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Body-mass Index and Health

Edited by Ayşe Emel Önal

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Meet the editor

I was born in 1960 in Istanbul. In 1985, I graduated from Istanbul University, Istanbul Medical Faculty. In 1995, I became a specialist of Public Health with my thesis titled "Relations of Activities of Daily Living and Instrumental Activities of Daily Living with Health Problems of the Elderly Teachers Living in Istanbul". I was an associate professor of Public Health in 2005. In 2007, I was an associate professor in the Environmental Health Department. I became professor in 2011. Since 2013, I have been the Director of the Department of Environmental Health and since 2016 I have been director of the Department of Public Health of Istanbul University, Istanbul Medical Faculty. I have a degree in French and English language.

Contents

Preface

Nearly eight billion people live in the world today. Close to one billion people live on the edge of hunger, and more than two billion people are obese or overweight. Two billion people are lacking essential micronutrients such as vitamin A and iron. One in three women of childbearing age is anemic. There are 150 million children under five years old that are short according to their age (ie stunted). There are 50 million children whose weight is less than average according to their height (ie wasted).

The most common diseases, and also the most deadly diseases of today, are cardiovascular diseases, cancers and respiratory diseases. They are directly or indirectly related to unhealthy diet. Obesity in children and adults, micronutrient deficiencies in children, pregnant women and the elderly, stunted and wasting in children are important nutritional problems in the world.

Beginning with life intrauterine, a healthy lifestyle and healthy eating habits protects individuals from many acute and chronic diseases. To be protected from acute and chronic nutrition related diseases, countries should prepare control programs and undertake screening for potential deficiencies or excesses, encourage breastfeeding, provide healthy nutrition guidelines for each age group and encourage the consumption of natural probiotics and prebiotic foods.

The body mass index has an important place in weight control. Attention should be paid to the regularization of anthropometric measures and to physical activity to protect from increasing obesity that is associated with chronic noncommunicable conditions, such as diabetes mellitus, cancers and cardiovascular diseases. Also, attention should be paid to the countries that are developing. The daily intake of calories, carbohydrates, oils and proteins, vitamins and minerals and clean water is essential for all individuals, especially for children and for pregnant women.

I would like to thank IntechOpen publishing house for giving me the opportunity to be editor of this book titled "Body-mass Index and Health" and to write this preface. I wish everyone fresh air, healthy water, healthy food and a healthy, long life.

Yours truly

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Introductory Chapter - Life, Health and Body Mass Index

Chapter 1

Introductory Chapter: Life, Health and Body Mass Index

Ayşe Emel Önal

Additional information is available at the end of the chapter

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1. Introduction

The main areas of interest of Public Health are physical, social, and psychological health promotion, protection from diseases, and reaching the longest life possible by the genetic structure of man. As is known, air, water, and food are essential for life. We take the energy we need for life from the food we consume every day [1, 2].

Primary health care is the minimum health care that governments have to offer as a result of a publicly funded spending. Improving the nutritional status of the community and providing clean water to the community is essential for the continuity of life. While good nutrition of individuals in health protection and prevention of diseases is one of the primary protection measures, governments need to ensure food control and safety in environmental measures [2, 3].

The methods used to diagnose diseases during periods of asymptomatic or mildly symptoms are called secondary protection or screening. With screening methods, risky individuals for diseases or diseases are identified and the treatment of diseases, if any, can be treated with no difficult, and the development of complications and disabilities are prevented [4].

A healthy nutrition is the adequate intake of the nutrients needed to ensure the growth, development and continuity of the daily functions of the body. If healthy nutrition does not occur, malnutrition, unbalanced nutrition, and overnutrition occur. There are many nutritional diseases within these groups. Early diagnosis can be made by calculating the body mass indexes of individuals who are susceptible to these diseases or who are at the initial stage of the disease. The diagnosis is then confirmed using definitive diagnostic methods so that it can be treated at an early stage. According to these calculations, if the person is not ill but the body mass index is outside the normal limits, primary prevention measures are applied.

Nutrition is the process from taking nutrients to digestion, absorption, transport to tissues, and use by cells. The number of calories that we have to take in pregnancy, lactation, infancy, childhood, adolescent age, adulthood, and old age are different and the principles of healthy nutrition show different characteristics in these periods. Childhood malnutrition leads to diseases of protein energy malnutrition such as marasmus and kwashiorkor. Adults often develop cachexia with a chronic degenerative disease such as cancer [5, 6].

Unbalanced nutrition usually lacks one or more nutrients. As in the past, vitamin D deficiency, iron, folate, vitamin B12 deficiency, and iodine deficiency are common in children and adults living in economic deprivation areas. Scurvy (vitamin C deficiency), infantile beriberi (deficiency of thiamin (vitamin B1)), aribofilavinosis (riboflavin (vitamin B2) deficiency), pellagra (niacin deficiency), and vitamin B6 deficiency, xerophthalmia (deficiency of vitamin A) are diseases seen in regions with economic deprivation and also in some severe acute infections or noninfectious chronic diseases [6, 7]. Osteoporosis, cataract, and mental dysfunctions in the elderly were associated with vitamin and mineral deficiencies [8].

From past to present, human nutrition has undergone a transformation over time. This transformation has changed from herbal nutrition to hunting, from ready food to genetically modified food [9]. This change and diversity has come to prominence especially in recent years. Nowadays, mostly foods have high glycemic index, too much salt, too much oil and energy, and little vitamins and minerals. Together with changing living conditions such as inactivity, have increased the frequency of obesity in the world and the incidence of obesity-related chronic noncommunicable diseases such as diabetes mellitus, cardiovascular diseases, cerebrovascular diseases, renal diseases, and peripheral artery diseases [10, 11].

Obesity is an energy metabolism disorder caused by excessive fat storage in the body and causing physical and psychological problems. Obtaining more energy than consumed is the most important cause of obesity, but physical activity habits, some environmental reasons, hormones, gut microbiota, and genetic structure are also effective in the development of obesity [12, 13].

The MONICA study was conducted by WHO in six different regions of Asia, Africa, and Europe and reported to have increased obesity prevalence in 10 years. There was a trend of increasing body mass index with half the female populations and two-thirds of the male populations [14].

The WHO Regional Office for Europe reported that overweight in the world affected 35% of adults over 20 years of age (BMI $\geq$ 25 kg/m^2) (34% men and 35% of women). According to this report, 12% of the world's population (10% of men and 14% of women) is obese. Between 1980 and 2008, the prevalence of obesity (BMI $\geq$30 kg/m^2) in the world has doubled [15]. Finucane et al. indicate that between 1980 and 2008, mean BMI worldwide increased by 0·4 kg/m^2 per decade for men and 0·5 kg/m^2 per decade for women [16].

Body mass index is the most commonly used method in adults to determine nutritional status (and therefore obesity). BMI, formerly called the Quetelet index, is calculated by proportioning the body weight to the square meter in meters (kg/m^2). The BMI value is considered to be normal between 18.5 and 24.9, overweight between 25 and 29.9, and obese at 30 and above [17].

Obesity in children is more commonly evaluated with percentiles. The recommended cutoffs are: >95th percentile: overweight, 85th–95th percentile: risk of overweight, and <5th percentile: underweight. However, there are also tables and graphs of the WHO and the Centers for Disease Control and Prevention (CDC) showing the BMI of the children's percentile values [18–20].

Other methods of obesity determination are weight scales arranged according to height-age-gender. Based on these standards, it is possible to decide whether the body weight is normal or not. Z score, waist-hip ratio, skinfold thickness measurement, and body fat percentage measurement are other methods used in the diagnosis of obesity.

Many studies have found a relationship between overweight and obesity and sleep disorders and physical activity limitation [21]. The relationship between depression and BMI has also been investigated. It has been found that BMI does not reduce depression, but there is no clear finding that it increases [22, 23].

The relationship between BMI and osteoporosis has also been investigated. Some studies concluded that increasing fat mass may not have a beneficial effect on bone mass [24]. Contrarily, some study concluded that obese women or obese elderly had lower prevalence of osteopenia compared with normal weight subjects and also with lower prevalence of osteoporosis as compared to normal- and overweight women [23, 25]. It is also reported that high BMI is associated with breast, colon, prostate, endometrium, kidney, and bladder cancers [26–29]. Obesity has also been reported to be associated with asthma, osteoarthritis, gout, bladder diseases, pancreatitis, dementia, nonalcoholic fatty liver disease [30].

In addition, BMI was also associated with mortality. Mortality rates increase with increasing degrees of overweight, as measured by body mass index [31, 32].

Ways to resolve health problems due to inadequate and unbalanced diet can be summarized as follows: the fight against poverty, the development of food policies by governments, the protective policies that health authorities will initiate and continue. Main foods, especially bread, must be enriched with vitamins and minerals whose deficiencies are frequently observed. Vitamins and minerals such as B2, B6, B12 vitamins, folic acid, iron, zinc, and calcium are nutrients that can be added to foods.

Many countries have initiated control programs to combat obesity. These programs have been reported to reduce both the prevalence of obesity and the associated chronic noncommunicable diseases. Having an active life, reducing energy intake, limiting salt and saturated fats and refined sugars, restricting processed food consumption are among the measures to combat obesity.

Finally, programs organized for the prevention of diseases related in a healthy diet and malnutrition consisting of Turkey are as follows, and all of them are based on weight control and BMI measurement.

- Breastfeeding and Baby Friendly Health Institutions Program [33]
- Breastfeeding Protection, Promotion of Prevention and Control of Iron Deficiency Anemia With Support Program "Turkey Strong as Iron Project," 2004- [34]
- Program for the Prevention of Vitamin D Inadequacy and Bone Health Development in Infants, 2005- [35]
- Turkey Complementary Nutrition Program, 1990- [36]
- Healthy Nutrition, Let's Protect Our Hearts Program, 2004- [37]
- Fight Against Obesity Program, 2010-2014 [38]

- Turkey 2010-2014 program on healthy eating and active lives [39]
- Turkey Excessive Salt Consumption Reduction Program, 2011-2015 [40]
- Turkey Diabetes Prevention and Control Program, 2011-2014 [41]
- Turkey Diabetes Program, 2015-2020 [42]

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Section 2

Intrauterine Period and Body Mass Index

Chapter 2

Body Mass Index (BMI) and Anthropometric Measurement of the Developing Fetus

Niranjan Bhattacharya and Priyodarshi Sengupta

Additional information is available at the end of the chapter

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Abstract

Medical and scientific study of the measurements and size of the human body is known as anthropometry. In anthropometry, body mass index (BMI) is one of the best indirect methods for the estimation of body fat and mass. Other methods of indirect methods include weight, stature, and abdominal circumference. Direct methods include total body water, total body counting, and criterion methods include body density. Other factors like the size and weight of the mother also influence the size and mass of the body. An earlier work was conducted by K.L. Mukherjee on the systemic anthropometric measurements of the aborted human fetus. The following chapter will deal with the importance of parental and fetal BMI and its influence on the development of the fetus at varying stages of development and their relationship with anthropometric measurements.

Keywords: anthropometric measurements, body mass index (BMI), fetal development

1. Introduction

Anthropometry is a technique implemented for the scientific study of the measurements of the human body. Over the years anthropometric measurements have become an important tool for clinicians and scientists in health assessment of the fetal development and growth [1]. One of the main parameters used in anthropometry to study the impact of the fetal growth through different phases of pregnancy includes that of the parental and the fetal body mass index (BMI), which is believed to affect the baby's growth, development, and birth weight [2].

Birth weight is also one of the important factors affecting the fetal anthropometric measurements, and any abnormality is strongly associated with the morbidity and even mortality of the infant.

A low birth weight of a neonate can be linked to impaired overall growth and development of the baby and overweight can be related to severe complications of the child during delivery [3]. Fetal and offspring overweight can also be related to obesity in children in later life [3, 4].

Apart from the weight of the neonate, factors such as the maternal height, weight, and metabolic rate are also important anthropometric parameters related to the growth and development of the fetus [5]. Small and selected studies have suggested that pre-pregnancy pre-BMI and weight during the gestation period of the mother are important factors that predict the outcome of the fetal weight and its development [6–11].

Normally it is gestational weight, which is indicative of both nutritional status and tissue development, whereas pre-pregnancy BMI only reflects the nutritional status [12]. However, the relationship between the two is still not clearly established including that of the maternal BMI and other anthropometric parameters related to the fetal growth and development in pregnancy [2].

An early pioneering study in Calcutta led by Prof. K.L.Mukherjee involving anthropometric measures of the aborted human fetus collected ethically from all the trimesters was conducted [13]. They found the weight of the liver decreased with increase in gestational period, whereas organs such as lungs increased in their size with increase in the gestational period [13, 14]. The adrenal glands in the first-trimester remain larger than the kidneys; however, after 12 weeks of gestation the kidney outweighs the adrenal gland.

The group was unable to detect any thymus tissue at 8 weeks of gestation in smaller fetuses. However, they could detect the presence of the thymus gland in larger fetuses weighing more than 5 g between the first and second trimester period. In 28 week old fetuses, the thymus could be easily detected indicating that with an increase in the gestational week, the thymus becomes observable because of its increase in weight and size [15]. In case of sexual organs, the growth and development of the tests were not uniform. However, a trend was observed where there was a decrease in the weight of the testes with an increase in the gestational period in the male fetuses and a similar pattern was also observed in case of the ovaries in female fetuses [13].

2. Relationship between the parental BMI and the anthropometric development of the fetus

Most of the studies conducted are based on the relationship of birth weight as an important anthropometric parameter and its measure of the fetal growth and development [16]. Ay et al., for the first time examined the relationship of maternal anthropometrics with the fetal growth and development at various stages of pregnancy through a large cohort study [2]. They showed that maternal pre-pregnancy BMI (pre-BMI) gestational weight and height has an influence on the fetal growth and development starting from mid-pregnancy onward [2]. These maternal parameters can be associated with the small and large size of the infants and are related to an increasing gestational age. The findings of the study were independent of the social factors such as the socio-economic condition and lifestyle of the mother [2]. Studies pertaining to the timing of the anthropometric development of the fetus have been focused mainly on the birth weight and fetal growth. However, third trimester studies till date remains inconclusive [6, 17–20].

Factors such as diabetes or insulin resistance have a strong effect on the high maternal pre-pregnancy BMI and weight gain and can lead to increased fetal glucose and an increased birth

weight along with a risk of cardio-metabolic disorder [20]. Maternal nutritional status is also an important criterion that can be strongly associated with the pre-pregnancy BMI and the outcome of the fetal weight [21]. However, further studies are important to prove this exclusively including the maternal anthropometric mechanisms which affect the fetal growth [2].

Another important study was conducted in Pune to find out the relationship of BMI and height on 557 pregnancies with fetal age between 17 and 29 weeks of gestation and observed through ultrasound method. The group reported that parental height was positively associated with an increase in the fetal head circumference and femur length [22]. In case of higher BMI rates in mothers, ultrasound images showed that the fetus in utero had a smaller head circumference at 17 weeks and it increased during the time of birth. In mothers having lower BMI rates, head to fetal body ratio was observed to be large at 17 weeks. The placental volume was also depended on the maternal BMI and the paternal height [22].

As mentioned before, pre-pregnancy BMI is an important parameter and marker for nutrition, energy, and tissue development [22]. In the above study, further, the group of clinicians found a positive correlation between the paternal height and placental volume at around 17 weeks of fetal development although the direct role of maternal BMI on the 17 weeks fetus was found to negative [22]. Better maternal nutrition is thought to provide the mother with a higher BMI, which helps in the placental development in early pregnancy resulting in greater fetal development in the final gestational phases [23]. Similarly like Goldberg et al., the study further found a positive relationship with head circumference growth in the 29 weeks to birth interval [24].

A study by Tahergorabi et al., showed a weak association of maternal BMI with respect to the sex of the first-trimester fetus [25]. They showed maternal BMI was related to the female fetus rather than the male fetus and maybe sex-dependent in nature [25]. Other factors that can influence the impact of maternal BMI on birth weight of the fetus include maternal age, ethnicity, gestational diabetes mellitus and insulin resistance, education and environmental factors, and hypertension including genetics [26, 27].

Until recently the relationship of BMI and its significant influence on the developing fetus was unknown. Studies and observations have come to acknowledge the fact that maternal weight, BMI including that of the fetus plays an important role in determining the fetal growth and development [2, 28–30].

Recently, the significance of paternal BMI and dietary behavior in animal studies have also shed light into the fact that paternal obesity including BMI can affect the offspring in a gender-dependent manner [31]. Chen et al., in one such pioneer study observed that paternal BMI during the time of conception can be sex dependent and can influence the male but not the female fetus through mechanisms hitherto unknown [31]. However, the above cannot be exclusively confirmed as of yet due to very few studies relating to paternal BMI and its relationship with the fetal development [32].

3. Importance of BMI in fetal growth

BMI is one of the important parameters used along with other measures such as waist circumference, waist to hip and height ratio, subcapsular thickness as a part of the classification of overweight, obesity although it fails to account for the overall fat distribution [33]. It is also an

important predictor to assess the healthy outcome of a baby. BMI can be directly correlated to neonate obesity, preterm birth complications, shoulder dystocia, and other complications [33]. Nonetheless, BMI still is an important factor that influences the growth and development of the fetus on a more general basis [34].

In third world countries where maternal nutrition has a profound effect on the fetal growth and development during pregnancy, the anthropometric parameter such as intrauterine growth (IUG) chart alone is not enough to assess the level of fetal malnutrition. BMI, which is based on weight to length ratio, is further an effective and sensitive method to assess the level of malnutrition [35]. As pregnancy is an important period for the fetal growth and development, any metabolic changes like maternal weight gain due to diabetes, dyslipidemia, or weight loss due to the chronic infections and diseases can affect the fetal health and development. Fetal macrosomia, limited or stunted growth of the fetus, pre-term delivery of the offspring are often the result of maternal pre-pregnancy BMI dysregulation [36]. Hence, maternal pre-pregnancy BMI can be an effective tool in poor countries to anticipate and predict neonatal health complications apart from nutritional care [36].

Glucose being one of the major energy substrates has shown to cross the placenta via facilitated diffusion mechanism but no evidence is present to show the feto-maternal placental exchange of insulin [37–39]. In a proposed model of diabetic pregnancy of Pederson, it was presumed that excess maternal glucose could pass through the blood-placental barrier and result in stimulation of endogenous fetal insulin production in the developing fetus rather than direct feto-maternal insulin exchange [40]. There are studies supporting this model where a positive correlation between the cord C peptide along with insulin production and weight of the infant has been shown [38, 39]. This exchange of excess glucose probably can be associated with the insulin resistance of the mother and thereby link the role of maternal BMI in controlling the level of the excess glucose production and its placental exchange leading to up-regulation of fetal insulin secretion and production of bigger babies [41].

4. Conclusion

It can be concluded that the maternal BMI plays a profound role and can be good indicators of birth weight and development of the fetus [42]. Apart from the risk factors associated with the delivery of a preterm and overweight baby, maternal BMI can be also an important indirect predictor of mothers at risk of delivering abnormal weight babies in developing, and poor countries [43, 44]. Also, nutrition plays a major role in fetal and maternal well being [42]. Increased risk of negative pregnancy outcomes like pre-term birth, low birth weight, intrauterine growth retardation (IUGR), small for gestational age (SGA) have shown to be associated with lower maternal pre-pregnancy BMI [45–48]. However, BMI alone cannot be an important anthropometric measurement factor for understanding the growth and development of the fetus. For a more detail understanding of the intrauterine fetal growth, other important factors like maternal height, weight, metabolic rate, total body water, and fetal body density should be also considered [5, 49].

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Chapter 3

Body Mass Index and Insulin Sensitivity/Resistance: Cross Talks in Gestational Diabetes, Normal Pregnancy and Beyond

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Additional information is available at the end of the chapter

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Abstract

Pregnancy is a complex of metabolic, physiological, biochemical, and immunological changes in women's body, usually reversible after delivery in normal pregnancy. Gestational diabetes mellitus (GDM) is defined as "any degree of glucose intolerance with onset or first recognition during the current pregnancy." The etiology of the GDM is multifactorial and not sufficiently elucidated. The overweight and obesity during prepregnancy and pregnancy are one of the main modifiable risk factors of GDM. Maternal obesity increases the risk of a number of pregnancy complications, adverse pregnancy outcome for mother and child, and related chronic conditions in women. The obesity prevalence is the greatest among children of obese mothers, and an independent association between maternal body mass index and offspring adiposity and insulin resistance exists. Although the underlying mechanism remains unclear, available evidence suggests that GDM pathogenesis is based on relatively diminished insulin secretion coupled with pregnancy-induced insulin resistance. Recent findings provide data that higher BMI leads to decreased insulin sensitivity and higher degree of insulin resistance and contributes to GDM development.

Keywords: gestational diabetes mellitus, pregnancy, body mass index, homeostasis model assessment, quantitative insulin sensitivity check index

1. Introduction

Normal pregnancy has typical significant changes in maternal insulin resistance and hyperinsulinemia together with progressively increasing insulin secretion during gestation. The

glucose metabolism regulation during pregnancy has a complex characteristic. The placenta plays a critical role in the delivery of nutrients and the regulation of normal fetal growth. It has a metabolic and endocrine function, and produces cytokines that influence on the fetal growth. Gestational diabetes mellitus (GDM) is a serious complication of normal pregnancy. It is defined as "any degree of glucose intolerance with onset or first recognition during the current pregnancy." The global prevalence ranges between 1 and 14%, depending on the population studied and the diagnostic tests applied. GDM represents nearly 90% of all pregnancies with diabetes [1] and is one of the most common complications with risks for the mother and fetus. GDM is not only associated with adverse pregnancy outcomes such as macrosomia, shoulder dystocia, stillbirth, hypertension, and other obstetric complications [2, 3], but is also a strong predictor of impaired glucose tolerance and transitioning to overt type 2 diabetes mellitus (T2DM) postpartum [4]. Although most of the women with previous GDM return to normal glucose tolerance after delivery, both GDM patients and their offspring are at a greater risk of developing T2DM later [5]. The exact cellular mechanisms involved in GDM development are not yet completely understood. Growing data provide evidence for common pathogenesis of different diabetes forms as a result of a progressive β-cell dysfunction, inadequacy to secrete insulin, and insulin resistance in peripheral tissues leading to hyperglycemia. Pancreatic β-cell dysfunction is one of the main pathogenetic GDM mechanisms [6, 7]. Although this defect likely precedes the pregnancy [8], first it is detected clinically as insufficient β-cell compensation of insulin resistance in late pregnancy. GDM occurs if pancreatic β-cells are unable to face the increased insulin demand during pregnancy with elevated glucagon-like peptide 1 (GLP-1) confirming the abnormal insulin secretion [9]. The β-cell defect in GDM women is still present in the postpartum period [10]. Pregnancy is a diabetogenic condition. Many causes are suggestive for insulin resistance or decreased maternal insulin sensitivity. Pregnancy is normally characterized by progressive insulin resistance with beginning near mid-pregnancy and progression during the third trimester to levels approximating the insulin resistance typical for type 2 diabetes mellitus (T2DM) [11]. Firstly, Ryan et al. [12], using the euglycemic clamp technique, demonstrate decrease in insulin sensitivity with a state of insulin resistance in pregnancy being more marked in gestational-onset diabetic women in comparison of non-diabetic control group in late pregnancy. These alterations could be due to placental factors, progesterone, and estrogen, having insulin-antagonistic effects [12]. It seems that gestational diabetes and T2DM are the faces of one and the same disease. Women who develop GDM probably have reduced insulin secretion and/or chronic insulin resistance before pregnancy [13, 14] with a substantially increased risk of developing T2DM later [15]. GDM is the most common pregnancy metabolic disorder with an increasing prevalence ranging from less than 1 to 28% [16–18] that parallels the worldwide epidemic of T2DM [19]. The frequency of occurrence depends on diagnostic methods, ethnicity, and body composition [20]. Some ethnic groups have been long associated with an increased risk of GDM, and the prevalence seems particularly higher among women from South Asia and South East Asia than from Caucasian, African-American, and Hispanic communities [21]. Several pathophysiological mechanisms for GDM development have been proposed as metabolic, inflammatory, autoimmune, and genetic ones with various biologic and molecular pathways for regulation of glucose levels involved. During pregnancy, fine balance between pro -and anti-inflammatory cytokines, necessary for the normal development, exists [22]. In particular, GDM seems to be linked to downregulation of adiponectin and anti-inflammatory cytokines, and to upregulation of adipokines as leptin and pro-inflammatory cytokines, implicated in insulin resistance [22].

2. Obesity and risk of GDM

2.1. Obesity before pregnancy

The etiology of GDM is multifactorial and not sufficiently elucidated. The overweight, obesity during prepregnancy and pregnancy, excessive gestational weight gain, excessive central body fat deposition, are among the main modifiable risk factors of GDM and contribute significantly to risk of pregnancy complications. Obesity and diabetes constitute worldwide threats to the public health [23] and health care systems and economies [24]. Obesity is a chronic inflammatory state. Pregnancy and especially GDM are associated with elevation in inflammatory markers thus the heightened inflammatory response may play a substantial role in pregnancy complications [22]. Obesity prevalence has been continuously grown, particularly in lower and middle-income countries, but in both, developed and developing countries, more women are obese at conception, and young women at fertile age are at high risk of excess weight gain driving obesity and related reproductive and metabolic complications [25]. The obesity in worldwide is epidemic. The number of individuals with obesity doubled between 1980 and 2014. Moreover, in 2014, over 1.9 billion adults (18+ years) were overweight, with over 600 million being obese [26]. Accumulating epidemiological data confirm that maternal obesity has short- and long-term implications for women and babies, with a threefold increased risk of GDM [27], large for gestational age babies [28], also increased probability of macrosomia and childhood obesity [29–31], and even of fetal death, stillbirth, and infant death [32]. GDM brings a sevenfold higher risk for future development of T2DM [15]. Excessive adiposity and weight gain are well-documented risk factors of type 2 diabetes in the general population [33–35]. Women who develop GDM are more likely to be overweight or obese at the time of the diagnosis in comparison to the general population. A larger part of them develop incident of overweight or obesity in later life. Women with a history of GDM are usually advised to control their weight after delivery [36].

2.2. Excessive gestational weight gain as risk factor for GDM

An excess body weight is a major health issue worldwide as the sixth significant risk factor contributing to disease, and the increased obesity level may result in a decline of life expectancy in the future [37]. The body mass index (BMI), or Quetelet index, is used to assess the degree of obesity/human body fat based on an individual's weight and height [38]. However, BMI values may have different connotations in individuals with diverse ethnic background, short/tall stature, or varied muscle mass, and do not reflect the regional distribution of fat in the body, i.e., subcutaneous versus visceral/central [39]. Both prepregnancy BMI and weight gain during pregnancy are positively associated with gestational insulin resistance [40, 41], with obesity being a risk factor for GDM [42] and increased risk of adverse maternal and perinatal outcomes [43]. In addition to high risk of GDM, excessive gestational weight gain (EGWG) and obesity in prepregnancy have further adverse risks of preeclampsia, eclampsia, cesarean delivery, macrosomia, etc. [44–48]. Because of increasing living standards, EGWG prevalence is higher than ever before with approximately 40% of pregnant women gaining more weight than is recommended [48]. These two factors—high prepregnancy BMI and EGWG—have been reported as well-established risk for adverse pregnancy outcomes [49–54]. Large studies, including different ethnic women in western countries, determine

increased risk for macrosomia in parallel with increasing EGWG in all prepregnancy BMI categories, and the risk varies in relation to degree of BMI [55–58]. Moreover, more underlined risk of macrosomia in overweight and obese before pregnancy women and in those who gain excessive weight during pregnancy has been proved [59]. Women with previous pregnancies complicated by GDM are at an increased risk of developing T2DM in the postpartum [15]. A meta-analysis evaluates 28 studies including women with previous GDM, with follow-up ranging between 6 weeks and 28 years after the end of pregnancy, and it reveals rates of T2DM between 2.6 and 70%, depending on ethnicity, diagnostic criteria, and the follow-up period [60]. Prepregnancy obesity and excessive weight gain from prepregnancy to postpartum increase postpartum diabetes and prediabetes risks among GDM women [61]. Women, failing to lose weight postpartum, are with a higher risk of subsequent long-term obesity [62]. The recent meta-analysis shows 18% increase in risk of diabetes per unit increase in BMI [63], and every kilogram of weight gain increases by 7% the risk of diabetes [64]. Several studies have indicated that body fat distribution, dependent on ethnicity, has a larger effect than general obesity in predicting the risk of diabetes [65, 66]. Asians are with smaller frames and lower body fat distribution than white Europeans for the same BMI [67]. In comparison to Europeans, Chinese, and South Asians have more abdominal adipose tissue, especially visceral adipose tissue [68]. In this regard, waist circumference (WC) is a simple and valid index to assess abdominal fat and has been proved to be an independent predictor of T2DM [69, 70]. In Caucasian women, WC is also an important predictor of GDM [71].

2.3. Obesity and adipose tissue

In the last decade, abundant data have indicated that adipose tissue is not just an energy storage depot but rather a metabolically active tissue [72]. Adipose tissue is considered to be an important and active organ for maintenance of systemic homeostasis through a complex network of auto-, para-, and endocrine cross talks to other tissues and organs [73] mediating the development of obesity and related diseases. During obesity, the number and size of adipocytes are increased [74]. Studies of adipocytes from women in different trimesters reveal alterations in lipolytic activity that promote maternal fat accumulation in early pregnancy and enhance fat mobilization in late pregnancy [75]. Hypertrophy of adipocytes can impair the functions of adipose tissue in association with excess amount of adiposity and leading to a dysregulated secretory profile [76]. Obesity in pregnancy has intense effects, causing systemic inflammation. Maternal obesity and GDM may be associated with a state of chronic, low-grade inflammation, referred as "meta-inflammation," opposite to an acute inflammatory response [77], or metabolically induced inflammation. Meta-inflammation is distinct from an acute pro-inflammatory response and is triggered primarily by metabolites and nutrients, leading to systemic insulin resistance [78]. The base of this chronic low-grade inflammation is a production of pro-inflammatory cytokines by adipocytes in obesity [79]. This elevation of circulating pro-inflammatory cytokines, originated from adipose tissue, may induce increased inflammatory cytokine secretion by the placenta and alter placental function [80]. During pregnancy, similar to gestational age, the size of the placenta is also in progress. The levels of pregnancy-associated hormones estrogen, progesterone, cortisol, and placental lactogen in the maternal circulation are elevated [81, 82] accompanied by an increasing insulin resistance. A healthy pregnancy outcome is highly reliant on tight physiological regulation

largely orchestrated by the placenta, an extremely complex and multifunctional materno-fetal organ [83]. The placenta like a transient endocrine organ with a secretion of various hormones and cytokines, affecting both maternal and fetal metabolism, plays a major role in the initiation and preservation of pregnancy. Maternal obesity significantly impacts the endocrine function of the placenta. Obese pregnancies have a dysregulated maternal cytokine profile with considerable rise in pro-inflammatory cytokines [84, 85]. Furthermore, such over expression of pro-inflammatory cytokines is also observable in GDM placenta. This alteration in normal secretion of adipocytokines is involved as an essential factor in GDM development [86–89].

2.4. Adipose tissue and adipokines in normal pregnancy and in pregnancy with GDM

Adipokines, secreted from adipose tissue, are involved in a wide spectrum of biological processes, including regulation of energy homeostasis, adipocyte proliferation and differentiation, inflammation, angiogenesis and regulation of coagulation, and vascular function [90–92]. Adipokines act locally in adipose tissue (auto- and paracrine manners), but they also mediate via the circulation the cross talks between adipose tissue and other key metabolic organs (endocrine manner). Some adipokines, such as leptin and adiponectin, are adipocyte specific, while others, like pro-inflammatory cytokines, to a higher degree are secreted by the nonfat cells in adipose tissue [76]. In obesity, dysregulation of pro- and anti-inflammatory cytokines released from adipose tissue is in the base of the chronic low-grade systemic inflammation as that leads to development of metabolic and cardiovascular disorders [93, 94] and promotes insulin resistance or GDM. Adipose tissue produces adipocytokines, including leptin, adiponectin, tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), as well as the recently discovered resistin, visfatin, and apelin [95, 96]. A study finds the circulatory levels of IL-6, interleukin-8 (IL-8), interleukin-1β (IL-1β), TNFα, and C-reactive protein (CRP) are higher in overweight and obese pregnant women, relatively to normal weight women during pregnancy and postpartum [97]. The expression of pro-inflammatory cytokines has also been reported to be dysregulated in the development of GDM introducing an altered cytokine profile in hyperglycemic pregnancies [98, 99]. These effects are all related to regulation of insulin resistance. Higher circulatory levels of CRP, IL-6, monocyte chemoattractant protein-1 (MCP-1), and interleukin-1 (IL-1) receptor antagonist (IL-1Ra) are significantly associated with maternal adiposity [100]. Increased circulation levels of pro-inflammatory cytokines, IL-6, TNFα, leptin, and decreased levels of adiponectin and anti-inflammatory markers such as interleukin-4 (IL-4) and interleukin-10 (IL-10) are seen in GDM pregnancies in comparison to normal pregnancies, regardless of BMI [99]. The elevated circulating levels of IL-6 and TNFα in maternal blood are consistently observed in maternal obesity as well as in GDM, in the presence or absence of obesity [101–103]. TNFα and leptin have been suggested as the strongest predictors of pregnancy-associated insulin resistance [104, 105]. Together with increased levels of serum cortisol, interleukins, and other factors, they can interrupt the insulin signaling pathway and lead to insulin resistance during normal pregnancy [104]. Additionally, TNFα has been established as the most significant predictor of pregnancy-induced insulin resistance, with higher synthesis and releasing by the placenta in comparison to IL-6 or IL-8 [106]. Hence, TNF-α is more likely to exert crucial effects on IR during pregnancy. Although the leptin is produced mainly by adipocytes, there is strong evidence that the placenta, rather than maternal

adipose tissue, contributes to the rise in maternal leptin concentrations during pregnancy [107]. Pregnancy is considered as a leptin-resistant state, but the results on circulating leptin levels in GDM are controversial. However, most studies have shown increased leptin in GDM [108–110]. Adiponectin, anti-inflammatory factor, is considered to have beneficial effects on insulin sensitivity and anti-inflammatory activities [99]. TNF-α, leptin, and adiponectin are produced by placenta [111, 112] and releasing into the maternal circulation contributes to the rise in maternal TNF-α and leptin concentrations during pregnancy [104], more pronounced in GDM than in normal pregnancy [99]. Increased circulating concentrations of TNF-α enhance leptin production, opposite, leptin increases the production of TNF-α and IL-6 by monocytes [113] and stimulates the production of CC chemokine ligands (CCL) [114]. Except this, TNF-α and other pro-inflammatory mediators suppress the production of adiponectin by adipocytes [115]. Something more, some studies find a significant positive correlation between BMI values and levels of TNF-α and leptin, and an inverse correlation between BMI and adiponectin levels in GDM [108, 116–118]. The increased secretion of pro-inflammatory cytokines, the relative hypoxia, and cell death due to hypertrophic adipocytes promote a high infiltration rate of monocytes into visceral adipose tissue and activation of macrophages [119]. In general, the increase in release of pro-inflammatory cytokines, infiltration of macrophages, as well as relationship between hypertrophic growth of adipose tissue and inflammation lead to the development of insulin resistance [120] and β-cell failure [121, 122].

2.5. Interaction between iron and adipocytes

Several recent studies have attempted to illuminate the effect of iron overload on adipocyte function. Although inflammatory cytokines can influence iron storage in various cell types, studies have shown that the link between elevated iron and obesity/diabetes is independent of inflammation [123, 124]. No central mechanism for the impact of iron on adipocytes is known; however, iron is known to influence adipocytes' mitochondrial function and adiponectin production [125]. Alterations in adipocyte mitochondrial iron content affect adipocyte differentiation and insulin sensitivity [126, 127]. Some studies have suggested that adipose tissue may be a primary target organ for the metabolic effects of iron. The results propose that stores of body iron and/or iron metabolism may be involved in the development of insulin resistance not only in liver or muscle but also in adipocytes [128]. Adipocytes require iron for normal function and differentiation. They also express specialized proteins involved in iron metabolism and this fact is well suited to possible adipocyte action as an iron sensor. Evidence that adipocyte iron levels regulate adiponectin transcription and serum protein levels is present. These data further highlight the role of the adipocyte as a key regulator of metabolism in all tissues, based on integrated sensing of nutritional stores and iron availability [129]. The hypothesis that adiponectin links iron and insulin resistance is attractive as decreased adiponectin levels are associated with insulin resistance during GDM, a relationship between its reduced concentration and β-cell dysfunction in GDM women [130]. Moreover, studies in mice, human, and cell culture have demonstrated that iron lowers adiponectin production and increases diabetes risk [129]. Serum ferritin levels, as indicator for tissue iron stores, reflect insulin resistance during diabetic pregnancy [131], with a higher level in GDM women in comparison to normal pregnant [132], and also with a risk of subsequent development of postpartum impaired glucose tolerance and overt T2DM [131]. Furthermore, intracellular iron excess

catalyzes the formation of reactive oxygen species (ROS), promoting oxidative stress [133, 134] thus leading to increased β-cells apoptosis, hepatic dysfunction, and insulin resistance, and in consequence, promoting the T2DM progression [135]. Research data verify that serum ferritin concentrations are among the best predictors of serum leptin under physiological conditions. More importantly, the relationship is causal, reflecting regulation of leptin transcription by iron [136]. Studies on relationship between ferritin and leptin have suggested a possible link which is independent of relationship with BMI and inflammation. Iron overload may lead to a decrease in leptin serum level [137] along with the destruction of the fat cell membrane and the dysfunction in adipose tissue [138]. Opposite to this suggestion—leptin with other stimuli, such as pro-inflammatory cytokines, can be added to the list of adipose-derived factors that may contribute to hypoferremia observed in the overweight and obese population [139]. The functional significance of iron accumulation in adipocytes and the reduced leptin level is not yet clear. One possible explanation is that while iron regulates the serum leptin level, at the same time, it could have an effect on leptin signaling to a change in leptin sensitivity [140]. This interplay between iron, leptin, and adiponectin is an intriguing subject for study in various population groups, including pregnant women with gestational diabetes.

Deficiency of vitamin D is associated with impaired glucose homeostasis during pregnancy [141]. New studies underline the key role of vitamin D in glucose homeostasis and insulin resistance: 1,25(OH)2D3, the active form of vitamin D, regulates circulating glucose levels by binding to vitamin D receptor of pancreatic β-cell and modulating insulin secretion [142, 143]; it promotes insulin sensitivity by stimulating the expression of insulin receptors and enhancing insulin responsiveness for glucose transport [144]; regulates the balance between the extracellular and intracellular calcium pools in pancreatic β-cell, [145]; it is responsible for the presence of vitamin response element in the human insulin gene promoter with stimulation of the expression of insulin receptor and for the effects on systemic inflammation by modulating the effects of cytokines on β-cell function [146], since insulin resistance and β-cell apoptosis could be induced by systemic inflammation. Vitamin D has a direct effect on pancreatic β-cells and is a prerequisite for the normal insulin secretion function of the endocrine pancreas [147, 148]. Probably, the active form of vitamin D decreases expression of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α involved in insulin resistance [149]. Some studies report a negative relationship between serum 25(OH) D levels, BMI [150–152], and HOMA-IR [147, 152]. Maternal overweight and obesity are among the highest modifiable risk factors. The prevalence of obesity is increasing, especially in women at reproductive age. In America, according to the data from Pregnancy Risk Assessment Monitoring System (PRAMS), one in five women is obese when they become pregnant, which presents the increase of the obesity prevalence by 70% compared to the previous decade [153]. Obesity is a risk factor for the development of GDM [154], and increased BMI is associated with a greater frequency of complications in pregnancy, at birth and postpartum [155, 156]. The most commonly studied index, body mass index, calculated by formula BMI = weight (kg)/height (m^2) [37], is for measure of total body fat [157]. BMI is derived from easy measurements of height and weight and it is not expensive. Usually, women are classified as underweight (BMI less than 18.5), normal weight (BMI 18.5–24.9), overweight (BMI 25.0–29.9), class I obese (BMI 30.0–34.9), class II obese (BMI 35–39.9), or class III obese (BMI 40.0 or greater), according to Institute of Medicine (IOM) [158]. There are some limitations maybe even more important when attempting to compare individuals from

different ethnic groups. The proposed BMI cut-off points ranging from 18·3 to 29·7 kg/m^2 for children and adolescents aged 5–19 years, which correspond to the adult obesity threshold of 30 kg/m^2.These cut-offs are on the base of data from the USA population [159]. The use of these global cut-off points to define overweight and obesity remains contentious. Given the marked variations in different world regions, countries, and populations within countries, the use of these values may underestimate the health hazards of adult obesity [160]. Current studies show that maybe visceral fat mass is a novel risk factor for predicting gestational diabetes in obese pregnant women [161]. Central obesity as assessed by early pregnancy waist-hip ratio (WHR) and visceral fat mass (VFM) measured by bioimpedance is an independent predictor of GDM in addition to classical risk factors [162]. In a prospective study of 485 women cohort in Canada, elevated first trimester visceral and total adipose tissue depth independently predict the risk of subsequent dysglycemia in pregnancy [163]. Measures of central/abdominal obesity such as WC and WHR have been compared to BMI for their association with adverse cardiovascular and metabolic consequences [164]. BMI and WHR are significant risk factors for development of gestational diabetes and IR, but this association varies among different ethnicities [165]. Results of meta-analysis of 20 studies show that the risk of developing GDM is about two, four, and eight times higher among overweight, obese, or severely obese compared with normal-weight women at the beginning of their pregnancies [166].

For every 1 kg/m^2 increase in BMI, the prevalence of GDM increases by 0.92% [42]. The increasing BMI index with 1 kg/m^2 increased the risk of GDM developing with 9.9% [167] Increasing trend in the risk of severe adverse obstetric outcomes, rising along with increasing maternal BMI, exists [168]. Maternal overweight and obesity, diabetes, and excessive gestational weight gain are associated with fetal overgrowth and large for gestational age (LGA), which then can lead to an increased risk in the offspring for later obesity and diabetes [169, 170]. It has been found that in Finnish obstetric population, the maternal morbidity rises markedly when comparing overweight (BMI ≥26–29 kg/m^2) vs. obese (BMI ≥ 30 kg/m^2) women: the incidence of maternal diabetes, hypertension, and other chronic diseases [171].

3. Insulin resistance and insulin sensitivity in normal and GDM pregnancy

Pregnancy is a normal physiological state of insulin resistance, and it presents a physiological stress model of pancreatic β-cells [172, 173]. It is associated with a decrease in insulin sensitivity of an approximate 50–60% by the latter half of pregnancy and a 200–250% increase in insulin secretion with purpose to maintain euglycemia in the mother [10]. The increased resistance is caused by post-insulin receptor events and is brought about by the cellular effects of the increased levels of some pregnancy-associated hormones [174]. In gestational diabetes, insulin resistance is not adequately compensated by insulin hypersecretion because of defective β-cell function. Insulin resistance during pregnancy reveals limitations in insulin secretion; on the other hand, increasing insulin resistance and subsequent insulin hypersecretion may worsen the level of β-cell failure [174]. As a result, pregnant women with GDM have a higher level of insulin resistance compared to healthy pregnant women.

Some studies demonstrate that the insulin secretion and sensitivity capacities of Asian women are different from those of women in Western countries. Since even in Asians, the pancreatic β-cell mass is relatively smaller than in Westerners, and insulin secretion capacity is also lower on the background of abdominal obesity is more common in Asians than in Westerners with similar body weights [175]. A study assesses the change in insulin resistance and β-cell function in a multiethnic population-based cohort of pregnant women. Pregnant women from East Asia and South Asia are more insulin resistant and show poorer β-cell function (HOMA-β) than Western Europeans [176]. The mechanisms leading to increased insulin secretion in pregnancy, primary or compensatory to resistance, are not entirely elucidated yet. They are partly related to metabolic effects of several hormones and cytokines which are elevated in maternal circulation during pregnancy [177]. Decreased insulin sensitivity or increased insulin resistance is defined as the decreased biological response of a nutrient to a given concentration of insulin at the target tissue, e.g., liver, muscle, or adipose tissue. Obesity is the most common risk factor related to decreased insulin sensitivity. During the pregnancy, it is related with maternal energy metabolism, and visceral fat accumulation has important biological meaning. In this relation, the influence of visceral fat, respectfully BMI, and insulin sensitivity are too important [178].

In healthy pregnant women, pancreatic β-cells increase their insulin production through hyperplasia, hypertrophy, and hyperfunction to compensate for the pregnancy-induced insulin resistance [176]. Maternal islets adapt to this increased demand mainly through enhanced insulin secretion per β-cell and increased β-cell proliferation [179]. Like other forms of hyperglycemia, GDM is characterized by pancreatic β-cell dysfunction that is insufficient to meet the body's insulin needs. Available data suggest that β-cell defects in GDM are a result from the same spectrum of causes that underlie hyperglycemia in general, including autoimmune disease, monogenic causes, and insulin resistance [180]. In normal pregnancies, the dynamic changes in glucose homeostasis and insulin sensitivity are in connection with alterations in lipid and protein metabolism. Longitudinal studies of glucose tolerance during gestation demonstrate an increased insulin response to oral glucose in the first trimester relative to prepregnancy values [10], with a subsequent progressive increased insulin responses in consistent with progressive IR [10]. Remarkably, there is an independent effect of pregnancy on β-cell function independent of the observed changes in insulin; but the etiology of this effect is at present unknown, although may include the role of incretins [181, 182]. The impact of obesity on these changes is significant; in particular, the decline in fasting glucose at early gestation is reduced, but not reduced at all in severely obese women [183]. In late gestation, the normal reduction in peripheral insulin sensitivity of 50% is reduced in obese women [10]. In addition to significant peripheral and hepatic insulin resistance, which manifests as reduced insulin-mediated glucose disposal, there is a large reduction in insulin-stimulated carbohydrate oxidation and a reduction in insulin suppression of endogenous glucose production, all of which are reversed in the postpartum period [184]. Importantly, the overall effects of this impaired insulin resistance are not influenced only on the glucose. In the postprandial state, this obesity-related insulin resistance overacts the normal circulatory increases in metabolic fuels, i.e., glucose, lipids, and amino acids. The fasting, postprandial, and integrated 24-h plasma concentrations of all basic macronutrients are affected by enhanced insulin resistance in obese pregnant women [185].

3.1. Homeostasis model assessment of insulin resistance (HOMA-IR)

The homeostatic model assessment (HOMA) is a method used to quantify insulin resistance and β-cell function, based on a single measurement of fasting glucose and insulin or C-peptide concentrations in the blood [186]. The easiest and most popular assessment of β-cell function is the homeostatic index HOMA-B. It is widely used because of its simplicity and it reflects the release of insulin under nonstimulated conditions [187]. HOMA model is considered as a structural model of the underlying physiological basis for the feedback loop between the liver and the β-cell in fasting [188]. HOMA-IR has been observed to have a linear correlation with the glucose clamp and considered as minimal model for estimations of insulin sensitivity/resistance in various studies [188, 189]. HOMA-IR determines the relationship between the liver and pancreas. This index reflects more the liver insulin resistance in comparison to peripheral insulin resistance [190], and it is a good indicator of overall insulin sensitivity during pregnancy. Although surrogate marker HOMA-B is less evaluated as an index, it provides high reliability in the measurement of β-cell function. Both indices, HOMA-B and HOMA-IR, submit better overall picture of the essential metabolic disorder [191]. Disadvantage of HOMA model is related to the fact that it underlines the lack of linearity at deepening of insulin resistance [192]. This model is a widely used and well correlates with the insulin sensitivity, as measured by the venous clamp technique in various studies [188, 189].

3.2. Assessment of insulin sensitivity by using quantitative insulin sensitivity check index (QUICKI) and HOMA2 variant insulin sensitivity (HOMA %S)

The quantitative insulin sensitivity check index (QUICKI) is an empirically derived mathematical transformation of fasting blood glucose and plasma insulin concentrations [193, 194]. QUICKI is a simple, robust, accurate, and reproducible method that appropriately predicts changes in insulin sensitivity after therapeutic interventions as well as the onset of diabetes [195]. QUICKI has been seen to have a significantly better linear correlation with glucose clamp determinations of insulin sensitivity than minimal-model estimates [196]. Its calculation is used to evaluate the insulin sensitivity [197] including during early and late pregnancy [190]. The index assumes that the circulating glucose and insulin are determined by a feedback loop between the liver and pancreatic β-cells [198]. Insulin sensitivity has been modeled by proportionately decreasing the effect of plasma insulin concentrations at both the liver and the periphery [199]. Other parameter to assess insulin sensitivity is HOMA-S%. The computer model can be used to determine insulin sensitivity (HOMA–S%) from paired fasting plasma glucose and insulin concentrations. The data from individual subjects determine unique combinations of insulin sensitivity (HOMA %S) and beta cell function (HOMA %B) from steady-state conditions [200]. HOMA can be used to track changes in insulin sensitivity and β-cell function in individuals. Also, it can be used in individuals to indicate whether reduced insulin sensitivity or β-cell failure predominates. Determination of HOMA-%S is used to establish the prevailing normal over a normoglycemic population in each comparative group [188]. Maternal obesity is associated with higher maternal glucose and GDM risk; its association with newborn size at birth is, in part, independent of maternal glycemia [201–204]. BMI is an indicator of the tissue quantity (weight) over the skeletal frame (height), including adipose tissue and muscle. BMI is known to increase blood volume and to reduce the concentration

of serum metal ions, such as, iron and zinc [205]. Maternal overweight (BMI ≥ 25 kg/m^2) has been shown to be the strongest risk factor for GDM. Two meta-regression analyses show that the odds ratios for developing GDM are 1.97–2.14 in overweight (BMI ≥ 25 kg/m^2), 3.01–3.56 in obese (most studies BMI ≥ 30 kg/m^2), and 5.55–8.56 in severely obese (BMI ≥ 35–45 kg/m^2) women compared with normal weight women [154].

3.3. The effect of BMI on insulin sensitivity indices

In late gestation, the normal reduction in peripheral insulin sensitivity of 50% [206] is reduced in obese women as determined by the quantitative insulin sensitivity check index and that insulin sensitivity in women with GDM worsened as gestation progressed [207]. The indexes of insulin sensitivity QUICKI and HOMA significantly correlated with a direct measurement of insulin sensitivity using the euglycemic-hyperinsulinemic clamp during pregnancy [208]. The mechanism for the decrease in insulin sensitivity in pregnancy is not fully understood and is part of the natural process during pregnancy, although the insulin signaling pathway can be interrupted by several factors, such as increased levels of serum cortisol, TNF α, and some interleukin cytokines, leading to insulin resistance, during normal pregnancy [104]. In this connection, it would appear that preconceptual fat mass is one of a major determinant, because lean women exhibit an inverse correlation between changes in insulin sensitivity and fat mass, which is not seen in obese women [209]. Obese women exhibit a negative relationship between the decrease in insulin sensitivity and accretion of fat mass from prepregnancy to late gestation [210]. Visceral fat volume in human body has important biological meaning, which is well expressed during the pregnancy. In this relation, the influence of visceral fat, respectfully BMI, on the insulin sensitivity is too important. A study has announced diminished insulin sensitivity in pregnant women with GDM compared to healthy pregnant women for BMI ($P > 0.05$) with significantly higher body fat percentage, expressed by connection QUICKI index-BMI ($r = -0.384$, $P < 0.01$) [211]. These results are similar to other author's results—lower level of insulin sensitivity index QUICKI in pregnant women with GDM in comparison to NGT $P = 0.001$, a reverse correlation between QUICKI index and BMI in the both of group ($r = -0.458$ for NGT and $r = -0.603$ for GDM) [167]. Insulin sensitivity measured during the clamp was higher during pregnancy in the NGT group than in the GDM group ($P < 0.05$) [208]. Values of QUICKI index in overweight women with normal glucose tolerance (NGT) and in women with GDM have been significantly lower ($P < 0.01$) than those in normal-weight women with NGT, and QUICKI in women with GDM has been decreased significantly ($P < 0.05$) during pregnancy, according to Endo et al. [207]. Furthermore, other authors have reported significant interaction between race and BMI (under/normal weight, overweight/obese) for glucose, insulin, and HOMA-IR at or above the 75th percentile and QUICKI less than the 25th percentile in mid-trimester [212]. Other authors have detected lower levels of QUICKI index in overweight compared to normal-weight women at third trimester of pregnancy [199]. Changes in insulin sensitivity are a hallmark of pregnancy and contribute to the metabolic changes, while nutrient transfer to the fetus impacts maternal metabolite levels [213, 214]. Studies show that values for HOMA-S% between pregnant with GDM and matched control NGT subject are highly significant different ($P < 0.001$) [215, 216]. Some authors found lower level for HOMA S% in GDM pregnant with prepregnancy BMI ≥ 25 kg/m^2 in comparison to GDM with prepregnancy BMI <25 kg/m^2 ($P < 0.001$) [217].

These values are not markedly different from those obtained in the other study [167]. In this study, there are statistically significant differences in HOMA-S% between the NGT and GDM groups (P = 0.002). It is found a reverse correlation between HOMA-S% and BMI in the both NGT and GDM patient groups (r = −0.467 and r = −0.679, respectively). The authors' hypothesis is that as higher is a BMI, stronger is its influence on insulin sensitivity, expressed by HOMA-S% index [167]. The current studies confirm that GDM is associated with increased insulin resistance and β-cell dysfunction, as well as reduced insulin sensitivity and secretion.

BMI, glucose, and insulin sensitivity are interrelated and alter maternal metabolism. A novel aspect of studies is identification of metabolic signatures uniquely associated with maternal BMI and glycemia, including differences in metabolites most strongly associated with these phenotypes [218]. The association of several plasma metabolites with maternal prepregnancy BMI across gestation in a cohort of 167 non-Hispanic and Hispanic ancestry women was reported [219]. Some of these metabolites have been found to have a role in aspects of metabolism such as insulin sensitivity and pancreatic β-cell function. A limited number of GDM metabolomics studies have been performed, evidence suggests that the metabolic signatures of T2D and GDM overlap [220]. Metabolomic studies of maternal metabolism during pregnancy are focused largely on normal pregnancy and GDM [221–227]. It is important to examine the associations of maternal BMI on the maternal metabolome, to consider estimated maternal insulin sensitivity as a predictor of the maternal metabolome. Furthermore, maternal BMI and insulin sensitivity impact a broad array of metabolites and have shared independent associations with the maternal metabolome [228].

3.4. The effect of BMI on homeostasis model assessment of insulin resistance (HOMA-IR)

Insulin resistance is, by definition, a disorder in the signal transduction of several known hormones [229]. Insulin resistance in peripheral tissues in women with GDM is exacerbated, but few studies have examined the extent of insulin resistance in placenta in this disease. It is possible that this insulin resistance could contribute to alter the placental transport of nutrients [230–232]. The degree of maternal insulin resistance manifested during pregnancy is theoretically associated with the degree of glucose flux from mother to fetus. Excessive insulin resistance during pregnancy is also observed in obese subjects without abnormal glucose tolerance [10]. Different studies found HOMA-IR values in the GDM group are significantly higher than in NGT patients, which indicated a significant insulin resistance [167, 215, 233–239]. Some studies report controversial results. They found that the HOMA-IR values are similar in GDM patients and healthy NGT controls [240–243]. Women with GDM in early pregnancy had significantly higher HOMA-IR values than those with GDM in later pregnancy or those with NGT [244] and results are similar to other from prior work [245]. Probably, higher BMIs among women with early-onset GDM are detected to at least partially explain this phenomenon [246]. An important goal is to identifying women with GDM during early pregnancy to minimize maternal and neonatal morbidity. One study reported that first trimester HOMA-IR values are independent predictors for the development of GDM in logistic regression analysis, and the HOMA-IR value is found to be a better marker (AUC ¼ 0.75; 95% CI, 0.67e0.83) than the other factors [247]. Another study detects borderline significance for risk of subsequent GDM for increased HOMA-IR values at gestational weeks 16–18, independent of other variables that

are associated with GDM [248]. Some researchers determined the predictability of GDM with a 90% sensitivity and 61% specificity by ROC analysis in patients whose HOMA-IR scores are >2.08 in the first trimester [249]. A study reports that HOMA-IR at 21–28 gestational weeks is reliable risky factor to development of IR (OR = 0.677, 95% CI = 0.573–0.781, P = 0.002, sensitivity 54.7%, and specificity 24.5%). HOMA-IR is found with statistically significant impact on developing of GDM-OR = 2.039 (95% CI = 1.427–2.914, P < 0.0001). The increasing HOMA-IR index with unit increases the risk of GDM developing about two times. The predictive threshold values for developing insulin resistance in gestational pregnant at 21–28 gestational weeks are HOMA–IR > 1.8 [250]. According to the International Diabetes Federation (IDF) criteria, the HOMA-IR cut-off point to differentiate low and high value of insulin resistance is 2.38. Several previous studies performed on smaller populations have demonstrated that HOMA-IR index assessed at diagnosis of GDM is ranged from 1.6 to 25 [130, 176, 251, 252]. HOMA-IR values of ≥1.29 at diagnosis may indicate insulin resistance in the studied population of women and are associated with a higher value of the prepregnancy BMI [177]. Maternal obesity-prepregnancy at the time of GDM diagnosis is in connection to enhance insulin resistance. A positive correlation between BMI and HOMA-IR in NGT group r = 0.485 and in GDM pregnant r = 0.594 has been established without statistical difference between two pregnant groups in second to third trimester [250]. The results are similar to those of others studies [253–255]. Other study obtains no significant correlations between BMI and markers of insulin resistance, indicating that BMI is not a confounder in the elevated insulin resistance among the enrolled GDM subjects [256]. The correctness requires to be noted some authors refer to BMI, especially in pregnancy, to be a poor index of fat mass, and it could be superseded in the statistical models by other anthropometric measures, three of which were independent predictors of GDM. These simple measures (age, fasting blood glucose, and subcutaneous fat), while are recognized in a few earlier reports, they are largely ignored in assessment of GDM risk [257–259]. Other study finds trimester-specific strongly positive association between HOMA-IR and prepregnancy BMI in each trimester (P < 0.001 in trimester 1 and 2, P = 0.004 in trimester 3). Also, the results from these analyses support the notion that the maternal metabolome is predominantly influenced by obesity and less by dietary intake during pregnancy [219]. However, it appears that beginning of the pregnancy in the obese state disturbs normal anabolic activity through early-gestational insulin resistance [260]. This may suggest that the obesity induces various metabolic and hormone fluctuations, rather than insulin resistance alone. This study demonstrates for the first time an association between prepregnancy BMI and a pattern of metabolites related to obesity, which differs from nonpregnant cohorts [219].

4. Conclusions

Undoubtedly, in recent years, the frequency of GDM is increasing in tandem with the dramatic increase in the prevalence of overweight and obesity in women of childbearing age, assessing by BMI. Another risk factor for GDM is the excessive weight gain during the pregnancy, assessing by use of BMI. The optimal weight increase in pregnancy is well established on the base of studies, and is different depending on BMI prior to pregnancy. Some studies show, that excessive weight gain is a significant risk factor for GDM in all categories of BMI, but the relationship is more stringent in obese individuals. Most of studies observed that higher BMI decreases the

insulin sensitivity, increases the IR and contributes to development of GDM. New guidelines into the mechanisms underlying maternal metabolism during pregnancy are being gained through the use of new technologies. Future studies on the base of integrated data from multiple technologies will allow a systems biology approach to maternal metabolism during pregnancy.

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Conflict of interest

The authors have declared that no conflict of interest exists.

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Section 3

Adult Body Mass Index and Related Factors

Chapter 4

Relationship between Human Body Anthropometric Measurements and Basal Metabolic Rate

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Additional information is available at the end of the chapter

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Abstract

Through the use of 3D body measurement technology and cardiopulmonary function test equipment, obtaining the body size data and basal metabolic rate of 116 young healthy subjects, this study aims to find the relationship between the size of human body and basal metabolic rate. Factor analysis, univariate analysis, and linear regression analysis were performed on 13 observed items (selected from 152 human data) by SPSS data analysis software. The 13 observed items include the largest abdominal circumference, waist circumference, chest circumference (horizontal), thigh circumference, hip circumference, weight, total shoulder width, neck circumference, height, waist height, high cervical point, hip height, and chest height. The results indicate that girth and height factors are correlated with the predicted basal metabolic rate as well as the measured basal metabolic rate. The predicted basal metabolic rate is significantly correlated with weight, height, hip circumference, and neck circumference. The measured basal metabolic rate is significantly correlated with the neck circumference as well as height.

Keywords: body measurement, basal metabolic rate, factor analysis, univariate analysis, linear regression analysis

1. Introduction

As the standard of living continues to rise, people are paying more attention to the relationship between their physical beauty and health. The appearance of the human body is a way of self-expression, and people's dissatisfaction with their body size will lead to psychological and physical changes. Study on human body anthropometric measurements is a branch of ergonomics, while the size of human body has a great influence on their physical beauty. In

the medical field, human body anthropometric measurement can be an important indicator for predicating diseases. The study mainly through comparing the correlation between several important human sizes and basal metabolic rate analyzes the anthropometric size with stronger correlation. Through literature searching, it is not difficult to find that many related fields have some research methods and findings that are worth learning and referencing. For example, studies on human sizes and diseases and studies on human physical beauty provide theoretical basis for further experiments to a certain degree.

1.1. Studies on the correlation between anthropometry and physical health

Many studies reveal that the size of the human body not only can indicate the beauty of the human body but also can predict the physiological parameters of the disease [1–3].

In 1996, Seidell et al. found that deaths from cardiovascular disease increased three times in 48, 287 Dutch with body mass index (BMI) greater than 25 kg/m2, indicating that measuring body mass index can, to a certain degree, predict cardiovascular disease [2]. In 2005, Shao et al. eliminated the influence of age and gender on blood glucose metabolism and the interrelationship between several measurement indicators and lipid metabolism indicators through experiments and researches. After that, the study showed that BMI value (anthropometric parameter) has significant positive correlations with fasting blood glucose and true insulin [4]. Meanwhile, neck circumference is also correlated with obstructive sleep apnea-hypopnea syndrome (OSAHS), metabolic syndrome (MS), and hyperandrogenism in women. In the studies of Onat et al., it is found that the correlation between neck circumference and metabolic syndrome is stronger than that between waist circumference and metabolic syndrome. It is also found that the evaluation point of neck circumference to metabolic syndrome is neck circumference >39 cm for men and >35 cm for women and the prediction accuracy can reach 67%. Furthermore, after correcting the components of the metabolic syndrome, neck circumference is still of significance [5]. In 2012, Liang et al. found that waist-height ratio is the best predictor of abnormal glucose metabolism in both men and women. Three thousand and eleven resident subjects over 20 years old were recruited in four cities, by comparing the predictive value of different genders, body mass index, waist circumference, and waist-height ratio for abnormal glucose metabolism [6].

1.2. Studies on the correlation between anthropometry and physical beauty

In terms of studies on physical beauty, people usually evaluate physical beauty based on attractiveness, and human size plays a decisive role in it. In 1986, studies of researchers Hatfield and Sprecher showed that people's attractiveness is attributed to individual qualities and personality [7]. Studies of Buss (1987) and Symons (1995) put forward a basic hypothesis of evolutionary theory of human mate choice, that is, physical beauty is a reliable clue that largely reflects the reproductive potential of women. Such perspective has been extended to many cross-cultural studies. People often evaluate the level of physical beauty of women according to their attractiveness, which is generally divided into nine levels. The first level represents the lowest score, meaning the least attractive and making people feel no sense of physical beauty. The ninth level represents the highest level, meaning the most attractive and

offering the most esthetic sense of physical beauty [8]. In the current correlation studies, the anthropometric parameters that are being widely used to judge attractiveness are waist-hip ratio (WHR), body mass index (BMI), and volume height index (VHI).

In 1993, Devendra Singh, PhD, from the University of Texas, USA, determined that the physical characteristics are sure signs of the reproductive potential of women, while the waist-hip ratio of human, i.e., WHR, is an important indicator. In addition, in the studies of Evans, Barth, and Burke in 1988, WHR was also an accurate predictor of health, and it could be involved in predicting the risk of severe diseases; the lower the ratio, the healthier the individual [9]. During the period from 1830 to 1850, Adolf Quetray, a Belgian scholar, invented body mass index (BMI), to measure fat content with the ratio of height to weight squared (m^2/kg). In the subsequent studies, Tové again verified that BMI is a better indicator to evaluate the physical beauty of women by studying the side and frontal images of women. BMI has been widely used in the medical field. This index was originally used to calculate the fat content of human body, and with the in-depth study on the beauty of human body, it has become an important indicator to evaluate the physical beauty of women. In 2004, Jintu Fan, PhD, from the Hong Kong Polytechnic University proposed a new indicator to evaluate the attractiveness of the 3D image of female body. He noted that volume height index (VHI) is a better indicator than BMI and WHR [10].

1.3. Introduction to basal metabolic rate and its influential factors

Basal metabolic rate refers to the basal metabolic energy consumed by the human body surface area per unit of time, and the unit is generally $kJ \cdot m^{-2} \cdot h^{-1}$ or kJ ($/m^2 \cdot h$) [11]. Basal metabolic rate is of great significance to the studies of human movements, and it can be used to evaluate the status and psychological condition of the human body. As regards medical field, the measurement of basal metabolic rate is a diagnostic method for health; meanwhile, basal metabolic rate is also an important indicator of thyroid disease.

Factors that influence basal metabolic rate are body size, age, gender, hormone, temperature, and surface area [12]. Compared with people who are fat and short, people who are tall and thin have higher basal metabolic rate, which is related to the lean body mass. Normally, the basal metabolic rate of children is higher than that of adults, while that of adults is higher than that of older people. Experiments showed that under the circumstances of same age and same surface area, the basal metabolic rate of men is higher than that of women, that is, because the lean body mass ratio of men is higher than that of women, generally 6–10% higher. And 10–15% higher is within the normal range. The basal metabolic rate of pregnant women is evidently increased, which is related to the increase in calories burned in the body. Furthermore, hormones also have a great impact on basal metabolic rate, and the secretion of hormones can regulate cell metabolism. For instance, hyperthyroidism will increase the basal metabolic rate, and when suffering from myxedema, the basal metabolic rate will decrease significantly [12]. Differences in seasons can also lead to differences in basal metabolic rates. Usually, the basal metabolic rate in winter is higher than that in summer. The basal metabolic rate is basically proportional to the body surface area and out of proportion to weight [11]. Therefore, body surface area is a standard to measure metabolic rate.

1.4. Calculation method of basal metabolic rate

In 1894, Rubner argued that the basal metabolic rate is relatively constant when represented by per body surface area, which is significantly associated with body weight and height [13]. Harris-Benedict established the initial equation of basal metabolic rate in 1919 [14]:

Male: P = 13.7516 m/1 kg + 5.0033 h/1 cm^{-6} × 7550a/1 year + 66.473

Female: P = 9.5634 m/1 kg + 1.8496 h/1 cm^{-4} × 6756a/1 year + 655.0955

In the equation, P represents the total body heat production in the state of rest, and its unit is kcal/day; m is the weight, and its unit is kg; h is the height, and its unit is cm; a is the age, and its unit is year. However, the maximum value of energy consumption calculated by such classic equation is hugely different from that calculated by the domestic calculation method in Chia (same gender, height, weight, and age), with the former significantly higher than the latter [15]. In 1928, Paul H. Stevenson published the findings of body surface area of Chinese in the Chinese Journal of Physiology [16]. With changes in the body of the Chinese people, their weight and height have also changed obviously. Songshan Zhao further explored the body of Chinese in 1983, and progress has been made in the correlation among human body surface area, weight, and height [16]. And the formula that can reasonably reflect the body surface area of adults in China so far has been obtained:

A = 0.00659H + 0.0126 W−0.1603 [16]

A represents the body surface area (m^2), H the height (cm), and M the weight (kg).

2. Methodology

2.1. Subjects

About 116 young healthy men and women at 18–26 years old were invited to participate in the study, embodying 95 females and 21 males. Through the relevant literature, we selected 13 human data as observations. **Table 1** shows the 13 basic dimensions and body mass index (BMI) of the 116 subjects, while **Table 2** demonstrates the experimental data on metabolic rate of 116 subjects.

2.2. Testing equipments

Voxelan (Hamano Engineering Co. Ltd. Japan) 8CCD 3D scanner obtained regional images through a camera and obtained relevant body data by converting the images into spatial points with a model software. Anthroscan (Scanworx) 3D image data processing software was used to purify, smooth, and triangular mesh reconstruct the scanning images to generate closed human body automatically, to extract human body size precisely and measure the size of human body interactively, including distance, circumference and angle. Therefore, it can extract the section image of the human body and analyze it arbitrarily. MetaMax 3B sports cardiopulmonary telemetry tester, a series of German CORTEX product, can collect

Testing items	Max	Min	Mean
Body height (cm)	176.0	152.0	162.2
Weight (kg)	82.2	40.3	54.6
Bust girth (horizontal) (cm)	119.0	78.0	87.9
Waist girth (cm)	115.9	60.5	71.7
Buttock girth (cm)	118.1	81.1	92.8
Maximum belly circumference (cm)	123.3	64.9	79.2
Mid-neck girth (cm)	38.6	28.3	32.8
Thigh girth (right) (cm)	64.5	43.8	52.3
Across shoulder (cm)	49.3	37.0	41.8
Bust height (cm)	128.4	102.2	117.0
Waist height (cm)	109.8	87.5	101.0
Neck height (cm)	150.8	122.1	138.2
Buttock height (cm)	89.2	69.4	80.5
BMI (kg/m^2)	30.2	16.2	20.2

Table 1. Body size and BMI index of 116 subjects.

Parameter	Max	Min	Means
Oxygen uptake (L/min)	0.326	0.127	0.228
Carbon dioxide output (L/min)	0.269	0.107	0.191
Respiratory quotient (%)	1.070	0.62	0.838
Heart rate (bpm)	111.000	57.000	77.731
Measured basal metabolic rate (%)	2260.000	902.000	1595.999
Predicted basal metabolic rate (%)	2070.000	1359.000	1549.148
Lipid oxidation rate (%)	84.000	0.000	43.426

Table 2. Experimental data on metabolic rate of 116 subjects.

gas metabolism parameters during exercising and breathing, such as VO2, VCO2, respiratory rate, heart rate, respiratory exchange rate, ventilation volume, and environmental temperature and atmospheric pressure.

2.3. Experimental protocol

This experiment was conducted in an artificial climate chamber (temperature, 25 ± 2°C; humidity, 50 ± 2%). All subjects were required to wear sportswear, of whom the female shall

put on the special underwear with gym short while the male shall wear the sport short only. Before starting the experiment, subjects were expected to fill in the basic personal information, such as age, gender, weight, and so on. When taking 3D body scanning, the subjects erectly stood on the scanner platform and spread feet 15 cm with arms lifting outward and smooth breathing. Scanning will be completed within 5–10 s. After that the body fat composition of the subjects would be measured. Besides, while taking the metabolic test, subjects sat in a quiet room with physical relaxation. The testing time varies from person to person, and about 15 min is required for most subjects.

After scanning with Voxelan 3D laser scanner, Anthroscan (Scanworx) 3D image data processing software was used for obtaining statistical data, importing the scanned.obj cloud point map into Anthroscan, reducing the scale by 1:500 and adjusting X, Y, and Z axes. Therefore, the human body was facing the right side for intelligent repair. After obtaining the complete human body models, human body anthropometric measurements were carried out. Such data and the data of metabolic measurements were imported into the Excel spreadsheet. Spss19.0 was finally used to analyze the data correlation. The images of part of the subjects that were scanned by the 3D scanner and processed by the Anthroscan (Scanworx) 3D image software are shown in **Figures 1** and **2**.

Figure 1. Part of 3D scanning images of female subjects.

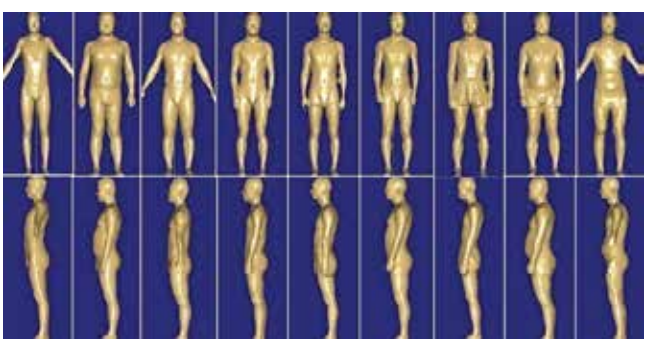

Figure 2. Part of 3D scanning images of male subjects.

3. Results and discussion

3.1. Factors

Factor analysis was carried out to analyze the maximum abdominal circumference, waist circumference, chest circumference (horizontal), right thigh circumference, hip circumference, weight, total shoulder width, mid-neck girth, height, waist height, cervical height, hip height, and chest height, so as to verify if the data were appropriate for correlation analysis.

The KMO value is greater than 0.05 and close to 1, sig. = 0.000 < 0.05, so the 13 observed items are suitable for factor analysis (**Table 3**). After preliminary analysis, it was found that the basal metabolic rate was not significantly related to gender, and therefore, 13 representative sizes of the subjects were analyzed. For **Table 4** reveals high communality of each factor, the extracted components can be well described by these variables. Meanwhile, in the light of **Table 5**, the eigenvalues of the first two factors are 6.985 and 3.833, respectively, accounting for 83.596% of the total variance. The first two factors explain the variance of 83.596% of the original 13 factors; hence, we will confirm to extract the two principal components.

In order to name these factors, we rotated the factors so that the coefficients were polarized to 0 and 1. By rotating the factor matrix, the factor can be named and interpreted (**Table 6**). Factor 1 is named the girth factor since it can represent waist girth, maximum belly circumference, bust girth (horizontal), thigh girth (right), buttock girth, weight, across shoulder, and mid-neck girth. Factor 2 is named the height factor as it can represent waist height, neck height, bust height, buttock height, and body height. The coefficient of principal component score is shown in **Table 7**.

Standardized first factor = 0.178 × maximum belly circumference + 0.171 × waist girth + 0.171 × bust girth (horizontal) + 0.166 × thigh girth (right) + 0.154 × buttock girth +0.135 × weight + 0.112 × across shoulder +0.104 × mid-neck girth − 0.017 × body height − 0.043 × waist height − 0.022 × neck height − 0.044 × buttock height − 0.037 × bust height.

Standardized second factor = −0.066 × maximum belly circumference − 0.036 × waist girth − 0.047 × bust girth (horizontal) − 0.059 × thigh girth (right) − 0.015 × buttock girth + 0.047 × weight + 0.023 × across shoulder + 0.051 × mid-neck girth + 0.189 × body height + 0.203 × waist height + 0.196 × neck height + 0.198 × buttock height + 0.200 × bust height.

3.2. Factors and predicted basal metabolic rate

According to **Figure 3**, the girth and height are highly related to the predicted basal metabolic rate with linear correlation. The correlation coefficients between predicted basal

Kaiser-Meyer-Olkin measure of sampling adequacy		0.843
Bartlett's test of sphericity	Approx. Chi-Square	2403.025
	df	78.000
	Sig.	0.000

Table 3. Kmo and Bartlett's test.

	Initial	Extraction
Maximum belly circumference	1.000	0.849
Waist girth	1.000	0.867
Bust girth (horizontal)	1.000	0.830
Thigh girth (right)	1.000	0.750
Buttock girth	1.000	0.768
Weight	1.000	0.919
Across shoulder	1.000	0.544
Mid-neck girth	1.000	0.629
Body height	1.000	0.930
Waist height	1.000	0.954
Neck height	1.000	0.974
Buttock height	1.000	0.901
Bust height	1.000	0.952

Table 4. Communalities.

Factor	Initial eigenvalues			Extraction sums of squared loadings			Rotation sums of squared loadings		
	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %	Total	% of variance	Cumulative %
1	6.985	53.729	53.729	6.985	53.729	53.729	5.741	44.165	44.165
2	3.883	29.867	83.596	3.883	29.867	83.596	5.126	39.431	83.596
3	0.853	6.560	90.156						
4	0.383	2.948	93.103						
5	0.247	1.899	95.003						
6	0.214	1.650	96.652						
7	0.135	1.040	97.693						
8	0.111	0.855	98.548						
9	0.067	0.517	99.065						
10	0.051	0.390	99.455						
11	0.041	0.315	99.770						
12	0.018	0.140	99.910						
13	0.012	0.090	100.000						

Table 5. Analysis on all variances.

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	Component	
	1	**2**
Waist girth	0.928	0.077
Maximum belly circumference	0.919	−0.070
Bust girth (horizontal)	0.911	0.017
Thigh girth (right)	0.865	−0.049
Buttock girth	0.862	0.156
Weight	0.848	0.448
Across shoulder	0.679	0.287
Mid-neck girth	0.674	0.418
Waist height	0.062	0.975
Neck height	0.171	0.972
Bust height	0.094	0.971
Buttock height	0.051	0.948
Body height	0.192	0.945

Table 6. Rotation component matrix.

	Component	
	1	**2**
Maximum belly circumference	0.178	−0.066
Waist girth	0.171	−0.036
Bust girth (horizontal)	0.171	−0.047
Thigh girth (right)	0.166	−0.059
Buttock girth	0.154	−0.015
Weight	0.135	0.047
Across shoulder	0.112	0.023
Mid-neck girth	0.104	0.051
Body height	−0.017	0.189
Waist height	−0.043	0.203
Neck height	−0.022	0.196
Buttock height	−0.044	0.198
Bust height	−0.037	0.200

Table 7. Component score coefficient matrix.

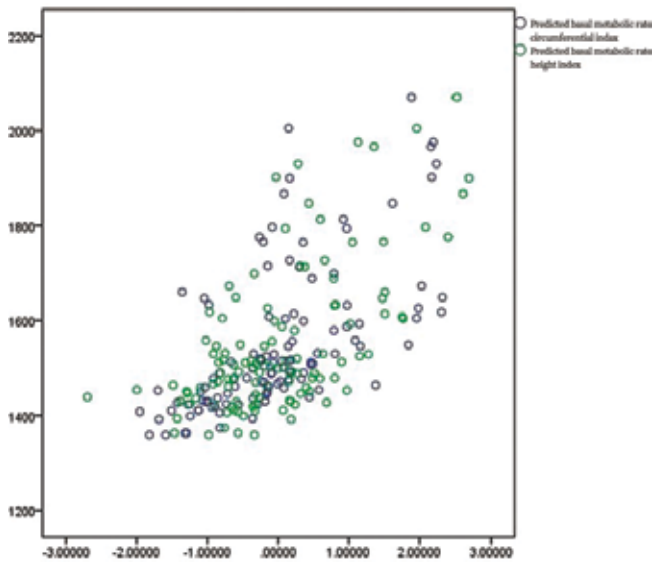

Figure 3. Simple scatterplot of factors and predicted basal metabolic rate.

metabolic rate and girth index and predicted basal metabolic rate and height index are 0.627 (sig. = 0.000 < 0.01, reject null hypothesis) and 0.634 (sig. = 0.000 < 0.01, reject null hypothesis), respectively. The results unveil that there is a significant correlation between predicted basal metabolic rate and girth index and predicted basal metabolic rate and height index, respectively (**Table 8**).

Table 9 [(a) predicator variable, height index; (b) predicator variable, height index and circumference index; (c) dependent index, predicted basal metabolic rate] lists the sources of variation, degree of freedom, mean squares, F value, and the significant test of F. The mean squares among group two models are far greater than that within the group. The statistical value of F is 216.155, sig. <0.05, so the regression equation established is valid.

According to **Table 10**, in model 2, dependent variable Y regression on the two independent variables X1 and X2 of the nonstandardized regression coefficients are 98.698 and 97.650, respectively, while T values of the corresponding saliency detection are 14.780 and 14.624, respectively, and the significant level of their regression coefficient (sig.) is 0.000, which is less than 0.05. Hence, it can be deduced that there is a definite linear relationship between the two factors and measured basal metabolic rate.

3.3. Factors and measured basal metabolic rate

The correlation between the weight index, height index, and predicted basal metabolic rate was analyzed. It can be observed from the scatterplot in **Figure 4** that there is a correlation between weight index, height index, and predicated basal metabolic rate, and the linear trend of the scatterplot is not obvious.

		Predicted basal metabolic rate	Circumferential index	Height index
Predicted basal metabolic rate	Pearson's correlation coefficient	1	0.627**	0.634**
	Sig. (two-sided)		0.000	0.000
	N	114	114	114
Circumferential index	Pearson's correlation coefficient	0.627**	1	0.000
	Sig. (two-sided)	0.000		1.000
	N	114	114	114
Height index	Pearson's correlation coefficient	0.634**	0.000	1
	Sig. (two-sided)	0.000	1.000	
	N	114	114	114

Table 8. Correlation analysis between two factors and predicted basal metabolic rate.

Model		Sum of squares	df	Mean square	F	Sig.
1	Regression	1100764.555	1	1100764.555	75.320	0.000[a]
	Residual	1636821.445	112	14614.477		
	Total	2737586.000	113			
2	Regression	2178287.472	2	1089143.736	216.155	0.000[b]
	Residual	559298.528	111	5038.725		
	Total	2737586.000	113			

[a]Predictor variables: height indicator.
[b]Predictor variables: height indicator and girth indicator.
[c]Dependent variable: predicted basal metabolic rate.

Table 9. Anova.

Coefficients[a]						
Model		Nonstandardized coefficients		Standardized coefficients	T	Sig.
		B	Std. error	Beta		
1	(Constant)	1551.000	11.322		136.985	0.000
	Height index	98.698	11.372	0.634	8.679	0.000
2	(Constant)	1551.000	6.648		233.294	0.000
	Height index	98.698	6.678	0.634	14.780	0.000
	Girth index	97.650	6.678	0.627	14.624	0.000

[a]Dependent variable: predicted basal metabolic rate.

Table 10. Regression coefficient.

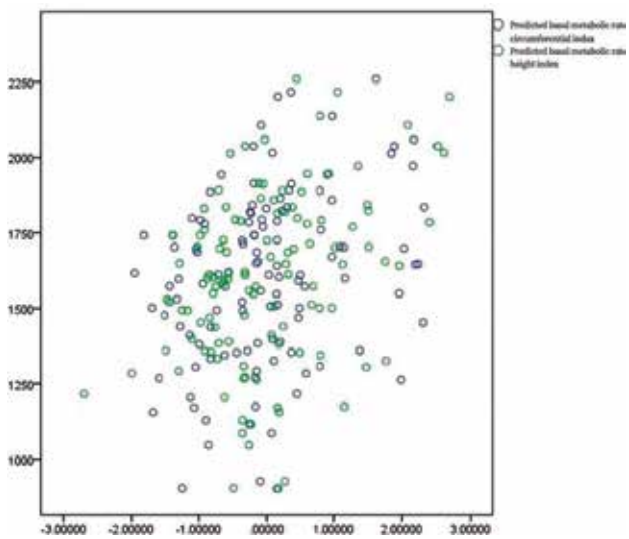

Figure 4. Simple scatterplot of factors and measured basal metabolic rate.

		Measured basal metabolic rate	Circumferential index	Height index
Measured basal metabolic rate	Pearson's correlation coefficient	1	0.303**	0.349**
	Sig. (two-sided)		0.001	0.000
	N	114	114	114
Circumferential index	Pearson's correlation coefficient	0.303**	1	0.000
	Sig. (two-sided)	0.001		1.000
	N	114	114	114
Height index	Pearson's correlation coefficient	0.349**	0.000	1
	Sig. (two-sided)	0.000	1.000	
	N	114	114	114

Table 11. Correlation analysis between two factors and measured basal metabolic rate.

The consequence indicates that the correlation coefficient between the measured basal metabolic rate and the height index, the measured basal metabolic rate, and the girth index are 0.303 (sig. = 0.001 < 0.01, reject null hypothesis) and 0.349 (sig. = 0.000 < 0.01, reject null hypothesis), respectively. Accordingly, we can conclude there is an insignificant correlation between the measured basal metabolic rate and the height index, measured basal metabolic rate, and the girth index, respectively (**Table 11**).

3.4. Univariate and predicted basal metabolic rate

Select the maximum abdominal circumference, waist circumference (horizontal), chest circumference, mid-neck girth, right thigh circumference, hip circumference, weight, total shoulder width, and height as independent variables, and select the predicted basal metabolic rate as dependent variable, and then regression analysis was performed.

According to **Table 12**, except for the right thigh variable, weight, height, hip circumference, and neck circumference variables are embedded into regression model.

Besides, there is high R square value on model 1, 2, 3, 4, 5, and 6, which unveils the dependent and independent variables are highly correlated (**Table 13**).

The F value in model 6 is 358.808, and sig in all models is 0.000, less than 0.01, which has a strong significance. Meanwhile, all the regression variances are greater than residuals, indicating the established regression equation is effective (**Table 14**).

It can be observed from **Table 15** that the multivariate regression equation should be F = 56. 615 + 15.131 × weight + 6.504 × height − 8.266 × hip circumference + 11.180 × mid-neck girth. However, because the sig. Value of the constant value is 0.772 > 0.1, the constant value is not significant. Therefore, there is no data in the column of constant value, which has been removed. So the standardized equation is Y = 0.771 × weight + 0.268 × height − 0.243 × hip circumference + 0.197 × mid-neck girth.

3.5. Univariate and measured basal metabolic rate

A linear regression analysis was performed on the nine independent variables and the dependent variable-basal metabolic rate. The nine independent variables are the maximum abdominal circumference, waist circumference (horizontal), chest circumference, mid-neck girth, right thigh circumference, hip circumference, weight, total shoulder width, and height.

Variables entered/removed[a]			
Mode	**Variables entered**	**Variables removed**	**Method**
1	Weight	—	Stepwise (criteria: probability-of-F-to-enter ≤ 0.005, probability-of-F-to-enter ≥ 0.100)
2	Thigh girth (right)	—	Stepwise (criteria: probability-of-F-to-enter ≤ 0.005, probability-of-F-to-enter ≥ 0.100)
3	Body height	—	Stepwise (criteria: probability-of-F-to-enter ≤ 0.005, probability-of-F-to-enter ≥ 0.100)
4	Buttock girth	—	Stepwise (criteria: probability-of-F-to-enter ≤ 0.005, probability-of-F-to-enter ≥ 0.100)
5	Mid-neck girth	—	Stepwise (criteria: probability-of-F-to-enter ≤ 0.005, probability-of-F-to-enter ≥ 0.100)
6	—	Thigh girth (right)	Stepwise (criteria: probability-of-F-to-enter ≤ 0.005, probability-of-F-to-enter ≥ 0.100)

Table 12. Modeling.

Model	R	R square	Adjusted R square	Std. error of the estimate
1	0.898[a]	0.806	0.804	68.926
2	0.943[b]	0.890	0.888	52.127
3	0.952[c]	0.906	0.904	48.245
4	0.959[d]	0.919	0.917	44.965
5	0.964[e]	0.930	0.927	42.170
6	0.964[f]	0.929	0.927	42.104

[a]Predictive variable: (constant), weight.
[b]Predictive variable: (constant), weight, thigh girth (right).
[c]Predictive variable: (constant), weight, thigh girth (right), body height.
[d]Predictive variable: (constant), weight, thigh girth (right), body height, buttock girth.
[e]Predictive variable: (constant), weight, thigh girth (right), body height, buttock girth, mid-neck girth.
[f]Predictive variable: (constant), weight, body height, buttock girth, mid-neck girth.
[g]Dependent variable: predicted basal metabolic rate.

Table 13. Model summary[a].

Model		Sum of squares	df	Mean square	F	Sig.
1	Regression	2205499.952	1	2205499.952	464.241	0.000[a]
	Residual	532086.048	112	4750.768		
	Total	2737586.000	113			
2	Regression	2435975.842	2	1217987.921	448.250	0.000[b]
	Residual	301610.158	111	2717.209		
	Total	2737586.000	113			
3	Regression	2481549.406	3	827183.135	355.379	0.000[c]
	Residual	256036.594	110	2327.605		
	Total	2737586.000	113			
4	Regression	2517200.603	4	629300.151	311.244	0.000[d]
	Residual	220385.397	109	2021.884		
	Total	2737586.000	113			
5	Regression	2545528.093	5	509105.619	286.286	0.000[e]
	Residual	192057.907	108	1778.314		
	Total	2737586.000	113			

Model		Sum of squares	df	Mean square	F	Sig.
6	Regression	2544352.653	4	636088.163	358.808	0.000[f]
	Residual	193233.347	109	1772.783		
	Total	2737586.000	113			

[a]Predictor variables: (constant), weight.
[b]Predictor variables: (constant), weight, thigh girth (right).
[c]Predictor variables: (constant), weight, thigh girth (right), body height.
[d]Predictor variables: (constant), weight, thigh girth (right), body height, buttock girth.
[e]Predictor variables: (constant), weight, thigh girth (right), body height, buttock girth, mid-neck girth.
[f]Predictor variables: (constant), weight, body height, buttock girth, mid-neck girth.
[g]Dependent variable: predicted basal metabolic rate.

Table 14. Anova.

Coefficients[a]						
Model		Nonstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. error	Beta		
1	(Constant)	591.996	44.975		13.163	0.000
	Weight	17.615	0.818	0.898	21.546	0.000
2	(Constant)	1164.971	70.904		16.430	0.000
	Weight	23.644	0.900	1.205	26.258	0.000
	Thigh girth (right)	−17.221	1.870	−0.423	−9.210	0.000
3	(Constant)	297.992	206.631		1.442	0.152
	Weight	19.243	1.298	0.981	14.829	0.000
	Thigh girth (right)	−11.486	2.162	−0.282	−5.313	0.000
	Body height	4.909	1.109	0.202	4.425	0.000
4	(Constant)	588.554	204.637		2.876	0.005
	Weight	20.533	1.248	1.046	16.455	0.000
	Thigh girth (right)	−5.100	2.525	−0.125	−2.020	0.046
	Body height	5.343	1.039	0.220	5.141	0.000
	Buttock girth	−8.278	1.971	−0.243	−4.199	0.000
5	(Constant)	142.712	222.059		0.643	0.522
	Weight	15.874	1.653	0.809	9.603	0.000
	Thigh girth (right)	−2.024	2.490	−0.050	−0.813	0.418
	Body height	6.055	0.991	0.249	6.111	0.000
	Buttock girth	−7.457	1.860	−0.219	−4.009	0.000
	Mid-neck girth	10.517	2.635	0.186	3.991	0.000

Coefficients[a]					
Model		Nonstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. error	Beta		
6	(Constant)	56.615	194.877		0.291	0.772
	Weight	15.131	1.375	0.771	11.001	0.000
	Body height	6.504	0.822	0.268	7.916	0.000
	Buttock girth	−8.266	1.569	−0.243	−5.269	0.000
	Mid-neck girth	11.180	2.502	0.197	4.469	0.000

[a]Dependent variable: predicted basal metabolic rate.

Table 15. Regression coefficient.

Variables entered/removed[a]			
Model	Variables entered	Variables removed	Method
1	Mid-neck girth	—	Stepwise (criteria: probability-of-F-to-enter ≤ 0.005, probability-of-F-to-enter ≥ 0.100)
2	Body height	—	Stepwise (criteria: probability-of-F-to-enter ≤ 0.005, probability-of-F-to-enter ≥ 0.100)

[a]Dependent variable: measured basal metabolic rate.

Table 16. Modeling.

Model	R	R square	Adjusted R square	Std. error of the estimate
1	0.473[a]	0.223	0.216	254.233
2	0.502[b]	0.252	0.239	250.619

[a]Measure variables: (constant), mid-neck girth.
[b]Measure variables: (constant), mid-neck girth, body height.

Table 17. Model summary.

According to **Table 16**, the mid-neck girth and body height variables can be embedded into the model. The goodness of fit of model 2 is better than model 1, but the R value of the model 2 is 0.252, which indicates that independent variable can explain the change of dependent variable 25.2% (**Table 17**). In the model regression analysis, the goodness of fit is general. In addition, for the probability of F value greater than F critical value (sig.) which is about 0.000, we can deduce that there are correlations between measured basal metabolic rate and the mid-neck girth, measured basal metabolic rate, and body height, respectively (**Table 18**).

In the light of **Table 19**, since P values of the two independent variables are 0.000 and 0.042, respectively, the mid-neck girth and body height are related to the basal metabolic rate. Meanwhile, after considering all the factors of the independent variable, we can deduce the final regression equation: Y = −1128.222 + 38.379 × mid-neck girth + 8.940 × body height.

Model		Sum of squares	df	Mean square	F	Sig.
1	Regression	2081624.638	1	2081624.638	32.206	0.000[a]
	Residual	7239032.599	112	64634.220		
	Total	9320657.237	113			
2	Regression	2348739.947	2	1174369.974	18.697	0.000[b]
	Residual	6971917.290	111	62810.066		
	Total	9320657.237	113			

[a]Measure variables: (constant), mid-neck girth.
[b]Measure variables: (constant), mid-neck girth, body height.
[c]Dependent variable: measured basal metabolic rate.

Table 18. Anova.

Coefficients[a]						
Model		Nonstandardized coefficients		Standardized coefficients	t	Sig.
		B	Std. error	Beta		
1	(Constant)	−22.175	287.115		−0.077	0.939
	Mid-neck girth	49.413	8.707	0.473	5.675	0.000
2	(Constant)	−1128.222	606.438		−1.860	0.065
	Mid-neck girth	38.379	10.114	0.367	3.795	0.000
	Body height	8.940	4.335	0.199	2.062	0.042

[a]Dependent variable: measured basal metabolic rate.

Table 19. Regression coefficient.

4. Conclusions

In this study, after undertaking the factor analysis, linear regression analysis, univariate analysis, and other analysis methods, we can draw the following conclusions:

1. There is commonality among three dimensional body measurement data, embracing maximum belly circumference, waist girth, bust girth (horizontal), thigh girth (right), buttock girth, weight, across shoulder, mid-neck girth, waist height, neck height, bust height, buttock height, and body height, which can be well divided into girth and height factor, with the waist girth, maximum belly circumference, bust girth (horizontal), thigh girth (right), buttock girth, weight, across shoulder, and mid-neck girth included in the girth factor, while waist height, neck height, bust height, buttock height, and body height contained in the height factor.
2. Girth and height factors are correlated with the predicted basal metabolic rate as well as the measured basal metabolic rate. They have a significant linear relationship with the

predicted basal metabolic rate, whereas there is no significant linear relation between the two factors and the measured basal metabolic rate.

3. There are several variables linearly related to the predicted basal metabolic rate and basal metabolic rate, embracing waist girth, maximum belly circumference, bust girth (horizontal), thigh girth (right), buttock girth, weight, across shoulder, mid-neck girth, and body height. The predicted basal metabolic rate is in a significant correlation with weight, body height, buttock girth, and mid-neck girth, while the basal metabolic rate is correlated with mid-neck girth and body height.

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Chapter 5

Body Mass Index and Colorectal Cancer

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Additional information is available at the end of the chapter

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Abstract

Colorectal cancer (CRC) is one of the most common cancers in the world. Obesity is an established risk factor for colorectal carcinogenesis. Many epidemiological and experimental studies support this link and tumor-promoting effects of obesity. Body mass index (BMI) is a marker of general obesity. Obesity is also a global health problem and is defined by World Health Organization as BMI > 30 kg/m^2. In this chapter, we give a general review about the mechanisms of obesity on colorectal carcinogenesis and the effects of obesity on clinical outcomes such as disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS), in adjuvant setting and metastatic disease, respectively.

Keywords: colorectal cancer, body mass index, obesity, carcinogenesis

1. Introduction

CRC is third most common cancer in men with age-standardized rate (ASR) 20.6 per 100,000 and second in women (ASR 14.3 per 100,000) in the world [1]. Approximately 1.4 million new cases and 693,900 deaths occurred in 2012. Wide geographical variation in its incidence is observed; the highest incidence is in Australia/New Zealand, the lowest is in Western Africa. Our country, Turkey takes place between them with ASR of 16.6 per 100,000 for both sexes. Environmental factors especially unhealthy lifestyle may increase the burden of CRC and important number of cases can be preventable by changing this lifestyle [2–5].

Obesity which is characterized by an excess of body fat is an established risk factor for colorectal carcinogenesis [6–12]. It is defined by World Health Organization (WHO) as BMI > 30 kg/m^2 [13]. BMI is the most widely used metric of adiposity in adults and classified by WHO in 1995, 2000 and 2004 (**Table 1**). Obesity is a global health problem and its prevalence has increased worldwide in all age groups [14, 15]. Overweight individuals account for

Classification	BMI (kg/m^2)
Underweight	<18.50
Normal range	18.50–24.99
Overweight	≥25.00
Pre-obese	25.00–29.99
Obese	≥30.00
Obese Class I	30.00–34.99
Obese Class II	35.00–39.99
Obese Class III (severely obese)	≥40.00

Table 1. The international classification of BMI (Source: Modified from WHO and AICR).

approximately 30% of the global population (1.9 billion), and more than 650 million people are classified as obese in 2016 [13]. In a large prospective mortality cohort study in the United States, 20% of all cancer deaths in women and 14% in men could be attributed to obesity in 2003 [16]. World Cancer Research Fund (WCRF), American Institute for Cancer Research (AICR) and US National Cancer Institute (NCI) are classified CRC, cancers of kidney, esophagus (adenocarcinoma), gastric cardia, gallbladder, liver, pancreas, thyroid for both sexes and postmenopausal breast cancer, endometrial and ovarian cancers in women as obesity-related cancers [17, 18]. Cohort studies and meta-analyses strengthened the evidence and demonstrate that obesity increases the risk of colon cancer up to 33% as compared to the risk of anybody with a normal BMI [8, 9, 15, 19–21] (**Table 2**).

Cancer site	Bergström et al. [19]	Renehan et al. [21]				AICR 2014	
	RR	Relative risk (RR)				% link to excess body fat	
		Men	P value	Women	P value	Men	Women
Ovarian	NR	—	—	1.03	NS	—	5%
Breast (post-menopausal)	1.25	—	—	1.12	<0.0001	—	17%
Endometrium	2.52	—	—	1.59	<0.0001	—	50%
Kidney	1.84	1.24	<0.0001	1.34	<0.0001	20%	28%
Gallbladder	1.78	1.09	NS	1.59	0.04	11%	28%
Esophageal adenocarcinoma	NR	1.52	<0.0001	1.51	<0.0001	32%	38%
Pancreas	NR	1.07	NS	1.12	0.01	17%	20%
CRC	Colon: 1.33	Colon: 1.24 Rectum: 1.09	<0.0001 <0.0001	Colon: 1.09 Rectum: 1.02	<0.0001 NS	17%	15%
Thyroid	NR	1.33	0.02	1.14	0.001	NR	NR

NS: not significant, NR: not reported

Table 2. Obesity-related cancers [17, 19, 21].

A recent linear dose-response meta-analysis of four prospective studies showed that each 5 kg increase in adult weight gain was associated with an approximately 6% increased risk of colon cancer (RR = 1.06, 95% CI = 1.03–1.10) [8]. Similarly, another meta-analysis of 30 prospective studies reported an increased risk of colon cancer by each 5-unit increase of BMI in both men (RR = 1.30, 95% CI = 1.25–1.35) and women (RR = 1.12, 95% CI = 1.07–1.18), and this association was stronger in men ($p < 0.001$) [9]. BMI was positively associated with rectal cancer in men, but not in women. In this study, they showed also that increasing waist circumference (per 10 cm increase) and increasing waist-hip ratio (per 0.1 unit increase) were associated with colon cancer risk in both men and women. This study underlines that the variation of the association between obesity and colon and rectal cancer risk is depending on sex and cancer site.

In this chapter, we first overview about the role of obesity in colorectal carcinogenesis and the effect of obesity on clinical outcomes such as disease-free survival (DFS), progression-free survival (PFS) and overall survival (OS), in adjuvant setting and metastatic disease, respectively.

2. The role of obesity in colorectal carcinogenesis

Obesity is a result of energy imbalance which is characterized by an overall rise in caloric intake and reduced physical activity caused by a sedentary lifestyle, besides genetic predisposition [22, 23]. Increased consumption of high carbohydrate food and beverages and dietary fat support total energy intake and priorities to reduce public obesity should focus on these environmental drivers. High BMI greater than 25 kg/m^2 reflects high body fatness [24]. The excess energy is stored as fat [23]. Obesity is associated with hyperplasia of the adipocytes which contain abnormally high free fatty acids (FFA) [25]. The exact pathophysiological mechanisms underlying the association between obesity and the risk of colorectal cancer are not fully understood but accumulated evidences coming from preclinical and clinical studies for the tumor-promoting effects of obesity has begun to illuminate many aspects of this connection [25].

2.1. Hyperinsulinemia and the insulin resistance

Adipose tissue excess or obesity, particularly abdominal obesity is linked to hyperinsulinemia, insulin resistance, hyperglycemia, and to the development of type 2 diabetes [9, 26]. High circulating insulin level is a well-established risk factor for cancer [27–29]. Epidemiological evidences indicate that high serum C-peptide which is a marker of pancreatic insulin secretion, and type 2 diabetes mellitus are associated with a greater risk of colorectal cancer [30–35].

Hyperinsulinemia is associated with elevated blood levels of free (unbound, bioavailable) insulin-like growth factor-1 (IGF-1) protein [36, 37]. Obesity-associated insulin resistance increases free IGF-1 levels in the postprandial state, unlike the reduction in insulin-sensitive lean people [38]. Inversely, IGF-binding protein-1 (IGFBP-1) concentrations decrease with increasing adiposity which may cause high concentrations of free IGF-1 [39, 40]. IGF-1 concentrations have been shown to be positively associated with colorectal cancer in prospective studies [30, 41–44].

Insulin is an anabolic hormone which coordinates glucose to either oxidation to provide energy or storage in the body after uptake in insulin-sensitive cells [45]. Insulin receptors (IRs) exist in IR-A, IR-B and IR-related receptor (IRR) isoforms and insulin has been shown also to have tumorigenic effects on preneoplastic cells which have insulin receptors [46, 47]. IRs and IGF receptors have an extracellular ligand-binding domain and an intracellular protein kinase domain. IGF-1 and insulin-like growth factor-2 (IGF-2) are mitogenic growth factors [46]. They have also metabolic functions. IGF receptors include IGF1R and IGF2R [48]. The binding of insulin and/or IGF ligands to cell surface receptors on cancer cells results in cell proliferation and survival [46, 49]. Upregulation of the IR and IGF1R has been demonstrated in human breast cancer and prostate cancer, respectively [50, 51]. IGF receptors are expressed physiologically in the mucosal and muscular layers of the colon and are overexpressed also in colon cancer cells [52, 53].

There are six high-affinity IGF-binding proteins (from IGFBP1 to IGFBP6); IGFBP1-IGFBP5 have higher affinities for IGF-1, whereas IGFBP6 has a higher affinity for IGF-2 [54]. IGFBPs affect the bioavailability of the IGFs in extracellular fluids [55]. IGFBP/IGF complexes first stabilize IGFs and protect them from degradation, and they inhibit the binding of IGFs to their receptors. Therefore, only released IGFs from IGFBPs by dissociation or protease-mediated cleavage can induce IGF signals [54, 56] (**Figure 1**).

The receptors (IRs, IGFRs) bind the ligands (Insulin, IGF-1, IGF-2) with different affinities (**Table 3**) [48, 57–59]. IR-A has a higher IGF-2 affinity than IR-B [59]. IRR is an orphan receptor; its binding ligand is unknown and participates as a heterodimerization partner of the ligand binding family members [60].

Insulin/IGFs ligand binding to their receptors activate two major signaling pathways "the phosphatidylinositol 3'-kinase (PI3 kinase)-Akt" and "RAS-RAF-MAPK" [57]. These are classical insulin signaling pathways [61]. In the first pathway, IRs and IGFRs interact with the intracellular insulin receptor substrate 1 (IRS1) after ligand binding and then promotes the PI3K/Akt cascade [62]. This pathway ultimately inhibits apoptosis [63, 64]. In the second pathway, another IRS protein Shc is phosphorylated by IR, and mediate signal transduction through the RAS-MAPK signaling pathway which plays a vital role in cell proliferation [65, 66]. There are several IRS proteins, including IRS1-6, Shc and Gab1 [61]. They are phosphorylated upon IR activation and the tyrosine-phosphorylated IRS sites function by docking with SH2 domain-containing proteins and mediate signal transduction to various downstream factors. **Figure 1** illustrates simplified signaling mechanisms of the "Insulin, IGFs/IR, IGFRs" axis. Chronic hyperinsulinemia may reduce the hepatic production of IGFBP resulting in increased level of free IGFs [8, 37]. Finally, insulin and bioavailable IGFs promote carcinogenesis by inhibiting apoptosis and stimulating cell proliferation (mitogenesis) [62–64].

Activation of the PI3 kinase pathway was also associated pro-invasive phenotype [55]. The role of cell-matrix adhesion molecules (integrins) and cell-cell adhesion molecules (E-cadherin/catenins complex) was investigated in the IGF-1 induced migration. Disruption of the E-cadherin/catenin complex by the activation of IGF1R upon IGF-1 stimulation was shown in human colonic adenocarcinoma cell-line [67].

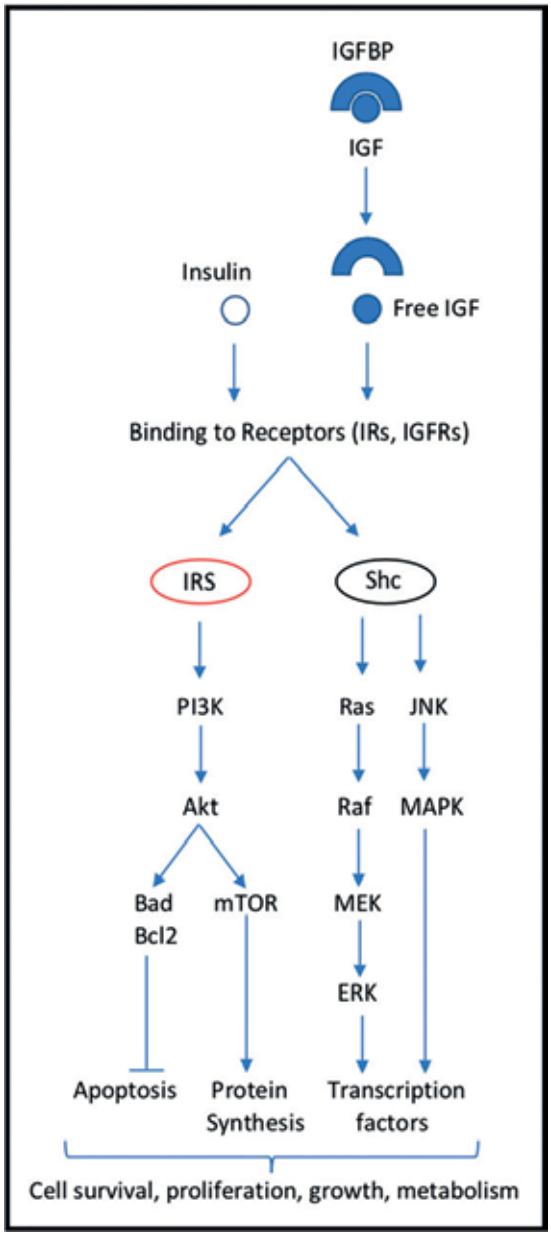

Figure 1. Schematic and simplified signaling mechanisms of the "Insulin, IGFs/IR, IGFRs" axis. Insulin and bioavailable IGFs promote carcinogenesis by inhibiting apoptosis and stimulating cell proliferation.

Cross talks of Insulin/IGF axis to other receptor tyrosine kinase pathways such as epidermal growth factor receptor (EGFR) pathway as well as IGF1R/EGFR heterodimers have also been demonstrated [55, 57]. These interactions may play a critical role in various cellular responses according to the growth factors, the ratio of the receptors and the microenvironment. Regarding mutations,

Receptors	Affinity		
	High	Low	Very low
IGF1R	IGF-1	IGF-2	Insulin
IGF2R	IGF-2 and other ligands*	IGF-1	Insulin
IR	Insulin	IGF-2	IGF-1

*Other ligands such as mannose-6-phosphate.

Table 3. Insulin, IGF ligands and their receptor affinities [48, 57–59].

when the mutation threshold in colon cancer was investigated, lower Kras mutations were detected in patients with high BMI [68]. But, in another study that evaluated associations of anthropometric factors with Kras and Braf mutation status in primary CRC, high BMI was found to be associated with the risk of Kras-mutated tumor in men, but not in women [69].

As a conclusion, obesity-related insulin/IGFs signaling pathways may result in evading apoptosis (or resisting cell death), sustaining proliferative signaling and activating invasion and metastasis, which are three of the ten hallmarks of cancer [70, 71].

2.2. Adipocyte-derived factors (leptin, adiponectin)

Adipose tissue is not inert storage depot for lipids, but it is an active endocrine organ [72]. It expresses and secretes a variety of bioactive peptides, known as adipokines. Besides adipocytes, adipose tissue contains connective tissue matrix, stromal and vascular cells, nerve tissue, and immune cells [73]. Adipocytes express and secrete specific endocrine hormones such as leptin and adiponectin; many other proteins are derived from the non-adipocyte fraction of adipose tissue [74].

Leptin is an adipocyte-specific hormone; it is a product of ob gene [75]. Leptin regulates food intake and body weight suppressing appetite and promoting metabolism. Obesity is associated with elevated serum levels of leptin and is often associated with leptin resistance [25]. Epidemiological studies show that high leptin levels are associated with an increased risk of colon cancer [76–78]. Leptin stimulates cell proliferation by probably MAPK phosphorylation and it is a promoter of cyclin D1 [25, 79, 80]. Leptin also promotes angiogenesis by the activation of PI3K and MAPK pathways [79]. Leptin receptors are expressed on normal epithelial and epithelial-derived tumor cells [81]. A study on obese mice that are genetically deficient in leptin receptors showed significant inhibition of colorectal tumor growth [82]. Leptin levels are correlated with high risk of tubular adenoma and the presence of 3 or more polyps [83, 84].

Other adipocyte-specific peptide hormone adiponectin is secreted mainly from visceral fat adipocytes and is inversely correlated with BMI [21]. It is most abundant adipokine and its circulating levels are higher in women than men. In contrast to leptin, adiponectin levels are significantly lower in obese individuals and a prospective study showed that low adiponectin concentrations was related to an increase in colorectal cancer risk [85, 86]. Physiologically, adiponectin enhances insulin sensitivity and glucose uptake [87]. Induction of insulin sensitivity reduces the circulating

levels of insulin and IGF-1. Besides this role in glucose metabolism, it stimulates also fatty acid oxidation [88]. Adiponectin has anti-angiogenic properties; it inhibits Vascular Endothelial Growth Factor-A (VEGF-A) [21, 25]. All of these observations support anti-cancer activity of adiponectin.

Adiponectin exerts its activity via two receptors: AdipoR1 and AdipoR2 [25]. Adiponectin inhibits colorectal cancer cell growth probably by downregulating mammalian target of rapamycin (mTOR) by adenosine monophosphate-activated protein kinase (AMPK) phosphorylation [89].

Inducing angiogenesis is another hallmark of cancer [70, 71].

2.3. Chronic inflammation

Chronic low-grade inflammation is a hallmark of obesity [90]. Increased production of lipids exacerbates inflammation. Increase in visceral adipose tissue (VAT) is accompanied by rising pro-inflammatory adipokines [tumor necrosis factor (TNF) alpha and interleukin (IL)-6 as well as leptin] [25, 81, 91, 92]. In contrary, as mentioned above, there is a decrease in the level of adiponectin which is an anti-inflammatory adipokine [91]. TNF-alpha expression is upregulated in parallel with the increase of BMI and this increase of expression of the TNF-alpha gene in white adipose tissue (WAT) establishes a link between inflammation, insulin resistance and hyperglycemia [93, 94]. Local and systemic chronic inflammation favors tumor initiation and progression [25]. One of the best examples of local chronic inflammatory conditions is inflammatory bowel disease which has an increased risk of colon cancer [95]. Free fatty acids (FFAs) coming from adipocytes are potent activators of macrophages that generate pro-inflammatory cytokines including IL-1beta, IL-6, TNF-alpha [96–98]. In this microenvironment of an obese host, the activation of nuclear factor (NF)-kappa B via Akt induces cell survival and promotes carcinogenesis [25, 55]. TNF-alpha may function in an autocrine and paracrine mode in the local adipose tissue, but a correlation was also shown between circulating TNF-alpha levels and colorectal adenomas [99, 100]. IL-6 stimulates PI3K/Akt pathway after binding IL-6 receptor (IL-6R), this leads to the expression of the cyclin D1 [101]. The action of IL-6 via JAK2/STAT3 signaling pathway may have a role in carcinogenesis by anti-apoptotic and proliferative mechanisms [102, 103]. Another inflammatory mediator is interferon gamma-inducible protein-10 (IP-10), also known as C-X-C motif chemokine-10 which is a chemo-attractant protein secreted by mature human adipocytes, and enhances local inflammation and tissue damage [104]. Like leptin, high levels of IP-10 are associated with the presence of polyps and tubular adenoma [83]. High serum concentrations of IP-10 are shown to be associated with poor prognosis in patients with CRC [105]. Inflammatory biomarker C Reactive Protein (CRP) and IL-6 were found to be correlated with the presence of CRC [106].

Adipose tissue contains high concentrations of CD4+ Th1, CD8+ lymphocytes with B cells and dendritic cells. In addition, high levels of anti-inflammatory Th2 and Treg cells exist [25]. In obese individuals, the net balance shifted to a pro-inflammatory state in tissue [107]. In this oncogenic micro-environment, the adipocytes can be seen to be surrounded by syncytium of phagocytic macrophages which is histopathologically described as crownlike structures (CLSs) [108, 109]. These adipocytes are undergoing necrosis, and subsequently, dead adipocytes are surrounded

by phagocytic adipose tissue macrophages (ATMs). Proinflammatory cytokine osteopontin (OPN) plays a role in the recruitment and accumulation of ATMs and the development of insulin resistance [110, 111]. Matrix metalloproteinase 9 (MMP9) is expressed and secreted into the circulation by ATMs, and it contributes to adipogenesis and angiogenesis [109]. Elevated leptin levels are also correlated with production of proangiogenic cytokines, such as VEGF, leading to angiogenesis [112, 113]. In fact, inflammation is a complex biological response to cellular stress [90]. Excess fuel or energy leads to cell stress at the level of organelles with increased reactive oxygen species (ROS) in the mitochondria due to FFA oxidation and the unfolded protein response in the endoplasmic reticulum caused by excess demands for protein synthesis for adipose tissue expansion [23, 114].

Glucose intake has also been shown to promote cancer growth via the inflammatory cascade, the 12-lipoxygenase pathway, in mice fed sucrose-enriched diet [115].

Chronic low-grade inflammation developing in adipose tissue during obesity can be transferred to other tissues such as liver, pancreas, skeletal muscle through the appearance of active inflammatory mediators in the bloodstream [116].

As a conclusion, tumor-promoting inflammation, which is one of the enabling characteristics, can contribute to multiple hallmarks of cancer including proliferative signaling, evading apoptosis, angiogenesis, invasion and metastasis [71]. It also supports mutations. This inflammatory biological state is thought to be associated with increased risk of obesity-related colon cancer [117].

2.4. Fat tissue and fatty acid metabolism

Adipose tissue depots are not metabolically equal [23]. In mammals, there are two kinds of adipose tissue: white adipose tissue (WAT) and brown adipose tissue (BAT) [116]. WAT has two compartments: visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) [108, 118]. In adult humans, BAT volume is small, and its deposits are essentially cervical supra-clavicular, supra-adrenal and para-spinal regions [119, 120]. BAT promotes energy expenditure by triggering thermogenesis and suppressing diet-induced weight gain [116, 121]. Decreasing BAT activity in mice was shown to be stimulating hyperglycemia, rising plasma triglyceride levels and insulin resistance [122]. In humans also, BAT activity was found to be inversely related to BMI [123]. TNF-alpha has been shown to induce brown adipocyte apoptosis, and VAT inflammation may be linked to the lower BAT volume [124]. Visceral fat compared to subcutaneous fat is associated with higher insulin resistance [108, 118]. The maximum adipocyte size is lower than in visceral (omental) fat as compared with subcutaneous fat [125]. Therefore, visceral adipocytes are less able to reach greater sizes before death after simple rupture under the increased pressures of their intra-abdominal environment [109]. The rate of death of overproduced fat cells is not increased which is approximately 8–9% per year, in obese individuals [109]. These findings support increased CLSs and necrotic adipocyte death in obese people [109].

BMI is a marker of general obesity, and the markers of abdominal obesity are waist circumference and waist-to-hip ratio [108]. On the other hand, visceral fat area or volume reflects visceral obesity.

Experimental studies on mice suggest that excess fat intake by diet may increase both the number of mammalian intestinal stem cells (ISCs) which are the cell-of-origin for the development of cancer and the proliferation rate of ISCs [126–128]. Ex vivo treatment of intestinal organoid cultures with fatty acid constituents of the high fat diet may enhance the self-renewal potential of these organoid bodies [127]. High fat diet may also enhance the ability of more differentiated enterocytes (transit-amplifying cells) which are derived from ISCs [127]. These effects appear to be mediated by peroxisome proliferator-activated receptor delta (PPAR-d) activation in colorectal epithelial cells [127, 128]. This activation may induce inflammation-associated colonic carcinogenesis [128].

A recent study suggested a link between obesity and sporadic microsatellite instability (MSI)-high CRC in women [129]. We know that fatty acid synthase (FASN) enzyme is involved in de novo lipogenesis catalyzing the reaction steps in the conversion of acetyl-CoA and malonyl-CoA to long-chain saturated fatty acids [130]. In one study using a large number of samples of CRC, FASN overexpression in CRC was found to be associated with MSI, independent of CpG island methylator phenotype (CIMP) [131]. FASN overexpression is commonly observed in human cancers, including CRC [132–134]. MSI-high CRC has a deficient mismatch repair system and has been associated with poorly differentiated and mucinous tumors [131, 134–136]. It is present approximately 15% of CRCs [131]. A possible association between obesity, FASN and MSI in CRC is very interesting. Another study showed that obesity and physical inactivity were associated with elevated risk of MSI-H colon cancer in men, but with non-MSI-H tumors in women [137]. An exact mechanism of these associations awaits further investigations.

Lipid metabolites function as cell signaling molecules directly related to the control of inflammation [90]. One example is sphingolipid metabolite sphingosine-1-phosphate (S1P) which is implicated in adenoma growth and is possibly involved in chronic inflammation and colon cancer via IL-6/STAT3/S1P-receptor 1 positive feedback link [138]. S1P/S1P kinase regulates cyclooxygenase-2 (COX-2), promoting arachidonate cascade which is implicated in colon carcinogenesis [139, 140]. Arachidonic acid (20:4ω6) is a precursor of prostaglandins (PGs) which are key mediators of inflammatory reactions [141]. High level of COX-2 expression is found in cancer cells. PGE2 is a major downstream effector of COX-2, and it inhibits apoptosis, favors invasion, motility and promotes angiogenesis. The efficacy of nonsteroidal anti-inflammatory drugs, especially selective COX-2 inhibitors, was shown in the reduction of colorectal polyps [142].

Feeding high-fat diet activates also the inflammasome and caspase-1 activation which controls adipocyte differentiation and insulin sensitivity [143].

Another new concept is the kynurenine pathway which is implicating in the metabolic syndrome [25]. Most foods contain amino acid tryptophan, and excessive food intake amplifies tryptophan catabolism. There is a clear correlation between plasma levels of tryptophan and its metabolites, leptin and BMI [144]. It seems that the increased tryptophan oxidation is an aspect of fat metabolism. Oxidative enzymes such as indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO) catalyze tryptophan to kynurenine. IDO is activated by interferon-gamma which is the response to immune system stimulation [145]. Kynurenine acts via the Aryl Hydrocarbon Receptor (AHR) to modulate transcription factors and microRNAs. The AHR is known to influence food intake to control body mass [25].

Growth factors	Pathways	Hallmarks of cancer
Insulin, IGFs	PI3K-Akt	Evading apoptosis (resisting cell death)
Insulin, IGFs	RAS-RAF-MAPK-Cyclin D1	Sustaining proliferative signaling
IGFs	Disruption of E-cadherin/catenin	Activating invasion and metastasis
Leptin	JAK2-STAT3-MAPK	Sustaining proliferative signaling
Leptin/VEGF	PI3K-MAPK	Inducing angiogenesis
Leptin, TNF-alpha, IL-6	Multiple pathways	Tumor promoting inflammation

Table 4. Obesity-related mechanisms of carcinogenesis.

Clustering of clinical findings made up of abdominal obesity (apple-shaped body), hyperglycemia with insulin resistance, dyslipidemia (high triglyceride, low high-density lipoprotein), and hypertension is accepted as metabolic syndrome [23]. It is clear that one of the consequences of metabolic syndrome is the increased risk of carcinogenesis.

Table 4 summarizes obesity-related mechanisms of carcinogenesis.

3. The effect of obesity on clinical outcomes

3.1. In the adjuvant setting

As we mentioned earlier, several studies have established a link between obesity and colon cancer risk, but there is little information about the effects of obesity on clinical outcomes after diagnosis and surgical treatment. In the first publication, Dignam et al. reported a significant increased risk for recurrence and death from colon cancer in very obese patients (BMI ≥35 kg/m^2) who receive adjuvant chemotherapy [146]. They investigated the association of BMI with the outcomes of 4288 patients with Dukes B and C colon cancer. This study cohort was from cooperative group clinical trials. They observed 2074 events in this study population and hazard ratio (HR) for risk of recurrence was 1.38 (95% confidence interval [CI] = 1.10–1.73), and HR for risk of mortality was 1.28 (95% CI = 1.04–1.57) in very obese patients compared with normal weight patients.

The Adjuvant Colon Cancer Endpoints database also compared the outcomes in patients (N = 25,291) with stage II and stage III colon cancer receiving adjuvant chemotherapy, and they showed inferior outcomes both for obese as well as underweight patients [147]. Men with class 2 and 3 obesity (BMI ≥ 35.0 kg/m^2) had a statistically significant reduction in DFS (HR: 1.16; 95% CI = 1.01–1.33; p = .0297) compared with normal-weight patients. These worse outcomes appeared to be cancer-related.

On the other hand, Cancer and Leukemia Group B (CALGB) 89803 trial investigators did not find any significant associations between an increased risk of recurrence and mortality and BMI in patients with stage III colon cancer [148]. In this study, they observed 369 events in 1053 patients. The difference between studies should be related to statistical power. Another

explanation is related to suboptimal adjuvant therapy (calculating dose according to a maximum body surface area of 2.0 m^2) in very obese patients in the study by Dignam et al.

3.2. In metastatic disease

In advanced colorectal cancer, there are more trials than in the adjuvant setting evaluating the role of obesity on clinical outcomes. In a pooled analysis from four large, prospective studies, among 6128 patients with metastatic CRC treated with first-line bevacizumab and chemotherapy, patients with the lowest BMI (<25 kg/m^2) experienced the lowest median OS [149]. This study is presented at the World Congress on Gastrointestinal Cancer 2015. This observation concerning the relationship between worse outcome and the lowest BMI does not mean that obesity is an advantage in patients with mCRC [150]. Probably, in patients with mCRC with a lower BMI, the effects of cancer-related cachexia may be more deleterious. These patients may have less tolerance to the treatments. According to another explanation, obesity may promote angiogenesis and bevacizumab, which is an anti-VEGF monoclonal antibody and may have a vital role in obese patients.

There are also other trials with contradictory results [151–155]. In a trial investigating the influence of BMI on outcomes in advanced CRC patients receiving chemotherapy with or without targeted therapy, BMI was shown as an independent prognostic factor for survival in patients receiving chemotherapy (CT), but not in patients receiving CT plus targeted therapy [151]. In patients receiving only CT, median OS was 19.5 months for BMI category >30 kg/m^2 versus 8 months for BMI category <18.5 kg/m^2 ($p = 0.001$). In patients receiving CT plus targeted therapy, median OS was 21.4 months for BMI category >30 kg/m^2 versus 16.6 months for BMI category <18.5 kg/m^2 ($p = 0.8$). In another trial, the authors speculate that higher circulating levels of VEGF may confer resistance to bevacizumab [152]. In our retrospective trial, we found better time to progression (TTP) in patients who have BMI < 25 kg/m^2 compared to patients who have BMI > 25 kg/m^2; median TTP was 11.7 months versus 6 months, respectively ($p = 0.004$) [153]. All patients had been treated with fluoropyrimidine-based combination CT plus bevacizumab. We think that patients with high BMI may require higher dosages. In another similar trial, the investigators compared OS across the BMI groups for CRC, and they found that the OS was shorter for patients who were underweight and overweight compared to normal in the group of patients receiving CT + targeted therapy. There was no difference in OS for CT alone [154]. In a recent multicentric study, we demonstrated that obesity serves as a prognostic factor for mCRC patients who have been treated with bevacizumab-based regimens. In particular, among Kras wild-type left-sided tumor patients with bevacizumab-based regimens, the prognosis could be worse for obese patients than that for non-obese patients [155].

4. Conclusion

High BMI or obesity is an established risk factor in colorectal carcinogenesis. Adipose tissue excess, particularly abdominal obesity is linked to hyperinsulinemia, insulin resistance,

hyperglycemia, and to the development of type 2 diabetes which are the components of metabolic syndrome. Chronic low-grade inflammation is a hallmark of obesity, and obesity supports many hallmarks of carcinogenesis. It is clear that one of the consequences of metabolic syndrome is the increased risk of carcinogenesis. Targeting obesity and metabolic syndrome should be beneficial in the prevention and the treatment of colorectal cancer.

Conflict of interest

Authors declare no conflict of interest.

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The body mass index has an important place in weight control. Attention should be paid to the regularization of anthropometric measures and to physical activity to protect from increasing obesity that is associated with chronic noncommunicable conditions, such as diabetes mellitus, cancers and cardiovascular diseases. Also, attention should be paid to the countries that are developing. The daily intake of calories, carbohydrates, oils and proteins, fibers, vitamins and minerals and clean water is essential for all individuals, especially for children and for pregnant women.

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