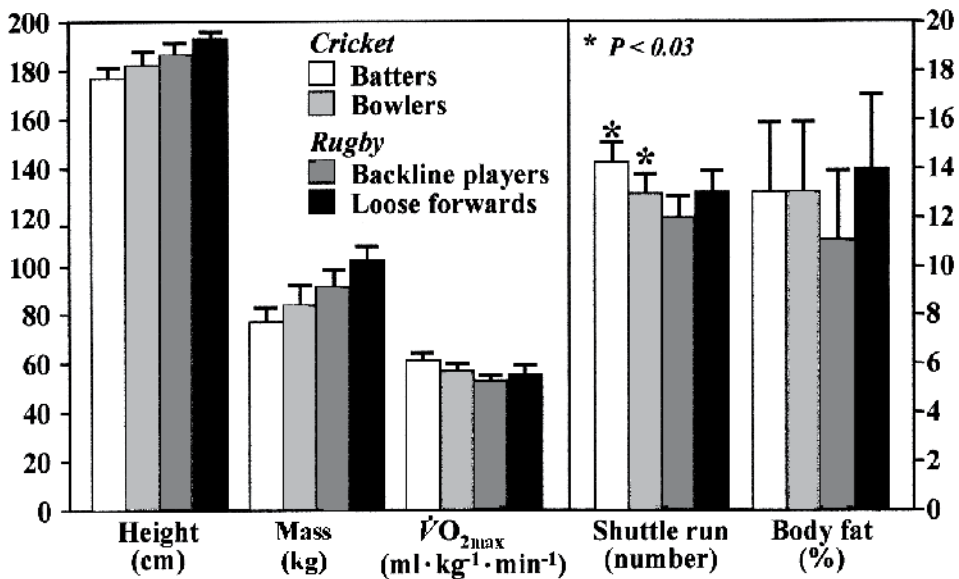

Fig. 1. Comparison of South African international cricket and rugby players (Taken from Noakes & Durandt, 2000).
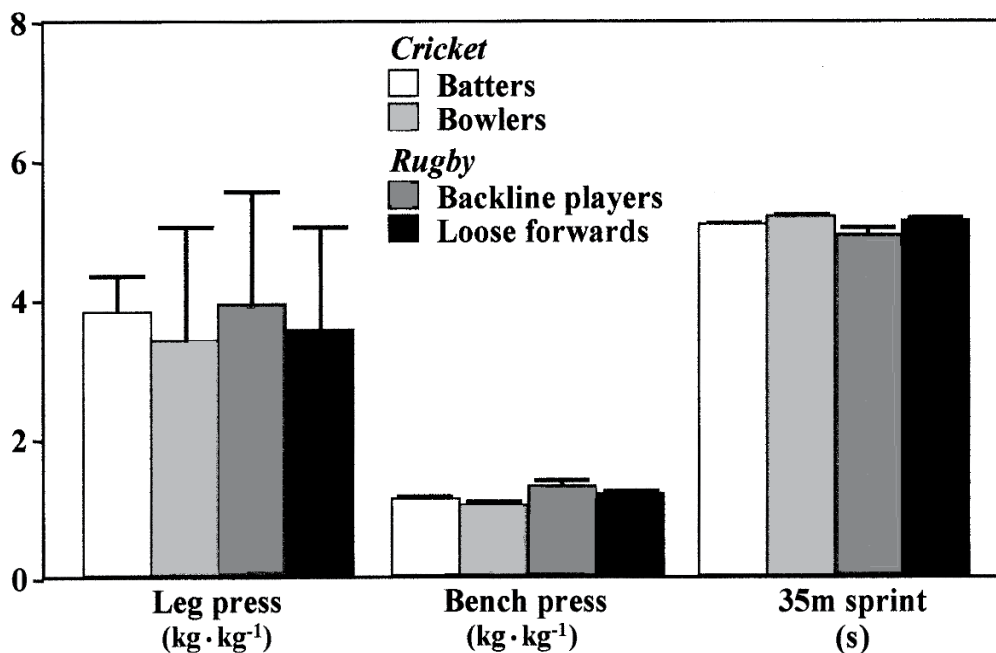
Fig. 2. Strength comparisons between elite South African rugby and cricket players (Taken from Noakes & Durandt, 2000).

3. Most frequent injuries in cricket

There have been many reports on the types of injuries incurred by elite teams worldwide (Orchard et al., 2006; Leary & White, 2000) with a more recent paper reporting on injuries at all levels of play including recreational cricketers (Walker et al., 2010). These latter authors found that of all age groups, the upper (36%) and lower (31%) limbs were most commonly injured. This was higher than that reported by Stretch (1995) who found a 23% occurrence of lower limb injuries in school boys. However, with respect to more adult and elite players, the incidence rate is higher and between 38% and 50% (Leary & White, 2000; Orchard et al., 2002). Walker et al. (2010) reported that contact with the ball or bat was the dominant mechanism of injury for those under age 50 while overexertion, strenuous or repetitive movement, slips and falls were the mechanisms for those over age 50 (Walker et al., 2010). Walker et al. (2010) showed that 35% of injuries to the lower limb areas were as a result of strains and sprains to muscles in the lower limb region. This was the highest percentage of all injuries to the lower limb region and was most obvious in the 30-39 year age group; the typical age at which cricketers 'peak' and are playing at top level. This is important considering the high demands placed on the lower limb musculature when sprinting and turning between the wickets and when sprinting and during the rapid acceleration and deceleration in the run-up and delivery of the ball when fast bowling (Christie et al., 2011b). It is contended that this repeated eccentric loading of the lower limb musculature is the real source of stress for cricket players (Noakes & Durandt, 2000) and which would reflect in more lower limb muscle sprains and strains. Injury research on bowlers has largely focused on low-back injuries in fast bowling and the current thinking is that the mixed technique results in the

most injuries (Bartlett, 2003). The loading on the bowler's musculoskeletal system at back-foot and front-foot strike is a potential risk for not only lower back injury (Bartlett, 2003) but also lower limb musculoskeletal strain. Peak vertical forces for back- and front-foot strike are 2.4 and 5.8 times body weight (Hurion et al., 2000). In terms of increasing playing hours and increased risk of injury, surprisingly, despite a 30% increase in player hours over more than a decade, match injury incidence has remained relatively constant (Orchard et al., 2006) which may reflect improvements in injury detection and treatment (Mansigh, 2006).

4. Physiological demands of cricket

One of the first studies which attempted to assess the energy cost of cricket calculated that the mean energy expenditure of cricketers, during a five-match test series, was 86.4 kcal.m^2.h^{-1} (Fletcher, 1955). This equates to an energy expenditure of approximately 650 kJ.h^{-1} for an average cricketer with a body surface area (BSA) of 1.8 m^2 (Christie et al., 2008). These calculations, together with data recorded using indirect calorimetry with cricketers playing in the nets, led to the development of Figure 3 (redrawn by Noakes & Durandt, 2000).
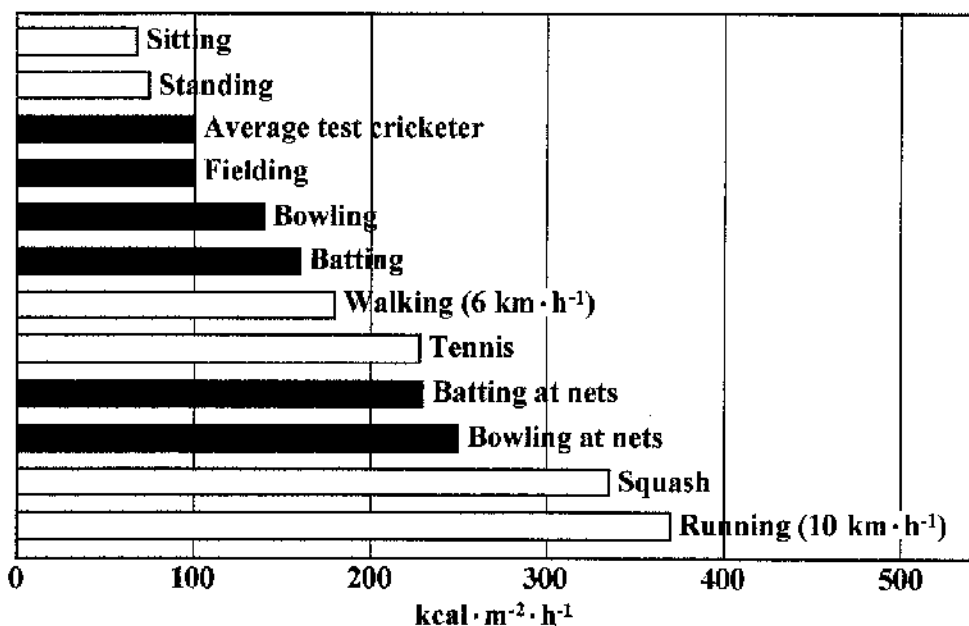
Fig. 3. The energy demands of different cricketing activities compared with other sports and activities. (Redrawn by Noakes & Durandt, 2000 from Fletcher, 1955).

Fletcher's data suggested that the energy demands of cricket are only slightly more than that required to stand (Christie et al., 2008) which led to the understanding that cricket was physically undemanding requiring more skill than "fitness" (Noakes & Durandt, 2000). However, it must be noted, that Fletcher included time spent sitting watching the game in his calculations (Petersen et al., 2010). Despite this, these findings were confirmed more recently by Rudkin and O'Donoghue (2008) who, after analyzing first-class fielding in the United Kingdom, concluded that cricket is physically undemanding. In contrast, studies

from our laboratory, simulating one day batting, have estimated much higher energy demands (Christie et al., 2008; Christie et al., 2011a).

4.1 Physiological demands of batting

Noakes & Durandt (2000) estimated that during a one-day game, a hypothetical player scoring 100 runs, made up of 50 singles, 20 twos, 10 threes and 20 fours, would cover a distance of 3.2 km in an activity time of 8 minutes. Average running speed would be 24 km.h^{-1} with at least 110 decelerations required (Noakes & Durandt, 2000). From this, these authors deduce that the physiological demands of batting in a one-day game are substantial. Players need to be well trained to do this as they are also required to field for 3.5 hours which adds to the stress placed on them.

The first study done in our laboratory, focusing specifically on the physiological demands of batting, looked at 10 batsmen receiving one delivery every 30 s with a total of 7 overs (42 deliveries) faced (Christie et al., 2008). After every 3rd delivery the player was required to complete one shuttle run at full pace. The two popping creases were set 17.68 m apart. The 2 by 2 singles run per over simulated the high work rate likely to be achieved after the 15th over in a high-scoring one-day match (King et al., 2001). The total distance run by each player was approximately 495 m. The 30 s period of inactivity between deliveries was to account for the bowler walking back to his 'mark'. The 1-minute break between each over was reflective of a change in bowler. The results were that heart rate increased significantly during the first three overs (Figure 4) and then more marginally for the remaining four overs during which mean heart rate was 152 bt.min^{-1} (Christie et al., 2008).
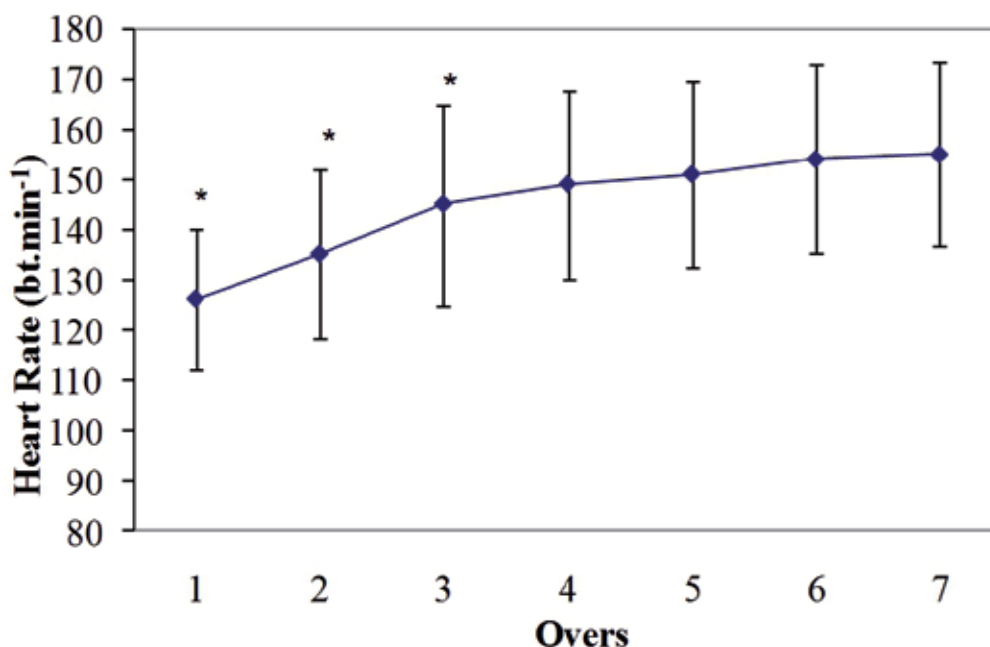

Fig. 4. Mean heart rate responses (bt.min^{-1}) from the first to the seventh Over. (* *Denotes a significant increase in heart rate for the first three Overs*)

Oxygen consumption during the first over (23.5 ml.kg^{-1}.min^{-1}) was significantly (P < 0.05) lower than the remaining six overs (mean of 27.3 ml.kg^{-1}.min^{-1}) which demonstrated a 'steady-state' response (Christie et al., 2008). Further, the mean energy cost of the work bout was 2536 kJ.h^{-1} (301 kcal.m^2.h^{-1}) (Christie et al., 2008).

This initial research in our laboratory therefore demonstrated that batting was a lot more physically taxing than previously thought. Further, these findings also contradicted the notion of Gore et al. (1993) that during a ODI a batsman's heart rate rarely rises above 128 bt.min^{-1}.

A subsequent study in our laboratory, with a slightly altered work bout due to more recent time motion analyses (35 second break between balls as well as a 75 second break between overs as well as a single sprint per ball), found even higher responses (Christie et al., 2011a). During the first over, heart rate increased significantly (p<0.01) to 142 bt.min^{-1} and then continued to increase until the end of the third over (161 bt.min^{-1}). Thereafter heart rate stabilised and remained between 161 bt.min^{-1} and 167 bt.min^{-1} (final over). Oxygen consumption and energy expenditure increased significantly (p<0.01) until the end of the second over after which both responses stabilised. VO$_2$ stabilised between 27 and 28 mlO$_2$.kg^{-1}.min^{-1} in the final six overs while energy expenditure remained constant at 11 kcal.min^{-1}. These studies confirmed our belief in the higher physiological demands of batting.

4.2 Physiological demands of bowling

Research on the physiological demands of bowling is sparse with the only studies available being those which included some physiological measures when assessing other aspects of the game. One study found heart rates of between 154 and 158 bt.min^{-1} during a 6-over fast bowling spell (Devlin et al., 2000). This was confirmed by Taliep et al. (2003) who found that heart rates during fast bowling ranged between 73% and 77% HR max. Burnett et al. (1995) reported peak heart rates of between 180 and 190 bt.min^{-1} during a 12-over fast bowling spell. To the author's knowledge, no in-depth physiological studies have been done on bowlers suggesting a need to investigate these demands further. During a 6 to 8-over spell, bowling speed remains unchanged while accuracy has shown some non-significant variation (Portus et al., 2000; Devlin et al., 2000). In contrast, Taliep et al. (2003) found significant reductions in bowling speed after the 6th over in a 12-over bowling spell and no change in accuracy.

5. Musculoskeletal demands of cricket

Noakes & Durandt (2000) speculate that the main cause of stress for cricket players is the repeated eccentric muscle damage resulting from multiple declarations that occur in batting and fast bowling. The stop-start nature of both sprinting between the wickets and fast bowling (during the 'run up' and delivery of the ball), contributes to early-onset fatigue indicators which, over time, results in a specific type of fatigue which negatively impacts performance and increases the risk of injury (Christie et al., 2011b). It has recently been shown that the physiological demands of batting in a one-day game are substantial and that players need to be well trained to optimally maintain this type of workload (Noakes & Durandt, 2000; Christie & King, 2008; Christie et al., 2008; Christie et al., 2011a

and b). With respect to bowling, although most of the research has focused on lower back injuries (Stretch et al., 2000), it is the view of Noakes & Durandt (2000), that the repeated eccentric actions during fast bowling are the real source of stress for fast bowlers and that this needs to be followed up and related to speed and accuracy of bowling as well as injury potential. Substantial muscle strength is needed to reduce muscle damage arising from these repeated actions (Thompson et al., 1999). The ability to cope with repeated eccentric loading such as during cricket may require substantial muscle strength in order to reduce the damage (Noakes & Durandt, 2000). Running research has shown that repeated eccentric actions produce a specific form of fatigue that requires substantial recovery time (Nicol et al., 19991). They alter muscle function particularly with respect to a reduction in elastic energy production which results in increased work during the push-off phase (Nicol et al., 1991). Recovery time from this damage can take up to 2 weeks post-marathon.

Although the research on eccentric load placed on cricketers is still in its infancy, a recent pilot study from our laboratory looked specifically at the strength decrements associated with repeated sprints between the wickets (Christie et al., 2011b). The protocol was exactly that of Christie et al. (2011a) but which assessed isokinetic (concentric and eccentric) strength changes.

Leg	Speed (deg.s^{-1})	QUADRICEP DECREASE (%)		HAMSTRING DECREASE (%)	
		Concentric	Eccentric	Concentric	Eccentric
Right	60	14.12	18.68	9.76	12.15
Left	60	7.53	6.07	8.79	13.36
Right	180	3.69	15.65	10.41	14.94
Left	180	7.58	6.66	11.19	9.33
	MEAN	8.23	11.77	10.04	12.45

Table 1. Representing the percentage decrease (%) in peak torque values.

Eccentric strength changes were greater than concentric changes (Table 1). Overall, the strength of the quadriceps decreased by 8.23% concentrically and 11.77% eccentrically while the strength of the hamstrings decreased by 10.04% concentrically and 12.45% eccentrically. This was evident in both legs and in both muscle groups (mean decrement of 11.77% and 12.45% in the quadriceps and hamstrings eccentric strength respectively). While concentric hamstring decrements ranged between 9.76% (Right leg at 60 deg.s^{-1}) and 11.19% (Left leg at 180 deg.s^{-1}) the range was much larger for the quadriceps concentrically. More specifically, there was a 14.12% decrement in concentric quadriceps strength at 60 deg.s^{-1} in the right leg and only a 3.69% in the same leg at 180 deg.s^{-1}.

As with the peak torque changes, there were similar decrements in work over time (Table 2). The greatest decrement in work was to the hamstring musculature eccentrically (decrement of 14.70%). This was followed by the eccentric work of the quadriceps muscle group

(11.13%). With respect to eccentric changes, although the hamstrings were affected similarly in both legs, the quadriceps showed greater decrements in the dominant, right leg and virtually no change in the non-dominant, left leg (Table 2).

Leg	Speed (deg.s^{-1})	QUADRICEP DECREASE (%)		HAMSTRING DECREASE (%)	
		Concentric	Eccentric	Concentric	Eccentric
Right	60	16.34	21.53	9.65	15.73
Left	60	11.74	1.56	5.65	14.12
Right	180	3.98	14.99	12.73	17.91
Left	180	10.27	6.44	8.47	11.04
	MEAN	10.58	11.13	9.12	14.70

Table 2. Representing the percentage decrease (%) in peak work values.

Strength losses are considered reliable indicators of exercise-induced muscle damage (Warren et al., 1999) which are likely after repeated eccentric muscle actions. When strength losses occur, there is a much higher chance of muscular strain and joint instability. Further, this could impact performance such as reduced ability to accelerate and decelerate when running between the wickets or could lead to more errors, increasing susceptibility to injury (Rhanama et al., 2003). The greater eccentric strength decline of the hamstrings may be due to the greater requirement of the hamstrings to control running actions and for stabilizing the knee joint during foot contact with the ground. If this is the case, then it could lead to less control and lower stability of the knee and greater risk of injury (Rhanama et al., 2003).

5.1 Eccentric loading and fatigue
In their book 'Art and Science of Cricket', Woolmer & Noakes (2008) provide a comprehensive section on what they consider to be the main cause of cricketing fatigue. Basically, they propose that eccentric actions alter muscle recruitment over time resulting in the inability to store the energy of landing and recover energy for the push-off phase of the running stride which follows. The brain must then decide to either recruit more fibres to assist in the push-off phase in order to keep the same speed of running or reduce running speed in order to cope. As the bowling spell or batting innings progresses, the way in which the muscles are recruited will change because of the body's natural desire to protect the vital organs from catastrophic failure, referred to as the 'central governor' (Noakes et al., 2001). Despite this, the player must still produce the same result.

So, according to the central integrative model of exercise regulation (Figure 5), the subconscious brain is making these choices, and altering the way in which it recruits the muscles (St Clair Gibson & Noakes, 2004). It sets the number of motor units activated throughout the exercise bout (1). Sensory feedback from various physiological systems results in an appropriate adjustment in muscle recruitment (2). At the start of the bowling spell or batting innings, the subconscious brain informs the conscious brain (3) of increasing

neural effort and this is interpreted as an increased sensation of fatigue (4) which can then also further influence the subconscious (5). Basically, the subconscious influences the conscious brain with sensations of fatigue (commonly seen in ratings of perceived effort) so the bowler or batsmen alters speed in order to ensure they have enough reserve to complete the bowling spell and/or innings.
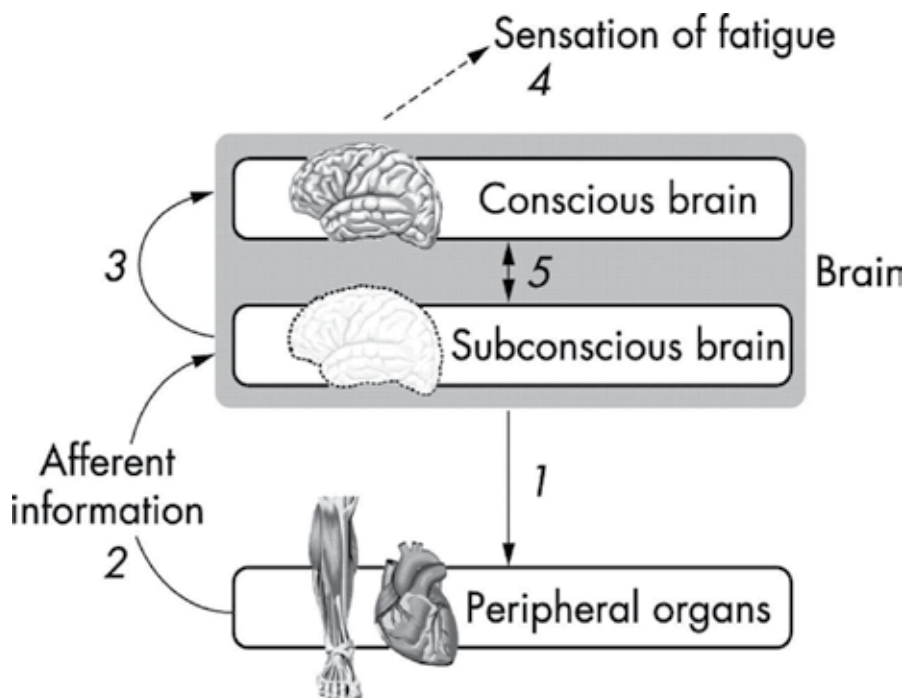
Fig. 5. The central integrative model of exercise regulation. (Taken from St Clair Gibson & Noakes TD, 2004).

If their theory is correct, then the main goal of training programmes should be on the development of eccentric training programmes to assist players in coping with this stress and hopefully reducing their risk of injury by delaying the onset of fatigue (Woolmer & Noakes, 2004).

6. Conclusion

Research on all aspects of the game of cricket is needed in order to better understand the demands being placed on players as well as to link these to fatigue indicators and injury risk. The sport has a long way to go in terms of linking science and practice evident in other sports such as football. Until more is understood of the demands of the game, training programmes will be merely based on trial and error and not grounded in science. This means that it is probable that players are not getting adequately prepared for play and as a result, are becoming injured more frequently. This is particularly the case for injuries which are more avoidable and linked to fatigue, such as sprains and strains. Further, there is a

need for more communication and cooperation between sports scientists involved in cricket research and coaches of the game to ensure mutual benefit. This chapter contends that the real source of stress for cricketers is the musculoskeletal demands and associated stressors and that research needs to consider linking appropriate eccentrically based training programmes with fatigue indicators, performance affects and injury risk reduction.

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Prediction of Sports Injuries by Mathematical Models

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1. Introduction

A number of different methodological approaches have been used to describe the inciting event for sports injuries. These include interviews of injured athletes, analysis of video recordings of actual injuries, clinical studies (clinical findings of joint damage are studied to understand the injury mechanism, mainly through plain radiography, magnetic resonance imaging, arthroscopy, and computed tomography scans), in vivo studies (ligament strain or forces are measured to understand ligament loading patterns), cadaver studies and simulation of injury situations, and measurement/estimation from "close to injury" situations. This chapter describes mathematical modeling approach and assesses its strengths and weaknesses in contributing to the understanding and prevention of sports injuries. This chapter demonstrates the relationship between structural measures and lower limb injuries.

Sports injuries can affect any and all parts of the body depending on the particular repetitive movement performed just like any repetitive motion injury. While there are factors that raise the risk of injury, there are also elements that predispose athletes to sports injuries. Rehabilitation and preventative efforts should be centered on a thorough knowledge of risk factor etiology as well as knowledge of how such factors contribute to sports injuries.

In most epidemiological studies directed toward identifying major sports injury causation factors, injured athletes have been compared with uninjured athletes through single variable techniques. However, many of the factors highlighted later in this paper through these analytical techniques either interact or are interrelated.

Multivariable statistical techniques have also been used to detail risk factor interaction (Mechelen, 1992), such as discriminatory analyses and stepwise logistic regression (Dixon, 1993). In this chapter we will identify potential predictive factors that can be used in logistic regression equations, the basic concepts of this mathematical study, and equations that have been developed to what they are today.

2. Predictive factors of sports injuries

Predictive factors of sports injuries are biological variables and the relations between them that can be indicators for creating a health profile or diagnosis. For example, weight can be a

predictive factor of diabetes, arteriosclerosis, and other metabolic illnesses. It is even more useful when associated with height, BMI, and waist-hip ratio since it can then be used in predicting hypertension, myocardial infarction, diabetes, and strokes. In order to effectively predict health complications, the WHO recommends using anthropometry to monitor risk factors of chronic diseases and to perform studies that define the association between the aforementioned factors and specific outcomes, such as arterial hypertension. Predicting factors of sports injuries can be grouped into two types of factors: Intrinsic factors and extrinsic factors.

2.1 Extrinsic factors

Sports injuries are most commonly caused by poor training methods; structural abnormalities; weakness in muscles, tendons, ligaments; and unsafe exercising environments**.** The most common cause of injury is poor training. For example, muscles need 48 hours to recover after a workout. Increasing exercise intensity too quickly and not stopping when pain develops while exercising also causes injury.

The most common cause of sports injuries is improper training whether from a technical or tactical point of view or simply training that is poorly planned and executed (Shaffer, 2006). The athlete exposes him or herself to possible sports injuries without adequate preparation for: exposure to potential danger, the playing position or type of activity, the duration of the competition or league, competition level, time dedicated to training and to rest. These variables can be quantified and turned into predictive factors (Ferrara, 2007). Among such:

2.1.1 Poor physical condition due to inadequate training (Mechelen, 1996).

2.1.2 Abrupt increments of training intensity or training load, resulting from overuse and overstress. These injuries tend to appear in underdeveloped locomotion devices, caused by unvaried and unbalanced sports practice especially after training intensification or excessive training. Aerobic training increments between 55% and 75% do not transmit negative effects and do not result in injury risk (Tate, 1995), although disproportionate increases in intensity can provoke anxiety and states of distress.

2.1.3 Premature competition and quasi-adult training performed by a child or adolescent expose the athlete to injuries from excessive force when pulling or pushing.

2.1.4 Resistance training, specifically in adolescents, without the appropriate battery of tests to identify the actual state of regulating and homeostatic mechanisms.

2.1.5 Performing new or unfamiliar exercises. This is common at the beginning of seasons, as well as upon introducing changes in the overall training regime. The same happens when sessions of active rest are planned in which the athlete reflects on unknown sports activities.

2.1.6 Environmental factors and atmospheric conditions, especially when weather conditions vary unexpectedly or unpredictably, the time of day and the season of the year (Mechelen, 1996).

2.1.7 The type and integrity of the playing surface, playing surface incline.

2.1.8 Game mediation: Judges and referees and the official game mediation. Competition among equals is typically promoted in most sports.

2.1.9 Sports and training equipment. Type and quality of protection, type of footwear, thermal and isothermal clothing. Before using a specific type of shoe, the athlete should know the structural morphology of his or her own feet. Advances in sports injury prevention technology has obligated sports brands to offer a wider variety of models, each model having specific characteristics that complement and correct potential foot dysmorphia.

2.1.10 Equipment protection, as well as player protection such as shin guards, ankle support, orthotic devices, mouth guards, helmets, prophylactic tape, etc...

2.1.11 Methodological training development and the level of physicality. Extrinsic factors associated with exposure to injurious situations are: potential dangers, playing positions, competition length, competition level, training time, training frequency, rest intervals or the frequency of exertion, weekly distance run or the number of jumps, hits, throws and impacts, number of trainings per week, training speed, number of competitions per year, absence of regularity in training, etc. All having to do with requirements for the level of physicality needed for different sports activities.

2.1.12 Prior years of sports training and experience under certain competition and training conditions.

2.1.13 Inadequate warm-up, whether insufficient or excessive. In some sports, the athlete is required to warm up over such a long period of time that he or she loses concentration on his or her movements and they consequently become ineffective.

2.1.14 Mastery of a sports technique, technical ability, skill and quality that contributes to the effectiveness of a movement.

2.1.15 Mental and psychological conditions: Intelligence and creativity, motivation and discipline that influence the precision of technical execution, skill level, previous experiences and the necessity of some athletes to take risks.

2.1.16 Intrinsic characteristics of common movements in sports activities, linked to structural, biomechanical, and functional characteristics of the athlete. In basketball, the height of the players, the number of jumps, sprints, stops, turning jumps, and backwards jumps can be determining factors in the occurrence of injuries (Grubbs, 1997; Shambaugh, 1991).

2.1.17 Nutritional and hydroelectric imbalances. (The most common cause of sudden death in marathons is overhydrating).

2.1.18 The type of sport, notably high-risk and contact sports as well as sports performed when unbalanced or in which unbalancing equipment is used.

2.1.19 Incorrect playing, inattention to game rules with an excess of rough play and the absence of fair play.

2.1.20 And, of course, muscular fatigue that stems from technical errors in execution and leads to injury.

2.2 Intrinsic factors

Everyone's bone architecture is a little different, and almost all of us have one or two weak points where the arrangement of bone and muscle leaves us prone to injury.

2.2.1 Age. There is an increase in the occurrence of injuries in children and adolescents' locomotion devices when they try to perform more ambitiously in hopes of improving their short-term performance. As age and competition level increase, so increases the risk of injury (Inklaar, 1996).

Nonetheless, in many studies, age is not a factor of predisposition, except when it relates to increased speed and distance in training that is significantly greater than that of an older athlete.

In children, the most frequent factors of predisposition to injuries are:

2.2.1.1 Intrinsic causes in children

2.2.1.1.1 Muscle tendon imbalance related to strength deficit, excessive flexibility and scant muscle volume.

2.2.1.1.2 Biomechanical alterations, curved, flat feet, femoral anteversion, and the genu valgum that promotes and increased deviation of the Q angle, lumbar hyperlordosis, and length difference between the lower limbs.

2.2.1.1.3 Abrupt weight modifications from growth, since injuries tend to happen from overexertion in growth zones (epiphisitis) when a sudden increase in bone length occurs without parallel adaptation of muscle tendon units.

2.2.1.2 Extrinsic causes in children

2.2.1.2.1 Derived from training errors, high-intensity and long-duration training involving frequent use of still developing structures.

2.2.1.2.2 Planning children's training as though it were adult training, modifying only the workload or volume.

2.2.1.2.3 Technopathies derived from incorrect use of footwear, overly large equipment for the child, hard surfaces, accessories and clothing that are generally inappropriate.

2.2.2 Sex. Not a determining risk factor per se, although there are substantial anatomical differences which, in women, are: a wide pelvis, a more pronounced Q angle, greater pelvis anteversion and greater flexibility (Plisky, 2007). Women's levels of training quality and quantity tend to be less intense than that of men due to women's lower muscle mass.

2.2.3 Structural, neuromuscular conditions that affect athletic performance. Especially noteworthy conditions are:

2.2.3.1 The alteration of axis lines in the rachis, lumbar curvature, and lower and upper limbs.

2.2.3.2 Lower limb dissymmetry greater than 1 cm.

2.2.3.3 Muscular imbalance: muscular hypotonia and hypertonia.

Genu varum and genu valgum, along with an accentuated Q angle, the genu recurvatum and a smaller intercondylar notch favor the occurrence of injuries in the knees, particularly, cruciate ligaments in women (Shambaugh, 1991). This and the spinal column become real limitations on physical exercise. An excessive Q angle, as well as femoral anteversion favor the occurrence of injuries (Heiderscheit, 1999). The intrinsic causes of jumper's knee, can be sought in the mechanical properties of tendons (resistance, elasticity and extensibility) rather than in morphological or biomechanical abnormalities of the knee extensor mechanism (Ferretti, 1986). Athletes with jumper's knee demon strated better performance in jump tests than uninjured athletes, particularly in ballistic jumps involving eccentric force generation (Lian, 1996). Bilateral patellar tendinopathy may have a different etiology from unilateral pathology (Gaida, 2004).

2.2.3.4 Functional instability and muscular imbalances in the ankle, ligamentous laxity, peronial musculature weakness that can diminish control of excessive ankle inversion (Arnold, 2006)). The arch index is a substitute for quantifying foot structure. High-arched runners are at a greater risk of foot injury. Low-arched runners risk soft tissue damage and knee injury (Howard, 2006). While the pronated foot is implicated as a risk factor for **sports injury** in some studies, others suggest that a supinated foot posture increases the risk of overuse lower limb **injuries**. Athletes in a given **sports** discipline may tend to have a similar foot morphology, which varies from that observed elsewhere. Further, the foot morphology that is beneficial for performance in a **sport** may be detrimental with regard to **injury**. (Cain, 2007). Mark (2006) suggest that there are certain factors, including foot pronation, **sport**, and a history of this condition, that are associated with an increased risk of exercise-related leg pain. However, according Barnes (2008) no definitive conclusions can be drawn relating foot

structure or function to an increased risk of tibial stress injuries. Extremes of foot types are likely to pose an increased risk of tibial stress injuries compared to normal arched feet.

2.2.3.5 Joint laxity is still the subject of much debate, although muscular elasticity and flexibility programs are recommended to increase ligaments 'defense. (Barber Foss, 2009; Kraemer, 2009)

2.2.4 Warm-up and stretching before competitions (Herbert, 2002, Andersen, 2005).

2.2.5 Height. Taller males are at risk of injury, using single variable logistic regression adjusted to age (Walter, 1989).

2.2.6 High BMI (<19,5 and > 27) relative to the sports activity in question. Simple anthropometric measurements, weight, and age can be effective indicators of future injuries (Backe, 2009). Rose (2008) was found out that students with body mass index (BMI) in the 50th to 90th percentiles had the greatest risk of sport injury. It is concluded that factors like location of residence, ethnicity, and BMI were predictors of sports injuries in adolescents. Men with a waist girth greater than 83 cm seem to be at greater risk of developing patellar tendon pathology. There may be both mechanical and biochemical reasons for this increased risk (Malliaras, 2007).

2.2.7 Deterioration of the senses, such as reduced peripheral vision, myopia or hyperopia, can increase the risk of injury when mistakenly judging the location of teammates, of opponents, the position of the ball or other obstacles.

2.2.8 Somatotype or constitutional type.

2.2.9 Strength and constitutional resistance achieved through training, as well as muscle tone and joint stability. The right- and left-hand power was higher for injured athletes in some sports (Dane, 2002).

2.2.10 Basic conditional qualities such as balance, agility, speed and coordination.

2.2.11 Reaction time and timing.

2.2.12 Physical maturity and posture alignment.

2.2.13 Previous injuries and incomplete recovery from the same before returning to train or compete at the desired tempo and intensity. In these cases, the causes of the injuries may persist, the healed tissue might not work with the required efficacy or the injury might not completely heal. Through a multiple logistic regression analysis, Walter (1989) demonstrated that previous injuries are one of the most indicative factors.

2.2.14 Previous and persisting systemic illness, general and local inflammation, chronic illness, rheumatic diseases, and connective tissue diseases, as well as dental cavities and tonsil stones.

2.2.15 Mental and psychological conditions: intelligence, creativity, motivation, discipline, level of distress, previous experience in the same sports activity, the need to take risks, excessive bravado, fervor, strict adherence to rules and fair play.

3. Predictive factors of injuries

When an injury occurs, biomechanical, kinematic, and body composition analyses tend to provide more predictive information than the analyses focused on training intensity, resistance, muscle tone, agility, physical maturity, previous injuries or training methods.

Unevenness in the length of lower limbs, misalignments, anatomical abnormalities, club foot, genu valgum, support type, or posture defects are typically factors cited as injury predictors.

Footprints have also been examined: the average arch, the foot's plantarflexion and dorsiflexion, excessive pronation, as well as the quadriceps' Q angle.

In this chapter we will also delve into constitutional defects in regards to an ideal constitution.

With the exception of the case of athletics, Watson (1987) states that constitutional and postural defects during practice, as opposed to during sports activities, have not received the attention they deserve. Watson points out the clear relation between postural defects and the risk of sports injuries, although it is difficult to prove and establishes a clear relation between foot anomalies and decompensation in the transmission of force in lower limbs, and future repercussions of injury depending on the player's dysmorphia.

3.1 The relationship between lower limb structure and sports injuries

Common predisposing factor in injuries to the ankles, legs, knees, and hips include:

Bilateral weight and structural symmetry, Quadriceps and calf girth, patella alta, a kneecap that's higher than usual, Q-angle of the knee (high Q angle: kneecap displaced to one side, as with knock knees), Forefoot varus, Rear foot valgus, true and apparent leg length, uneven leg length, excessive pronation (flat feet), cavus foot (over-high arches), bowlegged or knock-knee alignment.

Uneven leg length may lead to awkward running and increases the chance of injury, but many people with equal-length legs suffer the same effects by running on tilted running tracks or along the side of a road that is higher in the centre. The hip of the leg that strikes the higher surface will suffer more strain.

Pronation is the inward rolling of the foot after the heel strikes the ground, before the weight is shifted forward to the ball of the foot. By rolling inwards, the foot spreads the shock of impact with the ground. If it rolls too easily, however, it can place uneven stress on muscles and ligaments higher in the leg.

While an overly flexible ankle and foot can cause excessive pronation, a too-rigid ankle will cause the effects of cavus foot. Although the arch of the foot itself may be normal, it appears very high because the foot doesn't flatten inwards when weight is placed on it. Such feet are poor shock absorbers and increase the risk of fractures higher in the legs.

Bowlegs or knock knees add extra stress through knees and ankles over time, and may make ankle sprains more likely.

Other structural conditions that make sports injuries more common include **lumbar lordosis.**

Having some muscles that are very strong and others that are weak can lead to injury. If your *quadriceps* (front thigh muscles) are very strong, it can increase the risk of a stretched or torn hamstring (rear thigh muscle). Tight iliotibial bands may be the cause of knee pain for many athletes in running sports.

Overuse injuries are caused by repeated, microscopic injuries to a part of the body. Many long distance runners experience overuse injuries even after years of running. For road runners, the surface is hard and sometimes uneven, and the running movements are repetitive. In addition, there are usually both up- and downhill elements, and these increase the stress on tendons and muscles in the lower leg. You will more likely develop running injuries if you wear the wrong shoes or sneakers. You should use footwear that doesn't allow side-to-side movement of the heel, and that adequately cushions the foot.

Barnes (2008) have not found definitive results that can confirm that constitutional defects are risk factors for injury, while Ferretti (1986) demonstrates that 78% of knee injuries and 50% of spinal column and ankle injuries are closely related to anatomical alteration in static and dynamic foot postures. Regarding these constitutional defects, females could consider themselves at risk due to having a greater articular laxity and less muscle tone, although, at

the same time possessing greater coordination, laterality and body outline. Women also have certain anatomical aspects that can contribute to a greater disposition to injury: a wider pelvis, a greater femoral anteversion, less muscle development of the vastus internus in the quadriceps, a smaller intercondylar notch, a greater tendency towards genu valgum and ligament laxity, external tibial torsion and a higher number of misalignments in lower limbs.

4. Logistic regression equations

The purpose of regression techniques is two-fold:
1. **To estimate the relation between two variables** while taking the presence of other factors into account
2. **To construct a model that allows for the prediction of the value of the dependent variable** (in logistic regression, the probability of success) for specific values of a predicted group of variables

4.1 The concept of logistic regression

The benefit of logistic regression no doubt comes from its capacity to analyze clinical and epidemiological research data. The primary objective that this technique accomplishes is modeling how the presence, or absence, of diverse factors and their values influence the probability of the, typically dichotomic, occurrence of an event. This technique can also be used to estimate the probability of the occurrence of an event with more than two (polytomous) categories.

These sorts of situations are approached using regression techniques. Nonetheless, lineal regression methodology is not applicable since the outcome variable only provides two values (we will focus on the dichotomic case), such as the presence/absence of a knee sprain, or the presence/absence of injury.

If we classify the value of the outcome variable as 0 when the event does not occur (the absence of a knee sprain) and as 1 when it does occur (the athlete sprains his or her knee), and we look to calculate the possible relation between the occurrence of a sprained knee and, for example, the difference in the thickness of both thighs (considered a possible risk factor), we could fall into the temptation of using a linear regression:

$$\text{Knee sprain} = a + b * [\text{difference in thigh thickness}] \tag{1}$$

And, based on our data, gauge the coefficients *a* and *b* of the equation through the normal procedure of least squares. However, although this is mathematically possible, we arrive at nonsensical results; upon calculating the resulting equation for different values of thigh thickness, we will obtain results that generally differ from 0 and 1, while the only results actually possible in this case are 0 and 1. Since this restriction is not imposed in lineal regression, the outcome can theoretically take on any value.

If we use *p* as the dependent variable of probability that an athlete suffers a knee sprain, we can build the following equation:

$$\text{Ln}\frac{p}{1-p} \tag{2}$$

now we do have a variable that can take on any value, and we can therefore propose a traditional regression equation in order to find that value:

$$\ln \frac{p}{1-p} = a + b \text{ [difference in thigh thickness]} \qquad (3)$$

which, with a slight algebraic manipulation, can be turned into:

$$\text{Injury probability} = \frac{1}{1 + e^{\left[-a - b - \left(difference\ in\ thigh\ thickness\right)\right]}} \qquad (4)$$

And this is exactly the kind of equation known as a logistic model, where the number of factors can be greater than one. Therefore, in the denominator exponent, we could have:

$$b1.\text{difference in thickness} + b2.\text{age} + b3.\text{sex} + b4.\text{height} \qquad (5)$$

4.2 Logistic model coefficients as risk quantifiers

One of the factors that make logistic regression so interesting is the relation that logistic model coefficients preserve with a risk quantification parameter known in the field as an "**odds ratio**".

The odds associated with an event is the quotient of the probability of occurrence given the probability that it does not occur:

$$\text{Odds Ratio} = \frac{p}{1-p} \qquad (6)$$

with *p* being the probability of occurrence. Therefore, we can calculate the odds of an injury occurrence when the difference in thigh thickness is equal to or greater than a specific quantity, which determines how much more probable it is that an injury occurs than if it were not to occur in this situation. Likewise, we could calculate the odds of an injury occurrence when the difference in thigh thickness in less than that same figure. If we divide the first odds by the second, we will have calculated an odds quotient, or an odds ratio, which in some way quantifies how probable the occurrence of an injury is when the difference in thickness is greater than a specific figure (first odds) relative to when the difference in thickness is less. The notion being measured is similar to what we find in the **relative risk,** which corresponds to the probability quotient that an injury occurs when a specific factor is present (difference in thickness) compared to when it is not. In fact, when the prevalence of the event occurring is low (<20 %), the odds value ratio and the relative risk are very similar; but such is not the case when the occurrence of the event is quite common, a fact that is often ignored.

$$\text{Relative Risk} = \frac{\text{Probability of Injury the presence of the risk factor}}{\text{Probability of Injury the absence of the risk factor}} \qquad (7)$$

$$\text{Absolute risk Increase} =$$
$$\left(\text{post test probability if risk factors is present}\right) \qquad (8)$$
$$-\left(\text{post test probability if risk factors is present}\right)$$

If we have a dichotomic factor in the regression equation, for example if the subject is not a jumper, the *b* coefficient of the equation for this factor is directly related to the odds ratio *OR* of being a smoker compared to not being one:

$$OR= \exp (b) \tag{9}$$

where *exp(b)* is a measurement that quantifies the risk presented when the corresponding factor is present compared to when it is not, assuming that the rest of the model's variables remain constant.

When the variable is numerical, for example, age or body mass index, it is a measurement that quantifies the change in risk when a variable changes its value while the rest of the variables remain constant. Insomuch, the odds ratio that, in theory, moves from age *X1* to age *X2*, with *b* being the coefficient that corresponds to age in the logistic model is:

$$OR= \exp [b * (X2- X1)] \tag{10}$$

This is a model in which the increase or decrease of risk is proportional to the change in one factor's value to another. In other words, it is proportional to the difference between the two values, but not to the starting point, meaning that the change in risk, in the logistic model, is the same when we move from 20 years old to 30 years old as when we move from 40 to 50.

When the variable's coefficient *b* is positive, we obtain an odds ratio greater than 1 that therefore corresponds to a risk factor. On the other hand, if *b* is negative the odds ratio will be less than 1 and will correspond to a non-risk factor.

$$\text{Pre-test odds} = \frac{\text{pre-test probability of injury}}{1 - \text{pre-test probability of injury}} \tag{11}$$

$$\text{Pre-test odds} = \text{pre-test odds} \times \text{positive likelihood ratio negative - likelihood ratio} \tag{12}$$

Where

$$\text{positive - likelihood ratio} = \frac{\text{sensitivity}}{(1 - \text{specificity})} \tag{14}$$

$$\text{negative - likelihood ratio} = \frac{(1 - \text{specificity})}{\text{sensitivity}} \tag{15}$$

$$\text{Post - test probability} = \frac{\text{post - test odds}}{(\text{post-test odds} + 1)} \tag{16}$$

4.3 Qualitative variables in the logistic model

Given that the employed methodology for calculations with the logistic model is based on using quantitative variables, the same way as in any other regression process, it is incorrect that qualitative variables are used in regression processes, whether nominal or ordinal variables.

Assigning a number to each category does not solve the problem since the physical exercise variable has three possible answers: sedentary, sporadically performing exercise, frequently performing exercise; and we assign the values 0, 1, 2, respectively, to these variables. But then, performing frequent exercise has twice the value of performing exercise sporadically, which makes little sense. Even more absurd would be if a nominal variable, for example

civil status, did not have any ordering relation among the outputs. The solution to this problem is to create as many dichotomic variables as the number of outputs. These new variables, artificially created, are called "*dummy*", or indicator, internal, or design variables. Therefore, if the variable in question produces exposure data with the following outputs: *Never ran, Ex-runner, Runs less than 10 kilometers per day, Runs 10 or more kilometers per day*, we have 4 possible answers from which we will construct 3 dichotomic internal variables (values 0,1) with different possibilities for codification that lead to different interpretations. The most frequent of which is the following:

	I1	I2	I3
Never ran	0	0	0
Ex-runner	1	0	0
Runs less than 10 km per day	0	1	0
Runs 10 or more km per day	0	0	1

Table 1. Design variables.

In this type of codification the regression equation's coefficient for each design variable (always transformed with the exponential function), corresponds to the odds ratio for this category given the reference level (the first output). In our example, it quantifies how the risk changes given the situation of never having run. There are other possibilities, among which we will highlight an example with a qualitative variable and three outputs:

	I1	I2
Output 1	0	0
Output 2	1	0
Output 3	1	1

Table 2. Qualitative variable and three outputs.

With this codification, each coefficient is interpreted as an average of the change in risk upon moving from one category to the next. In the event that a category cannot naturally be considered a reference level, for example blood group, a possible classification system is:

	I1	I2
Output 1	-1	-1
Output 2	1	0
Output 3	0	1

Table 3. Classification system of category not natural.

Where each coefficient of the indicator variables has a direct interpretation as a change in risk regarding the average of the three outputs.

4.4 How to present logistic regression results

It is common to present logistic regression results in a table wherein each variable will be shown with a coefficient value, its standard error, a parameter (labeled *chi² Wald*), which allows us to check if the coefficient is significantly different from 0 and check the *p* value for this context. It also allows us to check the odds ratio of each variable, together with its confidence interval for 95% reliability.

Term	Coeff.	Stand. Err.	chi²	p	Interpretation
Indepen.	-1.2168	0.9557	1.621	0.2029	NO
Age	-0.0465	0.0374	1.545	0.2138	NO
Race *			* 5.684	0.0583	Almost (p < 0.1)
Race 1	1.0735	0.5151	4.343	0.0372	p < 0.05
Race 2	0.8154	0.4453	3.353	0.0671	Almost (p < 0.1)
Runner	0.8072	0.4044	3.983	0.0460	p < 0.05
Injury	1.4352	0.6483	4.902	0.0268	p < 0.05
Dissymmetry	0.6576	0.4666	1.986	0.1587	NO
Q Angle	0.8421	0.4055	4.312	0.0379	p < 0.05
Thigh Thickness	1.2817	0.4621	7.692	0.0055	p < 0.01

Table 4. Example of Logistic Regression Presentation.

Variable	Odds ratio	OR < 95%	OR > 95%
Age	0.95	0.89	1.03
Race 1	2.93	1.07	8.03
Race 2	2.26	0.94	5.41
Runner	2.24	1.01	4.95
Injury	4.20	1.18	14.97
Dissymmetry	1.93	0.77	4.82
Q Angle	2.32	1.05	5.14
Thigh Thickness	3.60	1.46	8.91

Table 5. Odds Ratio.

4.5 Goodness of fit

As long as we are dealing with a regression model, it is fundamental that the model be checked for an appropriate adjustment to the data used in the calculation before drawing conclusions (Bender, 1996).

In the case of logistic regression, a rather intuitive idea is to calculate the probability of an event, the occurrence of an injury or knee sprain in our case, for all athletes from the sampling. If the goodness of fit is acceptable, one would expect a high probability value to

be associated with the presence of an injury, and vice-versa, if the calculated probability value is low, one would likewise expect the absence of injury.

This intuitive idea is formally realized through the Hosmer-Lemeshow test , that basically consists in dividing the range of probability in deciles of risk (which would be injury probability ≤ 0.1, ≤0.2, and so forth up to ≤1) and calculating the distribution of both injured athletes as well as uninjured athletes that are calculated in the equation and actually observed. These distributions, both calculated and observed, contrast with each other through a chi² test.

In the final presentation of logistic regression data, a goodness of fit test should be included as well as a commented conclusion drawn from the same test. With these, the Hosmer-Lemeshow test would be more illustrative than the mere obtained distribution values.

5. Logistic regression equation and logistic regression analysis

Despite the fact that accidents are unavoidable in sports, injury prediction and prevention is a practical aspect of sports medicine considered to be the best treatment. Regression models encompass mathematical techniques that deal with measuring the relation between an outcome variable and predictive variables. When the outcome variable is continuous, the preferred model is logistic regression. However, when the outcome variable is dichotomic (injured/not injured) and the object of study is the relation between this and one or more predictive variables (right Q angle, left Q angle, the difference in thigh thickness, lower limb dissymmetry, age, sex, hours of training, kilometers run, etc...) the chosen regression model is a simple logistic regression model (for one factor) or a multiple logistic regression model (for more than one factor).

Therefore, the logistic regression analysis technique is used when it is suspected that one of the values of specific categorical variables depends on a series of predictive or independent variables, along with the goal of finding a mathematical function that expresses such a relation.

When the goal is to calculate the relation or association between two variables, the regression models allow for the consideration that there may be other factors that affect this relation.

So, if the possible relation between lower limb dissymmetry and the probability of suffering a knee injury is being studied as a risk factor, that relation can be different if other variables are taken into account such as age, sex, or body mass index. Because of this, these factors could be included in a logistic regression model as independent variables in addition to dissymmetry. In the resulting equation when considering *DISYMMETRY, AGE, SEX*, and *BMI* as independent variables, the *exp* (coefficient of the equation for *DISYMMETRY*) gives us the **adjusted or controlled odds ratio for the rest of the factors**, given the data for DISYMMETRY.

The other variables, in addition to the interest factor (in this example *AGE, SEX, BMI*), are called by several names: control variables, external variables, covariants, or **confounding variables**.

Interaction

When the relation between the factor being studied and the dependent variable is modified by the value of a third variable, we are then dealing with interaction. In our example, we assume that the probability of suffering **a sports injury** increases with age when there is lower limb dissymmetry. In this case we decide that there is an interaction between the variables of *AGE* and *DISSYMMETRY*.

If we focus only on the logistic model exponent, without considering interaction, we would have:

$$-b_0 - b_1 * \text{DISSYMETRY} - b_2 * \text{AGE} \tag{17}$$

If we want to consider the interaction between INJURY and AGE, the model changes:

$$-b_0 - b_1 * \text{DISSYMETRY} - b_2 * \text{AGE} - b_3 * \text{DISSYMETRY} * \text{AGE} \tag{18}$$

If the variable for *DISSYMETRY* is dichotomic (values 0 and 1), the relation between *INJURY* and *DISSYMETRY* will end up quantified by b1 in the first model while in the second…

$$-(b_1 + b_2 * \text{AGE}) * \text{DISSYMETRY} \tag{19}$$

In other words, the relation is modified in function of the value of *AGE.*

5.1 Precautions

The wide availability of programs that allow access to sophisticated statistical tests can lead to the improper and merely mechanical usage of these tests. Regression models require that the model constructor possess at least a minimal knowledge of the model's underlying philosophy, as well as not only a knowledge of the advantages of this technique, but also of its problems and shortcomings. The use of mathematical processes often convinces us that we are observing "objective" results, and to an extent this is true. However these techniques also carry an intrinsic subjectivity from the selection of a mathematical model to the selection of the variables inserted in that model

5.1.1 Independent variable and probability direction

One of the first considerations we must take into account is that the relation between the independent variable and the event probability doesn't change direction. In such a case, the logistic model doesn't work for us. This is something that does not typically occur in clinical studies, but because of that same fact, it is easier to ignore when it does occur.

A very clear example of this situation arises when we evaluate the probability of an athlete's sports injuries in relation to the age when he or she first began sports competitions. Up to a certain age, the probability can increase as the age at which the athlete began competing is earlier. And starting from a mature age, the likelihood of injury also increases compared to the older age at which an athlete competes. In this case, a logistic model would be inadequate.

5.1.2 Collinearity

Another problem that may arise in regression models, and not only logistic models, is that the variables involved may be correlated, which would lead us to a nonsensical model and therefore to some values of the coefficients that cannot be interpreted. This situation, with correlated independent variables, is called collinearity.

In order to understand it, let's look at an extreme case in which the same variable is introduced in the model twice. We would then have:

$$\exp(-b0 - b1 * X - b2 * X) \tag{20}$$

or

$$\exp[-b_0 - (b_1 + b_2) * X]\tag{21}$$

Where the sum of b1+b2 allows infinite possibilities when the value of a coefficient is divided into two addends, and therefore the calculation obtained from b1 and b2 doesn't make sense.

An example of this situation could be given if we include variables such as the length of the lower limbs and the length of the calves in the equation, two variables that are closely correlated.

5.1.3 Sample size

As a basic rule, it is necessary to have at least 10 participants, or (k + 1) cases to estimate a model with k independent variables; in other words, at least 10 cases for each dependent variable (the probability of the event).

It is useful to point out that the qualitative variables appear as c – 1 variables in the model, when constructing the corresponding internal variables based on the qualitative variables.

5.1.4 Model selection

When talking about models that can be multivariable, an interesting topic is how to choose the best set of independent variables to include in the model (Tsigilis, 2005)

The definition of the "best" model depends on the type and objective of the study. In a case where something will be predicted, the best model would be one that produces the most reliable predictions. And in a case where the relation between two variables is being calculated (correcting the effect of other variables), the best model will be one that obtains the most precise calculation of the coefficient of the variable in question. This is often forgotten and leads to completely different model strategies. Therefore, in the second case a covariant with a statistically significant coefficient, but whose inclusion in the equation does not modify the value of the coefficient of the variable in question, will be excluded from the equation since it doesn't deal with the confounding factor: the relation between the variable in question and the probability are not modified if that variable is taken into account. However, if the outcome of a predictive model is included in the equation, then we look for more reliable predictions.

5.1.5 Types of differences

Whenever data in analyzed, it is important to distinguish between numerical differences, statistically significant differences, and clinically relevant differences. These three concepts do not always coincide.

5.1.6 Number of variables

The first thing one must consider is the **maximum model,** or the maximum number of independent variables that can be included in the equation, while taking their interactions into account when appropriate.

Although there are different processes for choosing a model, there are only three basic mechanisms for doing so: start with only one independent variable and, one by one, add more according to the pre-established criteria (forward-moving process). Or also, starting with the maximum model, eliminate the variables one by one according to a pre-established criteria (reverse-moving process). The third method, called "*stepwise*", combines the two

previous mechanisms and, in each step, a variable already present in the equation can be eliminated or another can be added.

In the case of logistic regression, the criteria for deciding if we should choose a new model or stay with the currently used one at each step is established by the **models' likelihood ratio logarithm**.

5.1.7 The likelihood equation

A model's likelihood equation is a measurement of how compatible the model is with the actual outcome data. If upon adding a new variable to the model, the likelihood does not increase in a statistically significant way, then that variable will not be included in the equation.

To evaluate the statistical significance of a particular variable within the model, we will focus on the Wald chi2 value corresponding to the variable's coefficient and on its level of probability.

5.1.8 Sports monitoring

To develop this equation it is necessary to perform a prior monitoring of a representative group of athletes taking into account their age, sex, and sport during a sufficiently long observation period that could be called a season. During this period it is crucial to differentiate the subjects into two groups: injured and non-injured.

Consequently, the relation between the different measured variables and the final outcome of injury or no-injury is established.

In order to determine the predictive variables, we should identify those that show significant differences among the two groups, thus establishing the relation between the injury/no injury dependent variable given the distinct anthropometric and sports variables (activity time, training time, team position, etc...).

5.1.9 Sensitivity, specificity, positive predictive value and negative predictive value

It is useful to use control techniques to evaluate the fit of the outcome results. With the mathematical equations defined in the logistic regression analysis. The results should be analyzed in all studied subjects, for the studied group of athletes in question, and for a control group of both sexes and differentiating the success rate by sex.

5.1.9.1 Sensitivity

Proportion of injured subjects in relation to how many the equation predicted would be injured.

$$Sensitivity\,(Sn) = \frac{True\,Positive}{(True\,Positive + False\,Negative)} \tag{22}$$

The following table summarizes these calculations:

	POSITIVE TEST (T+)	NEGATIVE TEST (T-)
INJURY PRESENT (I+)	TRUE POSITIVE (TP)	FALSE NEGATIVE (FN)
INJURY ABSENT (I-)	FALSE POSITIVE (FP)	TRUE NEGATIVE (TN)

Table 6. Sensitivity.

$$Sn = P\ [T^+ \text{ if } D^+] \tag{23}$$

$$Sn = \frac{TP}{(TP + FN)} \tag{24}$$

5.1.9.2 Specificity

Proportion of uninjured subjects in relation to how many the equation predicted would not be injured.

$$Specificity(Sp) = \frac{True\ Negative}{(True\ Negative + False\ Positive)} \tag{25}$$

You can think of specificity as 1- the false positive rate. Notice what the denominator for specificity is the number of healthy players. Using conditional probabilities, we can also define specificity as:

$$Sp = P[Test\ is\ negative\ if\ Patient\ is\ healthy] \tag{26}$$

$$Sp = P\left[T^- if\ I^-\right] \tag{27}$$

The following table summarizes these calculations:

	POSITIVE TEST (T+)	NEGATIVE TEST (T-)
INJURY PRESENT (I+)	TRUE POSITIVE (TP)	FALSE NEGATIVE (FN)
INJURY ABSENT (I-)	FALSE POSITIVE (FP)	TRUE NEGATIVE (TN)

Table 7. Specificity.

$$Sp = P\ [T^- \text{ if } D^-] \tag{28}$$

$$Sp = \frac{TN}{(TN + FP)} \tag{29}$$

5.1.9.3 False positives

Proportion of uninjured subjects in relation to how many the equation predicted would be injured.

5.1.9.4 False negatives

Proportion of injured subjects in relation to how many the equation predicted would not be injured.

In order to know the probability of whether or not a subject injures him or herself in relation to the outcome injury ratio, we must know the positive predictive values (PPV) and the negative predictive values (NPV) that should be defined as the following:

Positive predictive values: The probability of an athlete injuring him or herself when predicted by the equation. To calculate this we use the equation:

$$PPV = \frac{(S*PL)}{(S*PL)(FL*PNL)} \qquad (30)$$

Where S: Sensitivity. PL: Probability of injury. FP: False Positives. PNL: Probability of non-injury.

The following table summarizes these calculations

	POSITIVE TEST (T+)	NEGATIVE TEST (T-)
INJURY PRESENT (I+)	TRUE POSITIVE (TP)	FALSE NEGATIVE (FN)
INJURY ABSENT (I-)	FALSE POSITIVE (FP)	TRUE NEGATIVE (TN)

Table 8. False negatives.

$$PPV = P \,[I+ \text{ if } T+] \qquad (31)$$

$$PPV = \frac{TP}{(TP+FP)} \qquad (32)$$

Negative predictive values: The probability that the athlete does not injure him or herself when the model has predicted a situation of non-injury. To calculate this we use the equation:

$$NPV = \frac{(E*PNL)}{(E*PNL)+(FN*PL)} \qquad (33)$$

	POSITIVE TEST (T+)	NEGATIVE TEST (T-)
INJURY PRESENT (I+)	TRUE POSITIVE (TP)	FALSE NEGATIVE (FN)
INJURY ABSENT (I-)	FALSE POSITIVE (FP)	TRUE NEGATIVE (TN)

Table 9. Negative predictive values.

$$NPV = P \,[I- \text{ if } T-] \qquad (34)$$

$$NPV = \frac{TN}{(TN+FN)} \qquad (35)$$

Where S: Sensitivity. PL: Probability of injury. FP: False Positives. PNL: Probability of non-injury.

It is always necessary to find false negatives and positives beforehand, as well as the probability of injury or non-injury for each athlete before determining the positive and negative predictive values.

In order to perform this type of calculation, the probability that an individual exhibits the characteristic in question (suffering an injury) is expressed in function of the predictive variable or variables; if we make P the probability, the model is expressed as follows:

$$P = \beta_0 + \beta_1 X \qquad (36)$$

Where β_0 y β_1 are the model parameters and X is the predictive variable. The probability (P) is equal to a constant β_0 plus the product of the other constant β_1 multiplied by the value of the predictive variable X.

The coefficient β_0 is an independent or constant term and it is the value of the outcome variable's average. The coefficient β_1 is the regression coefficient and it is interpreted as the change in the outcome variable's average by the unit of increase of the predictive variable. The change will be an increase if the regression coefficient value is positive and it will be a decrease if the value is negative.

It is possible that once the model parameters are calculated, the substitution of some values of the predictive variable gives way to values that aren't allowed for a probability. This is why one should perform a probability transformation for the probability of showing the characteristics in question. This logit transformation that consists in the logarithmic odd

$\dfrac{p}{1-p}$ that a characteristic will present itself, is modeled by the following formula:

$$\text{Log}\left[\frac{p}{1-p}\right] = \beta_0 + \beta_1 X \tag{37}$$

$$\text{The Log}\left[\frac{p}{1-p}\right] \text{ is called logit (P)} \tag{38}$$

In the logistic regression model, the coefficient $\beta1$ is the logarithm of the odds ratio (OR) between two individuals that are differentiated in a unit in terms of the predictive variable. Likewise, by raising **e** to β_1, we obtain the OR value between those two individuals.

$$\text{Log (O.R.)} = \beta_1 \tag{39}$$

Or:

$$\text{O.R.} = e^{\beta1} \tag{40}$$

where **e** is the number that serves as the base of the Napierian logarithm, approximately 2.72.

In the logistic regression model, β_1 is the OR logarithm between two individuals that are differentiated in a unit in terms of the predictive variable, or likewise, by raising **e** to β_1, one obtains the OR value between these two individuals. In the case where $\beta_1=0$, it is implied that the logit(P)= β_0 + (0) X= 0, in other words, it does not change with X. Or equally, O.R. = e^0 = 1, which indicates that the two variables are independent and there is no relation between them. The calculation of β_1 is called the logistic regression coefficient.

If we have several predictive variables and we try to study the relation between the outcome variable and the whole set of predictive variables simultaneously, a multiple logistic regression model will be used.

$$\text{Log}\left[\frac{p}{1-p}\right] = \beta_0 + \beta_1 X + \ldots + \beta p \, Xp \tag{41}$$

where P is also the probability of presenting the characteristic in question.

An alternative form of presenting the same model is:

$$P = \frac{e^{\left(\beta_0 + \beta_1 + \ldots + \beta_p X_p\right)}}{1 + e^{\left(\beta_0 + \beta_1 + \ldots + \beta_p X_p\right)}} \qquad (42)$$

Which allows the calculation of the probability that an individual with certain predictive values will exhibit the characteristic in question.

5.2 Logistic regression equations applied to sports
5.2.1 Shambaugh injury score

Shambaugh (1991) proposed the first logistic regression equation that would predict injuries occurring within a season with 91% accuracy. The variables initially proposed were the diameter of the thigh, diameter of the calf, the Q angle, ankle dorsiflexion, genu varum and valgum, the difference in supported weight, and the length of the legs. Ankle dorsiflexion and varum were more elevated in uninjured players, and therefore we reject them in the final equation.

When the outcome of the equation was positive, the subject was predicted to be at risk for injury. But one equation with so many relative coefficients and too many collateral effects was, aside from being difficult to design, too complicated to be reliable.

Shambaugh determined that there should only be three dependent variables selected, and since one of the fundamental goals was to find structural asymmetries or imbalances, he opted for the Q angle of the knees and the difference in supported weight between both legs, resulting in the following equation, applicable only to males:

SHAMBAUGH injury score (1991) =

$$\left(\begin{array}{l}\text{imbalance in bilateral weight* .36+right abnormal Q angle*0.48+} \\ \text{left abnormal Q angle*0.86}\end{array}\right)\text{-7.04} \qquad (43)$$

considering the weight imbalance between the right and left leg to be an absolute value and the abnormality of the Q angle for males beginning at 10º.

The value of the Shambaugh score would be directly proportional to the possibility of injury; the higher the score was, the greater the probability of including the athlete in the injury category. There was a 95% success rate. The player that obtained a higher score was also the one who incurred the most serious injury.

Grubbs (1997) studied the Shambaugh score in relation to its predictive value, calculating the statistical values of sensitivity, specificity and positive and negative prediction in men as well as women. Its results were less outstanding, upon inclusion of results for women, the abnormality value of the Q angle in women was set at 15º.

In 2000 he proposed a modification to his injury score, introducing 4 variables instead of the three original ones in his logistic regression equation. The new variable was the squared value of the difference between thigh thickness:

SHAMBAUGH Injury Score $\left(2000\right)\ =$

Weight Imbalance $*\ 0.27\ +\ 1.46*\ \left(\text{Difference in thigh thickness}\right)^2$

$+\ 0.22*\ \text{Difference in the Q angle of both knees}$ $\qquad (44)$

$+\ 0.94\ *\ \text{Right abnormal Q angle}\ -\ 6.46.$

5.2.2 Salazar injury score (Salazar, 2000)

Salazar (2000) expanded on the Shambaugh injury score by including data from exposure to injury at practice, training time, and game play time. He used the control sheets created by DeLee (1992):

$$\text{SALAZAR INJURY PROBABILITY SCORE} = \frac{1}{1 + e^{(0.1621 - 0.06344 * average\ Shambaugh\ score)}} \quad (45)$$

5.2.3 Fernández-de la cruz injury score (Fernández-Martínez, 2008)

$$\text{FERNANDEZ} - \text{DE LA CRUZ DE INJURY PROBABILITY SCORE} = \frac{1}{1 + e^{-\left(0.757 * AQI - 0.647 * DGM^2\right)}} \quad (46)$$

where AQI is the left knee Q angle and DGM[2] is the squared value of the difference in thigh thickness, demonstrating a 72.9% success rate for injury prediction (positive prediction at 75.68%; negative prediction at 70.73%). This equation is applicable to men as well as to women. The overall percentage of correct classification was 68.6%. The cutoff point (0.5) indicates that the subjects with values equal to or greater than 0.5 would be placed in the "at risk" category, while a value less than the cutoff point would place them in the "reduced risk for injury" category.

6. Conclusion

Logistic regression equations allow injury prediction for athletes, risk calculation, and the opportunity for establishing the most effective and appropriate measures to be taken. Its versatility and capacity for being applied to specific sports groups allows personalized attention for each group.

This chapter shows that the logistic regression analysis can be used as a valid method in determining anthropometric parameters related to sports injuries, while providing a reliable and simple method that can be used in the common practice of sports medicine.

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Intervention Strategies in the Prevention of Sports Injuries From Physical Activity

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1. Introduction

Injuries are a serious problem in the training-competition process, since their occurrence leads to the modification or interruption of the activity. Any injury alters training plans and is an important factor in training monitoring. Within the sports community, the most common intervention focuses on recovering from injuries in order to return to previous performance levels; a process that is expensive from both the economic and sporting points of view. However, in many sports, strategies aimed at injury prevention have not been systematically implemented, despite their proven effectiveness. The present chapter reviews some of preventive programs that must be incorporated in training schedules to minimize the impact of injuries. With regard to the introduction of intervention strategies in sport, through preventive measures from physical activity, it is necessary to review the power of the proposed measures and assess their effectiveness. There are numerous published papers on the subject, although it requires a careful study of them, both from the standpoint of methodology as adequacy of proposals, so as to adequately inform such interventions.

2. Multifactorial analysis of the model for injury prevention

One of the most important aspects of training and competition would be the control of the process and its development. The control of training comprehends all the aspects that permit the adaptation of the contents and the training load. One of the reasons why the modification of training programs becomes necessary is sports injuries, as they generate a partial or total interruption of the training process. It is a fact that is practically usual in the majority of sports, as a great number of sportsmen and women injury themselves at least once a season (Bahr & Krosshaug, 2005; Van Mechelen et al., 1992). The injuries constitute set-backs, which cannot be totally avoided, as the mere practice of sports carries with it the risk of injury happening. However, their impact could be lessened through the monitoring, controlling and analysing of the factors and their evolution by using adequate means of control.

The objective would be to ensure that the risk is lessened (prevention) or that its evolution is more favourable, and to ensure the incorporation of the sportsperson in as little time as possible (functional recuperation). Until a few years ago, efforts were centred on treating injure, paying special attention to the therapeutic process from a clinical perspective. However, in the last few years interest has become directed towards the development of strategies and multidisciplinary proposals related to the prevention of and the recovery

from sports injuries. Therefore, the intervention performed presents a model of general control, which includes a global evaluation of the specific sporting context (sport, characteristics of the sportsperson, training conditions, etc.), an adequate prevention in the face of multiple factors of injury predisposition (multifactorial model), and a systematic effort in case of the injure appearing, guaranteeing a full recovery.

2.1 Sequence of prevention

To establish a plan of prevention one must begin with Van Mechelen et al.´s proposal (1992) in a sequence of four steps: establishing the extent of the injury, identifying the factors and mechanisms of injury, introducing preventive measures and, lastly, evaluating their effectiveness (Figure 1). The last few decades have seen a significant increase in the epidemical studies contributing information on the first two steps: identifying injury incidence in each sport, along with the factors and mechanism involved in the production of the injuries, as well as establishing the possible factors provoking the injury, upon which to act in a preventive manner. To understand the importance of the problem it is necessary to know the injury profile for the different sports: injury frequency (number of injuries per 1,000 hours of training or competition), location of the different body structures, severity, typology and the rest of relevant aspects (Fuller et al., 2006). Meeuwisse (1994) developed a model to explain the different risk factors involved in producing sports injuries, rejecting approaches involving an only factor.

Model/Stage	TRIPP (Finch, 2006)	Van Mechelen et al. (1992)
1	Injury surveillance	Establishing extent of the problem
2	Establishing aetiology and mechanisms of injury	Establishing aetiology and mechanisms of injury
3	Developing preventive measures	Introducing preventive measures
4	"Ideal conditions"/scientific evaluation	Assessing their effectiveness by repeating stage 1
5	Describing intervention context to inform implementation strategies	
6	Evaluating effectiveness of preventive measures in implementation context	

Fig. 1. The "sequence of prevention" of sports injuries (Van Mechelen et al., 1992) and The Translating Research into Injury Prevention Practice, TRIPP (Finch, 2006)

Later, this proposal is completed by showing the complex interaction of the internal and external risk factors and the mechanisms that cause sports injuries (Parkkari et al., 2001). In recent years, the theoretical framework of research has been expanded with contributions from Finch (2006), increasing the number of steps in the sequence of prevention to the implementation and evaluation of injury prevention in a real context.

These injuries are associated to a series of risk factors that need to be identified so as to introduce preventive measures in training (Figure 2). This factors are classified in intrinsic factors (predisposal of the sportsperson) and extrinsic factors (exposal to factors of risk),

although in reality the process indicates that these factors are produced in a complex manner and they interact between them (Larson et al., 1996; Murphy et al., 2003; Peterson & Renström, 1988).
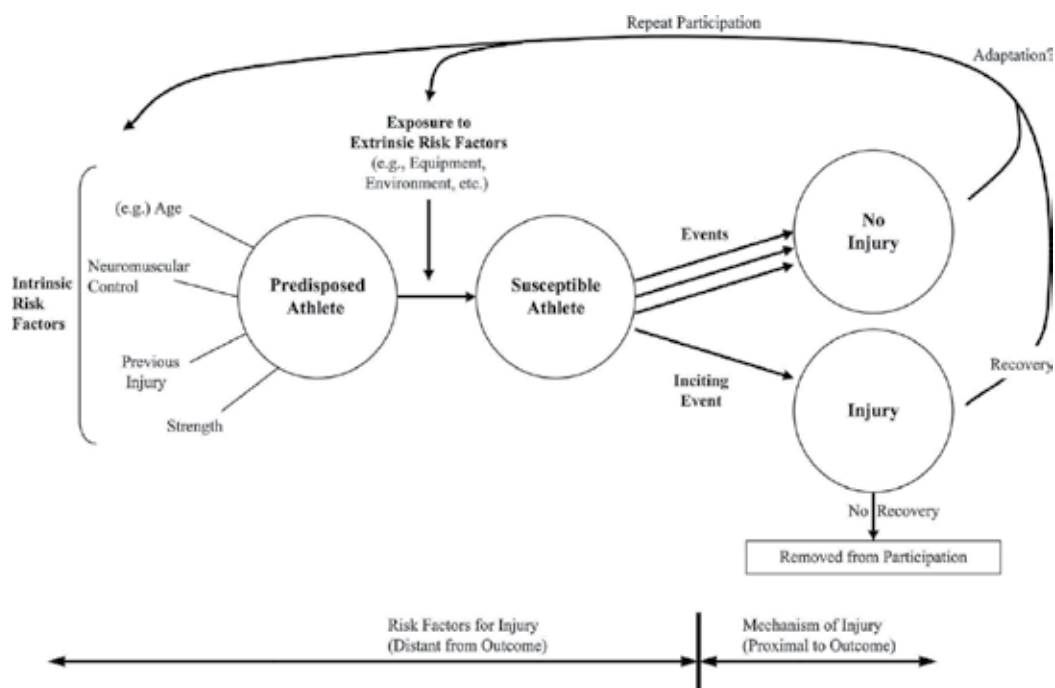

Fig. 2. Recursive model of aetiology in sport injury (Meeuwisse, 2007).

Among the most important intrinsic factors would be the existence of a previous injury and inadequate rehabilitation, age, the sportsperson's state of health, psychological state and aspects, etc. With regard to extrinsic factors, these are: type of activity and motive gestures specific to the sport, dynamics of the training load, training and competition exposition time, material and equipment, type of surface of the playing, environmental conditions and anatomic fatigue (Galambos et al., 2005; Junge & Dvorak, 2000).

Once the most frequent injuries of each modality and their risk factors are known, preventive measures can be introduced (Figure 3). The efficiency of these measures and their suitability from the methodological point of view (Finch, 2006; Shepard, 2005) are known beforehand. The prevention programs should be evaluated through more rigorous designs, with not only random experimental designs of group control, but also quasi-experimental designs that permit more representative samples (professional sportspeople) and more realistic practice contexts (training – competition processes), with truly ideal intervention programmes. Only in this way can the efficiency of the preventive intervention in sports be evaluated (Junge & Dvorak, 2004).

2.2 Different levels of sports injury prevention
2.2.1 Primary Level
The objective of the Primary Level of prevention is to avoid injury before it happens. It consists of a general preventive intervention taking into account the general factors and

mechanisms characteristic of a given person and their effect on a sportsperson with an injury risk. This level implies a change in beliefs, attitude, habits and behaviour towards prevention, and their training by both coaches and sportspeople.

The main measures are of an indirect type: they will control the type, quality and state of the training grounds and competition surfaces; the type of footwear that respects cushioning, traction and rotation upon the field; the use of protective elements; the organization of travel; sleeping and eating habits; the use of tapping as a possible factor in reducing ligamentous affectations; or hydration, controlling the number and quantity of liquid intake and the combination with other sports drinks.
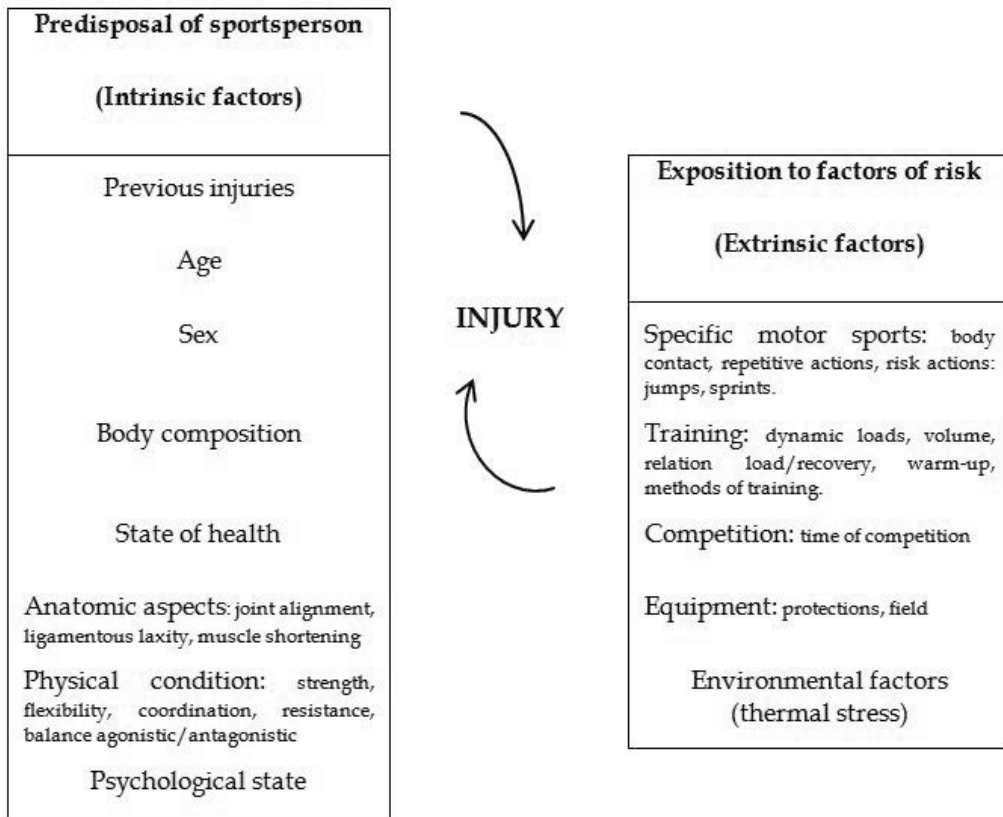
Fig. 3. Factors related to the occurrence of sports injuries (adapted from Bahr & Krosshaug, 2005; Meeuwisse, 1994; Parkkari et al, 2001; San Román, 2005).

2.2.2 Secondary Level

The Secondary Level of prevention constitutes an early level of detection in which intervention takes place in the stages immediately previous to injury or when it has already happened. At this level, one must be in contact with the sportsperson in risk of injury with the objective of diagnosing and detecting the injury once it has occurred by means of the appearance of signs and symptoms. Through the analysis and the discovery of the different risk indicators, there is the possibility of intervening by organizing programmes of intervention at an individual or group level (Muir & Fowler, 1990).

The tendency nowadays entails identifying risk values by means of an exhaustive process of evaluating and monitoring of the sportsperson. Clinical, physical and motor tests will be used to obtain risk indicators, as well as registering and analysing the clinical history of said sportsperson and his/her injuries in previous seasons. Age, competition experience, fatigue and overtraining will be taken into account with regard to exposal to training and competition, as well as psychological factors, reducing or controlling those situations which are potentially stressing for the sportsperson.

2.2.3 Tertiary Level

The Tertiary Level of prevention is the prediction and treatment of possible complications during the post-injure phase. This constitutes an individual level of prevention that involves reducing the grade of injury incidence by eliminating all those contents and work means that could worsen the injury or its consequences and executing programmes directed towards developing the elements of protection from a specific injury.

The elements of intervention at this level should be directed towards regulating and reducing mechanical, muscular, articular, ligament or tendon imbalance that a sportsperson may be exposed to after a specific injury.

3. Review of the basics of preventive measures through physical activity

3.1 Warm up

The efficiency of warm up in the training-competition process is explained by the change of the viscoelastic properties of tissues with increasing temperature or the improvement of metabolic conditions. Content such as joint mobility, jogging, stretching, and proprioceptive technical training (Figure 4) prior to the main activity provide an important preventive security (Fradkin et al., 2006).

Fig. 4. Examples of exercises with preventive content in warm-up.

Different studies have found a relation between the absence or deficient execution of warm-up and posterior injury in specific actions of the sport (Agre & Baxter, 1987; Ekstrand, 1983; Hopper, 1986; Seward & Patrick, 1992) and, in contrast, proposed tactics that introduce preventive contents, which include the previously mentioned elements, manage a decrease of the number of injuries (Dvorak & Junge, 2000; Ekstrand, 1983; Hewett et al., 1999; Olsen et al., 2005; Wedderkopp et al., 1999).

3.2 Strength

Strength plays an important role in the stabilisation of different bodily structures through the normal functioning of passive stabilizers (articular: ligamental structures and meniscus) and active stabilizers (muscles), as well as the interaction between both (Gleeson et al., 1998). The bibliography argues the protective factor that muscle can provide by contributing active stability to the different articular structures, as well as the correct balance between the different muscular groups, developing a fixative and balancing function which allows the individual to develop specific actions with the greatest safety possible, without risk of injury. The main goal of working strength as a means of prevention is to ensure the correct balance between the different bodily structures, thus permitting the safe development of the different actions specific to each sport (Árnason, 2008; Askling et al., 2003; Brooks et al., 2006; Croisier et al., 2005, 2008; Domínguez & Casáis, 2005; Hölmich et al., 2010; Mjølsnes et al., 2004; Parkkari et al., 2001; Thacker et al., 2003, 2004; Tyler et al., 2002).

3.2.1 The right artromuscular balance as preventive tool

The practice of sports implies the practice of certain structures in a repetitive manner, which generates a muscular imbalance between antagonistic/agonistic groups. Maintaining a correct artromuscular balance, permitting a lessening of the effects of muscle shortening and weakening, and maintaining the integrity of articulations would be the main preventive objective of strength work.

With this goal in mind, there are different evaluation measures, such as isokinetic appreciation, that can determinate the grade of functional balance between agonistic and antagonistic muscle (Table 1 and 2). The main investigations about this topic establish a ratio that connects both values, fundamentally in the thigh muscle (hamstrings/quadriceps) whose incidence is related to muscle injure and a protective function of the knee articulation (Aagard et al., 1995, 1996; Askling et al., 2003; Croisier et al., 2005, 2008).

Main investigations place adequate ratio values at the following reference values:

Kannus et al. (1988)	0.31 – 0.80 (recommended> 0.50)
Orchard et al, (1997)	< 0.61 larger injury risk
Clanton & Coupe (1998)	0.50-0,60
Brockett et al. (2004)	0.55
Benell et al. (1998)	0.59 – 0.69
Newton et al. (2006)	0.72 – 0.77
Holcomb et al. (2007)	0.78 (PD) – 0.92 (PND)
Lehance et al. (2008)	0.60

Table 1. Reference values of conventional ratio: H CONC/Q CONC < $60^{\circ}/s^{-1}$ and H EXC/Q CONC >$60^{\circ}/s^{-1}$ – $240^{\circ}/s^{-1}$ (Naclerio, 2007).

The value of functional ratio that discriminates the probability of injury is between 0.60 and 0.70 (Aagaard et al., 1995; Croisier et al., 2005). This same value is the one shown for an imbalance bearing a muscular recurrence.

Aagard et al. (1998)	$1 - 1.4$ ($240°/ s^{-1}$)
Tourney-Chollet et al. (2003)	0.8 ($60°/s^{-1}$) $- 0.88$ ($240°/ s^{-1}$)
Holcomb et al. (2007)	0.94 (PD) $- 1.11$ (PND) ($120°/ s^{-1}$)
Lehance et al. (2008)	>1.4 ($240°/ s^{-1}$)

Table 2. Functional ratio values: H EXC/Q CONC $>60°/s^{-1} - 240°/ s^{-1}$ (Naclerio, 2007).

Besides, recent investigations (Árnason et al., 2004; Hewett et al., 1999; Impellizeri et al., 2007; Newton et al., 2006) highlight the relationship between the balance of strength values between a dominant and non-dominant leg. It is established that a good balance should not exceed 10% between them, and in case of exceeding this percentage, the probability of injury would increase, and risk limit of bilateral asymmetry in the strength is at 15%.

In other muscle groups also involved in many sports, the normal ratios between agonist and antagonist muscles are in: adduction/abduction of hip, with hand-held dynamometer, between 0.96 and 1.4 depending on the rating, side lying position and supine position respectively (Hollman, 2006; Thorborg et al., 2010); and, concentric isokinetic $60°/s^{-1}$ and $120°/s^{-1}$ are between 0.68 and 0.76, also depending on the position in which the test is performed (Alexander, 1990; Pontaga, 2004). Concerning the shoulder joint, the ratios measured with isokinetic vary depending on the sport practiced so for the rotation ratio internal / external rotation, $60°/s^{-1}$ and $120°/s^{-1}$, between 1 and 1.3, but can reach a value of 2 for specialists sports pitches, both team sports and individual sports; and, for adduction/abduction and extension/flexion, normal values are 30% higher than for adduction to abduction, and 50% higher for extensors than for flexors (Codine et al., 2005).

Functional jump tests are also used to determine possible asymmetries associated to bilateral strength deficits. The majority of them are taken from evaluations of the functional state of the lower extremity after anterior cruciate ligament (ACL) injury, and many studies show their usefulness. Although jump distance tests do not contribute with the sophisticated analysis of the working of the lower extremity that can be obtained from studies of running and strength platforms, jump tests seem useful as an evaluation of early detection that does not require a specialised equipment, it can be done in a short time and uses opposite extremity as control. The highly specific nature and low number of false positives makes these tests useful in confirming asymmetries of lower extremities. By associating them with other clinical evaluating tools, they confirm the magnitude of functional limitations (Noyes, 1991).

It seems that both the progressive test (Shuttle Run) and the vertical jump have a low sensibility to detect functional limitations of the lower extremity (Noyes, 1991). Cates & Cavanaugh (2009), in their revision of lower extremities evaluation during rehabilitation, introduce different types of horizontal jumps (Figure 5) that imply a large coordinative component as a measure of evaluating dysmetrias, comparing the values established between one leg and the other, determining a symmetry index obtained after dividing the result of one extremity by the other and multiplying by 100.

One of the latest technologies applied to the analysis of muscle properties of the superficial muscles of each individual is Tensyomiography (TMG), which is a diagnostic method that observes the time parameters and the maximum displacement of muscles during contraction.

Its analysis could direct the strength work to be done on bodily structures (Dahmane et al., 2005). The evaluation permits a muscular symmetry or asymmetry to be established, Tc Time (the time that a muscle takes to contract) and Dm (muscular tone or volume), that adopts as lateral and functional symmetry between two muscles or muscle groups above 85%, although in certain muscle groups it can tolerate up to 30% Dm and 15-20% Tc (Table 3).

The implementation of preventive programs directed both at reforcing artromuscular structures as well as the tendinous have proved themselves as extremely efficient (Árnason et al., 2008; Askling et al., 2003; Croisier et al., 2005; Mjølsnes et al., 2004; Öhberg et al., 2004; Young et al., 2005).
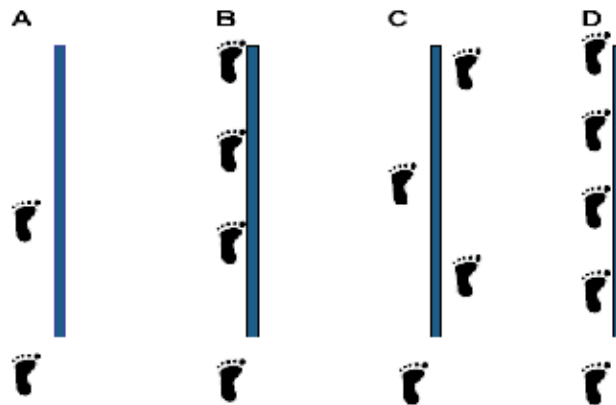

Fig. 5. Example of functional tests of one foot jumps in order to evaluate asymmetric functions; A: Single-leg hop for distance, B: Triple hop for distance, C: Crossover triple hop for distance, D: One-legged timed hop (Cates & Canavaugh, 2009).

VL (Vastus Lateralis)	Dm: 3 - 8 mm Tc: 17ms – 24ms
VM (Vastus Medialis)	Dm: 5-10mm Tc: 22ms – 28ms
RF (Rectus Femoris)	Dm: 3-10mm Tc: 22-30ms
BF (Biceps Femoris)	Dm: 2 – 6 mm Tc: 17-30 ms

Table 3. Range of Tc and Dm in TMG in the main high thigh muscle groups.

3.2.2 Eccentric work as preventive measure

In the last few years, numerous publications that establish the benefits of eccentric strength work with a double objective have appeared: improving the muscular strength values developed by the individual, and exerting a protective function for the prevention of sports injuries (Askling et al., 2003; Brockett et al., 2001). The positive effects of eccentric work on sports injuries are: the increase of the capacity to absorbe muscle tension, a higher hypertrophic level, a protective effect upon the tension-length parameters and the increase of sarcomeres in series (Brockett et al., 2001; Hortobagyi et al., 2001; Proske, 2001).

Taking into account that a great number of muscular injuries take place after eccentric contractions have been done (Thacker et al., 2003), it seems advisable to adapt muscle and tendinous structures to these requests that are produced during the specific actions of each sport, in order to avoid or minimize their seriousness. With the publications of Fyfe & Stanish (1992), the histological modification was established by observing the implications of eccentric training in the rehabilitation of tendinopathy. Later publications (Hortobagyi et al., 2001; LaStayo et al., 2003), confirm that the main effects of eccentric work on tissues allow an increase in elasticity, bringing about an increase in strength and in resistance of the tendon-muscle complex, as well as re-educated the proprioceptive sensibility.

In the last decade, studies by Alfredson et al. (1998) and by Young et al. (2005) have reaffirmed the proposals of Fyfe & Stanish (1992). They have suggested slight modifications, with more aggressive training, going from 10 to 15 repetitions, working on slow speeds, doing the program twice a day for at least 12 consecutive weeks, through "painful exercises".

One of the main biomechanical characteristics of eccentric muscle work is that muscular stretching is obtained whilst producing tension, which implies the stretching of the tendon – muscle, while increasing the levels of muscle strength and improving functional muscle properties at high speed movements. This basis is used in diverse published studies about the prevention of muscle injure in sportspeople, above all, directed at the hamstrings (Árnason et al., 2007; Askling et al., 2003; Croisier et al., 2005; Mjølsnes et al., 2004).

3.2.3 Scientific evidence of the work strength as preventive work

It is necessary to approach this section distinguishing those experiences centred on the protection of tendon structures and those directed towards muscle function.

At a tendon level, the main references to apply preventive work in sport to tendinopathy Achilles and patellar are by Mafi et al. (2001), Silbernagel et al. (2001) and by Young et al., 2005, with adaptations, following the steps indicated by Fyfe & Stanish (1992). The obtained results indicate that eccentric work improved the state of the tendon significantly in comparison to concentric work, especially if the eccentric work is done on inclined plane with 25º degrees overload.

The main studies that deal with eccentric work applied to muscular structures are centred mainly on the hamstrings (Árnason et al., 2008; Askling et al., 2003; Brooks et al., 2006; Dadebo et al., 2004; Mjølsnes et al., 2004), combining the flexibility exercises with FNP modalities and even using isoinertial devices, Yo-yo Technology (Figure 6).

3.3 Flexibility

The lack of muscle extensibility or the high tone of the antagonist muscle, are factors that enhance sports injuries, especially muscle injure.

3.3.1 Improved flexibility as preventive tool

Muscular injure where no external agent is involved generally occurs during the eccentric phase of muscle contraction. In this case, the muscle develops tension whilst increasing in length. Weakness and fatigue make muscle structures more susceptible to injure (Garret, 1996) when at a specific moment they are incapable of absorbing the generated tension.

When overstretching occurs in a muscle during a quick motor action, its ideal stretching tolerance may be surpassed, jeopardizing its integrity and allowing a possible injury (Askling et al., 2000, 2006). An imbalance in the level of flexibility in a muscular group, or in

the adequate range of movement for the normal actions in the sport , could predispose to injury (Knapik et al., 1991).

Achieving a correct balance of artromuscular and the structures that make up the locomotor system, as well as achieving an adequately wide level of movements will allow a more fluid movement and coordination in the execution of technical actions and displacements.

3.3.2 Scientific evidence of the use of flexibility

The use of flexibility as a prevention method has been a topic of much controversy in the last few years. There are two fundamental strategies that the studies follow to be able to determine the influence of flexibility levels on injuries and, on the other hand, whether improving flexibility could act as an element protective of and preventive from injuries (Thacker et al., 1999, 2003; Petersen & Hölmich, 2005).

Fig. 6. Examples of eccentric work exercises.

Diverse authors have found a predisposition to injury in sportspeople with low flexibility levels. Low flexibility levels put hamstrings and quadriceps muscles at risk; therefore, it would be interesting to find this type of deficiency to establish adequate prevention programmes (Ekstrand & Gillquist, 1983; Liemohn, 1978; Witvrouw et al., 2000; Worrell, 1991). The use of standard stretching programs, the stretching technique used, and the stretching maintenance time are probably involved in a complex synergism that can reduce muscle injure, modifying the patterns of modern training in professional sportspeople (Dadebo et al., 2004). In opposition to these authors, Orchard et al. (1997) and Hannessey & Watson (1993) found no correlation between flexibility levels and muscle injure.

Training and better flexibility are programmed to preserve sportspeople from possible muscular injuries through a stretching superior to the usual range required in the sport. It seems appropriate to achieve a good residual level of flexibility, to have a range of articulate and muscular reserve, in case an unexpected or unusual gesture is superior to the flexibility

or mobility of work. As an important part of muscular injuries in physical sport activities is found in the myotendinous junction, it would be advisable to improve the mechanical properties of this area. Kubo et al. (2001) has shown how repeated training of flexibility can alter the viscoelastic properties of the myotendinous junction, increasing its capacity to absorb to traction force especially in eccentric actions, a typical mechanism, in muscular injure (Witvrouw et al., 2004). In this sense, the stretching work with an eccentric dynamic phase or stretching in active tension or some modalities of FNP would be an interesting stimulus to allow the contractile component to better absorb these types of contractions so common in sports activities.

Witvrouw et al. (2007) and Mahieu et al. (2007) argue that the use of repeated dynamic stretching can improve the properties of the tendon just as eccentric training can, being an important weapon in the prevention of tendon injuries.

Stretching as part of a warm-up is one of the most extended practises in training, and permits the achievement of a series of adaptations that help in the performance and minimise the risk of injury, which is why they are a clear recommendation of the most prestigious associations of exercise prescription (Franklin et al., 2000; Holcomb, 2000). In the same way, it has been confirmed that stretching as part of warm-up content can prevent possible muscular injuries due to overstretching (Shellock & Prentice, 1985). Although there are contradicting opinions, perhaps due to the type of stretching techniques used (static stretching, FNP, rebounds) or to doing the same in different conditions (with or without previous increase of muscle temperature) (Shrier, 2002).

Nowadays, many studies are being published that fuel this important controversy about the type of stretching that should be done in warm-up of sports such as football, with explosive and velocity predominance (Cramer et al., 2004; Fletcher & Jones, 2004; Cometti, 2007). It is being pointed out that passive or static stretching have a contra productive effect, whilst the dynamic one would generate it in a positive way.

The majority of the existing investigation about static stretching focused on its application previous to exercise, reporting negative effects on explosive force when done 60 minutes before training or competition (Shrier, 2004), as well as an increase in time in a 20 meter sprint both in track runners and cross country runners who compete in power events (Nelson et al., 2005), making them inadequate for activities where the production of elastic-explosion and reactive power are decisive, as in the case of football, resulting inappropriate in their short-term effect (Barnett, 2006).

Static stretching reduces power peak, inhibiting the explosive properties of muscle, reducing reaction times and movement, and in some cases jumping capacity (Fowles et al., 2000; Cornwel et al., 2001; Young & Elliot, 2002; Behm et al., 2004; Cramer et al., 2004; Power et al., 2004; Mahieu et al., 2007). Therefore, it is not advisable as previous activity when preceding physical sporting activities dependant on rapid muscle tension or on explosive-elastic or reactive regime (Young & Behm, 2001; Cornwell et al., 2002; Cramer et al., 2004; Fletcher & Jones, 2004; Wittmann et al., 2005; Little & Williams, 2006; Cometti, 2007; Yamaguchi et al., 2007). In these cases, the practice of dynamic or ballistic stretching beforehand improves muscular provision, providing an increase in race speed, or agility actions.

3.4 Proprioception

A normal joint is dependent on the proper functioning of the neuromuscular control to avoid injury, as this allows dynamic control of the loads applied to it. Several authors have

highlighted the role of proprioception in the prevention and treatment of sports injuries. Work towards a better neuromotor control of movement has been shown to be effective, specially, in view of an articular injure, and there are very interesting proposals in this regard.

3.4.1 Fundamentals of proprioception as method of preventive work

Sherrington (1906, as quoted in Hewett et al., 2002) defined this concept as the culmination of the neural inputs originated in the different proprioceptors of the human body. However, this term has evolved, and as years have gone by the interaction between the sensorial, to which more importance was given before, and the motor, which is the formation of this somatosensorial system, has been included and studied and is a central theme of this section.

Actually, the present definitions of proprioception do not only include sensorial information but also position conscience and articular movements, speed and the detection of movement strength (Saavedra et al, 2003). We are therefore speaking of a source of sensorial information that anticipates information for intervening in the neuromuscular control with the objective of improving the functional articular stability (Lephart et al., 2003).

Proprioception consists of a ringlet from the stimulation of the sensorial receptors (cutaneous, articular, muscular) that are found in the visual, vestibular, and auditory systems that translates the mechanic event into a neurological signal (Saavedra et al., 2003) that goes through the spinothalamic tract.

The concept of proprioceptive training based on what has been explained, was initially introduced in the area of rehabilitation, with the objective of restoring the "neurological alteration" produced in the receptors when injury occurs (Freeman, 1965, as cited in Ergen & Ulkar, 2008), as it causes a destruction of proprioceptive of the injured tissue, these are not completely recovered (Griffin, 2003).

An injury produces a proprioceptive altercation, which reduces the neuromuscular control of this structure and those adjacent to it, which in turn causes general functional instability. The proprioceptive work in the field of rehabilitation restores the deficit caused by the injury incidence to values that do not generate functional instability. After recovering from it, the prevention work improves stability and neuromotor control and avoids a possible posterior relapse.

Parallel to previous investigations and in the last few decades, the advances in proprioceptive work in the prevention of injury were also aimed at achieving quicker reaction of the fixative musculature of the articulations after an imbalance. Because of this "anticipation" of the movements, a sportsperson can improve his/her performance by putting into action faster than their physical capabilities, such as strength.

The bibliography explains this phenomenon as anticipatory postural adjustments programmed beforehand without following the usual response steps, which predict possible disorders that can occur during the execution of said movement, acting as a "trigger" of the preparatory adjustments before even doing the movement, avoiding a loss of balance (De Guez, 1991, as cited in Del Abril, 2001). The proprioceptive work, as a learning process requiring repetitive practice and systematic movements, is capable of anticipating voluntary movement and do the bodily adjustments, which requires a previous muscular activation so as not to lose balance.

3.4.2 Scientific evidence as a preventive proprioceptive work

Over the last three decades this form of work has been introduced in the field of injury prevention, being one of the first studies published by Tropp et al. (1985). From the moment when this study was published and the following two decades, more studies were done showing that the most effective prevention of injury was by means of a prevention plan that had as principal content proprioceptive and neuromuscular training. Diverse studies have shown that there is a reduction of injury incidence when exercises on a stable and unstable plan are done, increasing the difficulty in balance within stability as a methodological progression, causing bipodal and unipodal support combining these with jumps (Bahr et al., 1997; Caraffa et al., 1996; Eils et al., 2001; Hewett et al., 2006; Knobloch et al., 2005; McGuine et al., 2006; Mohammadi et al., 2007; Myklebust et al., 1998; Paterno et al., 2004; Wedderkopp et al., 1999). In the same way, there are also some studies that find no significant differences in their results (Söderman et al., 2000; Petersen & Hölmich, 2005; Verhagen et al., 2004).

The publications related to proprioceptive training aimed at injury prevention that have obtained results present two different work angles (Figure 7):

1. Authors who emphasize "static" proprioceptive work (balance and rebalancing), mainly on unstable plan in bipodal and monopodal support, which at times is combined with technical elements (Tropp et al., 1985; Bahr et al., 1997; Caraffa et al., 1996; Eils et al., 2001; Knobloch et al., 2005; McGuine et al., 2006, Mohammadi et al., 2007; Vergahen et al., 2004; Wedderkopp et al., 1999).

2. Authors who emphasize dynamic proprioceptive work (neuromotor control) through specific actions which require a great control of the different bodily structures, like jumps and receptions, on bipodal and monopodal support, and on the stable and unstable plan (Heidt et al., 2000; Hewett et al., 1999, 2002, 2006; Myklebust et al., 1998; Paterno et al., 2004; Petersen & Hölmich, 2005; Zebis et al., 2008).

Proprioceptive work has shown itself useful for the decrease of injuries in sport, especially in the case of those of articular character in knees and ankles, particularly ACL (Caraffa et al., 1996; Hewett et al., 1999; Knobloch et al., 2005; McGuine et al., 2006; Mohammadi et al., 2007; Myklebust et al., 1998; Paterno et al., 2004; Wedderkopp et al., 1999); the common aspects of training load in the studies show (Table 4) that the positive results are:

Hewett et al. (1999, 2002, 2006) also suggest that for knee injury prevention, concretely ACL, proprioceptive work based on "static balance" was not effective, and that it needed to be combined with other techniques to obtain significant results in lessening ACL injuries (combining sports technique exercises, dynamic proprioception and/or plyometric, postural control and/or "core").

Surface	Stable and instable
Type of support	Monopodal and bipodal
Neuromuscular implication	Jumps and receptions
Number of weekly sessions	Season: 1-3 trainings/Preparatory period: 3-5 trainings
Session time	Between 15 – 20 minutes
Number of exercises	Between 2 and 12 exercises
Work time for each exercise	Between 15 and 45 seconds
Sensorial information	Without sensorial privation (SP) (eyes open)/with SP (eyes shut)

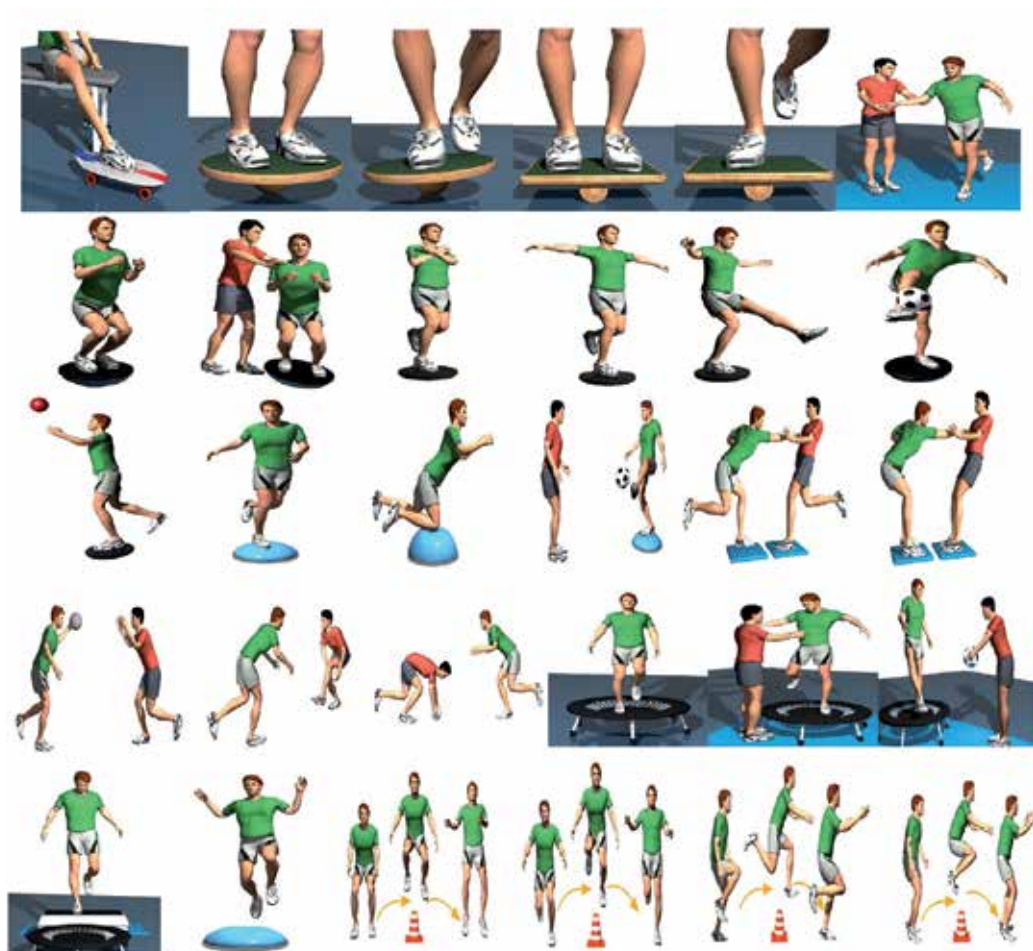Table 4. Common elements of training load in proprioceptive work.

Fig. 7. Examples of proprioceptive exercises on different surfaces.

4. General protocols for injury prevention in sports, intervention strategies: Group vs. individual

The measures successfully introduced in sports to prevent injuries and mentioned previously, allow adequate preventive programs to be designed for each context. This design and its application demand a profound prior reflexion regarding the specific needs of the sportsman/woman with whom the program is to be developed and the best way of tackling the problem.

When introducing a preventive program, one can organise the session or apply the contents of the preventive program in two ways: the first one more generally directed towards dealing with problems generated in each sport, data that will be extracted from the injury profile of the activity and the team sports, being able to organise these programs as parts of

the session (warm-up, main part and return to calm) in a group manner. The other direction is more specific and for its organization the individual needs of the sportsperson will be required. It can be done before training with individualised sessions, or reduced group sessions, so as to better attend to their needs.

4.1 Implementation of team sports prevention programs

Currently there are numerous published proposals that seek to encompass different prevention protocols in general, studying their effects in complex ways. The main general preventive published proposals based them on "multistation" work, putting together exercises that present scientific evidence directed towards the protection of muscular-tendon structures and the articular of the lower body.

One the most extended preventive programs in sport, directed towards ACL prevention is the Prevent Injury and Enhance Performance Program (PEP Program), designed by the Santa Monica Sports Medicine Foundation (SMSMF), and which i will be summarised below.

In terms of popularity, another programme by the Fédération Internacionale de Football Association (FIFA) is the F-MARC or "The 11", referring to the number of exercises designed in the program directed to reducing injuries in the lower body in football. One of the last programmes to appear, develop and be promoted by the Mayor Soccer League (MLS) and the SMSMF, the MLS Groin Injury Prevention Protocol, is directed at preventing injuries in the groin, through a protocol.

The programs directed towards general preventive aspects in sport, which try to influence the imbalances particular to the specialty, can be developed in training directed in a group or individual manner and can be developed in parts of the session or in complete sessions with the objective of prevention. The work could be organized in form of a circuit, with different work stations or organising the group in such a way as to have everyone doing the same task at the same time, during a warm-up session, for example.

Such programmes have been developed in elite sportspeople of different team sports such as football, handball and volleyball (Söderman et al., 2000; Myklebust, 2007; Olsen et al., 2005; Steffen et al., 2008). Besides, in schools there are models such as the iPlay Study, where they develop a school-based physical activity injury prevention programme (Collard et al., 2009; Emery et al., 2006).

4.2 Implementation of individual prevention programs

Individual prevention programs are those directed towards particular preventive aspects taking into account the characteristics of each individual, their injury history, previous evaluation and reports about sports life. They are developed in an individual manner, although it allows a greater grade of control by club technicians, a great implication of the player is necessary so that the proposed session has the necessary quality and brings about the desired effects.

The work contents must be individual and adjusted to the individual's injury history, with contents including one or various of the following aspects: rebalance of the strength values in the concentric and/or eccentric work, strengthening of the "core", adjustment of the levels of work flexibility to the specific sport, improving the postural stability through the neuromuscular control and proprioceptive work.

5. Conclusion

The measures indicated have been contrasted in terms of efficiency in different studies. Currently, there are numerous published proposals which aim to encompass them in different ways in protocols of general prevention, studying their effects in a complex way. In conclusion, it can be stated that the preventive measures that have greater scientific evidence are the use of functional bandaging, flexibility and strength training (with special attention paid to eccentric work), and proprioceptive work.

However, the programmes should be evaluated by more rigorous designs, not only with randomised experimental designs control group, but also quasi-experimental designs to use more representative samples (professional athletes) and more realistic practice contents (competition-training process), and intervention programs with really powerful measures. In this way, they must be valued with the rigour required of different preventive measures, thus usually refuting works quoted and taken as reference samples using insignificant and limited prevention protocols.

The next challenges in injury prevention should be to use the opportunities we have to implement methods of preventive work in a real context through programmes that take into account the evaluation of its effectiveness, in order to offer the sportsperson an anticipatory care, considering that the gain in injury prevention is given by the interaction of different changes in behavior and beliefs in all levels of sport. The future of intervention strategies in the prevention of injury from physical activity overcomes barriers to implementation and at each level should be designed in a different programme, adapted to each context.

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Part 4

Orthopedic and Skeletal Aspects of Sports Medicine

Pilates Based Exercise in Muscle Disbalances Prevention and Treatment of Sports Injuries

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1. Introduction

The Pilates method has today become more popular than ever. As a form of movement it serves as a basis for fitness, complements sports training and is also one of the methods of physiotherapy. Pilates method combines features typical both for Eastern systems (mind control during exercises, relaxation, increasing of elasticity, movement starting from body center, balance) and Western systems (forming strength, endurance, exercises having both global and local effects). The primary goals in muscle-strain rehabilitation include not only recovery of muscle strength and flexibility but also correction of muscle imbalances. In prevention of sports injuries complementary training regarding body awareness, economical breathing, neuromuscular coordination by executing fluent and precise movement starting from a strong core is suggested. The Pilates based exercise, performed under the supervision of a certified instructor serve these needs and can be part of prophylaxis and kinesitherapy in sport medicine.

2. Joseph H. Pilates – A sportsman and kinesitherapist

Joseph Humbertus Pilates (1880-1967) was born in Germany with poor health. The medicine at that time could not offer any antibiotics nor other modern cures. Human health depended mostly on being able bodied. Regular physical exercises were regarded as a prime method of prevention and treatment of many illnesses.

From his parents Pilates learnt how to run sport activities and incorporate physical exercises in the healing process to stimulate it.

In the 19th century there were two main gymnastic systems. The first one was developed by the German Friedrich Jahn. His system derived from ancient Greek gymnastics and was mostly focused on improvement of strength and fitness, which, according to Jahn, were directly connected with well being. The second system, created by the Swede Per Henrik Ling, emphasized rhythm and fluidity of movements. The purpose of these exercises was to

improve the endurance, strength and flexibility of muscles and joints, thereby improving the efficiency of the circulatory system. In Ling' exercise system it was breathing and movement coordination as well as conscious body control during practising were emphasised (Latey 2001). In his early youth J. Pilates gymnastic systems and some common elements can be found in his later invented system of fitness exercises. Since childhood, Pilates was dedicated to practising various physical exercises and developed his interest in human anatomy. As a role model, Pilates took the antic model of beauty, based on the harmonious development of body, mind and spirit. By practising reasonable and balanced sports Pilates became a perfect model for anatomy charts (Mętel & Milert, 2007).

As a young man, Pilates ran many sport activities, e.g. diving and skiing. He was interested in other gymnastic systems (e.g. Yoga) and martial arts (karate). In 1912 he moved to England, earning a living through boxing and as a self-defence trainer. During the World War I he was interned in a prison camp on the Isle of Man, where he organized conditioning exercises for fellow prisoners. It was during this period this Pilates formed his idea on health and healthy lifestyle. Pilates believed that the only way to health is to keep the balance of body and mind, whilst the modern, sedentary lifestyle, bad posture and inefficient breathing were the roots of poor health. Pilates dubbed this philosophy "Contrology", as described in 1934 in his book "Your Health".

Unable to keep practising floor exercises with his fellow camp interns, Pilates used bed springs in resistance exercises, whereby the war wounded could regain their health and fitness while still bed-bound (Sparrowe, 1994, as cited in Latey, 2001). The apparatus Pilates designed during this time served as forerunners of the exercise machines such as „Universal Reformer" and „Cadillac" (Trapeze table); spring-based equipment used in Pilates' exercise method.

Pilates returned to Germany after World War I, but in 1926 emigrated to the USA. In New York, together with his wife Clara, he opened his exercise studio. His clients were mostly dancers, with boxers and gymnasts also embracing his method. One of the reasons the method was enthusiastically welcomed by dancers was its similarity to dance in its pursuit of extreme range of movement with precision and control; something a dancer is always attempting to achieve (Latey, 2002). Pilates taught mat and apparatus classes, which required high physical fitness from trainees (McNeill, 2011). In his second book, "Return to Life Through Contrology" (1945), he included selected exercises to follow and practise at home and the development of his philosophy (Latey, 2001). By the time of his death Pilates had extended his system of fitness exercises, describing the principles of correct performance. Pilates stated that his physical exercises could prevent coronary heart disease, increase muscle power and reduce the risk of respiratory ailments. He claimed the efficacy of his method to be scientifically proven, but at the time no such investigation was performed (Lange et al., 2000).

Nowadays, many new Pilates exercises are created based on the elementary ones. They are modified and adapted to various levels of physical fitness, and to the health and age of the practitioner – including those with trauma and elite athletes. In ''Traditional'' or ''Repertory'' Pilates, the exercises are vigorous with a fast, dynamic rhythm and even with high level of concentration are not easy to perform properly. They rely on the client having a fairly healthy body with good level of flexibility and to achieve some of the desired positions or range of motion, some muscle groups are obliged to work very hard. This fact contradicts Joseph Pilates' belief in working all the muscles of the body evenly. However, Pilates' ability to keep the rest of an injured body strong and flexible, while allowing the injured body part to heal enables the client to return to work almost as soon as the injury is

repaired. This method of kinesitherapy remains highly relevant today and can be applied to people of all fitness levels (Lately, 2002).

Nowadays, applied Pilates based exercises have been influenced by other body-mind methods and improved by an improved understanding of the human body, new perspectives on illness, advances in medical treatment, new understandings in stress management, developments in psychology and teaching skills. We also support the statement of Lately (Lately, 2002) that updating the principles of the Pilates method has given physiotherapy a new direction, and influenced exercise prescription in many body work fields, including sports medicine. We mainly concentrate on the prevention of injury caused by muscle imbalances and post-acute rehabilitation.

3. Methodology and equipment in Pilates' system

Pilates' exercise system can be divided into two categories: floor mat exercises and professional Pilates' devices. Originally, J. Pilates invented a system of stretching and strengthening mat exercises. Later this was extended to include exercises designed using specially designed apparatuses, e.g. Universal Reformer, Cadillac (Trapeze Table), Wunda (Combo) Chair.

The basis of the Pilates system are mat exercises. Postural muscles are mainly strengthened and stretched in low positions, using gravity and the exercised parts of the body. Balanced development of these muscles promotes proper body posture during various activities of daily living and decreases the effects of long-lasting burden, caused by practicing diverse sport disciplines. This makes the Pilates method similar to spine stabilization exercises. It assumes that weakness or fatigue of postural muscles can lead to disturbances of stability in the lumbar spine, which in turn can lead to strain injuries and chronic back pain. A critically important element of this type of training is conscious activation of the profound muscles of abdomen - transversus abdominis (TrA) and pelvic floor muscles (PV), which should fire first for pre-movement stability, and recovering elasticity and eccentric work of superficial muscles.

Exercises on professional Pilates' devices are mainly resistance exercise performed with the aid of springs and pulleys, but also stress relief of certain parts of the body can be achieved. The machines can be customized to the needs of the practitioner. The resistance during the exercise allows movement to be isolated and performed in the proper plane. Additional resistance prevents automatic movements being responsible for injuries. The exercises using professional Pilates' devices can be performed in post-acute state of sports injuries.

Fig. 1. Multidimensional exercise with Pilates circle

Pilates method also utilises small equipment (balls, foam rollers, Pilates circle, balance boards, Thera-bands etc.). They can be used in intralimb and interlimb coordination exercises, or as an element making exercises more attractive. They can also help transferring the learnt exercises to the movement required to run particular sport activities. (e.g. catching or kicking the ball).

In physiotherapy praxis Pilates based exercises are also performed with a gymnastic stick, a gym ladder and a stool. Pilates based exercises using a Swiss ball are also very popular, as is sensoric massage with this tool.

Fig. 2. Sensoric massage with Swiss ball

Exercises are performed from low (lying prone, supine, side-lying, quadriped, sitting) medium and high (kneeling, standing) postures. Low postures ensure better stability during the exercises, used particularly at the early stage of movement learning. Such positions facilitate proper performance of complex movements of upper and lower limbs, aiding concentration on other aspects of exercises (e.g. breathing, precision, flow). In case of complaint such as after injuries or with chronic low back pain, low position stabilisation of the trunk prevents additional unwanted movements that could cause more pain during exercising. For this reason low positions are more often used in early stages of after-injury rehabilitation excluding exercises exerting long lever on the spine. The upper positions can be used at the later stages of rehabilitation. Regardless of the exercise type and position, the movements are performed slowly and deliberately, beginning by correcting the starting position using physical or verbal instructions.

The number of repetitions is usually limited to 5-10. Pilates claimed that the lesser the number of repetitions of the movement performed properly the better the therapeutic effect was. Excessive number of repetitions performed without concentration and awarness can be harmful and lead to injuries. From approximately 500 mat or device exercises that have been developed in Modern Pilates the training programs should be tailored to the practitioner on an individual basis, taking into account his movement abilities and needs (elasticity of tissues, muscle strength and endurance, coordination and concentration ability). The best results can be achieved when practicing one-on-one or in small groups.

The implementation of this method for sports training should start with introducing the so-called pre-Pilates exercises, which allows a moderate degree of difficulty to implement all the principles of this technique from the three-dimensional breathing, slowly adding body alignment, concentration, control, stamina and fluency in performing movement. Moreover,

in modern Pilates based exercise it is not recommended to start each session with an exercise called "The Hundred", as it used to be in traditional Pilates method. According to Lately (Lateley, 2002) this exercise is particularly arduous as an initial exercise, might be extremely dangerous for someone new to the method, and even under supervision can result in severe injury. The authors concur with Lately on this issue.

Fig. 3. Postural alignment in standing

Fig. 4. Stability and endurance training: core muscle activation with limbs exercises

4. Body-mind exercise system

The purpose of the system of fitness exercises developed by Pilates is to develop harmony of body, mind and spirit by improving muscle strength and increasing the elasticity of active movement structures. The movements are carried out slowly and fluently with focused attention. These exercises are referred to as a "body-mind exercise system". Other such systems include also Yoga, Tai Chi and Feldenkreis' method.

"Body-mind exercises" is not the name of the exercise, but rather a description of how an exercise should be performed. Their common features are: mind control during exercises, relaxation of muscles and joints not involved in exercise movement, and maintaining muscles' physiological elasticity, with movement starting from body centre.

Understanding one's individual optimal postural alignment (neutral posture) will allow economy of movement, a natural flow of compensatory patterns, so that no muscle is

overworked or misused, without aiming for perfect symmetry. Pilates explained the balance of body and mind as the conscious control of all muscular movements of the body. It is the correct utilisation and application of the leverage principles afforded by the bones comprising the skeletal framework of the body, a complete knowledge of the mechanism of the body, and a full understanding of the principles of equilibrium and gravity as applied to the movements of the body in motion, at rest and sleep. Concentration and awareness is one of the fundamental principles of Pilates' system. It determines movement in a particular muscle group. It is very important, especially when other sectors of locomotors apparatus do not act properly or are not in natural alignment because of trauma or sport injury. That is why Pilates' system is nowadays recognized as a relatively safe alternative for intensive aerobic or weight bearing exercises. (Latey, 2001, as cited in Latey, 2002).

Awareness of the performed movement improves its efficiency and quality of movements. According to the original assumptions of the Pilates' system it requires at least an elementary knowledge of biomechanics and functional anatomy by the practitioner. It facilitates the process of learning new movement patterns, especially those to be transferred into functional tasks such as walking, reaching, lifting and other daily living or sport activities (Lange et al., 2000).

Focusing on the therapeutic movement, particularly in the case of sport injuries helps to avoid errors in repeating the exercises without therapeutic supervision. Proper learning of movement can be also achieved with the help of hands-on guiding, assisting correct movement (touch can improve muscle engagement and relaxation). Verbal cues also play a very important role in increasing awareness of the therapeutic movement being performed and learnt. This applies particularly in the case of a limited amount of information such as typically used with elderly or stroke patients (Lange et al., 2000; Latey, 2000). Verbal cues of the Pilates based exercise instructor as well as his tactile stimulation (hands-on) aim to motivate the exercisers to increase the focus on how to perform movement and maintain the desired body position, so that sensorimotor integration is stimulated. Moreover, connecting the mind and body requires the exercising person to tune into their bodily sensory systems.

Fig. 5. "Hands on" for body alignment execution

Touch can improve muscle recruitment, a client's awareness and also introduce better body biomechanics and relaxation. Awareness of the sensations, touching the muscles and joints

helps to focus concentration. Awareness of the body also assists in reducing overwork, strain and tension. Sportsmen particularly need awareness of their body, particularly the muscular sensations, so as to direct mental and physical efforts efficiently. Attending to the feedback from the proprioceptor system makes the individual aware of what is being done. Precision assists coordination; this is the practical application of focused awareness.

Fig. 6. Manual stimulus for increasing body awareness and desired muscle recruitment

5. "Powerhouse" – The strong core

Popular weight lifting in a gym studio typically focuses on improving muscle strength by shortening the muscles; the complex role of the supporting muscles is ignored. However, as the body lengthens, the diagonally opposed supporting muscles also have to work well. Stretching the muscles is an important part of sport training and in order to regain muscle balance, with the muscles lengthening and working at the same time, eccentric muscle contractures with proper support from stabilizing deep muscles and the body centre is needed.

Major emphasis in the Pilates concept should be placed upon the muscles forming 'powerhouse'- the body centre. Joseph Pilates himself never set down in writing what the exact parameters of the powerhouse were and there does not seem to be exact agreement amongst the master teachers of Pilates today. In a recent legal decision, the ability to trademark the name Pilates, and consequently the sole right of certification of Pilates instructors was lost. This means that there is no longer one certifying or governing body that determines exactly what the Pilates method is or is not. As a result, the Pilates based exercise, along with the underlying biomechanical basis, has been diverging greatly in recent years. There are now many techniques within the Pilates world, some adhering strictly to the system of exercises developed by Joseph Pilates, and others that are incorporating changes into this system.

The powerhouse is the core centre of the body from which peripheral muscle actions are carried out. The idea of centring is to create not only a strong structural powerhouse, but also a flexible one. Indeed, Joseph Pilates had the following maxim on his business card: ''A man is only as old as his spine is inflexible''. Profound muscle strengthening is a very important supplementation for training in various sports disciplines where big, superficial

muscle groups are mainly reinforced. Skipping profound muscles in strength training leads to imbalance, which increases the risk of trauma, and often is the reason for serious sport injury. It is suggested that treatment of muscle imbalances should start with exercises that isolate specific core muscles and then progress into functional activities or complex sports movements where these muscle should act in synergy to stabilize the lumbo-pelvic region.

Pilates method of body conditioning may be generalized to have three major effects upon the powerhouse. First, Pilates affects the posture of the pelvis, which results in postural changes to the lumbar spine. Second, it works directly upon the musculoskeletal structure of the spine (the lumbar spine in particular) by strengthening, stretching, and lengthening the spine. Third, Pilates affects the structural integrity or tone of the abdomino-pelvic cavity as a whole. The posture of the pelvis largely determines the posture of the spine. The spine sits upon the base of the sacrum; therefore, any change in the sagittal posture of the pelvis will change the level of the base of the sacrum. The level of the base of the sacrum will in turn affect the curve of the lumbar spine. However, once the base of the sacrum is uneven to any degree, the spine must have a curve in it to compensate. This curve is necessary to eventually create a level base for the head to sit upon. This righting mechanism to create a level base for the head is necessary to place the eyes and the labyrinthine receptors of the inner ear on a level plane, this being necessary for proper static and dynamic proprioception of our body.

Fig. 7. Execution of strong core with body alignment before and during movement

One of the major emphases of Pilates is to address the posture of the pelvis by addressing the musculature of the pelvis. Pilates further corrects this imbalance by placing a strong emphasis on stretching the low back musculature. In this manner, Pilates aims to create a neutral pelvis, and thereby create a healthy lumbar lordosis. (Muscolino& Cipriani, 2004 as cited in Selby, 2002; Siler, 2000; Winsor, 1999).

6. Breathing in Pilates

Body posture has an impact on the functioning of the entire human organism. There are reasons to believe that correct posture is a prerequisite for correct breathing patterns (Fiz & Gnitecki, 2008). Deficient respiratory capacity reduces the amount of oxygen delivered to body cells, which hampers both physical and intellectual performance. Symptoms of oxygen

deficiency include headache, vertigo, lack of appetite as well as concentration and memory malfunctions. Lower oxygen levels have a negative impact on muscles, which are likely to work deficiently under such circumstances and tire faster, which can lead to general fatigue and listlessness. The body tries to compensate for the oxygen loss, involving additional breathing muscles in the respiratory process, which then requires higher energy consumption and reduces its efficiency. The entire body is involved in breathing. During respiration, the functioning of the breathing muscles changes the dimensions of the chest. Shoulders and particular backbone sections are also part of the breathing cycle. Any immobilization, disfigurement, pain, lesions or developmental defects of the chest, as well as breathing muscles palsy can have important consequences for mobility and thus reduce the lungs' ventilation range. It needs to be stressed that most pathological processes, not only such severe ones as pneumonia, bronchitis, chronic obstructive pulmonary disease and heart failure, but also those of lesser clinical importance, including meteorism, intercostal nerve pains, or shoulder neuralgia clearly change the breathing mechanics (Dyszkiewicz et al., 2003). Changes in posture and its incorrect models related to the synchronized functioning of the muscles of the neck, upper body, abdomen, shoulders and pelvis are crucial for breathing (and in consequence for chest mobility). Other remote factors, seemingly unrelated to chest biomechanics, include the impairment of the motoric function of the lower extremities and the backbone, with a modification of the movement patterns. Research carried out by Szczygieł (Szczygieł et al., 2010) on healthy people indicated that even momentary slightly forced posture distortions can have a strong impact on breathing parameters. The research was an attempt to specify the plane in which posture distortions most severely influence the functioning of the respiratory system. Results show that the body arrangement most likely to lead to a reduction of the VC is posture with counter-lateral head, shoulder and hip rotation. The position responsible for the greatest reduction of other factors (VC- Vital Capacity, FEV1- Forced Expiratory Volume in One Second, MEF75- Maximal Expiratory Flow at 75% of Force Vital Capacity, MEF50- Maximal Expiratory Flow at 50% of Force Vital Capacity, MEF25- Maximal Expiratory Flow at 25% of Force Vital Capacity and PEF- Peak Expiratory Flow) was frontal stooping. Positions with sagittal plane changes had the smallest effect on breathing mechanics. Therefore, optimum conditions for breathing require an axial arrangement of particular body segments.

According to Joseph Pilates "breathing is the principal art of life. Our life depends on it. Millions have never learned the art of correct breathing." From the day we were born, we have been breathing unconsciously, without worrying if our breathing is correct.

Correct coordination of breathing with a particular exercise is the rule of thumb applied while teaching the Pilates method. Correct breathing improves blood oxidation, brain function and movement control.

In Pilates, costal-diaphragmatic breathing is used, accentuating protracted exhalation with simultaneous drawing of the navel closer to the spine. While inhaling, the chest expands in three planes, and while exhaling, abdominal oblique muscles become involved. This is called "lateral breathing". Lateral breathing causes the chest to expand, and the air penetrates the back and lateral parts of the chest. This stimulates intercostal muscles, allowing them to expand and making the upper body more agile.

Normally, our breath is too shallow, and stress compounds the problem, making our breathing faster and even shallower (Rakowska, 1990). Women tend to breathe with the tip or the upper part of the lungs, raising their shoulders and the upper body. Men are more likely to breathe using their diaphragm, making their abdomen expand with every breath.

An important element of the Pilates method is being able to expand the ribs laterally, which helps you to draw in your abdomen, at the same time relaxing the upper body. While accentuating the axial arrangement of the body, the method ensures the optimum conditions for the respiratory system and helps to stabilize the backbone. This is of crucial importance for people practicing sports, who are likely to adopt forced body posture. This increases the risk of overload changes in the body, and hampers the functioning of the respiratory system (Bliss et al., 2005). Unlike other exercises based on passive breathing, the Pilates breathing method involves active respiration. It activates outer intercostal muscles and abdominal muscles. The most efficient muscle participating in breathing out, and thus in increasing the pressure in the abdominal cavity is the transverse abdominal muscle (Zocchi et al., 1993).
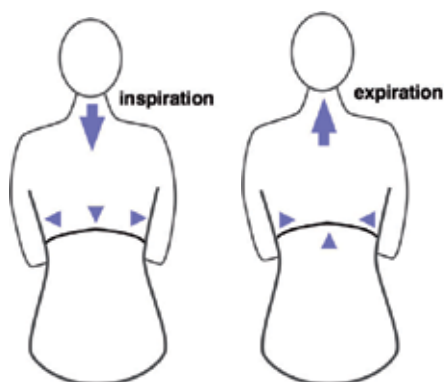

Fig. 8. Pilates method breathing

Deep breathing is an important element of exercise optimisation. The fact that the basic movements in the exercise are made while breathing out, sets the method apart from others. In addition, prolonging exhalation helps to counteract the occurrence of undesirable tension (protracted additional respiratory muscle cramps) and ensures greater stabilization in the most difficult phases of the exercise. While considering reports on the effectiveness of the method, an issue that must be mentioned is the case of diaphragm rupture while breathing deeply using the Pilates method (Yang et al., 2010). Cases of such spontaneous diaphragm rupture, without prior antecedents in patients, are extremely rare. They may occur e.g. with abrupt coughing. They account for ca. 1% of similar diaphragm problems (Gupta et al., 2005). The causes are related to a rapid increase in abdominal pressure. Weighted against the benefits of the method, such cases seem to be of marginal importance.

Meanwhile, both scientific magazines and popular science publications frequently look at bronchial asthma in athletes. Statistics regarding asthma indicate that it occurs more frequently in athletes than in the general population (Weiler et al., 1998). This topic is quite controversial. On the one hand, it is suggested that prolonged intensive training may lead to the development of bronchial asthma (Weiler et al., 1998) and (Helenius et al., 1998). At the same time, the issue of the use of medicines by asthmatic athletes in the context of pharmacological doping is raised. In light of the above, the Pilates breathing method may be a valuable element of physical training. There is no doubt that optimum breathing allows for longer and more intensive training without running the risk of excess fatigue. The asthma debate is exhaustively discussed in an article by Wroński. The author believes that Pilates breathing exercises can be used to complement drug therapy in children and young people with bronchial asthma (Wroński& Nowak ,2008).

7. Muscle imbalances and Pilates practising by sportsman

The muscle balance in any joint is determined by the ratio of torques between agonist and antagonist muscle groups. The coordination of movements depends on the coordinated actions of muscles on the opposite sides of a joint. This prevents injuries of muscles, tendons, and joint elements during fast movements. The deficiency of strength in one muscle or muscle group can lead to imbalance in the joint actions, which in turn can cause traumas of muscles and joints due to the anomalous distribution of mechanical stresses and strains.(Pontaga, 2003) The terms muscle balance or imbalance do not refer to equal or unequal torque values, but to the balance between the torque ratios of agonistic and antagonistic muscle groups (Gioftsidou et al., 2008). There is a failure of the agonist-antagonist relationship and to their balance between the torque ratios. Muscle imbalances resulting in overloaded movement apparatus can result from frequent repetition of movement patterns specific to the sport's discipline. Static overload refers to the maintenance of posture of the body for a longer period of time such as the trunk flexion in cycling, downhill, speed skating, alpine skiing. Dynamic overload can result from forced movement which is typical of the discipline, leading to the development of muscle imbalances. Because the human physiological motor activities take place in the area of the force of gravity to align the existing muscle imbalances Pilates method offers exercises in various starting positions with multidimensional movements in which skeletal muscle are activated in a manner conducive not only to development of their strength but also endurance, flexibility and neuromuscular coordination. Therefore, this system, with appropriate supervision and adjustment of the degree of difficulty of the exercises to be performed without losing the flow of movement and dynamic stabilization of the deep muscle system appears to be appropriate in the eradication of unwanted muscle imbalances. Recent studies hypothesized a common muscle imbalance pattern of weakness in gluteus medius and tightness of the iliotibial band in chronic musculoskeletal pain syndromes in the lumbar-pelvic-hip area such as chronic low back pain. Investigators categorized muscles, based on their primary functions, as "phasic" or "postural", and indicated that in response to dysfunction or overuse, the phasic muscles tend to be inhibited or weakened; while the postural muscles tend to develop higher tone and ultimately shorten. [Jull&Janda, 1987, Janda 1992,1993 as cited in Arab&Nourbakhsh, 2010] Tight muscles are activated more readily during movement patterns and become overactive. Once the phasic and postural muscles are no longer activated in balance, they are unable to protect the body's joints from the effects of gravity.(Page, 2005)

In this classification, the gluteus medius; primary muscle for hip abduction, is categorized as phasic and the tensor fasciae latae and iliotibial band the synergist muscle, is categorized as postural muscle. It is speculated that the iliotibial band shortness in patients with low back pain is a compensatory mechanism following hip abductor weakness. (Jull&Janda, 1987 as cited in Arab&Nourbakhsh, 2010). Controversial results have been reported in the studies which examined the relationship between hip abductor strength and the iliotibial band syndrome in runners. Some researchers concluded after conducting a study with runners with the iliotibial band problems that strengthening of the hip abductors has been recommended for symptom improvement in subjects with the iliotibial band dysfunction (Fredericson&Weir, 2006, MacMahon et al. 2000 as cited in Arab&Nourbakhsh, 2010) while others in contrast (Grau et al., 2008 as cited in Arab&Nourbakhsh, 2010) concluded that weakness of hip abductors does not seem to play a role in the etiology of the iliotibial band

syndrome in runners. Some reports have also demonstrated an association between LBP and hip abductor muscle weakness.

Considering the above reports and the promising results of research on the effects of Pilates exercises to reduce chronic low back pain seems to be a reasonable recommendation to use Pilates techniques for athletes with low back pain. Note, however, that the scientific evidence demonstrating the efficacy of this method in the treatment of back pain are incomplete. Modern group sports such as soccer is marked by a faster speed of play than in the past, and this inevitably translates into an increase in the intensity of practice sessions. This may justify an increase in the percentage of muscle strains occurring during practice.

We suggest an assessment whether it is observed that a player's muscle imbalances is only an adaptive response to the athlete's body to the demands of the discipline and is tolerated by him, or results of biomechanical changes in articular' trajectory caused by the development of the areas in the body with reduced resistance to overload (locus minores resistanci). It is worth to check if after previous trauma protective mechanisms of the damaged area have extinguished and not result in persistently maintaining the stiffness and the development of undesirable tissue compensation. Because such mechanism may change a whole myofascial chain and neuromuscular coordination it is possible that pain may also occurs in a place located far away from the primary pathology. Also, persistent pain or fear of its occurrence may lead to changes in motor programs resulting in the development of muscle imbalance syndromes, particularly in muscle tone and their flexibility. For example, examining the strength and elasticity of muscles of lower limbs, often stated gluteal muscles weakness and their function of the hip' extension is overtaken by hamstring muscles which results in excessive tension and shortening. In turn, the weakening of the abductors and external hips' rotators, usually cause the hypertone in the area of iliotibial band. Certain muscles in the human body are especially subjected to strain traumas, for example, the posterior muscle group of thigh. The simultaneous extension of the hip joint and flexion of the knee stretch the posterior muscle group of thigh and, if the movements are very fast and forceful (sprinting, bobsledding, jumping, and other athletic sports), these muscles can be injured.(Pontaga, 2003). In the study analysing muscle injuries suffered in Italian major-league soccer team during the period 1995–2000 it was found that among the overall injuries, muscle accidents were the most frequent, representing 30% (103 cases), followed by contusions (28%), sprains (17%) and tendinopathies (9%). Proposed causes of muscle strains were: lack of training, insufficient warming up, excessive fatigue, strength imbalances, flexibility deficiencies, muscle weakness and insufficient rehabilitation. (Volpi et al., 2004)

A study of the role of eccentric muscular work in the development of muscle strains found a residual eccentric-strength deficit in sprinters with a history of hamstring injury compared to runners with no injuries. (Jonhagen et al. 1994 as cited in Volpi et al., 2004)

Factors increasing the risk of developing acute muscle injuries, include decreased muscle strength, mainly eccentric muscle strength and muscle imbalance (decreased eccentric work of antagonist to concentric work of agonist (Schwellnus, 2004 as cited in Gioftsidou et al., 2008). In running and kicking there is an important eccentric activation of thigh muscles. When decelerating in running, the hamstrings act eccentrically to slow extension at the knee, and the quadriceps act eccentrically to control the lowering of body weight when athletes approach a stop. In kicking muscles, activation follows "the soccer paradox" meaning that

flexor activity is dominant during extension and extensor activity dominates during flexion. Quadriceps activity is greatest during the loading phase when it is antagonistic to the movement and hamstrings are most active during the forward swing when they are antagonistic to the movement (Volpi et al., 2004).

There is no knee extensor activity immediately prior to ball contact. The eccentric activation of knee flexors reduces the angular velocity at the knee. Such a mechanism protects the knee from hyperextension, but it is extremely stressful for hamstrings. (Robertson&Moshe,1985 as cited in Volpi et al., 2004). Electromyography studies have confirmed hamstring peak activity near the time of ball contact. (Wahrenberg et al., 1978 as cited in Volpi et al., 2004)

Recuperation of flexibility (Kujala et al., 1997 as cited in Volpi et al., 2004), amelioration of muscle strength (Worrell, 1994 as cited in Volpi et al., 2004) and correction of muscle imbalances (Welsch, 1988 as cited in Volpi et al., 2004) represented the primary goals in muscle-strain rehabilitation. It is important to underline that prevention of recurrences, not speed of recovery, is the primary goal in muscle- strain rehabilitation. It is suggested that athletes who have suffered a muscle injury must never give up eccentric work for the rest of their careers (Volpi et al., 2004).

As Pilates method offers different eccentric exercises for trunk and leg muscle e.g. rolling the spine in different position with or without using the equipment or tools (Swiss ball, Thera-band) in our opinion this method can be suggested as a complementary sport training. Elasticity of the leg muscles, especially hamstrings, iliopsoas, quadriceps, hip rotators, plays very important role in maintaining the proper body posture both in rest and in motion. Weakness and contractions of this muscles lead to improper pelvic alignment in standing position, and consequently in spine and total body. In athletes practicing e.g. cycling, leg muscles work intensively in contracting position, while complementary Pilates training provides the eccentric exercises.

It is indicated that fatigue of the shoulder complex muscles, which may occur in overhead athletes or workers with regular exposure to overhead work, is proposed to be a neuromuscular alteration that contributes to shoulder pathology. Acute muscle fatigue may create short-term muscle force imbalances and disrupt normal synergistic activation of the muscles at the shoulder region. These activation imbalances may in turn result in the scapulothoracic kinematic alterations. Acute fatigue of the serratus anterior may be particularly problematic as this muscle has been noted to be the primary contributor to both normal three-dimensional scapula rotations and scapulothoracic stability. In addition, the serratus anterior is considered to be one component of several muscle synergies at the shoulder complex and its fatigue may alter the balance of these synergies. (Szucs et al., 2009)

Precise control of movement at the shoulder complex during upper extremity use is considered critical to the health of the shoulder region. In Pilates based exercise it is strongly recommended to keep scapulas in position of "soft V" at starting positions so the intention is to voluntarily "fix" the scapula in the position of posterial depression. It is generally accepted that serratus anterior and the trapezius (upper and lower) should work with proper timing to provide normal, three-phases humero-scapular rhythm. In first phase upper trapezius should be relaxed and scapula fixation should be provide by lower trapezius. In second phase scapula external rotation is achieved by the activation of serratus anterior and at last upper trapezius with other scapula's elevators need to fire to lift the scapula up. (Horst, 2010)

Fig. 9. Push-up exercise on Swiss ball, starting position without "locked elbows"

Fig. 10. Push-up exercise on Swiss ball , movement with activation of strong core

It was found that the upper trapezius and serratus anterior are under differing cortical control mechanisms, with trapezius but not serratus demonstrating both contralateral and ipsilateral responses to cortical magnetic stimulation. Increased upper trapezius tone and constant readiness to activate disturbs the humero-scapular rhythm and is also an indication of fatigue or compensation of serratus anterior. As muscle fatigue can be a central phenomenon as well as a peripheral phenomenon, the upper trapezius may have been recruited differently during or after the task. (Alexander et al., 2007, Hunter et al., 2006 as cited in Szucs et al., 2009) It is ball, important that performing Pilates Push-up, which is an exercise in close kinematic chain, serratus anterior muscle should be activated rather than a dominant role of upper trapezius muscle which can be achieved by the alignment of spine, unlocked elbow joints, lower – costal breathing and touching stimulus of an instructor during execution of an exercise.

The Push-up exercise has been recommended as a rehabilitative exercise for individuals with shoulder pathology because it strongly activates serratus anterior while minimizing upper trapezius co-activation (Ekstrom et al., 2005, Lear&Gross 1998, Ludewig et al., 2004 as cited in Szucs et al., 2009). Using this task as a rehabilitative exercise may be too strenuous for most patients, but it may have potential as an assessment tool to help determine the success of serratus anterior strengthening and endurance training or the readiness for return to high demand overhead work. (Szucs et al., 2009)

The results of the controlled study with 19 participants show that a 12-week long Pilates training program was effective in improving core strength and posture (exercising subjects showed smaller static thoracic kyphosis during quiet standing) as well as certain aspects of

scapula and upper trunk displacement during a shoulder flexion task. As deficits in neck–shoulder biomechanics have previously been associated with symptoms in the neck–shoulder region, these results could support the use of the Pilates method in the prevention of neck–shoulder disorders.(Emery K., 2010)

In our opinion Pilates can be recommended as a complementary exercising method for many sports discipline to reduce muscle imbalances, increase body awareness, sensomotoric coordination, economical breathing, body aligment, precision and fluency in movement however deep understanding and proper implementation in the practise the main Pilates principles under close supervision of certified and experienced Pilates instructor is needed.

8. Pilates method in evidence based medicine

Current state of neurophysiological and biomechanical knowledge has caused that classical Pilates technique evaluated into Pilates based exercises which are recommended for use by people of varying age and physical proficiency. We conducted database searches (SPRINGER LINK, SCIENCE DIRECT, EBSCO HEALTH SOURCE, MEDLINE, PUBMED, COCHRANE, EMBASE) up to the June 2011 to investigate the application and effectiveness of this method using the key word "Pilates".

8.1 Pilates based exercise programs effects in different age population

Rogers and Gibson explains that studies concerning Pilates method primary concentrated on its effects in rehabilitation or to increase specific component of movement – such as tennis serve velocity (Sewright, 2004 as cited in Rogers&Gibson, 2009), leaping ability (Hutchinson 1998 as cited in Rogers&Gibson, 2009) or muscular strength and endurance in specific population.

In a controlled experiment of Rogers and Gibson with healthy, young objects (n=28) in which novice practitioners (n=9) participated 3–times a week, 1-hour session in 8-week traditional mat Pilates program, it was concluded that in experimental group body composition, muscle endurance and flexibility improved compared to participants of university wellness centre forming the control group. (Rogers&Gibson, 2009)

In the controlled study of Siqueira Rodriges with 52 elderly females, 27 persons formed the Pilates group participating in Pilates exercises twice a week for eight weeks. The researchers concluded that the practice of the Pilates method can improve the functional autonomy and static balance of elderly individuals (Siqueira Rodrigues et al., 2010)

In pilot study with 7 older adults who participated in a novel Pilates inspired exercise program specifically designed to improve balance in an upright position, referred to as postural stability it was indicated that the effect in relation to static balance can be a consequence of postural stability, reached by the harmony of opposing muscle groups. (Kaesler et al., 2007)

Siqueira Rodrigues introduce Pilates as a method consisting of a physical exercise that uses resources such as gravity and the resistance of springs, either to resist or assist movement execution (Gagnon, 2005 as cited Siqueira Rodrigues et al., 2010). It aims to prevent automatic movements, which are responsible for unwanted muscle activity that can cause injuries (Petrofsky et al., 2005 as cited in Siqueira Rodrigues et al., 2010). Siqueira Rodrigues also indicates that Pilates method has been studied in relation to its positive effects on posture (Blum, 2002 as cited in Siqueira Rodrigues et al., 2010), pain control (Gladwell et al.,

2006 as cited in Siqueira Rodrigues et al., 2010), improved muscle strength (Schroeder et al., 2002 as cited in Siqueira Rodrigues et al., 2010), flexibility (Segal et al., 2004 as cited in Siqueira Rodrigues et al., 2010), and motor skills (Lange et al., 2000 as cited in Siqueira Rodrigues et al., 2010).

The positive influence of Pilates exercise on dynamic balance and personal autonomy in healthy adults was assessed in the controlled study with the 17 participants of 10 Pilates-based exercise sessions performed on a Reformer and including a tall arm series, open leg rocker, leg press series and tall kneel arm series. After the Pilates training significant change in dynamic balance was found in the Functional Reach Test, while control, non-exercising group (n=17) demonstrated no significant change. These findings suggest that Pilates-based exercise may be a useful tool for clinicians and trainers to incorporate with their patients and clients who are looking to improve their dynamic balance and also benefit athletes who are seeking small gains to improve performance through precise, controlled movements. (Johnson et al., 2007)

Some authors indicates that Pilates encouraged the importance of proprioceptive stimulation for motor learning improvement using the powerhouse exercise (transversus abdominus, obliques, and multifidi muscles) and repetition of correct movement to achieve the training standard, leading to a better motor performance and less risk of injuries. (Anderson & Spector, 2000 as cited in Siqueira Rodrigues et al., 2010)

An observational study was conducted to assess and compare the contraction of the transversus abdominis muscle among 36 healthy females (mean age 36.2) trained in Pilates, traditional abdominal curls and a control group. To indirectly measure contraction of the transversus abdominis muscle and to monitor lumbar–pelvic stability, a stabilizer pressure biofeedback unit (Chattanooga Group Inc.) was employed and a tester, blinded to group category, conducted the measurements. For the lumbar–pelvic stability test, only 5 (42%) Pilates group subjects passed this test, with all others failing this test, leaving 14% overall who were able to stabilize the lumbar–pelvic area. The authors concluded that females who train in Pilates may be better able to recruit and utilize their deep abdominal muscles and stabilize the pelvic area compared to those not trained in Pilates. (Herrington & Davies, 2005)

In the controlled, experiment with 34 pain-free health club members with no Pilates experience who were randomly assigned to an unsupervised twice weekly of eight weeks Pilates mat exercises or strength training it was concluded that transversus abdominis activation increased following a programme of unsupervised Pilates mat exercises that is practical and requires no special equipment, however, there was no change in abdominal muscle activation during functional postures. The researchers suggested that supervision of exercises and progression to more functional exercises may be required to increase functional abdominal activation. (Critchley et al., 2011)

Performing Pilates exercise might prove to be a useful means of increasing activity and thereby curbing the obesity epidemic of female teenagers. It was proven in a randomised, controlled study that 4 weeks long physical training with the Pilates technique lowered the BMI percentile of 10- to 12-year-old girls. (Jago et al., 2006)

8.2 Pilates method and low back pain

Two systematic reviews of all controlled clinical trials of Pilates to treat low back pain were recently conducted. In the most recent review the search strategy was filled up to May 2010

and generated a total of 199 references, of which 51 were considered potentially relevant. Study quality was assessed using the Oxford scale. Four eligible randomized controlled clinical trials (n ¼ 4) involving Pilates for the management of low back pain were included. They originated from the United Kingdom (Gladwell et al., 2006 as cited in Posadzki et al., 2010), the United States (Head et al., 2006 as cited in Posadzki et al., 2010), Italy (Rydeard et al., 2006 as cited in Posadzki et al., 2010) and Canada (Vad et al., 2007 as cited in Posadzki et al., 2010). Although some of the authors of the reviewed studies conclude that Pilates yielded better therapeutic results than usual or standard care, the findings of this review suggest that the evidence available for its clinical effectiveness is inconclusive. (Posadzki et al., 2011)

The second systematic review published this year with meta-analysis aimed to compare pain and disability in individuals with persistent nonspecific low back pain who were treated with Pilates exercises compared to minimal or other interventions based on 7 randomized controlled trials. In conclusion they stated that Pilates-based exercises are superior to minimal intervention for reduction of pain in individuals with nonspecific low back pain. However, Pilates-based exercises are no more effective than other forms of exercise to reduce pain. In addition, Pilates exercises are no more effective than minimal intervention or other exercise interventions to reduce disability related to chronic low back pain. (Lim at al., 2011)

These two systematic reviews show that the evidence base for Pilates method effectiveness in treatment of chronic low back pain remains scarce and therefore larger and better-designed clinical trials are needed.

8.3 Pilates based exercise in post-surgery rehabilitation

Pilates practice applied in post-surgery rehabilitation were found in conference review, preliminary report and case study article.

It possible to use different tools and special equipment when incorporating Pilates based exercise into treatment process. In the review which aims was to establish an evidence-based approach to the postoperative rehabilitation of the knee following anterior cruciate ligament reconstruction, arthroscopic meniscectomy and meniscal repair surgery exercises performed with the use of Pilates Reformer machine were investigated.

The authors emphasized that there has been a gradual move away from traditional methods towards accelerated rehabilitation programs for anterior cruciate ligament reconstruction following the observation that patients who had been noncompliant with traditional rehabilitation progressed more rapidly. (Decarlo et al., 1992, Shelbourne et al., 1990 as cited in Atkinson et al., 2010) They claim that accelerated rehabilitation programs, which aim to overcome the common post-surgical problems of prolonged knee stiffness, anterior knee pain, difficulty gaining full extension and delays in the strength recovery, maintaining knee stability may include following types of exercise: closed and open kinetic chain, eccentric, concentric, isometric, isokinetic, plyometric, sport-specific and Pilates method. The Pilates Reformer machine exercises allowing the patient to be positioned in such way as to help to remove gravity from the equation and other equipment exercise for core stability strength and co-ordination are included after the 4-week in post-operative anterior cruciate ligament reconstruction protocol. The author indicates that additional use of Pilates Reformer machines according to the principles of the Australian Physiotherapy and Pilates Institute may allow for earlier progressive load

bearing and introducing squatting or lunging activities in treatment process. The theory behind this approach is to introduce consistent motion and defined joint ranges early in the rehabilitation period, using zero-gravity spring-based resistance. This allows for exact functional patterns and muscle memory to be retrained and thus, when the patient is ready to weight bear into a squat or lunge, the motion has already been learned. Though there is currently little scientific data to support this new approach, it may shorten rehabilitation by as much as 4 weeks, with the largest effect seen within the first 2 months. The authors of the survey proposed at the 3-month post-operative review functional exercise for neuromuscular coordination and also Pilates exercises for core stability and strength with the application of all equipment. (Atkinson et al., 2010)

In a preliminary report with 38 participants Pilates method was introduced into modified exercises programme developed to account for the postoperative precautions and needs of total hip and knee arthroplasty. At 1 year follow up, review of patient charts and follow up telephone calls revealed; 25 patients were extremely satisfied and 13 were satisfied with their outcome and use of Pilates in their rehabilitation. From these observations of a small number of patients it was concluded that this technique can be utilized without early complications, however, further studies are necessary to confirm its utility and safety. (Levine et al., 2009)

Other report which documented the use of the Pilates method in medical rehabilitating of postsurgical patients and for recuperation of musculoskeletal condition was case study concerning treatment of scoliosis of adult woman who had progressive severe low back pain. She had worsened over the years after her surgery and had prevented her from activities such as carrying her son or equipment necessary for her job as a photographer. The patient was provided a series of Pilates exercises used to overcome her chronic habituation and muscle weakness. It was concluded that addition of Pilates based exercise to therapy can be useful to care for patients with chronic low back pain and deconditioning (Blum, 2002).

8.4 Pilates based exercise in specific disorder treatment

In a randomized clinical trial comparing pelvic floor muscle training to a Pilates exercise program for improving pelvic muscle strength 62 women with little or no pelvic floor dysfunction were randomized to Pilates or a pelvic floor muscle-training. The results of the study demonstrated only the feasibility of a Pilates exercise program for strengthening the pelvic floor muscles with the important note that these findings are only relevant to those women who can "find" their pelvic floor muscles however are encouraging and may eventually lead to widespread use of Pilates-based exercise programs to treat and prevent pelvic floor dysfunction. (Culligan et al., 2010)

In a randomised, controlled trail with 52 breast cancer patients and also in one pilot study of with 4 women who had undergone axillary dissection and radiation therapy for breast cancer it was concluded that Pilates exercises are safe and efficient for women with breast cancer but there is a need for further studies to confirm these statements. (Eyigor et al., 2010, Keays at al., 2008)

In a randomized, prospective, controlled, and single-blind trial with 55 participants the effects of Pilates on pain, functional status, and quality of life in patients with ankylosing spondylitis were investigated. Pilates exercise program of 1 h was given by a certified trainer to 30 participants of experimental group 3 times a week for 12 weeks. It was the

first clinical study designed to investigate the role of Pilates method in ankylosing spondylitis treatment with a conclusion that this exercise technique is as an effective and safe method to improve physical capacity in ankylosing spondylitis patients. (Altan et al., 2011)

9. Conclusion

Studies concerning effects of performing Pilates based exercise suggest its beneficial influence on body posture, pain control, muscle strength, endurance, flexibility, body composition, static balance, functional autonomy, motor skills and specific component of sport activities. There is an increasing number of scientific reports suggesting application of Pilates method into modern, mind-body post-operation rehabilitation treatment. Despite a lack of convincing evidence to date to prove its medical effectiveness, the results of reports are promising and we suggest further studies to be carried out using a more representative sample and a longer period of intervention, to more precisely evaluate the results of practising Pilates based exercises.

10. Acknowledgment

11. References

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Physical Management of Pain in Sport Injuries

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1. Introduction

The number of people both young and old engaging in sporting activities has increased in the recent times. Apart from the economic benefits of sports which drive youths to engage in competitive sports, adults and seniors are now aware of the health benefits of recreational sports. Inactivity has been linked to many chronic diseases including cardiovascular disease which is leading cause of death worldwide. Health educators are now encouraging the public to be involved in physical activities in order to promote their health. Unfortunately sports are associated with injuries whether it is for leisure or competition. Those who overdo or who are not properly trained are prone to sports injuries. Many sports injuries can be prevented if proper precautions are taken (Lachmann 1989).

If injuries are not properly managed, it could reduce the optimal performance or inability of an athlete to continue participation in sports. Nowadays many sports injuries can be treated effectively and most people who suffer injuries can return to a satisfying level of physical activity after an injury due to advancement in medical management. However, many athletes tend to ignore minor injuries or result into self-management. This always led to more damage to the body structures and makes the injury worse.

Majority of injuries sustained during sporting activities involve musculoskeletal system which include; bones, joints, tendons, ligaments and tendons (Ebnezar, 2003). The injury may be as a result of trauma from external force as it is in contact sports. This is direct trauma also known as macro trauma. Indirect trauma is due to pathology resulting from repeated sub maximal loading. Fracture of bones is less common but not unlikely (Kisner and Colby, 2007).

Signs and symptoms that follow injuries include; pain (from the chemicals released by damaged cells), swelling (from an influx of fluid into the damaged region), loss of function (because of increased swelling and pain), redness (from local vasodilation) and heat (from increased blood flow to the area), which are features of inflammatory reaction.

Pain is the major reasons why many people seek medical attention. International Association for the Study of Pain defined pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage (IASP, 1994). Pain experienced from soft tissue injuries is usually related to the extent and type of trauma sustained as well as to the structures involved and an individual's perception and expression of it (O'Sullivan and Schmitz, 1994). Pain and inflammation

continue into the sub-acute phase and may fade out in the chronic stage subsiding with healing in 1 to 3 months (Schnedler, 1990).

Management of soft tissues injury is patterned along with the phases of injury.

Inflammatory phase (acute): It can last up to 72 hours. Where there are musculotendinous injuries, there is myofilament reaction and peripheral muscle fiber contraction within the first two hours.

Regeneration and repair phase (sub-acute): This fibro-elastic and collagen-forming phase lasts from 48 hours up to 6 weeks. During this time structures are rebuilt and regeneration occurs. Fibroblasts begin to synthesize scar tissue. These cells produce type iii collagen, which appears in about four days, and is random and immature in its fiber organization. Capillary budding occurs, bringing nutrition to the area, and collagen cross-linking begins. As the process proceeds, the number of fibroblasts decreases as more collagen is laid down. This phase ends with the beginning of wound contracture and shortening of the margins of the injured area.

2. Remodeling phase (Chronic stage)

This phase lasts from 3 weeks to 12 months. There is evidence of cross-linking and shortening of the collagen fibers promote formation of a tight, strong scar. It is characterized by remodeling of collagen so as to increase the functional capabilities of the muscle, tendon, or other tissues. Final aggregation, orientation, and arrangement of collagen fibers occur during this phase (Kisner and Colby, 2007).

Sports injuries are usually treated with pharmacological and non-pharmacological methods. Non pharmacological methods involve conservative methods such as physical therapy and surgery.

Physical therapy is most essential in managing the majority of the soft tissue injuries. Physical therapy should commence early so as to speed up the healing of damaged tissues and to prevent complications that could develop during chronic stage. The athlete may return to full functional activities if the treatments commence early.

3. Cryotherapy

Cryotherapy also known as cold therapy has been reported to be one of the least expensive and most used therapies recommended in the immediate treatment of the skeletal muscle injury. Among chiropractic practitioners it is the most often utilized passive adjunctive therapy.

Cryotherapy is capable of reducing effects related to the damage process, such as pain, edema, haemorrhage and muscle spasm after soft tissue injuries. Although cryotherapy may not reduce edema once it is formed but when used immediately after injury, it can prevent formation of edema. Cold is capable of diminishing secondary hypoxic injury, so there is less free protein in the tissues decreasing the tissue oncotic pressure leading to tissue swelling by decreasing metabolism and lowering permeability rate (Enwemeka et al, 2002).

The mechanism of pain relief after application of ice is not clear. The prevailing theories such as decreased nerve transmission in pain fibres, reduction of the activity of free nerve endings, increase in the pain threshold, release of endorphins and cold sensations which over-ride the pain sensation are plausible reasons provided in the literature.

One of the physiological effects of ice is vasoconstriction. When the blood vessels narrow, the amount of blood delivered to the injured area is reduced thereby reducing bleeding during injuries. Muscles always respond to injury through spasm to protect itself and prevent further damage. Ice, is also beneficial in reducing muscle spasms (Chesterton et al, 2002).

There are several procedures of application of cryotherapy ranging from gel, spray, ice packs, and immersion. Among these ice packs are most popular and safe as it prevent frost bite because of the protection of body tissue by the plastic bag (Martinez et al, 1996).

3.1 Methods of application of cryotherapy

Ice packs: Ice in this method are crushed, shaved, or chipped and put in a plastic bag applied directly to the injured area. Several authors agree that some form of protection be used to prevent frostbite. Ice pack with temperature at 0 o C (32 o F) can be applied directly to the skin to maximize the effectiveness of the cold application.

Cold-gel packs: A gelatinous substance enclosed in a vinyl cover containing water, and antifreeze (such as salt).

Chemical cold packs: These consist of two chemical substances, one in a small vinyl bag within a larger bag. Squeezing the smaller bag until it ruptures and spills its contents into the larger causes a chemical reaction producing the cold. They are ideally utilized for emergency use.

Ice immersion: A container is filled with ice and water, and the body part is immersed in it. Immersion is recommended for extremities.

Ice massage: A cube of ice is rubbed over and around the underlying muscle fiber until numb.

Ice should be used for a period of 5 minutes if being used as first aid. Prolong period of application could cause blood vessels dilation resulting into increase in hemorrhage.

At chronic stage of injury, ice may be used for 10 minutes. An individual experiences cold-burning sensation-aches-numbness during the application of ice (Erith et al, 2002).

When an exercise or manual therapy is to be used for a patient, ice are usually applied to serve as local anesthesia to reduce pain.

4. Reduction of bleeding

By cooling the surface of the skin and the underlying tissues, ice causes the narrowing of blood vessels, a process known as vasoconstriction. This leads to a decrease in the amount of blood being delivered to the area and subsequently lessens the amount of swelling. After a number of minutes, the blood vessels dilate allowing blood to return to the area. This phase is followed by another period of vasoconstriction- this process of vasoconstriction followed by dilation is known as the Hunting Response.

Although blood still flows into the injured area the amount of swelling is significantly reduced if ice is not applied. Decrease in swelling allows more movement in the muscle and so lessens the functional loss associated with the injury (Eston and Peters, 1999). The swelling associated with the inflammatory response also causes a pressure increase in the tissue and this leads to the area becoming more painful. The effects of ice causing vasoconstriction after application led to decrease in pain. Equally the conduction velocity of the nerve is reduced, thereby limiting the pain transmission of the peripheral nerves (Goodall and Howatson, 2008).

5. Reduction of muscle spasm

By reducing the cells metabolic rate, ice reduces the cells oxygen requirements. Thus when blood flow has been limited by vasoconstriction then the risk of cell death due to oxygen demands (secondary cell necrosis) will be lessened.

6. Transcutaneous electrical nerve stimulation

Electrical currents are generated by stimulating the device of transcutaneous electrical nerve stimulation (TENS) and delivered it across the skin through electrodes Figure 1. TENS is a non-invasive treatment modality that involves the application of a low-voltage electrical current for pain relief. TENS is now a popular modality in the field of physical therapy and sport medicine for managing pain.

There are much available clinical evidence concerning the use of TENS for various types of conditions relating to musculoskeletal disorders and other type of pain, such as sympathetically mediated pain, bladder incontinence, neurogenic pain, visceral pain. Although this claim has been challenged by many experts about the degree to which TENS is more effective than placebo in reducing pain (Adedoyin et al, 2005).

Melzack and Wall in 1965 provided the explanation on the mechanism of the analgesia produced by TENS in their pain gate-control theory. Their explanation was that gate is usually closed, inhibiting constant nociceptive transmission via C fibers from the periphery to the T cell. When painful peripheral stimulation occurs, however, the information carried by C fibers reaches the T cells and opens the gate, allowing pain transmission centrally to the thalamus and cortex, where it is interpreted as pain. The gate-control theory postulates a mechanism by which the gate is closed again, preventing further central transmission of the nociceptive information to the cortex. The proposed mechanism for closing the gate is inhibition of the C-fiber nociception by impulses in activated myelinated fibers.

The Pain Gate can also be shut by stimulating the release of endogenous opioids (endorphins, enkephalins, and dynorphins), which are pain-relieving chemicals naturally released by the body in response to pain stimuli. Opioids are a naturally occurring hormone in the body. They are released in response to an injury or physical stress to reduce pain and promote a feeling of wellbeing. Much like Morphine, and related medications, opioids have a similar chemical structure, which explains their strong painkilling effects.

TENS has not only been found to be indicated for relieving both acute and chronic pain following sports injuries but also found to be enhancing tissues healing. TENS machine is very simple to use. It can be used at home by the athletes without special training. It could be applied to the painful site between 30 to 60 minutes; the machine could also be attached to the body during the performance of daily activity.

One of the main benefits of a TENS machine is that it can be used at home. Unlike most analgesic drugs TENS has little or no side effects. Pain relief drugs are effective but they can lead to several complications including: nausea, headaches, liver damage, and erosion of cartilage, stomach bleeding and stroke. Drug addiction and abuse can also be associated with the use of drugs. This is the reason why conservative treatments such as TENS are becoming more popular. TENS should not be used for people who are on pacemaker and those that develop arrhythmia of the heart.

Fig. 1. TENS Machine with electrodes placement

7. Interferential current therapy

In recent past faradic current has been used in the treatment of sport injuries for muscle re education. It is usually prescribed at early stage of injuries and when active contraction of muscles is hindered (Goats, 1990). Faradism is believed to increase muscle bulk and muscular strength especially when the muscle is made to work against resistance. Faradic current is capable of stimulating the motor nerves and cause tetanic contraction of muscles. Contraction of muscles when maintain for a period of time is capable of increasing the metabolism, with a consequent increase in the oxygen demands and nutrients and an increase of waste products, including metabolites. By the action of contraction and relaxation of muscles, there is increase in the pumping action of the veins and lymphatic vessels lying within the muscles. This mechanism is helpful in enhancing good venous and lymphatic return.

However, faradic currents like other direct and low frequency alternating currents (<1 KHz to <10 KHz) usually encounter a high electric resistance in the outer layers of the human skin. This makes the treatment of deep structures painful because a large transcutaneous current passes deeply (Adedoyin et al, 2002). Interferential current (IFC) was therefore designed to overcome this problem. Interference current is a medium-frequency current that delivers currents to deep-seated structures in order to relief pain. The machines are designed to generate an amplitude-modulated interferential wave, called beat frequency. The wave is created by two out-of-phase currents that collide with each other to generate an interferential wave with frequency between 1Hz and 250Hz.

Inferential current is primarily used to relief pain in musculoskeletal injuries. The mechanism of pain relief is similar to that of TENS. The duration of treatment should be between 30-60 minutes. Inferential currents can be applied via 2 or 4 electrodes. Quadripolar application of IFC is claimed to be created deep within the tissues whereas bipolar application is said to be distributed similarly to conventional electrical stimulation with maximal current intensities underneath the electrodes, progressively decreasing with distance (Goats, 1990).

Interferential current has been reported to be liked with stimulation of muscles, reduction of swelling and improved blood circulation and healing process. Many experts believed that TENS and IFC produced analgesic effects in a similar manner while few believed the IFC is better than TENS.

Interferential Currents should be avoided over the trunk or pelvis during pregnancy; and should be placed over the carotid sinuses and epiphyseal region in children. It should not be used for patient with pacemakers.
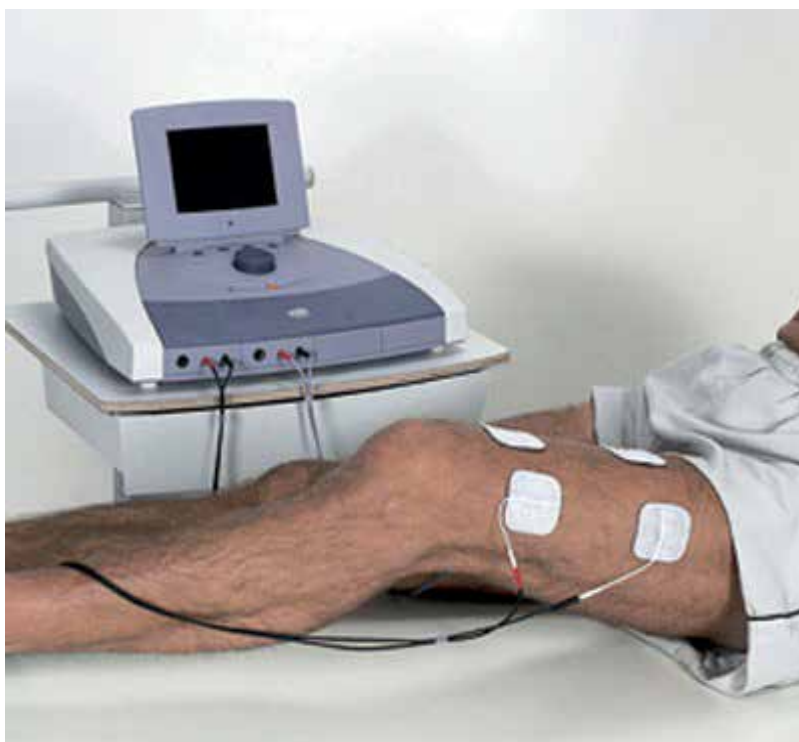

Fig. 2. Interferential Current Machine and Electrodes Placement

8. Therapeutic exercise

There is strong evidence for the use of exercise in the management of soft tissue injuries. In fact other physiotherapeutic modalities such as electrotherapy (Faradism, TENS), thermotherapy (Short wave diathermy), Actinotherapy (Ultrasound) are considered adjunct treatments. Exercise should be encouraged as soon as possible to prevent complications such as reduced range of motion, contractures, adhesions, muscles wasting and reduced strength.

Active movement can improve the integrity of joints and enhance good scar formation in muscles, tendons and ligaments, and improve the tensile strength of the mature scar.

Resisted exercise training would improve muscular strength, muscular hypertrophy, muscular endurance and power. It could also improve dynamic postural stability as related to standing balance and mobility. Resisted exercise is based on overload principle which states that for a muscle or muscle group to increase in strength, it must, on regular basis, be

challenged to overcome resistances that are greater than those that are usually encountered (Nyland, 2006).

Where a joint is immobilized, isometric exercise may be encouraged in order to protect the integrity of the joints. By contracting the muscle fibres without moving the joint, the muscle fibres are stimulated. This improves blood supply to the joint and also prevents intra articular and peri articular adhesions

Balance and coordination could also be impaired during musculoskeletal disorder because of deviation of gait especially injuries involving ankle joints. Exercise on wobble board is usually encouraged to improve static balance and strength of the lower extremities. Figure 3. Apart from being useful in stimulating the proprioceptive system and re-educate reflex posturer control, wobble board may improve the symmetry of weight distribution on the lower extremities of individuals (Adedoyin et al, 2009).

All these exercises have been found to bring about relief of pain with or without any other therapeutic analgesic modalities (Adedoyin et al, 2009).

Fig. 3. Wobble Board

9. Ultrasound

Therapeutic ultrasound is one of the most common treatments used in the management of soft tissue injuries. Ultrasound therapy is widespread in sports physiotherapy and physical therapy practice (Khanna et al, 2009).

Ultrasound consists of inaudible high frequency vibrations created when a generator produces electrical energy that is converted to acoustic energy through molecular collision and vibration. It undergoes a progressive loss of intensity of the energy during passage through the tissue (attenuation) (Tee Haar, 1987). Ultrasound frequency, wavelength,

intensity, amplitude, continuous/pulsed therapy, coupling medium, movement and angle of transducer and frequency, tissue composition and duration of treatment affect the dosage of ultrasound delivered to target tissue (Tee Haar, 1987, Speed 2001).

Ultrasound produces thermal and non-thermal physical effects (Low and Reeds, 2000). Thermal effects lead to increased blood flow, reduction in muscle spasm, increased extensibility of collagen fibres and pro-inflammatory response. Non-thermal effects of ultrasound including stable cavitation and acoustic streaming and micro massage; which are more important than thermal effects in the treatment of soft tissue lesions (Dyson and Suckling, 1978).

The sound waves are capable of penetrating into the skin and surface layers and cause tendons and soft tissues to vibrate, producing gentle healing vibrations within the affected area that soothe inflammation and relieve pain. Ultrasound waves also cause tendons and tissues to relax and increase blood flow to help reduce local swelling and chronic inflammation (Khanna et al, 2009).

The choice of parameters depends on the condition being treated. Continuous ultrasound therapy is used to treat muscle spasms, pain and to relax tense muscles. In this type of ultrasound, the sound waves transmitted create friction as they pass through muscle fibers, which in turn produce heat in the injured area. The body increases blood circulation to that area to cool it down, and this increased blood flow speeds up the healing process.

Whereas pulse ultrasound is used treat inflammations such as tendinitis and bursitis. This method of ultrasound therapy works through cavitation by transmitting vibrations that stimulate cell membranes, resulting in more rapid repair. No adverse effects have attributable to the use of appropriate therapeutic doses of ultrasound in literature. However, people with pacemakers and other electronic implants should not use ultrasound.

Other hear modalities that commonly used at chronic stage include infra-red, short wave diathermy and hot packs. Many experts believed that heat therapy can reduce pain and muscle spasm following some types of injury. Heat is sometimes recommended prior to exercise for athletes with 'stiff' muscles or in the treatment of chronic conditions in which restricted muscle or joint motion may interfere with recovery. Heat has also been found to enhance stretching of tissues by applying it to the muscles before the stretching is carried out. However, the application of heat to injured parts of the body has also been linked with increases in tissue swelling (oedema), and heat can spur metabolic activity and increase capillary blood flow, effects which may be counterproductive in the early treatment of some injuries.

10. Massage

Massage is the systematic, mechanical stimulation of the soft tissues of the body by means of rhythmically applied pressure and stretching using hands. It's performed to produce mechanical or reflexive effects such as improved range of motion, to increase circulation and lymphatic drainage, to induce general relaxation and reduce pain (Johnson, 2000). Massage has been used in managing athletes since the first Olympic games up until now. In sports, it is usually used in achieving and maintaining peak performance and to support healing of injuries (Fritz, 2004). Massage techniques include effleurage or stroking, petrissage or kneading, tapotement or percussion. Massage techniques involving effleurage, and kneading are used before sport. Massage can also be used after sport to improve the athlete's psyche and during sport in treatment of injuries. In treatment of muscle strain, massage is facilitates healing at the sub-acute and chronic stage. Controlled soft tissue

massage of scar tissue along fiber direction towards injury will promote development of mobile scars at the sub-acute stage of healing, while cross-fiber friction of scar tissue coupled with directional stroking along the lines of tension away from injury will increase strength and alignment of scar tissue at the chronic stage (Fritz, 2004).

If properly applied massage therapy can provide pain relief, Improves the flow of nutrients to muscles and joints, accelerating recovery from fatigue and injury, soothe stiff sore muscles, reduce inflammation and swelling. Massage and gentle stretching can help to maintain range of motion of joints.

The choice of the massage is specific to the athlete's sport of choice and is often focused on area prone to injuries. Sport massage is gaining popularity as useful components in a balanced training regimen. Sports massage can be used as a means to enhance pre-event preparation and reduce recovery time for maximum performance during training or after an event. There is evidence that specially designed massage promotes flexibility, removes fatigue, improves endurance, helps prevent injuries, and prepares athletes to compete at their absolute best.

11. Orthotic devices

Orthotic devices are needed during early onset of sport injuries in order to provide rest and support for the damaged structures especially joints. The devices provide support, or correct deformities and improve the movement of joints, spine, or limbs. They also provide stability of joints by limiting abnormal or excessive joint mobility. Excessive movement can worsen the injured parts and increase the pain. Knee and Ankle joints are more prone to injury than any other joints in the body. Ankle foot orthosis is commonly used to protect the ankle joints at acute stage (Figure 4).

Fig. 4. Ankle Foot Orthosis

For injuries involving the lower limbs, full weight bearing is usually discouraged as this could lead to more tissue damage. Physical therapists usually prescribe cane or crutches for non-weight or partial weight bearing during ambulation.

12. Conclusion

Individuals who engage in regular sporting activities or exercise could be involved in injuries. Injuries can have serious negative impact on athletes in their sport performance as they are affected physically, mentally and emotionally. Pain is one of the major complaints after injuries and it is the reason why athletes seek medical attention. Effective management however depends on correct diagnosis based on history and evaluation. Relieve of pain could restore function and enhance fitness, health and quality of life. Injured athletes can be effectively managed through pharmacological and non pharmacological approaches. Non pharmacologic means involve surgery and conservative managements. Surgery is usually considered when other treatments have failed. Non steroidal anti-inflammatory drugs (NSAIDs) are most commonly prescribed with success. However, these drugs have been reported to have deleterious effects on some body structure especially cartilage. Athletes are enjoined to seek physical therapy, as it plays major roles in pain management of sport injuries with little or no side effects.

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Better Association Between Q Angle and Patellar Alignment Among Less Displaced Patellae in Females with Patellofemoral Pain Syndrome: A Correlation Study with Axial Computed Tomography

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1. Introduction

Q angle, as an isolated clinical tool, is of uncertain and limited clinical value. [1] The Q angle, defined as the angle between the lines joining the anterior superior iliac spine, the center of the patella, and the center of the tibial tubercle, has been studied widely [2,3]. As a routine assessment tool in physical examination for clinical knee problems, with great inherent diversity in serving as a relevant clinical tool, the Q angle has long met debates in day to day orthopaedic practice. An increase in Q angle has long been looked as a pathologic factor in PFPS [4, 5]. Presumably the larger the Q angle, the larger the lateral pulling force on the patella [2], but reportedly Q angle rarely correlated with patellofemoral pain syndrome(PFPS)[6, 7]. Livingston and Mandigo [7] reported that no correlations between the Q angle measures and the magnitude of discomfort experienced in unilateral knee pain sufferers; while these relationships were weak yet significant in bilateral knee pain sufferers.

Since last decade, computer tomography (CT) has become an important diagnostic tool for better assessment of patellofemoral disorders [8, 9, 10]. Biedert and Warnke [6] have carried out a correlation study between the Q angle and the patella position by axial CT evaluation in patients with PFPS, but failed to establish the diagnostic relevance of the Q angle in the related patellofemoral disorders [6]. Other studies have revealed no significant correlation between Q angle and the position of patella in patients with PFPS. It has been stated that the

patella may be translated laterally in patients with patellofemoral malalignment and thereby articially affect the measurement.[1] Reider has found a decrease in Q angle in chronic recurrent dislocation of patella, an increase in Q angle in the classic patellar pain pattern, often called "chondromalacia patella, and a normal mean Q angle in subluxated patellae.[11] Lin et al had a disclosure of a more apparent statistic trait via a deep exploration into the patellar alignment subtypes in a study of PFPS.[12] Given this; we speculated that patellar displacement exerts an effect on the Q angle to some extent. Since lateral displacement of the patella was found in most patients with PFPS, the Q-angle might be undervalued over the already laterally displaced patellae in patients with PFPS[13]. A deep exploration into the effect of lateral patellar displacement on Q angle measures might render a better disclosure of how the measure of Q angle and related clinical implication were affected by patellar displacement. The current study is thus aimed to execute a deeper prospective study of the correlation between Q angle and patellar alignments by treating the more displaced patellae and less displaced patellae separately to see whether Q angle might be varied with difference in patellar displacement. The hypothesis of this study was that the interaction dynamics between Q angle and patellar alignment may be varied with various status of patellar displacement.

Clinical Relevance: To endorse Q angle with a certain clinical value is important to clinical assessment of PFPS that prevails among females.

2. Materials and methods

2.1 Subjects

Among 50 female PFPS patients enrolled in the current study, there were 28 patients with PFPS over their both knees and 22 patients with PFPS unilaterally. All patients were examined with axial computed tomography for all knees. All PFPS knees came into the current study to explore the probable correlation between the Q angle and the patellar position. The inclusion criteria of PFPS were patients who were suffering from pain with more than three kinds of knee-flexing activities as sitting, getting up from sitting, walking upstairs or downstairs, squatting, getting up from squatting, running, kneeling, or jumping. The exclusion criteria included the presence of any major medical disease, rheumatoid arthritis, or gouty arthritis; past history of previous knee surgery, image findings of osteoarthritis, or any deformity of lower limbs. All were measured for body weight, body height, BMI, and Q angle. The Q angle was measured, with the patient lying supine, as the angle between the lines joining the anterior superior iliac spine, the center of the patella, and the tibia tubercle [2, 3]. The same goniometer was used for every patient and the same senior doctor taking all of the measurements. All patients underwent CT imaging of the knees in the same way as Gigante's methods [9].

2.2 CT imaging

Computed tomography was performed with a Pace General Electric machine (GE Medical Systems). The patient was in the supine position and the scans were obtained in knee extension with the quadriceps relaxed. The ankles were restrained with felt strips to prevent external rotation of the foot. An axial image was obtained through the widest diameter of the patella, which allows the best view of the patellofemoral joint for the related measurement of patellar alignment [9].

2.3 CT measurements of patellar displacement

Lateral patella shift of Sasaki (LS)[14], used to represent patellar positions, is the ratio of the lateral portion of transverse patellar line relative to the medial one (AC /BC). "C" is the point on the transverse patellar line (AB) intersected by a line that is drawn from the most convex point of the lateral femoral condyle and perpendicular to the line (Line D) along the anterior border of femoral condyles.. (Figure 1) The interrelation between the Q angles and CT measurements were investigated.
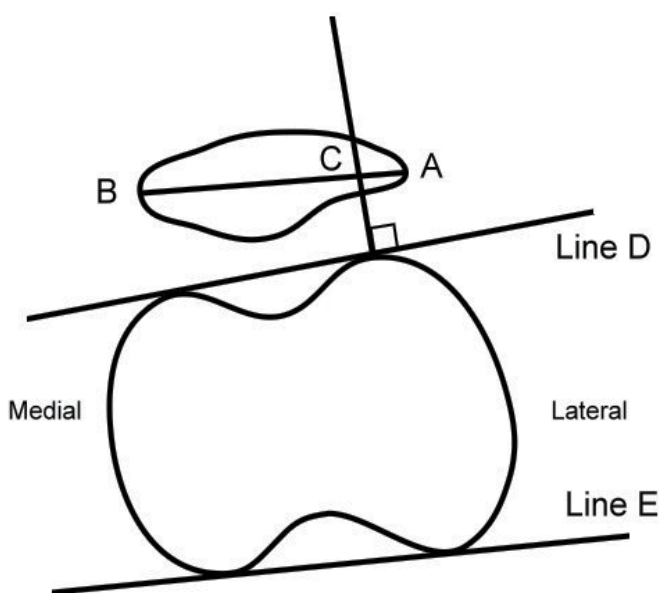
Lateral Shift of Sasaki (LS): AC/BC*100%

Fig. 1. Measurement made from CT images for lateral patella shift of Sasaki (LS). "LS" is the ratio of the lateral portion of transverse patellar line relative to the medial one (AC /BC). "C" is the point on the transverse patellar line (AB) intersected by a line that is drawn from the most convex point of the lateral femoral condyle and perpendicular to the line (Line D) along the anterior border of femoral condyles.

2.4 Statistical analysis

SPSS (version 11.5, SPSS Inc, Chicago, IL) statistical soft ware was used to execute all statistical analyses. The statistic tool used includes t test for the difference in measurement between study groups. The Pearson's correlation was used to investigate the relation between the Q angle and the measurement for patellar displacement, LS. For all statistical tests, the significance level was set at $p < .05$. To further examine the relationship between the Q angle and the measurements for patellar positions, the whole sample was grouped as: group 1 that was divided into those knees whose mean LS were below 20 percentiles of the whole sample and those knees whose mean were over 20 percentiles, group 2 that was divided into those knees whose mean LS were below 30 percentiles of the whole sample and those knees whose mean were over 30 percentiles, and group 3 that was divided into those

knees whose mean LS were below 40 percentiles of the whole sample and those knees whose mean were over 40 percentiles. And a test with ROC curve was done for the specificity and sensitivity of the presence of patellar pain relative to Q angle. The area under the ROC curve was used to anticipate the pathognomonic potential of the Q angle. (Figure 2)
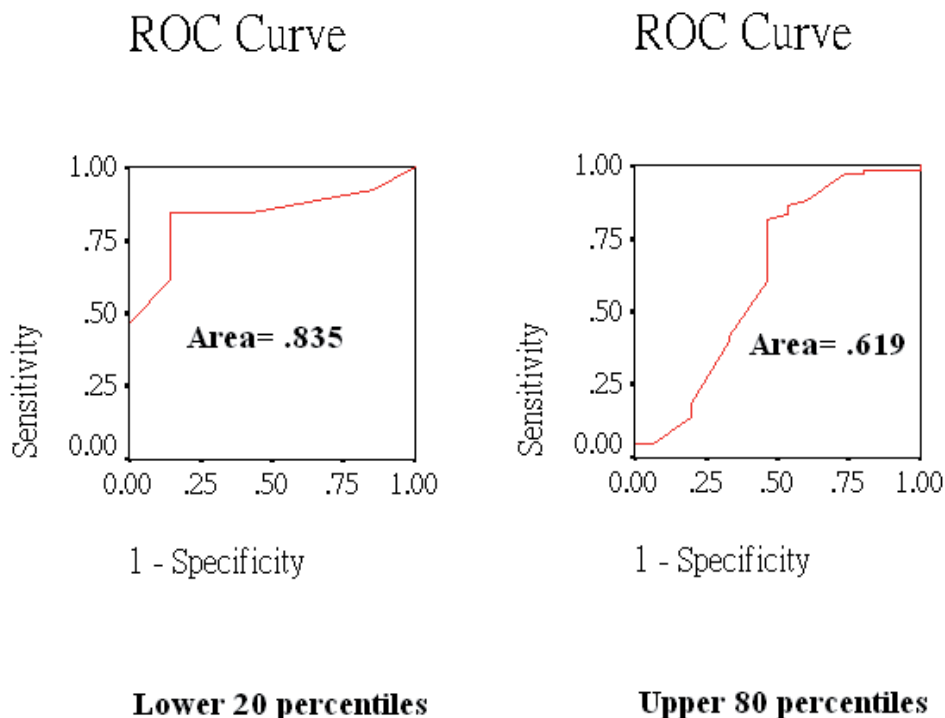

Fig. 2. Test with ROC curve for the specificity and sensitivity of the presence of patellar pain relative to Q angle.

3. Results

Q angle was significantly correlated to the measure of patellar displacement, LS, in the less displaced half of LS measures of each group. And an area of .730 to .835 was revealed by the test with ROC curve in the subgroups of less displaced patellae.

In total, the subjects aged 40.14±9.99 years, and their the basic demographics was: body weight, 57.18±8.55 kg, body height, 158.48±5.48 cm, and BMI, 22.75±3.09. The Q angle was 23.98±7.61 degrees, and LS, 35.99±14.03 in %. The Q angle and LS measures in each group and subgroup were shown in Table 1. There was no significant difference in Q angle between the subgroups in each group. (*p < 0.05*) (Table 1)

Statistic correlation was undertaken to explore the probable correlation between Q angle and patellar position, measured in LS. There was no correlation between Q angle and LS when the whole sample of 100 knees was calculated as a whole. After analysis into subgroups of different cutoff, a significant correlation was disclosed between Q angle and LS in the subgroup of knees with less displaced patellae in each group of respective way of cutoff. (*p < 0.05*) (Table 2)

	Group 1 Cutoff 20%: 24.00mm		Group 2 Cutoff 30%: 27.87mm		Group 3 Cutoff 40%: 32.16mm	
	Lower 20 percentiles (n= 20)	Upper 80 percentiles (n= 80)	Lower 30 percentiles (n= 30)	Upper 70 percentiles (n= 70)	Lower 40 percentiles (n= 40)	Upper 60 percentiles (n= 60)
Q angle (deg)	21.45±6.08	24.61±7.85	23.37±7.09	24.24±7.86	24.35±7.83	23.72±7.52
LS (%)	18.60±4.28**	40.33±12.10	21.11±5.06**	42.36±11.58	23.34±5.90**	44.42±11.24

There was significant difference in LS between any two subgroups within any group ($p< 0.01$).
There was no significant difference in Q angle between the subgroups within any group. ($p< 0.05$)

Table 1. Measurements of Q angles and patellar position (LS) in study groups

Via the test with ROC curve for the specificity and sensitivity of the presence of patellar pain relative to Q angle, an area of .730 to .835 was revealed in the less displaced half of LS measures of each group, indicating that Q angle would be more pathognomonic of PFPS among patients or knees of less displaced patellae. (Figure 2, Table 2)

	Group 1 Cutoff 20%: 24.00mm		Group 2 Cutoff 30%: 27.87mm		Group 3 Cutoff 40%: 32.16mm	
	Lower 20 percentiles (n= 20)	Upper 80 percentiles (n= 80)	Lower 30 percentiles (n= 30)	Upper 70 percentiles (n= 70)	Lower 40 percentiles (n= 40)	Upper 60 percentiles (n= 60)
Correlation coefficient[a]	0.481*	-0.175	0.502**	-0.142	0.453**	-0.096
Area under ROC curve[b]	0.835	0.619	0.780	0.634	0.730	0.657

[a]: Correlation coefficient between Q angle and lateral shift of patella (LS)
[b]: Diagnostic tests: probability of correctly distinguishing between painful and non-painful knees
*: $p <0.05$; **: $p<0.01$

Table 2. Correlation coefficient between Q angle and lateral shift of patella (LS). And diagnostic tests between subjects with and without painful knees.

4. Discussion

We have hypothesized that the interaction dynamics between Q angle and patellar alignment may be varied with various status of patellar displacement. After deep exploration into the subgroups of LS, the current study has demonstrated that Q angle was significantly correlated to the measure of patellar alignment, LS, in the less displaced half of LS measures of each group of respective cutoff point for LS. And via the test with ROC curve for the specificity and sensitivity of the presence of patellar pain relative to Q angle, an area of .730 to .835 was observed to be under the ROC curve in the less displaced half of LS measures of each group, indicating that Q angle would be more pathognomonic of PFPS among patients or knees of less displaced patellae.

Reportedly, a decrease in Q angle has been observed in chronic recurrent dislocation of patella, an increase in Q angle in the classic patellar pain pattern, often called

"chondromalacia patella, and a normal mean Q angle in subluxated patellae.[11] While, Biedert and Warnke's reported failure to conclude any correlation between the Q angle and the patellar displacement in their experiment[6]. Quite similar to Biedert and Warnke's work [6]. Our current study also showed no correlation between the Q angle and the patellar displacement when analyzing all the subject knees of PFPS as a whole. When the more displaced patellae and the less displaced half were evaluated separately, a significant correlation was observed between the Q angle and the patellar displacement among those with less displaced patellae in our study.

The concept of the "larger the Q angle, the larger the lateral pulling force on the patella" has been challenged, one after another, in the literature. Dandy has reported that an unstable, subluxated patella lies more laterally than normal, thereby decreasing the Q angle[15]. By statistically treating the more displaced patellae and the less displaced ones separately in the 3 ways of cutting off for the LS measures, the current study has revealed a positive correlation between Q angle and patellar displacement among those with less displaced patellae. The Q angle has been presumed to be responsible for the bowstring effect [3], whereby the patella tends to move laterally as the quadriceps contracts. Actually it is the underlying valgus vector force of the Q angle, rather than the Q angle per se, that dominates the way that the instantaneous bowstring assumes. As thus the Q angle and the instantaneous center of the patella landmarks the way the instantaneous bowstring assumes. Apparently Q angle failed to mean a comparable degree of the valgus vector across the knee of PFPS. As revealed in the current study, Q angle was equivocally obscured by patellar displacement that was the presumed result of the valgus across the knee. As thus the degree of valgus across the knee could be better represented by Q angle together with patellar displacement. In the current study there was no significant difference in Q angle between the subgroups in each group. We failed to observe Q angle as being undervalued by patellar displacement even if a consistent trait of negative association between Q angle and patellar displacement (LS) has been demonstrated in each subgroup of more displaced patellae in each group. (Table 2) We failed to verify Post's concept that the patella may be translated laterally in patients with severe patellofemoral malalignment and thereby artificially decrease the measurement of the Q angle[1, 2].

The natural valgus of the lower limb and the lateral pulling vector of the quadriceps migrates the patella laterally.[15, 16] An abnormal or increased Q angle is considered a relevant pathologic factor in patellofemoral disorder [6]. When the Q angle exceeds 15-20° it is thought to contribute to knee extensor mechanism dysfunction by increasing the tendency for lateral patella malpositioning [17]. Previous investigations of the quadriceps angle (or Q angle) and its relationship to knee disorders have yielded equivocal results.[6, 9, 10, 18] Reportedly Q angle failed to dictate the PFPS symptom and the presumed patellar malalignment leading to PFPS. Previous studies from various investigators have failed to correlate Q angle measurements with patient complaints. Fairbank et al have demonstrated no significant difference between painful and pain free knees [19]. There is no specific correlation between patellar symptomatology and an increased Q angle, as thus the clinical value of measuring the Q angle has been much controversial [20]. In the current study, via the test with ROC curve for the specificity and sensitivity of the presence of patellar pain relative to Q angle, an area of .730 to .835 was observed under the ROC curve in the less displaced half of LS measures of each group of respective cutoff point, indicating that Q angle would be more pathognomonic of PFPS among patients or knees of less displaced patellae. Likewise, the

current study has endorsed Q angle with a certain clinical value among people who are with less displaced patellae. The result will be important to clinical assessment of PFPS that prevails among females and athletes[20].

For the time being, the diagnostic relevance of the Q angle is highly equivocal. The Q angle has been subjected to a radical modification in order to play a positive clinical tool and provide a certain clinical value. Fithian et al has proposed a modified Q angle by measuring it in 30° of knee flexion with the patella manually reduced into the trochlea [21]. By analyzing all subject knees into different subtypes of patellar displacement to reveal an association between Q angle and patellar alignment and to endorse the Q angle with a promising pathognomonic value among PFPS patients or knees of less displaced patellae, the current study would help motivate further revision and endorsement of the Q angle in regard.

Reportedly a significant difference in Q angle between sides has led to a statement that symmetry in right versus left lower limb Q angle measures may be erroneous. And this is why both knees of PFPS patients with bilateral knee pain were enrolled into the current study instead of one person one knee [7, 22] Additionally, in our series, there was a significant difference in Q angle between sexes in our unopened observations (*p< 0.01*) This is why the male were excluded from the current study. As thus the current design merely focused on female population. Women have been stated to have higher Q angles than men, on the basis of a wider pelvis [23, 24]. Some has reported minimal difference in the Q angle measure between men and women [3]; while some has reported higher Q angle in men [19, 25].

The limitation of this study is failure to execute the interaction dynamics between Q angle and patellar position under weight bearing condition. A further study with open MR would make possible the related study under weight bearing condition.

In conclusion, Q angle was significantly correlated to patellar alignment among people with less displaced patellae. Q angle was more pathognomonic of patellar pain in those people with less displaced patellae.

5. Acknowledgements

6. References

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Syndesmotic Injuries in Athletes

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1. Introduction

Ankle injuries are the most common presenting injury in the athletic population, with the ankle sprain accounting for 10% to 30% of all single-sport injuries [1-4]. Lateral ankle sprains make up a majority of these injuries, and the literature describes a high degree of success with quick return to play afterward. Injuries to the syndesmotic ligaments occur far less frequently, with reported values between 1% and 18% of all ankle sprains [5-8]. However, the incidence of these "high ankle sprains" has been increasing recently due to an increase in the knowledge and understanding of the clinical diagnosis, biomechanics, and cause of syndesmotic injuries. More recent reports have the incidence ranging from 17% to 74% of all ankle injuries in young athletes [9-11]. Despite the improved awareness for this injury, there still exists a paucity of information on optimal conservative and operative management. In a recent survey, health care providers caring for professional athletes identified syndesmotic injuries as the most difficult foot and ankle injury to treat [12]. Athletes have shown a delayed return to play, higher incidence of chronic pain, and significant long-term disability compared to lateral ankle sprains [8, 13, 14]. A study from the United States Military Academy found that involvement of the syndesmosis was the most predictive factor of chronic ankle dysfunction six months after an injury [14]. This review will describe the anatomy of the biomechanics of the distal tibiofibular ligament, followed by an assessment of the clinical evaluation and diagnosis of syndesmotic ligament injuries. Finally, the indications and treatment options for both nonoperative and operative intervention will be discussed and evaluated with a current review of the literature.

2. Anatomy

A syndesmosis is defined as a fibrous joint in which two adjacent bones are linked by a strong membrane or ligaments [15]. The distal tibiofibular joint is a syndesmotic joint between the tibia and fibula, linked by four ligaments: the anterior inferior tibiofibular ligament (AITFL), the interosseous ligament (IOL), the posterior inferior tibiofibular ligament (PITFL), and the inferior transverse ligament (ITL). The distal tibiofibular joint employs both its bony and ligamentous structure for stability (FIGURE 1).

The architecture of the bony components of the syndesmosis provide significant stability to this joint. The fibula sits in a groove created by bifurcation of the lateral ridge of the tibia into the anterior and posterior margins of the tibia, approximately 6-8cm above the level of

the talocrural joint [16]. The anterior margin ends in the anterolateral aspect of the tibial plafond called the anterior tubercle, or Chaput's tubercle. The posterior margin ends in the posterolateral aspect of the tibial plafond called the posterior tubercle, or Volkmann's tubercle. The apex of this fibular notch is the incisura tibialis, which has a depth that varies from concave (60-75%) to shallow (25-40%) [17, 18]. Its depth varies from 1.0 to 7.5mm [19, 20] and is a little less in women than in men [21]. A shallow notch may predispose to recurrent ankle sprains or syndesmotic injury with fracture-dislocation [15]
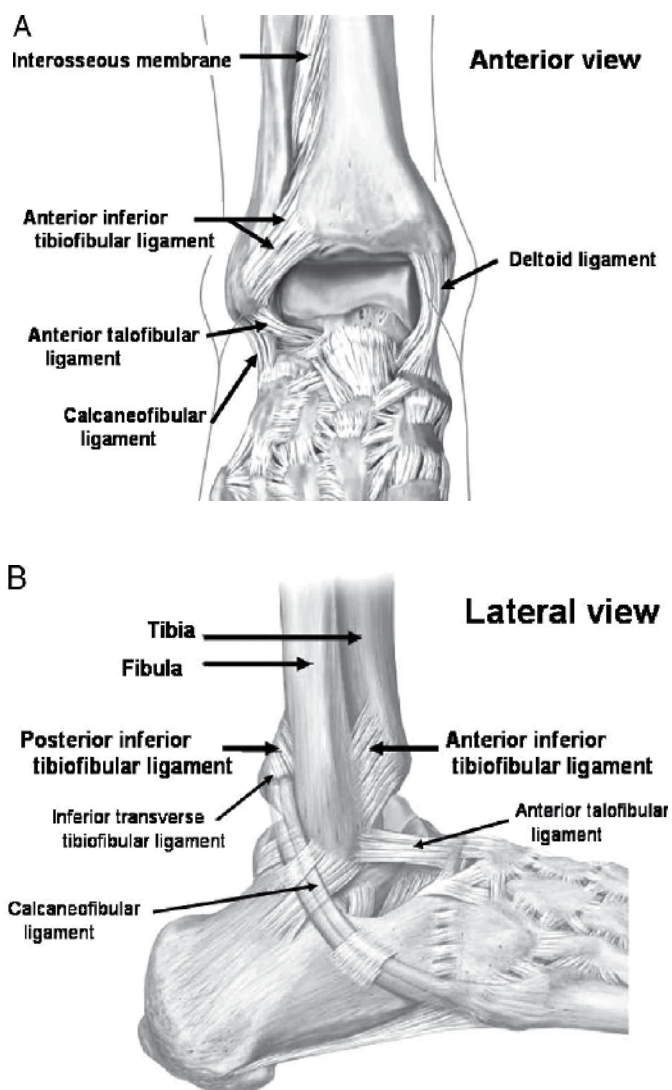

Fig. 1. Anatomy of syndesmosis, A) anterior; B) lateral. AITFL = anterior tibiofibular ligament; IOL = interosseous ligament; PITFL = posterior tibiofibular ligament; ITL = inferior tibiofibular ligament. (Reprinted from Browner B, Jupiter J, Levine A, Trafton P. Skeletal Trauma: Fractures, Dislocations, Ligamentous Injuries, 3rd edition. Philadelphia: Saunders, 2002; p. 2307Y74. Copyright * 2002 Saunders.

The bony architecture of the fibula mirrors that of the fibular notch. The medial aspect of the fibula forms a convex structure that complements that of the tibia, with an anterior and posterior margin, as well as a ridge that bifurcates that margins and aligns itself with the incisura tibialis.

The AITFL originates from the anterior tibial tubercle and runs distally and laterally in an oblique fashion to insert onto the anteromedial distal fibula. This ligament has a width of approximately 18mm, length between 20 and 30mm, and a thickness of 2 to 4 mm. It is the most commonly sprained ligament in syndesmotic injuries and is always disrupted with joint space widening or frank diastasis [15]. It is often multifascicular, and its most inferior fascicle has been described as a discrete structure called the accessory AITF ligament. The fibers can be seen during ankle arthroscopy and have been reported to be a source of impingement [22]. The PITFL originates on the posterior aspect of the fibula and runs horizontally to Volkmann's tubercle (FIGURE 5). This ligament has an approximate width of 18mm and a thickness of 6mm and is the strongest component of the syndesmosis. Because of its extensive breadth of attachment coupled with elasticity, the PITFL is able to withstand greater forces without failure than the AITFL and reaches maximal tension during dorsiflexion [23, 24]. The inferior transverse ligament is deep and inferior to the PITFL, extending over to the posterior aspect of the medial malleolus. The inferior transverse ligament is often difficult to distinguish from the PITFL as it runs just distally in the same plane. It forms the most distal aspect of the articulation. A portion of this ligament lies below the posterior tibial margin preventing posterior translation of the talus and deepening the ankle mortise to increase joint stability by functioning as a labrum. The interosseous ligament spans the space between the lateral tibia and medial fibula and is confluent with the proximal interosseous membrane. It is the main restraint to proximal migration of the talus between the tibia and the fibula [25] (FIGURES 2 and 3).
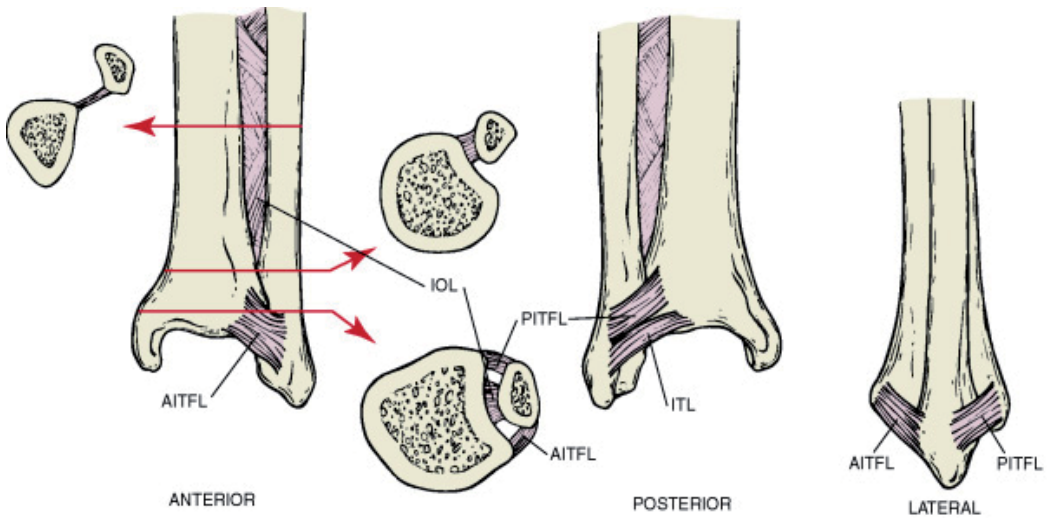

Fig. 2. The anatomy of the ankle syndesmosis in anterior, posterior, lateral positions; anterior inferior tibiofibular ligament (AITFL), interosseous ligament (IOL), posterior inferior tibiofibular ligament (PITFL), inferior transverse ligament (ITL). Copyright: Mark Hutchinson, University of Illinois
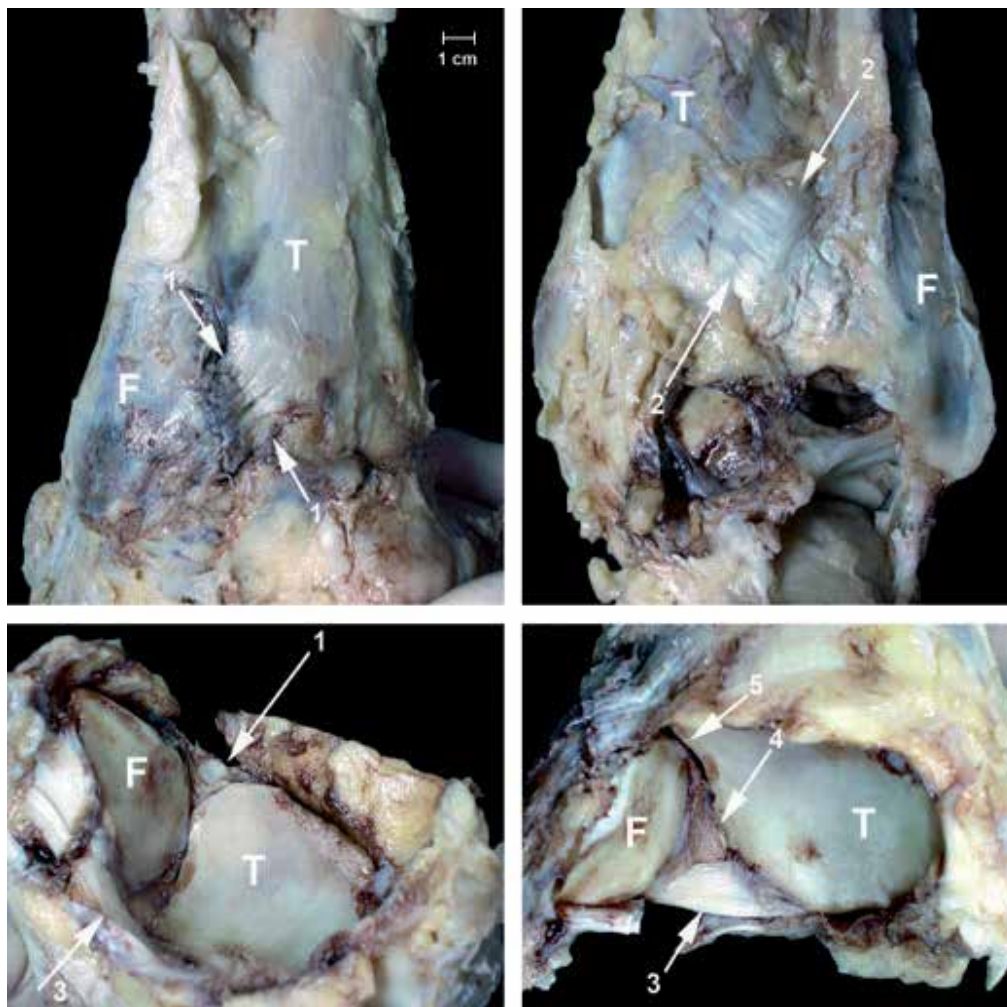
Fig. 3. Exposure of syndesmotic ligaments ina dissected right ankle (male, 92 years). (A) The trapezoid multifascicular anterior tibiofibular ligament (AITFL) (1) runs obliquely upwards from the anterior fibular tubercle towards the anterior tibial tubercle. (B) The band-like posterior tibiofibular ligament (PITFL) (2) runs obliquely upwards from the posterior fibular tubercle towards the posterior tibial tubercle. (C) View from below after removal of the talus shows the curved and horizontally running transverse ligament (3) and the inferior margin of the AITFL. In (D) fat (4) from the synovial fold is visible in the tibial incisure between the transverse ligament and the small contact area between the tibia and fibula (5). F, fibula; T, tibia. Picture courtesy of:

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3. Biomechanics

The ankle joint undergoes extreme loading which places stresses upon the bones, ligaments and dynamic stabilizers. Failure or injury to any of these components can lead to instability and pain. As a weight-bearing joint, the ankle can experience a multitude of different forces, reaching up to 6 times body weight at times [23]. The syndesmotic ligamentous complex maintains the integrity of the ankle mortise necessary to perform its hinge and glide movements. In simple terms, the ligaments stabilize the syndesmosis by preventing lateral displacement of the fibula. If any or all of the structures fail and the lateral malleolus displaces laterally, the talus usually follows. When the syndesmosis is disrupted, the normal gliding and rotational motion of the talar dome within the distal part of the tibia is altered. In addition to maintaining the integrity between the tibia and fibula, the syndesmosis complex resists axial, rotational, and translational forces. The deep portion of the deltoid ligament also contributes to the stability of the syndesmosis and must be evaluated after injury [26].

Normal motion exists between the distal fibula and tibia. The fibula can move medially, laterally, proximally, and distally in small increments. It also has a rotational component in relation to the tibia. The ankle joint undergoes triplanar motion from plantarflexion to dorsiflexion [27]. The movements require the talus and malleoli to remain in intimate contact. The superior portion of the talus is wider anterior vs. posterior, often described as a trapezoid. In dorsiflexion, the wider portion of the talus is set between both malleoli, providing maximum stability. The reverse process happens with plantarflexion. The syndesmotic ligaments provide such strong stabilization to the articulation that the fibula only rotates externally about 2 degrees, and the intermalleolar distance widens only about 1mm when the ankle joint is brought from full plantar flexion to full dorsiflexion [28]. The talus rotates an average of 5 degrees with dorsiflexion. The fibula moves approximately 2-4 mm distally with weight bearing. Mechanical disruption of the syndesmosis may result in increased compressive stresses seen by the tibia, increased likelihood of lateral subluxation of the distal fibula, and incongruence of the ankle joint articulation [29]. The relative joint position of the talus under the tibial plafond and dynamic joint motion would be altered with resulting abnormalities in contact pressures and a medium for development of degenerative joint disease.

Radiostereometric analysis of normal ankles by Beumer et al [30] showed that with an external rotation moment of 7.5N-m applied to the foot, the fibula externally rotated between 2-5 degrees, translated medially between 0 and 2.5mm, and moved posterior between 1 and 3.1mm. The extremes of motion are seen in the stance phase of gait. Oglivie-Harris et al. performed a biomechanical study to determine the relative contribution of each of these ligaments during 2 mm of lateral displacement of the fibula [31]. Their results showed the AITFL contributed 35% of the restraining force, the inferior transverse ligament contributed 33%, the intraosseous ligament contributed 22%, and the PITFL contributed 9%. They proposed that injury to two of the ligaments may lead to instability. Another study used cadaver specimens to determine the effects of sequential sectioning of the syndesmotic ligaments to resistance of an external rotation force. The distal tibiofibular diastasis was 2.3mm after sectioning of AITFL, 5.5mm with the additional sectioning of distal 8cm of the intraosseous ligament, and 7.3mm after division of the PITFL [29]). Sectioning of all 3 ligaments allowed for close to 5 degrees of pathologic external rotation at ankle joint. The AITFL has been found to prevent excess fibular movement and rotation of the talus and

maximum tension is achieved in plantar flexion. The posterior ligaments are able to withstand greater forces without failure than the AITFL and reach maximum tension during dorsiflexion [23]. The posterior structures combination of strength and elasticity make them the last structures to tear in an injury [24]. The IOL is the shortest but primary bond between tibia and fibula [32]. The IOL restrains posterolateral bowing of the fibula and transmits a small portion of the weight bearing load to the fibula [33]. It is thought to behave as a spring, allowing for slight separation of tibia and fibula during dorsiflexion [34]. Normal axial loading within the leg segment during walking involves a transfer of between 6% to 15% of the compressive axial load from the tibia to the fibula through the distal interosseous ligament and membrane [27].

4. Mechanism of injury

Athletes may present with a variety of mechanisms for injury. The exact mechanisms are not known for certain and despite the fact that researchers have been unable to duplicate the lesions of a syndesmotic sprain, most syndesmotic injuries are caused by external rotation [29, 35, 36]. Any measure that widens the mortise may damage the syndesmosis. Most proposed mechanisms of injury were based on the observations of clinicians who have interviewed patients with these injuries. The mechanism of external rotation is supported by multiple biomechanical studies that demonstrate increased external rotation of the talus and fibula upon sequential sectioning of the ligaments involved [37]. With this external rotation moment, the fibula separates from the tibia, causing initially a disruption of the AITFL. Commonly, the medial deltoid ligament is also injured. Nussbaum produced a study of 60 athletes with syndesmotic sprains without diastasis [38]. 55% of the injuries occurred when an athlete collided with another with a planted foot in external rotation; after the contact, the player fell forward, dorsiflexing the ankle and further externally rotating the foot. 37% caught their toe and twisted their ankle without receiving contact. No significant correlation existed between the mechanism of injury and the severity of   injury. External rotation of the talus also occurs, with possible injury to the deltoid ligament medially. The severity of the force and the duration are determining factors on how far the injury extends; sometimes the proximal extent of the fibular injury component results in a fracture.

Clinicians should be aware of other possible mechanisms of injury. Others have reported on syndesmotic injuries that were due to hyperdorsiflexion, inversion, and plantarflexion [39-42]. Brosky reported that when maximal tension is achieved with external rotation, either dorsiflexion or plantarflexion may result in damage [43]. Other more recent cadaveric studies have looked at whether syndesmotic injuries can cause result from and cause multidirectional instability [44].

Mechanisms during individual sporting activities have been described. Fritschy noted that despite the protection offered by the rigid ski boot, syndesmotic injuries were common among elite skiers because of extremely rapid turns and sudden forceful external rotation of the foot. The external rotation forces acting on the individual ski are caused by a relatively long moment arm [45]. Skiers typically catch the inner edge of the ski which causes forceful external rotation of the foot. Football players often encounter 2 possible scenarios involving contact for high ankle sprains. One involves a direct blow to the lateral leg with a planted foot causing interal rotation of the leg relative to the foot. The other scenario involves a blow to the lateral knee with the foot planted in external rotation relative to the body being

internally rotated [9]. (FIGURE 4) Other injuries include falls, twisting weight-bearing injuries, and motor vehicle accidents. Athletes often are incapable of providing an exact mechanism; but they often recognize that the injury is not consistent with a typical ankle sprain.

Fig. 4. The mechanism of syndesmotic injury typically seen in sports such as (a) soccer and (b) football is a direct or indirect external rotation force placed on the foot relative to leg and trunk. Figures copyright is owned by Jeffrey R. Thormeyer. Artist: Matthew Mendoza
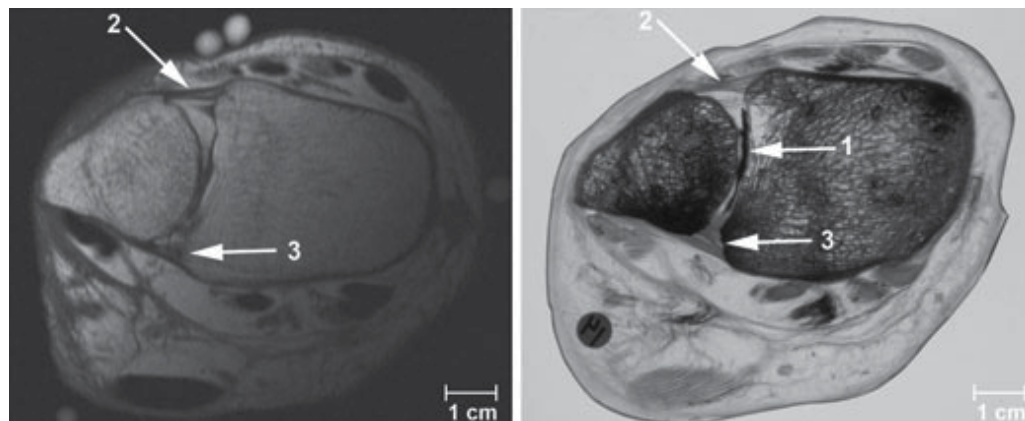
Fig. 5. Correlation between MR image (left) and plastinated slice (right) at the same level through the tibiofibular syndesmosis (female, 84 years). The intra-articularly injected green dye is visible in the tibiofibular recess (1), which extends between the anterior (2) and posterior (3) tibiofibular ligament. As the MR image is obtained without intra-articular contrast, the recess is not visible here. The incisura fibularis is shallow with an irregular contour.

Picture courtesy of :

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5. Epidemiology

Isolated ankle syndesmosis injuries are not very common disruptions. They are seen more often in conjunction with deltoid ligament injury and fractures in the malleoli. The real prevalence of ankle syndesmosis injuries is likely underestimated because many are missed or are not treated in a timely fashion. Hopkinson and colleagues suggested that ankle syndesmosis injuries account for 1% of all ankle injuries in the United States military. This was a study of cadets at West Point, who must participate in a contact sport, and showed 15 syndesmotic injuries out of a total of 1344 total ankle sprains [39]. Fallat and colleagues followed all ankle injuries that presented at a local emergency department and a primary care clinic prospectively for 33 months. The diagnosis of a high ankle sprain was made on physical examination alone. Of 639 patients who had 547 soft tissue injuries and 92 ankle fractures, the prevalence of syndesmosis injuries was 5% [46].
In populations of high-level sports participation or high impact activities, the incidence has shown to be higher [10, 47]. In ice hockey and skiing syndesmotic sprains are occurring more frequently than lateral ankle sprains most likely due to the rigid nature of the footwear as observed by Fritschy in world class skiers [45]. Boytim and colleagues reported a prevalence of 18% for syndesmosis injuries in a prospective study of 98 ankle injuries, and close to 40% of ankle sprains in an American professional football team [9]. Vincellete and

colleagues showed that close to a 1/3 of Canadian football players had calcification of the syndesmosis, documenting evidence of old, chronic, syndesmotic injuries [48]. A retrospective study by Wright et al showed syndesmotic sprains accounting for 74% of ankle sprains in two professional hockey teams over 10 years [11]. A study using arthography demonstrated high incidences (50% direct and 36% indirect signs of syndesmotic injury) [49]. In a retrospective study using MR to assess injuries to the ankle in 90 severe sprains, Brown et al. found a syndesmotic injury in almost 2/3 (24% acute; 38% chronic) [50].

Syndesmosis injuries are increasing in incidence in the athletic population, and in collision sports such as football, hockey, and rugby. They account for an increasingly significant proportion of ankle sprains. For athletes, the increase in risk stems from the intensity of play, twisting and cutting demands, as well as risk of contact and collision. Risk factors were identified in a study performed with data over 4 years looking at injuries sustained by cadets at the United States Military Academy. Syndesmotic and medial ankle sprains accounted for about 12% of ankle sprains in this young, athletic population. Important risk factors noted included male sex, higher level of competition, and exposure to selected sports such as football, team handball, basketball and soccer [51]. Using all available data, the incidence of high ankle sprains in the general athletic population is increasing as a percentage of all ankle sprains and is higher with more intense sporting activities.

Despite syndesmotic injuries being less common, they are often more difficult to diagnose than lateral or medial ankle sprains and recovery from the injury can be very protracted. Common complications of syndesmotic sprains are heterotopic ossification or frank synostosis, prolonged dysfunction of the ankle, and diastasis. Taylor and colleagues reported the findings on 50 syndesmosis injuries in 44 football players [52]. Reported that Hopkinson [39] reported that 90% of syndesmotic injuries showed HO (although asymptomatic), while Boytim [9]demonstrated a 75% rate. McMaster and Scranton found radiographic evidence of synostosis in seven patients who had persistent pain 3 to 11 months after a high ankle sprain [53]. Veltri et al. reported 2 cases of symptomatic synostosis in 2 football players [54]. A different study conducted by Bassett et al [52] reported that 50% of players who sustained syndesmotic injuries had evidence of HO and that their recovery period was on average 11 additional days as compared to those without HO. In a survey of NFL head athletic trainers, the mean return to play time was 30 days with a range of 5-56 days [55]. Boytim et al reported that football players with a high ankle sprain averaged 6.3 missed or limited practices (range 2-21) and averaged 1.4 missed games (range 0-5) as compared to 1.1 missed or limited practices and 0.04 games missed for lateral ankle sprains [9]. Difficulties in ankle function become apparent as soon as the athlete returns to high demand activities such as cutting, twisting, turning, jumping or pushing off. A study revealed that an ankle syndesmotic sprain requires a recovery period almost twice as long as that of a severe lateral ankle sprain [39]. Furthermore, residual chronic pain is more common than in an isolated lateral ankle sprain [38, 56]. Failure to reduce or stabilize a syndesmotic injury and the associated lateral talar translation may cause abnormal joint mechanics, diastasis, and degenerative changes. Accordingly, early recognition and treatment of high ankle sprains is paramount for a normal non-antalgic gait and return to sport.

6. Clinical evaluation

As with all injuries, a thorough history and physical exam are mandatory. Paramount within the history is relevant information concerning mechanism of injury and prior ankle

injuries or instability. It is important to detail the time interval between injury and evaluation. A simple classification system into acute (<3 weeks), subacute (3 weeks to 3 months), or chronic (> 3 months) is useful. Because many ankle injuries can appear similar on initial presentation, an understanding of the mechanism of injury is crucial. A grade III lateral ankle sprain (non-surgical) from an inversion type injury can look similar to an unstable syndesmotic injury (surgical). Differential diagnoses begins with mechanism of action, location of injury, type of sport, position of limb, direction of forces, and magnitude and velocity of injury. Elapsed time from injury allows correlation with amount and timing of swelling. Severity of injury can be correlated with ability to bear weight. Athletes complain of generalized pain with weight-bearing or push off during gait if they are able to bear weight. A heel-raise gait pattern may be observed to avoid excessive ankle dorsiflexion and to avoid pain during pushoff [43]. In chronic situations, the athlete may complain of stiffness and feelings of instability, especially on rough or uneven terrain [57] Patients with chronic injuries may show prolonged recovery as compared to those with ordinary lateral ankle sprains [56].

Inspection may reveal edema and ecchymoses about the lateral aspect of the ankle. Palpation is necessary for differentiation. Palpation is necessary as the patient will often have well-localized anterolateral pain located over the anterior syndesmosis of the ankle. The pain and swelling in acute syndesmotic injuries are often more precisely localized than in patients with the common inversion lateral ankle sprain. Careful palpation over the anterior talofibular and calcaneofibular ligaments should reveal minimal if any tenderness. The degree of swelling tends not to be as substantial as with lateral inversion injuries. Note any tenderness along the interosseous membrane and the length of the tenderness. Nussbaum et al found that days lost from competition could be predicted by measuring the distance over which the interosseous membrane was tender to palpation [38] There may be tenderness about the medial aspect of the ankle if they injury involved an abduction component. Fites et al. recommend that if swelling about the joint between tibia and fibula occurs less than 24 hours after injury, consider it a syndesmotic injury until proven otherwise [58]. The deep deltoid ligament and posterior syndesmotic ligaments are structures deep within the ankle and difficult to palpate independently. Each may be ruptured without isolated palpable tenderness. Because of the uncertainty with presentation, repeat clinical exams are often necessary to delineate between stable and occult unstable injuries. A missed, unstable injury that is undertreated can lead to a poor result. Range of motion is often limited in both directions of sagittal plane motion with an empty or painful end feel at terminal dorsiflexion [55] If the athlete is unable to bear weight, the Ottawa fracture rules should be applied to determine the need for radiographs before provocative stress tests are performed [59].

To evaluate syndesmotic injuries, numerous clinical exam tests have been described. However, the accuracy, prognostic potential, ability to detect severity of injury, or capability to correlate with the degree of instability present have not been well established [55]. A number of exam tests have been developed that include the external rotation test, the Cotton test, the fibular-translation test, the squeeze test, and the crossed-leg test [60].

The squeeze test is performed by compressing the tibia and fibula at midcalf level [61]. Pain in the area of AITFL is a positive test and may herald a syndesmotic injury (FIGURE 6). Teitz et al confirmed that compression of the two bones proximal to the midpoint of the calf

caused separation at the origin and insertion of the AITFL [62]. Reliability remains in question with reported low positive predictive value as well as poor intra-examiner reliability [63, 64]. Studies have indicated that a positive test is correlated with a prolonged recovery time or presence of heterotopic ossification [39, 52].

Fig. 6. The squeeze test. The tibia and fibula are compressed at the level of the mid-calf. Pain at the ankle joint indicates a positive test. The examiner should palpate the fibula along its entire length. Copyright: Mark Hutchinson, University of Illinois

The external rotation test is performed with the patient sitting facing the examiner with hips and knees at 90 degrees. The leg is stabilized and an external rotation force is applied to the ankle with the foot in dorsiflexion (FIGURE 7). The largest displacement of the syndesmosis and creation of tension within the ligamentous structures occurs here as the broadest portion of the talus is present in this position. Reproduction of pain in the syndesmotic area is a positive test. Medial sided pain points toward a deltoid ligament injury. Alonso [63] reported a high degree of inter-tester agreement, low rate of false positives and a protracted recovery if coupled with palpatory tenderness and a positive squeeze test.

Fig. 7. The external rotation test. With the knee bent to 90- and keeping the leg steady, an external force is applied to the ankle. Pain at the ankle indicates a positive test. Copyright: Mark Hutchinson, University of Illinois

The fibular-translation test is performed by applying an anterior and posterior drawer force to the fibula with the tibia stabilized. Increased translation as compared to contralateral side accompanied by pain defines the test as positive. This test has shown poor correlation to syndesmotic injury both in cadaveric sectioning studies as well as clinically [55].

The Cotton or shuck test is done by attempted translation of the talus within the mortise in a lateral direction. The distal lower extremity is held steady with one hand while the plantar heel is grasped with the other hand and the heel is moved side to side. Increased translation or pain may be indicative of a syndesmotic injury along with a concomitant deltoid injury. A high degree of false positives secondary to subjective interpretation has been shown. Excessive translation is more often seen with the most severe injuries [65, 66].

The crossed-leg test is a more recently described test. The patient rests the midtibia of his affected extremity on the knee of the other extremity, in a figure 4 type position. The patient then applies a downward force on the medial side of the knee. The test is positive if pain is felt in the syndesmotic region. The authors reported 7 of 9 patients with radiographic abnormalities tested positive with this maneuver [67].

The heel thump test was described as a test to target ligamentous injury in the absence of a fracture. The patient rests with leg dangling over edge of table or chair with the foot in gravity induced equinus. The examiner delivers a firm thump to the heel in line with the long axis of tibia with the intention of delivering talus into the mortise. A positive test is aggravation of pain above the ankle briefly. The utility of this test may lie in the ability to

examine the structures when swelling precludes palpation or ligamentous stressing [68]. However, the test is not specific as it has been described as a method for identifying tibial stress fractures also [69].

Stability of the ankle joint may be further examined by asking the patient to perform some active maneuvers including performing a toe raise, walking and jumping. Spaulding found in gait analysis that syndesmotic injury decreased the ability to effectively push off the toes while walking [70]. The above mentioned actions should be painful or prevent normal motion if a syndesmotic injury is present. Improvement with these measures by tightly taping the ankle just above joint is an adjunctive test described by Williams and Amendola [71] to further confirm suspicion. Additionally, functional ability may be assessed by having the athlete perform a single leg hop. Disability was defined by Nussbaum as an inability to hop 10 times without significant pain [38] Nussbaum concluded that 4 parameters may help determine severity of the syndesmosis injury: AITFL tenderness, the length of tenderness along the interosseous membrane, a positive external rotation test, and functional disability. This study reported 55 out of 60 patients had a positive external rotation test which also required longer rehab and return to play time. They also found that return to play time could be correlated directly with the tenderness length with a 95% confidence interval.

Although the presence of positives with any of these tests should generate suspicion to a syndesmotic injury, there are no good studies demonstrating that one test is reliably predictable as to the severity of the injury. Beumer and colleagues al performed a biomechanical evaluation of 5 special tests (squeeze, fibula translation, Cotton, external rotation, and anterior drawer) to determine the degree of distal tibiofibular displacement induced by each test in intact cadaveric ankles and after sectioning of the anterior talofibular ligament, the posterior talofibular ligament, and the deltoid ligament [60]. The average increase in displacement after sectioning of all ligaments was only approximately 1 mm. This study showed that the degree of distal displacement between tibia and fibula exhibited with specific exam maneuvers combined with creation of syndesmotic specific ligament injuries failed to show that any of the tests can be used to predict extent of injury.

7. Imaging

Evaluation of the syndesmosis should include three views (AP, lateral, mortise) of the ankle as well as orthogonal views of the entire tibia and fibula especially if any tenderness along the proximal leg exists. A mortise view taken with the patient positioned in unilateral weight bearing is the most accurate way to assess instability radiographically but many patients with mortise instability may not be able to tolerate unilateral standing due to pain [72]. Bilateral weight-bearing or non-weight bearing radiographs can be considered instead. Weight bearing films provide physiologic stress to unveil occult unstable injuries. CT scans and MRI scans may be of value in more subtle cases. Radiographs are evaluated for the relationship of the tibia and fibula as well as for fractures along the entire lengths of the bones. Disruption of the normal relationship between distal tibia and fibula is often representative of a syndesmotic injury. Radiographic evaluation with full length views of the leg is needed to evaluate pronation or external rotation injuries resulting in a Maisonneuve type fracture. The more proximal the fibular fracture, the greater risk for syndesmotic injury and resulting instability. Beumer et al [30] studied motion of the distal fibular before and after syndesmotic injuries on cadavers. The fibula tended to externally rotate after disruption but this was difficult to see on plain radiographs. Posterior

translation on the lateral view was described as a secondary pathology. Radiographic parameters have been developed to help identify syndesmotic injuries: increased tibiofibular clear space decreased tibiofibular overlap, and medial clear space widening.

Tibiofibular clear space is defined as the distance between the medial border of the fibula and the lateral border of the posterior tibia as it extends into the incisura fibularis. This distance is measured at 1 cm proximal to the tibial plafond and should be less than 6mm in both the AP and mortise projections. This measurement provides the most reliable indicator of injury to syndesmosis [73]. Tibiofibular overlap is the overlap of the lateral malleolus and the anterior tibial tubercle. This is also measured 1 cm above the plafond. The overlap should be greater than 6mm in the AP view, and greater than 1 mm in the mortise view. Medial clear space is defined by the distance between the lateral border of the medial malleolus and the medial talus at the level of the talar dome (FIGURE 8). With the ankle in neutral, the clear space should be less than or equal to the space between talar dome and tibial plafond. A widening of the medial clear space correlates with a concomitant deltoid ligament injury [61]. Avulsion fractures may occur and aid in identification; calcification above syndesmosis or at tibial attachment of PITFL may also aid in diagnosis.
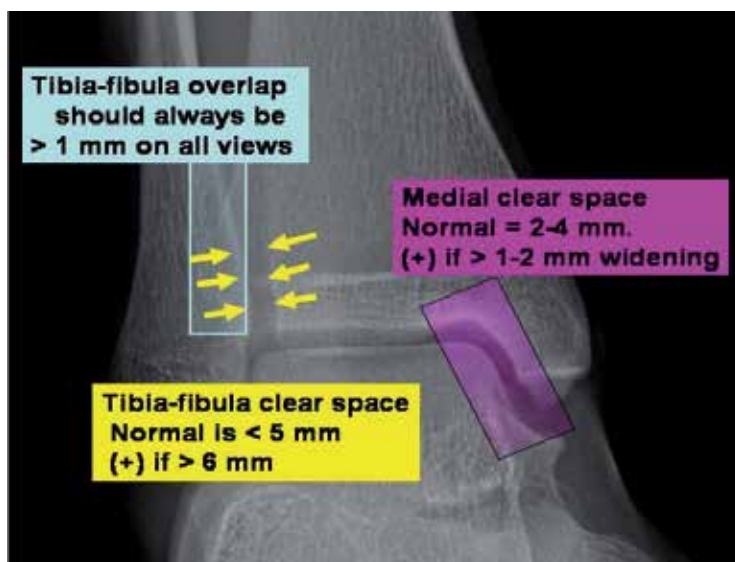

Fig. 8. Diastasis of the tibiofibular clear space greater than 6 mm is considered one of the most reliable indicators of syndesmotic injury. There should be at least 1 mm of tibiofibular overlap on all views. The medial clear space of greater than 4 mm or greater than 2 mm difference compared with the opposite side is indicative of instability. Copyright: Mark Hutchinson, University of Illinois

Reliability of evaluation of syndesmotic injuries by measuring diastasis of the tibia-fibula interval and tibia-fibula overlap on standard radiographs has been questioned. There is considerable variation in the size and depth of the notch which can make radiographic interpretation of separation difficult [74]. Absolute values of distances do not take into account anatomic differences in size or with gender. To account for these, Ostrum et al. introduced the concepts of measurements based on ratios [75]. They concluded that there was an injury to the syndesmosis if the ratio of the tibiofibular overlap: fibular width was

greater than 24%; ratio of tibiofibular clear space: total fibular width less than 44%. In addition to gender differences, rotation effects measurement of tibiofibular overlap. Pneumaticos et al [76] demonstrated that overlap changed with rotation but the clear space remained same during rotation from degrees of external rotation to 25 degrees of internal rotation. They concluded that the tibiofibular clear space is the most reliable parameter for measuring widening on plain radiographs. Takao et al. published results of ankle arthroscopy in tibiofibular syndesmotic rupture [77]. Evaluating 38 patients who had Weber B ankle fractures, they identified disruption on AP and mortise radiography in 42% and 55% respectively. During arthroscopy, the diagnosis actually increased to 87% [78]

Some authors have suggested stress radiographs to aid in identification; stress radiography with an external rotation force placed on the foot is a useful imaging approach (FIGURE 10). It may require local anesthesia to obtain these views. Alternatively, a gravity stress view may be obtained by performing an AP radiograph with the leg horizontal and without support under the foot/ankle. The resultant displacements are then compared to the uninjured side. Lateral views may allow for easier interpretation to assess possible posterior and lateral displacement of the fibula [29] . However, studies evaluating translation after rotation forces applied show that after sectioning of ligaments, distance is negligible and stress views cannot be reliable used for predictive purposes because of the high false negative rate.

CT scans are more sensitive than plain radiography in detecting syndesmotic injuries based on diastasis. Ebrahiem et al noted that CT is more effective at picking out 2-mm and 3-mm diastasis[79]. Avulsion fracture may occur on either the anterior or posterior aspect of the tibia and have been noted to occur in up to 50% of syndesmotic injuries. CT imaging utilized in this case can pick up avulsion fractures without evidence of diastasis [80].

MRI can be used for diagnosis and has shown to effectively display the components of the syndesmotic complex with high interobserver agreement [81]. A study by Takao et al. revealed 100% specificity and 93% sensitivity of injury of AITFL and 100% specificity and sensitivity for PITFL as compared to arthroscopy in acute studies [82]. While useful for confirmation, it is unclear if MRI imaging has shown to alter treatment plans or prognosis. MRI allows for the grading of ligamentous injuries. Grade 1 injuries represent stretching of the ligament without fiber disruption. The ligament is intact on MR imaging but often has edema present adjacent to the ligament and within overlying soft tissues. Grade II injuries represent partial tearing of the ligament. MR images demonstrate thickening of the ligament with partial fiber disruption and associated edema within the ligament and overlying soft tissues. Grade III injuries represent discontinuity of the ligament. MR images demonstrate this along with extensive edema. The normal AITFL is dark on all MR sequences and has an oblique course. This structure may have normal fenestrations and accessory fascicles[83]. MR imaging findings of acute injuries include abnormal T2 signal with thickening, waviness, or disruption of the AITFL and interosseous membrane, usually with fluid extending superiorly within the distal tibiofibular joint. MR imaging findings of more chronic injuries include thickening, attenuation or disruption without associated edema. Associated injuries also are common with these injuries and are picked up by MR imaging. Brown et al looked at associated injuries in 59 patients with acute and chronic injuries. AITFL injuries were present in 74%; bone contusions in 24%, osteochondral lesions in 28%, joint incongruence in 33%, and osteoarthritis in 10% [50].

Recent interest has been garnered for the use of ultrasound with its inherent advantages as a method of diagnosis. Ultrasound can be performed in the office setup in both real time and dynamic modes. It is inexpensive, fast and does not have radiation exposure (FIGURE 9). Mei-Dan et al conducted ultrasound evaluations on athletes with syndesmotic injuries and compared them to athletes who sustained lateral ankle sprains as well as a control group without injury. The results were encouraging for accurately diagnosing a syndesmotic injury in cases of latent high grade syndesmotic sprains. Exams within two weeks of injury increased the ability of ultrasound to detect injury [84]. Milz et al compared US examination and MRI studies for lateral ligament injuries and syndesmotic injuries. The study showed a sensitivity of 66% and specificity for AITFL of 91% [85].
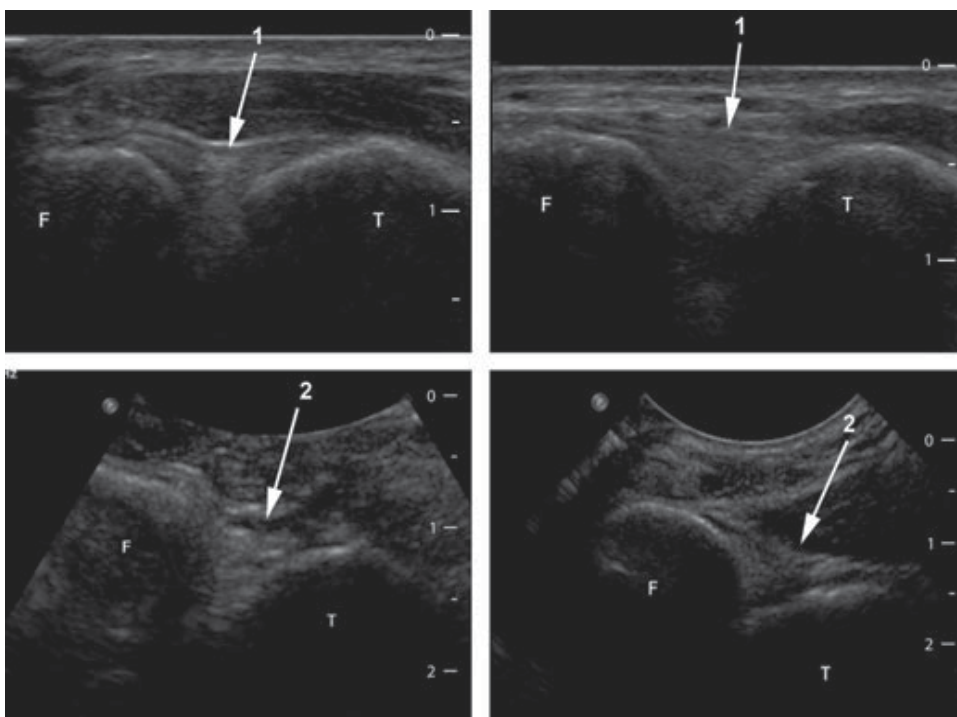

Fig. 9. Ultrasound images of anterior (1) (A,B) and posterior (2) (C,D) tibiofibular ligament (female, 20 years). F, fibula; T, tibia. In plantar flexion the ATIFL is slack (A). In dorsiflexion the talus pushes the tibia and fibula outwards, with stretching of the anterior tibiofibular ligament as a result (B). The same mechanism applies for the PTIFL. In plantar flexion the ligament is slack with a resulting increase in echogenicity (C). In dorsiflexion the fibres are stretched and are more longitudinally aligned (D). F, fibula; T, tibia
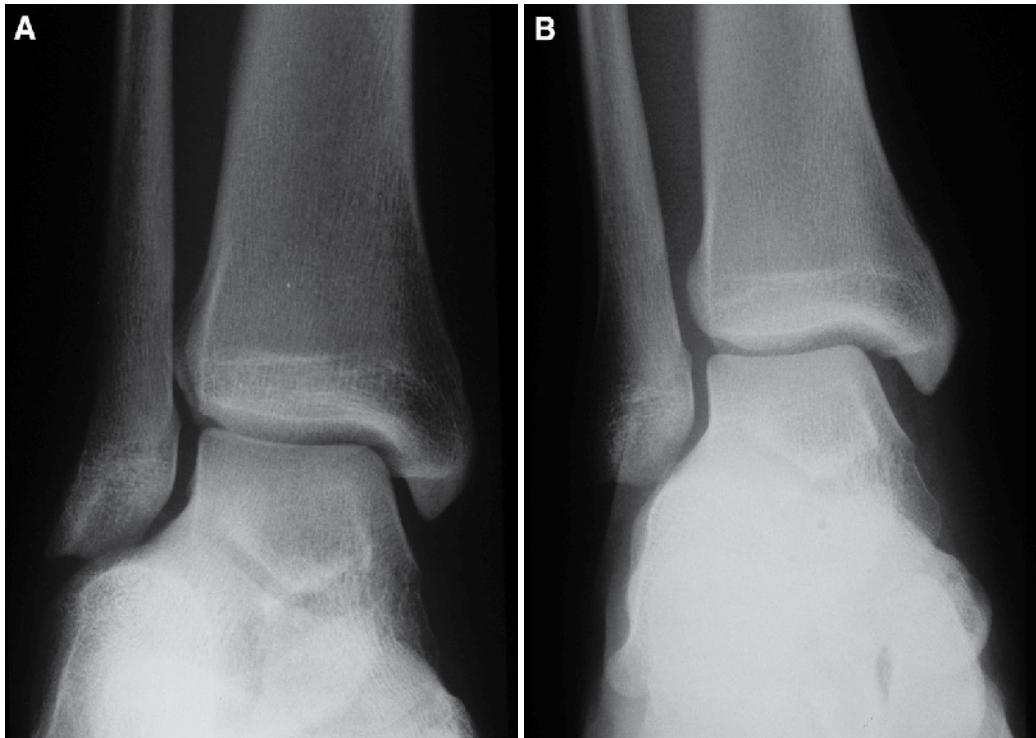
Fig. 10. Mortise radiographs of subject 1, 1 day after injury. (A), at rest, there is a suggestion of widening of the syndesmosis without widening of the medial clear space. (B), with external rotation stress, there is obvious widening of the medial clear space and distal syndesmosis

8. Classification

There are two classification systems for syndesmotic injuries. The West Point Ankle Grading system provided by Gerber and colleagues is more applicable to athletes [10] and is based on amount of edema, tenderness, ability to bear weight, stress testing, and abnormal radiographic parameters. It distinguishes the following categories of pure ligamentous syndesmotic injuries: grade I—no evidence of instability (partial tear of the AITFL; grade II—no or slight evidence of instability (tear of the AITFL, partial tear of the IOL); and grade III—definite instability (complete tear of the syndesmotic ligaments). A grade II injury poses a particular diagnostic challenge because the extent of injury and its occult instability often

requires provocative measures to recognize. Underestimating or undertreating the injury can have devastating consequences.

The other classification system is based on whether diastasis is acute or latent. Based on radiographic findings, Edwards and DeLee [86] classified traumatic syndesmotic sprains into latent diastasis (seen on stress radiographs only) and frank diastasis, which is obvious on plain radiographs.

Because the existing classification systems do not offer a clear therapeutic algorithm, clinical and radiographic examination should focus on detecting and documenting the amount of latent and frank diastasis, as well as documenting the time course of injury. Traumatic injuries can be catergorized into acute, subacute, and chronic. Acute injuries, identified within three weeks of injury, are divided into sprains without diastasis, sprains with latent diastasis, and sprains with frank diastasis based on clinical examination, routine radiographs, stress radiographs, and futher imaging studies. Injuries to the syndesmosis of longer than 3 weeks' duration are considered subacute. Syndesmotic injuries more than 3 months old are considered chronic. The latter two entities can be further subdivided based on variables such as presence of arthritic changes, and presence or absence of a synostosis.

9. Management

(TABLE 1) Treatment intervention is based on the severity of the syndesmotic injury. Grade 1 injuries are treated with non-surgical management. Symptomatic treatment includes a period of rest, ice, and immobilization for comfort and assistance with rehabilitation. For mild injuries in athletes, casting is generally not required and may impede course of therapy because of risk of disuse atrophy and stiffness. Patients often utilize crutches only 1 to 2 weeks for comfort in a controlled ankle motion walker boot. This immobilization allows

	Grade I	Grade II	Grade III
Clinical	Stable exam	Mid laxity	Unstable exam
	Good end point	Soft but positive end point	No end point
			Gross instability
X-rays	Stable on stress radiographs	0-1 mm laxity on stress x-rays	Unstable stress radiographs
Treatment	Rest, ice		
		Consider surgery; Cast immobilization may be 6-8 wk	
	Bracing and crutches for comfort	Return to play may be delayed for 6-8 wk until able to pass functional testing	Followed by functional bracing
	Functional brace at 2-4 wk	Take another x-ray at 2-3 wk to ensure no displacement	After surgery, follow same return to play as Grade II
	Return to play when no symptoms appear on functional testing	Then treat the same as Grade I injury	

Table 1.

athlete early mobilization but protects against external rotation. The athlete is then switched to a functional brace usually between weeks 2 and 4. Exercises are initiated during this transition. They include gradual increases in range of motion and stretching with eventual balance and bicycle program additions. Of note, patients need repeat examinations and radiographs every 1 to 2 weeks during this initial period to determine continued stability [87].

Nussbaum et al[38] and Williams et al [71] have described a 3-phase approach to rehabilitation. The acute phase aims at protecting the joint and decrease pain and swelling through immobilization and pain control. The subacute phase includes an increase in exercise intensity with goals of restoration of strength and basic functional motion. This includes cardiovascular conditioning. The final stage has its goal of returning the patient back to sport participation with strengthening, neuromuscular training, and sport-specific exercises. Determining the timing of return to sports is difficult and is based on examination as well as ability to perform sport specific tasks.

Grade II and III injuries are inherently unstable. The consensus concerning Grade III injuries is that operative fixation is necessary to maintain anatomic reduction of the mortise. The optimum treatment plan for Grade II injuries is less clear [88]. Nonoperative treatment for this injury includes initial splinting and protection from rotation as well as strict non-weight bearing status. Once swelling has retreated and the syndesmosis remains reduced on exam, the patient is transitioned to a short leg cast for 6 to 8 weeks. The athlete is then transitioned to progressive weight bearing in a walking cast, and then eventually to a soft ankle brace. If conservative approach is undertaken, again, serial evaluations are needed to ensure maintenance of reduction. Rehabilitation should focus on range of motion, balance, proprioception, strength, and return to play exercises specific to his/her sport [32]. Some investigators have suggested more aggressive treatment in athletes, including arthroscopic debridement and percutaneous screw fixation; however, this approach has not yet been substantiated by biomechanical or clinical data ([89] Early anatomic reduction and fixation ensures that the ligaments are in an optimal position for healing. Early fixation avoids the potential of a subtle missed diagnosis or for a delayed slip while attempting cast immobilization.

10. Operative treatment

10.1 Indications

The goal of surgical stabilization is to restore and maintain the normal tibiofibular relationship to allow appropriate healing of the ligamentous structures of the syndesmosis. Therefore, any sign of instability, either frank diastasis on radiograph or diastasis on stress radiographs, direct treatment towards syndesmotic fixation. However, these clear indications for surgical intervention represent a small percentage of the population. Taylor et al [90] noted that only 0.25% of ankle injuries and 1.7% of syndesmotic sprains are Grade III injuries with unstable radiographs. In addition, stress radiographs have been shown to be unreliable [91, 92] on biomechanical studies with a high false negative rate [32].

Chronic sprains with recalcitrant pain and functional instability are another indication for surgical fixation of the syndesmosis. Often times, these patients present with chronic ankle pain of an unknown etiology requiring an ankle arthroscopy to make the appropriate diagnosis [93, 94]. Thus, arthroscopic evidence of syndesmotic instability is another indication for surgical intervention. However, this modality is mostly used for chronic ankle pain, as it is unrealistic to perform an ankle arthroscopy on every ankle injury without radiographic signs of instability.

The challenge becomes identifying those patients with injuries that will result in prolonged recovery, recurrent symptoms, or chronic pain and instability despite normal radiographs. Amendola et al[95] performed a systematic review of syndesmotic sprains, and was only able to find six prospective studies investigating isolated syndesmotic sprains without radiographic widening or associated fracture in athletes. The average amount of time lost due to injury between studies was from 10 days to 52 days, but the range of missed time was from 0 days to 137 days. Surgical intervention was required in only two of these studies, with Wright et al [13] reporteding 1 out of 14 cases and Hopkinson et al [5] reporting 1 out of 15 cases. Recurrent or prolonged symptoms were not recorded in all the studies, but Hopkinson et al [5] noted no recurrences, Nussbaum et al [96] documented a 6% recurrence and Taylor et al [97] a 43% recurrence of ankle instability. Because of the small size, varied follow-up and heterogeneous outcome measures of these studies no conclusion could be made regarding risk factors or prognostic signs regarding prolonged symptoms, recurrent symptoms, or surgical intervention.

11. Surgical implants

There are a multitude of different implants employed for syndesmotic fixation. Metal screws are the most common hardware utilized, however recently the development of bioabsorbable screws and suture-button fixation has been analyzed as alternatives. Each mode of fixation has its own advantages and disadvantages, and several biomechanical studies are available in the literature evaluating each implant, as well as comparing different methods of fixation.

Fig. 11. Proper orientation of syndesmotic screws. Copyright: Mark Hutchinson, University of Illinois

There are multiple different methods to choose from when using a metal syndesmotic screw, such as composition of the screw, size of the screw and number of cortices of fixation (FIGURE 11). Several biomechanical studies have evaluated these parameters, and for the most part no difference in strength of fixation was found. Beumer et al[98] evaluated the difference between stainless steel and titanium screws, and found no difference in strength of fixation. The same study also noted no difference between three and four cortical fixation. No biomechanical advantage was found using a 4.5-mm screw over a 3.5-mm screw in tricortical fixation of the syndesmosis [99]. However, with quadricortical fixation the 4.5-mm screw did show improved resistance to shear stresses during axially loading compared to a 3.5-mm screw [100].

Syndesmotic fixation of the tibiofibular joint prevents its normal physiologic movement that occurs during normal weight bearing and ankle range of motion. Needleman et al [101] demonstrated that quadricortical fixation with a 4.5-mm screw decreases tibiotalar external rotation, and may result in fatigue fracture of the screw [102]. Three cortical fixation may decrease the rigidity of fixation and increase physiologic motion, but may also lead to hardware loosening [103]. Other complications associated with the metal screw include inferior tibiofibular synostosis [104] and osteolysis around the implant [102].

To avoid the hardware complications associated with metal screws, bioabsorbable screws have been proposed as an alternative mode of fixation. The goal of the bioabsorbable implant is to temporarily hold the tibiofibular joint in place while the syndesmosis heals, but over time hydrolyze and degrade to the point of failure after weight bearing as started to allow for normal physiologic motion of the ankle. Two cadaveric, biomechanical studies compared the load to failure and stiffness of fixation between a stainless steel screw and a polylactide bioabsorbable screw of the same size [105, 106]. Both studies found no difference in syndesmotic fixation between the metal and bioabsorbable screw group. Two randomized, clinic trials evaluating bioabsorbable and metallic screws found no loss of reduction in either group, with no different in subjective and objective outcomes between the two groups [107, 108]. In fact, patients were more likely to return to their previous level of activity when treated with a bioabsorbable screw rather than a metal screw [108].

The material of these bioabsorbable screws has caused concern regarding possible biologic reactions with the body. Several studies have reported osteolysis [109], foreign-body reaction [110, 111], late inflammatory reaction [112] and osteoarthritis due to polymer debris entering the joint [113] with use of bioabsorbable screws. However, these studies were either case reports, or involved treatment of ankle fractures or talar neck fractures. In the previous four studies comparing metal and bioabsorbable screws, there was no osteolysis or inflammatory reaction recorded.

Another alternative to screw fixation is the suture button. This method resists tibiofibular diastasis while allowing for some movement at the distal tibiofibular joint (FIGURE 12). Proponents of this technique believe that it is simple, safe and effective when compared to the syndesmotic screw [114, 115]. Several biomechanical studies have been published recently comparing this technique to metal syndesmotic screws. These studies were in agreement that the metal screw has on average increase strength to failure compared to the suture button, but that the suture button has more consistent strength [114, 116, 117]. Failure of the suture button occurs through the button, whereas failure of the screw is relative to

cortical thickness. Forsythe et al [118] found the suture-button was not as strong, with increased diastasis compared to a metal screw.

However, the studies did not agree on the amount of motion that suture-button allowed. Klitzman et al [119] noted in their biomechanical analysis that suture-button fixation allowed more physiologic motion of the fibula in the sagittal plane when compared to tricortical screw fixation. On the other hand, Soin et al [117] denied observing a difference in fibular motion during cyclic loading for the suture-button and syndesmotic screw. They described ankle motion for both constructs as being similar, and stated that neither was normal.

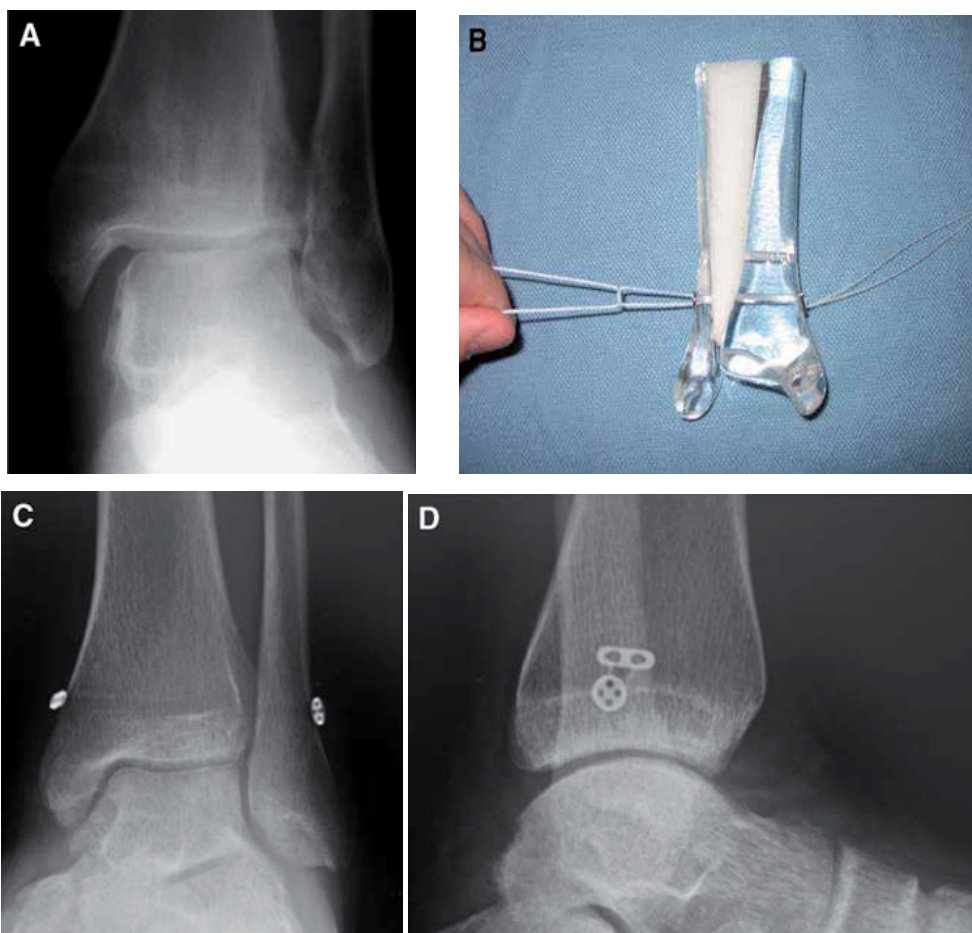Fig. 12. (A) Anteroposterior (AP) view of a widened syndesmosis. (B) TightRope system for syndesmosis fixation.(C, D) AP and lateral weight-bearing radiographs 6 months after a TightRope fixation of a syndesmosis disruption

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12. Surgical intervention

The AO technique for syndesmotic fixation recommends that diastasis screws be placed parallel and 2cm to 3cm above the ankle joint angled 20° to 30° anteromedially to match the anatomic relationship of fibula and tibia axially [120] (Figure 14). Two different cadaveric studies evaluated the level of placement of fixation, yielding conflicting data. McBryde et al examined syndesmotic fixation at 2 cm and 3.5 cm above the tibial plafond, and found 2cm above the tibial plafond gave improved syndesmotic fixation. Miller et al [121] found improved holding strength and decreased displaced with fixation at 5cm above the tibial plafond compared to 2cm regardless of using tricortical metal screws or suture button. The AO technique also warns about placing screws within 2cm of the tibial plafond for fear of inferior tibiofibular synostosis, although Kukreti et al [104] did not find a significant difference in synostosis when placed within 2cm of the ankle joint and between 2 – 5cm from the joint. Therefore, no conclusions can be made regarding the appropriate height of diastasis fixation.

No recommendations have been made between tricortical and quadricortical fixation. As previously discussed, there is no biomechanical difference between three cortical and four cortical fixation [98]. A prospective, randomized trial comparing two tricortical screws with one quadricortical screw showed improved subjective outcomes at three months for tricortical fixation [122]. By one year, the outcomes were not statistically different. Ankle motion between the two groups was equivalent at all time periods. All quadricortical screws were routinely removed at two months, while tricortical screws were removed in two patients because of discomfort.

The AO technique recommends one screw for syndesmotic fixation, with an additional screw being used with concurrent multiple fractures of the fibula [120]. Biomechanical studies have shown two screws increase the fixation strength of the tibiofibular joint [123], but there are no clinical studies comparing one-screw versus two-screw fixation. Another biomechanical study evaluated single versus double suture-button fixations[124]. The second suture-button added very little strength to the construct, which was still significantly less than an intact syndesmosis. However, this study did show that an "anatomic" suture-button fixation provided significantly improved strength compared to the original technique that was equivalent to the intact syndesmosis. This technique provides fixation at the posterior cortex of the fibula to the anterolateral edge of the tibia (FIGURE 13).

Traditional, syndesmotic fixation has been performed with the ankle in maximum dorsiflexion [101, 125]. This maneuver accounts for the narrower posterior talus engaging in the mortise during plantarflexion, which theoretically could cause overtightening of the mortise and prevent dorsiflexion when the wider anterior talus attempt to engage into the mortise. Lately, recent studies have shown that fixation in any amount of ankle flexion results in equivalent range of motion [126, 127].

13. Postoperative management

Most biomechanical studies evaluated in this review report fixation of the tibiofibular syndesmosis does not restore the strength or diastasis of the normal syndesmosis during normal weight bearing conditions. The only study that published data suggesting full strength and resistance to diastasis with loading is Teramoto et al [124] with use of their "anatomic suture-button" technique. However, their study also showed metal screw fixation that was stronger than the intact syndesmosis, which is contradictory to every other study regarding syndesmotic metal screw fixation. Because normal weight bearing results in
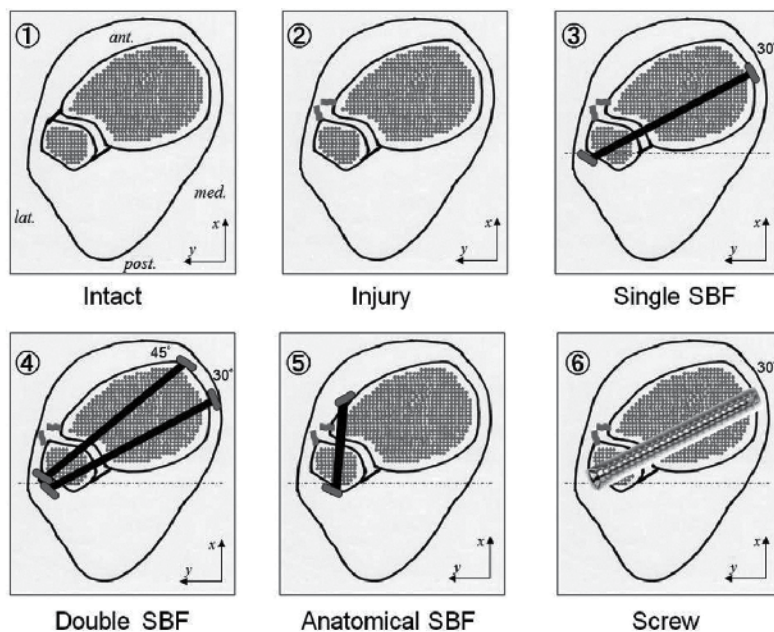
Fig. 13. Axial View of Different Fixation Devices for Ankle Syndesmosis. (1) Intact syndesmosis (2) Injured syndesmosis (3) Single Suture Button Fixation (4) Double Suture Button Fixation (5) Anatomic Suture Button Fixation (6) Screw Fixation
Reference: Figure 13 is from Teramoto A et al. Comparison of Different Fixation Methods of the Suture-Button Implant for Tibiofibular Syndesmosis Injuries. AJSM October 2011.
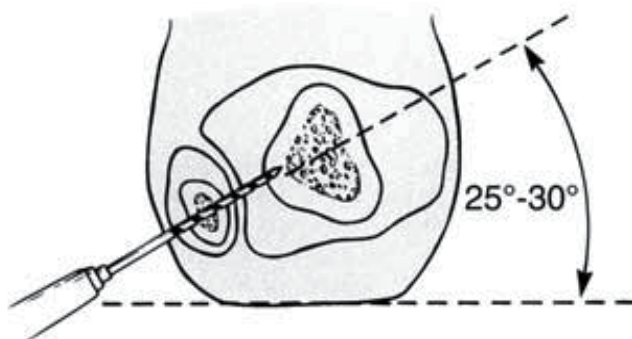
Fig. 14. Is from Browner BD, Jupiter JB, Levine AM, Trafton PG (eds). Skeletal Trauma ed 3. Philadelphia PA, WB Sauders, 2003, vol 2, p 2309.

increased diastasis regardless of surgical technique or implant, non-weight bearing is recommended for the first six weeks to allow the syndesmotic ligaments to heal. Weight bearing is then slowly progressed as tolerated.

Another controversy specific to metal screws is their removal postoperatively. As described previously, metal screws are at risk to loosen with tricortical fixation or break with quadricortical fixation. Other complications, such as symptomatic hardware, osteolysis and synostosis, are also possible postoperatively. Bell et al [102] retrospectively reviewed

patients with syndesmotic screws, and compared those that had the screw removed versus those in which the screw was maintained. There was no statistical significance between the two groups in ankle scores, range of motion or functional outcome. The only difference was a higher incidence of osteolysis and screw breakage in the retained screw group. Manjoo et al retrospectively divided patients into two groups: patients with intact screws and patients with fractured, loosened or removed screws. An intact syndesmotic screw was associated with worse function scores compared to loose, fractured or removed screws. No difference was noted in functional outcomes between patients with loose, fractured or removed screws. Intact syndesmotic metal screws are routinely removed as early as 8-12 weeks postoperatively [25, 128], but should not postpone weight bearing or limit rehabilitation. De Souza et al[129] did not show any adverse clinical outcomes to patients that began weight bearing prior to screw removal.

Rehabilitation can progress to functional activities when the patient demonstrates the ability to perform activities of daily living, ambulate on uneven/soft surfaces, and ascend/descend stairs without difficulty. Patients may return to sports participation when they demonstrate the ability to perform aggressive sports-specific tasks like running, jumping, kicking, and cutting/pivoting at competition/practice speed without noteworthy symptoms during or after participation. The expected time frame to return is around 12 to 14 weeks.

14. Outcomes

The literature has many outcome studies evaluating syndesmosis fixation in patients with concurrent ankle fractures. Most of these studies are retrospective case series. They show the most important predictor of functional outcome is accurate reduction of the syndesmosis [130-132]. A cadaveric study showed that 1mm of lateral talar displacement is associated with a 42% decrease in tibiotalar contact area [133].

Fewer studies have evaluated surgical fixation of pure syndesmotic injuries, and most of these studies are retrospective case series. There is a paucity of published data comparing the clinical results of different methods of surgical fixation. Edwards and DeLee[134] and Taylor et al[90] both published their case series of six patients with isolated, unstable ankle syndesmotic injuries that were treated with syndesmotic screw fixation. Edwards and DeLee reported 4 excellent and 2 good results, but no other information regarding functional outcome and return to sports. Taylor et al treated six intercollegiate athletes, and using aggressive rehabilitation was able to get the athletes to return to full activity in 41 days on average.

Degroot et al[135] followed 24 patients with suture button repair for syndesmotic injuries for an average of 20 months. Syndesmotic parameters returned to normal after surgery and remained normal throughout the followup period. However, one in four patients required removal of the suture endobutton device due to local irritation or lack of motion. Osteolysis of bone with subsidence of the device was noted in four patients, and three patients developed heterotopic ossification. This is somewhat surprising as the main advantage of suture button devices was the lack of hardware problems seen with metal screws. This study illustrates the point that clinical studies need to be performed to fully investigate outcomes of these devices. Although there is a significant amount of biomechanical data available, without good clinical evidence true recommendations regarding the best implant and technique for syndesmotic fixation will remain in question

15. Conclusion

Controversy surrounds almost every aspect of syndesmosis injuries from diagnosis to treatment to return of play. More research will help in defining these areas more clearly as the awareness has increased recently. Isolated injury to the syndesmosis is associated with chronic pain, prolonged recovery, recurrent sprains, and the heterotopic ossification. The delay in fixation that can occur with either a delayed or missed diagnosis with resultant instability takes the athlete out of the crucial period of ligamentous healing where the response to surgery is often decreased. Optimizing outcomes from these complex injuries requires early recognition through awaremess of mechanism of injury, a detailed physical exam, and appropriate imaging to assess for subtle changes. Successful treatment depends on early identification and timely intervention; anatomic reduction is required of any treatment modality. While the injury is difficult one, appropriate management can return the athlete to preinjury levels of participation, although their return will likely be delayed compared to lateral ankle sprains.

16. Acknowledgment

17. References

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Consequences of Ankle Inversion Trauma: A Novel Recognition and Treatment Paradigm

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1. Introduction

Diseases associated with physical inactivity (i.e. hypokinetic diseases) include, but are not limited to: cardiopulmonary disease, hypertension, obesity, metabolic disorders, non-smoking related cancers, and osteoporosis.(Admirall et al., 2011; CDC, 2009; Liu et al., 2008; Sesso, Paffenbarger, & Lee, 2000; Steanovv, Vekova, Kurktschiev, & Temelkova-Kurktschiev, 2011; Weiderpass, 2010) Physical inactivity remains one of the most important public health concerns as objective measures demonstrate that less than 5% of Americans participate in the recommended amount of physical activity necessary for health benefits.(Troiano et al., 2008) Additionally, physical inactivity is currently identified as the second leading actual cause of death, implicated in more deaths than the next seven causes of death combined.(Mokdad, Marks, Stroup, & Gerberding, 2004) Further, injury associated with sport, exercise, and recreation is a leading cause for the cessation of regular physical activity.(Koplan, Powell, Sikes, & Campbell, 1982; Pate, Pratt, Blair, & al., 1995) With lateral ankle sprains (LAS) being the most commonly occurring orthopedic pathology (Fernandez, Yard, & Comstock.R.D., 2007; Hootman, Dick, & Agel, 2007), and with such a high percentage of disability occurring after the initial injury(McKay, 2001; Verhagen, de Keizer, & Van Dijk, 1995) its role in potentially limiting physical activity is significant.(Verhagen et al., 1995) Despite the obvious public health problem that ankle sprains represent, no significant inroads have been made at preventing the injury and/or treating the associated sequelae using traditional treatment paradigms. Thus the evidence regarding the presentation and treatment of the consequences associated with LAS will be described within the context of a new recognition and treatment paradigm known as the PCL(McKeon PO, Medina McKeon JM, Mattacola CG, Lattermann C. Finding, 2011) (patient-, clinician-, laboratory-oriented) model which addresses the sequelae of lateral ankle sprains from a holistic perspective. Further, this model will be situated within the dynamic systems theory to provide the framework for understanding how all of the individual post-injury adaptations create a singular pathology that predisposed an individual to fall into a continuum of disability that will affect them for the remainder of their lives.

2. Ankle sprain epidemiology

2.1 Observation and description of the clinical phenomenon

Lateral ankle sprains are the most common injuries associated with physical activity and athletic participation. (Fernandez et al., 2007; Hootman et al., 2007) Forceful plantar flexion and inversion is the most common mechanism of injury causing damage to the passive lateral ligamentous structures of the ankle.(Baumhauer, Alosa, Renstrom, Trevino, & Beynnon, 1995) Specifically, the anterior talofibular ligament (ATFL), reported to be the weakest, is the first ligament injured.(Brostrom, 1964) Rupture to the ATFL is followed by damage to the calcaneofibular ligament (CFL) and finally to the posterior talofibular ligament (PTFL).(Brostrom, 1964) Isolated injury to the ATFL occurs in 66% of LAS while ATFL and CFL ruptures occur concurrently in another 20%.(Brostrom, 1964) The PTFL is not commonly injured because of the large amount of dorsiflexion needed to strain the ligament places the ankle in a closed packed and thus more stable position. The current literature suggests it takes over 6 weeks for ligament damage to heal, (Avci & Sayh, 1998; Brostrom, 1966; Cetti, Christensen, & Corfitzen, 1984; Freeman, 1965b; Konradsen, Holmer, & Sondergaard, 1991; Munk, Holm-Christensen, & Lind, 1995) however, studies have also documented joint laxity 6 months after injury.(Brostrom, 1966; Cetti et al., 1984) In addition to the lateral ligamentous structures of the talocrural joint, the subtalar ligaments can also be injured. However, injury to the subtalar joint often occurs in combination with injury to the lateral ankle ligaments as evidenced by the estimated 75 to 80% incidence of subtalar instability in those with CAI.(Hertel, Denegar, Monroe, & Stokes, 1999; Meyer, Garcia, Hoffmeyer, & Fritschy, 1986) Damage to the ligaments of the ankle can lead to the development of an unstable or hypermoble ankle joint which ultimately leads to an increase in the accessory motion available at a joint. Increased accessory motion places further strain on the injured ligaments and it is hypothesized that increased mobility of the talus, due to hypermobility, may lead to the axis of rotation becoming more anterior or posterior in the frontal plane.

With injury to ligaments, mechanoreceptors may also be damaged. If damaged, the afferent (i.e. sensory) input from ligamentous mechanoreceptors may be altered and further disrupt the axis of joint rotation causing the injured individual to compensate in an effort to maintain proper function.(Konradsen & Magnusson, 2000) However, there is a lack of consistent empirical data to confirm that alterations in function are due to the loss and/or disruption of afferent input from ligament mechanoreceptors.(Hubbard & Hertel, 2006a) Despite the inconsistency of the literature, evidence does exist to suggest that a loss of afferent information from the lateral ligaments can have both local and global consequences on sensorimotor function in both asymptomatic individuals (Myers, Riemann, Hwang, Fu, & Lephart, 2003; McKeon, Booi, Branam, Johnson, & Mattacola, 2010) and those with CAI.

In addition to ligamentous mechanoreceptors, musculotendinous mechanoreceptors may also become altered with ankle instability.(Freeman, 1965a) Increased mobility of the talus stresses the joint capsule (Wilkerson & Nitz, 1994) which then negatively affects (via the gamma motorneurons) the activation threshold of the muscle spindles in muscles and tendons that cross the ankle joint. Further, the gamma motor neurons may also increase co-contraction levels (Wilkerson et al., 1994) resulting in altered afferent signals being sent to the central nervous system. Evidence of these altered afferent signals are the early recruitment of proximal muscles such as the gluteals to help provide stability (i.e. the development of a hip strategy).(Beckman & Buchanan, 1995; Bullock-Saxton, janda, &

Bullock, 1994) A vicious and continuous cycle is thus put into motion when proper healing and joint alignment are not restored due to inappropriate treatment.(Hubbard et al., 2006a) Unfortunately, inappropriate or totally absent treatment occurs far too often for lateral ankle sprains. Indeed, LAS are often erroneously considered to be an inconsequential injury with no lasting consequences. However, LAS account for approximately 60% of all injuries during interscholastic and intercollegiate sports in the United States.(Fernandez, Yard, & Comstock, 2007; Hootman et al., 2007) Further, more than 23,000 LAS are estimated to occur per day in the United States which equates to approximately one sprain per 10,000 people daily.(Kannus & Renstrom, 1991) In addition, health care costs for acute LAS have been estimated to be over $4 billion dollars annually in the United States alone when accounting for inflation in 2011.(Soboroff, Pappius, & Komaroff, 1984) Another consequence of societal insignificance assigned to LAS is the high percentage of people (~55%) who sprain their ankle and do not seek treatment from a health care professional.(McKay, 2001) As a result, the true incidence of injury may be much greater than what has been previously reported.

Even more troubling is the fact that about 30% of those who suffer a first time LAS develop CAI; however this number has been reported as high as 75%.(Anandacoomarasamy & Barnsley, 2005; Peters, Trevino, & Renstrom, 1991; Smith & Reischl, 1986) This translates to at least 1 out of every 3 individuals who sprain their ankle will go on to suffer residual symptoms (i.e. CAI) indefinitely. Indeed, the residual symptoms that define CAI significantly alter an individual's health and function by causing them to become less active over their life span.(Verhagen et al., 1995) Further, a clear link has been established between CAI and post-traumatic ankle osteoarthritis (OA). Post-traumatic ankle OA is the most common cause, accounting for more than 70% of all ankle OA cases (Valderrabano, Hintermann, Horisberger, & Fung, 2006a) and both ankle joint fractures (Horisberger, Valderrabano, & Hintermann, 2009b) and ligament lesions associated with CAI (Hirose, Murakami, Minowa, Kura, & Yamashita, 2004; Valderrabano et al., 2006a) are a significant cause of post-traumatic ankle OA. Indeed, a high percentage (66-78%) of patients with CAI go on to develop post-traumatic ankle OA.(Hirose et al., 2004; Valderrabano et al., 2006a)

3. Pathophysiology: Perspectives of the patient, clinician, and laboratory scientist

3.1 Acute ankle sprains
3.1.1 Patient-oriented evidence
Anyone who has ever suffered a lateral ankle sprains knows that it is a painful and disabling injury. The published literature also supports this belief across a wide range of self-report questionnaires/scales.(de Vries, Kingma, Blakevoort, & van Dijk, 2010; Evans, Hertel, & Sebastianelli, 2004) For example, Brostrom (Brostrom, 1966) reported 20% of patients reported their ankle feeling unstable a year after an initial ankle sprain. Further, a prospective investigation performed by Evans et al.(Evans et al., 2004) indicated that self-assessed disability (as measured by two independent scales) did not return to baseline (i.e. pre-injury) levels until twenty-one days post injury.

3.1.2 Clinician-oriented evidence
The hypermobility associated with acute LAS can be assessed qualitatively and empirically using various clinical techniques such as manual stress tests, instrumented arthrometry and stress radiographs. Manual stress tests are one of the most common means to assess laxity

after an ankle sprain. To date, evidence indicates that 30% of patients have had a positive anterior drawer 2-weeks post injury and 11% had a positive anterior drawer 6-weeks post injury.(Avci et al., 1998)   Additionally, 12% have been shown to have a positive anterior drawer at 8-weeks post injury. (Cetti et al., 1984)   Similarly, significantly more anterior displacement and inversion rotation was shown via an ankle arhtrometer 8-weeks after an acute LAS.(Hubbard & Cordova, 2009a) Another study showed that 42% and 33% of subjects from separate treatment groups had an increased talar tilt compared to their uninvolved healthy ankle at 3-months post injury using stress radiography. (Freeman, 1965b) At 1-year post injury, ~30% of patients had a positive anterior drawer. (Brostrom, 1966) Using a more objective outcome, 5% of patients presented with pathologic stress radiography values 3-months post injury.(Konradsen et al., 1991)   Further, over 50% of patients who sprained their ankle between 9-13 years prior, had mechanical laxity on stress radiographs.(Munk et al., 1995)

In addition to hypermobility, LAS can also cause hypomobility. Hubbard and Hertel (Hubbard & Hertel, 2008), using simple lateral radiographs of the ankle, found that the distal fibula has been pulled anteriorly, relative to the tibia, from a 'normal' position seen in healthy uninjured adults (i.e. a positional fault had occurred). Similarly, a decreased posterior talar glide (Denegar, Hertel, & Fonseca, 2002) has been observed in those with acute LAS suggesting that a talar positional fault may also be present. Since normal osteokinematic motion cannot occur without propoer arthrokinematics, these studies support the commonly observed limitations in ankle range of motion (ROM) following acute LAS.(Aiken, Pelland, Brison, Pickett, & Brouwer, 2008; Youdas, McLean, Krause, & Hollman, 2009) These studies have shown that: 1) active dorsiflexion ROM returns to 'normal' values between 4- and 6- weeks post injury (Youdas et al., 2009) and that clinical measures of ROM are not as sensitive as laboratory measures (e.g. isokinetic dynamometer).(Aiken et al., 2008)

3.1.3 Laboratory-oriented evidence

There have been numerous investigations that have quantified deficits in sensorimotor function in those with LAS using laboratory-oriented evidence. In short, grade II or III acute LAS have been reported to cause deficits in ankle inversion joint position sense for up to 12- weeks post injury when compared to the uninjured limb.(Konradsen, Olesen, & Hansen, 1998)   In addition, isometric strength deficits have been reported, in multiple planes of motion, as long as 6-weeks post injury.(Holme et al., 1999; Koralewicz & Engh, 2000) The most commonly studied sensorimotor outcome is postural control. Recent systematic reviews demonstrated that postural control is impaired on the involved limb (McKeon & Hertel, 2008a; Wikstrom, Naik, Lodha, & Cauraugh, 2009) and uninvolved limb following acute LAS.(Wikstrom, Naik, Lodha, & Cauraugh, 2010c)   These findings are supported by prospective data indicating that balance deficits on the uninjured limb resolve in about 7- days while balance deficits on the involved limb take about 21-28 days to fully resolve.(Evans et al., 2004)   Given the above mentioned impairments, as well as the obvious pain and dysfunction associated with LAS, it is not surprising that both the temporal and spatial parameters of gait are also impaired.(Crosbie, Green, & Refshauge, 1999)

3.2 Chronic ankle instability

Based on the above presented information, it is clear that there a numerous consequences of acute LAS and that those consequences are multi-factorial in nature. While the exact

physiological mechanism of CAI remains unknown, evidence suggests that it is multi-factorial in nature. Therefore, while ankle ligamentous damage is the most obvious result of a LAS, the laxity itself is not likely to be the sole cause of CAI. Rather, the true mechanism is most likely linked to a number of adaptations and impairments which cause a cascade of events that ultimately leads to CAI (Figure 1).(Hertel, 2008) One consequence that has been, for the most part, ignored is the loss of relevant sensory (i.e. afferent) information from those damaged ligaments, and surrounding tissue, that is associated with the continuum of disability.(McKeon, 2010; McKeon et al., 2010) As mentioned above, the deafferentation theory (Freeman, 1965a), has been refuted in the literature because of inconsistent support and because the link between local mechanical instability and global functional disability in those with CAI has not been clearly established. One factor that remains clear however, is that those with CAI have a decreased ability to cope with changes in task and environmental demands. This inability to effectively cope is thought to be most commonly manifested in episodes of giving way.
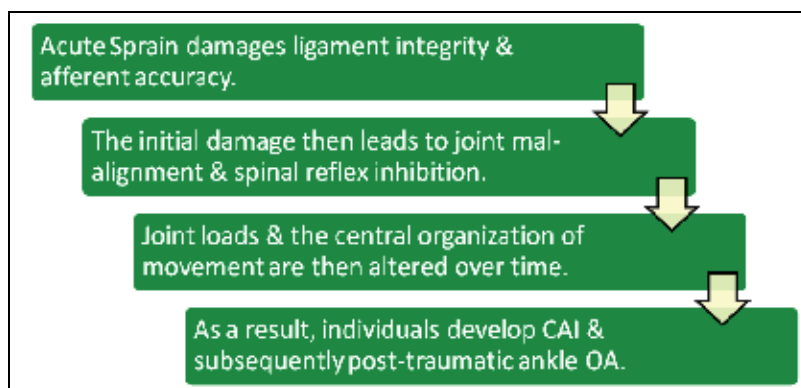

Fig. 1. Hypothetical cascade of events that causes the development of CAI and post-traumatic ankle OA based on the available evidence.

3.2.1 Patient-oriented evidence

The most commonly reported symptom across the continuum of disability associated with CAI is decreased functional performance due to repeated episodes of 'giving way'.(Hertel, 2002; 2008) It is crucially important to assess how impaired sensorimotor control due to CAI, often measured with laboratory-oriented outcomes, manifests into patient-reported activity limitations and participation restrictions. In other words, how does the instability a patient experiences at the ankle move from a local ankle instability to a global disability in function? Gaining the patient's perception of disability is very important in developing a thorough understanding of the impact of CAI on quality of life. These patient-oriented tools can be used to both assess the impact of CAI and the effects of rehabilitation strategies on function. Overall, patient-oriented measures of function provide the opportunity to gain insight into how the patient experiences disability due to ankle injuries.

Numerous scales/questionnaires have been developed in the sport injury literature to quantify the impact of CAI on patient-oriented function. Each scale assesses functional ability differently and has unique grading/weighting systems but all scales contain questions related to an individual's ability to complete both activities of daily living and

sport. The Ankle Joint Functional Assessment Tool (AJFAT), Cumberland Ankle Instability Tool (CAIT), Foot and Ankle Outcome Score (FAOS), the Foot and Ankle Disability Instrument (FADI), and the Foot and Ankle Ability Measure (FAAM) are some of the more commonly reported scales in the literature. In 2007, Eechaute et al.(Eechaute, Vaes, Van Aerschot, Asman, & Duquet, 2007) performed a systematic review of the clinimetric qualities of these scales and found that the FADI and the FAAM are the most appropriate scales to use for the assessment of function in those with CAI. Further, a self-reported loss of at least 10% of function during activities of daily living and at least a 20% loss of function during sport-related activities are the current recommendations for classifying those with CAI when using the FADI and/or FAAM.(Hale & Hertel, 2005)

3.2.2 Clinician-oriented evidence

Capturing the deficits that patients report associated with CAI in measurable clinical tests is crucial for the development of objective outcomes for diagnosis, prognosis, and rehabilitation. Several clinical tests have been developed to assess the effects of CAI across a wide range of outcomes and some of the more commonly reported will be discussed below.

There have been numerous studies which have reported mechanical instability in those with CAI. Tropp et al.(Tropp, Odenrick, & Gillquist, 1985) reported 42% of subjects with CAI had a positive manual anterior drawer test. More recently, Hertel et al.(Hertel et al., 1999) illustrated ankles with CAI demonstrated significantly greater laxity during an anterior drawer test and greater talar tilt angles upon supination stress than did uninjured ankles. Significantly greater talar tilt values have also been shown in those with CAI compared with a healthy reference group.(Lentell et al., 1995; Louwerens, Ginai, Van Linge, & Snijders, 1995) Similar results have also been reported using an instrumented ankle arthrometer (i.e. more anterior translation and inversion stress in those with CAI relative to uninjured ankles).(Hubbard, Kramer, Denegar, & Hertel, 2007) Further, those with CAI, relative to uininjured controls, have been shown to have an anterior positional fault of the distal fibula (Hubbard, Hertel, & Sherbondy, 2006b) and talus.(Wikstrom & Hubbard, 2010b) These results using different techniques demonstrate that mechanical instability and structural adaptations are present in patients with CAI and similar to those reported following a LAS.

The weight-bearing lunge test (WBLT) is a clinical measure of the amount of dorsiflexion available in a weight-bearing environment.(Hoch & McKeon, 2011) It has been demonstrated that those with CAI have a dorsiflexion deficit on their affected limb during functional activities.(Drewes, McKeon, Kerrigan, & Hertel, 2009) The WBLT and the anterior reach of the Star Excursion Balance Test (SEBT) are highly correlated in healthy people, but not correlated as highly in those with CAI suggesting that those with CAI adopt a new movement strategy to complete the test. The SEBT has been the most extensively studied clinical measure of balance.(Gribble, Hertel, & Denegar, 2007; Hertel, 2008; Hertel, Braham, Hale, & Olmsted-Kramer, 2006; Olmsted, Olmsted, Carcia, Hertel, & Shultz, 2002) It has been consistently shown that those with CAI have a reduced ability to maintain balance on their injured leg and maximally reach with the opposite limb in different directions. Currently, it is recommended that the anterior, posteromedial, and posterolateral directions be used because each present a unique contribution to the assessment of dynamic postural control deficits and because these directions can elucidate postural control deficits associated with CAI.(Hertel, 2008; Hertel et al., 2006) Another test for the assessment of balance in those with CAI is the Balance Error Scoring System (BESS) (Docherty, McLeod, & Shultz, 2006). The premise of the

BESS is that individuals attempt to maintain balance under a series of postural challenges and the clinician counts the number of errors committed during the test. Further, the BESS provides a clinical assessment which utilizes the manipulation of different postural control tasks and environments to explore the sensorimotor system's ability to cope with changing demands. Out of the six conditions of the BESS, it has been found that the single limb stance on a firm surface and a foam surface provide the most relevant information associated with clinically relevant postural control deficits in those with CAI.(Docherty et al., 2006)

3.2.3 Laboratory-oriented evidence

Ankle instability has been shown to result in a host of functional impairments. These impairments have included local effects thought to be a direct consequence of the joint damage described above including deficits in ankle joint position sense and movement detection, evertor muscle strength, peroneal and soleus motor neuron pool excitability, and peroneal muscle reaction time in response to perturbation (see Hertel, 2008) for further review). In addition to local effects around the joint, CAI has also been associated with global deficits in sensorimotor function, specifically alterations in proximal muscle and joint control as well as alterations in stereotypical movement patterns. For example, those with CAI have decreased hip extension and abduction strength.(Hubbard et al., 2007) and have diminished levels of alpha motorneuron pool excitability at the knee.(Sedory, McVey, Cross, Ingersoll, & Hertel, 2007) The use of motion analysis systems has also identified an increased use of knee flexion ROM while landing from a jump (Caulfield & Garrett, 2002) and altered hip biomechanics during the SEBT in those with CAI.(Gribble, Hertel, & Denegar, 2007) Differences have also been seen in stereotypical movement patterns which are now believed to be the result of a constrained sensorimotor system. For example, those with CAI have altered movement patterns during the swing phase of walking gait (Delahunt, Monaghan, & Caulfield, 2006; Monaghan, Dean, & Caulfield, 2006) and throughout the entire running gait cycle.(Drewes et al., 2009) More recently neuromuscular and biomechanical control alterations have been seen during gait initiation (Hass, Bishop, Doidge, & Wikstrom, 2010) and gait termination.(Wikstrom, Bishop, Inamdar, & Hass, 2010a) These most recent investigations clearly demonstrate that the global deficits associated with CAI negatively affect the central nervous system as both gait initiation and termination are mediated via supraspinal motor control mechanisms.(Wang et al., 2009). Cumulatively, these deficits and/or alterations in proximal muscles and joint control as well as stereotypical movement patters indicate global deficits in sensorimotor function. However, the link between local and global impairments in sensorimotor control is poorly understood at this time and this link must be a focus of future investigations if more effective treatments are to be developed.

3.3 Post-traumatic ankle OA

Only recently has there been an impetus to investigate the impairments associated with post-traumatic ankle OA because the diagnosis of ankle OA is becoming more common (Saltzman et al., 2005) and because ankle replacement procedures are anticipated to increase at a rate of about 5% a year.(Jeng, 2006) However, there is a limited amount of information available regarding patient-, clinician-, and laboratory-oriented evidence for those with ankle OA at this time. The vast majority of post-traumatic ankle OA research has been focused on patient-oriented evidence and the results consistently show, regardless of the

scale used, that those with post-traumatic ankle OA have greater levels of self-reported disability relative to age matched controls.(Horisberger, Hintermann, & Valderrabano, 2009a; Hubbard, Hicks-Little, & Cordova, 2009b; Khazzam, Long, Marks, & Harris, 2006; Messenger, Anderson, & Wikstrom, 2011; Valderrabano et al., 2007; Valderrabano et al., 2006b) Clinical-oriented evidence shows similar impairments as those associated with acute LAS and CAI. Specifically, decreases in ankle muscle strength and increased mechanical stiffness have been observed relative to age matched controls.(Hubbard et al., 2009b) Laboratory-oriented evidence is also similar to the impairments associated with acute LAS and CAI. For example, static postural control (i.e. plantar pressure distributions and COP displacements) have been reported to be altered and/or increased (Horisberger et al., 2009a; Hubbard et al., 2009b; Messenger et al., 2011) and walking gait velocity, cadence, and stride length are all reduced in those with ankle OA.(Khazzam et al., 2006; Valderrabano et al., 2007) Most recently, Messenger et al.(Messenger et al., 2011) illustrated that post-traumatic ankle OA alters gait initiation relative to uninjured age-matched controls. This evidence further illustrates that the long term sequela of LAS are global in nature and can negatively influence the central nervous system.

4. Finding context

Based on the information provided above from the PCL model, those with acute LAS, CAI, and post-traumatic ankle OA report significant and similar limitations in patient-, clinician-, and laboratory-oriented outcome measures. By examining all 3 sources of evidence, it is clear that an ankle sprain is more than just a peripheral musculoskeletal pathology with only local consequences. Further, examining the interaction of specific deficits on global function will help elucidate the cascade of events that leads to the development of CAI (Figure 1) and more importantly identify effective evidence-based treatment protocols that can address not only the isolated impairments but also the complex interactions among them. By developing context through the PCL model, a more thorough understanding of the consequences of injury and rehabilitation can be gained. What remains needed is a working theoretical construct to link these sources of evidence in a meaningful way. In the next section, we provide the theoretical construct that we believe will allow a more thorough understanding to be obtained.

5. Ankle instability and impaired sensorimotor control

The human body is a system composed of many interacting parts which can be organized in a variety of ways to accomplish movement goals.(Davids & Glazier, 2010) The hallmark of this system is its ability to adapt to changing demands both internally and externally. The sensorimotor control theory that captures the dynamic nature of this system is known as the dynamic systems theory of motor control.(Davids, Glazier, Araujo, & Bartlett, 2003) According to dynamic systems theory, the organization of the sensorimotor system is constrained, or shaped, by the interaction of 1) the health of the person (organismic constraint), 2) the task being performed (task constraint), and 3) the environment in which a movement goal is executed (environmental constraint) (Hoch & McKeon, 2010b; McKeon & Hertel, 2006) (Figure 2). Rather than having preprogrammed pathways to accomplish a movement goal, the dynamic systems theory states that the sensorimotor system is free to develop and change strategies based on its current state as it interacts with the

environment.(Davids et al., 2010) For example, an individual will use different gait strategies when walking on a sidewalk compared to walking in soft sand on a beach because the individual is interacting with different environments. In this way, coordination within the sensorimotor system changes based on the constraints related to the movement goal. Because of this freedom of spontaneous (goal-oriented) self-organization, a healthy sensorimotor system can accomplish a movement goal in a variety of ways based on the interaction with the tasks performed and the environmental cues received.(Hoch et al., 2010b) If there are changes in the task or environment, the sensorimotor system can reorganize to adopt a new strategy to achieve the movement goal. More strategies translate to an enhanced ability to successfully accomplish the movement goal and cope with change. This has been referred to as invariant results through variant means, also known as functional variability.(Latash, Scholz, & Schoner, 2002)
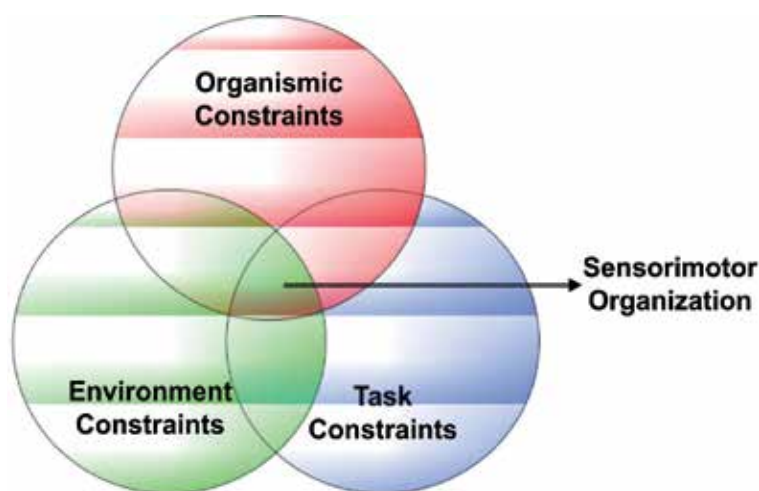

Fig. 2. Sensorimotor organization based on the interaction of constraints as described by the Dynamic Systems Theory

Ankle injury, which introduces organismic constraints, can significantly hinder the sensorimotor system in its ability to accomplish movement goals.(Hoch et al., 2010b) Ankle injuries result in mechanical and functional alterations within a component part of the sensorimotor system.(Hertel, 2002) Consequently, injured parts of the system cannot be used in movement solution development. This then reduces the functional variability of the sensorimotor system—in other words; it is constrained in its ability to cope with change. The result of this decrease in sensorimotor control is a reduction in functional performance. Ankle injury epidemiological evidence supports this framework in that the primary risk factor for an ankle sprain is a previous history of one. (Beynnon, Renstrom, Alosa, Baumhauer, & Vacek, 2001) Based on this information, it is apparent that there is the potential for a continuum of disability associated with CAI (McKeon, 2010) (Figure 3). Poor control may predispose a person to injury and injury significantly constrains sensorimotor control. To gain understanding into this continuum as it relates to CAI, we will discuss management strategies that address different points along the continuum and present recommendations to help improve treatment options that may attenuate the effects of organismic constraints on sensorimotor control.
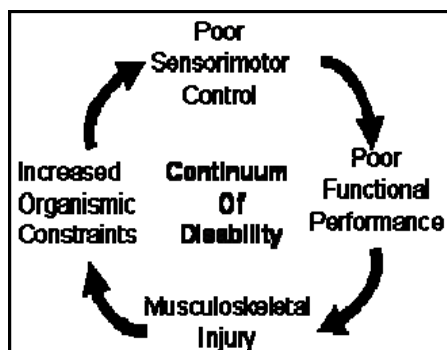
Fig. 3. Continuum of Disability

6. Management strategies through the continuum

Acute LAS management typically involves rest, ice, compression, elevation (RICE) and functional rehabilitation (i.e. early mobilization with support).(Mattacola & Dwyer, 2002) In more severe cases, LAS are treated with crutches and are typically immobilized for a short period of time.(Mattacola et al., 2002) To date, numerous investigations have assessed the efficacy of rehabilitation techniques on short-term patient-oriented outcomes including: pain, ROM, and return to work/activity. However, the high percentage of re-injury occurrence (up to 70%) and development of CAI (up to 75%) (Anandacoomarasamy et al., 2005; Peters et al., 1991; Smith et al., 1986) after an LAS, suggests that further research of both short and long-term outcomes following rehabilitation is needed to investigate not only specific mechanical and/or sensorimotor impairments but the interactions among them by examining patient-, clinician-, and laboratory-oriented evidence.

6.1 Acute care/immobilization – Overcoming the constraints of a damaged joint

Immediately after a LAS the primary goals are to manage pain, control inflammation and protect the joint. In the acute phase of healing, the most important structures to protect are the lateral ligaments of the ankle because the traumatic mechanism has caused increased laxity. In the past, the majority of the literature has focused on functional rehabilitation (i.e. early mobilization with support) but the high recurrence rates of LAS and development of CAI suggest that functional rehabilitation may not allow adequate time for the ligaments of the ankle to heal and stability to be restored. Indeed, increased laxity has been reported using both patient- (ankle giving way, or feelings of instability) and clinician-oriented (manual stress tests, radiographs) outcomes.(Hertel et al., 1999; Hubbard et al., 2007; Lentell et al., 1995; Louwerens et al., 1995) Unfortunately, ankle laxity often persists despite treatment as positive anterior drawer tests were still present in 3%-31% of subjects 6-months after injury (Cetti et al., 1984; Konradsen et al., 1991) and feelings of instability were present in 7%-42% of subjects up to 1-year after injury.(Brostrom, 1966; Munk et al., 1995) Cumulatively, these studies provide strong evidence that better and longer protection of the ankle joint after an acute LAS is needed to help restore mechanical stability. If mechanical stability is not restored, increased laxity could lead to further mechanical adaptations, deficits in sensorimotor control, recurrent injury and decreases in global function as a maladaptive compensation of the changes in joint laxity and/or sensorimotor control.

To help examine the effects of immobilization, a multi-center prospective randomized control trial was conducted examining three different mechanical supports (Aircast brace, Bledsoe boot, and 10-day below the knee cast) compared with that of a double-layer tubular compression bandage (current standard of care) in promoting recovery after severe LAS.(Lamb, Marsh, Nakash, & Cooke, 2009) A total of 584 patients with LAS were followed over nine months with the primary outcome being the quality of ankle function measured using the Foot and Ankle Score (i.e. a patient-oriented outcome). The below-knee cast caused a more rapid recovery than the tubular compression bandage with clinically important benefits in quality of ankle function at 3-months post injury.(Lamb et al., 2009) Based on the data, a short period of immobilization in a below-knee cast or Aircast ankle brace (2nd best results) may result in faster recovery than the current standard of care. Additionally, the authors recommended the below-knee cast because it showed the widest range of benefit. However, future research is needed to determine if similar benefits will be found in clinical and laboratory measures such as ligament laxity and postural control.

An earlier study (Beynnon, Renstrom, Haugh, Uh, & Barker, 2006) also examined the type of immobilization that had the best outcomes. The authors stratified acute LAS based on the grade (I, II, or III) and randomized patients to undergo functional treatment with different types of ankle immobilization. They compared an elastic wrap (current standard of care), Air-Stirrup ankle brace, Air-Stirrup ankle brace with an elastic wrap and fiberglass walking cast. They reported treatment of grade I and II ankle sprains with Air-Stirrup brace combined with elastic wrap allowed patients return to pre-injury function, as measured by both patient- and clinical-oriented evidence, quicker than the other immobilizers.(Beynnon et al., 2006) For grade III sprains, there were no differences between the Air-Stirrup brace and the fiberglass walking cast. The subjects in the Lamb et al.(Lamb et al., 2009) study were considered to have severe ankle sprains, which may be why the below-knee cast was more favorable.

Based on the research available to best treat acute LAS, some form of immobilization needs to be used to help protect the joint and allow ligament healing to occur. Thus, elastic or tubular wraps are not recommended because research suggests that they do not provide adequate protection to allow restoration of function. An Air-Stirrup brace with elastic wraps for grade I and grade II, and below-knee casts for grade III appear to be the best treatment strategy based on the current literature. After a period of controlled immobilization functional exercises are necessary to rehabilitate the joint and two of the more commonly used adjunctive therapies are discussed below.

6.2 Joint mobilizations

To date manipulative therapy techniques; including Maitland's mobilizations,(Maitland, 1985) Mulligan's mobilizations with movement,(Mulligan, 2004) and High-Velocity Low-Amplitude (HVLA) thrusts,(Bleakley, McDonough, & MacAuley, 2008; van der Wees et al., 2006) have all been postulated to be effective treatments for acute LAS. Indeed, manipulative therapy techniques are theorized to reduce pain (patient-oriented), improve function and increase ROM via the restoration of arthrokinematic motions (i.e. roll, glide, spin) (clinician-oriented),(Maitland, 1985) and improve spatiotemporal postural control in single limb stance (laboratory-oriented); thus recommendations to use these techniques make intuitive sense.

Patient-oriented outcome measures have improved following manipulative therapy. For example, multiple manipulative therapy treatment sessions result in improvements in self-report levels of pain and function.(Coetzer, Brantingham, & Nook, 2001; Green, Refshauge,

Crosbie, & Adams, 2001; Pellow & Brantingham, 2001; Whitman et al., 2009) Further, a single treatment session, involving multiple osteopathic and manipulative techniques, immediately reduced self-reported pain in patients with acute LAS.(Eisenhart, Gaeta, & Yens, 2003) Based on this evidence, it appears that multiple treatment sessions are needed to consistently see improvements in a variety of patient-oriented outcomes, regardless of the specific manipulative therapy technique used, in patients with acute LAS. However, the exact number of treatments and dosage within each treatment session remains unknown.

The available literature also indicates that both active and passive ROM (clinician-oriented evidence) are improved following the delivery of multiple treatment sessions.(Green et al., 2001; Pellow et al., 2001) Additionally, significant improvement in non-weight bearing range of motion (ROM) was reported after the delivery of a variety of manipulative therapy techniques over a 2-week intervention.(Coetzer et al., 2001) Thus, the cumulative data suggest that multiple treatment sessions are needed to see ROM improvements in patients with acute LAS. However, significant improvements in dorsiflexion ROM have been reported after just a single treatment session of Maitland's (AP talocrural) mobilizations in patients who underwent a prolonged period of ankle immobilization for a variety of pathological conditions.(Landrum, Kellen, Parente, Ingersoll, & Hertel, 2009) Thus, it appears that even if acute LAS patients are immobilized (i.e. casted) following injury, ankle joint mobilizations could be used to help restore ROM.

Similarly, a single treatment session consisting of two manipulative therapy techniques lead to an immediate redistribution of foot loading patterns (laboratory-evidence) during static stance relative to a placebo laying of hands procedure in patients with acute grade II LAS.(Lopez-Rodriguez, Fernandez de-las-Penas, Alburquerque-Sendin, Rodriguez-Blanco, & Palomeque-del-Cerro, 2007) There is also evidence to suggest that a single bout of anterior-to-posterior talocrural joint mobilizations (Maitland Grade 3 oscillations) improves ROM measured by the WBLT (clinician-oriented evidence) and spatiotemporal measures of postural control (laboratory-oriented evidence) in those with CAI.(Hoch & McKeon, 2010a; c) By combining these results with the patient-oriented evidence above, there appears to be strong indications that joint mobilization has the potential to be an excellent rehabilitation intervention for those with acute LAS and CAI. However, no investigation has directly compared the effectiveness of different manipulative therapy techniques on any outcome measures in patients with acute LAS or those with CAI. Thus direct comparisons of manipulative therapy techniques should be the focus of future research endeavors.

6.3 Balance exercises

One of the most commonly examined sensorimotor outcome measures following a LAS is single leg postural control and recent systematic reviews have demonstrated that postural control is impaired on both the involved limb (Arnold, De La Motte, Linens, & Ross, 2009; McKeon et al., 2008a; Wikstrom et al., 2010c) and the uninvolved limb (Wikstrom et al., 2010c) relative to an uninjured control group within six weeks of a LAS. The presence of bilateral balance impairments (Wikstrom et al., 2010c) suggest that global impairments as a result of a peripheral injury have occurred. Further, impaired postural control is associated with an increased risk of ankle injury (McGuine, Greene, Best, & Leverson, 2000; McKeon et al., 2008a) and because of this strong association, balance training is a common component of therapeutic intervention programs used by allied health care practitioners to treat acute LAS. Fortunately, balance training is effective at improving postural control scores in

subjects with acute LAS (McKeon & Hertel, 2008b; Wikstrom et al., 2009) and at reducing the risk of recurrent LAS.(McKeon et al., 2008b; McKeon & Mattacola, 2008d) The effectiveness of balance training is hypothesized to be due to the modality's ability to restore and/or correct feed-forward and feedback neuromuscular control alterations that have occurred as a result of a LAS. Indeed, neural adaptations occur at multiple sites within the central nervous system as a result of balance training intervention programs.(Beck et al., 2007; Taube et al., 2007) In other words, balance training capitalizes on the incredible plasticity of the central nervous system and enhances a patient's ability to react to both internal and external perturbations.

Balance training programs have been shown to improve self-reported function (patient-oriented), enhance the performance on the SEBT (clinician-oriented), and improve center of pressure and spatiotemporal measures of postural control (laboratory-oriented).(Hale, Hertel, & Olmsted-Kramer, 2007; McKeon et al., 2008c) While balance training improves postural control, the exact treatment dosage needed to cause balance improvements and reduce the risk of recurrent injury remains unknown. However, the generally accepted timeframe for improvements to be observed is 4-6 weeks of balance training.(McKeon et al., 2008b; McKeon et al., 2008d). Bahr et al. (Bahr, Lian, & Bahr, 1997) reported that the longer a balance training program is implemented the greater preventative effects accrue from the program. To date, published balance training investigations primarily use prospective cohort designs where the baseline measures represent postural control prior to the intervention but not pre-injury postural control values. So while the literature indicates that balance training improves postural control, it is not clear if balance training restores postural control to pre-injury balance values.

When designing a balance training program, it is important to consider the dynamic systems theory of motor control (Figure 2). Specifically, this chapter has focused on the organismic constraints as defined by both mechanical adaptations and sensorimotor dysfunction associated with LAS, CAI, and post-traumatic ankle OA. In order to overcome the effects of these constraints on the sensorimotor system, a systematic process of purposefully manipulating task and environmental constraints must be employed.

6.3.1 Cultivating functional variability

In rehabilitation, it becomes imperative that the clinician is very specific when identifying the desired movement goal for the patient.(McKeon, 2009) Rather than focusing on the task to be performed (task-oriented rehabilitation), the functional activities should be associated with the quality of the movement goal execution (goal-oriented rehabilitation). The most important elements for the development of functional variability are to incorporate: 1) a systematic progression through the exercises, 2) a logical manipulation of task and environmental constraints at each level of the progression, 3) specific outcomes that capture improvements and help the clinician determine when patient progression is appropriate, 4) an ability to reduce the outcomes into a decision as to whether the patient has overcome the continuum of disability, and 5) ensure that the process is replicable by documenting the systematic, logical, empirical, and reductive elements.

In order to present the systematic and logical process of program development, we have included examples of a published balance training protocol used for patients with CAI.(McKeon et al., 2008c) Further information associated with this program, including the full description of activities, progressions, outcomes used, and results can be found in the published manuscript.

6.3.2 Task constraints in balance training

Changing the demands of the balance training task results in changes within the component parts of the sensorimotor system to accomplish the movement goal.(McKeon, 2009) The complexity of the task will govern the variability of movement solutions the sensorimotor system can use. An example of this is balancing in single limb stance. In order to accomplish this movement goal (i.e. maintain single limb stance), the sensorimotor system can develop several movement solutions from its many component parts (e.g. ankle muscles, knee muscles, hip muscles, etc.) and is readily afforded the freedom to correct for any errors introduced in executing the movement goal. However, when a person lands from a jump on one leg and attempts to regain balance there are fewer solutions available to accomplish the movement goal, because of the increased task demands (e.g. increased 3-dimensional forces, momentum acting on the body, etc.). As a result, there is an increased likelihood of errors being committed. If an error in postural control is introduced during physical activity and/or athletic event, it can potentially have severe consequences, such as an ankle injury. As stated above, an ankle injury would result in increased organismic constraints and subsequently increase the likelihood of errors in the future, starting a vicious cycle. However, the introduction of errors in a controlled training environment gives the sensorimotor system time to develop either 1) more/new movement solutions or 2) enhance the efficacy of existing movement solutions so that the likelihood of committing errors and the consequences of those errors can be diminished over time.

6.3.3 Purposeful manipulation of task constraints

When progressing an individual through a balance training program, it becomes essential for the movement goals to be meaningful to the individual.(McKeon, 2009) Balance training has been shown to be beneficial at improving functional outcomes associated with CAI.(Holmes & Delahunt, 2009; McKeon et al., 2008b; McKeon et al., 2008d) From the dynamic systems perspective, the most important consideration in functional rehabilitation program development is the clarity of the movement goal.(McKeon, 2009) The task constraints then can be structured to challenge the sensorimotor system as it spontaneously organizes (i.e. develops new solutions) to accomplish the movement goal.

An example of the strategic manipulation of task constraints in the referenced balance training program is the "Hop to Stabilization" activity compared to the "Hop to Stabilization and Reach" activity (McKeon et al., 2008c). For both activities, the movement goal was to regain single limb stance as fast and effectively as possible after landing from a hop. In the first activity, subjects performed single limb hops to a target, stabilized single limb stance, and then hopped back to their starting position. In the "Hop to Stabilization and Reach" activity, subjects hopped to the target, stabilized, and reached back to the starting position with their opposite leg. Although the movement goal was the same, the tasks resulted in the development of different solutions for goal achievement. In order to keep patients on the cusp of failure (i.e. continuously challenge the sensorimotor system), the task constraints were increased when each patient could perform 10 error-free repetitions in the current task constraints. An important note is that each patient in the program progressed to higher levels based on their ability to execute the movement goals. This was done by increasing the distance of the hop target. To add additional task constraints for each activity, the patients hopped in eight different directions. Each direction presented unique task constraints that challenged the sensorimotor system to develop

movement solutions to accomplish the movement goal and ultimately make the patient more adaptable to unexpected perturbations (e.g. a mid-air collision with another player) that occur during athletic events.

6.3.4 Environmental constraints in rehabilitation

Environmental constraints (or cues) are essential components for the organization of the sensorimotor system.(McKeon, 2009) Rather than viewing the environment as such things as grass versus sidewalk, the cues from the environment should be considered for the predictability they offer to the sensorimotor system.(McKeon, 2009) More predictable environmental cues allow for greater freedom for the development of strategies to accomplish movement goals. Less predictable environment cues constrain the sensorimotor system's ability to develop movement goal strategies. An example of this is performing sport-specific activities in a rehabilitation environment compared to sport-specific activities during actual participation in athletic events. In the rehabilitation environment, environmental cues are based on the room, the performance of the activities, and the interaction with the therapist, and are much more predictable compared to real life performance. Once the patient returns to participation in athletics, the interaction with the playing surface, teammates, and opponents provide significantly more unpredictable environmental cues. This is one of the reasons that an athlete might pass a functional screen performed by a health care provider, but still struggle upon their return to actual competition.

With increased exposure to task and environmental constraints, the sensorimotor system can develop new strategies to accomplish movement goals and cope with change over time. Therefore, to maximize the efficacy of the sensorimotor system in those with ankle inversion trauma, it is essential to adjust the environmental and task constraints to keep the patient on the cusp of failure (i.e. continually manipulate the constraints so that patients have to provide near maximum physical and psychological effort to complete the assigned activities) throughout the rehabilitation program. When challenged in this way, the sensorimotor system develops greater flexibility in achieving its motor goals, and this translates into better outcomes of the movement goal and potentially a decreased risk of injury.(McKeon, 2009; McKeon et al., 2008c)

6.3.5 Purposeful manipulation of environmental constraints

The environmental constraints used in balance training should also be associated with specific movement goals.(McKeon, 2009) Initially, a predictable environment allows the sensorimotor system the freedom to explore a variety of strategies to accomplish a specified movement goal. The more unpredictable the environment becomes, the less free the sensorimotor system becomes to explore strategies. Consequently, a valuable balance training activity has a systematic progression from hopping to a predictable target, as described above, to an unpredictable one. In the example above of the hopping activities, patients started by hopping to a predictable target. The environmental constraints were then manipulated by having the subjects perform the same types of hops in an unpredictable environment in the "Unanticipated Hop to Stabilization" activity. In the Unanticipated Hop to Stabilization, patients were presented with a random sequence of numbers on a grid set up like a large phone pad that represented the order of targets to which they would hop and

stabilize in single limb stance. For each number sequence, the subjects had a specified amount of time to get the next target before the next number in the sequence was shown to them and the sequence changed each time they performed this activity. As performance improved and subjects began to make their target times, the environmental constraints were increased by decreasing the amount of time allotted to complete the task. From the dynamic systems perspective, this change in the number sequence is a form of environmental constraint. The cues subjects received from the environment (the number in the hopping sequence) shaped the strategies that the sensorimotor system needed to use to accomplish the movement goal. The reduction in time challenged the sensorimotor system to adapt to the unpredictable environment in which the movement goal was being executed.

It is important to note that with the systematic and logical progression, each patient progresses through the balance training program at their own rate based on their individual ability to accomplish the movement goal in each activity. Upon completion of the program, patients reported significant improvements in their ability to engage other task and environmental constraints in activities such as running, cutting, and participating in their desired activities.(McKeon et al., 2008c) The goal of balance training and functional rehabilitation from the dynamic systems perspective is to restore the sensorimotor system's ability to cope with change during the execution of movement goals, thus improving sensorimotor control and functional performance. Once a movement/rehabilitation goal can be accomplished without error, the constraints can again be systematically increased. Purposeful and logical manipulation of task and environmental constraints include the logical progression from single limb balance activities to more functional activities such as hopping, landing, rapidly changing direction, etc. In order to accomplish more advanced movement goals effectively, more degrees of freedom (i.e. using more joints, muscles, etc.) are necessary to correct for errors introduced during goal execution. By freeing more degrees of freedom to correct errors, the Continuum of Disability (Figure 3) can be broken. The clinician can utilize the principles of the purposeful manipulation of task and environmental constraints to guide the progression of rehabilitation. By doing so, it is possible to tailor a program to a patient's ability to achieve movement goals and restore sensorimotor system freedom.

Lastly, it is imperative to utilize outcome tools that have been shown to capture patient-oriented, clinician-oriented, and laboratory-oriented aspects of changes within the sensorimotor system. In the study referenced in this section, (McKeon et al., 2008c) those in the balance training group experienced significant improvements in self-reported function (patient-oriented evidence), dynamic postural control as assessed through the SEBT (clinician-oriented evidence), and spatiotemporal postural control (laboratory-oriented evidence). By assessing self-reported function through the FADI or FAAM, dynamic balance through the BESS or SEBT, and potentially instrumented measures of postural control and/or gait when available, it is possible to determine if a rehabilitation program has an impact on taking a patient out of the Continuum of Disability.

7. Summary

When evaluating patients with ankle inversion trauma and/or instability, clinicians should consider the Continuum of Disability rather than simply local instability. Buchanan et al.

(Buchanan, Docherty, & Schrader, 2008) has provided the best example of why the PCL model is more appropriate than the examination of deficits in isolation to date. The authors had individuals with CAI and healthy controls complete clinical measures of functional performance (i.e. hop tasks) and asked the subjects if their ankle "felt" unstable during the tasks. The initial results indicated no group differences in performance but a secondary analysis compared those with CAI that "felt" unstable to those with CAI that "felt" stable and healthy controls. This secondary analysis, that combined patient- and clinical-oriented outcomes, revealed that the CAI subjects who "felt" unstable during the tasks had performance deficits relative to the other groups. This investigation demonstrates how the combination of a patient- and clinician-oriented outcomes are more revealing than either outcome in isolation. We recommend using the constraints-led approach to guide decisions about comprehensive sensorimotor system evaluation, the development of rehabilitation progressions, and safe return to participation. Most importantly, as presented throughout this chapter, an ankle sprain is not simply a local joint injury; it results in a constrained sensorimotor system that leads to a continuum of disability and life-long consequences such as high injury recurrence and decreased quality of life.

8. References

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Treatment of Talar Osteochondral Lesions Using Local Osteochondral Talar Autograft – Long Term Results

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1. Introduction

Osteochondral lesion of the talus (OLT) is a broad term used to describe an injury or abnormality of the talar articular cartilage and adjacent bone. A variety of terms have been used to refer to this clinical entity including osteochondritis dissecans, osteochondral fracture, and osteochondral defect. Whether OLT of the talus is a precursor to more generalized arthrosis of the ankle remain unclear, but the condition is often symptomatic enough to warrant treatment. Above one third of cases conservative treatment is not successful and a surgery is indicated. Several surgical options have been described including: debridement, isolated or combined with drilling, excision and curettage, abrasion arthroplasty, microfracture technique arthroscopically or not, internal fixation with screws, autologous chondrocyte implantation and implantation of osteochondral autograft using single or multiple cylinders of articular cartilage and subchondral bone. The optimal solution remains uncertain. Furthermore smaller lesions are symptomatic and untreated OCDs can progress, current treatment strategies have not solved the problem

The goal of this study was to retrospectively evaluate the long-term results of 23 patients who underwent local osteochondral talar autograft for the treatment of OLT.

2. Materials and methods

From March 2005 to December 2008 a series of 58 patients were retrospectively evaluated. Thirty seven male and twenty one female with age ranged from 19 to 53 (mean 38) years. Sports related injury concerned 37 patients and the duration of symptoms was mean 65 months (range 6 to 98). Mean follow-up was 22,1 months (range 14 to 32). Preoperative evaluations included a clinical history, physical examination of the foot and recording of American Orthopaedic Foot and Ankle Society (AOFAS) Ankle- Hindfoot score. Special radiological studies performed preoperative, MRI (58 patients), CAT (58 patients), Bone Scan 3 patients (ordered by other doctors, because we don't need it for detection OLT) and weight-bearing radiographs to all of them to evaluate the injury. The majority of lesions n=41 were on the medial aspect of talus, 17 on the lateral talar dome and 4 medial and lateral lesions. The graft was harvested from the medial or lateral talar articular facet on the same side of the lesion depended by the geometry of the lesion. Graft sizes ranged from four

to eight millimeters in diameter. More specific 4 mm 6, 6mm 28, 8mm 24. So, this operation is used for stages 3 and 4 lesions according to Berndt and Hardy classification and for stages 1 and 2 in symptomatic patients that failed previous surgical treatment. (table 1).
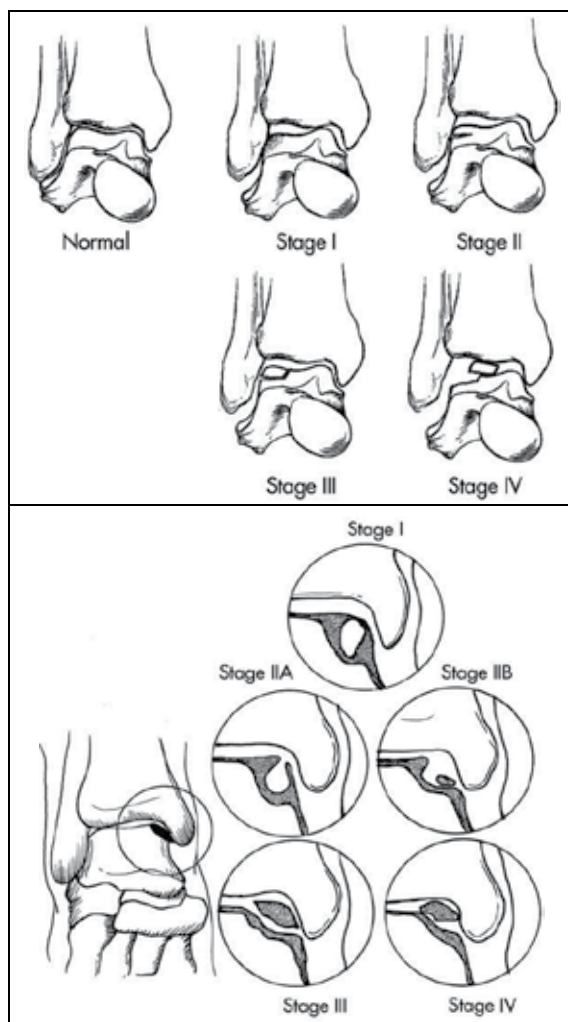

Table 1. Berndt and Hardy classification

Associated findings after the preoperative control (table2) was 17patients with Pes Planus, 11 patients with arthritis, 8 patients with Achilles tendinopathy, 3 with Tibialis Posterior Dysfunction, 3 with Hallux Rigidus, 13 with lateral ankle instability and 2 patient with previous pinning controlateral ankle. Additional procedures were an FHL tenosynovectomy and repair, excision of a lipoma, lateral ligaments reconstruction (Brostrom modification), TAL lengthening, synovectomy and AAI removal. Preoperative and postoperative results evaluated used the AOFAS hindfoot score. The result of the score was classified in excellent, good, fair and poor and additionally patients have been asked about their satisfaction following the procedure. Statistical analyses were performed using SPSS software.

Pes planus	17
Arthritis	11
Achilles tend	8
Tib.Post Dysf.	3
Hallux Rigidus	3
Lateral Ankle Instability	13
Previous pinning contr	2

Table 2. Associated Findings & History

3. Surgical technique

All procedures were performed with the patient in the supine position under tourniquet control. An arthrotomy was performed through a 7cm antero-medial or antero-lateral incision as required. The lesion is approached by removing a bone block from the tibia including the articular surface. To accomplish with this a wedge shaped bone block, 10mm wide, 20mm deep and 30mm in height is made at the distal anterior tibia articular surface on the side of the osteochondral lesion. Vertical parallel saw cuts are made with a high-speed micro oscillating saw. Care is taken to avoid injuring the uninvolved talar articular surface. The saw was then used to connect the two vertical parallel cuts proximally in the metaphysis. A 10mm wide thin osteotome is then driven from the superior portion of the transverse saw cut inferiorly to the articular surface of the tibial plafond 10 to 20mm deep depending on the location of the lesion on the talar dome. The tibial fragment is removed and set aside to be replaced later (figure 1). The defect created in the tibia following removal of the bone fragment permits direct access to the lesion from above. The lesion is delivered into the field by plantar-flexing the ankle. It is prepared by first debriding the loosened cartilage fragments. The lesion is then drilled using the appropriate size drill. Care is taken to ensure that the drill is perpendicular to the articular surface of the talus directly over the lesion. Drill sizes are matched to the diameter of the defect 4, 6 or 8mm to the size of the defect determined from the MRI. The osteochondral graft is harvested from the anterior aspect of the ipsilateral talar articular facet. A total of 15 grafts were harvested: two 4mm, six 6mm and seven 8mm (figure 2). This is performed through the same incision as the tibial osteotomy. The graft is harvested using the core-harvesting device (figure 3). The cutter was positioned over the talar facet near the anterior border ensuring that it was perpendicular to the articular surface. The inferior border of the talar facet flares outward slightly and the harvesting tube is oriented so that the flared margin can be identified and oriented toward the medial or lateral talar dome respectively. This ensures that the graft shape will approximate the saddle shape of the talar dome more closely. It is then tapped with a mallet until the cutter reaches the desired depth. The harvester is then rotated and removed with graft held in the harvester tube. The outer cutter is removed leaving the graft plug inside the harvester tube and a delivery guide is screwed onto the harvester tube. A plunger is inserted into the proximal end of the tube. The assembled harvester tube, guide and plunger

are positioned perpendicular to the talar done over the prepared site in the talus orienting the outer flair of the graft toward the outer edge of the dome. The plunger is tapped gently pressing the osteochondral graft plug into the hole (Figure 4). The graft is inserted until it is flush slightly proud to the surrounding cartilage overhanging. For the true medial lesions a Chevron-type medial malleolar osteotomy was performed at the end the osteotomy fixed with 2 screws. The approach to lateral lesions performed with anterolateral incision by taking down the ATFL and CFL. At the end a modified Brostrom performed. The postoperative treatment was immobilization for 4 weeks, walker boot for next 4 weeks and weight bearing at six weeks. Range of motion exercises was allowed once the surgical incision healed.
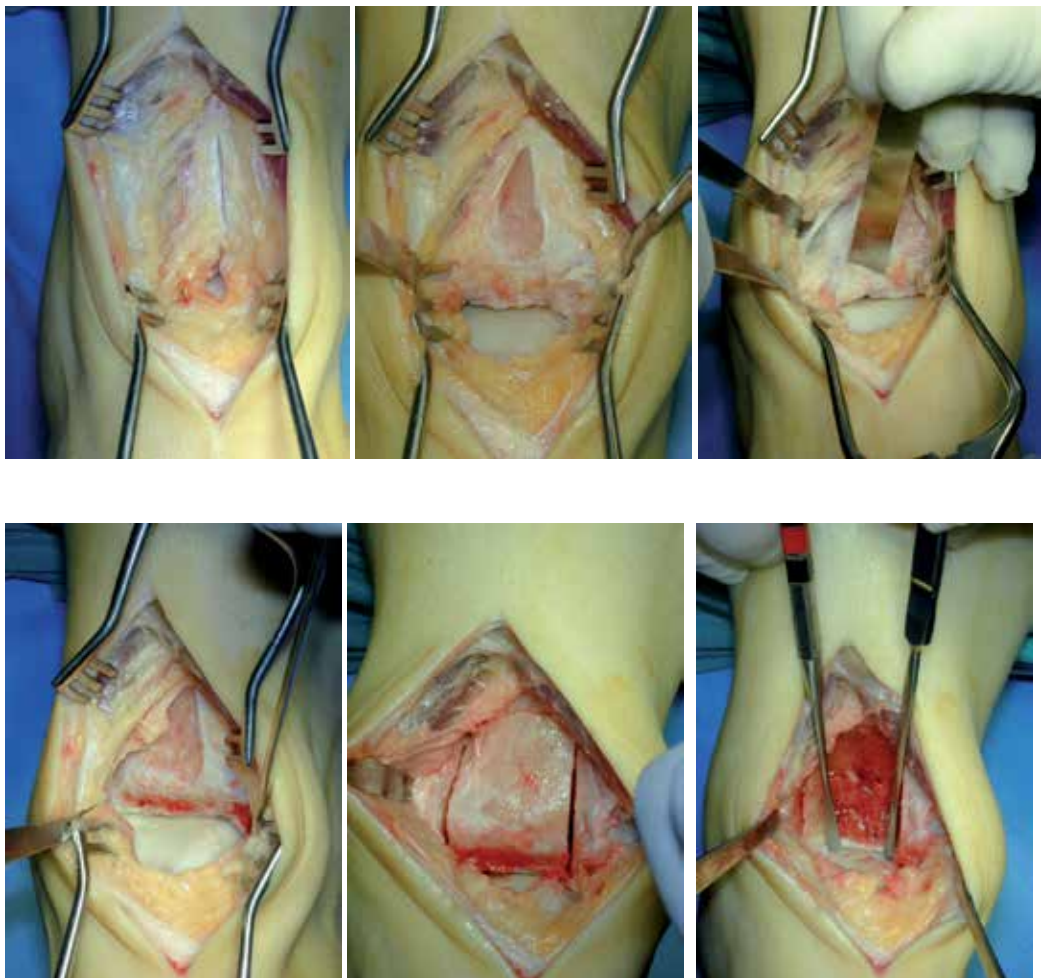

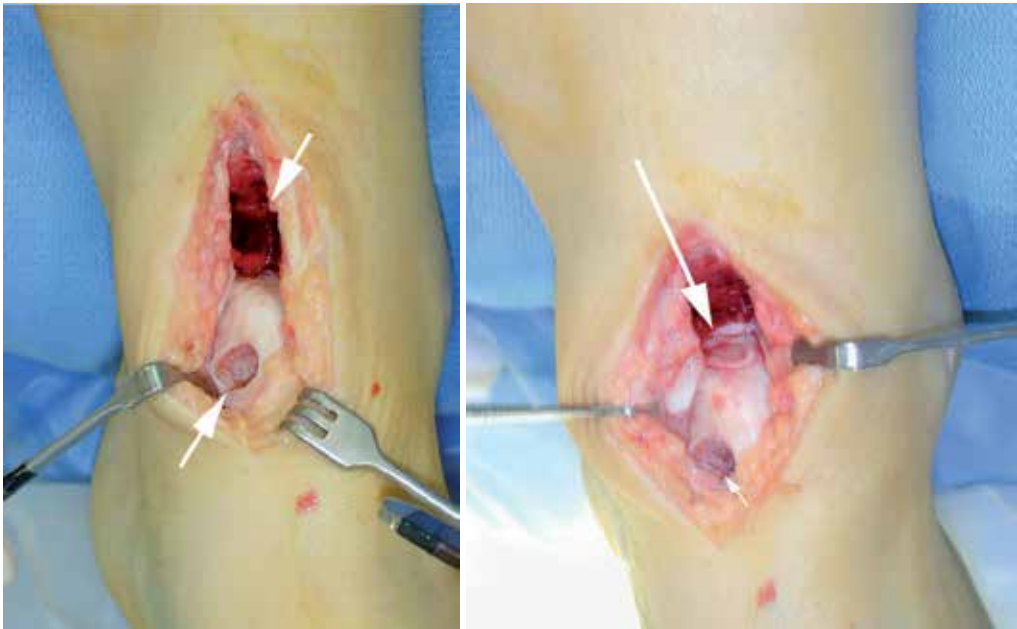Fig. 1. Tibial osteotomy trapezoid wedge shape for perpedicular access to the recipient sit

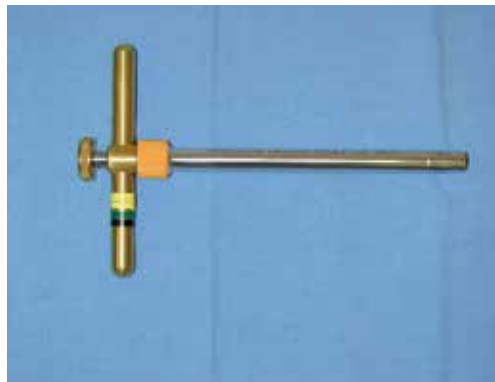Fig. 2. Donor medial talar facet-recipient site with the local garft altready inserted
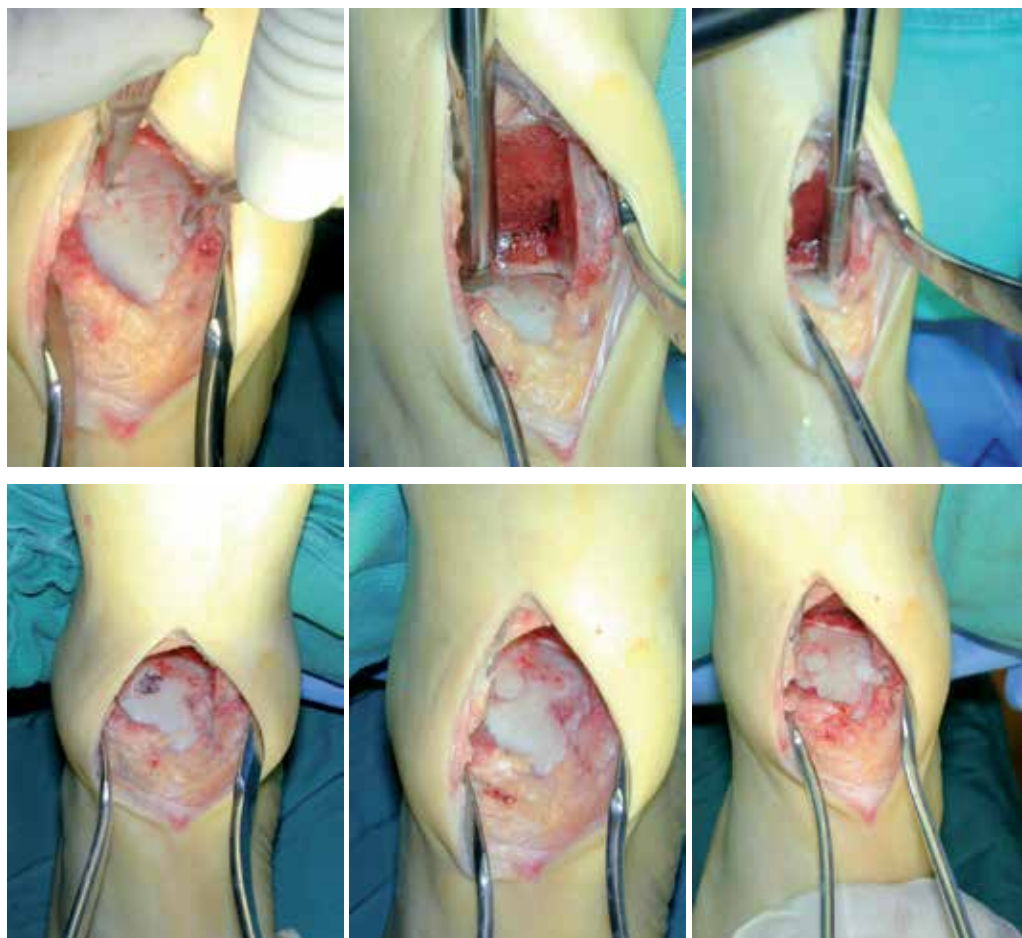

Fig. 3. Instrumention

Fig. 4. Perpedicular access to the recipient site a case with 2 lesions

4. Results

Patients were evaluated both intraoperatively and postoperatively. Operative findings included: degenerative joint disease in six cases, lipoma in two cases and lateral ankle ligament instability in two cases.

Preoperative AOFAS scoring using the ankle and hindfoot score was 65 average. At follow up, 41 months (average). Postoperative was 89 average. The patients under the age of 40 had higher average AOFAS scores postoperatively, compared to the patients over the age of 40. (table 3) The presence of degenerative arthritis yielded a lower AOFAS score in. However, the difference between these small subgroups was not significant. No reciprocal "kissing lesions" were encountered on the tibial articular surface opposite the osteochondral lesion. There was no deterioration in the overall functional improvement in patients underwent additional procedures. There were no perioperative complications. Long term, the most common complaint in patients over time was mild aching over the anterior aspect of the ankle, although this did not decrease activities of daily living or sports. All patients stated they would undergo the procedure again.

	Pre-operative	Post-operative
AOFAS	65	89
Under 40 years	69	92
No Arthritis	68	91
Arthritis	63	86

Table 3.

Evaluation of postoperative x-rays revealed no evidence of decreased joint space in the ankle. X-ray findings also revealed that the cyst visible preoperatively was no longer visible at the last follow up visit. No increase in arthritis was noted. Clinical examination postoperatively revealed improved range of motion, muscle strength, gait pattern and endurance. Patients returned to their work 8 months following surgery, without restrictions. Two patients underwent surgery subsequent to the index procedure, one had arthroscopy and removal of impinging osteophytes from the lateral malleolus six months following surgery and one had arthroscopy with debridement of the anterior tibial margin at the site where the tibial bone block had been removed twelve months following surgery (Figure 5). In both cases the cartilage of the graft appeared to have grown into the surrounding cartilage of the talar dome. The tibial articular cartilage on the tibial plafond had also healed without articular surface defects. It appeared that the use of talar osteochondral graft does not adversely affect the joint surface and easily incorporates into the surrounding surface cartilage.
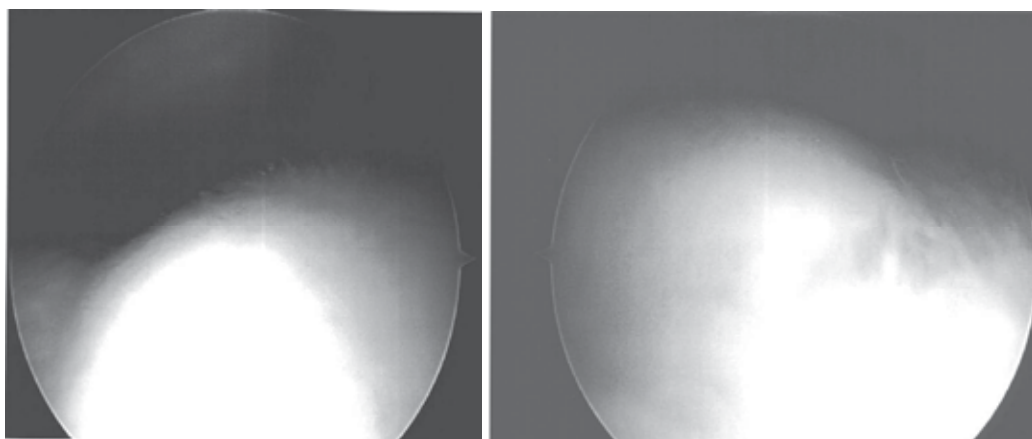
Fig. 5. Second look arthroscopy with a good incorporation of the local graft same quality and thickness cartilage

5. Discussion

The result of non-operative treatment of stage III and IV osteochondral lesions of the talus have been poor[1, 3]. Berndt and Harty reviewing 200 cases from the literature and adding 24 of their own found 73.9% poor results with non-surgical treatment. Of the fifty-six treated surgically 78.6% had good results[3]. O`Farrell and Costello (1982)[9] reported on 24 patients treated surgically and found the results were better with early diagnosis and treatment. This

report was further substantiated by Pettine and Morrey (1987)[10] who retrospectively reviewed 68 patients at average follow-up of 7.5 years and concluded that a delay in diagnosis and surgery resulted in a poor outcome. Whilst a high percentage of satisfactory results can be obtained with non-surgical treatment for Stage I and II lesions most stage III and IV lesions require surgery. Canale and Belding (1980)[4] recommended stage IV and III lateral lesions be treated surgically but that III medial lesions be treated non-surgically initially. All lesions in our study were stage III or IV and two/thirds were related to sports injuries. The surgical treatment for osteochondral lesions of the talus includes excision, excision and curettage with or without drilling, microfracture, cancellous bone grafting, internal fixation and osteochondral grafting. Review of the literature suggests a higher percentage of good and excellent results with excision and curettage with or without drilling the base of the lesion[14]. Mosaicplasty autogenous osteochondral grafting has been recently introduced and has evolved from treatment of osteochondral lesions of the knee. Hangody et al (1997)[7] reported their results in 11 patients treated with mosaicplasty autogenous osteochondral grafting for talar dome lesions using the knee as a donor site with a high success rate. However donor site morbidity can occur in up to 15% -16% of cases in an asymptomatic joint[8]. We feel this increased morbidity can be avoided. By harvesting the graft from a location on the talar dome, which carries minimal loads, the risks of the procedure are reduced. The graft is taken from the anterior part of the medial or lateral talar facet. Since the graft size is relatively small the integrity anterior dome is maintained. There was no incidence of collapse of the talus either at the donor site or at the site of the lesion. The two patients on whom arthroscopy was performed revealed the graft well incorporated on the surface of the joint. The chondral border of the graft revealed no line of degeneration or necrosis. Also, there was no additional change noted on the medial or lateral facet either at the site of the lesion or at the donor site.

The removal of a portion of the anterior tibial plafond to access this lesion has been previously described[6]. However, osteochondritic lesions are often large and located farther back in the talar dome so that they are inaccessible unless a large portion of tibia is removed. This makes the method described by Flick and Gould[6] impractical since the amount of bone needed to be removed is significant, ten mm. and will decrease the tibial load bearing capacity of tibial plafond if it not replaced. Moreover the location of such lesions is often so far posterior that removal without replacing tibial bone to access the lesion would significantly weaken the tibial plafond and medial malleolus. In addition, this method cannot be used laterally unless the lesion is located anteriorly. The use of a medial malleolar osteotomy carries the risk of nonunion and malunion and the results may deteriorate with time[2]. The securing of the malleolus with screws leaves the heads of the screws at the tip of the malleolus and these may require removal later. Our method allows access to either side of the ankle directly even if the lesion is located toward the posterior third of the dome. The defect is visualized from above after the bone block has been removed. The bone block is then replaced and secured with an absorbable pin. There is no risk of malunion since the block is replaced in the same position from which it was removed. No fractures occurred in the tibia. The tibial graft held in place without any fixation only by gentle tapping, since it holds the bone block in place but not carry any loads.

Moreover we use same quality osteochondral graft, the cartilage of the knee is thicker than the talus cartilage hence cannot incorporate precisely like the talus cartilage.

There are some lesions that are difficult to access even with this method. These are located in the posterior 20 to 30% of the talar dome, particularly in the lateral posterior region of the talus. For these less common lesions, not included in this report, we expose the talus through a posterolateral incision and performed the grafting using a second anterior incision to harvest the graft.

Additionally for the true medial lesions we still perform an osteotomy of the medial malleolus(figure 6) because it is difficult to have perpedicular access to the recipient site through the wedge shaped bone block, at the distal anterior tibia articular surface on the side of the osteochondral lesion.

For the true lateral lesions sometimes is needed to approach the lesion through an anterolateral incision we have to take down the anterior tibiofibular ligament (ATFL) and the calcaneofibular ligament (CFL) in order to have perpendicular access again to the recipient site (figure7), then we have to reconstruct the ligament with a standard modified Brostrom technique.

Fig. 6. Medial malleolus osteotomy for true medial site lesions

Fig. 7. Lateral OLT Approached through an anterolateral incision, with takedown of ATFL and CFL. Reconstruction with modified Brostrom

The overall improvement in the AOFAS score in our study was 24 points at an average follow up of 41 months. Improvement can be expected for as long as eighteen months postoperatively[12]. Canale and Belding (1980)[4] found 15 out of 31 cases (50%) developed degenerative joint changes at an average 11.2 years. The long-term success of preventing late joint degenerative changes has yet to be determined using our technique.

In this study our mid term results suggest that stage III and IV talar dome lesions can be treated successfully using local autogenous osteochondral grafts from the medial or lateral talar articular facet This procedure is combined with removal of a tibial bone block and its subsequent replacement and does not yield complications experienced with other procedures.

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Proprioception and the Rugby Shoulder

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1. Introduction

Rugby union is an international sport played by two teams of 15 players (8 forwards and 7 backs) over two 40 minute halves. It is ranked internationally, as a football code, second to soccer, and is the most popular world wide team contact sport involving collision (IRB, 2004). Professional rugby league is a contact sport involving two teams of 13 players (6 forwards and 7 backs), also played over two 40 minute halves. Each tem has a set of six tackles to advance the ball downfield (Gissane *et al.,* 2003).

Little is known about the level and pattern of injuries occurring since rugby union became a professional sport, and the number of prospective studies among elite players is small (Brooks, *et al*., 2005). Prior to Brooks et al., (2005), there have been several prospective cohort epidemiological studies of injuries sustained in professional Rugby Union (Bathgate, *et al.,* 2002; Garraway, *et al.,* 2000. Targett, 1998).

The mean incidence of injuries recorded from three studies within professional rugby union is 86.4 injuries per 1000 player hours (Holtzhausen, 2001). Pooled data analysis of injury incidence in rugby league, found an overall injury rate of 40.3 injuries per 1000 player hours (Gissane *et al.,* 2002).

Brooks et al., (2005) conducted the England Rugby Injury and Training Audit, which included all 12 Premiership rugby union teams, and England, England 'A', Under 21 and England 7's teams, during the 2002-2003 and 2003-2004 seasons. They used the operation definition which had been used previously by one of the authors in research into injuries in professional football; "any injury which prevented a player from taking a full part in all training activities typically planned for that day and match play for a period equal to or greater than 24 hours, from midnight of the day the injury was sustained" (Hawkins, and Fuller, 1999).

Detailed analysis of this audit, with respect to shoulder injuries, reports that the average number of tackles carried out during a Premiership match is 250, and that 65% of all shoulder injuries occurring during a match are to the shoulder. During the 2005-2006 season the number of days lost to training or playing due to reported shoulder dislocation or instability was 176 days per 1000 hours play (Heady et al., unpublished). Thus the tackle appears to be the phase of play associated with the greatest risk of injury overall. (Brooks et al., 2005; Bird et al.,1998; Garraway and Macleod ,1995; yet there appears to be scant published research regarding the affect on shoulder joint position sense within rugby players, in general, and the effect that tackling has on it.

Stability within the glenohumeral joint is maintained via anatomical factors such as the degree of bony congruity, integrity of the capsuloligamentous structures and neuromuscular feedback loops involving the joint and musculotendinous mechanoreceptors that are integrated within the central nervous system (Suprak, Osternig, van-Donkelaar, & Karduna, 2006).

Despite this highly integrated passive and active control system the glenohumeral joint is regarded as one of the least stable joints within the body.

The passive ligamentous and capsular structures are often exposed to deleterious loads due to the failure of the active muscular control systems of the glenohumeral joint. This failure of active muscular control system reported in the literature has in part at least been blamed on a failure of proprioception (Janwantanakul, Magarey, Jones, & Danise, 2001).

The term ''proprioception'' was introduced by Sherrington in 1906 who described it as a type of feedback loop from the limbs to the central nervous system; afferent information arising from peripheral areas of the body contribute to joint stability, postural control and motor recruitment patterns. It has more recently been described as a combination of joint position sense (JPS, the ability of a person to identify the position of a limb in space) and kinaesthesia (the perception of active and passive motion) (Aydin, Yildiz, & Yanmis, 2001).

The awareness of the position of the joint (JPS) is obviously an important aspect of proprioception. An intact JPS has been shown to be necessary for normal muscle coordination and timing, and this has been shown to be especially evident where active muscle forces play a significant role, as in glenohumeral joint stability Blasier, Carpenter, & Huston, 1994; Cain, Mutschler, Fu, & Lee, 1987). JPS contributes to the maintenance of muscle stiffness and coordination about t a joint to produce smooth limb movements, and has been found to be affected by ligamentous trauma, surgical intervention, and rehabilitation programmes (Lephart, Warner, Borsa, & Fu, 1994) Muscle fatigue, trauma and hyper laxity can be responsible for damage to the mechanoreceptors (deafferentation), which can reduce the afferent supply so that the central nervous system receives inaccurate information, and hence, responds with inaccurate output responses.

In the current literature it is generally agreed that tension in muscles, capsuloligamentous structures, and skin at a joint varies at the different points in the joint's range of movement (Allegrucci, Whitney, Lephart, & Fu, 1995; Dover, Kaminski, Maister, Powers, & Horodyski, 2003) Janwantanakul et al., 2001; Sullivan, Hoffman, & Harter, 2008). Because mechanoreceptors in tissues are activated by tension exerted on them, their activation would be expected to vary at different points in range as the tension in tissues around the joint varied. Consequently, position sense acuity may alter from one joint position to another. The accuracy of joint position reproduction at different criterion angles during JPS testing has been found to vary in studies involving the shoulder (Janwantanakul et al., 2001). In addition, Allegrucci et al. (1995) and Blasier et al. (1994) noted greater movement sense acuity at the shoulder complex, measured by the threshold for detection of movement test, at the end of range than in the mid joint range.

Joint position sense has been demonstrated to differ between participants in different sports and non-sporting individuals. Dover et al. (2003) showed baseball pitchers to have significantly decreased JPS at the extreme of external shoulder rotation than controls. This lack of awareness of joint position could potentially expose the glenohumeral joint to deleterious loading and result in injury.

Several factors have been reported to influence JPS including training, joint range, and fatigue (Myers & Lephart, 2000). Herrington, Horsley and Rolf (2007) and others (e.g.,

Dover, Kaminski, Meister, Powers, & Horodyski, 2003) have shown the level of training or nature of sports performance has a significant effect on JPS, with for instance, rugby players showing superior shoulder JPS to matched controls (Herrington et al., 2007). Janwantanakul et al. (2001) found that the joint angle set as the criterion angle to be matched had a Significant effect on JPS, with JPS improving towards the end of the range position as the capsular structures became taut. Several authors (Carpenter, Blasier, & Pellizzon, 1996; Tripp, Boswell, Gansneder, & Schultz, 2004: Voight, Hardin, Blackburn, Tippett, & Canner, 1996) found fatiguing activities to have a significant effect on shoulder JPS, causing a decrease following fatiguing activity. The consensus from these papers was that muscle fatigue somehow decreases the sensitivity of the capsular receptors and thus decreases proprioception indirectly. Fatigue, as in the decreased ability to generate the required force, leads to a production of substances, such as lactic acid and bradykinins, which exhibit affects via the nervous system which lengthen the muscle spindles. Hence, when the stretch stimulus arrives, the muscle spindle is not at the expected length, and affects the spindle output. If this situation is repeated, then the resulting sub-optimal motor response may be responsible for anatomical injury. This injury may itself contribute to deafferentation in a cyclic response (Voight, Hardin, Blackburn, Tippett, Canner, 1996). It has yet to be investigated if fatiguing tasks influence the angle-specific effect outlined above. It could be hypothesised from the above studies that end of range JPS could be preferentially decreased following a fatiguing task. This would then potentially expose the passive structures of the shoulder to increased loading and injury. Herrington, Horsley and Rolf (2007) assessed the effect of a simulated tackling task on shoulder joint position sense in rugby players, and also attempted to assess if differences in JPS occurring between mid range and end of range JPS, and if the tackling task had angle-specific effects on these values, utilizing a repeated measures design with 22 asymptomatic professional rugby players. JPS was assessed using two criterion angles in the 90degrees shoulder abduction position (45degrees and 80 degrees external rotation) prior to and following a simulated tackling task against a tackle bag.

They concluded that JPS was significantly reduced following a fatiguing task. But this change was only true for the end of range position, with JPS in the mid range not changing. If the mechanoreceptors are unable to accurately report shoulder position in the outer range (stretch) position due to repetitive tackling, then there is a potential for the anterior structures to become stressed before any compensatory muscle contraction can take place. These results highlight the presence of sensorimotor system deficits following repeated tackling. These deficits were proposed to contribute to overuse injuries and micro-instability of the glenohumeral joint which may be related to the increasing rate of shoulder injuries in rugby.

Following this, the same authors repeated a similar study using 15 asymptomatic professional rugby union players, 15 previously injured professional rugby union players, 15 asymptomatic matched non-rugby playing controls and assessed their joint position sense, with the aim of identifying whether joint position sense (JPS) in the shoulder differed between un-injured rugby players, matched control subjects and previously injured rehabilitated rugby players. The study found a significant difference between groups in error score ($p = 0.02$). The testing angle also had a significant effect on error score ($p = 0.002$), with greater error scores occurring in the mid range position. They concluded that rugby players have better JPS than controls, indicating JPS might not be related to injury risk. Poor JPS appears to be related to injury, players having sustained an injury have decreased JPS despite surgery and/or rehabilitation and returning to sport without incident.
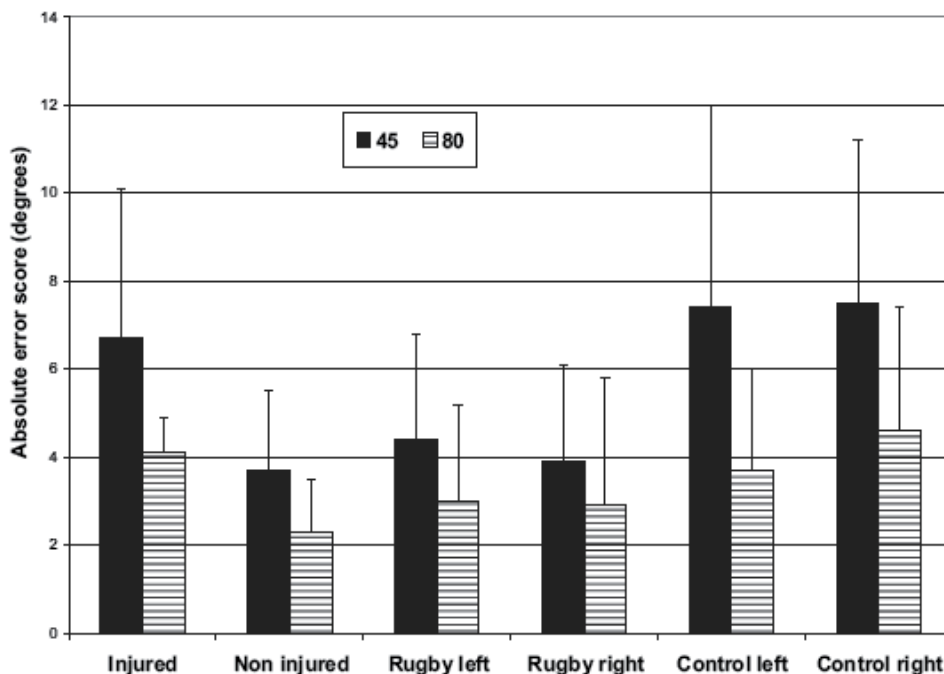
Fig. 1. Absolute error scores for the three groups.

Joint position sense can be defined as the ability to appreciate and recognise where a joint or a limb is in space (Ellenbecker, 2004). It has been reported in literature that joint position sense has great importance in avoiding non-physiological joint movements, such as extremes of movement – thus providing injury prevention and co-ordinates complex movement patterns (Jerosch and Prymka, 1996).

The mechanoreceptors found with in the capsule of the glenohumeral joint aid in providing afferent proprioceptive input via both slowly and rapidly adapting receptors (Vangsness et al. (1995). The rapidly adapting receptors respond to sudden changes in tension within the passive joint structures, although decrease their input into the central nervous system if the tension remains the same, in order to process acceleration and deceleration within the glenohumeral joint.

Proprioceptive feedback in not only produced from the passive restraints of the shoulder but from contractile structures too (Myers and Lephart, 2000; Nyland et al., 1998). The muscles which span the joint have three methods of assisting with joint stability by activation of various muscular contraction reflexes (Jerosch et al., 1997) (Jerosch et al., 1993), regulation of muscular contraction (Speer and Garrett 1993). The feedback is via the muscle spindles and golgi tendon organs. The muscle spindles provide feedback to enable effective motion execution via the monitoring of muscle length and joint position, and the sensitivity of the muscle receptors can be altered via efferent input from higher brain centres (Nyland, et al., 1998). The feedback from the golgi tendon organs registers changes in muscle tension and joint position, which induces agonist relaxation and contemporary increased activity within the antagonist, as a method of protection.

Processing of this information is carried out within the central nervous system at spinal level, brain stem, cerebellum, or cerebral cortex (Lephart and Henry 1996) and affects the

function of the dynamic restraints surrounding the glenohumeral joint. This is via feed forward (anticipatory) and feed back (reactive) loops (Ghez, 1991). These two loops work in harmony, within the healthy shoulder, to indicate the actions of the dynamic restraints, which themselves are responsible for maintaining appropriate force couples across the joint, reflex action and regulating muscle stiffness (Myers and Lephart, 2000).

During the rugby tackle high trauma, or repeated minor trauma, could compromise the stability of the shoulder joint via increased joint laxity has decreased proprioceptive acuity compared to subjects with less joint laxity (Blaiser et al 1994). This laxity could bring about a cycle of events; described by Lephart and Henry (1996) as shoulder functional joint stability paradigm. Figure 2
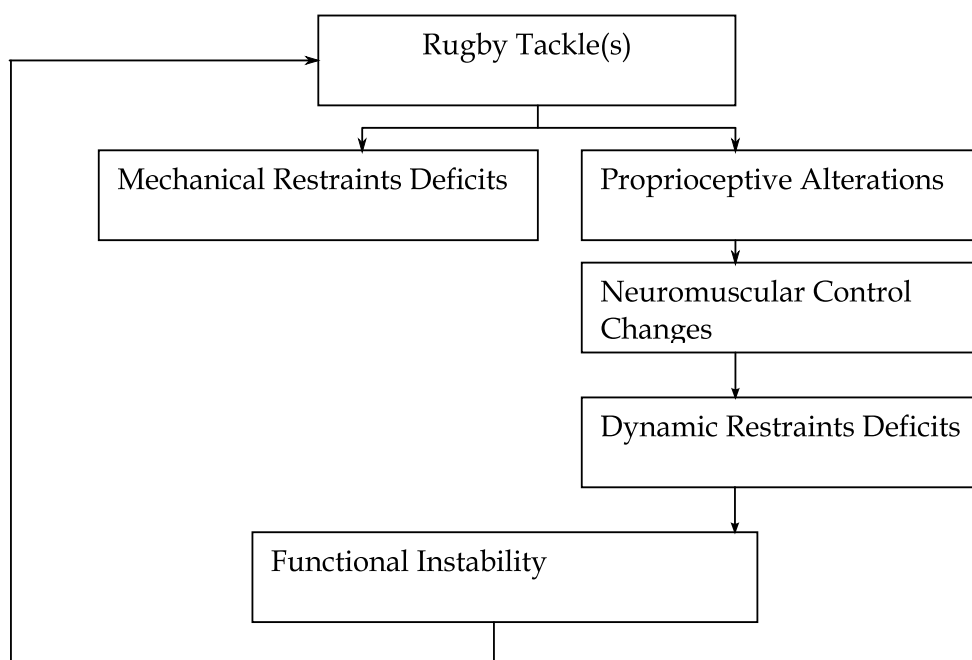
Adapted from Lephart and Henry (1996)

Fig. 2. Functional joint instability due to a Rugby Tackle.

Patients lacking proprioception have demonstrated an inability to perform multi-joint movements, suggesting that deficits in joint position sense detrimentally affects the co-ordinated movements at other joints along the kinetic chain (Riemann and Lephart, 2002) Following trauma to the shoulder joint through a heavy tackle of repeated contacts to the shoulder, proprioceptive input appears to be disrupted – which in turn affects neuromuscular co-activation deficits (Myers and Lephart, 1994).

Rehabilitation following injury to the glenohumeral joint should take into consideration not only pain relief, reduction of inflammation and restoration of optimal muscle strength and joint range of motion, but should include functional movements which replicate the demands of the sport in order to increase proprioceptive awareness, dynamic stabilization, feed forward mechanism (through anticipatory muscle responses), and sound reactive

muscle function to athletic demands (Lephart and Henry, 1995). Proprioceptive training has been suggested as re-connecting the afferent pathways from the joint to the central nervous system with the production of complimentary afferent responses as a compensation for the joint position deficits produced by fatigue and/or injury (Myers and Lephart, 2000).

With shoulder joint injury there is much more than the soft tissues which are damaged; the sensorimotor system which is responsible for motor control and proprioception, and as has been demonstrated following shoulder injuries in rugby (Herrington, Horsley, Rolf, 2007).

2. Restoration of the sensorimotor system

Following disruption of the sensorimotor system it is imperative that restoration of functional joint stability is carried out as quickly as possible, in order to minimise the deleterious consequences. This rehabilitation needs to be able to replicate the demands placed on the joint, under controlled conditions but identifying deficits within the sensorimotor system in a clinical setting is not easy. Within scientific literature many sophisticated devices such as isokinetic dynamometers and motion analysis have been utilised. But these devices are not readily available in a clinical setting and thus render these techniques impractical.

The assessment of proprioception using "reproduction of passive positioning" is a valid and established method reported by Barrett (1991) Clinically joint angular replication tests – whereby the shoulder is placed in a position and the patient holds it in that position and consciously registers this position, then the arm is returned to a resting position. The subject is then asked to return the arm to the test position. This test has been described by Davies and Hoffmann (1993) and assesses both the static and dynamic shoulder joint stabilisers providing a thorough afferent pathway assessment (Lephart & Fu, 2000). Other examples of open kinetic chain exercises are;

Joint angle repositioning, whereby the shoulder joint is taken to a specific position in space (generally a combination of abduction and external rotation) by the examiner. The subject (who has their eyes closed in order to negate visual cues) is asked to hold this position for 5 seconds, then the limb is moved to the starting position, and the subject is asked to move to the test position. The degree of error from the stated position is recorded.

Contra lateral limb mirroring; the subject's uninvolved shoulder is placed in a position in space (whilst they have their eyes closed) and the subject is asked to mirror that position with the "involved" limb. Once again the degree of error between the two sides is noted.

Rehabilitation:

The goals of neuromuscular rehabilitation according to Borsa et al., (1994) are:

- To improve cognitive appreciation of the shoulder relative to position and motion.
- To enhance muscular stabilisation of the joint in the absence of passive restraints.
- Restore synergistic muscular firing and coordinated movement patterns.

The progression of the rehabilitation programme should progress along continuum (table 1) of difficulty with respect to the sport or desired activity (Guido and Stemm, 2007) and evolve from bilateral to unilateral, supported to unsupported (Kennedy et al., 1982), utilising active and passive movement, with and without load. The act of gripping has been shown to activate reflex contraction of the rotator cuff muscles which will stimulate glenohumeral mechanoreceptors. (Shumway-Cook and Woollacott, 2001).

	Early Stress	End Stage
Support	Supported Bilateral	Unsupported Unilateral
Surface Stress	Stable Minimal Capsular Stress Mid Range	Unstable Maximal Capsular Stress Outer Range
Speed	Slow	Fast
Stress Application	Predetermined Stress	Random/ Sudden Stress
Movement Pattern	Simple Co-ordination	Complex Co-ordination

Table 1. Rehabilitation Continuum

Weight bearing exercises through the limb (closed kinetic chain exercises) facilitates the activity of the rotator cuff muscles, and can be utilised in positions of forward lean standing or in four point kneeling from a four point kneeling position joint position reproduction can be utilised (figure 3). These can be progressed to a three point position (by extending the other arm or either leg) and further progressed to two point weight bearing which will facilitate the posterior chain to aid with scapular stabilisation.

Fig. 3.

Further progression would be to change the surface from solid surface, to a wobble board or Swiss ball. The quality of the movement and exact local joint control needs to be monitored, as it is important to remember that arm movement, reflex stabilisation, postural control, and

somatosensory perception are not separate events but rather different parts of an integrated action. (Guido and Stemm, 2007). Only the number of repetitions that the patient can carry out correctly with consistency should be carried out, rather that dictating a pre-determined number of repetitions and sets. Thus each exercise repetition is bespoke for that patient to avoid fatigue – as motor control decreases rapidly with fatigue, as does joint position awareness.

Fig. 4.

Another possibility of improving the cognitive awareness of shoulder JPS, is to challenge the patient to find the balance point (figure5) whereby in side lying, they are challenged to place their arm directly perpendicular to the glenoid and, initially, maintain this position against gravity. Dynamic balance can be further enhanced by asking the patient to maintain this position with a Swiss ball balanced on their hand (figure 6). To progress this exercise the patient is asked to stand from this position maintaining balance of the Swiss ball overhead.

The addition of externally applied forces (perturbations) will promote glenohumeral joint co-contraction, and rhythmic stabilisation (where by the patient's shoulder joint is place in position and isometrically resists externally applied focus of the therapist , take advantage of the stretch reflex creating a change in the desired muscle length producing local muscular splinting.

As soon as it is applicable the exercises need to be carried out in more functional positions such as sitting and standing (rather than the early stage of lying positions), as body position has a significant influence on a patient's ability to replicate a target position and to be aware of upper limb movement (Janwantanakul et al., 2003).

Fig. 5.

Fig. 6.

Another alternative to assess and rehabilitate proprioceptive acuity is to utilise a laser pointer. Targets can be placed on a wall, and a laser pointer attached to the arm that is being rehabilitated (fig 7). The patient is instructed to either follow a set path (such as a line) or land the pointer on a predefined mark.

Fig. 7.

3. Proprioceptive neuromuscular facilitation (PNF)

Improvements in the neuromuscular response can be improved by utilising PNF exercises to stimulate the muscle spindles and golgi tendon organs. (Borsa et al., 1994). These movements occur in diagonal plans, against some form of external resistance, and require movement at the glenohumeral joint at all three planes (Voss and Ionta, 1985) and are designed to stimulate normal physiological movement.

Shoulder	Flexion External Rotation Adduction
Forearm	Supination
Wrist	Radial Deviation
Fingers	Flexion

Table 2. D1 flexion Joint Specific Movements

Shoulder	Extension Internal Rotation Abduction
Forearm	Pronation
Wrist	Ulnar Deviation
Fingers	Extension

Table 3. D1 Extension Upper Extremity Joint Specific Movements

Shoulder	Flexion External Rotation Abduction
Forearm	Supination
Wrist	Radial Deviation
Fingers	Extension

Table 4. D2 Flexion Upper Extremity Joint Specific Movements

Shoulder	Extension Internal Rotation Adduction
Forearm	Pronation
Wrist	Ulnar Deviation
Fingers	Flexion

Table 5. D2 Extension Upper Extremity Joint Specific Movements

The basic principles of PNF include utilisation of manual resistance (which varies throughout the range in response to the muscle strength), verbal cues, visual stimulus, and proprioceptive input via specific hand placement on the skin, stretch and timing order.

4. Plyometric exercises

Polymeric exercises involve an eccentric load or pre- stretch followed by a concentric contraction, (Borsa et al., 1994) which is induced via the myotactic reflex. This, then, facilitates reflex joint stabilisation. It has been proposed that movement towards the end of

the shoulder range stimulates joint mechanoreceptors, as well as facilitating muscle spindle activity and decreasing GTO activity from the length – tension changes occurring at the musculotendinous structures (Swanik et al., 2002)

Common plyometric exercises include throwing motions trunk motions, resistive band exercises ball/ wall drills and plyometric push ups (Borsa et al., 1994).

A plyometric push up involves starting from the lower position of the press up, with the chest neat the floor, and rapidly extending the elbows with force, so that both hands leave the floor, then controlling the movement back to the start position eccentrically.

It is essential to demonstrate excellent dynamic control around the shoulder, through full range, with good proprioceptive acuity before progressing to these demanding exercises. (Gibson, 2004).

5. Compression

It has been reported that tactile sensations (along with vestibular and visual) aid with joint repositioning (Allegruci et al., 1995). Compression garments are believed to enhance sensory and proprioceptive awareness leading to an increase in proximal stability (Gracies et al., 1997) and stimulate mechanoreceptors to enhance joint positioning sense and body awareness (Hylton and Allen, 1997) (Ulkar et al., 2004). There is a reduced contribution of cutaneous proprioceptive information in proximal areas such as the glenohumeral joint (Grigg 1994) and the provision of compressive force stimulates mechanoreceptors within the skin to provide joint position sense to the central nervous system (Barrack et al., 1983) and has been reported to promote the cognitive feeling of joint stability (Jerosch and Prymka, 1996; Barrack 1983).

Functional stability of the shoulder is dependent on co activation of the musculature as well as reactive neuromuscular characteristics. Injury to any of the soft tissue structures has been postulated as a cause of disruption of this neuromuscular mechanism. Treatment of such a dysfunction needs to consider proprioceptive training and rehabilitation, since the function of the shoulder joint is optimal when proprioception is normalized.

6. Summary

Injuries to the shoulder are becoming increasingly more frequent in professional rugby. It has been cited that this is due to the increased intensity and frequency of the contact/tackle phase (Brookes et al., 2005). Recent studies have provided at least a partial explanation of why this is occurring. professional rugby players to have superior JPS than controls, indicating JPS might not be related to injury risk, when assessed in a rested state Following a tackling task JPS was significantly decreased in the outer range position potential exposing to the anterior structures of the shoulder to increased loading. JPS would appear to be significantly affected by injury, players who have sustained an injury having inferior JPS, compared to their peers These results highlight the presence of sensorimotor system deficits following repeated tackling. These deficits are proposed to contribute to overuse injuries and micro-instability of the glenohumeral joint (Lephart & Henry, 1996). Thus, it would appear advisable, when appropriate, to restrict shoulder joint activity following repeated tackling. One way of achieving this would be to place tackling drills at the end of the training sessions and not to match tackling with heavy upper body weight training sessions.

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Tibial Stress Injuries: Aetiology, Classification, Biomechanics and the Failure of Bone

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1. Introduction

Stress fractures (SFs) were originally recognised in 1855 by Breithaupt, a Prussian military surgeon, who noticed that young military recruits suffered painful swelling of the forefoot after long marches (Carlson and Wertz, 1943). Initially called March Fractures, he believed the condition to be inflammatory, but in 1897 the bony nature of the affliction was identified when Stechow performed Roentgen studies on the metatarsals (Carlson and Wertz, 1943).

During World War II, the incidence of March fractures was prominent in new military recruits who were unaccustomed to long route marches with heavy packs (Carlson and Wertz, 1943; Bernstein and Stone, 1944). When the training programme became more intense, it was noticed that the frequency of the injury increased (Bernstein and Stone, 1944; Bernstein et al., 1946). By this time, 'March' fractures were also known as insufficiency, exhaustion, fatigue and creeping fractures (Hullinger, 1944). Although diagnosed in bones other than the metatarsals, they were still called March fractures (Carlson and Wertz, 1943; Hullinger, 1944; Bertram, 1944). The classic military type March fractures, however, are found in the neck and the mid-shaft of the second metatarsal.

Medial Tibial Stress Syndrome (MTSS) was probably first identified in 1913 when Hutchins discovered what he called 'spike soreness' in runners (as they were wearing running spikes). He described it as an area of tenderness in the posteromedial distal tibial region sustained in new athletes learning running techniques, or athletes altering their training regimens. Although there was no name for the injury at the time, Hutchins noticed the involvement of the periosteum and attributed the cause of pain to the flexor digitorum longus (FDL) tibial origin (Hutchins, 1913).

MTSS was not originally recognised as a separate entity to an overt stress fracture (SF) of the tibia, which is not surprising as at the time, patient examination and radiographs were the only clinical tools available for the diagnosis of these injuries. Usually MTSS patients demonstrated no abnormal signs on plane X-rays, but this common observation was due to lack of refinement of the imaging technology available at the time.

Devas (1958) was one of the first clinicians to extensively study tibial SFs and 'shin soreness' in athletes by using clinical observations in conjunction with plane radiographic interpretations. Assuming only one type of injury under study, Devas (1958) described a

'shin soreness type of SF involving a disruption of the periosteum over a varying distance' and described other symptoms i.e. tibial tenderness with soft tissue 'thickening' of the subcutaneous surface of the tibia and periosteal oedema. He also noted that plane radiological changes in this type of so-called SF were either of late onset, or not seen at all.

The term *shin splints* was originally used as a non-specific clinical term to describe distal tibial pain caused by repeated impact in the absence of any other injuries to the region. However, an improved understanding of the aetiology in conjunction with advances in nuclear medicine diagnostic techniques led researchers and clinicians to realise that shin splints, later defined more specifically as MTSS, was a separate condition which could be differentiated from other forms of distal leg pain such as SFs or compartment syndrome.

The distinction between tibial SFs and MTSS was becoming clearer and in 1966, the American Medical Association (AMA) defined the shin splint syndrome as "pain and discomfort in leg from repetitive running on hard surface or forcible excessive use of foot flexors; diagnosis should be limited to musculotendinous inflammations, excluding fatigue fracture or ischemic disorder" (AMA, 1966). It was not until the late 1960s and in the 1970s that a large range of Technitium-99 labelled radiopharmaceuticals were developed (Seibert, 1995), making Triple Phase Bone Scintigraphy (TPBS) available as a diagnostic tool. TPBS was initially believed by some clinicians to be of no advantage in the diagnosis of MTSS as it was claimed that the uptake of radionuclide was related to increased activity of the patient rather than being specific to a particular pathology (Rorabeck et al., 1983; Wallensten, 1983; Allen, 1996). However, abnormal scintigraph findings in patients with clinical signs of MTSS who did not subsequently develop a SF lead to the scintigraph definition of MTSS (Holder and Michael, 1984).

About this time, probably the first comprehensive and now classic clinical study of SFs was published (Matheson et al., 1987). Using plane film radiography coupled with nuclear medicine imaging, the pattern of SFs in athletes was found to differ from military recruits, with the most common SF type in athletes being the tibia (49.9%). This was followed by the tarsus (25.3%), metatarsus (8.8%), femur (7.2%), fibula (6.6%), pelvis (1.6%), sesamoids (0.9%) and lastly, the spine (0.6%). Bilateral stress fractures were observed in 16.6% of the cases. The femoral and tarsal SFs were more frequent in older athletes, whilst the fibula and tibial stress fractures were more common in the younger athletes. Matheson et al. (1987) radiographed 43.3% of these cases at presentation, and only 9.8% were abnormal. They recognised tibial periostitis ('tibial stress syndrome') as a separate entity to a tibial SF. This supported earlier studies such as Mubarak et al. (1982), who found that MTSS was due to periostitis rather than elevated compartment pressure or an overt tibial SF.

In the 1980's, a series of nuclear medicine studies on MTSS was published, leading to more specific diagnostic criteria for the injury. These criteria included recognising that MTSS had a characteristic scintigraphic appearance comprising of an elongated linear deposition of medium intensity radionucleotide along the posterior medial cortex of the tibia (Deutsch et al., 1997; Holder and Michael 1984; Matin, 1988). This differed from the more intense localised fusiform pattern typical of a SF (Matin, 1988), and highlighted that MTSS was a specific injury rather than just a precursor to a SF (Macleod, 1999). Despite these advances in nuclear medicine, MTSS is still used as a generic term for distal tibial pain. However, this perception is changing as more studies are published on the nature of this injury.

2. Diagnosis and classification

2.1 Definitions

From an aetiologic perspective, stress fractures can be divided into two types: insufficiency/pathological fractures and fatigue fractures. An insufficiency fracture occurs when normal loads are applied to bone which has mineral or elastic resistance deficiencies, such as in the case of osteoporosis, where there is a loss of normal bone per unit volume of bone tissue. On the other hand, fatigue fractures develop in normal bone which is exposed to atypical and/or more frequent loading. It is believed that this load alteration causes muscular fatigue, which then results in an altered stress state in the bone, initiating a microfracture. The muscular fatigue assumption is supported by the fact that non-weight bearing bones such as the ribs, humerus, radius and ulna, e.g. in tennis players, can sustain SFs (Devas, 1975; Bruckner, 1998).

Less is known about the aetiology of MTSS. Initially believed to be only tibial periostitis, current evidence indicates it is, at least in many cases, also a bone injury (Johnell et al., 1982; Magnusson et al., 2001; Magnusson et al., 2003, Franklyn et al., 2008). Additionally, clinical data indicates that there is more than one type of MTSS, with specific aetiology and injury mechanisms for each type. This is discussed further later.

2.2 Diagnosis and classification of tibial SFs

All tibial SFs fall into several different categories depending on location and fracture type/injury mechanism (Table 1). This was first recognised by Devas (1975), who initially categorised tibial SFs into two different types, compression and distraction (i.e. tensile) SFs, based on X-ray findings and clinical studies. Tensile tibial SFs were then further subdivided into transverse, oblique and longitudinal fractures.

Tibial SF type	Incidence	Most common age	Most common location
Compression	50%	Children or elderly	Upper third in children or lower third in elderly
Transverse	2.5%	Young adults, particularly physically active ones	Shaft
Oblique	42.5%	Young adults, particularly athletes and military recruits	Lower third
Longitudinal	5%	Mature adults	Shaft

Table 1. Various classifications of tibial stress fractures as defined by their characteristics, incidence and location (reproduced from material contained in Devas, 1975).

Devas found that young active individuals are likely to sustain either transverse or oblique tibial SFs. The transverse SFs, which he observed in the tibial shaft, were prevalent in athletes who performed plyometric activities, e.g. ballet or jumping sports, where powerful plantar-flexion of the foot occurs. He attributed these SFs to the dynamic pull of the calf muscles (Soleus and Gastrocnemius) loading the tibia, causing the tibia to bend and become more convex anteriorly; subsequently producing high tensile stresses on the anterior tibial mid-shaft. On the other hand, Devas (1975) believed oblique SFs of the distal third of the tibia, found in athletes and military recruits, to be the result of bending forces which subject the injury site to excessive tension. He found that the propagation of the oblique crack generally begins at the posteromedial border of the tibia and occurs in conjunction with

mild inflammation around the bone and a small swelling on the medial tibia. He also noted that thickening of the cortex may occur around the SF site due to an associated attempted healing periostitis.

Much of Devas's original observations form the basis for the current knowledge regarding SFs. In the current clinical setting, focal tenderness (due to periosteal swelling and probable attempted bone repair with cortical thickening) is the key for diagnosis of a SF. In the tibia, the whole anteromedial surface of the bone is subcutaneous; hence, there may be overt anteromedial subcutaneous pitting oedema on firm digital palpation reflecting the underlying response of the periosteum to micro-fracture formation (Johnell et al., 1982; Matin, 1988). Additionally, there is sometimes linear tenderness along the whole anterior margin of the tibia to which the deep fascia of the leg has a strong attachment for the anterior compartment. The tenderness sometimes also extends to the posteromedial longitudinal tibial margin or border, where the deep fascia also attaches in addition to the origin of the FDL. Medial tenderness may also arise from the medial belly of the Soleus, which is attached to the proximal medial tibial and the deep fascia. Intense localised posteromedial margin tenderness in addition to significant oedema and early callus formation may be palpable in athletes who have a delayed presentation of several weeks.

In addition to the above observations, the clinical exam of a potential tibial SF patient should also include an examination of lower limb alignment and foot types. The presence of foot pronation, and in particular, weak inverter muscles (Hinterman et al., 1998; Oakes, 1993), has been shown to predispose the running athlete's tibia to excessive medial torque during weight bearing, thus potentially altering the stress distribution in the tibia (Figure 1).

2.3 Diagnosis and classification of MTSS

MTSS has been defined as a condition resulting in intermittent pain in the lower extremities, in particular, tibial periostitis associated with a specific scintigraphic appearance (Macleod, 1999; Macleod et al., 1999). Probably the most widely accepted definition of MTSS is a condition comprising of tibial anteromedial surface subcutaneous periostitis in the vicinity of the junction of the middle and distal thirds on the medial border (Holder and Michael, 1984; Macleod, 1999) due to an osteoblastic irritation and stimulation of the periosteum (Deutsch et al., 1997). Oakes proposed that this was also potentially associated with outer cortical bone microfractures (Oakes, 1988).

The research of Holder and Michael (1984), which was later verified by other studies (e.g. Matin, 1988) is used by most medical imaging specialists as the standard reference for the correct definition and diagnosis of MTSS, and was supported by the British Medical Journal (Macleod, 1999). Holder and Michael (1984) described shin splints to be exercise-induced pain and tenderness to palpation along the posterior medial border of the tibia. In a study of 10 patients (5 males and 5 females), they described the injury as:

1. Exercise-induced pain initially relieved by rest and exacerbated by exercise;
2. Usually subacute onset of pain, initially dull and aching;
3. Pain and palpable tenderness along the posterior medial border of the tibia in the distal region of the middle third; diffuse and less focal than with an acute SF;
4. Hindfoot abnormality with heel valgus and excess pronation of the forefoot.

Foot pronation has been consistently identified as a significant risk factor for MTSS (Matheson et al., 1987; Moen et al., 2009), although not in all affected patients. As discussed by Hinterman et al., (1998), individuals with overuse lower limb injuries typically have a 2-4 degrees greater pronation than those with no injuries, although 40-50% of runners with excessive pronation have no overuse injuries.
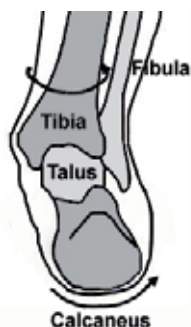
Fig. 1. Posterior view of the right foot. Notice the calcaneal eversion, which is associated with forefoot pronation and principally occurs at the subbtalar and midtarsal joints. This movement of the forefoot is associated with medial tibial rotation.

Using Cybex isometric leg muscle testing, Oakes demonstrated that MTSS patients had weaker inverter muscles than uninjured control subjects. He hypothesised that the weak inverters lead to excessive foot pronation due to eversion of the foot at the subtalar joint and subsequent medial rotation of the tibia (Oakes, 1993). Other authors have supported this injury mechanism (e.g. Hinterman et al., 1998), stating that the tibial rotation leads to injuries on the medial aspect of the tibia. This rotation would result in altered stress distribution in the bone, potentially increasing the tension on the medial border.

In-shoe orthotics can be beneficial for MTSS patients as they attempt to statically raise the medial arch of the foot, thereby preventing excess medial tibial torque or rotation by attempting to minimise forefoot pronation. However, orthotics have not consistently shown to be effective (Craig, 2008), which is not surprising, as not all MTSS patients show excessive pronation. This highlights the importance for the treating physician to identify the type of MTSS and therefore ensure correct management. It also emphasises that medial arch maintenance is mainly under the dynamic muscle control of the tibialis posterior and cannot be corrected optimally in the athlete by the use of simple static medial arch orthotics.

2.4 Nuclear medicine and imaging tibial SFs and MTSS

SFs and MTSS have been classified by both nuclear medicine and by clinical findings. Matin (1988) used a five-stage classification, where the initial two stages are defined as MTSS and the final three stages are a SF (Table 2). It is important to note that although there is bone involvement in Stages I and II, MTSS is not considered to be a precursor to a tibial SF in this system. Accuracies of 75% or greater have been found for scintigraphy (Lieberman and Hemingway, 1980; Allen, 1996; Gaeta et al., 2005), although false positives do occur, thus highlighting the need for a clinical diagnosis in conjunction with nuclear imaging.

Stage of injury	Percentage of bone cross-section involved	Description
I	0-20%	Minimal periosteal reaction
II	20-40%	Moderate periosteal reaction
III	40-60%	Early stress fracture
IV	60-80%	True stress fracture
V	80-100%	Full thickness stress fracture

Table 2. Classification of a stress fracture and MTSS using nuclear medicine techniques (Matin, 1988).

Figure 2 demonstrates a TPBS image from a patient showing three features of interest: a SF of the fourth metatarsal, MTSS, and bone bruising (i.e. increased bone oedema due to greater water content as a result of bone micro-damage or micro-fracture) of the calcaneus, where the patient had pronounced clinical symptoms of the SF and MTSS. The focal uptake at the location of the SF and the diffuse uptake at the MTSS site are readily apparent. Although the uptake at the calcaneus is considerable, the patient only experienced periodic mild tenderness at this site.
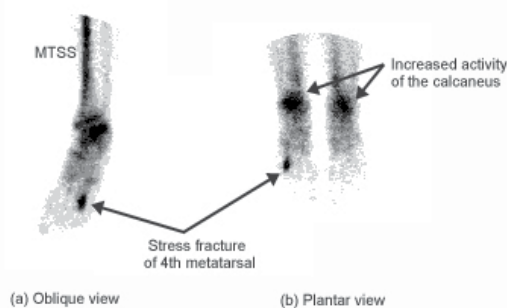

Fig. 2. Patient scintigraph illustrating three conditions (1) MTSS, (2) stress fracture of the fourth metatarsal and (3) mildly symptomatic bone bruising of the calcaneus.

Based on extensive clinical observations, Oakes (1988) proposed there were two distinct types of MTSS, where they can occur in isolation, or in conjunction to form a third type:

1. Tenderness on the distal tibia which when overt, can result in subcutaneous oedema or periostitis on the anteromedial surface of the distal third of the tibia. He proposed this was a result of tibial flexion from contraction of the two heads of the Gastrocnemius and the Soleus muscle causing tibial bending moments during the push-off stage of running. This type of MTSS subsequently results in microtrauma (microcracks between Haversian systems or osteons) to the underlying cortical superficial cortical bone and potentially a tibial SF at the thinnest tibial profile (i.e. the lowest tibial total cortical cross-sectional area).

2. Posteromedial linear pain and tenderness, predominantly due to the strong deep fascia of the posterior calf muscle compartment attaching to the linear posteromedial border of the tibia, but also from the tibial origin of the FDL. The cause of this longitudinal pain is tension in the tibial attachment of the deep fascia in conjunction with the origins of the powerful action of the Gastrocnemius and Soleus muscles proximally.

3. A combination of the above seen in serious long and middle distance runners.

As discussed further later, the authors have observed that some cases of MTSS may lead to a tibial SF, while most cases will not.

In two complementary studies, the first involving ten athletic patients diagnosed with MTSS by a TPBS and the second where anatomical dissection was performed on the lower limb of fourteen cadavers; Holder and Michael (Holder and Michael, 1984; Michael and Holder, 1985) found both pain and abnormal tracer accumulation were present at the origin of the Soleus. This study supports the Soleus involvement in MTSS, although Holder and Michael believed this to be the only cause of the injury. They further postulated the periosteal irritation stimulated afferent pain nerve fibres and activated an osteoblastic response. This

can be observed clinically from distal tibial tenderness, and possibly oedema, over the subcutaneous surface of the tibia.

Matin (1988) attributed the bony changes in MTSS to the insertion of Sharpey's fibres. He suggested that abnormal stress on the Sharpey's fibres not only led to the periosteal reaction with an elongated radionucleotide pattern, but also resulted in increased bone remodelling. He further postulated that Sharpey's fibres, which originate from muscles and other fasciae, increase stress on the superficial region of the tibial cortex as the fibres extend through the periosteum into the mineralised bone matrix of the outer circumferential cortical lamellae.

Radiographic findings are likely to be absent in the case of MTSS (Matin, 1988; Deutsch et al., 1997) with some clinicians stating they will always be radiographically occult (Matin, 1988). As opposed to a TPBS where bone turnover/remodelling is positively imaged due to increased bone vascularity, radiography relies on bone density changes for visualisation of pathology. Therefore, a tibial SF will be several millimetres in length and thus provides sufficient density contrast for radiographic visualisation, but only with optimal imaging conditions required for 'early' SF identification. On the other hand, even when MTSS is associated with microfractures, it is likely that they will never be large enough to be visible on plane radiography.

More recently, CT and MRI have been used to classify both SFs (Bergman and Fredericson, 1999; Deutsch et al., 1997; Feydy et al., 1998; Matin, 1988; Reeder et. al., 1996) and MTSS (Matin, 1988; Deutsch et al., 1997; Beck, 1998; Bergman and Fredericson, 1999). The main advantage of CT is that it provides a good delineation of fine bone detail (Feydy et al., 1998) so both SFs and partial SFs can be more easily observed. Unlike X-ray scans, cross-sectional images are possible using CT as this imaging modality uses a large number of X-ray beams to reconstruct a slice of bone. However, like radiography, the fracture line cannot always be observed readily as visualisation of the fracture line depends critically on the views imaged.

Fredericson et al. (1995) first reported MRI to be significantly better than other techniques for the early diagnosis of tibial and other SFs. They performed a study on 14 runners with 18 symptomatic legs within 10 days of referral for radiology. A TPBS and an MRI exam were also performed and the three imaging modes were compared. From this small number of patients, they concluded that MRI was more sensitive and more accurate in its correlation with the clinical symptoms and signs than a TPBS.

The main limitation with MRI is the lack of sensitivity in the assessment of cortical bone. Although Fredericson et al. (1995) found MRI to be superior to other imaging techniques in their 1995 study, SFs are often present without the fissure being observable, and the absence of a fracture line is considered a negative diagnosis (Bergman and Fredericson, 1999). The main advantages with MRI are that the patient is not subjected to ionising radiation and soft tissue changes can be easily depicted (Deutsch et al., 1997) as well as 'bone-bruising'. However, like TPBS, positive MRI images are possible in the absence of clinical symptoms (Kiuru et al., 2005). Additionally, oedema visible on MRI can be due to other conditions e.g. osteomyelitis.

In the original MRI study by Fredericson et al. (1995), the images were graded into four groups (Table 3). This was further modified by Pomeranz (2011) by dividing Group 4 into two separate categories: Group 4a (partial cortical fracture) and Group 4b (complete cortical fracture.

Grade	Clinical Exam	MRI
1	Periosteal tenderness at the distal 1/3-1/2 of the anteromedial tibial surface. Requires **firm** palpation with thumb.	Periosteal oedema: mild to moderate on T2 weighted images. Marrow normal on T1 and T2-weighted images.
2	Tenderness as above. Requires **less firm** palpation with thumb & may have linear tenderness along the posteromedial tibial border.	Periosteal oedema: moderate to severe on T2 weighted images. Marrow oedema on STIR or T2-weighted images. T1 normal.
3	Tenderness as above. Requires **less firm** palpation and may have linear tenderness as above. May have subcutaneous anteromedial tibial oedema.	Periosteal oedema: moderate to severe on T2 weighted images. Marrow oedema on T1 & STIR-T2-weighted images.
4	Tenderness as above. Requires **less firm** palpation and may have linear tenderness as above. A discrete region of maximal tenderness/thickening (early callus formation) over the fracture site will be palpable. Obvious tibial subcutaneous oedema is usually present.	Periosteal oedema: moderate to severe on T2 weighted images. Marrow oedema on T1-STIR or T2-weighted FS images. Fracture line clearly visible as low fuzzy incomplete (4a) or complete (4b) line. May see oedema in proximal tibial origins of Tibialis Posterior, FDL and Soleus.

Table 3. Modified by Oakes from Fredericson et al. (1995) and Pomeranz (2011).

As shown by the categories in Table 3, MRI can be used for the early detection of periosteal oedema, which is a reflection of microcracks between and through the Haversian systems in cortical bone in the region subjected to excessive repetitive loading. Fredericson et al. (1995) noted that the average marrow oedema extended over 5.2 cm and penetrated the outer one third of the marrow diameter. This indicated endosteal oedema as well as periosteal oedema.

For the managing physician, MRI can also be used to determine rehabilitation protocols and return to activity time without fear of reoccurance of a further episode of disabling bone pain due to inappropriate premature activity by often over-enthusiastic athletes, especially high-earning athletes. The soft-tissue sensitivity in detecting oedema due to microfractures can be used to determine the level of injury, as the extent of the bone oedema is a direct reflection of the strain damage to the tibial cortical bone. As a guide, Grade 1 injuries may be able to return to activity within 4-6 weeks if the aetiology of their stress reaction or SF is rectified. The most severe injuries, Grade 4a and 4b, can take as long or even longer to heal than the more conventional tibial fractures depending on the cause. For example, if the patient has poor biomechanical lower limb alignment coupled with excessive pronation due to unilateral weak inverter muscle groups (i.e. Tibialis Anterior and Posterior), 12 weeks or more might be needed for full recovery as the muscles will need strengthening prior to full safe return to activity or competition. Shoe orthotics can be beneficial in partial prevention of excess forefoot pronation and therefore excess medial tibial torque or rotation; however, the weak inverter musculature must also be addressed as outlined above.

2.5 Differential diagnosis

As a positive scintigraph is a non-specific finding (i.e. fracture lines cannot be observed) and MRI has a number of limitations, a differential diagnosis should be considered:

1. Insufficiency fracture: described earlier, in this case the bone has normal loading or low-level repetitive loading but is weak due to loss of bone mass, mineral or elastic resistance. The prime aetiological cause is osteoporosis (i.e. a loss of normal bone volume), and it should be considered as a potential diagnosis, particularly in older female patients.

2. Anterior tibial compartment syndrome: this condition is not common; however, it should be suspected when the pain is localised to the proximal anterior muscle compartment following intense exercise. This injury is aggravated by impact exercise and relieved when the exercise ceases. A measurement of compartment pressure during leg exercise can be used to confirm this diagnosis.

3. Popliteal artery entrapment syndrome (rare): muscle ischaemia from stenosis of the popliteal artery, which may pass through the medial head of Gastrocnemius. As with anterior tibial compartment syndrome, this condition also worsens during exercise. Dopler flow studies of the popliteal artery may help confirm the diagnosis prior to the use of femoral artery angiography.

4. Tibial tumours: Both benign and malignant tumours are possible. These tumours can usually be identified by X-ray; therefore, in order to exclude bone tumour, X-ray should be performed prior to scintigraphy.

5. Bone infection/osteomyelitis: This should be suspected in young athletes, especially if it involves the proximal tibial epiphysis. MRI can be used to establish the diagnosis and its exact location and extent.

Clinical symptoms and patient history should be used in conjunction with medical imaging for correct diagnosis of these injuries.

3. Mechanics of the tibia and bone failure

Numerous risk factors have been associated with tibial SFs (e.g. Burr, 1997; Bennell et al., 1999; Brukner et al., 2000), and to a lesser extent, MTSS (e.g. Moen et al., 2009). As these have been extensively published in the literature, they are not discussed here. The following sections focus on the biomechanical cortical bone parameters relating to tibial stress injuries, bone failure under various loading conditions, and *in-vivo* tests on humans and animals.

3.1 Tibial cortical bone parameters

The preponderance of the literature on cortical bone parameters originates from research on Israeli and US military recruits, with some studies having been performed on athletes. Most of this work has focused on male rather than female populations; hence the significant bone geometry related factors in females are less well understood. In male military cohorts, parameters which have been associated with tibial SFs include a narrow mediolateral (ML) width at the narrowest tibial cross-section (Giladi et al., 1991; Giladi et al., 1987) and small diaphyseal dimensions relative to body weight (Beck et al., 1996). In both male military cohorts and male athletes, a low cortical bone cross-sectional area (Beck et al., 1996; Crossley et al., 1999; Franklyn et al., 2008), small second moments of area (Milgrom et al., 1989;

Franklyn et al., 2008) and a small section modulus (Beck et al., 1996; Franklyn et al., 2008) have been associated with increased tibial SF risk.

A major limitation with many of these studies is that only basic cross-sectional dimensions have been measured from the images, and when they are then used to calculate parameters such as the cross-sectional area, introduce significant error for an irregularly shaped object such as a tibial section. Additionally, in some instances, the correct mechanical parameter has not been measured. This is most obvious in the case of the section modulus, which is often described as the cross-sectional area divided by the half-width of the cross-section. Lastly, using a formula to approximate tibial cross-sections to a shape such as en ellipse introduces a similar error; this error is compounded by the fact that tibial cross-sections can differ considerably from subject to subject (Figure 3).

Using a sample of 130 tibial CT cross-sections derived from a population of athletic and sedentary subjects, both male and female, Franklyn (2004) demonstrated that for irregularly-shaped sections such as tibial cross-sections, use of a formula involves a highly statistically significant degree of error. In this study, a series of cross-sectional parameters were calculated using various formulae from the literature and compared to the values of the parameter computed numerically by a validated code. For example, Milgrom et al. (1989) used a formula to calculate second moments of area about two planes; these moments are cross-sectional properties related to bending strength. Franklyn (2004) found that the formula for the second moment of area about the ML axis resulted in an overestimation by 1.09 (p = 3.15E-19), while the formula for the second moment of area about the anteroposterior (AP) axis resulted in an underestimation of 1.23 (p = 9.87E-32) when compared to the values of parameters computed numerically, with the error being larger for bigger sections. Other formulae in the literature tested resulted in similar levels of error. As these errors depend on both the parameter and the formula used, there was no one mathematical transformation which could be used to correct these values for all cross-sectional parameters.
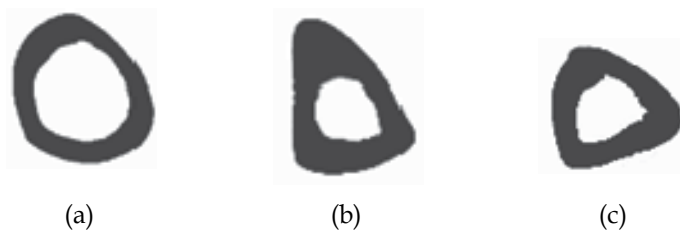

(a)   (b)   (c)

Fig. 3. Normal variation observed in cross-sections of the human tibia at the same cross-sectional level (a) elliptical, (b) triangular and (c) a hybrid of both shapes.

If basic methods are used to calculate tibial parameters, the error introduced is generally not a problem if, for example, cross-sectional areas are compared between groups of subjects within a specific study. However, problems arise when specific values need to be compared (i.e. values compared between two different studies) or the magnitude of the parameter is needed to better understand the injury mechanisms. It introduces doubt as to whether, for instance, an accurate cross-sectional area or section modulus is actually being calculated. Conclusions drawn from a particular study should be considered in light of the error implicit in the method used.

A further concern is the type of imaging modality used to scan the bone. Some imaging types, e.g. DEXA (Dual Energy X-ray Absorptiometry), have poor cortical bone resolution, but the technique has previously been used in a number of military or marine studies to calculate bone dimensions (e.g. Beck et al., 1996). DEXA was designed for bone mineral density (BMD) computation; hence dimensions measured from these images are likely to involve considerable error. DEXA can be used to directly compute geometric properties, but this technique also has error: a series of scan lines is performed through the bone at a specific cross-section, producing a profile of bone content in that section. For each line, the bone content is summed over the region; hence the distribution of bone cannot be determined (see Figure 4).
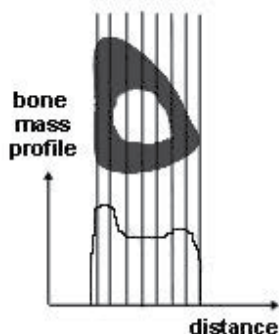

Fig. 4. DEXA uses a series of scan lines to produce a profile of bone content.

In order to overcome some of the abovementioned limitations, the current authors examined tibial geometry in athletes using CT imaging in conjunction with numerical methods to compute the true mechanical parameters (Franklyn et al., 2008). Bone geometry of MTSS patients was also analysed in order to make comparisons with the tibial SF patients. These results are discussed in detail later.

4. Bone alterations due to injury

It is now evident that MTSS involves alterations to at least the cortical bone of the tibia (Johnell et al., 1982; Magnusson et al., 2001; Magnusson et al., 2003; Franklyn et al., 2008; Murrihy, 2009), although whether the trabecular bone is also involved is unknown. This was first evident in the study by Johnell et al. (1982), where cortical bone and soft tissue biopsies were obtained from control (non-injured) patients and patients with chronic MTSS. The MTSS patients, who had one month's rest prior to the biopsies, were diagnosed by patient history and clinical examination in conjunction with radiography to exclude those with a stress fracture (scintigraphy was not widely available at the time).

Johnell et al. (1982) found there were no bone or inflammatory changes in any of the control subjects, while patients with MTSS had alterations such as increased osteoblastic activity at the medial surface of the tibia (where the biopsies were performed) and vascular ingrowth in conjunction with the soft tissue inflammatory changes. These findings were consistent with nuclear medicine studies at the time which demonstrated that MTSS patients had positive scintigraphy, indicating changes in bone metabolism (Matin, 1988). However, not all bone biopsies demonstrated changes: from a total of 35 cortical bone biopsies, 22 specimens had at least one sign of bony changes, but 13 did not. Consequently, they concluded that microfractures were a cause of MTSS, but not necessarily in all cases.

In other research performed since this time, BMD and cortical bone geometry in MTSS and tibial SF patients have been examined. These studies provide corroboration that MTSS involves alterations to the cortical bone, at least in many cases of MTSS, but not necessarily identical changes to those seen in tibial SF patients.

4.1 Bone mineral density in tibial SF and MTSS patients

In previous studies, BMD has been found to not differ between tibial SF patients and exercising controls subjects in most cases. This has been shown in male military recruits (Giladi et al., 1991; Milgrom et al., 1989), male marine recruits (Beck et al., 2000), male athletes (Crossley et al., 1999) and female athletes (Bennell et al, 1999). However, BMD differences have been found between female marine recruits with and without a tibial SF, (Beck et al., 2000). Nevertheless there is strong evidence to suggest the differences found in female subjects are due to hormonal effects such as menstrual irregularities or use of oral contraceptives (Myburg et al., 1990).

There are only a few studies where BMD has been analysed in MTSS patients. Magnusson et al. (2001) measured BMD in 18 male athletes sustaining clinically and scintigraphy-diagnosed MTSS, 18 competitive athletic controls (exercising 3-15 hours/week) and 16 control subjects who exercised at the non-professional level (0 to 5 hours per week). The authors demonstrated that at the injury site, male athletes with chronic MTSS had localised decreased BMD, and this reduction was bilateral even when the injury was unilateral. Additionally, they found that BMD normalises after recovery from the injury (Magnusson et al., 2003). At other sites of the tibia, the MTSS patients had higher BMD than the control group but lower BMD than the athletic control group.

The Magnusson study was limited by several factors. Firstly, subjects in the control group performed some exercise and were comprised of both manual and non-manual workers; hence they were not a true sedentary control group. A second limitation was the large range in number of hours of exercise per week, and both control groups contained a combination of subjects with manual and sedentary occupations; hence the groups were not uniform with regards to exposure. It is known that BMD increases due to impact exercise (e.g. Etherington et al., 1996), but these results show that BMD is reduced at the injury site in MTSS patients. It is likely that the reduced BMD is not inherent but develops in conjunction with the symptoms.

Differences in BMD at the injury site have not only been found between (male) MTSS and non-injured control subjects, but also between (female) MTSS and SF patients at the injury site. The authors of this chapter measured BMD from DEXA scans on 5 SF patients ($n = 10$ scans) and 10 MTSS patients ($n = 20$ scans), all of whom performed impact exercise a minimum of 3 to 4 times per week and had a minimum training history of 2 years (study criteria was described in Franklyn et al., 2008). All scans were performed at the same medical clinic with a Norland XR-36 scanner (Norland Medical Systems Inc.), and each subject was scanned in three regions 2.1 cm in length. Although only a small number of subjects, it was found that MTSS patients had significantly lower localised BMD (1.46 g/cm²) than tibial SF patients (1.63 g/cm²) at the injury site, but not at sites in the proximal and distal tibia (Table 4 and Figure 5).

Hence, from these studies, it can be concluded that male MTSS patients have localised low BMD at the injury site compared to non-injured exercising controls, and the BMD returns to normal after the symptoms have resolved. Also, at the injury site, female MTSS patients

have lower BMD than female tibial SF patients. As subjects with a tibial SF have been shown to have normal BMD, MTSS patients clearly have reduced BMD at the injury site.

BMD (g/cm²)	SF (n = 10)	MTSS (n = 20)	Significance
Proximal	1.2757	1.2139	0.136
33% level (injury site)	1.6354	1.4598	0.013[a]
Distal	0.9439	0.9023	0.403

[a] Statistically significant p < 0.05

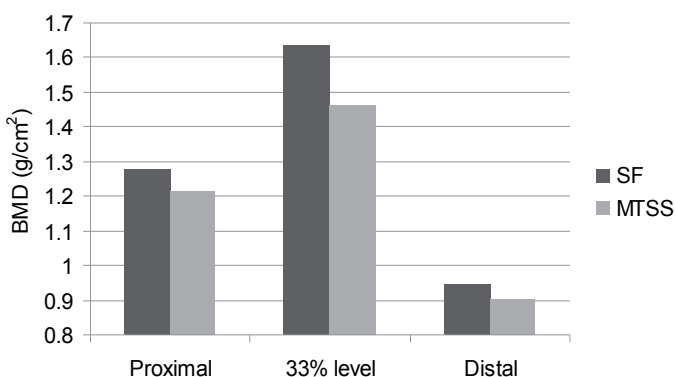Table 4. Statistical analysis of BMD in female tibial SF and MTSS patients (Oakes and Franklyn, 1998).

Fig. 5. BMD in female tibial SF and MTSS patients at three tibial sites (Murrihy, 2009).

4.2 Bone geometry in tibial SFs and MTSS patients

It has been shown that tibial SF and MTSS athletes have lower values of some cortical bone geometrical properties when compared to uninjured aerobic control subjects (Franklyn et al., 2008). These findings may imply that MTSS and tibial SFs are a continuum of injury, with MTSS being the precursory state of a tibial SF, and some researchers and clinicians believe this is the case. However, it is the belief of the authors that tibial SFs and MTSS are two separate injuries with some common aetiology and mechanisms. This is probably most strongly evidenced by the fact that not all cases of MTSS lead to a tibial SF. If they were one injury on a continuum, all MTSS patients would eventually sustain a tibial SF with continued exposure to the same impact forces, yet this does not occur. Additionally, tibial SFs are a localised injury whereas MTSS is diffuse. Lastly, it has never been demonstrated that MTSS and tibial SFs fall on a continuum of injury.

The results of the study by Franklyn et al. (2008) showed that the tibiae of male athletes with a tibial SF or MTSS have less cortical bone cross-sectional area (A) than uninjured athletes, resulting in lower values of some other mechanical parameters such as the polar moment of area (J), the maximum and minimum second moments of area (I_{max} and I_{min} respectively) and the section modulus (Z). These mechanical parameters determine the strength of a beam, such as bone, under different types of loading (see Table 5).

Parameter	Symbol	Type of loading it represents
Cross-sectional area	A	Axial loading
Polar moment of area	J	Torsion
Maximum second moment of area	I_{max}	Maximum bending rigidity
Minimum second moment of area	I_{min}	Minimum bending rigidity
Section modulus	Z	Pure bending

Table 5. Geometric parameters with engineering denotations and meanings.

Thus, injured males are less adapted to axial loading, torsion, maximum and minimum bending rigidity and pure bending (a state where there are no axial, shear or torsional forces). The lower values of these parameters in the injured males were due to less cortical bone in the medullary region (primarily in the AP medullary region) rather than from differences in external tibial widths. These results suggest that in males, cortical bone loss occurs from the medullary region prior to, or as a result of, these injuries.

In this study discussed above (Franklyn et al., 2008), it was found that females with a tibial SF or MTSS had smaller section moduli than uninjured females, but as other cross-sectional parameters did not differ, it was not due to less cortical bone area. Instead, injured females are less adapted to pure bending, but the results show that this occurs by a redistribution of the cortical bone about the centroid (centre of mass) so that bending forces are less tolerated by the tibia. Figure 6 shows typical tibial cross-sections from injured male and female subjects compared to uninjured control subjects.

Male AC
A=355mm²
Z=1,331mm³
$Imax$=18,700mm⁴
c=14.0mm

Different A thus differences in other parameters (but similar c)

Male SF
A=325mm²
Z= 1,291mm³
$Imax$=18,235mm⁴
c=14.1mm

Female AC
A=259mm²
Z=1,447mm³
$Imax$=10,840mm⁴
c= 7.5mm

Similar A but differences in other parameters due to varying bone distribution

Female SF
A=256mm²
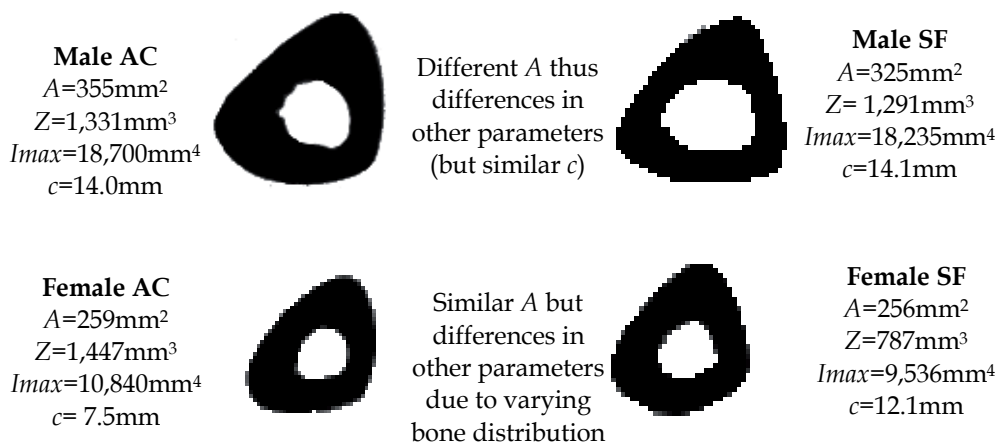Z=787mm³
$Imax$=9,536mm⁴
c=12.1mm

Fig. 6. Examples of typical male and female cross-sections from the mid-distal junction of the tibia showing the characteristic differences in geometry AC = aerobic control.

In mechanics, Z is a measure of a specific type of bending (pure bending). It depends on both the amount of material (cortical bone area) as well as its distribution, and is defined as:

$$Z = I_{max} / c$$

where c is the distance from the centre of mass to the outmost fibre of the cross-section (on the anterior border or tensile side). This outermost point is important as it is where the stress is highest under bending and therefore where failure is predicted to occur. If Z is larger, the structure can support a greater load under bending. This can occur due to a higher value of I_{max} (due to more bone) or lower value of c (the bone is closer to the centre of mass). In the study by Franklyn et al. (2008), the lower values of Z in the injured males were predominately due to lower values of I_{max}, whereas in the females, it was from higher values of c, consistent with the fact that injured males had less cortical bone area, but injured females had a different bone distribution less favourable for bending forces.

Alterations in bone shape can occur as osteoblasts in the periosteum create compact bone around the external bone surface while osteoclasts in the endosteum remove bone on the internal medullary cavity. Two mechanisms in which bone can adapt to mechanical loading have been proposed in the literature: (1) periosteal expansion (reshaping) and (2) redistribution of bone mineral from trabecular to cortical components (Adami et al., 1999), although the validity of the former has been disputed (Jarvinen et al., 1999). Although not a longitudinal study, the results from Franklyn et al. (2008) suggest in injured males, cortical bone could be lost to trabecular bone either before or during the injury, whereas in females, cortical reshaping may occur in conjunction with the injury. It is difficult to hypothesise further on these mechanisms; however, it is apparent that longitudinal studies examining cortical bone alterations prior to and during injury progression are needed.

4.3 Conclusions on bone characteristics and tibial stress injuries

These more recent studies on cortical bone and tibial stress injuries clearly demonstrate MTSS is, in many cases, an injury involving microfractures in the cortical bone in addition to low BMD, and cortical bone geometry which is less adapted to some mechanical modes of failure such as bending. Matin (1988) suggested that in MTSS patients, the deposition of radionuclide around the injured region was due to the response of the periostium to the developing abnormality in the cortical bone. However, he also proposed that abnormal stress on the Sharpey's fibres from the tissues increases stress on the outer circumferential lamellae of cortical bone, implying the tissue response may occur first. It seems unclear as to whether the cortical bone alterations occur before the inflammatory response of the tissue. In cases of MTSS which do not involve microfractures (Oakes Type II), the periosteal response would have to be due to, or a result of, a factor other than bone microfractures.

Most previous studies have shown BMD does not differ between uninjured control subjects and tibial SF patients. However, patients sustaining MTSS have reduced BMD at the site of the injury, and lower BMD than tibial SF patients at the injury site (consistent with tibial SF patients having normal BMD). This provides further evidence that MTSS and tibial SFs are two distinct injuries. Both MTSS and tibial SF patients have cortical bone geometry which is less adapted to dynamic mechanical loads imparted by the musculature. In males, there is less cortical bone area, which results in a decreased ability to tolerate different loading conditions such as axial load, torsion and various bending loads. In injured females, cortical bone area is not affected but there is decreased ability to tolerate pure bending. More work is needed in this area as there is a lack of longitudinal studies to provide more information on cortical bone changes and development of both MTSS and tibial SFs.

5. Cortical bone failure and fatigue

5.1 Bone as an engineering material

Bone is composed of two types of osseous tissue: cortical bone and trabecular bone, where the main distinction between the two is the density and the degree of porosity (Carter and Hayes, 1977). Compared to trabecular bone, cortical bone is quite stiff. Hence it is able to endure greater stress (force per unit area) but less strain (deformation) before failure. On the other hand, trabecular bone can withstand greater deformation before failure, and as a result, has a large capacity for energy storage (Keaveny and Hayes, 1993). In a long bone, a SF occurs in cortical bone as this tissue type is subjected to higher stresses, particularly around the external or superficial surface. Under the right conditions, this eventually leads to cracks (failure).

In engineering, materials can be classified as ductile i.e. have the ability to deform, such as in a soft metal, or brittle i.e. breaks with little deformation, for example, glass. As shown in Figure 7, each type of material has a typical fracture type: a ductile material has a characteristic 'cup and cone' fracture shape, while a brittle material has little yield and then fractures at an oblique angle.

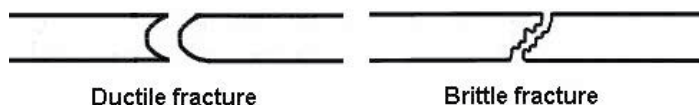
Ductile fracture   **Brittle fracture**

Fig. 7. Typical fractures of a ductile material and a brittle material.

Cortical bone does not act like a typical engineering material; it fractures in an oblique plane like a brittle material, but it also displays ductile behaviour. In addition, cortical bone demonstrates anisotropic properties i.e. the properties vary in different directions. For example, when subjected to tension transversely, cortical bone displays brittle behaviour, while if it is subjected to tension longitudinally, it appears to be ductile. Therefore, the type of behaviour depends on the loading conditions and the bone microstructure.

Although mechanical failure theories can be used to understand bone behaviour, like most biological materials, cortical bone exhibits unique characteristics that are different to standard engineering materials, and as such there are no mechanical theories of failure. Additionally, as the skeleton is subjected to complex loading conditions, it can be difficult to predict when and where failure will occur.

5.2 The biological basis for bone failure

According to the clinical evidence presented by Burr (1997), the most likely biological explanation for the initiation and/or propagation of a stress fracture is adaptive bone remodelling. This strain-mediated process is outlined below:

1. The stress is applied to the bone;
2. Osteoclastic resorption, which occurs as a part of the normal bone remodelling process, creates a reabsorption space that increases the bone porosity, reduces bone mass and exponentially decreases bone strength and stiffness. Osteoclasts reabsorb areas of bone, thereby forming hollow channels;
3. There is less bone, hence the strains on remaining bone increase;
4. The increased stress on the bone causes a new remodelling cycle to commence.

At Stage IV, there are two possibilities (Matin, 1988). First, the bone is allowed to rest so that osteoblastic bone regeneration can occur, with more dense bone replacing the lost bone so that the stress site is strengthened. Alternatively, at Stage IV, if there is no rest, the bone becomes weaker after the period of strain and resorption. This leads to the individual bone trabeculae eventually collapsing, subsequently causing microfractures in the bone which then may eventually lead to an overt SF.

In the initial osteoblastic stage, immature bone is laid down and eventually matures over time. Johnson (1963) found that it takes 90 days to fill a reabsorption space with mature bone. According to Reeder et al. (1996), the cross-sectional area decreases during this time period, which consequently subjects the bone to a potentially higher local stress. As a result, it is probable that the weakened state of the bone during the 90-day reparative period is when the bone is most susceptible to an injury such as a SF. Robling et al. (2001) demonstrated the importance of recovery time in restoring mechanosensitivity (i.e. the capability of sensing and responding to mechanical forces) to bone cells. Loading rat bones *in situ* using a four-point bending apparatus, tissue histology was examined when the rats were killed at various days after the loading commenced. They found that approximately 8 hours of recovery was required in the rat tibia to restore full mechanosensitivity to the cells after the cells had been desensitised from the application of repetitive mechanical loads for an extended period.

The theory outlined above is supported by other research. For example, Li et al. (1985) conducted an experiment where 20 rabbits were induced to run and jump by subjecting them to an electrical impulse at various intervals for a period of 60 days. Using radiographic and histological analyses on this group and a control (non-exercising) group, the authors found that osteoclastic reabsorption occurred before the presence of any cracks in the cortical bone. Furthermore, only some rabbits developed cracks in the bone after the period of exercise, suggesting that in the majority of cases, the rabbit tibiae adapted to changes in the applied stress.

Martin et al. (1997) performed a study *ex vivo* on deceased racehorses using the common SF site of the third metacarpal. Using the contralateral bone as a control, they found that if three-point cyclic bending loads were applied to the right bone for as many cycles as a racehorse would experience during its training and racing lifetime, then the elastic modulus and yield strength were not affected. This suggested that equine bone was not weakened by this loading *ex vivo*, and that SFs are not simply fatigue failure, but a result of the inability of the repair mechanism (remodelling) to sustain a level of equilibrium with the damage produced by fatigue. This implies that another mechanism, such as adaptive bone remodelling, is involved in SF development *in vivo*.

5.3 Fatigue failure in cortical bone specimens

In mechanics, ductile materials generally fail from a tensile load rather than a compressive load. Similarly, bone can withstand greater loads under compression than under tension; therefore, bone generally fails due to tensile stress. Hence, under *static* bending of a symmetrical specimen, bone will yield from tensile stresses rather than compressive stresses as bone is weaker in tension (Evans, 1957).

Currey and Brear (1974) tested cortical bone specimens under (non-fatigue) loading at different strain rates; some of the samples were subjected to compressive loads, while others were subjected to different types of bending loads. They demonstrated that cortical bone can fail under both tension and compression, but the modes of failure differed. When cortical bone

is compressed longitudinally, shear lines develop at an angle of approximately 30 degrees with respect to the load line (rather than 45 degrees, as in a normal isotropic material) due to the anisotropy of bone). These shear lines are believed to be due to buckling of the bone lamellae. However, cortical bone under tensile stress does not develop shear lines (Currey and Brear, 1974), but instead tensile lines that show yield (Caler and Carter, 1989).

In mechanics, failure of a structure is often from a time-varying load rather than from a constant load; this type of failure is known as *fatigue failure*. In this case, failure of the structure will occur at a *lower* stress level than would otherwise be the case for a standard static load. Most materials under cyclic loading fail as a result of a crack which develops from *tensile* stress. This crack then leads to stress concentrations, which subsequently initiate unstable crack propagation in the material. Alternatively, cracks will tend to form at any pre-exiting stress concentrator (imperfection) in the material, leading to crack propagation.

This mechanism differs in cortical bone, which fails under both tension and compression, i.e. there are two separate fracture regions, although the tensile failure occurs first. This was demonstrated by Carter and Hayes (1977) and Carter et al. (1981) who found that under cyclic loading, *tensile* loads result in *tensile stresses* which cause failure at osteon cement lines so that the osteons debond from the surrounding interstitial bone. On the other hand, *compressive* loads result in the formation of oblique microcracks along the planes of high *shear stress* before the crack from the tensile load had extended throughout the entire specimen. The shear stress tends to initiate near blood channels (Currey and Brear, 1974), which can act as stress concentrators in bone and therefore initiate crack propagation.

The studies described above do not take into account the remodelling process, which is a critical difference between bone and standard engineering materials. This was examined by Pattin et al. (1996), who studied energy dissipation under fatigue failure. Using human femoral cortical bone specimens, they performed fatigue to fracture testing under different types of cyclic loading. They found that above specific strain thresholds, tensile-loaded fatigue specimens dissipate 6-7 times more energy than compressive loaded fatigue specimens when subjected to the same loading magnitude. These results suggest that bone remodelling may be favoured under tensile load, since more energy is available to activate a remodelling response. This is consistent with other studies showing that SFs occur due to tensile failure.

Failure of cortical bone specimens are also affected by other factors such as the frequency of loading (Caler and Carter, 1989) and the strain range (amplitude). However, the mean strain and maximum strain do not affect the fatigue life (Caler and Carter, 1989; Carter et al., 1981). Compared to most engineering materials, cortical bone has a poor fatigue resistance, but a longer fatigue life than trabecular bone (Carter and Hayes, 1977).

In summary, the fact that cortical bone fails in tension under cyclic loading is not surprising, as according to mechanical engineering theory, tensile loads cause fatigue crack propagation in ductile materials (although bone is neither ductile or brittle). However, it is apparent that bone differs from most mechanical structures in that it demonstrates failure from both tensile and compressive components of a cyclic load, although the tension load will cause failure before the compressive component. Under each of these load types, the mode of failure is different. The bone specimen tests described above can describe the behaviour of cortical bone under load; however, they do not factor bone remodelling, which will influence the number of cycles to failure. Additionally, the applied loading to bone is likely to reduce when a crack initiates as continued loading becomes painful for the individual, consequently leading to a reduction in physical activity.

5.4 Fatigue failure in cortical bone *in-vivo*

Using patient X-rays and clinical examinations, Devas (1975) was probably the first to hypothesise that the tibial SFs which occur in athletes and military recruits, i.e. oblique SFs at the junction of the mid and distal thirds of the tibia, are the result of bending forces subjecting the site to excessive tension. This is a similar mechanism to the Oakes Type I MTSS (Oakes, 1988) mentioned earlier, where he proposed that the gastrocnemius and soleus muscles caused bending moments in the tibia, subsequently resulting in injury at the smallest tibial cross-sectional profile.

Lanyon et al. (1975) bonded a strain gauge rosette to the anteromedial aspect of the tibial midshaft of a 35-year-old human male, measuring the principal strains in the bone (i.e. the maximum and minimum strains, which are the most tensile and the most compressive strains respectively). When the subject was running with shoes, the maximum tensile strain, which occurred during the push-off phase, was greater than the maximal compressive strain, and the tensile strain was in-line with the long axis of the bone. This finding suggests that tibial SFs which occur at the midshaft are due to tensile forces causing tensile stress, and is consistent with the cortical bone specimen experiments mentioned earlier by Carter and Hayes (1977) and Carter et al. (1981), who found that tensile loads result in tensile stresses, which then cause failure at osteon cement lines.

The principal strains from the Lanyon et al. (1975) study were converted into principal stresses by Carter (1978). Carter found that the longitudinal stress on the anteromedial aspect of the tibial midshaft during running was primarily compressive at the heel-strike stage, while during the push-off stage, the longitudinal stress was highly tensile. On the other hand, the transverse and shear stresses were found to be small throughout the entire running gait. This suggests that if bone does fail under tensile stress when subjected to cyclic loading, then loads from the push-off stage are a significant contributor to the development of microcracks which lead to a tibial SF.

Milgrom et al. (1999) attached strain gauges directly to the mid-diaphysis of the medial cortex of the tibia in five male and three female subjects and measured strain magnitude and strain rates. They found that, in general, both strain magnitude and strain rate increased due to muscular fatigue, but values were not presented for different stages of the gait cycle. Similarly, Burr et al. (1996) conducted a study where strain gauges were attached to the medial tibial cortex at both the tibial midshaft and 2 cm distal to the first gauge in two male subjects, although data was only presented for the midshaft. Strains and strain rates where shown to be higher when running than walking, but the phase of the gait cycle producing these strains was again not presented.

5.5 Fatigue failure in cortical bone in animals

A number of experimental studies on rabbit tibiae have been performed to determine the aetiology of stress fractures. In humans, it is ethically difficult to instrument bone then load it until fatigue or injury; however, this is possible in animals.

As mentioned in Section 5.2, Li et al. (1985) conducted an experiment where rabbits were induced to run and jump for approximately 2 hours per day by being subjected to a pulse via an electric cage, where the frequency and period of the pulse was controlled. Radiographic and histological changes in the bone were examined over a 60-day period after sacrificing the exercising rabbits at various stages during the test. Two rabbits were also sacrificed from a control group, the first at the beginning and the second at the

conclusion of the experiment. From the radiographs, Li et al. (1985) found that there was a progressive periosteal reaction in 18 of the 20 rabbits, whereas the remaining tibiae showed soft tissue swelling with no radiographical changes (changes were found in 16 tibial midshaft, 3 distal and 1 upper third). Osteoclastic reabsorption was evident as early as the seventh day after exercise commenced, but cracks were not visible until the tenth day after loading. The histological analysis demonstrated that cracks developed on the cement lines of the Haversian systems, particularly on the anterior and medial aspects of the tibia, and that fracture lines were subsequently formed by convergence of adjacent cracks from the Haversian systems.

The experiment by Li and colleagues provided *in-vivo* verification of the early cortical bone specimen tests under cyclic loading performed by Carter and Hayes, which were discussed earlier under Section 5.3. Carter and Hayes found that tensile failure occurs first under cyclic loading, and that the tensile stresses caused failure through osteon debonding at the cement lines. Li et al. (1985) did not specify which types of cracks (longitudinal, transverse or oblique) occurred in the different locations of the tibiae. However, they did observe that most cracks occurred in the midshaft, which is consistent with other research to date on tensile stresses and tensile failure at this site.

Burr et al. (1990) applied cyclic loads to the hind limbs of 31 rabbits; one limb was subjected to compressive loads while the other limb acted as a control. The loads were applied using a specifically designed apparatus designed to apply cyclic loading of 1.5 times the body weight of the rabbit to simulate running. SFs were successfully produced in 68% of the rabbits within 6 weeks of loading and were verified by scintigraphy. Burr and colleagues stated that 89% of the SF were in the midshaft (implying that 11% were distal) and 74% were anteromedial; however, it was not clear how many of the midshaft SFs were anteromedial. As rabbit bones are quite small, it would have been difficult to visualise exact locations using scintigraphy. In addition, the rabbits were not under anaesthetic; hence their muscles could involuntary contract. This means that the loading applied to the tibia was not purely compressive as the involuntary contractions apply other loads to the bone such as bending.

Burr's group followed-up the above work with another rabbit experimental study analysing strain rate versus strain magnitude. Strain gauges were bonded to the midshaft and mid-distal third of the medial, lateral and posterior aspects of the tibia, but not the anterior border. The authors concluded that SFs were a result of increased strain rate at the mid-distal third of the tibia; however, the data presented showed that both strain rate and strain magnitude were higher in this location than in the midshaft. Hence, it could not be deduced from the results whether strain magnitude or strain rate is most likely to be associated with tibial SFs, or if both parameters in combination are significant.

6. Computer models of the tibia

More recently, computer models such as Finite Element (FE) models have been developed to examine the stresses in the tibial bone. FE models are advantageous in that the stresses can be analysed in any region of the bone modelled, loading and other boundary conditions can be readily controlled, and unlike human and animal experiments, a large number of loading conditions can be analysed.

In Section 5.5, a rabbit experimental model developed by Burr et al. (1990) was discussed. Burr and colleagues subsequently developed an FE computer model of the rabbit tibia (Burr, 1997; Burr 2001) where compressive loading only was applied. However, there were a

number of discrepancies with this model. For example, the model did not have any other loads from the musculature applied other than compression, yet it is probable that the tibia was subjected to other loads such as bending in the rabbit experiments. Additionally, the results of the FE model showed that high compressive stresses occurred on the anterior border of the tibia, yet from clinical research and knowledge of fracture types at this site, SFs on the anterior border are a result of tensile failure due to tensile or bending forces. Lastly, to produce compression on the anterior border, the applied compressive load would need to be significantly anterior to the centroidal axis of the tibia, particularly as the tibia is bent anteriorly and the rabbit leg is partially flexed. However, this is not consistent with the load position being applied to the heel in the experiment.

Using an MTSS patient, Franklyn (2004) developed a human tibial FE model to examine the relationship between ground reaction forces, bone geometry and maximum principal stress (Figure 8). The model was analysed similar to a 'free-body' analysis in engineering, where a section of the tibia was modelled, and the forces acting on the free body (tibial model) were applied. The forces were derived from gait analysis data of ground reaction forces which were then mathematically transposed to the equivalent forces acting on the free body. The major muscle forces were included. The model was then validated using *in-vivo* strain gauge data available in the literature such as the data from Lanyon et al. (1975), although this validation was not extensive due to the lack of *in-vivo* cyclic loading data available in the literature for all regions of the tibia.

The model was analysed using different time steps in the running gait cycle. It was found that the highest magnitude of principal stress was tensile, disperse, located on the external surface of the cortical bone on the medial tibial midshaft and occurs during the push-off stage of the gait cycle. This high stress region was due to a specific combination of high transverse and compressive loads during the latter part of the gait cycle. These findings are all consistent with previous work where bone fails in tension, and the push-off stage of the gait cycle has been shown to result in maximal tensile strain at the midshaft during running (Lanyon et al., 1975). Additionally, cracks have been shown to initially develop on the exterior cortical surface, which is also consistent with mechanical theory, which predicts stresses are greatest on the external surfaces.
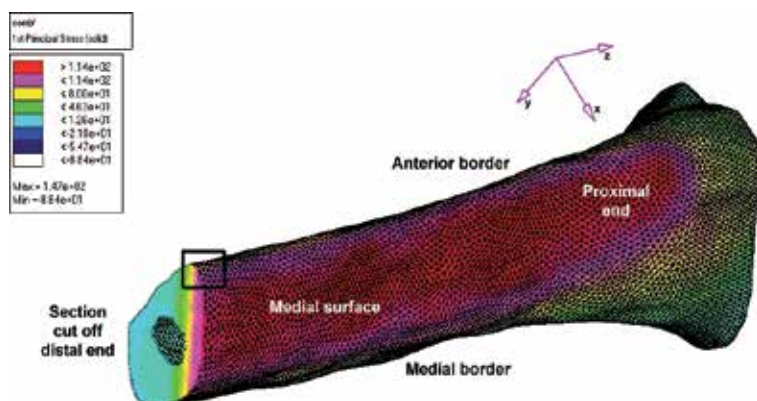

Fig. 8. Tibial FE model of an MTSS patient sectioned at the midshaft. Maximum principal stresses on the medial surface are diffuse and originate from the exterior surface (Franklyn, 2004).

Franklyn (2004) also conducted a preliminary analysis on load versus bone geometry in the FE model to replicate the stress pattern typical of a tibial SF. It was found that a localised SF pattern could not be produced by altering the loads alone, but only by changing the geometry. These results suggest that bone geometry is more influential than loading conditions in the development of tibial SFs and indicate that graded training programmes may be the most effective countermeasure for SF prevention.

7. Conclusion

Current knowledge of the aetiology and mechanics of tibial SF and MTSS development has come from a combination of clinical research, cohort studies, *in-vitro* cortical bone specimen experiments and *in-vivo* tests on both humans and animals. More recently, FE computer models have been used to better understand the relationship between tibial bone geometry, applied loads and stress distribution in the cortical bone.

Although there has been considerable research on the mechanisms behind these injuries, they are still not fully understood. However, a number of conclusions are evident. SFs of the tibial midshaft, which are longitudinal or transverse, arise from tensile and bending loads respectively. These loads produce tensile stresses which cause osteons to debond from the surrounding tissue, resulting in cracks between and through Haversian systems. On the other hand, SFs of the mid-distal junction are oblique; hence they could be due to shear stress and subsequent lamellae buckling from compressive loads, or from tensile stresses in an oblique plane due to torsional load. Clinical findings suggest tensile failure occurs at this site; hence torsional load appears to be a more likely mechanism.

Cortical bone geometry is significantly different between injured patients and non-injured control subjects. It is probable that the bone geometry alters due to impact loading rather than being inherent, but longitudinal studies are needed to determine if bone geometry alters prior to the injury or as a result of the injury. These types of studies may lead to the development of reliable prediction tools for tibial stress injuries.

Despite some common aetiology and mechanisms between tibial SFs and MTSS, it is unlikely that they are one injury on a continuum. However, it is evident that more research is needed in this area, as prevention of these debilitating injuries remains a problem which can affect successful sporting and military careers as well as the large recreational athletic population.

8. Acknowledgements

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For the past two decades, Sports Medicine has been a burgeoning science in the USA and Western Europe. Great strides have been made in understanding the basic physiology of exercise, energy consumption and the mechanisms of sports injury. Additionally, through advances in minimally invasive surgical treatment and physical rehabilitation, athletes have been returning to sports quicker and at higher levels after injury. This book contains new information from basic scientists on the physiology of exercise and sports performance, updates on medical diseases treated in athletes and excellent summaries of treatment options for common sports-related injuries to the skeletal system.

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