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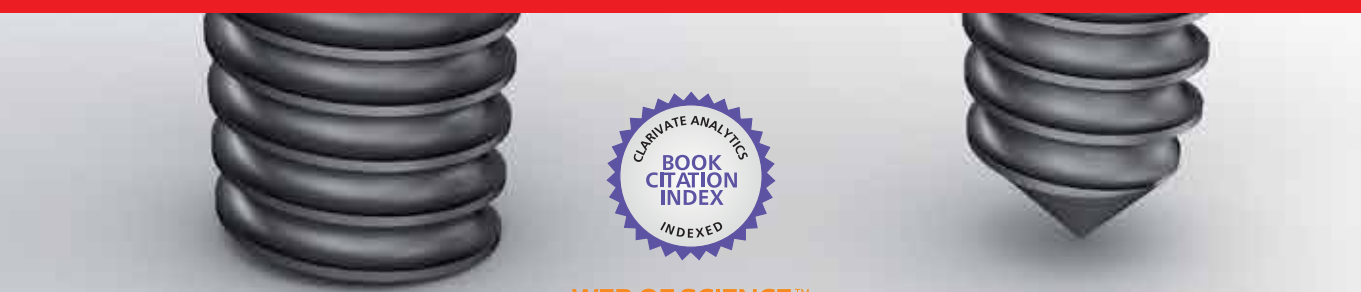
Implant Dentistry
A Rapidly Evolving Practice

Edited by Ilser Turkyilmaz



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Notice

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Meet the editor

Dr. Ilser Turkyilmaz obtained his dental degree from Hacettepe University, Ankara, Turkey in 1998. Immediately after graduation, he started his PhD program in the Department of Prosthodontics, Hacettepe University. He completed that program in 2004 and kept working as an instructor in the same department. Dr. Turkyilmaz then was invited by Goteborg University, Goteborg, Sweden for research collaborations. He worked in the Department of Biomaterials, Institute of Clinical Sciences, Sahlgrenska Academy, Goteborg University, Goteborg, Sweden in 2005. He returned to Hacettepe University in the end of 2005 and then worked in private practice in Ankara from February 2006 to May 2007. He was accepted for an implant prosthodontic fellowship program in the Department of Restorative and Prosthetic Dentistry, The Ohio State University, Columbus, Ohio, and worked in that university as an implant prosthodontic fellow from June 2007 to October 2008. He took up a full-time position as an assistant professor in the Department of Prosthodontics at the University of Texas Health Science Center in San Antonio, Texas, USA on November 1, 2008. Dr. Turkyilmaz maintains a private practice in the school's faculty practice. He treats patients with esthetic and reconstructive needs using implants, veneers, crowns, fixed partial dentures, complete dentures, and partial dentures. Dr. Turkyilmaz is particularly interested in dental implant studies regarding early/immediate loading protocols, implant stability measurements using resonance frequency analysis, bone density evaluations using computerized tomography (CT), flapless implant surgeries using CT-generated surgical guides, and the biomechanical aspects of implants. He has currently 50 scientific articles published in well-known international journals. He has also given lectures including dental implants at local, national and international meetings. He is currently serving as an editorial board member or reviewer for several international dental journals. Dr. Turkyilmaz earned Diplomate status within the International Congress of Oral Implantologists in 2011, which is the highest honor showing efforts in education, research and actual clinical experience with dental implants.

Contents

Preface

Implant dentistry has come a long way since Dr. Branemark introduced the osseointegration concept with endosseous implants. The use of dental implants has increased exponentially in the last three decades. As implant treatment became more predictable, the benefits of therapy became evident. The demand for dental implants has fueled a rapid expansion of the market. Presently, general dentists and a variety of specialists offer implants as a solution to partial and complete edentulism. Implant dentistry continues to evolve and expand with the development of new surgical and prosthodontic techniques.

The aim of *Implant Dentistry: A Rapidly Evolving Practice*, is to provide a comtemporary clinic resource for dentists who want to replace missing teeth with dental implants. It is a text that relates one chapter to every other chapter and integrates common threads among science, clinical experience and future concepts. This book consists of 23 chapters divided into five sections.

The first section of the book, *Oral Anatomy, Osseointegration Concept, and Implant Surfaces*, includes four chapters and presents basic information regarding oral anatomy, bone physiology, and bone response to various and enhanced implant surfaces.

The second section of the book, *Biomechanics in Implant Dentistry*, consists of four chapters, and helps readers better understand stress distribution in the jawbone, load transfer along the bone-implant interface, and implant stability.

The third section of this book with five chapters, *Computer-aided Implant Dentistry, and Digital Imaging*, concentrates on specific state-of-the-art computer software (NobelGuide) for treatment planning, and the value of computer software in more predictable implant placement. Chapters in this section describe the clinical application of digitally-engineered dental implants, computer-guided surgeries, and intuitive surgical navigation system in implant dentistry.

The fourth section of the book consists of six chapters, *Clinical Applications of Implants*, and considers variables affecting implant treatment outcomes, soft tissue management for more esthetic results, and implants supporting facial prostheses.

The last section of this book, *Risk Factors and Complications in Implant Dentistry*, consists of four chapters and focuses on risk factors that need to be considered before implant treatment, complications that might be encountered, and how to avoid/manage these complications.

We believe that, *Implant Dentistry: A Rapidly Evolving Practice,* will be a valuable source for dental students, post-graduate residents, general dentists and specialists who want to know more about dental implants.

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Part 1

Oral Anatomy, Osseointegration Concept, and Implant Surfaces

1

Oral Territorial Neurovascular Considerations in Implant Surgery

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1. Introduction

The anatomy of the intrabony course of the inferior alveolar nerve (IAN) is very important for dentists, neurologist, radiologists and pathologists to aid in diagnosis, treatment, planning surgery, and the application of local anesthesia (Polland et al., 2001).
IAN damage negatively affects the quality of facial sensibility and the patient's ability to translate patterns of altered nerve activity into functionally meaningful motor behaviors. The sensory alteration can be attributed to anatomical or functional changes within the nerve after resolution of inflammation and edema in and surrounding the nerve (Essick, 2004; Becerra et al., 2006).
Standardization of assessment methods would facilitate the identification of diagnostic criteria for different types of neurosensory impairment. Assessment of sensory changes can be evaluated using three types of measures: (i) objective electrophysiological measures of nerve conduction, (ii) sensory testing measures and (iii) patient report (Takazakura et al., 2007).
The request of replacing missing teeth with dental implants is increasing, and as a result, incidence of postoperative complications is increasing concomitantly (Kim et al., 2009). When the height of bone between alveolar crest and inferior alveolar canal is insufficient, implant placement in the posterior mandible is limited. One of the most difficult surgical challenges to the implant surgery is severe resorption of the posterior mandible processes (Ardekian et al., 2001). Understanding of the intrabony distribution of the IAN is important in the accurate preoperative planning for the placement of mandibular implants (Kieser et al., 2002). There are several treatment options for patients with inadequate bone height superior to the inferior alveolar canal. There are lots of alternative reconstruction methods of atrophic dental arch: use of autogenous bone grafting, allografts, xenogenic, or alloplastic materials with or without guided bone regeneration, distraction osteogenesis, IAN lateralization (McAllister & Haghighat 2007; Hashemi 2010). Placing the implants to the buccal side of the IAN or lateralization of it are the two of them (Misch & Resnik 2010). An ideal alveolar ridge with adequate bone height and width is essential for a successful dental rehabilitation (McAllister & Haghighat, 2007).
The placement of dental implants to the posterior mandible with severe resorption can cause damage to the IAN. The technique of nerve repositioning has been used to create the

opportunity of insertion dental implants of adequately length in those cases. In cases with atrophic posterior mandibular ridges, the IAN repositioning technique is an acceptable alternative to augmentation procedure prior to dental implants placement (Ardekian et al., 2001).

Patients often desire fixed dental implant restoration of missing posterior teeth in the mandible, defined for the present report as the region posterior to the mental foramen. Placement of implants in the posterior mandible is limited by the height of bone between the alveolar crest and IAN transposition or lateralization is a treatment option for patients with an edentulous posterior mandible with inadequate bone height superior to the IAN (Scarano et al., 2011).

Nevre lateralization carries a risk of epineurial damage or ischemic stretching. İmplant compression can cause neuropathy and drill punctures can result in neuroma formation of all types. In some cases it can cause centralized pain syndrome. Two patterns of neuropathy can be seen as a result; hypoaesthesias with impaired sensory function, often seen with phantom pain, and hyperaesthesias with minimal sensory impairment but presence of much-evoked pain phenomena (Gregg, 2000).

Damage to the alveolar nevre is largely due to insufficient information about the location of the mandibular canal and it is one of the most frequent complications. Such damage can also occur in the absence of knowledge about the traveling courses of the IAN, artery, and vein within the mandibular canal (Kim et al., 2009).

Neuropathic pain associated with implant placement is rare in literature. In the implantology literature, complications related to nevre are mentioned as 'sensory disturbances', focusing on the occurrence of paresthesia and dysesthesia, eventually accompanied by transitory pain sensations during bone drilling or implant placement (Hashemi, 2010).

The first published report of IAN replacement for the insertion of dental implants appeared in 1987. In that study, , sensory function of the IAN returned to normal 5 weeks after surgery according to subjective criteria (Jensen & Nock, 1987).

2. Anatomy of the mandibular nerve

The trigeminal nerve, which is the largest cranial nerve, is the sensory supply to the face, greater part of the scalp, the teeth, the nasal and oral cavity, the dura mater, the blood vessels of cerebrum. Additionally it gives the motor supply to the masticator muscles, and the mylohyoid and the anterior belly of digastric muscles. It has three divisions as ophthalmic, maxillary and mandibular nerves. It has been reviewed the functions of the widespread peripheral connections between the facial and trigeminal and facial nerves. The trigeminal nerve arises from the anterior surface of the pons, near its upper margin, as a large sensory and a small motor root, the latter lying ventromedial to former. On entering the pons, the fibers of the sensory root run posteromedially towards the principal sensory nucleus situated at this level before reaching the nucleus about %50 of fibers divide into ascending and descending branches. Fibers from the ophthalmic root lie posterolaterally, those from the mandibular lie posteromedially, and the maxillary fibers lie between them.

In Wallenberg's syndrome, plug of posterior inferior cerebellar branch of cranial the vertebral artery leads to loss of pain and temperature sensation in the ipsilateral half of the face with retention of common sensation. Symptomatic trigeminal neuralgia is caused by a

demonstrable structural lesion other than vascular compression, typically posterior fossa tumors or multiple sclerosis (Standring et al., 2005; Ordas et al., 2011).

Fibers of sensory root are principally axons of cells in the semilunal (trigeminal) ganglion, which occupies a recess in the trigeminal cave of Meckel, in the trigeminal impression near the apex of the petrous part of temporal bone. The ganglion placed on a depth of nearly 5 cm from lateral surface of the head deep to posterior end of the zygomatic arch. Axons of unipolar cells in the trigeminal ganglion divide into central and peripheral branches, the former being grouped to from ophthalmic and maxillary nerves and the sensory part of the mandibular nerve. The central branches composed the fibers of the sensory root (Standring et al., 2005). The motor nucleus of trigeminal nerve contains characteristic large multipolar cells interspersed with smaller multipolar cells. It lies in the superior part of pons medial to the principal sensory nucleus, separated from it by fibers of the trigeminal nerve. The motor nucleus receives fibers from both corticonuclear tracts. It also receives afferents from the sensory nuclei, reticular formation, red nucleus and tectum, the medial longitudinal fasciculus and locus coeruleus.

The detailed anatomy of the trigeminal nerve and its three branches and also their course excited early clinical interest since it was known that dissociated sensory loss could occur in trigeminal region. The superior and smallest trigeminal division is the ophthalmic nerve, which is the first branch of the trigeminal, is wholly sensory. It supplies the eyeball, conjunctiva and lacrimal gland, part of nasal mucosa, skin of nose, eyelids, forehead and part of scalp. It originates from the ventromedial end of trigeminal ganglion. It divides into lachrymal, frontal and nasocilliary branches. The maxillary nerve, the intermediate division of the trigeminal, is also wholly sensory. It gives off two large branches to pterygopalatine ganglion, then gives of the branches, which distribute nose, palate and pharynx. It gives off zygomatic and posterior superior alveolar branches nearly outside the orbital periostium. About halfway between the orbital apex and the orbital rim, the nerve enters the infraorbital canal as the infraorbital nerve.

The mandibular nerve, the third and the largest branch of the trigeminal nerve which supplies the teeth and gums of mandible, the lower lip, the lower part of face and the muscles of mastication, the mucosa of both presulcal parts of tongue and oral cavity, skin of the temporal region, part of the auricle including the external meatus and tympanum. It has a large sensory root, which proceeds from lateral part of trigeminal ganglion to emerge almost at ones from the foramen ovale, and a small motor root, which passes under the ganglion to unit with the sensory root just outside the skull. The nerve immediately passes between the tensor veli palatini muscle and the lateral pterygoid. Just beyond this junction a meningeal branch and the nerve to the medial pterygoid leaves the medial side of the nerve, which then divides into a small ventral and large dorsal trunk. As it descends from the foramen ovale, the nerve is about four cm from the surface and little anterior to neck of the mandible. The ventral trunk of the mandibular nerve gives rise to the buccal nerve, which is sensory, and the masseteric, deep temporal and lateral pterygoid nerves, which are all motor. The dorsal and larger mandibular trunk is mainly sensory but receives a few filaments from the motor root to mylohyoid muscle. It divides into auriculotemporal, lingual and inferior alveolar (dental) nerves (Standring et al., 2005).

The topographic anatomic landmarks, course and the surface making of the IAN from the inside of the oral cavity is particularly significant in giving nerve blocks for maxillofacial surgeons. Dentists frequently give anesthesia to the nerve before repairing or removing the premolar or molar teeth of the mandible. The IAN might be damaged during the extraction

of impacted lower third molar tooth. The roots of such teeth are commonly grooved and, very rarely, perforated by the nerve. It is also frequently damaged in fractures of the posterior tooth-bearing part of the mandible (Standring et al., 2005; Snell, 2011). So, it is important to know course of the nerve and its relation to adjacent anatomical landmarks in detailed.

The nerve descends medial to the lateral pterygoid muscle and then, at its lower margin, passes between the sphenomandibular ligament and the mandibular ramus to enter mandibular canal by the mandibular foramen.

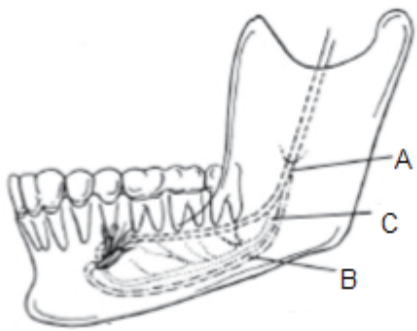

Fig. 1. Classification of the topography of the IAN. (A = the nerve has a course near the apices of the teeth, B = the main trunk is low down in the body, C = the main trunk is low down in the body of the mandible with several smaller trunks to the molar teeth.

Below the lateral pterygoid muscle it is accompanied by the inferior alveolar artery, a branch of maxillary. The artery also enters the canal. In the canal the IANlies downward and forward, usualy below the tip of the teeth until below the first and second premolars, at this point it divides into incicive and mental branches as the terminal branches. It continues forward in the canal or in a plexiform distrubition and giving off branches to the first premolar, canine and incisor teeth, and associated labial gingiva. Just before entering the mandibular canal the IAN gives off mylohyoid branch which pierces the sphenomandibular ligament and occurs a shallow groove on the medial surface of the mandible. It passes below the origin of mylohyoid muscle to lie on the surface of the muscle (Standring et al., 2005; Snell, 2011). The mandibular foramen opens into the mandibular canal, which carries the IAN. The mandibular foramen placed on midway between the ventral and dorsal magrin of ascending ramus of mandible nearly 1 cm above the occlusal surface of the lower teeth. The small triangular lingula guards the anterior border of the mandibular foramen and prvides attachments for he sphenomandibular ligament from which the mandible swings. The mylohyoid groove, immediately inferior to the lingula and lying just inferior to the mylohyoid line, carries the mylohyoid branch of the IAN. The ascending ramus diverges from the sagittal plane from front to back, once the needle engages the medial surface at this level it should be diverted laterally. At a higer level, near the base of coronoid process, the nerve is sufficiently medial to be accessible to a needle in the sagittal plane. With method the buccal and lingual nerves can be blocked (Standring et al., 2005; April, 1990; Snell, 2011). Variations in nerve architecture like these are of importance to clinicians who deal with surgery of the facial skeleton. Morphological changes of mandibular or mental foramen and variations of the nerve have also been described by many authors (Ramadhan et al., 2010;

Prado et al., 2010; Manikandhan et al., 2010; Siéssere et al., 2009; Oktem et al., 2008; Levine et al., 2007).

In many cases there is a single nerve which runs a few millimeters below the roots of teeth, nearly equal number of the nerve lies much lower in the mandible to continue near the lower border of the bone, or sometimes it is plexiform. The nerve can lie on the lingual or buccal side of the mandible (Standring et al., 2005; Snell, 2011). The MN, a branch of the IAN, when emerges through the mental foramen and then divides into three branches that supply the skin of the chin and mucous membrane of the lower lip and gum. Two of them pass upward and forward nearby the mucosal surface of the lower lip. The third one passes through the intermingled fibers of platysma and depressor anguli oris muscles to harvest the skin of the lower lip and chin. As the MN is one of the two terminal branches of the IAN, it is understandable why one's chin and lover lip on the affected side lose sensation, as well. (Standring et al., 2005; Snell, 2011).

Sensory fibers of mandibular nerve and its inferior alveolar branch transmit impulses from the teeth and gums of the lower jaw, skin of the chin and mylohyoid muscle via its mylohyoid branch (Van de Graaff, 1998).

There are numerous congenital anomalous, trauma or cancers of the oral region may affect the IAN throughout its trace. Mandibular fractures through the mandibular canal almost always produce paralysis of inferior alveolar or MNs, as well as numbness of the teeth. Injuries to the inferior alveolar or MNs can also occur during the elevation of skin or mucosal flaps in the region (Cummings et al., 1993). The tumors should be evaluated before surgical procedure or performing anesthesia with regard to size and degree of infiltration and particularly in defining the relationship to the nerve. The trigeminal nerve is the principle nerve relating to the practice of dentistry. Before teeth are filled or extracted, anesthetic is injected near the appropriate nerve to block sensation. A mandibular nerve block desensitized the lower teeth, which was performed by injecting anesthetic near the IAN as it enters the mandible through the mandibular foramen. Important complications may include damage to IAN and its branches during operation or injecting anesthetic. (Paparella et al., 1991; Van de Graaff, 1998).

An entrapment neuropathy is a nerve lesion caused by pressure or mechanical irritation from anatomic structures next to the nerve. This can occur where the nerve passes through a fibro-osseous canal or foramen like mental foramen and is relatively fixed, from impingement by an anatomic structure, or from entrapment of the nerve between the soft and hard tissues. Thus, it is important to know the anatomy of inferior alveolar nerve and its major branches with relation to their vulnerability to entrapment (Piagkou et al., 2011)

The IAN normally descends medial to the lateral pterygoid muscle passes between the sphenomandibular ligament and the mandibular ramus, and then enters the mandibular canal through the mandibular foramen. In the mandibular canal it runs downward and forward, generally below the apices of the teeth until below the first and second premolars, where it divides into the terminal incisive and mental branches (Khan et al., 2010; Krmpotic-Nemanic et al., 2001).

The mylohyoid nerve branches from the IAN, as the latter descends between the sphenomandibular ligament and the mandibular ramus. The mylohyoid nerve passes forward in a groove to reach the mylohyoid muscle and the anterior belly of the digastric muscle. (Loughner et al., 1990).

Topographically, the IAN may pass close to the medial part of the condyle. As such, a medially displaced disccould interfere mechanically with this nerve. This could explain the

sharp, shooting pain felt locally in the joint with jaw movements as well as the pain and other sensations projecting to the terminal area of distribution of the nerve branches near thetemporomandibular joint, such as the ear, temple, cheek, tongue, and teeth (Piagkou et al., 2011; Johansson et al., 1990).

The MN exits the mandible through the mental foramen, divides into three branches deep to the depressor anguli, oris muscle, and supplies the skin and mucous membrane of the lower lip, the skin of the chin, and the vestibular gingiva of the mandibular incisor (Standring et al., 2005; Moore, 1983; April, 1990; Woodburne & Burkel 1994).

The MN is significant during surgical procedures of, the chin area such as genioplasty and mandibular anterior segmented osteotomy (Westermark et al.,1998; Seo et al., 2005; Gilbert & Dickerson 1981), and it can also be damaged during dental procedures such as dental implant surgery, orthodontic treatment, and endodontic treatment.

Mental neuropathy also may be caused by systemic diseases and tumors (Bodner et al., 1989; Klokkevold et al., 1989; Chand et al., 1997). Severe pain or sensation disturbance may occur when the MN is entirely or partially injuried after such applications. A relatively common problem is the use of an inappropriate attachment depth or path during the insertion of dental implant fixtures, which may injury the IAN and MN. The incidence of permanent sensory disturbance to the lower lip after dental implant insertion in the mental foramen region is reportedly 7% to 10%. (Wismeijer et al., 1997; Mardinger et al., 2000). Complications such as loss of lip and chin sensation may result in lip biting, impaired speech, and diminished salivary retention, deficits that have a significant impact on a cases' activities of daily living (Deeb et al., 2000; Smiler, 1993) . The MN can be preserved during dental implant or flap surgeries by repositioning the IAN or ridge augmentation (Hu et al., 2007).

Anatomical anomalies of the mandibular canal may have clinical implications, such as an increased risk of injury to the IAN in case of removing a mandibular third molar and inadequate local anesthetics such as bifid and trifid mandibular canal (Mizbah et al., 2010).

The IAN can be damaged secondary to the injection of a local anesthetic into the pterygomandibular space or the MN when injecting in the region of the mental foramen. Although the exact pathophysiology of this injury remains unknown, there are three possible causes as firstly direct intraneural injection with mechanical injury to the nerve such as severance of axons, partial or total, scar tissue or neuroma formation, Wallerian degeneration, and so forth, secondly interruption of vessels of the mesoneurium with perineural and intraneural hemorrhage and secondary scar formation, and thirdly chemical toxicity of the anesthetic solution from a sterilizing solution in a leaky carpule. Regardless of its cause, it is recommended that aspiration be done before all local anesthetic injections. If there is a bloody aspirate or the patient complains of a paresthesia as typically, an electric shock-like sensation, the needle is withdrawn a few millimeters and aspiration is repeated. If there is now no bloody aspirate, it can be assumed that the needle tip is no longer in contact with a blood vessel or nerve, and the injection is completed. A note of such an occurrence should be routinely entered in the cases' chart. This method may prevent direct injection into a vascular space, but does not necessarily prevent deposition of the anesthetic within the epineurium. Because the diameter of the IAN is 4–5 times greater than the associated inferior alveolar artery or vein. Nerve injury secondary to local anesthetic injection is not common. It may be difficult to differentiate from damage related to the placement of the dental implants, particularly if the case was under sedation or general anesthesia and, therefore, unable to report a paresthesia at the time of the injections (Meyer & Bagheri, 2011).

Damage to the IAN as a consequence of bone preparation or implant placement may be caused by errors in radiographic planning, drilling, or direct contact of the implant with the nerve. Drill injuries to the IAN may be difficult to diagnose. Damage caused by drilling, the extent of injury of the IAN caused by the implant itself is related to the degree of encroachment of the implant into the IAC or its direct contact with the IAN. Nerve injury caused by implant placement may occur, despite correct osseous preparation, when the implant is inserted beyond the vertical confines of the prepared bone, compressing or breaching the superior wall of the IAC and forcing bone into the canal. Consecutive, extension of drilling into the IAC may favor over insertion of the implant cylinder beyond its intended depth and into the IAC, making direct contact with the IAN (Meyer & Bagheri 2011).

The MN ranges in the mandibular buccal soft tissue and is at risk of injury during incisions. Recognition of the changing anatomy of the edentulous mandible is especially helpful in minimizing risk of damage to the MN. As the cases ages, the alveolar bone in an edentulous area resorbs, and the position of the mental foramen becomes closer to the crest of the alveolar ridge. In some cases there is actual rupture of the IAN and the MN come to lie on the alveolar ridge crest. Placement of an incision must, therefore, take these anatomic changes into gravity. During the retraction of a mucoperiosteal flap it is potential to exert continuous improper pressure on the underlying IAN and MN. Gentle soft tissue retraction with frequent short relaxation of retraction pressure is advised nerve (Meyer & Bagheri 2011).

For reconstruction of an atrophied posterior mandible, different therapeutic options have been proposed, such as autologous bone grafting, guided bone regeneration for vertical ridge augmentation, and IAN mobilization with simultaneous implant placement. The possible dehiscence of soft tissues covering the surgical zone makes the first and second techniques unpredictable. Moreover, two surgical sites are necessary and a long treatment time as nearly 12 months is required. With IAN mobilization, only one surgical intervention is required and the total treatment time is shorter as about about 6 months. However, this method risks irreversible damage to the IAN, with consequent functional alterations. Recent studies have shown extreme variability in the examination of functionality of the neurovascular bundle after its mobilization. This variability can be attributed both to the methodology used for the tests, which evoke subjective answers from the case, and to the surgical procedure, which is highly dependent on surgeon method. Nerve injury may be the result of an overstretched mucoperiosteal flap in the premolar region to achieve optimal visibility of the operative zone (Bovi, 2005).

Less common causes of nerve damage are related to placement of autologous or allogenic or also xenogenic bone grafts during simultaneous implant placement. In cases of complex implant reconstruction, the bone graft material may be placed into the donor site with additional force, thus severely compressing or even crushing the IAN. The authors have decelerated several cases of particulate bone graft material within the IAC that caused important nerve compression, and other cases of severe scarring, similar in clinical configuration to a chemical burn, when calcium hydroxyapatite came in direct contact with the nerve (Meyer & Bagheri, 2011; Ferrera & Chandler, 1994).

During surgical resection of tumors of the oral cavity, head and neck surgeons are often faced with the challenge of achieving complete resection margins while preserving a functional and anatomical features to avoid nerve injury. Injuries to peripheral branches like IAN during the removal of third molar teeth are known and accepted risks in oral and

maxillofacial surgery practice. These risks might be reduced by modifications of evaluation or surgical methods depending on the operators' judgment in individual ceses. If a nerve damages, prompt recognition, subjective and objective valuing, and forming a treatment plan, if the sensory deficit fails to resolve in a rational period and is not acceptable to the cese, give the case the best chance of achieving recovery of sensory function in the distribution of the damaged nerve. Microneurosurgery may produce return of useful sensory function or complete sensory improvement if done in a timely fashion by an experienced operator, in greater than 80% of cases who prevent nerve damages during the removal of the third molar teeth (Meyer & Bagheri, 2011).

3. Mechanisms of nerve injury

3.1 Nerve morphology

The nerve trunk is surrounded of four connective tissue sheaths. These are the mesoneurium, epineurium, perineurium, and endoneurium from the outside inward (Polland et al., 2001). The mesoneurium is a connective tissue sheath which is analogous to the mesentery of the intestine. It encloses the nerve trunk within the soft tissue, contains the segmental blood supply of the nerve, it continues with the epineurium. The epineurium is the loose connective tissue sheath which protects the nerve trunk against mechanical stress. Fascicles are marked out by the perineurium, which surrounds the axons and endoneurial sheaths. The fascicular pattern can be monofascicular (one large fascicle), oligofascicular (2-10 rather large fascicles) or polyfascicular (more than 10 fascicles of different sizes). Individual nerve fibers and their Schwann cells are surrounded by the endoneurium. The perineurium and endoneurium provide elasticity together. Polyfascicular nerves with many small fascicles such as the IAN resist stretch more than monofascicular or oligofascicular nerves (Sunderland, 1951). The nerve fiber is the functional component of the peripheral nerve and it is responsible for transmitting stimuli. The nerve fiber consists of axon, a Schwann cell, and a myelin sheath in myelinated nerve fibers. The axon is a segment of a neuron and can be characterized by morphology, conduction velocity and function.

A-alpha fibers are the largest myelinated fibers. They are encoded for the transmission of muscle spindle and tendon organ afferents and skeletal muscle efferents. The A-beta fibers are the second largest myelinated axons. The sensation of touch is transmitted to these axons. The A-delta fibers are the smallest of the myelinated fibers, which transmit stimuli encoded for temperature and pain. The smallest axons are the unmyelinated C-fibers. They transmit stimuli encoded for slow or second pain, temperature, and efferent sympathetic fibers (LaBanc, 1992).

In 1943, Seddon described a triple classification of mechanical nerve injuries to characterize the morphophysiologic types. Seddon's classification includes neuropraxia, axonotmesis and neurotmesis and is based on the time course and completeness of sensory recovery (Seddon, 1943).

3.1.1 Neuropraxia

Neuropraxia represents the mildest form of nerve injury. It is characterized by a conduction block, almost complete return of sensation or function, and no degeneration of the axon. The continuity of the epineural sheat and the axons is lasts and morphologic alterations are minor. Trauma to the endoneurial capillaries causes intrafascicular edema, resulting in a conduction block. The sensation or function returns to normal within 1 to 2 days following

the resolution of intrafascicular edema, generally within 1 week following nerve injury. The function deficit recovers spontaneously and usually complete within 3 to 4 weeks (LaBanc, 1992).

3.1.2 Axonotmesis

Axonotmesis is a more severe nerve injury with disruption of the neuronal axon but with maintenance of the myelin sheath. This type of nerve damage may cause paralysis of the motor, sensory, and autonomic functions.

It involves loss of the relative continuity of the axon and its covering of myelin, but preservation of the connective tissue framework of the nerve (the encapsulating tissue, the epineurium and perineurium, are preserved). Because of the loss of axonal continuity, wallerian degeneration occurs. An axonotmesis is characterized by axonal injury and continues with degeneration or regeneration. Traction and compression are the usual mechanisms of this type of injury. This may cause severe ischemia, intrafascicular edema, or demyelination. Although the axons are damaged, there is no disruption of the endoneurial sheath, perineurium, or epineurium. Complete recovery takes place in 2 to 4 months, but improvement leading to complete recovery may take as long as 12 months.

It is important to know that within 2 to 4 months following injury, signs of sensation or function begin and continue to improve over the next 8 to 10 months. Anesthesia followed by a paresthesia is the psychophysical response to an axonotmesis as recovery begins (LaBanc, 1992).

3.1.3 Neurotmesis

Neurotmesis is the most severe lesion with potential of recovering. A neurotmesis is characterized by severe disruption of the connective tissue components of the nerve trunk. The etiology of nerve injury is traction, compression, injection injury, chemical injury, local anesthetic toxicity or in a complete distruption of the nerve trunk laceration and avulsion. In this type of nerve injury, sensory and functional recovery is never complete.

The psychophysical response to these injuries is an immediate anestesia. This may be followed by paresthesia or possibly neuropathic responses such as allodynia, hyperpathia, hyperalgesia, or chronic pain. This type of nerve injury has a high probability of development of a central neuroma (LaBanc, 1992).

4. Inferior alveolar nerve lateralisation

4.1 Surgical procedure

IAN lateralisation is a new technique. In the literature of implantology, the techniques described are partial and located at the anterior part of the nerve, near the foramen mentalis. Total lateralisation technique can be used in dental prosthesis in mandibular posterior edentulism when the alveolar bone is reduced and when the prosthesis compresses the nerve in the foramen region. This technique can also be used in implantology when terminal implant restitution is needed. On patients with benign tumors when the horizontal branch of the mandible is resected total lateralisation technique is a choice.

The procedure starts with the soft tissue incision slightly buccal to the crest of the residual alveolar ridge.The incision begins at the retromolar region and continues forward to the mesial portion of the cuspid tooth area, where a vertical relaxing incision is made. A full thickness mucoperiosteal flap is elevated to the inferior border of the mandible. For

performing IAN lateralization, the corticotomy starts usually 3–4 mm distal to the mental foramen. Corticotomy should be extended 4–5 mm distal to the most distal implant position. To remove the trabecular bone and gain access to the neurovascular bundle, only hand instruments such as small curettes are used. The MN is mobilized from its position. After the nerve is completely released from the canal, half a rubber piston from a dental anaesthetic cartridge or a piece of aluminum foil is inserted between the nerve bundle and the bone.

Once the drilling is completed, the implant is inserted while the nerve bundle remains retracted in situ ensuring that the apical ends of the implants are positioned inferior to the canal. Once the implants are in position, the nerve is repositioned over the lateral aspect of the implants. The surgical protocol for IAN transposition, followed by implant placement, presented excellent results, with complete recovery of the sensitivity within 6 months after the surgical procedure.

4.2 Case report

45 year-old female patient applied to Gulhane Scholl of Medicine, Department of Oral and Maxillofacial Surgery, with missing teeth in the mandibula. As she couldn't use removable partial denture, we evaluated posterior mandibular area. But mandibular posterior bone height was inadequate for implant placement. A preoperative panoramic radiograph (Fig 2) and computerized tomograhic (CT) scan revealed only 5 mm. of bone between the alveolar crest and the inferior alveolar canal.

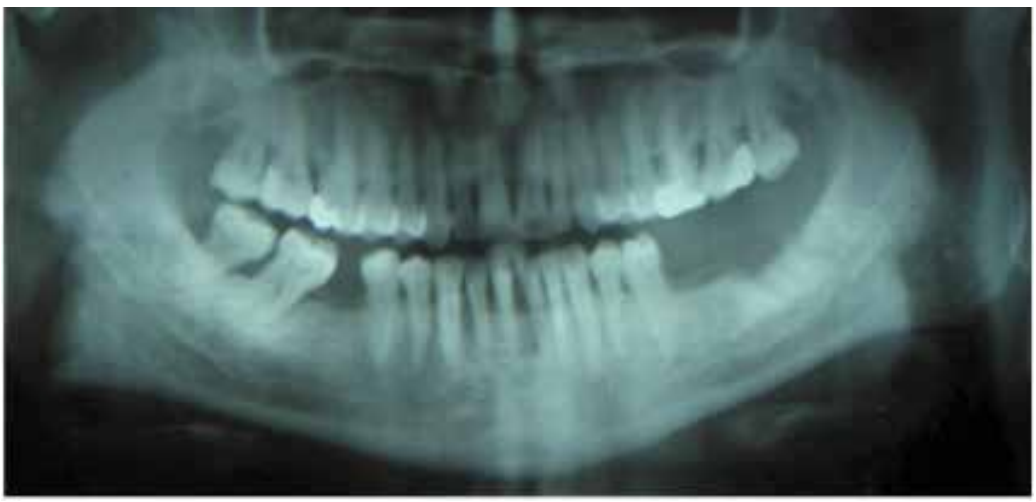

Fig. 2. Preoperatif panoramic radiograph.

We planed alternative methods including IAN lateralization technique at this place. The surgical procedure was performed under local anesthesia. A full thickness mucoperiosteal flap was elevated to the inferior border of the mandible. For performing inferior alveolar nerve lateralization, the corticotomy started 4 mm distal to the mental foramen. A small round bur in a straight hand piece with high torque and copious amount of water irrigation was used to prepare the corticotomy site. To remove the trabecular bone and gain access to the neurovascular bundle, only hand instruments (small curettes) were used. The IAN was

mobilized from its position. After the nerve was completely released from the canal and before starting to drill, half a rubber piston from a dental anaesthetic cartridge or a piece of membrane was inserted between the nerve bundle and the bone where the drill was expected to reach (Fig 3). At second premolar and second molar region, we placed 3.5x12 mm. MIS implant (Fig 4).

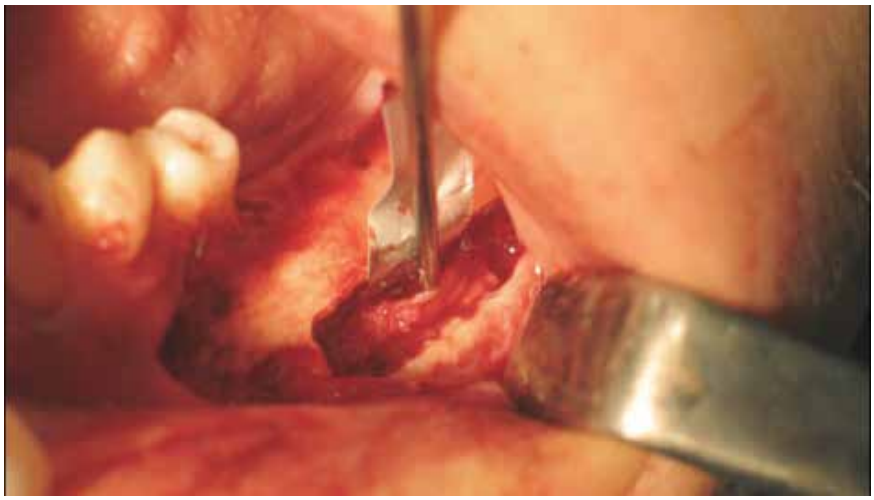

Fig. 3. Nerve retraction with a retractor.

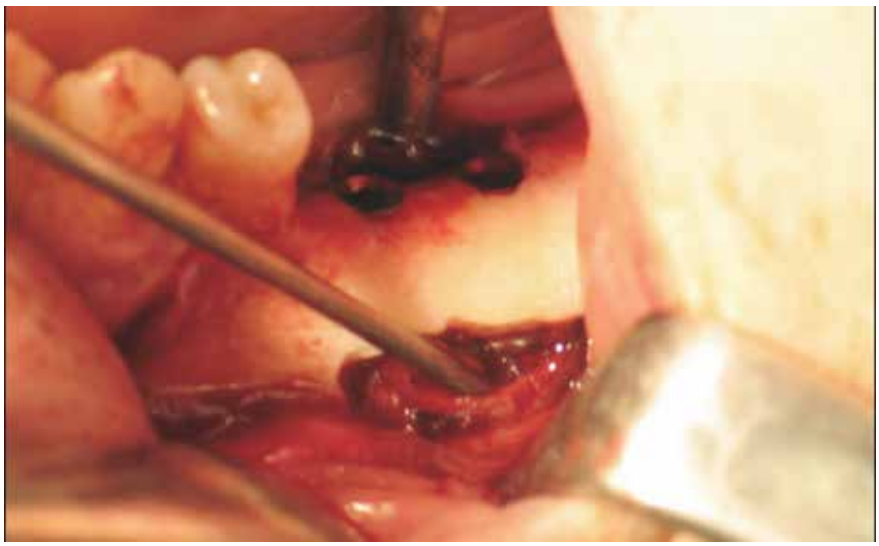

Fig. 4. Two implants was placed after nerve retractions.

The releasing incisions were carried out and mucoperiostal flap were sutured by using 3.0 silk. CT scan and panoramic radiograph (Fig 5) were taken after placing the endosseos implants. Surgical exposure and moving the nerve laterally results in a high incidence of sensory nerve disturbance and an excessive crown-to-root ratio of the prosthesis.

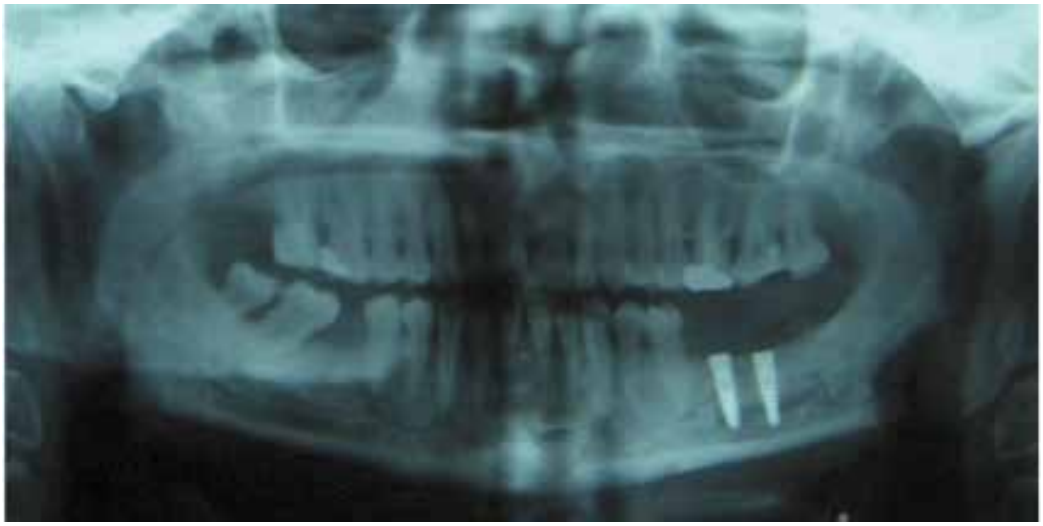

Fig. 5. The ends of the implants are positioned inferior to the canal.

We didn't examine any neurologic disturbance at postoperative controls. The present study investigated neurosensorial disturbances related to IAN lateralization for up to 6 month follow-up. Subjective criteria, sensory function of the IAN returned to normal 6 weeks after surgery. IAN lateralization is a precise technique requiring high clinical competence, which should only be carried out by specialists. IAN lateralization is a useful method for managing the atrophic posterior mandible with dental implants. The risk of permanent damage of the IAN appears to be small.

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2

Dental Implant Surfaces - Physicochemical Properties, Biological Performance, and Trends

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1. Introduction

Pure titanium and titanium alloys are well established standard materials in dental implants because of their favorable combination of mechanical strength, chemical stability, and biocompatibility (Brunette *et al.*, 2001). Integration of titanium implants with the surrounding bone is critical for successful bone regeneration and healing of dental implant.
The concept of osseointegration was discovered by Brånemark and his co-worker and, has had a dramatic influence on clinical treatment of oral implants. The first generation of successfully used clinical titanium implants, which were machined with a smooth surface texture, now approach 50 years in clinical use. Since then, implant surfaces have long been recognized to play an important role in molecular interactions, cellular response and osseointegration, and scientists all over the world have developed the second generation implants with surfaces which can accelerate and improve implant osseointegration. These second generation of clinically used implants underwent mechanical blasting coupled or not, with acid etch, bioactive coatings, anodized and, more recently, laser modified surfaces. (Cochran et al., 1998; Jansen et al., 1993; Palmquist et al., 2010; Brånemark et al., 2010). These implants have been extensively documented in vivo, including long-term clinical studies and experimental histological and biomechanical evaluation in animal models. For more knowledge in clinical results of commercially available implants the reader is referred to the following literature (Esposito et al., 2005; Esposito et al., 2003; Albrektsson & Wennerberg, 2004b).
The main objective for the development of implant surface modifications is to promote osseointegration, with faster and stronger bone formation. This will likely confer better stability during the healing process, which, preferentially, will improve the clinical performance in the area of poor bone quality and quantity. Furthermore, such promotion may, in turn, accelerate the bone healing and thereby allowing immediate or early loading protocols.
Recently growing micro and nano- technology is rapidly advancing surface engineering in implant dentistry. Such advances in surface engineering technologies have resulted in more

complicated surface properties from micro- and nanometer scales, including the morphology, chemistry, crystal structure, physical, and mechanical properties. Such surfaces, intentionally modified with respect to microscale and nanoscale features, may represent a next generation of oral implant systems if possible to transfer to complex three-dimensional geometries. Hitherto, micro- and nano-fabricated surfaces have not reached the clinical evidence stage. However, it is not known whether the improved bone response is due to surface roughness or the surface composition. Furthermore, somewhat surprisingly, there is yet not enough hard evidence (randomized clinical trials) to tell whether the second generation of the implants has a better clinical performance than the machined implants used earlier. Nevertheless, experimental evidence from in vitro and in vivo studies strongly suggests that some types of surface modifications promote a more rapid bone formation than machined surfaces.

It has been proposed that increasing osteoconductivity by these surface design strategies is related to the altered implant topography resulting in enhanced osteoblast and preosteoblast adhesion, thereby leading to accelerated bone formation (Chehroudi et al., 1992; Cooper et al., 1998). However, it is well known that titanium implantation in bone results in contact of the titanium surface with complex environment including blood components and other cells, not only the osteogenic ones. Recently, it has been shown that changes in the physico-chemical properties of the titanium results in significant modulation of cell recruitment, adhesion, inflammation and bone remodelling activities in addition to regulation on bone formation response (Omar, 2010).

These different methods for implant surface modification may lead to different and unique surface properties that might affect the host-to-implant response.

This chapter reviews the state of art of development in dental implant surfaces and current trends in surface modifications that aim to accelerate the osseointegration of dental implants. This chapter also contains an overview of the most popular surface textures, chemical modifications including nano-surface design based on nanoscale modification of the implant surface, but also briefly describe the interface biology of oral implant is also discussed. Finally, it concludes with a summary and future outlook.

2. Surface roughness of titanium implants

Surface roughness has been identified as an important parameter for implants and its capacity for being anchored in bone tissue. There exist a variety of different manufacturing methods to increase the surface roughness of the implant, where the most commonly used are: Machining, Sandblasting, Acid etching, Anodic oxidation, Laser modification or a combination of these. Further, commercially available implants have been categorized according to the roughness value (S_a) into 4 groups (Albrektsson & Wennerberg, 2004a), smooth (S_a < 0.5 μm), minimally rough (S_a = 0.5-1.0 μm), moderately rough (S_a = 1.0-2.0 μm) and rough (S_a > 2.0 μm). The S_a value represents the mean height of peaks and pits of the surface, while another important parameter is S_{dr}, which represents the developed surface area compared to a perfect flat area. With a larger surface area a larger contact to the bone tissue could be obtained. There exists another 50 some direct or combined surface roughness parameters (Gadelmawla et al., 2002) however, it is unknown to what extent these are important. For S_a measurements different factors will affect the outcoming result as the type of equipment used, the area of analysis, the filtering process of the raw data, the cut-off values as well as where on the implant the measurements are performed. To obtain more

comparable values in the literature guidelines for measurements have been published (Wennerberg & Albrektsson, 2000). Further, it is important to acknowledge that the surface chemistry and surface phase composition of the implant surface will change by altering the surface roughness (Kasemo & Lausmaa, 1988).

2.1 Machined surface

The first generation of osseointegrated implants had a relatively smooth machined surface (Branemark et al. 1969). The machined implant surface is solely turned and considered to be minimally rough (Figure 1). Different roughness values have been published using different measuring techniques. Moreover, manufacturing tools, bulk material, lubricant and machining speed will influence the resulting surface topography. Typical S_a values for machined surfaces are 0.3-1.0 μm. The surface oxide consists of a 2-10 nm thick mostly amorphous layer of TiO_2 (Lausmaa, 1996). Depending on the sterilization method the oxide layer could be crystallized into rutile structure (Jarmar et al., 2008). Further, the thickness and temperature is important on the phase composition (Radegran et al., 1991).
The bone responses to machined surfaces have been extensively evaluated in different animal models as well as clinical trials. The machined surface was the first used surface in clinical dental applications and has excellent long time follow-up (Adell et al., 1981; Brånemark et al., 1977). Further, other extra oral applications with bone anchored implants use machined implants, such as bone anchored hearing aids (Brånemark et al., 2001) and bone anchored amputations prosthesis for major limbs as legs and arms (Robinson et al., 2004; Rydevik, 1997).
The healing around the implant is characterized by an increase in bone-implant contact starting at the implantation while the biomechanical stability slightly decrease over the first weeks, possible due to inflammation and bone remodeling, and being fully recovered after 4 weeks in rat tibia (Brånemark et al., 1997). Endosteal down growth of bone tissue covering the implant threads occurs in the marrow cavity and reach up to 70% bone implant contact after 16 weeks in rat tibia which could be compared to clinically stable oral implants retrieved up to 16 year after implantation where the bone-implant contact was measured to 56-85% (Sennerby et al., 1991). Eighty-five % bone-implant contact was observed for a clinically stable bone anchored amputations prosthesis retrieved after 11 years (Palmquist et al., 2008). Further, in the latter study it was shown that hydroxyapatite forms directly at the implant surface shown in high-resolution transmission electron microscopy (TEM).

2.2 Sandblasted surface

Increased roughness of an implant could be achieved by blasting the surface by small particles, usually called sandblasting or grit blasting (Figure 2). When the particles hit the implant surface it will create a crater. The surface roughness is hence dependent on the bulk material, the particle material, the particle size, the particle shape, the particle speed and the density of particles. The resulting surface roughness is usually anisotropic consisting of craters and ridges and occasionally particles embedded in the surface.
The surface roughness increases with the size of the particles used (Wennerberg et al., 1992) where 25 μm particles blasted surfaces were rougher than the machined surface while smoother than 75 μm and 250 μm blasted surfaces. Typical S_a values are 0.5-2.0 μm. Further, implants blasted with 25 μm and 75 μm particles show higher removal torque compared to a machined implant surface after 12 weeks of healing in either rabbit tibia or femur (Wennerberg et al., 1995).

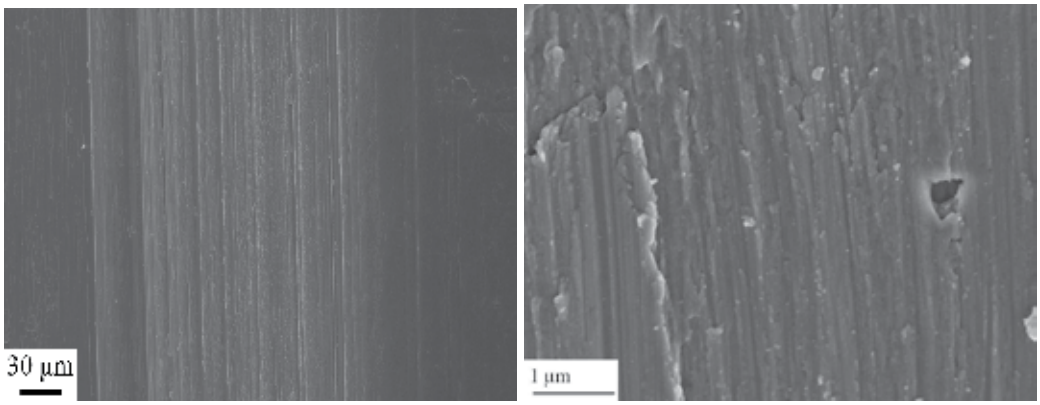

Fig. 1. Scanning electron micrograph of machined implant surface.

Significantly higher bone-implant contact was observed for the 25 µm blasted surface compared to machined surface while the bone area within the threads were significantly higher for the machined surface after 12 weeks (Wennerberg et al., 1995) and 1 year healing (Wennerberg et al., 1997). The blasting particle material, either TiO_2 or Al_2O_3 with a size of 25 µm, didn't show any difference in bone response with respect to removal torque, bone-implant contact and bone area after 12 weeks healing (Wennerberg et al., 1996a). Similar removal torque while significantly higher bone-implant contact and bone area was observed for implants blasted with 25 µm particles compared to 250 µm particles (Wennerberg et al., 1996b). The biological response to blasted implants show a optimal bone response with regards to removal torque values and bone implant contact to implants when a roughness of 1.5 µm is a achieved (Wennerberg, 1996). No ultrastructural studies of the interface between bone and implant surface have been found in the literature for blasted implants.

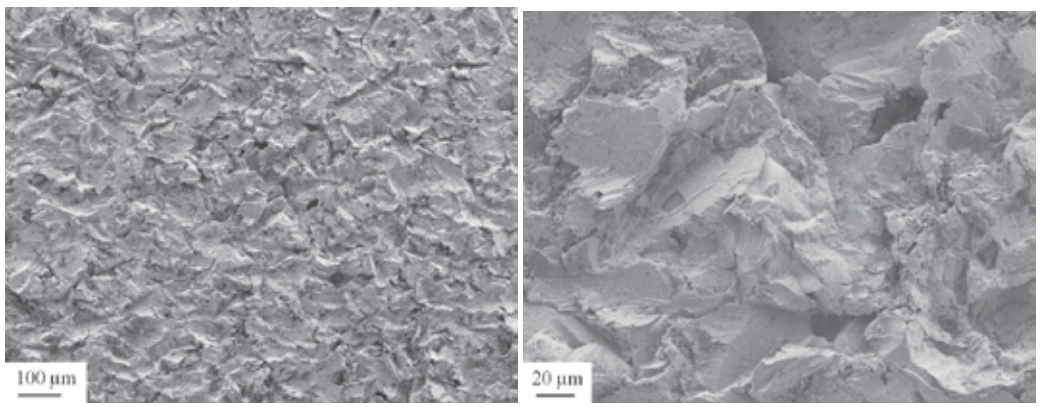

Fig. 2. Scanning electron micrograph of sandblasted surface.

2.3 Acid etched surface

With acid etching the surface is pitted by removal of grains and grain boundaries of the implant surface, as certain phases and impurities are more sensitive to the etching a selective removal of material is obtained (Figure 3). The resulting roughness is dependent on the bulk material, the surface microstructure, the acid and the soaking time. The surfaces are

generally considered minimally rough as the typical S_a values are 0.3-1.0 µm. Few analyses of the surface layer have been found, but speculative a titanium hydride layer could form due to the presence of hydrogen ions in the acid. The surface oxide has been found to be a native amorphous titanium oxide with a thickness of around 10 nm (Sul et al., 2006). The dental implant with acid etching presented implant surface morphology similar to Master Plus R (Conexão Sistemas e Protese) and Frialit Plus R (Maillefer, Swaziland).
The bone response to acid etched implants has been compared to machined implants in animal models. Significantly higher bone-implant contact was observed for acid etched implants compared to machined implants in a rabbit model after 1 and 2 months, while no difference was found after 14 days (Celletti et al., 2006). Also significantly higher bone-implant contact was observed in a poor bone quality dog model after 4 months healing while no difference in bone area was obtained (Weng et al., 2003). Significantly increased removal torque was needed to remove acid etched implants compared to the machined implant after 1, 2 and 3 months healing in rabbit while significantly lower removal torque was needed when comparing to titanium plasma sprayed implants (Klokkevold et al., 2001). Significantly lower bone-implant contact, bone area and removal torque was observed when comparing acid etched implants to anodic oxidized implants in rabbit tibia after 6 weeks healing (Gottlow et al., 2000).
On the ultrastructural level a number of publications have utilized the fracture technique for sample preparation. The interfacial bone tissue was composed of an electron dense zone (20-50 nm) closest to where the implant had been in the section followed by either mineralized bone tissue or an intermediate layer of finely fibrilar mineralized zone (100 nm) which was found at areas with ongoing bone remodeling (Steflik et al., 1992, 1997, 1998). It was further found that osteocyte cellular processors was extending towards the implant surface (Steflik et al., 1994).

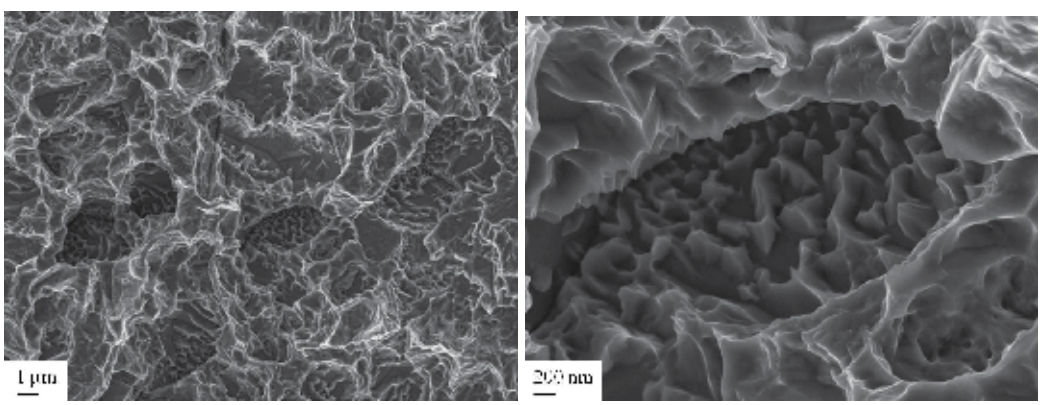

Fig. 3. Scanning electron micrograph of acid etched titanium surface.

2.4 Sandblasted and acid etched surface (SLA)

Commercially available dental implants are usually both blasted by particles and then subsequent etched by acids. This is performed to obtain a dual surface roughness as well as removal of embedded blasting particles. The etching reduces the highest peaks while smaller pits will be created and the average surface roughness will be reduced.
By the beginning of the 90s, intensive research had already shown that the sandblasted and acid etched surface had advantages compared to nearly every other type of implant surface,

including the titanium plasma spray surface which, until that time, had been the standard for ITI implants (Buser et al., 1991, Schroeder et al. 1981).
Typical S_a values for blasted and acid etched implants are 1-2 μm. The chemical process of the acid etching will change the surface structure and it has been reported a creation of a titanium hydride layer with a thickness of 1-2 μm intermediate the surface oxide and the bulk metal (Conforto et al., 2004). Further, by rinsing the SLA implant in a nitrogen atmosphere and storing in saline solution until installation, the amount of carbon contamination could be reduced and improving the hydrophilicity of the implant surface (Rupp et al., 2006). The result of this procedure is creating a new hydrophilic surface (SLActive) (Figure 4). This procedure allows the SLActive to maintain a chemically active surface that conditioned to the human body.
Also the anions from the acid could be incorporated in the oxide layer such as fluoride ions if etched in hydrofluoric acid (Figure 5) (Cooper et al., 2006).
The bone response to blasted and etched implants has been compared to different implant surfaces. Higher removal torque was needed to unscrew the dual modified surface compared to solely acid etched implants in a pig model with 10 weeks of healing (Szmukler-Moncler et al., 2004).Significantly higher removal torque was obtained compared to machined surface while similar values compared to titanium plasma sprayed implants while no differences was observed in the bone density around the 3 different implant types (Buser et al., 1999). Significantly higher removal torque and higher bone-implant contact has been observed for blasted and fluoride modified implants compared solely blasted implants in a rabbit model after 1 and 3 months healing (Ellingsen et al., 2004).
Several studies have shown that SLActive implants achieve a higher bone contact and stability at earlier time points (6 weeks) when compared with SLA implants, and dramatically reduced healing times from 12 to 6 weeks (Buser et al., 2004; Schwarz et al., 2007). No ultrastructural studies of the interface to sandblasted and acid etched implant have been found in the literature.

2.5 Anodized surface

The anodized surface (TiUnite) is a partial crystalline and phosphate enriched titanium oxide characterized by a microstructured surface with open pores in the low micrometer range (Figure 6). Anodization or anodic oxidization as it's also called is an electrochemical process carried out in an electrolyte. The structural and chemical properties could be tailored by varying different process parameters, such as anode potential, electrolyte composition, temperature and current (Lausmaa, 2001). Further, depending on the electrolyte composition, different ions could be integrated in the oxide layer, such as phosphorous (Hall & Lausmaa, 2000), calcium (Frojd et al., 2008) and magnesium (Sul et al., 2005). At lower voltages, below the dielectric breakdown limit, a rather constant oxide growth is obtained, while at higher voltages, an increased gas evolution is obtained rendering the surface oxide porous (Lausmaa, 2001). The crystalline structures of anodized oxides are amorphous with crystalline grains of anatase (Jarmar et al., 2008).
The bone response to anodized implants has been evaluated in different species and healing times and most often compared to the original machined surface. Significant higher bone to implant contact has been reported as well as increased biomechanical removal torque values for phosphorous containing anodized surfaces compared to machined surfaces in dog and rabbit (Albrektsson et al., 2000; Henry et al., 2000). The phosphorous containing anodized

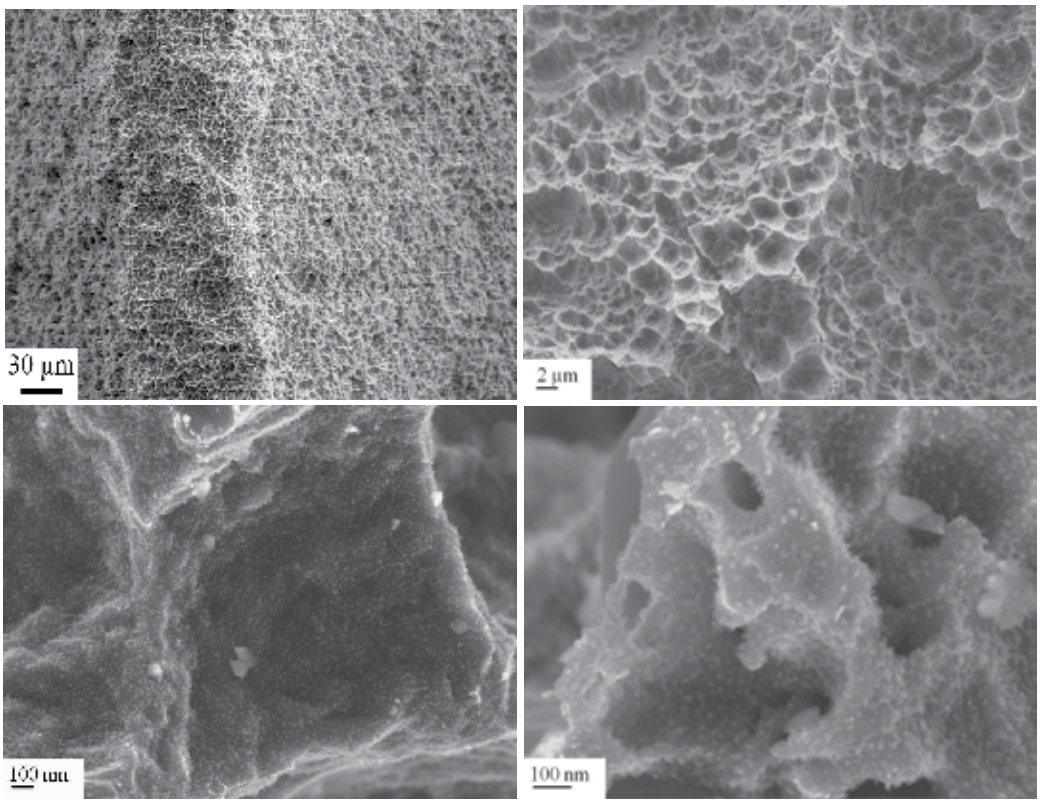

Fig. 4. Scanning electron micrograph of Straumann® Sandblasted and acid etched implant surface (SLA). Nanofeatures on the SLActive implant surface.

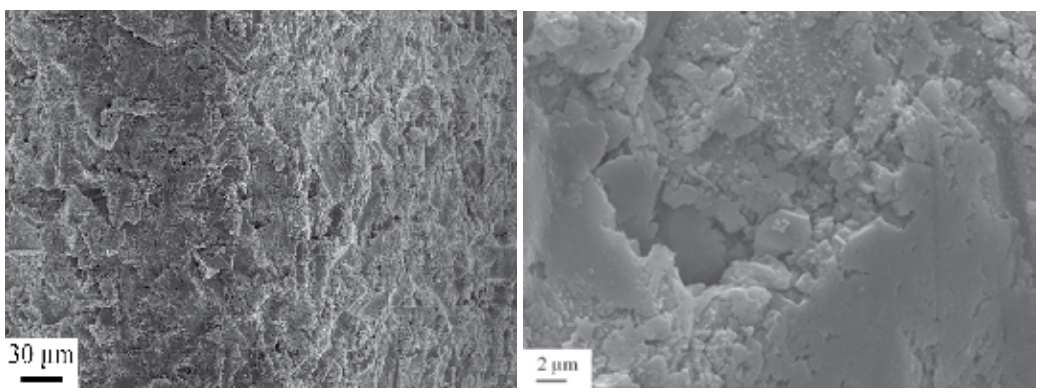

Fig. 5. Scanning electron micrograph of titanium dental implants in a fluoride modified surface (osseospeed® implant).

surface has also been shown to promote the early molecular events taking place at the immediate implant surface (Omar et al., 2010). Further, increased bone implant contact was obtained when calcium ions were incorporated in the anodized oxide compared to non

calcium containing anodized oxide surface in the rabbit (Frojd et al., 2008) as well as higher removal torques were observed for magnesium incorporated oxides compared to non magnesium oxide surfaces (Sul et al., 2005a). One study have been performed on the ultrastructural level of oxidized implants, where a failed TiUnite (NobelBiocare) implant was removed prior to stage 2 surgery due to lack of osseointegration. TEM analysis of FIB prepared samples showed an amorphous zone between the bone tissue and the implant surface (Giannuzzi et al., 2007). Furthermore, in the later study, interdiffusion of titanium, phosphorus and calcium between the bone and the coating where intimate bone-implant contact was observed, suggested that chemical bonding also exists within this interface. The remove torque to anodized implants has been compared to sandblasted, acid etched, and machined implants in animal models. Significantly higher removal torque was observed for anodized implants compared other groups in a rabbit model after 12 weeks (Elias et al., 2008).

A higher clinical success rate was observed for the anodized titanium implants in comparison with turned titanium surfaces of similar shapes (Jungner et al., 2005). Two mechanisms have been proposed to explain this osseointegration: mechanical interlocking through bone growth in pores, and biochemical bonding (Schupbach et al., 2005; Sul et al., 2005b).

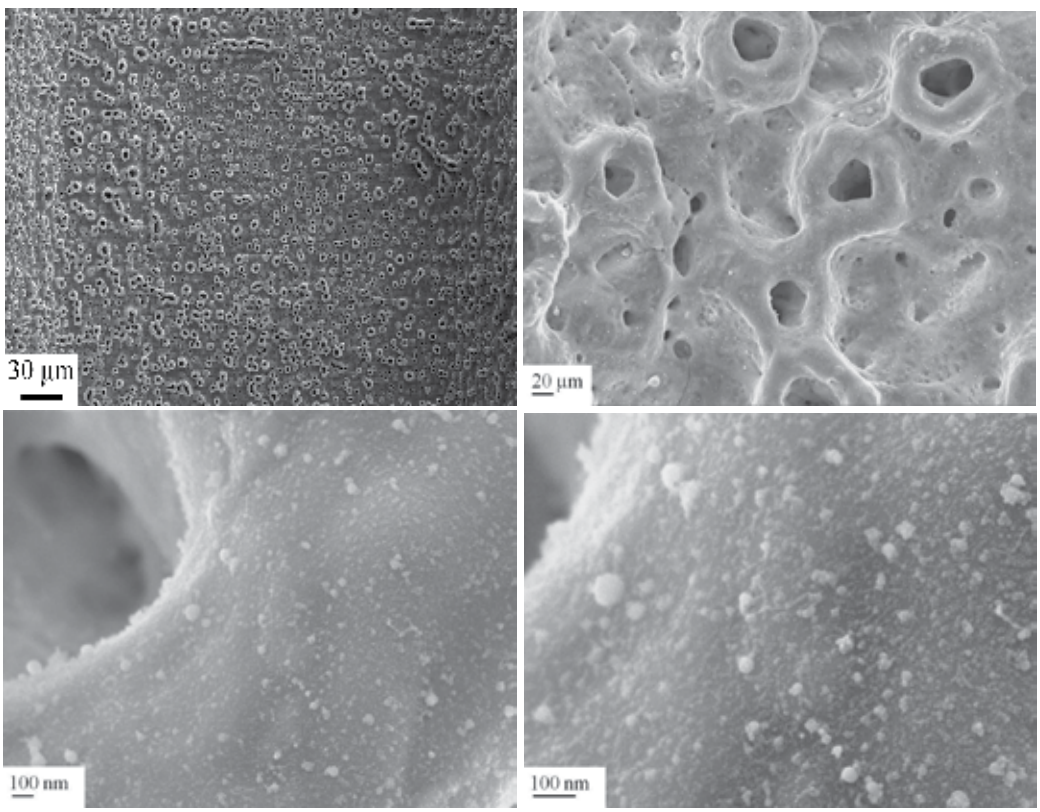

Fig. 6. A) Scanning electron micrograph of an anodized TiUnite® implant surface, B, C) the presence of pores with dimensions around 1-10 µm, and smaller pores with diameters below 1 µm, D) nanofeatures on the anodized implant surface.

2.6 Laser modified micro- and nano-structured surface

Laser is an emerging field for use as a micromachining tool to produce a 3-D structure at micrometer and nanometer level. The technique is a method of choice for complex surface geometries. The technique generates short pulses of light of single wavelength, providing energy focused on one spot. It is rapid, extremely clean, and suitable for the selective modification of surfaces and allows the generation of complex microstructures/ features with high resolution. These advantages make the technique interesting for geometrically complex biomedical implants.

The Brånemark BioHelix Implant (Figure 7) has surface modified with laser micromachining process to create micro- and nano-structured surface roughness in only the inner part of the thread. The inner part of the thread is believed to be more suitable for bone formation than the outer part (Thomsson & Esposito, 2008).

The laser technique has several advantages, add no chemicals and can be used in routine manufacturing. Only the valley and parts of the flank of the implant threads was laser treated while the remaining part was left as-machined. The idea behind this design is that the flack portion of the implant thread, which might have the higher risk to expose to the

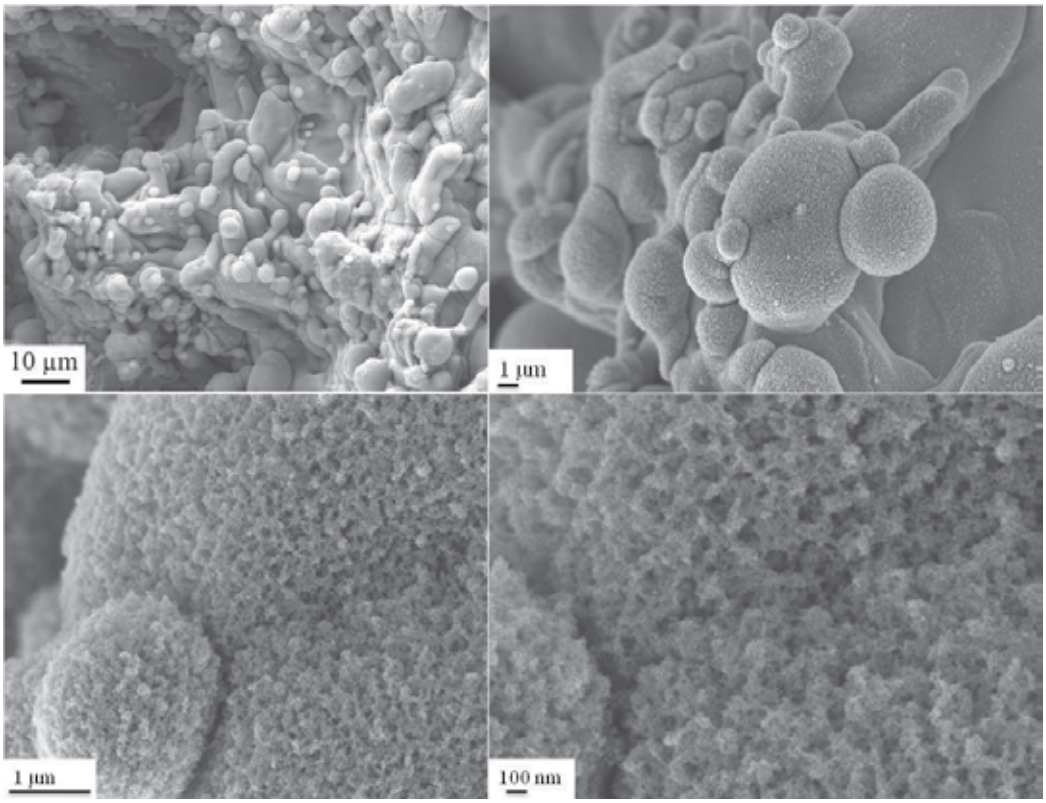

Fig. 7. Scanning electron micrograph of Brånemark BioHelix implant. The bottom portion of the threads is modified by laser processing, whereas the parts of the flanks and the tops are as machined. Higher magnification of the laser modified surface, showing the nanotopography.

microorganism and plaque, is characterised by relatively smooth surface to minimize the incidence of peri-implantitis, whereas the valley part of the implant threads has the rougher surface.

Short-term, experimental *in vivo* studies of laser-modified titanium implants with nano-scale surface topographical features have demonstrated a significant increase in removal torque and different fracture mechanisms (Palmquist et al., 2010; Brånemark et al., 2010). Of clinical importance is that nanostructured surfaces promoted long-term bone bonding and interface strength *in vivo* as determined by a coalescence between mineralized bone and the nanostructured surface and a substantial increase in removal torque (Palmquist et al., 2010).

One 1-year retrospective case series showed excellent clinical results of Brånemark BioHelix dental implants placed according to conventional procedures (Thomsson & Esposito, 2008). However, randomized clinical trials with suitable controls are needed to confirm these preliminary results.

3. Calcium phosphate coatings on titanium implants

Some surface reactive materials have shown the ability to form an interfacial chemical bond with surrounding tissues through a series of biophysical and biochemical reactions, causing 'bioactive fixation' of the implant (Cao & Hench 1996). Bioactive materials can be biostable (i.e. synthetic hydroxyapatite) or bioresorbable (i.e. bioactive glasses and glass-ceramics). Some bioactive ceramics like bioactive glasses of certain compositions have been claimed to have a real chemical bonding ability with soft tissues (Wilson et al., 1981). However, bioactive ceramics in the bulk form are not suitable for load-bearing applications as their flexural strength, strain-to-failure and fracture toughness are less than that of bone and their elastic moduli are greater than that of bone. For these reasons they are usually applied as coatings on metallic implants that possess superior mechanical properties. Calcium phosphates (CaP) are the most common family of bioceramics well-known for their use in biological application. CaP in the crystallographic form of apatite is an important mineral constituent of bone. Calcium phosphate ceramics are integrated within bone following a well known sequence of events (Frayssinet, et al. 1993). They are considered to be bioactive and osteoconductive. Bioactivity would be due to epitaxial nucleation of carbonated apatite crystals at the surface of ceramic grains. This layer of biological apatite might contain endogenous proteins and might serve as a matrix for osteogenic cell attachment and growth (Davies 2003).

Different types of methods have been introduced to prepare calcium phosphate coatings on dental implant (table 1 & 2). These methods can be divided to two groups: physical and chemical methods. Sometimes they can also be called dry and wet methods. Typically physical techniques include plasma spraying deposition, physical vapour deposition, magnetron sputtering deposition, ion beam assisted deposition, pulsed laser deposition, and hot isostatic pressing. Chemical techniques include sol-gel method, biomimetic process, electrochemical deposition, micro-arc oxidation (MAO) and electrophoretic deposition.

Physical techniques are widely used for preparation of calcium phosphate coatings. The bonding strength between coatings and implants is higher than those prepared by chemical methods. However, most of these methods have difficulties in coating of complex 3D

geometries such as rough screw-shaped dental implants. Chemical methods can be used to treat the implants with complex geometries. The treating temperature of chemical methods is low. The most important thing is that bioactive molecules and drugs can be incorporate into calcium phosphate coatings via chemical methods, such as biomimetic process.

Technique	Characteristics	Properties
Plasma spraying deposition (PS)	(1). High temperature >1000°C (2). Reproducible (3). High deposition rate (4). Atmosphere: Air, vacuum (popular), low pressure	(1). 2D (2). No homogeneity of crystallnity (3). Promote fast and strong fixation and bone growth in vivo and clinically (4). Bacteria adhesion
Magnetron sputtering deposition (MS)	(1). High deposition rate (2). Metallic and non-metallic substrates (3). DC and RF	(1). 2D (2). Ion doped hydroxyapatite and composites coatings
Ion beam assisted deposition (IBAD)	(1). The coating is amorphous, and needed to be heat treated further (2) The final crystallinity is dependent on the time, temperature and amount of water vapour present during the coating. (3). Low deposition rate compared to PS	(1). 2D (2). High adhesive strength (3). Graded crystallinity
pulsed laser deposition (PLD)	(1). Fast deposition rate (2).Multi-component and metastable materials	(1). 2D (2) HA, OCP, α, β-TCP
Hot isostatic pressing (HIP)	(1). High temperature and pressure	(1). 2D

Table 1. Physical techniques for implant coatings

In the last four decades, continuous research on HA and CaP have not only focused on tissue-coating interface, but also on the problems associated with the coating process and optimization of coating properties for maximum tissue response (Sun et al., 2001). A major dilemma for evaluation the bone tissue response of CaP coating compare to uncoated titanium implants (Morris et al. 2000; Barrere et al. 2003), is that the process of surface chemical modifications are often associated changes in topography and visa-versa. In addition, several factors may have influenced the results of *in vivo* evaluation at the interface of CaP coated implants.

Technique	Characteristics	Properties
Sol-gel method	(1). Combine with different coating process, such as dip and spinning coatings, following sintering (2).Substrates with complex geometry (3).Metallic and non-metallic substrates (4). Thin film	(1). 3D (2). Easy to control the composition (3). High sintering temperature for HA coatings
Biomimetic process	(1). Low temperature (2). Different types of substrates which could induce HA formation, such as metallic implants, bioceramics, polymers	(1). 3D (2). Bone-like crystal structure (3). Ion doped HA (4). Low bonding strength (5) Porous structure (6). Incorporate bio-molecules and drugs
Electrochemical deposition	(1). Conducting substrates (2). Chargeable particles (3). Low temperature	(1).3D (2). Low boding strength between coatings and substrates (3). Composite coatings (4). (4). Thick and cracked coatings
Electrophoretic deposition	(1). Conducting substrates (2). Chargeable particles (3). Low temperature	(1). 3D (2). Low boding strength between coatings and substrates (3). Composite coatings (4). Thick and cracked coatings
Micro-arc oxidation (MAO)	(1). Ambient temperature (2). Substrates with complex geometry (3). Electrolytic oxidation	(1).3D (2). HA and ion doped HA
Ultrasonic spray pyrolysis	(1). Ambient temperature (2). Continuous and pulse spray	(1). 2D (2). Cracks in coatings (3). The bonding strength of coatings prepared by pulse spray is better than that by continuous spray

Table 2. Chemical techniques for implant coatings.

3.1 Plasma spraying

HA coatings were first introduced in the middle 1980s for improved fixation between bone and implant (Furlong and Osborn, 1991). Since that time, these materials have been extensively used in orthopaedic and dental implants. Plasma-spraying is commercially the most frequently used method for deposition of calcium phosphate coatings, such as HA, onto implant materials to improve their bioactivity.

The thickness of hydroxyapatite coatings produced by plasma-spray varies from 100 to 300 μm (Willmann, 1997). With plasma spraying processing the surface area of titanium implant has increased up to approximately six times than the original surface. The arithmetic average roughness (R_a) for hydroxyapatite coated by plasma-spraying process is 5.0 ± 1.0 μm.

The bone tissue responses to plasma sprayed hydroxylapatite (HA) coatings on titanium implant have been well documented. Several earlier experimental studies have shown a higher percentage of bone-implant contact for HA-coated implants when compared with titanium implants in different species and types of bone (De Groot et al., 1987; Denissen et al., 1990). The histological findings demonstrated that the cortical bone reaction to titanium and HA-coated titanium was similar, but the HA-coated surfaces induced more bone deposition in areas on non-cortical bone contact than uncoated surfaces. Based on findings of a substantial reduction of the HA coating thickness after 12 weeks (Jansen, et al., 1991). Other studies in animal model have shown that the chemical composition of HA coating has a positive influence on the bone response, while, the influence of roughness is less evident (Vercaigne, et al., 1998).

In reference to the interfacial strength, the HA-coated implants were reported to have higher push-out strength in compared to non-coated implants (Cook et al., 1987). HA coated implants have also exhibited a greater torque removal value compare to Ti screw implants (Carr et al., 1995).

On the ultrastructural level, newly formed acicular crystallites were adjacent to the larger HA crystals of the plasma-sprayed coating. Needle-like crystals seemed even to grow at the surface and in the smallest holes of the HA coating. Collagen fibrils were not observed in the bonding area. The tiny crystals of the newly formed mineralized tissue developing in the cavities of the implanted material appeared to be more or less randomly oriented, thus resembling woven bone (Hemmerle, et al. 1997).

However, despite clinical success, it has been recognized that the plasma-spraying method has several disadvantages, including poor long-term adherence of the coating to the substrate material, non-uniformity in thickness of the deposited layer, and variations in crystallinity and composition of the coating. Other significant factors causing implant failures include microbial infection (Rosenberg et al., 1991; Verheyen et al., 1993).

3.2 Sputter-deposition

Sputtering process has been shown to be a particularly useful technique for the deposition of bioceramic thin films (based on Ca–P systems), due to the ability of the technique to provide greater control of the coating's properties and improved adhesion between the substrate and the coating.

Scanning electron microscopy showed that the deposited films had a uniform and dense structure (Figure 8). The calcium phosphate has been reported to range from 1.5 and 2.6. The *in vitro* dissolution appeared to be determined by the degree of the coating's crystallinity

(Ong & Lucas, 1998; Ong et al, 1997). The disadvantages with sputter coating is extensive time consuming, produces amorphous coatings and Ca/P ration of the coating is higher than of synthetic HA.

The thickness of hydroxyapatite coatings produced by sputter process varies from 0.5 to 3.0 μm (Ding, 2003). With sputter processing the surface roughness of the coating depends on the roughness of the substrate (Hayakawa et al., 2000). The arithmetic average roughness (R_a) for hydroxyapatite coated by sputter process is 3.0 ± 1.2 μm.

In a study using TiO2-gritblasted and sputtered CaP implants, the sputtered CaP coatings showed improved initial fixation and healing response when implanted into the trabecular bone of the goat (Vercaigne et al., 2000; Hayakawa et al., 2000). In a separate study comparing sputtered CaP coatings to plasma-sprayed HA coatings, the ultimate interfacial strength observed for the sputtered CaP-coated implants (as-sputtered and sputtered followed by post- deposition heat treatment) was not significantly different from the plasma-sprayed HA coated implants 12 weeks after implantation, suggesting that sputtered CaP coatings are comparable to plasma-sprayed HA coatings with respect to ultimate interfacial strength. This was supported by the histological findings that indicated no statistical difference in percent bone contact length between plasma-sprayed HA-coated implants and the as-sputtered CaP-coated implants at 12 weeks after implant placement (Yang et al., 2005).

Further, sputtered calcium phosphate coated titanium implants have showed higher removal torque compared to control uncoated titanium implants after 3 weeks of healing. This difference in the removal torque strength was no longer evident after 12 weeks of healing (Ong et al., 2002).

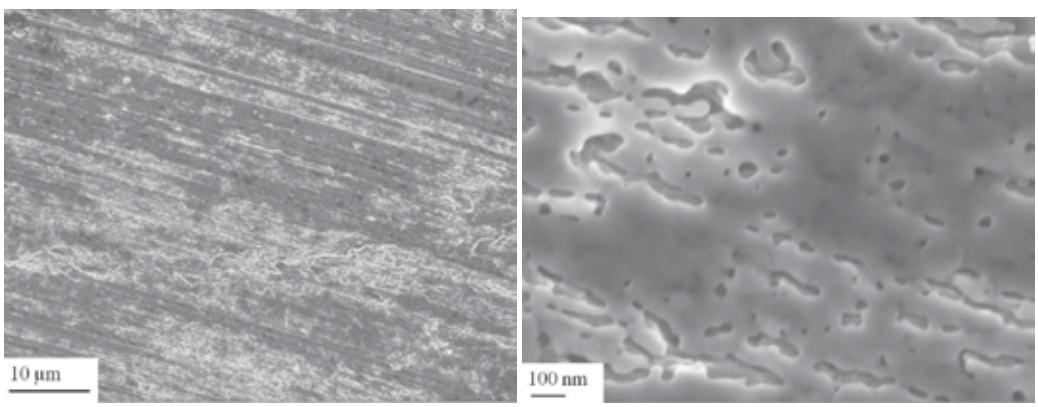

Fig. 8. Scanning electron micrograph of sputter CaP coated titanium implant.

3.3 Biomimetic precipitation

Biomimetic deposition of calcium phosphate onto surfaces of implant materials is a technique originally developed by Kokubo and co-workers (Kokubo et al, 1990). This method allows hydroxyapatite and other calcium phosphate surfaces to be deposited on substrates in a simulated body fluid (SBF) under physiological conditions of temperature and pH, on complex geometrical shapes.

The classical biomimetic Ca–P coating normally requires an immersion period of about 14–28 days with replenishment of SBF solution. It is observed that the thickness of the apatite

layer increases as the immersion period increases. In very recent years efforts have been made (Habibovic et al., 2002; Ma et al., 2003; Barrere et al., 2004; Muller et al., 2004) to make this process fast to increase its practical utility.

In the biomimetic method, a layer of usually rough and porous, calcium-deficient apatite will grow on the surface of implants. The Ca/P ratio for HA biomimetic coating was 1.51 (He et al, 2007), and the thickness of HA coatings produced by biomimetic process varies from 20 to 25 μm (Yang et al., 2005).

It is well known that the tissue and cell response could be considerably influenced by the composition and topography of the implant surfaces.[14] Biomimetically produced apatite surfaces may, therefore, be useful in facilitating early bone ingrowth into porous surfaces without the potential for coating debris, macrophage infiltration, fibrous tissue encapsulation, and eventual coating failure as may occur with the plasma-sprayed hydroxyapatite coating.[15]

Little information is available on bone tissue responses to biomimetic coatings on titanium implant. Very few experimental studies have shown the biomimetic HA coating did not have any positive effect on new bone formation and on the shear strength at the early bone healing stage (Fuming, et al, 2008; He et al, 2009; Yang, et al, 2009).

Recently, it has been found that the morphology of the biomimetic apatite surfaces changed by adding ions as substitutes to HA such as strontium (Sr), and silicate (Si) ions (Zhang & Zou, 2009; Xia et al., 2010).

Adding Sr ion change the morphology of biomimetic apatite from plate-like for the pure HA to sphere-like (Figure 9). Surface analysis results showed that 10-33% of Ca ions in the apatite have been substituted by Sr ions, and that the Sr ions were chemically bonded with apatite and successfully incorporated into the structure of apatite (Xia et al., 2010).

Our recent findings have showed that biomimetically prepared Sr and Si-ion substituted apatite films deposited on Ti implants provide bioactive surfaces which promote early bone formation. The mechanisms behind these responses may be release of Sr ions, and the nature of bonding of Si ions in the HA structure, whose fast hydrolysis is deemed to contribute to the surface hydrophilicity, respectively (Ballo et al., 2010).

3.4 Bioactive glass coatings

Originally introduced by Hench (Hench et al., 1971), silica-based bioactive glasses are slowly resorbing synthetic osteoconductive materials which are able to form strong chemical bond with bone. Several methods have been applied to obtain a bioactive glass coating on the load bearing part of the implants (Hench & Andersson, 1993). Several attempts have been made to create bioactive glass coatings on alumina (Greenspan & Hench 1976), stainless steel (Schepers et al., 1989), Co-Cr-Mo alloy (Lacefield & Hench, 1986), fiber-reinforced composite (Ballo et al. 2009, 2011), and titanium alloys (West et al., 1990, Kitsugi et al., 1996). Application of a double glass coating has been suggested to solve the problem of differences in thermal expansion coefficients. Recently, several attempts were made to prepare bioactive glass coatings on titanium and Ti6Al4V (Bloyer et al., 1999, Saiz et al., 2002). Application of a ground layer prepared from inert glass with a thermal expansion coefficient close to that of Ti6Al4V provided good adhesion to the substrate (Oku et al., 2001). This ground coating can be used in combination with more surface reactive glass coatings (Gomez-Vega et al., 2000a), with embedded hydroxyapatite and/or bioactive glass particles (Gomez-Vega et al., 2000b), or a sol-gel-derived silica coating (Gomez-Vega et al., 2001). Reactive plasma spraying

(Schrooten et al., 2000) or processing with infra-red laser (Moritz et al., 2004) have also been attempted to create bioactive glass coatings on titanium and its alloys.

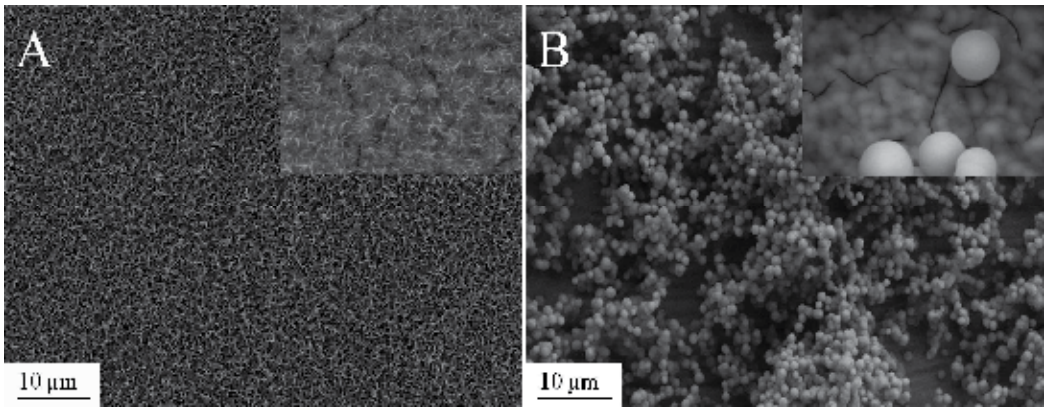

Fig. 9. Scanning electron micrograph of biomimetic apatite surface modification of titanium implants. A) Pure apatite with plate-like structure, B) Sr-HA with sphere-like structure.

Several experimental studies have shown that titanium implants coated with BAG were integrated into host bone without a connective tissue capsule and significantly greater osseointegration and high removal torque in compare to the control uncoated titanium implants (Moritz et al., 2004). Also significantly higher bone-implant contact was observed for BAG coated titanium implants than those in both the uncoated and HA coated titanium implants after 4, 12, and 24 weeks of healing (Xie et al., 2010).
Recently, one 1-year comparative clinical study showed that bioactive glass coated implants were as equally successful as hydroxyapatite in achieving osseointegration and supporting final restorations (Mistry et al., 2011). However, further clinical studies are needed to confirm these preliminary results.

4. Biological response to titanium implant surface modification

Osseointegration is the fortunate outcome of bone tissue healing around titanium implant. It is a biological process in which a direct anchorage is established by formation of bone tissue around the implant without the growth of fibrous tissue at the bone-implant interface (Branemark, Adell et al. 1969; Branemark, Hansson et al. 1977). Despite the wide use of osseointegrated titanium implants and the substantially growing research on the development of new titanium surfaces and/or modification of existing surfaces, a detailed understanding of the mechanisms of osseointegration is still lacking. The current knowledge on the process of healing at different titanium implants is predominantly gained from histological and biomechanical data and correlation with normal fracture healing. The histological and biomechanical studies strongly advocate that bone would respond differently by alteration of the implant surface properties (Larsson, Esposito et al. 2001).Consequently, great attention has been given to study, *in vitro*, the cellular and molecular activities on different substrates and to extrapolate the results to the actual interfacing between implant and living bone tissue. Based on results from the *in vitro* studies, the surface influences the initial sequences of protein adsorption, platelet adhesion and haemostasis, complement activation, inflammation and osteogenic cell response

(Nygren, Tengvall et al. 1997; Park and Davies 2000; Masaki, Schneider et al. 2005; Tan, Qian et al. 2006). Taking into account the important information acquired from these studies, however, they remain to large extent unrepresentative for the actual paradigm of the *in vivo* implantation scenario. For instance, early *in vivo* studies revealed that that the process of bone formation at titanium implants is preceded by recruitment of cells of different types and at different levels of morphological differentiation (Sennerby, Thomsen et al. 1993; Sennerby, Thomsen et al. 1993). However, the functional activities of the different cells and the roles of cells other than osteogenic ones in the healing process have not been clearly defined. A key question is how early molecular and cellular events are influenced by material surface properties *in vivo*, and how these early events influence the organization of the surrounding tissue and its interlocking or bonding with the material surface and, in turn, the capacity of this interface to adapt to long-term continuous load interactions.

The new advances in research technologies have made it possible to apply molecular techniques to analyze the interface between the living tissues and implant surface. Such tools can be used at high degree of precision to discover mechanisms that govern osseointegration including events of early inflammation, mesenchymal stem cells (MSCs) recruitment and cell-cell communication. Nevertheless, the advent of these approaches requires establishing reliable procedures to collect cell samples from within the *in vivo* interface in the way that their spatial distribution can be determined. Using the highly sensitive quantitative polymerase chain reaction (qPCR) in conjunction with the well documented rat tibia model, it has been revealed that gene expression of the interfacial implant-adherent cells is immediately and differently influenced by titanium implants depending on their surface properties (Omar, Lenneras et al. 2010; Omar, Svensson et al. 2010). The model was further combined with immunohistochemistry and SEM to confirm the presence of specific cell types at the interface. Ultimately, the regulations of inflammation, bone formation and bone resorption processes were correlated to the strength of the early formed bone-implant interface, by measuring the removal torque (Omar, Lenneras et al. 2011) (Table 3).

The inevitable early inflammation and the processes of cellular recruitment and adhesion to titanium implants in bone are obscure and have not received similar attention as that given during soft tissue integration. In soft tissue healing around titanium discs, higher release of tumor necrosis factor-alpha (TNF-α) was observed in response to porous titanium with and without plasma protein layer compared to machined titanium after 3 hours (Jansson, Kalltorp et al. 2002), as well as for machined titanium compared to copper after 12 hours of implantation (Suska, Esposito et al. 2003). The soft tissue data presented strong evidence on the modulation of inflammatory cell responses by titanium surface roughness and composition, respectively. The local releases of inflammatory mediators, in addition to the modulatory role of the implant surface, initiate the cascade that controls early inflammatory events. These events involve the release and regulation of primary acute phase cytokines. By activation of their target cells, these cytokines generate a second wave of cytokines, including members of the chemokine family.

In bone, higher expression of the chemokine, monocyte chemoattractant protein-1 (MCP-1), was revealed at machined implant surface compared to anodically oxidized implant (Omar, Lenneras et al. 2010). This was coupled with higher expression of pro-inflammatory cytokines TNF-α (3 hours and 1 day after implantation) and interleukin-1beta (IL-1β) (1 day and 6 days after implantation) at the machined implants (Omar, Lenneras et al. 2010; Omar, Svensson et al. 2010). The temporal expression profile for MCP-1 was similar to the

expression of pro-inflammatory cytokines telling that the recruitment of inflammatory cells was accompanied by cytokine activity at both surfaces. The immunohistochemical sections for the same time period showed CD163-labeled monocytes/macrophages at both surfaces. However, a general SEM observation in all samples was that a large amount of fibrinous material covered the machined implants (Figure 10). Fibrin has been shown to enhance the pro-inflammatory response to biomaterials (Tang and Eaton 1993) which might explain the upregulated pro-inflammatory cytokine expression at the machined surface as early as 3 and 24 hours (Omar, Lenneras et al. 2010) and at later time periods (Omar, Svensson et al. 2010).

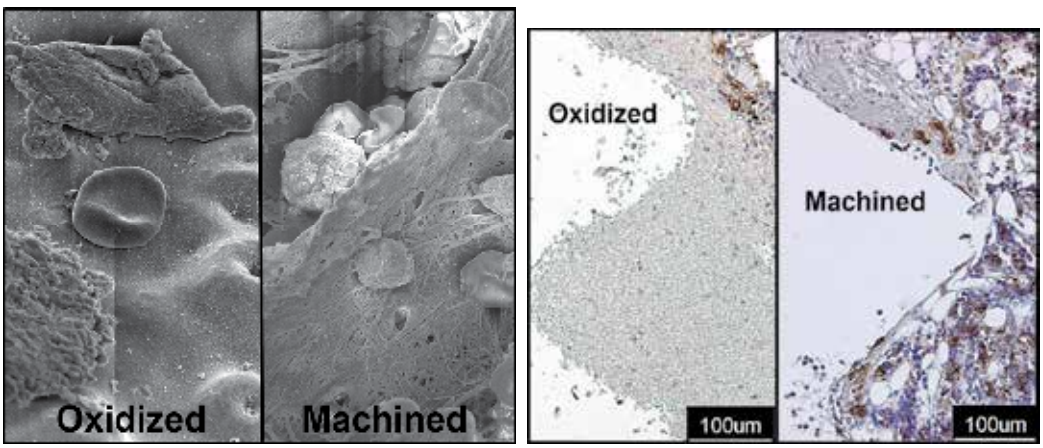

Fig. 10. Left, scanning electron microscopy images of oxidized and machined implant retrieved 24h after implantation. Right, immunohistochemical sections of the interface 24h after implantation showing CD163-positive monocytes/macrophages in the interface zone. Biological material adherent the machined implant was highly fibrinous with numerous erythrocytes and leukocytes compared to the oxidized implants.

One of the major observations during the initial 24 hours after implantation in bone was the significant modulation of the chemokine receptor CXCR4 (Omar, Lenneras et al. 2010). These results provided the first set of data on the role of this chemokine receptor at titanium implants in bone. After 12 hours of implantation, 11-fold higher CXCR4 expression was demonstrated at the oxidized implants compared to the level at machined implants. CXCR4 together with its exclusive ligand, stromal derived factor-1alpha (SDF-1α), has recently gained significant attention as a major axis for local and systemic recruitment of MSCs to sites of tissue repair and regeneration (Yu, Li et al. ; Ceradini, Kulkarni et al. 2004; Shichinohe, Kuroda et al. 2007; Wang, Deng et al. 2008). Blocking of CXCR4 significantly inhibited *in vivo* migration of circulating alkaline phosphatase (ALP) positive osteoblast progenitor cells to subcutaneously implanted BMP-2 containing collagen pellets (Otsuru, Tamai et al. 2008). Other studies have also demonstrated that MSC migration to a fractured tibia site is highly dependent on CXCR4 in a time- and dose-dependent manner (Granero-Molto, Weis et al. 2009). The revealed upregulation of the chemokine CXCR4 at the oxidized implant surface was corroborated by SEM and immunohistochemical observations showing the predominance of mesenchymal stem cells at that surface.

At the *in vivo* bone implant interface, the cellular attachment is meditated via protein rich layer to which cells adhere using variety of surface receptors, mainly form integrin family. The modulation of expression of specific integrins may reflect specific temporal and

conformational changes in protein adsorption influenced by the physico-chemical properties of the surface. T-shaped hollow titanium implants treated with sulphuric and hydrochloric acids showed higher expression and peak of β1 and β3 integrins in the surrounding bone after 1 week in rat femur compared to machined titanium and non implant defect (Ogawa and Nishimura 2003). Cells adherent to oxidized surfaces showed upregulation of integrin-β1 during the 24 hours of implantation (Omar, Lenneras et al. 2010). Since CXCR4 exhibited association with integrin-β1 at the oxidized implants, this together with the increased expression of osteogenic markers, such as ALP and osteocalcin (OC), and the higher number of mesenchymal cells, as shown in SEM observations, altogether suggested that the oxidized implant was associated with higher recruitment of MSCs through mechanisms which involve modulation of CXCR4 chemokine receptor and integrin-β1expression (Figure 11).
Integrin-β2, expressed mainly by leukocytes (Stewart, Thiel et al. 1995) and not by cells of osteoblastic lineage (Hughes, Salter et al. 1993), was higher at the oxidized implants after 12 hours of implantation. This integrin has also been shown to be expressed by osteoclast progenitors (Hayashi, Nakahama et al. 2008). Results showing a higher expression of osteoclastic marker (cathepsin K; CATK) at the oxidized surface (Omar, Svensson et al. 2010) suggested that the higher expression of β2 integrin may be due to the early presence of osteoclasts in the interface.

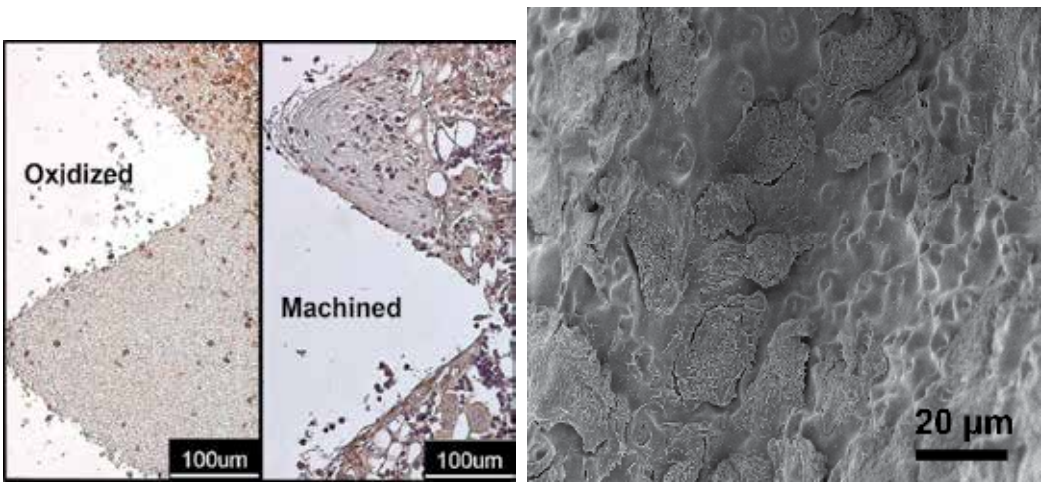

Fig. 11. Left, immunohistochemical sections of the interface 24h after implantation showing periostin positive mesenchymal and osteoprogenitor cells. Right, scanning electron microscopy of oxidized implant retrieved 24h after implantation. On the oxidized implants, mesenchymal cells were frequently seen.

Peak expression for ALP, OC, tartrate resistant acid phosphatase (TRAP) and CATK was detected 3 days after implantation in rat bone (Omar, Svensson et al. 2010). Previous studies in bone fracture model (without implants) in similar animal model have shown that ALP and OC expression attained their peaks after 5 and 11 days, respectively (Jingushi and Bolander 1990). Osteoclastic gene expression levels of TRAP and CATK have been shown to attain their earliest peaks between 7 – 14 days (Uusitalo, Hiltunen et al. 2000; Nagashima, Sakai et al. 2005). The observations that the peak expression of osteogenic and osteoclastic markers was detected as early as 3 days at the implant surface and that oxidized implants were associated with significantly higher levels than machined implants indicate, firstly,

that bone remodeling around implants starts much earlier than what has previously been assumed (mainly based on conclusions from fracture models and *in vitro* experiments with one cell population), and, secondly, that the implant surface has an influence on the level of expression of bone differentiation and remodeling markers. Possible mechanisms for the accelerated implant-associated bone response include multiple cell participation and cross-talk, influenced by material surface physicochemical properties and topography of the implanted surfaces.

The regulation of gene expression at implant surfaces *in vivo* is a complex process. It is probably that material properties influence the gene expression of several factors, in addition to the secretion, organization and remodelling of the extracellular matrix components. Thereby these events may further affect key-factors, such as Runx2, which is crucial transcription factor for osteogenic differentiation and bone formation. The higher expression of osteoblast markers, (ALP) and (OC), and osteoclast marker, (CATK), was in parallel to a higher expression of Runx2 at the oxidized surfaces compared to machined ones after 3 days of implantation (Omar, Svensson et al. 2010). Similar results were demonstrated for hydrofluoric acid (HF) etched surface in comparison to similar surface without acid etching (Guo, Padilla et al. 2007). In the latter study, Runx2 expression was evident after 7 days in rat tibia and was associated with higher expression of ALP and bone sialoprotein (BSP). Regulatory effect on the expression of Runx2 was also confirmed for the HF surface in rabbit cortical bone concurrently with higher expression of collagen 1 and OC after 8 weeks of implantation (Monjo, Lamolle et al. 2008). At the implant surface, collagen-rich matrix organization together with increased expression of integrin-β1 may characterize an important pathway for Runx2 activation and consequently the downstream osteogenic activity and bone formation (Figure 12).

The performance of dental implants is best evaluated with respect to their stability into the implantation site. The *in vivo* interfacial gene expression model has been successfully combined with removal torsion analysis to determine possible relationship between the molecular events and torque strength at the interface (Omar, Lenneras et al. 2011). Significantly higher and constant increase in removal torque was registered for the oxidized implants throughout the period of 6 – 28 days of implantation (Figure 13). At the same time, the increased biomechanical strength at the interface of the oxidized implants was in association with higher expression levels of bone formation genes (OC and Runx2). The increased expression of bone formation genes during this period was coupled with upregulated expression of bone resorption genes (TRAP and CATK). The high expression of bone formation and bone resorption indicated an active remodelling throughout the time periods concomitant with an increasing biomechanical strength of the interface. In agreement, other studies compared the expression of different genes and pull-out force of coin-shaped implants with different hydrofluoric acid modification after 4 weeks in rabbit (Lamolle, Monjo et al. 2009; Taxt-Lamolle, Rubert et al. 2010). The test implant group that showed increased pull-out values, revealed higher expression of OC, collagen 1 and TRAP and decreased expression of TNF-α and IL-6.

On the other hand, low and unchanged values were observed in removal torque strength for the machined implants during the evaluation periods 6, 14 and 28 days. Machined implants were associated with an increased expression of pro-inflammatory cytokines (TNF-α and IL-1β) during the early (week) phase of osseointegration (Omar, Lenneras et al. 2010; Omar, Svensson et al. 2010), observations which were extended also to the later stages of osseointegration (Omar, Lenneras et al. 2011). It has previously been suggested that the

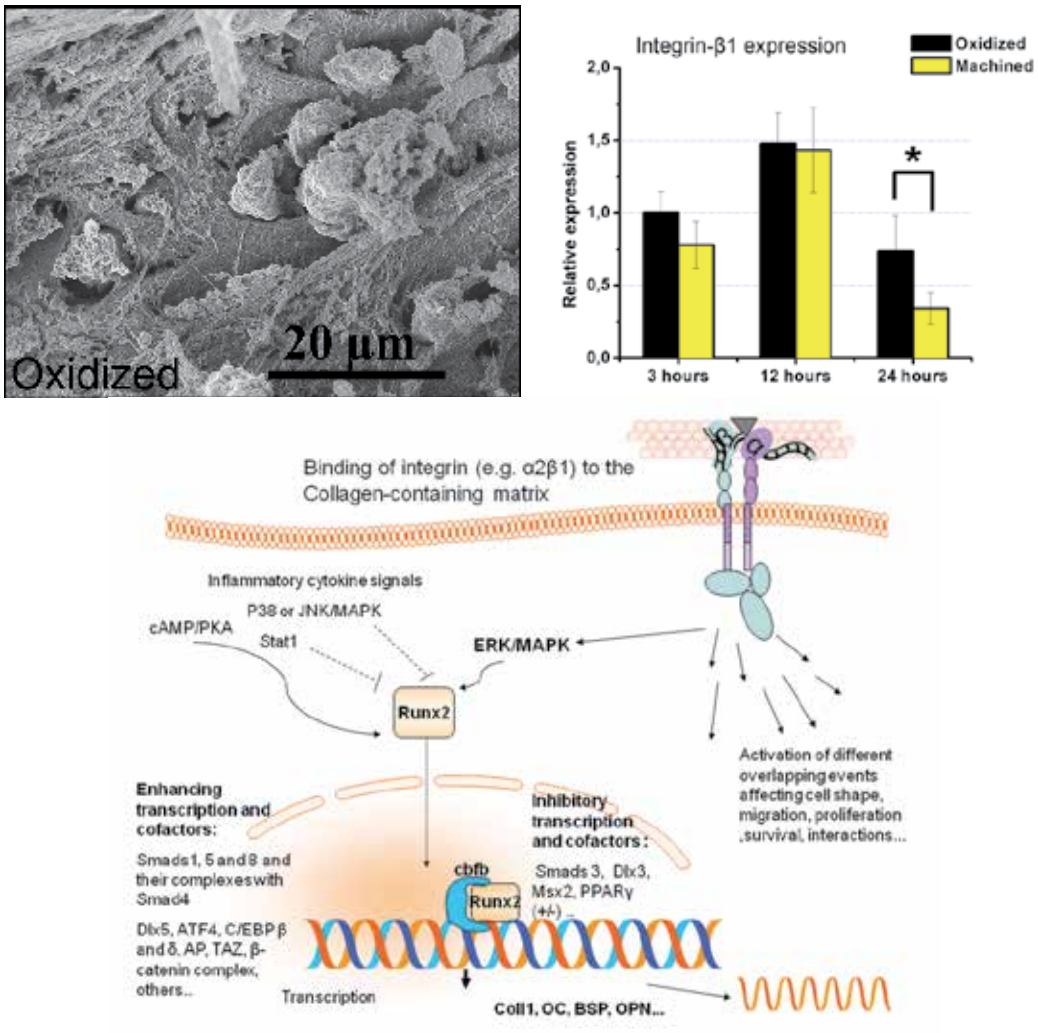

Fig. 12. Upper left, SEM image of oxidized implants retrieved 6d after implantation. Well-organized collagen network with numerous mesenchymal cells were observed on the oxidized implant. Upper right, a graph showing significantly increased expression of integrin-β1 at oxidized implant after 1d of implantation. The lower drawing illustrates activation of osteogenic response by mechanisms involving binding of integrin-α2β1 to collagen-rich matrix.

initial reduction and plateauing of the biomechanical strength of machined implants could be a manifestation of post-surgical inflammation and the remodelling activity (Branemark, Ohrnell et al. 1997). This is partly supported by the present results, given that machined implants, which were associated with higher expression of pro-inflammatory cytokines, did not reveal any increase in the biomechanical strength between 6 and 28 days. Whereas the increase in remodelling activity coupled with increased bone forming activity were in line with increased interface resistance for similar time periods.

		Initial phase		Early phase			Late phase	
		3h	12h	1d	3d	6d	14d	28d
qPCR	TNF-α	2-fold at machined	No differnce	2-fold at machined	No difference	3-fold at machined	No difference	3-fold at machined
	IL-β1	No difference	No differnce	5-fold at machined	No difference	3-fold at machined	2-fold at machined	2-fold at machined
	MCP-1	No difference	No difference	2-fold at machined	Not analyzed	Not analyzed	Not analyzed	Not analyzed
	CXCR4	No difference	12-fold at oxidized	No difference	Not analyzed	Not analyzed	Not analyzed	Not analyzed
	Intg-β2	No difference	2-fold at oxidized	2-fold at oxidized	Not analyzed	Not analyzed	Not analyzed	Not analyzed
	Runx2	Not analyzed	Not analyzed	No difference	6-fold at oxidized	No difference	No difference	2-fold at oxidized
	ALP	Not analyzed	Not analyzed	No difference	5-fold at oxidized	2-fold at oxidized	No difference	No difference
	OC	Not analyzed	Not analyzed	No difference	5-fold at oxidized	5-fold at oxidized	3-fold at oxidized	3-fold at oxidized
	CATK	Not analyzed	Not analyzed	No difference	4-fold at oxidized	2-fold at oxidized	2-fold at oxidized	No difference
	TRAP	Not analyzed	Not analyzed	No difference	2-fold at oxidized	2-fold at oxidized	2-fold at oxidized	2-fold at oxidized
Scanning electron microscopy (SEM) and backscattered SEM		-Higher proportion of fibrinous material adherent to machined. -Larger proportion of mesenchymal cells firmly anchoring to oxidized.		- Fibrinous material with entrapped leukocytes were evident throughout the 6 days at the machined. -Fairly organized collagenous network and many mesenchymal cells scattered all over the oxidized at days.			-mineralized lamellar bone and areas of newly formed bone for both. - Machined implant: separated from bone by a narrow gap. -Oxidized implant: direct contact with bone. Bone ingrowth into micropores.	
Histology and Immuno--histochemistry		-Hematoma organization. -Prominent fibrin mesh at machined. - CD163 positive cells (Monocytes and macrophages) at both implants. -Periostin positive cells (mesenchymal and osteoprogenitors) at both implants.		-Tissue organization with different cellular populations. -Higher degree of vascularity and organization at oxidized. -CD163 positive (Monocytes and macrophages) at both. -Periostin reactivity (osteoprogenitors and osteoblasts) and throughout regenerated tissue at both implants. -Bone formation (woven bone)			-Woven bone remodeled. -Mature bone forming the interface.	
Biomechanical stability		Not analyzed		-Oxidized implant demonstrated higher magnitude and significant increase in biomechanical resistance during the first 28 days. -Machined implant showed lower magnitude and non-significant increase in biomechanical resistance during the first 28 days. - The oxidized implant showed a fracture-like breakpoint while the machined implant showed the typical curve with mainly separation in the immediate bone-implant interface.				
Biological processes		Clot formation, hematoma organization, initial inflammation, multiple cell chemotaxis and recruitment and adhesion		Downregulation of inflammatory phase, growth factor production, tissue organization, differentiation of osteogenic and osteoclastic cells, coupled bone formation and remodeling			Mature osteoclasts and osteoblasts, continuous coupled bone formation and remodeling (maturation), later abating of remodeling, Steady inflammatory milieu.	

Table 3. Summary of cellular and molecular activities at oxidized and machined implant during the first 4 weeks of implantation in rat tibia. The biological activities were correlated to the biomechanical stability of oxidized and machined implants in the same animal model.

5. Ultrastructure characterization of bone-implant interface

In order to further understand the bonding mechanisms that occur between living bone tissue and implant surface, analytical tools with sufficient resolution for ultrastructural analysis are needed. This especially important with the emerging nano-structured implant surfaces. Further, not only the structural aspect should be considered but also the chemical nature of the interface layer is of importance. The tool of choice is transmission electron microscopy (TEM) where various analytical tools often are readily used in high resolution. The electron-solid interaction generates different contrast phenomena, depending on crystal structure and atom number as well as interactions with the sample electrons generating energy-losses of the primary electron beam and secondary x-rays for chemical analysis. Further, elastic scattering and interference contrast could also be used for structural analysis. Hence, TEM is a versatile tool alloying structural and chemical analysis with high lateral and volumetric resolution. However, the literature of biomedical implants in bone tissue using TEM is scarce where the main reason is the sample preparation, especially for metallic implants. The sample should be around 100 nm thick to be electron transparent. Further a balance between contrast and overlapping information occurs, where less contrast is obtained when the sample becomes thinner, while the amount of overlapping information in the sample increases with the thickness.

5.1 TEM sample preparation methods

Different methods for sample preparation have been developed and are often optimized for each branch of research. Within the materials research field, polishing techniques, etching and broad ion milling are often employed, while the ultramicrotome is often used for

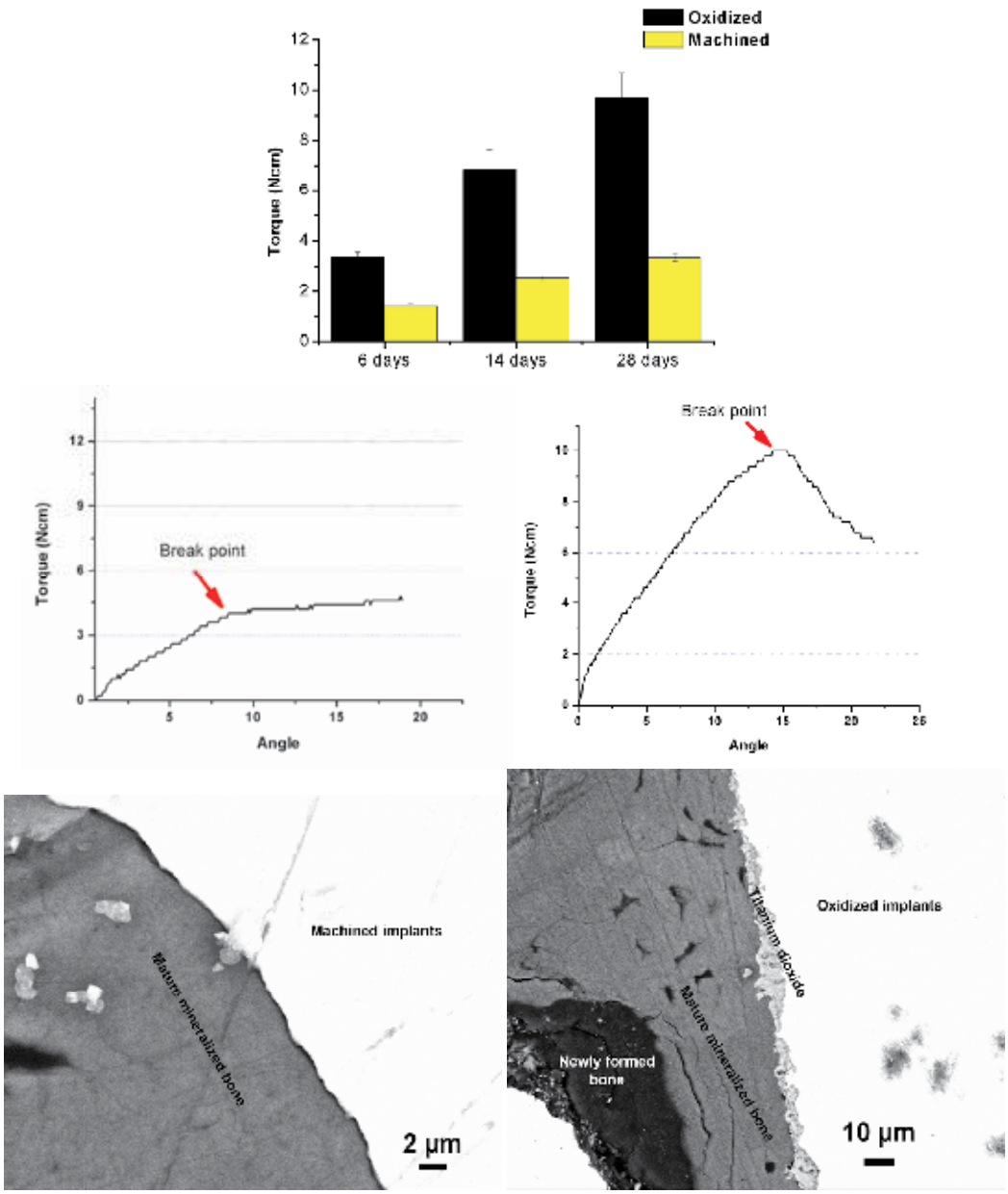

Fig. 13. Upper, a graph showing significant increase in the removal torque values for oxidized implants during early osseointegration. The middle graphs show the load-deformation curves of machined (left) and oxidized (right) implants after 28d of implantation. The deformation of the machined implant interface is mainly due to separation whereas a fracture-like pattern is registered for the oxidized implant. The lower backscattered SEM images show machined implant (left) was separated from bone by a narrow gap. Direct contact of the bone with the oxidized implant (right) was detected with generalized bone ingrowth into different sized micropores.

tissues. Within the field of biomaterials, the samples are composed of both hard materials as metals and ceramics and tissues as bone and soft tissue, therefore a different strategy has to be employed, as the diamond knife in the ultramicrotome could not cut through the hard implant material and the grinding, etching and broad ion milling will destroy the tissue.
Different strategies have been introduced where the main focus has been focused on removing the uncuttable implant material allowing the use of the ultramicrotome. One of these methods used experimental implants made of plastic which were coated with a thin enough layer of the material that was tested so it was still cuttable with the ultramicrotome. Different metal coating has been used such as titanium, zirconium, gold and steel (Albrektsson et al., 1985, 1982a, 1982b). This method was restricted to experimental studies, as the plastic implants did not posses clinically acceptable mechanical properties. Other methods were developed to be able to evaluate implants from clinical situations where different solutions to remove the implant were used. One method was based on gently fracture away the implant material either during the decalcification step (Steflik et al., 1992) or after resin embedding (Thomsen & Ericson, 1985). Uncertainties of the integrity of the interfacial tissue remained as the material was completely removed. A strategy for keeping the oxide layer intact, having an intact interface, while removing the bulk properties of the implant allowing ultramicrotome sectioning was developed. By electrochemical dissolution of the metallic titanium the oxide layer was still present in the section (Radegran et al., 1991), however, this technique demineralized the tissue (Sennerby et al., 1991). Another metod used was sawing and grinding to remove the bulk metal leaving the surface layer of the implant intact (Leize et al., 2000), this may be useful for thicker surface coatings as plasma-sprayed titanium, but with most commercially available dental implant rather thin oxides are present. With the use of focused ion beam (FIB) intact bone-implant interfaces could be prepared, allowing both material and tissue analysis (Engqvist et al., 2006).

5.2 Interface analysis of different surfaces

Quit few ultrastructural analysis of the bone-implant interface are presented in the literature as compared to the total amount of articles using bone anchored implants. The most published literature evaluates the machined surface or similar smooth surface using mainly the plastic implant replica model or the fracture method. The fracture method has also been used for acid etched implants, while the FIB has mainly been used for the laser-modified implant surface. Some articles evaluate plasma-sprayed surfaces and oxidized surfaces.

5.2.1 Smooth implant surface

Different interfaces have been described for machined implants, some dependent on the healing time and some depending on sample preparation method. Most of the analysis showed that an interposed amorphous electron lucent layer of approximalty 20-50 nm was found between the mineralized bone and implant surface (Albrektsson et al., 1985, 1982; Linder et al., 1983). This was often with a poorly mineralized zone of a few hundred nm containing collagen fibrils prior to the mineralized bone tissue (Albrektsson et al., 1985, 1986). Others found instead an electron dense layer of similar thickness prior to the mineralized bone tissue, either directly at the implant surface (Ayukawa et al., 1998) or with a larger amorphous zone in direct contact with the surface (Sennerby et al., 1991, 1992). Also a direct contact between mineralized bone tissue and implant surface has been reported using different sample preparation techniques (Albrektsson et al., 1981; Brunette et al., 1991;

Meyer et al., 2004). By the use of high-resolution TEM crystalline hydroxyapatite was found precipitated directly at the implant surface of a machined titanium implant retrieved after 11 years of clinical loading (Palmquist et al., 2008). The sample preparation technique seem to be essential where plastic implant replicas seem to show a predominance for an intervening electron lucent layer, while the fracture technique show a predominance for an electron dense layer and a thicker amorphous zone. With FIB difficulties in sample preparation for smoother implant surfaces is separation between the tissue and implant (Palmquist et al., 2009)., most likely due to shrinkage of the tissue during dehydration (Lawton et al., 1995) and resin embedding, on the other hand this suggests that the separation for the fracture technique occurs at the immediate interface, and it has been shown that low amount of remnants were found on the implant after fracture (Lausmaa & Linder, 1988).

5.2.2 Roughened implant surface

The most studies have been performed using an acid etched surface, increasing the roughness by pitting and the creation of craters in the surface. The results using the fracture technique of acid etched surfaces showed an electron dense layer interposed between the implant surface and the mineralized bone tissue (Steflik et al., 1992a, 1992b, 1998). Further, at areas of less mature bone tissue a zone of mineralized collagen fibril layer was found between the mineralized bone and the electron dense layer (Steflik et al., 1992b, 1998). Further, the use of high-voltage TEM has enabled tracking of the canaliculus which reach the implant surface (Steflik et al., 1992a, 1994). For plasma-sprayed implants and plastic implant replicas of plasma-sprayed implants a direct bone-implant contact has been described at most places as well as an intervening layer with indistinct structure reaching up to 1 µm in thickness (Leize, 2000; Hemmerle & Voegel, 1996). By combining micro and nano topography by the use of laser ablation, an intimate contact between mineralized bone tissue and implant surface oxide has been described (Palmquist et al., 2010) using the FIB technique. Further, elemental analysis showed the presence of calcium and phosphorous in the nano structured surface oxide (Palmquist et al., 2011). The FIB has also been used to analyse the bone-implant interface of a failed dental implant retrieved with smaller amount of bone tissue, the results showed an electron lucent layer closest to the implant surface as well as bone ingrowth in the porous oxide (Giannuzzi et al., 2005, 2007).

5.2.3 Bioactive implant surface

The use of bioactive coating may enable a chemical bond between the implant surface and surrounding bone tissue. Most frequently used bioactive coating is hydroxyapatite. Thin sputtered and Plasma-sprayed HA coatings has been shown to form an intimate contact with bone tissue (Engqvist et al., 2006; Grandfield et al., 2011a, 2011b) with minor resorption of the coating. The use of calcium aluminate coating showed also an intimate contact with bone tissue, where different crystalline phase was observed in the coating while the outermost layer of the coating facing the bone tissue was calcium deficient (Palmquist, et al., 2009). Ultrastructural analyses of hydroxyapatite scaffolds and bone tissue have shown the formation of an apatite layer between the collagenous bone and implant surface (Grandfield et al., 2010a). Further, this layer was shown to have a distinct difference in crystal direction from the crystals in the collagenous bone tissue with the used of electron tomography (Grandfield, et al., 2010b). Further, the incorporation of ions in the hydroxyapatite has shown to influence the rate of dissolution and also the rate of bone formation (Porter et., 2004a, 2004b, 2005).

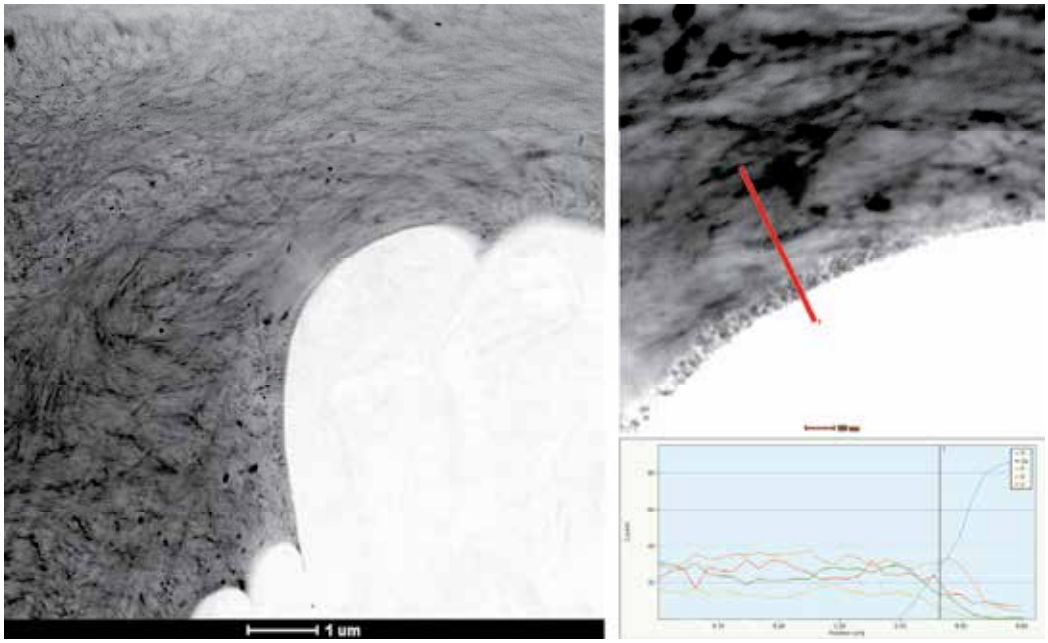

Fig. 14. HAADF-STEM micrographs of laser modified titanium implants after 6 months healing in rabbit, the left image show an overview where bone tissue are found with an intimate contact to the implant surface, collagen banding is observed close to the implant surface. Right, a closer view of the interface, where the enlarged surface oxide is clearly observed with intimate contact to the bone tissue. The EDS line scan along the red line show the presence of Calcium and Phosphorous in the bone tissue, and Titanium in the bulk metal. An overlap zone observed where calcium, phosphorous, titanium and oxygen are seen simultaneously indicating bone ingrowth in the nano structured surface oxide.

6. Summary

The new generation dental implants exhibit a large variation in surface properties, both in terms of structural and chemical compositions. The selection criteria for the first generation of dental implants were mainly based on their mechanical properties and corrosion resistance under physiological conditions. The current surfaces have mainly underwent topographical modification and, to a lesser extent, alteration in chemical composition. The aim of surface modifications was to achieve an enhanced biological response. Experimental studies and clinical experience provided extensive empirical knowledge about the role of such surface modifications for biological responses. However, comprehensive understanding of the biological response at the bone-implant interface is still lacking and further research is required to understand the biological processes taking place at the interface, and how these are influenced and can be controlled by specific surface properties.

7. Future prospective in dental implant surfaces

Future development of the next, third generation of dental implants should be based on increased knowledge about the interface biology on cellular and molecular levels. The

development of future generations of oral implants for compromised tissue conditions will, most probably, entail tailored modifications of material surfaces. Implant surfaces, selectively, designed for drug and/or cell releases represent promising candidate strategy. Other surface modifications, such as selective ion substitutions of biomimetic surfaces may further improve the biological response to those surfaces. Further, as the bacterial infection is a major challenge which may jeopardize the success of osseointegrated implants, implant modification resulting in antibacterial activity might be of importance to reduce such complications.

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3

Osseointegration and Bioscience of Implant Surfaces - Current Concepts at Bone-Implant Interface

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1. Introduction

The high success rates for the dental rehabilitation of patients with endosseous implants have resulted from many research approaches with the aim of enhancing and accelerating bone anchorage to the implant, thereby providing optimal support for the intraoral prosthetic devices. This revolutionary breakthrough has first evolved from the research efforts of the Brånemark group in the late 1960s by pioneering the insertion of machined screw-type commercially pure titanium (cpTi) implants with minimum surgical trauma and a consolidation period for the healing of the bone (Albrektsson et al., 1981; Brånemark et al., 1969). This first endosseous titanium implant was produced with an industrial turning process, which led to surfaces with minimally rough topographies at the micron level. The bone bonding ability, termed as "osseointegration" by Brånemark *et al.* (1977), of this machined implant was mainly the result of the proper surgical technique providing macro-stability to the implant and the biocompatible nature of the bulk titanium. In the past three decades, much has been learned about the concept of osseointegration and significant improvements on the design and surface of implants were done to eliminate the important challenges of the implant dentistry.

Osseointegration was first defined as a direct contact between living bone and the surface of a load-carrying implant at the histological level (Brånemark, 1983) and, in clinical terms, as a biomechanical phenomenon whereby clinically asymptomatic rigid fixation of the implant is achieved and maintained in bone during functional loading (Albrektsson & Johansson, 2001). Typically, an implant is considered to be osseointegrated when there is an absence of movement between the implant and bone under normal conditions of loading following a defined healing period. This clinical state is the result of direct bone apposition to an implant surface without formation of a poorly vascularised collagenous capsule, termed as fibrous encapsulation. Although the concept of "osseointegration" was first put forth to define the connection between bone and titanium, it has been shown that bone anchorage can also be achieved with the use of other materials without an adverse tissue reaction (Wenz et al., 2008). Thus, osseointegration is currently accepted as a general term for bone-implant surface contact. However, the quality of the host bone/foreign implant interface is

mostly affected by the characteristics of the material. Especially, titanium has been shown to have a closer contact with the calcified tissue and to be covered by a thinner proteoglycan structure compared to zirconium and stainless steel (Albrektsson et al., 1985, 1986). Various studies have also suggested that titanium exhibits a better biocompatible nature and less foreign body reaction compared to other conventional materials (Eisenbarth et al., 2004; Hallab et al., 2003). It has been stated that osseointegration of titanium does not result due to a positive tissue reaction, instead it occurs in the absence of a negative tissue response (Stanford & Keller, 1991). Therefore, the bioinert character of titanium is the main reason of its enhanced bone bonding behaviour. Now, osseointegration of titanium is widely accepted as the prerequisite for dental implant success in dentistry. Although the reported success rates are higher than 90% in controlled clinical trials (Henry et al., 1996; Jemt et al., 1996), important challenges, such as the long latency period between implant placement and loading, remain to be elucidated. Also, achieving high success rates in specific patient groups (e.g. diabetics, oncology patients, smokers) seems to be elusive (Esposito et al., 1998). Over the past two decades, elevating the local quality and quantity of the host tissue for an optimal osseointegration was the major goal of implant dentistry in order to overcome these drawbacks. Therefore, various approaches have focused on finding alternative methods to accelerate and optimize osseointegration, aiming at sufficient mechanical integrity to withstand occlusal forces at an early period (Morton et al., 2010).

During the first 10–20 years of understanding the healing mechanisms of traumatized bone where implants are placed, the concept that successful osseointegration was the result of titanium implant biocompatibility dominated clinical thinking. Subsequently, implant surface modifications encouraged new considerations of improvements in bone formation at the implant surface. Since the biological mechanisms at the bone-implant interface determine the fate of the implant, characteristics of the implant surface play a central role in challenging the process of osseintegration with early loading. Upon insertion, premature loading can disrupt the healing process and may result in early failure of the implant. Enhancing the biological response using a surface science approach therefore has attracted the attention of many research groups (Ramazanoglu et al., 2011; von Wilmowsky et al. 2009). It is well established that characteristics of the implants surface, such as nano- and micro-topography, and physicochemical composition, have a major influence on the outcome of osseointegration, especially at the histological level, aiming at biological and morphological compatibilities (Mendonça et al., 2008).

In general, the implantation of devices for the maintenance or restoration of a body function imposes extraordinary requirements on the materials of construction. Foremost among these is an issue of biocompatibility. It was found, after extensive literature review, that there are three major required compatibilities for placed implants to exhibit biointegration to receiving hard tissue and biofunctionality thereafter. They include biological comatobility (in short, called as biocompatibility), mechanical compatibility, and morphological compatibility to receiving host tissues (Oshida et al., 1994; Oshida, 2000; Oshida et al., 2010). Accordingly, numerous studies have been conducted to meet aforementioned requirements for successful implant systems (i.e., mechanical compatibility, biological compatibility, and morphological compatibility) by altering surface characteristics for overcoming the potential drawbacks of the implant therapy (Oshida, 2007; Oshida et al., 2009). This chapter focuses on essential mechanisms governing the peri-implant healing and surface science approaches for enhancing osseointegration. The future of the implant surface science and prospective

tissue engineering attempts for the biological constitution of the peri-implant area are also topics of this chapter for providing ideas for forthcoming studies.

2. Healing around the endosseous implant

Ossification mechanisms that occur following the placement of the implant are very important for understanding the biologic response to endosseous implants. Osborn (1979) categorized this bio-response into the following three groups: (1) biotolerant type, characterized by distance osteogenesis, the implant is not rejected from the tissue, but it is surrounded by a fibrous connective tissue, (2) bioinert type, characterized by contact osteogenesis, the osteogenic cells migrate directly to the surface where they will establish de novo bone formation, and (3) bioreactive type, the implant allows new bone formation around itself, thereby exchanging ions to create a chemical bond with the bone. Upon insertion, various implant materials exhibit different biologic responses. While biotolerant materials, such as gold, cobalt-chromium alloys, stainless steel, polyethylene and polymethylmethacrylate, exhibit distance osteogenesis, titanium and titanium alloys are accepted to be bioinert according to their surface oxides (Kienapfel et al., 1999). Besides, the rutile-type oxide, which is formed on titanium as a titanium dioxide, is described as a stable crystalline form similar to ceramics in its bioreactive behaviour (Zhao et al., 2005). Although titanium has superior characteristics compared to other implant metals, the ostoconductivity of titanium is lower than calcium phosphate (CaP) based bioceramics (Kilpadi et al., 2001). Therefore, CaP based ceramics are referred to be bone-bonding materials, whereas titanium is a nonbonding material to bone (Hench & Wilson, 1984). Therefore, approaches have mainly focused on enhancing the bioactivity of titanium and providing a higher osteoconductivity to the bulk material by altering the surface properties.

The character of the host tissue also plays an important role on the ossification mechanism following implantation. Understanding the different peri-implant healing cascades of the cortical and trabecular bone is crucial for better orientating the osseointegration in poor quality bone (Davies, 1996). Following surgical trauma, the vascular injury of the cortex results in death of the peri-implant cortical bone, and followed by a slow proceeding osteoclastic remodelling. The removal of the injured tissue by osteoclasts and the subsequent formation of the new bone is a long lasting process. Therefore, the healing around the implant in cortical bone results in distance osteogenesis. Although this slow remodelling phase provides early stability in cortical bone leading to low rate of implant failure (Adell et al., 1981), especially in the parasymphyseal mandible, it is a handicap for the surface science approaches for enhancing the osseointegration histologically. On the other hand, the trabecular bone enables the migration of osteogenic cells due to its marrow component. The colonization of differentiating progenitor cells on the implant surface and *de novo* bone formation provides the evidence that peri-implant healing in trabecular bone occurs via contact osteogenesis. Actually, the presence of osteprogenitor populations in the spongious bone, which is characterized to be of poor quality in implant dentistry (Lekholm and Zarb type III and IV bone), favours the migration and bone forming activity of these cells directly on the surface when the implant is considered to be bioinert (Marco et al., 2005). In the recent decades, the development of novel osteoconductive titanium surfaces, that increased the local quantity and quality of osseous tissue at the interface, thereby improved the success of implants, especially in regions of the jaw such as the edentulous posterior maxillae where the cortical thickness is frequently insufficient for the primary stability.

The surgical placement of the implant results in injury of the host bone. If the implant is considered to be bioinert, the body responds to this injury with physiological mechanisms similar to the bone fracture healing. Following implant placement, the implant surface first gets in contact with the blood originating from the injured vessels facing the implant cavity. After several seconds, the surface is completely covered with a thin layer of serum proteins. This protein modification of the surface occurs for all implant materials in the same way. However, the type and surface characteristics of the material have a major influence on the structure and conformation of this protein layer (Dee et al., 2002). Shortly after protein adsorption, the surface becomes associated with thrombocytes. As a result of thrombocyte aggregation and degranulation on the surface, coagulation mechanisms take place and cytokines (e.g. transforming growth factor-β (TGF-β) and platelet derived growth factor (PDGF)) and several vasoactive factors (e.g. serotonin and histamine) are released from cytoplasmic granules of thrombocytes. These chemoattractants stimulate proliferation and migration of various cells, thereby orientating the peri-implant healing mechanisms (Dereka et al., 2006). For example, PDGF has important mitogenic and migrative effects on several cell types, such as inflammatory leukocytes, osteoblasts, smooth muscle cells and fibroblasts (Heldin & Westermark, 1999).

Polymorphonuclear neurophils (PMNs) are also first group of cells that play an important role in the inflammatory response. PMNs dominate the bone-implant interface at the first and second days. The number of PMNs tends to decrease when bacteria and endotoxins are not present at the interface. At the second day of healing, monocyte migration and macrophage accumulation starts to take place (Davies, 2003). PMNs and macrophages remove dead cells, extracellular matrix (ECM) residues and bacteria. Beside their role on the initial inflammatory phase, another mission of macrophages is the expression of cytokines, such as fibroblast growth factor (FGF), PDGF and vascular endothelial growth factor (VEGF). Thus, they provide important signals in order to stimulate the recruitment of osteogenic and endothelial progenitors for the next proliferative phase. The release of vasoactive amines, thrombocyte and leukocyte infiltration, the establishment of the coagulum and fibrin network, macrophage actions are important events that occur at the inflammatory phase. This first phase, which can sometimes extend to five days, is followed by the removal of the coagulum by PMNs and subsequently by monocytes, at the same time angiogenesis starts also to take place (Stanford & Keller, 1991). The growth of new capillaries into the fibrin network is mostly stimulated by the growth factors (primarily FGF and VEGF) expressed by macrophages and endothelial cells as a response to hypoxic and acidic nature of the bone-implant interface (Schliephake, 2002). In this way, the proliferation, maturation and organization of endothelial cells to new capillary tubes take place, thereby providing oxygen and nutrients to the newly formed tissue at the interface.

The behaviour of blood cells inside the fibrin-based structural matrix has a major impact on the healing mechanisms at the bone-implant interface. Besides, the quality of bone healing around an implant is also affected by the capacity of osteogenic cells to proliferate and migrate. Meyer et al. (2004) have demonstrated that the osteoprogenitor cells started to attach the implant surface after one day following insertion. This was a similar finding, as stated by Davies (1996), showing that early recruitment and colonization of mesenchymal stem (MSCs) cells occur on an implant surface in a short time through modulation of white blood cells, fibrin network and thrombocytes (Park & Davies, 2000). The three dimensional structure of fibrin matrix and the migrating effects of growth factors expressed by the first arriving cells play an important role in the establishment of an osteoprogenitor reservoir at

the interface. Therefore, the chemistry of the implant material and its surface characteristics are of special interest in implantology, since they initially influence the binding capacity of fibrin and the release of growth factors, thereby affecting the migration of mesenchymal cells directly (Puleo & Nanci, 1999).

Titanium implant materials possess ideal fibrin retention on their surface. Through this fibrin matrix, osteogenic cells having the migration ability arrive the implant surface and start to produce bone directly on the surface. Davies (2003) termed this phenomenon as *de novo* bone formation through contact osteogenesis. Upon arrival to the surface, the differentiated osteogenic cells secrete the collagen-free matrix (cement lines / lamina limitans) for the mineralisation through calcium and phosphate precipitation. This layer, where the initial mineralisation occurs, consists of non-collagenous proteins (mostly osteopontin and bone sialoprotein) and proteoglycans (Klinger et al., 1998). Following calcium phosphate precipitation, the formation and mineralisation of collagen fibers take place. Thus, a non-collagenous tissue is established between the implant surface and the calcified collagen compartment through contact osteogenesis. This intermediary tissue is very important for the understanding the bonding mechanism between bone and a bioinert titanium implant.

Following the establishment of the calcified matrix on the implant surface, woven bone formation and organization of the bone trabeculae start to take place for the reconstitution of the damaged bone at the peri-implant area (Marco et al., 2005). Since the woven bone mostly consists of irregular shaped and loosely packed collagen fibers, it does not provide sufficient mechanical stability compared to the organized the lamellar bone. However, most of woven bone usually remodels in three months and replaced by the lamellar bone. At three months of healing the implant is mostly surrounded by a mixture of woven and lamellar bone (Chappard et al., 1999). The formation and remodeling of the new lamellar bone around the implant occur more rapidly in the regions where there is denser marrow component present. Therefore, the biologic fixation of the implant is achieved faster in the trabecular bone, while a better primary stability is obtained in the cortical bone following implantation.

An implant surface is considered to be clean following fabrication processes. If not stored under special conditions, contaminations (e.g. hydrocarbon, sulphur dioxide and nitric oxide) occur from the atmosphere (Kasemo & Lausmaa, 1988). In order to decrease and eliminate such risk of contamination, commercial implant surfaces are usually subjected to passivation treatments and stored carefully in optimal packages until usage. If such an implant is placed into the bone, its surface first get in contact with the blood, which is mostly composed of water molecules. Differently from the liquid water, the water molecules bind to the surface and form water mono- or bi-layer (Kasemo & Gold, 1999). The organization of water molecules differs according to the wettability characteristics of the surface (Lim & Oshida, 2001). While on hydrophilic surfaces the interaction with water molecules results in the dissociation of molecules and in the formation hydroxyl groups, the water binding capacity of hydrophobic surfaces is very low. Following the establishment of water overlayer, the ions (e.g. Cl^- and Na^+) enter the layer and become hydrated. The characteristics of an implant surface have a major implant on this arrangement of ions and their water shells. After the establishment of an intermediate layer composed of ions and water molecules, the biomolecules arrive at the surface in milliseconds. Proteins absorb first onto the surface, then change their conformation, denaturize and desorb from surface leaving their place to other proteins that have more affinity to the surface. Thus, a biologic layer having a different arrangement and conformation surrounds the surface.

It is well known that surface characteristics have an important effect on the adsorption of biomolecules by changing the arrangement of water molecules and ions (Puleo & Nanci, 1999). While on hydrophobic surfaces proteins bind with their hydrophobic regions, on hydrophilic surfaces the connection is established with the help of hydrophilic regions Kasemo & Gold, 1999). This protein overlayer is never considered to be static. It is subjected to structural and conformational changes in time. Normally the protein, which is found in higher concentration in the biological fluid, reaches and adsorbs to the surface first. Usually, this protein is afterwards replaced with another one that has a more affinity to the surface, although its concentration is low in the biological fluid. As a result of these adsorption and desorption mechanisms, a diverse layer which is composed of different protein is formed and maintained at the surface. The major role of this protein layer is the attachment of functionary cells of the healing process. If a bone implant is planning to be developed, the establishment of a surface, that generates an optimal protein composition and conformation for the attachment of osteogenic cells on itself, is one most important strategies of the production.

Several proteins (e.g. fibronectin, vitronectin, laminin, serum albumin and collagen) facilitate the attachment of osteogenic cells on titanium surfaces (Park et al., 2005; Yang et al., 2003). Therefore, the protein binding capacity of an implant surface is considered to be an important factor for as successful osseointegration, since surface properties, such as micro- and nano-topography (Lee et al. 2010), physicochemical composition (Park et al., 2005) and surface free energy (MacDonald et al., 2004), have an influence on the extend of protein adsorption. It has been documented that osteogenic cells preferably attach to the specific protein sequences, such as the arginine-glycine-aspartic acid (RGD) motif. This motif is found in various ECM proteins, including fibronectin, vitronectin, laminin and osteopontin (Ruoslahti, 1996). Osteogenic cells attach to these binding motifs using their membrane receptors, termed as integrins. Integrin mediated cell attachment is crucial for physiological and pathological mechanisms, such as the embryonic development, maintanance of tissue integrity, circulation, migration and phagocytic activity of leukocytes, wound healing and angiogenesis. Integrins are obligate heterodimers composed of two distinct glycoprotein subunits; α and β subunits (Hynes, 2002). Integrin subunits cross the plasma membrane with a long extracellular ligand, while generally a very short domain remains in the cytoplasm. For the integrin family eighteen α and eight β subunits have been characterized in mammals until now. Through the combination of these different α and β subunits, 24 distinct integrins can be assembled. A cell can modulate more than one integrin receptor and change their location, thereby modifying its capacity to bind to different protein sequences (Dee et al., 2002).

As mentioned before, adhesion-promoting proteins in blood (e.g. fibronectin, vitronectin and various collagen types) bind to integrins through an RGD-dependent pathway (Ruoslahti, 1996). But, there are also different domains within these proteins that have the ability to bind to integrins and provoke integrin-mediated cellular signalling cascades. Briefly, integrin-mediated cell attachment to ECM initiate several intracellular events, including protein kinase C and Na^+/H^+ antiporter, phophoinositide hydrolysis, tyrosine phosphorylation of membrane and intracellular proteins (Plopper et al., 1995). These mechanisms result in mitogen stimulated protein kinase activation by altering the cellular pH and calcium concentration. Thus, intracellular communication is established and the extracellular signal is transmitted to the nucleus. The cell responds to this integrin-mediated signal through migration, proliferation and differentiation (Sawyer et al., 2005). The

response of osteogenic cells to the initial protein layer on the implant surface is very important for the activation of osteoblastic pathways through integrin-mediated signalling, thereby for optimal osseointegration. Therefore, the development of an implant surface, that favours an osteogenic protein conformation on itself, has been one of the major areas of implant surface science. In the recent decades, various approaches have focused on understanding the effect of the surface characteristics on the protein dependent mechanisms of cell adhesion, proliferation, differentiation and bone matrix deposition, aiming at the development of novel implant surfaces.

3. Surface treatments for enhanced osseointegration

The surface of a titanium implant plays a crucial role in determining the biological response of the host bone for several reasons (Fig.1.). The surface of titanium is the only region in contact with the bone, and is always different in characteristics from the bulk. Therefore, mainly the characteristics of the surface govern the healing mechanisms at the bone-implant interface. For enhancing the biomechanical anchorage of the implant and for promoting osseointegration at the histological level, the modification of surface topography or the coating of titanium with bioactive materials has captured the interest of many scientists, clinicians, and manufacturers as well (Oshida, 2007). Commonly used techniques to alter surface properties of titanium are as follows: sand-blasting (Rosa &Beloti, 2003), acid-etching (Juodzbalys et al., 2007), alkali-etching (Kim et al., 2000), plasma spraying (Vercaigne et al., 1998), electropolishing (Harris et al., 2007), anodic oxidation (Yamagami et al., 2005), hydroxylapatite (HA) (Dalton & Cook, 1995) and calcium phosphate (CaP) (Liu et al. 2004) coatings, etc. Such modifications have, in general, resulted in several changes in surface properties, including morphology, physicochemical composition and surface energy. Although various studies have shown that surface alterations, such as the resulting roughness, have improved the outcome of osseointegration (Abrahamsson et al., 2001; Buser et al., 1991), it is still poorly understood that either this enhancement was caused due to topographical reasons or fabrication-related changes in surface composition and wettability characteristics. Furthermore, the majority of published papers lack of an adequate surface characterization, as stated in the literature (Wennerberg & Albrektsson, 2009), that makes the evaluation of the effect of unique surface properties on osseointegration. However, general observations using different *in vitro* and *in vivo* studies can be still made to evaluate the effect of surface properties *per se* (topography, composition, crystal structure and wettability) on osseointegration. Commonly, two categories of surface properties are suggested to be the most important aspects for affecting the tissue response to the implant: surface topography and chemical composition. Therefore, this chapter focuses mainly on these two categories.

3.1 Topographical features of titanium surfaces

Any dental implant, once inserted into the host bone, first comes into contact with tissue fluids. The adsorption of biomolecules and the subsequent interactions of cells on an implant surface determine the fate of the implant. For many years, the "machined" surface of the Brånemark implant was the gold standard for implant surfaces. However, the decreased success rates of these smooth textured implants at compromised sites (Jaffin & Berman, 1991), especially at the posterior maxillae, motivated the approaches for finding better implant surfaces promoting bone formation. In the search for methods modifying

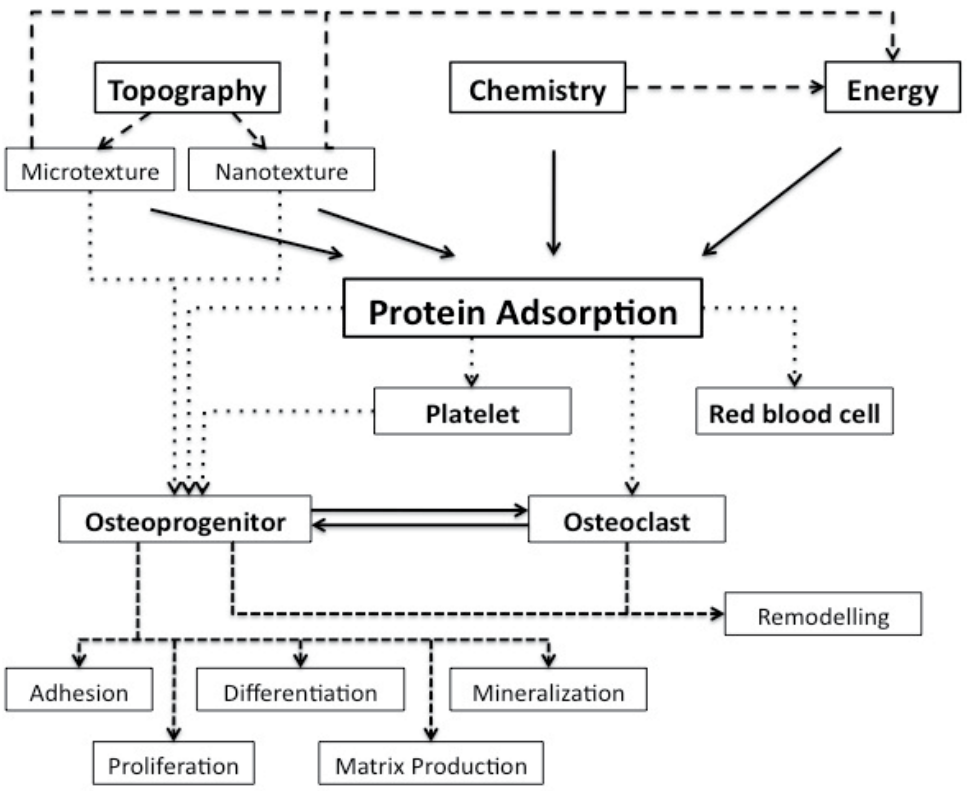

Fig. 1. Effect of submacron surface characteristics of the implant on the osteogenic response

surface properties to achieve better osseointegration, much attention has been focused on increasing the surface roughness for improving the interfacial retaining mechanics. The main idea behind the establishment of such a rough topography was to increase the surface area of the implant adjacent to the bone and to improve the cell adhesion to the surface, thereby achieving higher bone-to-implant contact and better biomechanical integrity (Oshida et al., 1994; Cooper, 2000). Until now, extensive number of papers has been published on this topic. Numerous studies have shown that moderate roughness and complex microtopographies are important for the likely development of bone-implant interfaces and for the enhanced osseointegration of titanium implants (Abrahamsson et al., 2001; Buser et al., 1991). Compared with smooth surfaces, implants with rough surfaces exhibited greater contact with bone (Al-Nawas et al., 2008). However, systematic reviews (Shalabi et al., 2006) and the Cochrane collaboration (Esposito et al., 2007) were not able to find any clinical evidence supporting the positive effect of increasing surface roughness on osseointegration. Although it has been suggested that a moderate rougness value (R_a, between 1 and 2 μm) is optimal for bone-implant interactions (Wennerberg & Albrektsson, 2000), there is still no suitable roughness to specific metallic biomaterials. The effect of surface topography, especially the microroughness, on bone response around dental implants has been reviewed intensively elsewhere (Cooper, 2000; Oshida, 2007; Wennerberg & Albrektsson, 2009).

From an *in vitro* standpoint, the response of cells and tissues at implant interfaces can be affected by the surface topography (Gaydos et al., 2000; Moore et al., 2000). Culture models

provide better conditions to test the direct interactions between the implant surfaces and cells. Surface roughness in the range from 1 to 10 μm influences the interface biology, since it is the same order in size of various cell types responsible for bone-implant healing. The literature contains plentiful information about the effects of micro-scale textures on cells and tissues. However, due to multiplicity of roughening protocols and cell culture models in literature, it is difficult to draw an ultimate conclusion about the effect of microroughness on cellular activities. In order to obtain ideal cell colonization on the surface, an increase in cell proliferation is an important parameter when evaluating the effectiveness of surface micro-morphology. There are limited studies that documented better cellular proliferation on surfaces with microrough topography (Deligianni et al., 2001; Marinucci et al., 2006). Mustafa et al. (2001) blasted the machined titanium surfaces with 63-90 μm, 106-180 μm and 180-300 μm TiO2 particles and obtained test models having different microtopographies. They showed that on all microrough surfaces the cell proliferation was better compared with machined surfaces and they found an insignificant increase in cell proliferation parallel to increasing roughness. However, most studies until now argued that surface microroughness influenced cell proliferation negatively (Anselme et al., 2000a; Linez-Bataillon, 2002; Sader et al., 2005). Anselme et al. (2000b) mechanically polished and sand-blasted Ti-6Al-4V surfaces with 500 μm or 3mm alumina particles, so they created surfaces having increased roughness values. They documented that increasing roughness caused a significant decrease in cell proliferation and they based this negative correlation upon the change in surface elemental composition (AlO_x contamination) after blasting with alumina particles. However, there are also studies that didn't found any negative relation between alumina contamination and biological response (Wennerberg et al., 1996).

To evaluate the effect of surface microtopography on osteogenic cell functions, Boyan and her colleagues (Boyan et al., 1998, 2001; Schwartz et al. 2001a) established an experimental study design that consists of pure titanium disks having increased roughness values. They produced dual acid-etched (PT), dual acid–etched and corrundum-blasted (SLA) and titanium plasma sprayed (TPS) test groups. Other researchers (Lossdörfer et al., 2004) that were using the same protocol revealed that on rough surfaces such as SLA and TPS, the cell attachment and ^{3}H-tymidin incorporation, an important finding of cell proliferation, was decreased compared with smoother PT surfaces. Kieswetter et al. (1996) asserted that this decrease in cell proliferation was a sign of a more differentiated cellular phenotype in culture, as described in the theory by Lian and Stein (1992). To test this hypothesis, Boyan et al. (2002) cultured fetal rat calvarial cells on PT, SLA and TPS surfaces and documented that after 14 days of culture on rough surfaces, in spite of decreased cell proliferation, the bone nodule formation and ALP specific activity which is an early marker of osteogenic differentiation was significantly increased. Besides, it has been shown that on surfaces with rough microtopographies, osteoblasts secrete factors, such as osteoprotegerin (OPG), receptor activator of nuclear factor kappa B ligand (RANKL), prostoglandins (PGE_1 and PGE_2) and TGF-β1, that enhance osteoblast differentiation while decreasing osteoclast formation and activity (Lossdörfer et al., 2004). These results indicate that on rough surfaces osteoblasts exhibit a more differentiated phenotype, even though the proliferation is negatively affected.

The mechanism by which topography influences osteoblast differentiation appears to be mediated by integrin signaling (Olivares-Navarrete et al., 2008) and mitogen-activated proteine kinase (MAPK) pathways (Schwartz et al., 2001b). The topography has also an effect on subsequent expression of transcription factors, ECM protein genes and cytokines

(Balloni et al., 2009; Marinucci et al., 2006). However, the *in vivo* interaction of osteogenic cells with an implant surface is different from the *in vitro* culture studies. Therefore, two essential aspects should also be taken into consideration when testing titanium surfaces under *in vitro* conditions. First, the osteoblast-surface interaction studies do not provide information about the role of surface topography on the initial platelet activation within the associated blood clot. The platelet adhesion on the surface and the subsequent release of platelet-derived growth factors is critical for the recruitment of bone-forming cells into the interface. Park et al. (2001) have demonstrated, that platelet adherence, platelet-derived microparticle (MP) formation and P-selectin expression were enhanced on microrough surfaces, and suggested that this increased activation of platelets may be the reason for up-regulation of osteogenic responses during bone healing. Second, the initial adsorption of blood-derived molecular factors influences the attachment of osteogenic cells on titanium implants. The plasma protein adsorption behaviour is also affected by the surface topography. The effect of surface roughness on protein adsorption was investigated by determining the adsorption of bovine serum albumin (BSA) and fibronectin, from single protein solutions on rough and smooth Ti-6Al-4V surfaces (Deligianni et al, 2001). It was reported that the rough substratum bound a higher amount of total protein (from culture medium supplied with 15% serum) and fibronectin (10-fold) than did the smooth one. Sela et al. (2007) showed that the increase of the 3D surface area through acid-etching and blasting of titanium has resulted in increased adsorption of plasma proteins.

In general, a huge number of animal investigations also agree on the positive effect of surface roughening protocols on osseointegration. Numerous animal models and surgical protocols were performed to evaluate the bone response around dental implants. Until now, the majority of the studies have focused on commercially available implant surface designs and compared them mostly with machined controls. Various microrough profiles established by different surface methodologies, such as blasting, etching, blasting/etching, plasma spraying and oxidation, were found to be stronger integrated in bone when compared with machined surfaces (Wennerberg & Albrektsson, 2009). Unfortunately, it is very difficult to compare different studies, because wound healing conditions and kinetics differ between animal models. Also, the topographical parameters vary between different microrough surfaces among previously published studies; therefore, it is impossible to obtain and establish an appropriate roughness profile of titanium for better osseointegration. Besides, it should be not neglected that procedures for the establishment of microroughness also result in changes in the surface chemistry and hence it makes the evaluation of the unique effect of roughness on the bone response (Wennerberg & Albrektsson, 2009).

3.2 Physicochemical composition of titanium surfaces

Beside topographical features of titanium surfaces, the chemistry, wettability and charges are also important parameters affecting the extent of bone response (Elias et al., 2008). If a titanium implant is inserted into the host bone, titanium dioxide should be considered as an interacting surface, rather than its bulk. Due to high affinity to oxygen, a very thin oxide film is formed on titanium when exposed to air (Kasemo & Gold, 1999). Titanium dioxides are different from the metallic Ti and have properties similar to ceramics. The biocompatibility of titanium is therefore the result of the chemical stability and corrosion resistance of its dense and protective oxide film (Healy & Ducheyne, 1992). The crystal structure of this film is believed to be important for the success of implant integration.

Although marketed biomedical titanium implants mostly exhibit anatase or rutile type crystal phase, amorphous structure can be also formed on titanium following electrochemical procedures. For example, Sul et al. (2001, 2005) investigated several microarc oxidized implant surfaces having different crystal structures (amorphous, anatase, anatase-rutile mixture) in rabbit tibia model. Both anatase and anatase/rutile surfaces exhibited better torque resistance values compared with amourphous ones. It has been stated that, beside the titania crystal structure, also the microporous topography and oxide thickness has a positive effect on the positive outcome of bone response. These results were also confirmed by other *in vitro* studies. Anatase or rutile surfaces showed better cellular responses, such as increased adhesion, proliferation, expression of osteoblastic markers (procollagen type I peptide, osteocalcin and alkaline phosphatase) and mineralized nodule formation, compared with amorphous ones (Li et al., 2004; Saldana et al., 2005).
While the crystal structure of titanium can be changed following various thermal and non-thermal treatments, the wettability characteristics of the surface is also altered with respect to this modification. Also, various attempts have tried to find an optimal surface wettability profile for achieving better bone response. According to the literature, highly hydrophilic surfaces are proposed to be more desirable than hydrophobic ones (Junker et al., 2009; Schwarz et al., 2009). Preliminary *in vitro* studies indicated the hydrophilic nature of titanium surfaces significantly influences the cell differentiation and growth factor production positively (Rausch-Fan et al., 2008; Zhao et al., 2007). Besides, animal studies also shown that on hydrophilic surfaces osseointegration can be established at an early period (Bornstein et al., 2008; Buser at al., 2004; Schwarz et al., 2007). However, there are also contradictory results from other *in vitro* studies. For example, Kern et al. (2005) sintered titanium surfaces at 750° C for 90 min to transform amorphous crystal structure into anatase and found no significant differences in osteoblast adhesion despite of changes in hydrophilicity and oxide structure. Le Guehennec et al. (2008) cultured MC3T3-E1 cells on alumina blasted, biphasic calcium phosphate blasted (BCP-Ti) and commercial SLA surfaces and were not able to demonstrate any significant differences between hydrophobic SLA and hydrophilic BCP-Ti surfaces in their MTS and ALP assays. Bauer et al. (2008) cultured rat MSCs on nanotubular titanium surfaces having different wettability characteristics and found an increased cell attachment on super-hydrophobic surfaces compared with super-hydrophilic ones. Due to the ambiguous results in the literature, it is difficult to state that the hydrophilicity of surface is the only reason for enhanced outcomes. The microtopography, chemistry and wettability must be taken together into consideration.

4. Novel trends at the bone-implant interface

4.1. Biomimetic coating of titanium surfaces with calcium phosphates

Beside its excellent biocompatibility and biomechanics, titanium itself is not bioactive. To overcome the limited bioactivity of titanium and to improve the *de novo* bone formation around these implants, research was focused on preparing calcium phosphate (Ca-P) coatings on titanium and its alloys. It has been well established that the Ca-P based coating of titanium favours the bone response compared with the uncoated titanium (Chang et al., 1999a; Wheeler, 1996). Additionally, Ca-P based surfaces bind more attachment proteins, such as fibronectin and vitronectin, for the integrin mediated binding action of osteoprogenitors compared to titanium surfaces (Kilpadi et al., 2001). Several techniques were described for the deposition of Ca-P coatings on titanium implants, including ion beam

deposition, plasma spraying, sol-gel methods, laser deposition, radiofrequency sputtering, biomimetic deposition and electrostatic spray deposition (Ong & Chan 2000). Among these procedures, plasma spraying is the most popular method for the deposition of Ca-P coatings on titanium implants. But this technique has some drawbacks, including the difficulty in controlling the coating structure, the weakening of the coating-implant interface and the high temparature of the deposition process (Cofino et al., 2004; Dalton & Cook, 1995)

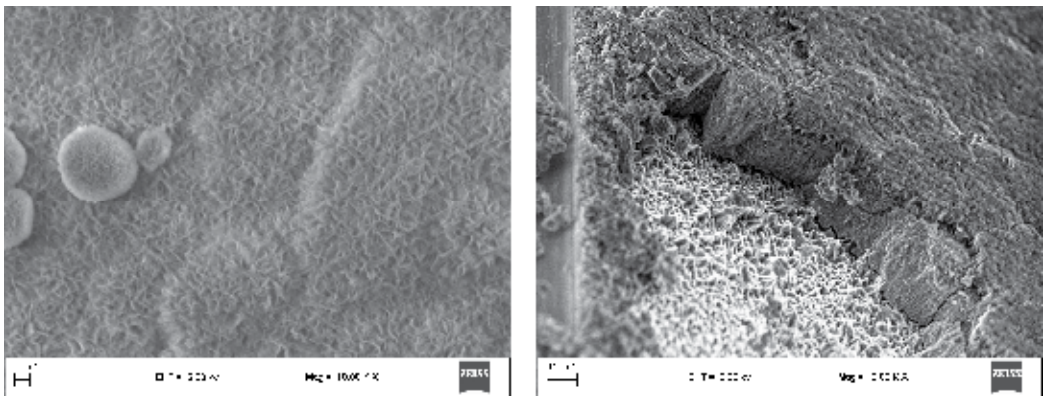

Fig. 2. Top and cross sectional SEM images of biomimetic Ca-P coatings

Biomimetic calcium Ca-P coating procedure, first introduced by Kokubo et al. (1990), is one of the novel approaches for preparing bioactive calcium phosphate layers on titanium surface. This technique involves the precipitation of bone like apatite crystals from a simulated body fluid (SBF) onto titanium surfaces under physiological temperature (37^{o}C) and pH (7.4) that mimics the normal conditions in human blood plasma. To shorten the immersion period of the substrate within calcium phosphate containing solution, the method was further revised by a group of investigators (Barrere et al., 2001; Liu et al., 2004) Thus, a calcium phosphate lattice can be formed on titanium surfaces in order to provide osteoconductive properties to the substrate (Fig. 2.). Another advantage of this simple and economical procedure is that the biomimetic surface acts as a tissue-engineering scaffold and this process can be combined with deposition of signalling molecules, like growth factors and bone morphogenetic proteins (Liu et al., 2004, 2007; Ramazanoglu et al., 2011).

4.2 Biomolecular coatings of titanium surfaces

Beside the topographical and physicochemical modifications, biochemical approaches to immobilize different bioactive molecules, peptides, proteins and others on dental implants attracted the interest of many scientists. The main idea behind these methodologies was as follows: (1) to eliminate the adsorption of proteins that would result in the adhesion of unspecific cells leading to fibrous integration; (2) to enhance the specific attachment of osteogenic cells for the establishment of a tight bone-implant interface; (3) to provide integrin-mediated signals for provoking the bone healing mechanisms. For this purpose, various immobilization methods were utilized, including physical adsorption (Wikesjö et al., 2008), incorporation into Ca-P lattice (Liu et al., 2004, 2007; Ramazanoglu et al., 2011), covalent attachment (Bagno et al., 2007), self-assembly of monolayers (Heijink et al., 2008) and electrochemical methods (Beutner et al., 2010). Complete description of these methods is beyond the scope of this chapter and reviewed intensively elsewhere (Beutner et al., 2010).

However, the organic molecules used for bio-functionalization of titanium-based materials are of importance for orientating the tissue response. Especially, extensive studies have been performed on binding ECM proteins and their peptide sequences to titanium to promote osteogenic cell adhesion. Although the coating of titanium with a single protein has resulted in enhancement of cellular adhesion (MacDonald et al., 2004), research has mainly focused on immobilizing short cell binding motifs within these ECM molecules due to their structural integrity (Morra, 2006). In particular, the RGD motif, as discussed before, is one of the most studied protein sequence capable of promoting cell adhesion and thereby initiating intracellular signalling cascades through multiple integrins including $\alpha_v\beta_3$ and $\alpha_5\beta_1$ (Ruoslahti, 1996). This motif is usually covalently attached to titanium using silanization (Bagno et al., 2007) or functionalized using polymer chemistry (Tosatti et al., 2004), and has been reported to increase osteoblast attachment and proliferation (Schuler et al., 2006). While several *in vivo* studies (Elmengaard et al., 2005; Kroese-Deutman et al., 2005) demonstrated better osseointegration results, others did not find any significant enhancement for the RGD functionalization (Petrie et al., 2008; Schliephake et al., 2009).
Another approach for enhancing the osseointegration is the delivery signalling molecules, especially the osteogenic growth factors. The concept of coating implant surfaces with osteogenic growth factors, such as bone morphogenic proteins (BMPs), to enhance osseointegration has been documented in several studies using different delivery strategies (Becker et al. 2006; Sykaras et al. 2004; Wikesjö et al. 2008). The bone forming potential of BMPs around implants have been shown in an experimental study using an atelopeptide type-I collagen carrier as a coating (Bessho et al. 1999). However, other studies utilizing a collagen/chondroitin sulphate (CS) carrier system on titanium found an enhancement of bone volume density (BVD) and bone-implant contact (BIC) around coated implants, but they were not able to show any significant difference between bare collagen/CS and BMP integrated coatings (Schliephake et al. 2005; Stadlinger et al. 2007). Due to the variation of findings between different studies, it can be stated that there is still a need for an optimal 3D carrier on the implant surface to provide sufficient retention of BMPs at the repair site. As mentioned before, the biomimetic coating method has been shown to have the potential of being an appropriate BMP carrier on the titanium surface. It has been demonstrated that BMP-2 incorporated in calcium phosphate coatings can induce bone formation at an ectopic site and the sustained release of BMP-2 from this coating has an important effect on the osteoinductivity of the material (Liu et al. 2005). However, studies using this methodology failed to show a significant effect of biomimetic coated implants with incorporated BMP-2, VEGF or their combination on osseointegration, and it has been stated that an ideal dose of BMP-2 or VEGF, which resembles the growth factor release from natural bone matrix should be achieved for enhancing the osseointegration (Liu et al. 2007; Ramazanoglu et al., 2011).

4.3 Nanotopographical modification of titanium surfaces

The structures encountered by osteoblasts in the human body are not only in micrometer scale, since bone is made up by nanostructures. Thus, there is a need to produce better implant materials having also nanometer roughness. Several studies have suggested that nanophase materials produced from various chemistries, such as metals, polymers, composites and ceramics, improved cellular activities when compared with conventional microrough materials (Gutwein & Webster, 2004; Webster & Ejiofor, 2004). Nanobiomaterials have an increased percentage of atoms and crystal structures, and also

provide a higher surface area than the conventional ones. Thus, nanoscale surfaces possess high surface energy leading to increasing initial protein adsorption that is very important in regulating the cellular interactions on the implant surface. Webster et al. (2001) suggested increased osteoblast adhesion on nanophase materials. Numerous studies have shown that osteoblasts cultured on nanophase biomaterials exhibited better osteogenic behaviour, including adhesion, ECM production and mineralization, than on conventional materials (Elias et al., 2002; Price et al., 2003).

In recent years, several methods have been also developed to produce nanoscale structures on titanium surface. While irregular nanomorphologies can be established using solution chemistry (Mendonça et al., 2010), the electrochemical anodization of titanium is the most popular and novel strategy to produce controlled structures (including nanotubes, pillar-like nanostructures, and nanodots) on implant surfaces for load bearing approaches (Oh et al., 2006; Sjöström et al., 2009). Especially, the titania nanotube arrays are one of the most promising candidate of titanium nanosurfaces for dental implantology (Fig. 3.). Several *in vitro* studies have demonstrated that cells cultured on these nanotubular surfaces showed higher adhesion, proliferation, ALP activity and bone matrix deposition (Oh et al., 2006; Popat et al., 2007a).

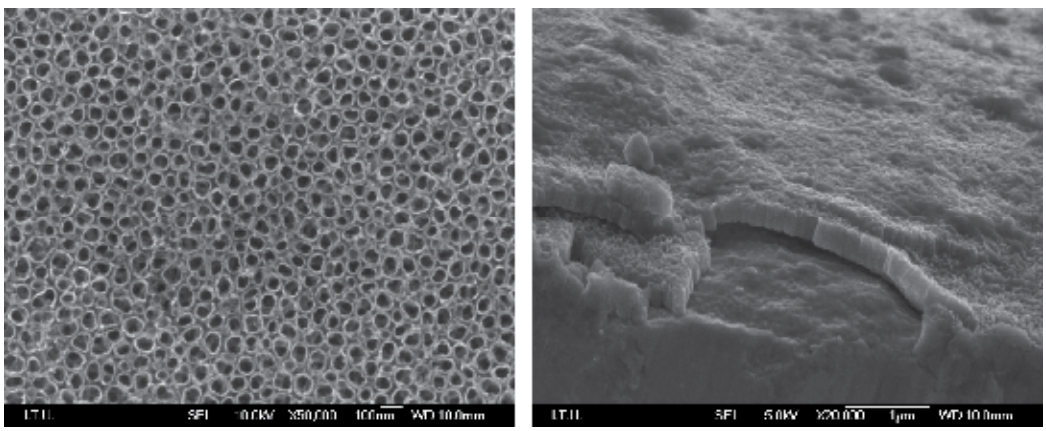

Fig. 3. Top and cross sectional SEM images of titania nanotubes

These increased *in vitro* cellular activities for titania nanotubes also translated to *in vivo* bone bonding. Nanotubular surfaces significantly improved bone bonding strength by as much as nine-fold compared with gritblasted surfaces, and histological analysis revealed greater bone-implant contact and collagen type I expression confirming the better *in vivo* behaviour of titania nanotubes (Bjursten et al., 2008; von Wilmowsky et al., 2008). It has been also shown that various nanomorphological features of titania nanotubes, such as length, diameter, wall thickness, have a major impact on the cellular reponses, providing the evidence that cells are susceptible to nanoscale dimesions (Brammer et al., 2009; Park et al., 2009). Besides, nanotubular structures on titanium provide a suitable infrastructure for loading and subsequent releasing of antibiotics (Aninwene et al., 2008; Popat et al., 2007b) or for immobilizing biosignalling molecules for better osseointegration (Balasundaram et al., 2007). However, there is still a need for additional studies that would optimize the fabrication of nanotubes for better bioactivity.

5. Future trends and concluding remarks

Nowadays, patients can be treated dental implants with a success rate above 97 %. Although novel approaches were able to accelerate and enhance the osseointegration, the healing limits of the body, which make the immediate loading challenging, should not be neglected. Osseointegrated or ankylotic titanium implants don't behave like natural teeth. Since they lack a periodontal ligament, they only had tenth of the mobility of the natural teeth (Schulte, 1995). Axial and horizontal loads bellow a subjective tolerance limit can be compensated by the natural periodontium, but such loads on osseointegrated implants would lead to local disruption of the bony interface. Additionally, it has been reported that the defensive capacity of the peri-implant tissue against bacterial invasion is inferior to that of the natural tooth, that make them more prone to bone loss (Chang et al., 1999b). A third disadvantage of the osseointegrated implant is the absence of a periodontal neurophysiological mechanoreceptive system for the biocybernetic control of the stomatognatic system (Jacobs & Van Steenberghe, 2006).

Considering these drawbacks, establishment of a periodontal ligament surrounding an implant, termed as bio-root, would provide the ideal condition for implant-supported treatments in future. To overcome the above mentioned disadvantages of the dental implants, several *in vivo* experiments attempted to create a periodontal ligament around these implants by placing them adjacent to retained tooth roots (Urabe et al., 2000; Warrer et al., 1993). Although they were able to partially regenerate the periodontal ligament consisting of cementum, periodontal ligament and alveolar bone, the application of these methods in patients seems to be impossible due to technical and physical factors. Furthermore, several studies have reported that periodontal ligament cells cultured on titanium implants can produce a periodontal ligament-like tissue when placed in the jaws of animals (Choi, 2000; Gault et al., 2010; Lin et al., 2011). Although it has been shown that generating a periodontal-like tissue around implants may be experimentally possible, also in human trials (Gault et al., 2010), approaches until now were not able to innovate a predictable and feasible method for producing dental implants with periodontal-like ligament.

Furthermore, gradient functional concept (GFC) on materials and structures has been receiving special attention not only in industrial applications, but in dental as well as medical fields. Particularly, when such structures and concepts are about to be applied to implants, its importance becomes more clinically crucial. For example, the majority of implant mass (implant core portion) should be strong and tough, so that occlusal force can be smoothly transferred from the placed implant to the receiving hard tissue. However, the surface (implant case portion) needs to be engineered to exhibit some extent of roughness. From such macro-structural changes from bulk core to the porous case, again the structural integrity should be maintained. The GFC can also be applied for the purpose of having a chemical (compositional) gradient. Ca-, P-enrichment is not needed in the interior materials of the implants. Some other modifications related to chemical dressing or conditioning can also be utilized for achieving gradient functionality on chemical alternations on surfaces as well as near-surface zones (Oshida, Y.; 2007).

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4

Dental Implant Surface Enhancement and Osseointegration

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1. Introduction

The long-term success of dental implants largely depends on rapid healing with safe integration into the jaw bone. Geometry and surface topography are crucial for the short- and long-term success of dental implants. Implant surfaces have been developed in the last decade in a concentrated effort to provide bone in a faster and improved osseointegration process. Several surface modifications have been developed and are currently used with the aim of enhancing clinical performance, including turned, blasted, acid-etched, porous-sintered, oxidized, plasma-sprayed and hydroxyapatite-coated surfaces, as well as combinations of these procedures. Among the several parameters influencing the success of the implants, implant-bone interface plays an important role in prolonging the longevity and improving the function of the implant-supported prosthesis. There are several modalities to improve implant-bone interface to promote faster and more effective osseointegration.

Osseointegration, defined as a direct structural and functional connection between ordered, living bone and the surface of a load-carrying implant, is critical for implant stability, and is considered a prerequisite for implant loading and long-term clinical success of endosseous dental implants. Osseointegration of titanium implant surfaces is dependent upon both physical and chemical properties (Sul *et al.*, 2005). This structural and functional union of the implant with living bone is strongly influenced by the surface properties of the titanium implant. As titanium and its alloys cannot directly bond with living bone, modification of the implant surface has been proposed as a method for enhancing osseointegration.

Scientific research works to assess the influence of implant surface properties on bone healing have identified several factors which are important for osseointegration. The surface characteristics of implant which influence the speed and strength of osseointegration include surface chemistry, topography, wettability, charge, surface energy, crystal structure

and crystallinity, roughness, chemical potential, strain hardening, the presence of impurities, thickness of titanium oxide layer, and the presence of metal and non-metal composites. Among these, wettability and free surface energy of an implant surface are considered to be very crucial. The implant surface, including topography, chemistry, surface charge, and wettability, has been described as an important factor to influence osseointegration. The influence of physical properties such as surface topography and roughness on osseointegration have translated to shorter healing times from implant placement to restoration (Cochran *et al*., 2002). The biologic basis underlying these clinical improvements continues to be explored (Kim *et al*., 2005, Lossdorfer *et al*., 2004). Albrektsson *et al*. (1981) suggested six factors that are particluarly important for the establishment of reliable osseointegration: implant material, implant design, surface conditions, status of the bone, surgical technique, and implant loading conditions.

2. Biology of wound healing following implant placement

Wound healing involves a highly orchestrated sequence of events which is triggered by tissue injury involving soluble mediators, blood cells, extracellular matrix and parenchymal cells. Ultimately, it culminates in either partial or complete regeneration or repair. Fracture healing in bone occurs in four phases which include inflammation, soft and hard callus formation, and remodeling. Following a fracture, blood coagulation and hematoma formation takes place. This is followed by inflammation. Various chemical mediators such as thrombin and growth factors released by activated leukocytes and platelets in the hematoma serve as chemotactic signals to many cell types which play an important role in bone healing. Unlike soft tissue healing, bone healing does not lead to scarring. Instead it leads to restoration of the bony tissue. During successful implantation, insertion of metal implants into cortical bone eventually leads to complete healing. Following implant placement, unlike in fracture healing, implants extend into and persist in the marrow spaces and this may have a bearing on the healing process. Although implant healing must to some extent adjust to the presence of the implant, ultimately, sound bony tissues will be completely restored during wound healing. This adjustment involves imbedding the implant surface in a layer of bone, continuous with the original bone.

Wound healing around a dental implant placed into a prepared osteotomy follows three stages of repair- Initial formation of a blood clot occurs through a biochemical activation followed by a cellular activation and finally a cellular response(Stanford and Schneider, 2004). During surgery, dental implant surfaces interact with blood components from ruptured blood vessels. Within a short period of time, various plasma proteins such as fibrin get adsorbed on the material surface. Fibrinogen is converted to fibrin and the complement and kinin systems become activated. As in fracture healing, the migration of bone cells in peri-implant healing will occur through the fibrin of a blood clot. Since fibrin has the potential to adhere to almost all surfaces, it can be anticipated that the migration of osteogenic cell populations towards the implant surface will occur. However, as the migration of cells through fibrin will cause retraction of the fibrin scaffold, the ability of an implant surface to retain this fibrin scaffold during the phase of wound contraction is critical in determining whether the migrating cells will reach the implant surface. Activation of platelets occurs as a result of interaction of platelets with the implant surface as well as the fibrin scaffold and this leads to thrombus formation and blood clotting.

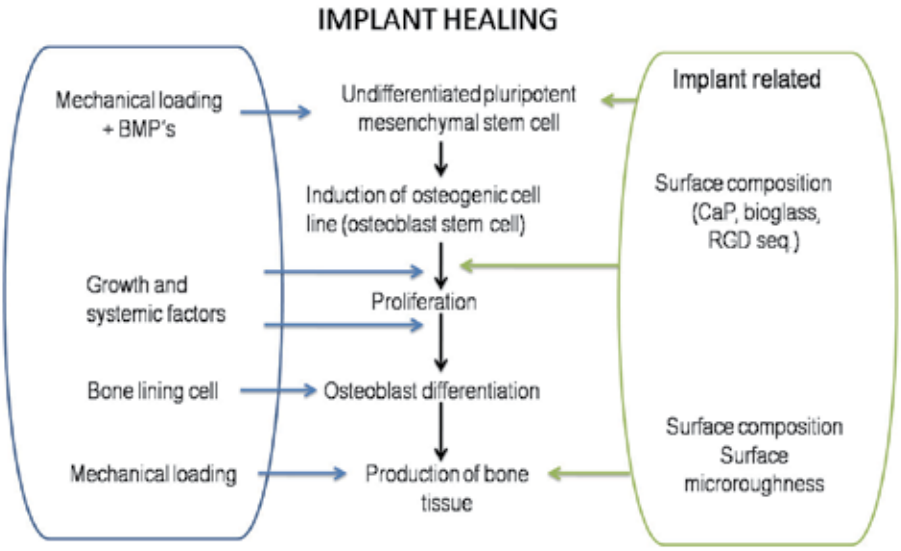

Fig. 1. The implant healing process - The surface composition, roughness and topography are interrelated surface characteristics that influence the biological response to an implant.

Moreover, platelets are a rich source of many growth and differentiation factors which play a key role in the wound healing process by acting as signaling molecules for recruitment and differentiation of the undifferentiated mesechymal stem cells at the implant surface. Plasma also contains dissolved substances such as glucose, amino acids, various ions, cholesterols, and hormones which are needed for the viability of cells and tissues. Blood interactions with implants lead to protein adsorption, which is dependent on the surface properties of the material. As hydrophilic surfaces are better for blood coagulation than hydrophobic surfaces, dental implants have been developed with high hydrophilic and rough implant surfaces which exhibit better osseointegration than conventional ones. Adsorption of proteins such as fibronectin and vitronectin on the surface of dental implants could promote cell adhesion and osseointegration. During the initial remodeling, a number of immune cells mediate early tissue response followed by migration of phagocyte macrophages. These cells initially remove the necrotic debris created by the drilling process and then undergo physiological changes which lead to expression of cell surface proteins and production of cytokines and pro-inflammatory mediators. This cytokine-regulated cellular recruitment, migration, proliferation and formation of an extracellular matrix on the implant surface can be influenced by the macrophages. These cells express growth factors such as fibroblast growth factor (FGF-1, FGF-2, FGF-4), transforming growth factors, epithelial growth factor as well as bone morphogenetic proteins (BMPs). The end result of this complex cascade is promotion of a wound healing process that includes angiogenesis.

3. Influence of implant surface topography on osseointegration

Dental implant quality depends on the chemical, physical, mechanical, and topographic characteristics of the surface (Grassi *et al.*, 2006). These different properties interact and determine the activity of the attached cells that are close to the dental implant surface.

Dental implants have been designed to provide textures and shapes that may enhance cellular activity and direct bone apposition (Huang *et al*., 2005). Osteogenesis at the implant surface is influenced by several mechanisms. A series of coordinated events, including cell proliferation, transformation of osteoblasts and bone tissue formation might be affected by different surface topographies (Shibli *et al*., 2007). Amount of bone-to-implant contact (BIC) is an important determinant in long-term success of dental implants. Consequently, maximizing the BIC and osseointegration has become a goal of treatment, which is enhanced by implant surface roughness (Soskolne *et al*., 2002).

Albrektsson et al (1981) recognized that among the factors influencing BIC such as topography, chemistry, wettability and surface energy the most important is wettability. Surface wettability is largely dependent on surface energy and influences the degree of contact with the physiological environment (Kilpadi and Lemons, 1994, Zhao *et al*., 2005). Several evaluations have demonstrated that implants with rough surfaces show better bone apposition and BIC than implants with smooth surfaces (Buser *et al*., 1999, Cochran *et al*., 2002).

Surface roughness also has a positive influence on cell migration and proliferation, which in turn leads to better BIC results, suggesting that the microstructure of the implant influences biomaterial–tissue interaction (Matsuo *et al*., 1999, Novaes *et al*., 2002). Implant surface properties are likely to be of particular relevance to the chemical and biological interface processes in the early healing stages after implantation. It is generally accepted that these early stages are likely to have an effect on the host response to the implant and, therefore, the long-term outcome and success of the treatment. Surface chemistry has the potential to alter ionic interactions, protein adsorption, and cellular activity at the implant surface (Schliephake *et al*., 2005). These modifications may subsequently influence conformational changes in the structures and interactive natures of adsorbed proteins and cells. Furthermore, within the complexities of an *in vivo* environment containing multiple protein and cellular interactions, these alterations may differentially regulate biologic events. Modifications to the implant surface chemistry may lead to alterations in the structure of adsorbed proteins and have cascading effects that may ultimately be evident at the clinical level.

In vivo evidence has supported the use of alterations in surface chemistry to modify osseointegration events. Specifically, an investigation utilizing sandblasted, large-grit, acid-etched (SLA) surfaces that were chemically different but had the same physical properties was conducted to assess BIC as a measure of osseointegration. The chemically enhanced SLA surface demonstrated significantly enhanced BIC during the first 4 weeks of bone healing, with 60% more bone than the standard SLA surface after 2 weeks (Buser *et al*., 2004). The chemical modifications for the test SLA surface resulted in increased wettability (ie, in a hydrophilic surface rather than a hydrophobic one). Water contact angles of zero degrees were seen with the chemically enhanced surface compared to 139.9 degrees for a standard SLA surface, and the hydrophilicity was maintained after drying. The chemical composition of the surface was also altered, including a 50% reduction in carbon concentration compared with the control implant surface (Rupp *et al*., 2006).

4. Interaction between cells and the surface of the dental implants

Since surface properties of biomaterials are important parameters influencing cellular reactions towards artificial materials, the properties of dental implant surfaces are extremely important in influencing the healing process leading to osseointegration and ultimate

clinical success of the implant. Surface morphology modulates the response of cells to a dental implant, and surfaces with defined microstructures may be useful for enhancement of the stable anchorage (Elias and Meirelles, 2010). Surface chemistry involves adhesion of proteins, bacteria, and cells on implants. Wettability and surface energy influence the adsorption of proteins, and increase adhesion of osteoblasts on the implant surface. The cell behavior on a hydrophilic surface is completely different from that on a hydrophobic one. A hydrophilic surface is better for blood coagulation than a hydrophobic surface. The expressions of bone-specific differentiation factors for osteoblasts are higher on hydrophilic surfaces. Consequently, dental implants manufacturers have developed high hydrophilic and rough implant surfaces which in turn exhibited better osseointegration than implants with smooth surfaces.

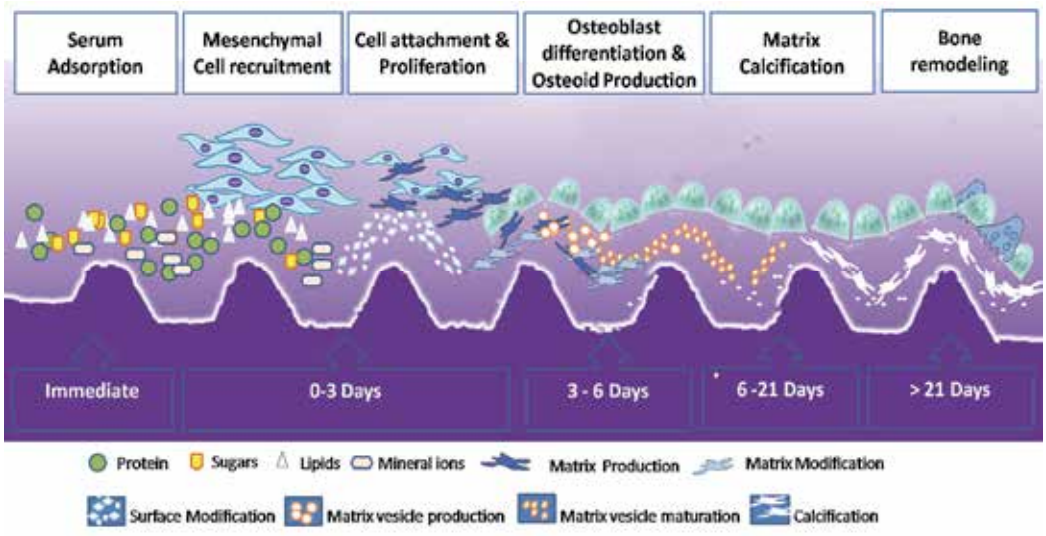

Fig. 2. Illustration showing the cellular phenomena at the implant bone interface during healing of implant

5. Implant surface topography

Implant surface topography refers to macroscopic and microscopic features of the implant surface. Although commercially pure titanium is the prime material of dental implants, the success rates of different commercially available implant systems vary. The exact reason for this is not clear. Several implant-related factors such as implant surface topography, chemical composition and surface roughness that influence osseointegration have been studied. It has been shown that titanium implants with adequate roughness may influence the primary stability of implants, enhance bone-to-implant contact, and may increase removal torque force (Wennerberg and Albrektsson, 2009).

The surface roughness of the implants can significantly alter the process of osseointegration because the cells react differently to smooth and rough surfaces. Fibroblasts and epithelial cells adhere more strongly to smooth surfaces, whereas osteoblastic proliferation and collagen synthesis are increased on rough surfaces (Boyan *et al.*, 2001). Investigators have demonstrated that while the adhesion of fibroblasts is lesser on rough surfaces, the adhesion and

differentiation of osteoblastic cells are enhanced (Wennerberg and Albrektsson, 2000). It is not clear whether the height of surface irregularities is more important than the distance between them, and which combination of these factors could improve osseointegration. Although the increase in surface roughness promotes greater mechanical anchorage, the implant–bone interface strength will not increase with the continuous increase of surface roughness.

Fig. 3. The machined and nano etched implant surface

6. Surface roughness

Surface topography plays an important role in the osseointegration of titanium implants (Le Guehennec *et al.*, 2007). In vitro and *in vivo* studies have shown that titanium surface roughness influences a number of events in the behavior of cells in the osteoblastic lineage, including spreading and proliferation, differentiation, and protein synthesis (Sammons *et al.*, 2005, Zhao *et al.*, 2006). Implant surface roughness is divided, depending on the dimension of the measured surface features into **macro, micro, and nano-roughness.**

Macro roughness comprises features in the range of millimeters to tens of microns. This scale directly relates to implant geometry, with threaded screw and macro porous surface treatments. The primary implant fixation and long-term mechanical stability can be improved by an appropriate macro roughness. This will enhance the mechanical interlocking between the macro rough features of the implant surface and the surrounding bone (Wennerberg *et al.*, 1996, Shalabi *et al.*, 2006).

Micro roughness is defined as being in the range of 1–10 μm. This range of roughness maximizes the interlocking between mineralized bone and implant surface. Studies supported by some clinical evidence suggest that the micron-level surface topography

results in greater accrual of bone at the implant surface (Junker *et al.*, 2009, Shalabi *et al.*, 2006). The use of surfaces provided with **nanoscale topographies** are widely used in recent years. Nanotechnology involves materials that have a nano-sized topography or are composed of nano-sized materials with a size range between 1 and 100 nm. Nanometer roughness plays an important role in the adsorption of proteins, adhesion of osteoblastic cells and thus the rate of osseointegration (Brett *et al.*, 2004).

6.1 Nanotopography

Surface properties play a key role in biological interactions between the implant surfaces and the host bone. Modifying surface roughness has been shown to enhance BIC and improve the clinical performance of implants. The nanometer-sized roughness and the chemistry have a key role in the interactions of surfaces with proteins and cells. These micromechanical features influence the process of secondary integration (bone growth, turnover and remodeling). At the nanoscale, a more textured surface topography increases the surface energy which in turn increases the wettability of the surface to blood, adhesion of cells to the surface, and facilitates binding of fibrin, matrix proteins, growth and differentiation factors. Nanotopography, by modulating cell behavior, can influence the process of cell migration, proliferation, and differentiation. These surfaces thus enhance the process of osseointegration by hastening the wound healing following implant placement (Dohan Ehrenfest *et al.*, 2010).

Various surface modification treatments create a nanometer-scale topography that allows the bone to grow into and maintain the implant surface under elevated shear forces. Grit blasting, anodisation, and acid etching, are the commonly used methods for modifying surface roughness of metal implants. Topographical features in the nanometer ranges may be helpful in the healing process as related to protein adsorption and cell adhesion as surface properties control the steps of adhesion, proliferation, and differentiation of mesenchymal stem cells and, thus, condition tissue integration.

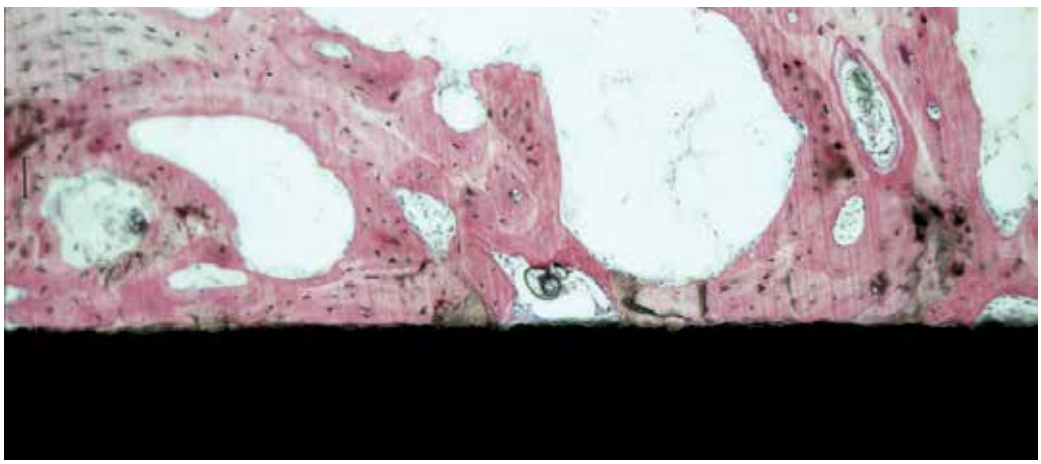

Fig. 4. Showing bone healing at the nanorough surface

Nanotopography modifications are commonly described in the literature both as nanoroughness and nanofeatures. Overall surface roughness will be modified when features are added to the surface, that is, by adding nanofeatures the surface roughness will also be

modified. However, the modifications commonly used to produce the so-called nanorough materials do not intentionally produce such nanofeatures. Reproducible surface roughness in the nanometer range is difficult to obtain with chemical treatments. Although, all surfaces may show nanotopography, not all of them will have significant nanostructures. A nanostructure is an object of intermediate size between molecular and micrometre-sized structures, and often defined between 1 and 100 nm (Dohan Ehrenfest *et al.*, 2010). Nanofabricated samples have well-defined dimensions that aim to modulate cell activity, such as migration, attachment, proliferation and differentiation.

Several investigators have revealed that nanoscale topography also influences cell adhesion and osteoblastic differentiation (Dalby *et al.*, 2008, Webster *et al.*, 1999). These findings reiterate observations demonstrating that nanotopography may directly influence adherent cell behavior (Webster *et al.*, 2000). Nanotechnology can alter the implant surface at an atomic level (Oh *et al.*, 2005) and may influence the chemical composition of these surfaces. Nanorough titanium and nanostructured titanium can enhance osteoblast adhesion and differentiation compared to their nanosmooth control. Surfaces with micro- and nanopores have also been shown to greatly enhance osseointegration. The micro- and nanoscale surface properties of metal implant, including chemistry, roughness, and wettability, could affect bone formation. It has been shown that grit-blasting with biphasic calcium phosphate (BCP) ceramic particles gave a high average surface roughness and particle-free surfaces after acid etching of titanium implants. Studies have shown that BCP grit-blasted surfaces promoted an early osteoblast differentiation and bone apposition as compared to mirror-polished titanium. By the process of anodic oxidation, nanoscale oxides may be deposited on surfaces of titanium implants. The nanoscale properties can be controlled by adjusting the parameters for anodization such as voltage, time, and shaking. Osseointegration of dental implants can be improved by the application of calcium phosphate (CaP) coating by plasma spraying, biomimetic and electrophoretic deposition. While plasma-sprayed hydroxyapatite (HA)-coated dental implants have disadvantages related to coating delimitation and heterogeneous dissolution rate of deposited phases, an electrochemical process consisting of depositing CaP crystals from supersaturated solutions releases calcium and phosphate ions from these coatings. This process helps in the precipitation of biological apatite nanocrystals with the incorporation of various proteins, which in turn, promotes cell adhesion, differentiation into osteoblast, and the synthesis of mineralized collagen, the extracellular matrix of bone tissue (Sandrine *et al.*, 2010).

Osteoclast cells are also able to resorb the CaP coatings and activate osteoblast cells to produce bone tissue. Thus, these CaP coatings promote a direct bone-implant contact without an intervening connective tissue layer leading to a proper biomechanical fixation of dental implants. Currently, titanium is the standard material for dental implants because of its excellent biocompatibility and osseointegration properties. On account of the influence of surface modifications of the titanium implants on osseointegration, such modifications have been successfully exploited to influence bone integration and long-term stability of the implant.

7. Methods of surface modifications of implants

The methods employed for surface modifications of implants can be broadly classified into 3 types-mechanical; chemical; and physical. These different methods can be employed to change the implant surface chemistry, morphology, and structure. The main objective of

these techniques is to improve the bio-mechanical properties of the implant such as stimulation of bone formation to enhance osseointegration, removal of surface contaminants, and improvement of wear and corrosion resistance.

7.1 Mechanical methods

The mechanical methods include grinding, blasting, machining, and polishing. These procedures involving physical treatment generally result in rough or smooth surfaces which can enhance the adhesion, proliferation, and differentiation of cells.

7.2 Chemical methods

Methods of surface modification of titanium and its alloys by chemical treatment are based on chemical reactions occurring at the interface between titanium and a solution. The chemical methods of implant surface modifications include chemical treatment with acids or alkali, hydrogen peroxide treatment, sol-gel, chemical vapor deposition, and anodization. Chemical surface modification of titanium has been widely applied to alter surface roughness and composition and enhance wettability/surface energy (Bagno and Di Bello, 2004).

The process of acid treatment serves to remove the surface oxide and contamination which leads to a clean and homogenous surface. The acids commonly used include hydrochloric acid, sulfuric acid, hydrofluoric acid, and nitric acid. Acid treatment of the surfaces of titanium implants results in uniform roughness with micro pits ranging in size from 0.5-2 μm, increase in surface area, and an improvement in bioadhesion. Acid treatment of implants enhances osseointegration as these implants can facilitate migration and retention of osteogenic cells at the implant surface (Takeuchi *et al.*, 2003).

Alkali treatment involves immersion of the implants in either sodium or potassium hydroxide followed by heat treatment by rinsing in distilled water. This results in the growth of a bioactive, nanostructured sodium titanate layer on the implant surface. The surface acts as a site for the subsequent in vitro nucleation of calcium phosphates when immersed in simulated body fluids (SBF). This involves an initial formation of Ti-OH by release of sodium ions from the sodium titanate layer by the process of ion exchange. This is followed by formation of calcium titanate as a result of reaction with the calcium ions from the fluid. Being negatively charged, Ti-OH groups react selectively with the positively charged calcium ions in the SBF to form calcium titanate. Phosphate and calcium ions get incorporated into this calcium titanate and get transformed into apatite which can provide favorable conditions for bone marrow cell differentiation.

Chemical treatment of implant surfaces with hydrogen peroxide results in chemical dissolution and oxidation of the titanium surface. When titanium surfaces react with hydrogen peroxide, Ti-peroxy gels are formed. The thickness of titania layer formed can be controlled by adjusting the treatment time and it has been demonstrated that, when immersed in SBF, thicker layers of titania gel are more favorable for the deposition of apatite (Tavares *et al.*, 2007).

Anodization is a process by which oxide films are deposited on the surface of the titanium implants by means of an electrochemical reaction. In this process, titanium surface to be oxidized serves as the anode in an electrochemical cell with diluted solution of acids serving as the electrolyte. The thickness of the oxide layer can be altered by altering the parameters

of the electrochemical process and it has been shown that these anodized surfaces demonstrate improved adhesion and bonding.

The sol-gel process used to deposit ceramic coatings can be employed to deposit HA coatings on the implant surface. This results in thin layers of less than 10 μm thickness. This process improves the biological activity of the titanium implants and contributes to enhanced bone formation and osseointegration. Materials such as TiO_2, CaP, TiO_2-CaP composite, and silica-based coatings can be deposited on the titanium surface by this technique. Chemical vapor deposition involves chemical reactions between chemicals in the gas phase and the surface of the substrate which results in the deposition of a non-volatile compound on the substrate.

7.3 Physical methods

The physical methods of implant surface modification include plasma spraying, sputtering, and ion deposition.

Plasma spraying includes atmospheric plasma spraying and vacuum plasma spraying. This is used for creating titanium and CaP coatings on the surfaces of titanium implants. One major concern in the use of plasma sprayed coatings is the resorption and degradability of HA in the case of HA (PSHA) coated implants and loosening of the titanium particles in the case of titanium plasma sprayed (TPS) implants. This can affect the stability of the implants as well as pose a health hazard.

Sputtering, a method employed to deposit thin films, has been used to deposit thin films on implant surfaces to improve their biocompatibility, biological activity, and mechanical properties such as wear resistance and corrosion resistance.

8. Surface treatment of titanium implants

8.1 Turned surface (machined dental implants)

The first generation of dental implants, termed the turned implants, had a relatively smooth surface. After being manufactured, these implants are submitted to cleaning, decontamination and sterilization procedures. Scanning electron microscopy analysis showed that the surfaces of machined implants have grooves, ridges and marks of the tools used for their manufacturing. These surface defects provide mechanical resistance through bone interlocking. The disadvantage regarding the morphology of non-treated implants (machined) is the fact that osteoblastic cells are rugophilic – that is, they are prone to grow along the grooves existing on the surface. This characteristic requires a longer waiting time between surgery and implant loading. The use of these implants follows a protocol suggested by Brånemark i.e., 3-6-month healing or waiting time prior to loading.

These are the best documented implants with several reports suggesting good long-term clinical outcomes on all indications when used in sites with good bone quality using a two-stage procedure. The success rates of turned implants in challenging situations such as low bone density has been reported to be lesser than when placed in areas with good bone quality. Studies on animal models, clinical studies, and systematic reviews have suggested a positive correlation between surface roughness and BIC (Wennerberg and Albrektsson, 2010, Junker *et al.*, 2009). With experimental studies clearly indicating that significantly greater amount of new bone is formed around HA coated, or oxidized implants, it has been suggested that these implants should be preferred over turned implants in sites with poor bone quality. Owing to

morphological characteristics and lower resistance to removal torque, machined dental implants are becoming commercially unavailable. However, clinical cases in which turned implants were placed in poor bone have reported good long-term results. Although studies have shown lower primary stability for the turned implants, they demonstrated secondary stability values and clinical success rates similar to modified implants.

8.2 Etched surface dental Implants

Etching with strong acids is another method for roughening titanium dental implants. Acid etching of titanium removes the oxide layer and parts of the underlying material. The extent of material removed depends on the acid concentration, temperature and treatment time. The most commonly used solutions for acid etching of titanium includes either a mixture of HNO_3 and HF or a mixture of HCl and H_2SO_4 (MacDonald *et al.*, 2004). Acid treatment provides homogeneous roughness, increased active surface area and improved bioadhesion (Braceras *et al.*, 2009). This yields low surface energy and reduces the possibility of contamination since no particles are encrusted in the surface. This type of surface not only facilitates retention of osteogenic cells, but also allows them to migrate towards the implant surface. The manufacturers have their own acid etching method regarding concentration, time and temperature for treating implant surfaces. Roughening of implants by acid-etching produces micro pits on titanium surfaces and has been shown to promote rapid osseointegration with long term success (Wong *et al.*, 1995, Cho and Park, 2003).

8.3 Dual acid-etched technique

Immersion of titanium implants for several minutes in a mixture of concentrated HCl and H_2SO_4 heated above 100 °C (dual acid-etching) is employed to produce a micro rough surface. The dual acid- etched surfaces enhance the osteoconductive process through the attachment of fibrin and osteogenic cells, resulting in bone formation directly on the surface of the implant (Park and Davies, 2000).

The dual acid-etched surface produces a microtexture rather than a macrotexture. It has been found that dual acid-etched surfaces enhance the osteoconductive process through the attachment of fibrin and osteogenic cells, resulting in bone formation directly on the surface of the implant (Orsini *et al.*, 2000). Advantage of the dual acid-etched technique is in higher adhesion and expression of platelet and extracellular genes, which help in colonization of osteoblasts at the site and promote osseointegration. Experimental studies have reported higher BIC and less bone resorption with dual acid-etched surfaces compared to machined or TPS surfaces (Cochran *et al.*, 1998, Cochran *et al.*, 2002). It has been hypothesized that implants treated by dual acid-etching have a specific topography which enables them to attach to the fibrin scaffold, to promote the adhesion of osteogenic cells, and thus to promote bone apposition (Trisi *et al.*, 2002). High temperature acid-etching methods produced a homogeneous micro-porous surface which showed increased cell adhesion and higher BIC than TPS surfaces. The wettability of the surface has also been proposed to promote fibrin adhesion. This fibrin adhesion provides contact guidance for the osteoblasts migrating along the surface (Buser *et al.*, 2004).

8.4 Hydroxyapatite coated implants

Hydroxyapatite is one of the materials that may form a direct and strong binding between the implant and bone tissue. The coating with hydroxyapatite (Ca10(PO4)6(OH)2) can be

considered as bioactive because of the sequence of events that results in precipitation of a CaP rich layer on the implant material through a solid solution ion exchange at the implant-bone interface (Ducheyne and Cuckler, 1992). The CaP incorporated layer will gradually be developed, via octacalcium phosphate , in a biologically equivalent hydroxyapatite that will be incorporated in the developing bone (Ogiso *et al.*, 1992). Synthetic form of hydroxyapatite has also been widely investigated due to the similar chemical composition to the mineral matrix of bone, which is generally referred to as hydroxyapatite (Ducheyne and Cuckler, 1992).

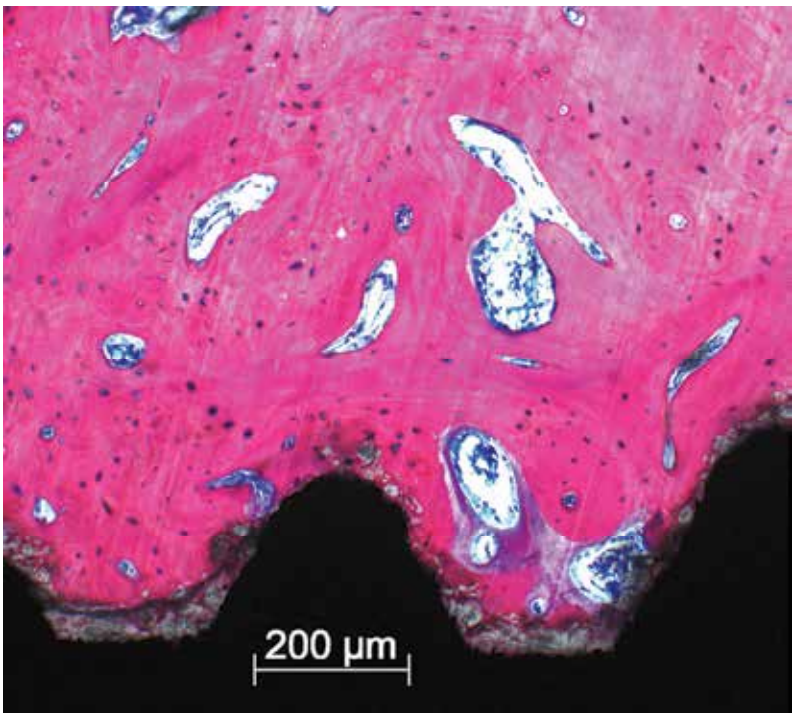

Fig. 5. Showing accelerated bone formation on the coated implant surface

Several methods have been described for applying hydroxyapatite coatings onto metals and different material properties may result from each method. Plasma-spraying is the most important commercially used technique for coating metals, especially titanium. In a so-called plasma gun, an electric arc current of high energy is struck between a cathode and an anode. Plasma spraying technique results in a coating thickness of 40-50 µm.

8.5 Sol-gel coated implants

The sol-gel method represents a simple and low cost procedure to deposit thin coatings with homogenous chemical composition onto substrates with large dimensions and complex design. The high mechanical strength and toughness of titanium alloys are the most important advantages over bioactive HA ceramics. A system that join both materials has the mechanical advantages of the underlying (metallic) substrate and biological affinity of the HA. Coating metallic implants with bioactive materials, like HA, may accelerate bone formation during initial stages of osseointegration and thereby improving implant fixation

(Vidigal *et al.*, 1999). Thin HA film on titanium substrates can be prepared using sol–gel (Xu *et al.*, 2006) or electrophoresis techniques (Wang *et al.*, 2002).
The sol-gel and electrophoresis methods are capable of improving chemical homogeneity in the resulting HA coating to a significant extent, when compared to conventional methods such as solid state reactions, wet precipitation and hydrothermal synthesis (Milev *et al.*, 2003). These methods are also simple and less expensive than the plasma spraying method that is widely used for biomedical applications. Sol-gel titania films may be prepared using a dip coating or spin coating process (Gan *et al.*, 2004). *In vivo* bone tissue evaluations of surfaces modified using the sol-gel method have shown better osseointegration with no adverse reaction (Gan *et al.*, 2004, Gil-Albarova *et al.*, 2004). However, the behavior of sol-gel modifications of loaded osseointegrated implants in the long term remains unknown.

8.6 Sandblasted and acid-etched (SLA) implants

This type of surface is produced by a large grit 250-500 μm blasting process followed by etching with hydrochloric/sulfuric acid. Sandblasting results in surface roughness and acid etching leads to microtexture and cleaning (Galli *et al.*, 2005). These surfaces are known to have better bone integration as compared to the above-stated methods (Bornstein *et al.*, 2008).

8.7 Grit-blasted surface

The grit blasting technique usually is performed with titania or alumina particles. The final surface roughness may be controlled by varying the particle size selected. Titanium implants blasted with alumina and titania particles with sizes of 25 μm and 75 μm demonstrated enhanced bone formation compared to turned implants. TioBlast implants (AstraTech) surface modification included grit blasting with titania particles. The success rate of TioBlast implants reported in a prospective study after 7 years was 96.9% with the same survival rate at 10 years. Compared to turned implants, TioBlast implants demonstrated lower bone loss and higher overall success rates (Engquist *et al.*, 2002, van Steenberghe *et al.*, 2000). Grit blasting represented the first clinically applied surface modification of titanium implants; the technique has then been further modified with acid etching, such as: SLA (Straumann) and Osseospeed (AstraTech).

8.8 Oxidized surface

Alteration of the topography and composition of the surface oxide layer of the implants can be achieved by a process of anodization. Anodic oxidation is an electrochemical process that increases the TiO_2 surface layer and roughness. The oxidation process changes the characteristic of the oxide layer and makes it more biocompatible (Gupta *et al.*, 2010). The implant is immersed in a suitable electrolyte and becomes an anode in an electrochemical cell. When a potential is applied to the sample, ionic transport of charge occurs through the cell, and an electrolytic reaction takes place at the anode, resulting in the growth of an oxide film. This results in a surface with micropores which demonstrates increased cell attachment and proliferation (Gupta *et al.*, 2010). The anodization process is rather complex and depends on various parameters such as current density, concentration of acids, composition and electrolyte temperature. The tissue healing process around anodized implants is quicker than in machined implants. In a study performed on canine models to evaluate bone healing

at oxidized and turned implant surfaces, Gurgel *el al.* (2008) reported a higher percentage of BIC and bone density for anodized implants.

8.9 Plasma-spray coating

Plasma Sprayed (PS) Titanium coating is an optimized way to achieve a surface topography and morphology. The advantage of plasma coating is that these coatings give implants a porous surface that bone can penetrate more readily. Osseointegration was shown to be fastest and most effective for rough surfaces with open structure that varied between 50 to 400 μm.

Titanium plasma spraying (TPS) method consists of injecting titanium powders into a plasma torch at high temperature. The titanium particles are projected on to the surface of the implants where they condense and fuse together, forming a film about 30 μm thick. This processing results in a substantial surface area increase compared to the other commercially available surfaces. It has been shown that this three-dimensional topography increased the tensile strength at the implant-bone interface. Based on that, TPS implants have been often recommended for regions with low bone density. Studies have shown that the implant-bone interface formed faster with a TPS surface than with machined implants (Al-Nawas *et al.*, 2006, Lossdorfer *et al.*, 2004, Novaes *et al.*, 2002). Rough surfaces, obtained by TPS and grit-blasted/acid-etched have shown torque to failure values significantly higher than implants with machined profiles (Piao *et al.*, 2009, Bratu *et al.*, 2009, Schneider *et al.*, 2003).

8.10 Plasma sprayed hydroxyapatite

The addition of calcium and phosphorous based materials as coatings have received significant attention due to the fact that these elements are the same basic components of natural bone and coatings can be applied along the implant surfaces by various industrial processing methods (Kirsch, 1986). Most commercially available bio-ceramic coatings are processed as a 20–50 μm thick Plasma Sprayed Hydroxyapatite (PSHA) coatings. PSHA coatings normally rely on mechanical interlocking between a grit-blasted or etched metallic surfaces and the ceramic-like PSHA biomaterial for physical integrity during implant placement and function (Knabe *et al.*, 2002).

The osseointegration of the dental implant with plasma-sprayed HA is faster than uncoated implants. *In vivo* studies on rabbit femoral condyles have demonstrated a higher level of osseointegration for the HA-coated samples compared to the uncoated ones. Bone maturation was reported to be more significant at the bone-implant interface and coating of titanium with HA lead to improved maturation of newly formed bone tissue (Clark *et al.*, 2005). These observations were attributed to the presence of porous HA in the coated samples. Due to the high biocompatibility and osteoconduction of CaP materials, they have been widely used for different hard tissue applications such as HA-coated metallic implants and bone substitute materials.

8.11 Fluoride treatment

Titanium is very reactive to fluoride ions, forming soluble TiF_4 by treating titanium dental implants in fluoride solutions. This chemical treatment of titanium enhances the osseointegration of dental implants. An in vitro analysis of fluoride modified implants on human mesenchymal cells revealed no difference in cell attachment between the fluoride modified and control (grit-blasted) implants. Moreover, decreased cell proliferation was

observed after 7 days on the fluoride modified compared to control (grit-blasted) implants. It has been shown that this chemical surface treatment enhanced osteoblastic differentiation in comparison with control samples (Ellingsen, 1995). The results of osteoblast differentiation showed increased expression of Cbfa1, osterix and bone sialoprotein to fluoridated implants (Cooper *et al.*, 2006, Isa *et al.*, 2006). Fluoridated rough implants also withstood greater push-out forces and showed a significantly higher removal torque than the control implants (Ellingsen *et al.*, 2004).

8.12 Laser deposition

The surface characteristics of titanium implants have been modified by additive methods, such as titanium and hydroxyapatite plasma spray, as well as by subtractive methods, such as acid etching and laser ablation. The laser ablation technology for surface preparation already has numerous industrial applications. This process results in titanium surface microstructures with greatly increased hardness, corrosion resistance, and a high degree of purity with a standard roughness and thicker oxide layer (Gaggl *et al.*, 2000, Hallgren *et al.*, 2003). Biological studies evaluating the role of titanium ablation topography and chemical properties showed the potential of the grooved surface to orientate osteoblast cell attachment and control the direction of ingrowth (Frenkel *et al.*, 2002).

8.13 Sputter deposition

Sputtering is a process whereby atoms or molecules of a material are ejected in a vacuum chamber by bombardment of high-energy ions. There are several sputter techniques and a common drawback inherent in all these methods is that the deposition rate is very low and the process itself is very slow (Jansen *et al.*, 1993). The deposition rate is improved by using a magnetically enhanced variant of diode sputtering, known as radio frequency magnetron sputtering.

Radio frequency sputtering (RF) : Radiofrequency (RF) magnetron sputtering is largely used to deposit thin films of CaP coatings on titanium implants. RF magnetron sputtering is a very suitable technique to deposit standardized CaP coatings on titanium substrates. The advantage of this technique is that the coating shows strong adhesion to the titanium and the Ca/P ratio and crystallinity of the deposited coating can be varied easily. Studies in animals have shown higher BIC percentages with sputter coated implants (Vercaigne *et al.*, 2000a, Vercaigne *et al.*, 2000b). Studies have shown that these coatings were more retentive, with the chemical structure being precisely controlled (Ong *et al.*, 2002).

Magnetron sputtering: Magnetron sputtering is a viable thin-film technique as it allows the mechanical properties of titanium to be preserved while maintaining the bioactivity of the coated HA. Films were deposited in a custom-built sputter deposition chamber at room temperature. This technique shows strong HA titanium bonding associated with outward diffusion of titanium into the HA layer, forming TiO_2 at the interface (Wolke *et al.*, 1994).

9. Biologically active drugs incorporated dental implants

Several attempts have been made to improve and accelerate osseointegration by modification of surface properties, such as introducing bioactive factors to titanium surfaces. Of these, some osteogenic drugs have been applied to implant surfaces. Incorporation of bone antiresorptive drugs, such as bisphosphonate, might be very relevant in clinical cases lacking bone support.

9.1 Bisphosphonates

Bisphosphate-loaded implant surfaces have been reported to improve implant osseointegration. Bisphosphates are antiresorptive agents that have beneficial effects for the patients on preventing further bone loss, and their effects on increasing the bone mass is modest (Kwak *et al.*, 2009, Yoshinari *et al.*, 2002). It has been shown that bisphosphonate incorporated on to titanium implants increased bone density locally in the peri-implant region (Josse *et al.*, 2005) with the effect of the antiresorptive drug limited to the vicinity of the implant. Experimental *in vivo* studies have demonstrated the absence of negative effects, but only a slight increase in dental implant osseointegration (Meraw and Reeve, 1999, Meraw *et al.*, 1999). Other experimental studies using PSHA-coated dental implants immersed in pamidronate or zoledronate demonstrated a significant increase in bone contact area (Yoshinari *et al.*, 2001, Kajiwara *et al.*, 2005). The main problem lies in the grafting and sustained release of antiresorptive drugs on the titanium implant surface. Due to the high chemical affinity of bisphosphonates for CaP surfaces, incorporation of the antiresorptive drug on to dental implants could be achieved by using the biomimetic coating method at room temperatures. However, the ideal dose of antiresorptive drug will have to be determined because the increase in peri-implant bone density is bisphosphonate concentration-dependent (Peter *et al.*, 2005).

9.2 Simvastatin

Statins are commonly prescribed drugs that inhibit 3-hydroxy-3-methylglutaryl coenzyme reductase to decrease cholesterol biosynthesis by the liver, thereby reducing serum cholesterol concentrations and lowering the risk of heart attack (Goldstein and Brown, 1990). Simvastatin, could induce the expression of bone morphogenetic protein (BMP) 2 mRNA that might promote bone formation (Mundy *et al.*, 1999). Simvastatin given per-orally to adult rats increased cancellous bone mass and increased cancellous bone compressive strength (Oxlund *et al.*, 2001).

Ayukawa *et al* (2009) confirmed that topical application of statins to alveolar bone increased bone formation and concurrently suppressed osteoclast activity at the bone-healing site. In addition, clinical studies reported that statin use is associated with increased bone mineral density (Edwards *et al.*, 2000, Montagnani *et al.*, 2003). Du *et al* (2009) investigated the effect of simvastatin by oral administration on implant osseointegration in osteoporotic rats and found that it significantly improved bone integration with the implant. Another animal study showed that the intra-peritoneal administration of simvastatin increased BIC ratio and bone density and implied that simvastatin might have the potential to improve the nature of osseointegration (Ayukawa *et al.*, 2004). In an in vitro study Yang *et al* (2010) showed that simvastatin-loaded porous implant surfaces promote accelerated osteogenic differentiation of preosteoblasts, which have the potential to improve the nature of osseointegration.

9.3 Antibiotic coating

Antibacterial coatings on the surface of implants that provide antibacterial activity to the implants themselves have been studied as a possible way to prevent surgical site infections associated with implants. **Gentamycin** along with the layer of HA can be coated onto the implant surface which may act as a local prophylactic agent along with the systemic antibiotics in dental implant surgery (Alt *et al.*, 2006).

Tetracycline-HCl treatment has been regarded as a practical and effective chemical modality for decontamination and detoxification of contaminated implant surfaces.

Tetracycline-HCl functions as an antimicrobial agent capable of killing microorganisms that may be present on the contaminated implant surface. It also effectively removes the smear layer as well as endotoxins from the implant surface. Further, it inhibits collagenase activity, increases cell proliferation as well as attachment and bone healing (Herr *et al.*, 2008). Tetracycline also enhances blood clot attachment and retention on the implant surface during the initial phase of the healing process and thus promotes osseointegration (Persson *et al.*, 2001).

10. Future directions in implant surface modifications

Several growth factors and cytokines have also been suggested to stimulate a deposition of cells with the capacity of regenerating the desired tissue (Liu *et al.*, 2007, Sigurdsson *et al.*, 2001). An enhanced proliferation and differentiation of undifferentiated mesenchymal cells, osteoprogenitor cells, and preosteoblasts into osteoblasts may improve bone response and subsequently osseointegration of titanium implants (Chappard *et al.*, 1999). The adhesion of plasma proteins on the surface of titanium implants has been reported to play an essential role in the process of osseointegration (Eriksson *et al.*, 2001). The specific pattern of adsorbed proteins determines the type of tissue that will develop at the interface between the implanted material and the host (Walivaara *et al.*, 1994).

Polypeptide growth and differentiation factors and cytokines have been suggested as potential candidates in this regard to stimulate a deposition of cells with the capacity of regenerating the desired tissue (Liu *et al.*, 2007, Sigurdsson *et al.*, 2001). Biologically active implants surfaces may have the potential to enhance the proliferation and differentiation of undifferentiated mesenchymal cells and osteoblasts which can improve bone response and subsequent osseointegration of titanium implants (Chappard *et al.*, 1999). Researchers have shown that growth factors released during the inflammatory phase have the potential of attracting undifferentiated mesenchymal stem cells to the injured site. These growth factors include PDGF, EGF, VEGF, TGF-β, and BMP-2 and BMP-4. These factors are released in the injured sites by cells involved in tissue healing. The surface of titanium dental implants may be coated with bone-stimulating agents such as growth factors in order to enhance the bone healing process locally. Members of the transforming growth factor (TGF-β) superfamily, and in particular bone morphogenetic proteins (BMPs), TGF-β1, platelet-derived growth factor (PDGF) and insulin-like growth factors (IGF-1 and 2) are some of the most promising candidates for this purpose. Among these, bone morphogenetic protein (BMP), has shown considerable potential to stimulate bone formation both in extra skeletal sites and in defect models in different species (Avila *et al.*, 2009, Becker *et al.*, 2006, Sigurdsson *et al.*, 2001). The effects of rhBMP-2 on the osseointegration of titanium implants have also been investigated in experimental animal studies (Sigurdsson *et al.*, 1996, Wikesjo *et al.*, 2002).

Experimental data, in which BMPs were incorporated into dental implants, have been obtained from a variety of methodologies. Besides individual growth factors, the effects of incorporating a "cocktail" of these factors have also been evaluated. In an animal study assessing the potential effects of humidifying and bioactivating titanium dental implants with liquid preparation rich in growth factors (PRGF) on implant osseointegration in the goat model, 26 implants were inserted in the tibiae of the goats. Before installation, 13 implants were carefully humidified with liquid PRGF with the aim of bioactivating the implant surface, whereas the other 13 implants were placed without PRGF treatment (Anitua *et al.*, 2009). After 8 weeks, the animals were sacrificed and histological and

histomorphometric tests were performed. Histological and histomorphometric results demonstrated that application of liquid PRGF increased the percentage of BIC by 84.7%. The whole surface of the PRGF-treated implants was covered by newly formed bone, whereas only the upper half was surrounded in the control implants. This suggested that PRGF can accelerate bone regeneration in artificial defects and improve the osseointegration of titanium dental implants.

A clinical study in which 1391 implants were placed in 295 patients after bioactivating the surface with PRGF, stability and implant survival were evaluated, and it was reported that 99.6% of the implants treated with PRGF were well osseointegrated suggesting that the clinical use of this technique in oral implantology can improve the prognosis (Anitua, 2006).

Animal studies in which platelet-rich plasma in liquid form was applied to the implant surface by dipping the implant in PRP prior to placement have demonstrated that PRP in a liquid form showed a tendency to increase bone apposition to roughened titanium implants (Nikolidakis *et al.*, 2008, Nikolidakis *et al.*, 2006).

Nikolidakis *et al* (2006) investigated the effect of local application of autologous platelet-rich plasma (PRP) on bone healing in combination with the use of titanium implants with 2 different surface configurations - CaP coated and non-coated implants. PRP fractions were obtained from venous blood sample of 6 goats and applied via gel preparation and subsequent installation in the implant site or via dipping of the implant in PRP liquid before insertion. Thirty-six implants (18 non-coated and 18 CaP coated) were placed into the goat femoral condyles (trabecular bone). The animals were sacrificed at 6 weeks after implantation, and implants with surrounding tissue were processed for light microscopic evaluation. Significantly more interfacial BIC was observed for all 3 groups of CaP-coated implants and the titanium / liquid group (non-coated implant with PRP liquid) than for the other 2 non-coated titanium groups (with PRP gel or without PRP). The evaluation of the bone mass close to implant surface indicated that all the groups induced a significant increase of the bone mass except the PRP gel groups. On the basis of the observations, it was concluded that magnetron-sputtered CaP coatings can improve the integration of oral implants in trabecular bone. Although the additional use of PRP did not offer any significant effect on the bone response to the CaP-coated implants, PRP in a liquid form showed a significant effect on bone apposition to roughened titanium implants during the early post-implantation healing phase.

The role of the osteoinductive TGF-β1 application to CaP implant surfaces have been studied in animals using a goat model. It was observed that, although the BIC was highest in the TGF-β1 loaded implants, the beneficial effects of the growth factor were only marginal (Schouten *et al.*, 2009). The limiting factor regarding the use of growth factors in surface treatment of implants is that the active product has to be released progressively and not in a single burst. Although the possibility of incorporation of a plasmid containing the gene coding for a BMP exists, it is associated with disadvantages related to poor efficacy and a possible undesirable overproduction of BMPs.

11. Conclusion

The endosseous dental implant has become a scientifically accepted and well documented treatment for fully and partially edentulous patients. Titanium and its alloys are the materials of choice clinically, because of their excellent biocompatibility and superior mechanical properties. The composite effect of surface energy, composition, roughness, and

topography on implant determines its ultimate ability to integrate into the surrounding tissue.

Surface modification technologies involve preparation with either an additive coating or subtractive method. Cell migration, adhesion, and proliferation on implant surfaces are important prerequisites to initiate the process of tissue regeneration, while modifications of the implant surface by incorporation of biologic mediators of growth and differentiation may be potentially beneficial in enhancing wound healing following implant placement. These topographical modifications have boosted the success rate of the implant therapy, especially in patients with poor bone quality sites, and have significantly reduced the healing period. The cellular mechanisms involved in this faster and improved osseointegration are yet to be fully determined. Further research should be directed to explore the biologic basis underlying the clinical improvement with altered implant surfaces.

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Part 2

Biomechanics in Implant Dentistry

5

Implant Stability - Measuring Devices and Randomized Clinical Trial for ISQ Value Change Pattern Measured from Two Different Directions by Magnetic RFA

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1. Introduction

Implant stability plays a critical role for successful osseointegration, which has been viewed as a direct structural and functional connection existing between bone and the surface of a load-carrying implant(Bränemark, et al. 1977, Sennerby & Roos 1998). Achievement and maintenance of implant stability are prerequisites for successful clinical outcome(Sennerby & Meredith 2008). Therefore, measuring the implant stability is an important method for evaluating the success of an implant. Implant stability is achieved at two different stages: primary and secondary. Primary stability of an implant comes from mechanical engagement with cortical bone. It is affected by the quantity and quality of bone that the implant is inserted into, surgical procedure, length, diameter, and form of the implant(Meredith 1998).

Secondary stability is developed from regeneration and remodeling of the bone and tissue around the implant after insertion but is affected by the primary stability, bone formation and remodeling(Sennerby & Roos 1998). The time of functional loading is dependent upon the secondary stability. It is, therefore, of an utmost importance to be able to quantify implant stability at various time points and to project a long term prognosis based on the measured implant stability(Atsumi, et al. 2007).

2. Measuring analyses of implant stability

Presently, various diagnostic analyses have been suggested to define implant stability. Primary implant stability can be measured by either a destructive or a non-destructive method. Histomorphologic research, tensional test, push-out/pull-out test and removal torque test are classified as destructive methods. Non-destructive methods include percussion test, radiography, cutting torque test while placing implants, Periotest®(Siemens AG, Benshein, Germany), and resonance frequency analysis(RFA)(Meredith 1998).

2.1 Tensional test

The interfacial tensile strength was originally measured by detaching the implant plate from the supporting bone(Kitsugi, et al. 1996). Bränemark later modified this technique by applying the lateral load to the implant fixture(Bränemark, et al. 1998). However, they also addressed the difficulties of translating the test results to any area- independent mechanical properties(Chang, et al. 2010)(Fig. 1a).

2.2 Histomorphometric analysis

Histomorphometric analysis is obtained by calculating the peri-implant bone quantity and bone-implant contact(BIC) from a dyed specimen of the implant and peri-implant bone. Accurate measurement is an advantage, but due to the invasive and destructive procedure, it is not appropriate for long-term studies. It is used in non-clinical studies and experiments.

2.2 Push-out/pull-out test

The 'push-out' or 'pull-out' test is the most commonly used approach to investigate the healing capabilities at the bone implant interface(Brunski, et al. 2000). In the typical push-out or pull-out test, a cylinder-type implant is placed transcortically or intramedullarly in

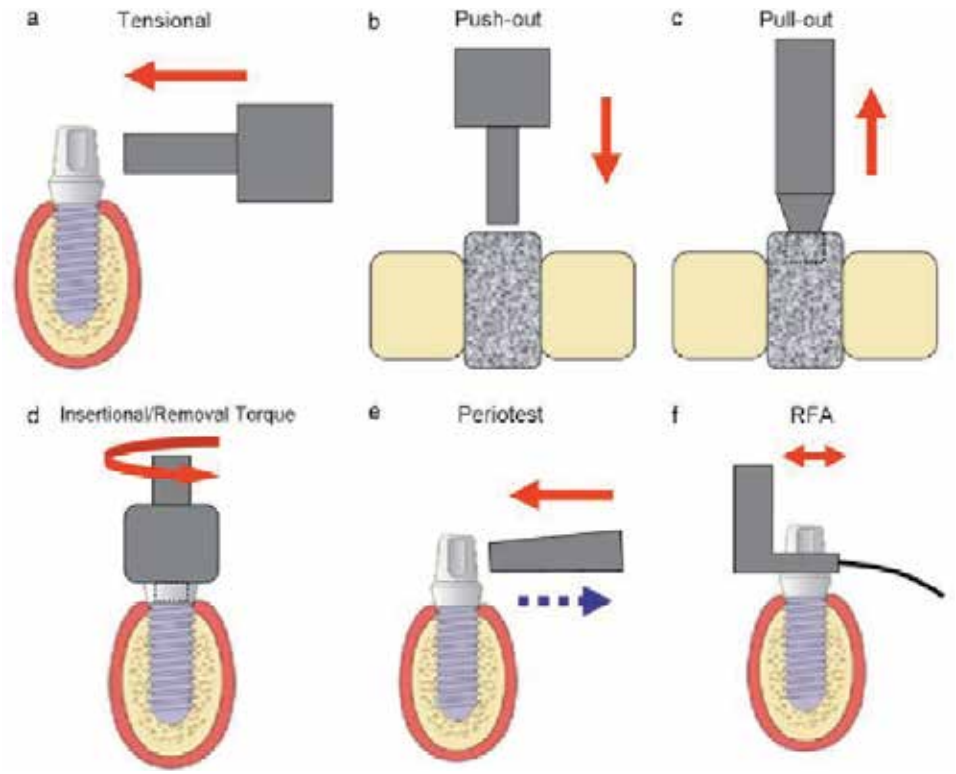


Fig. 1. Stability analyses for oral implant osseointegration from Chang, P. C., Lang, N. P. & Giannobile, W. V. (2010). "Evaluation of functional dynamics during osseointegration and regeneration associated with oral implants." Clinical Oral Implants Research 21: 1-12. (a) tensional test, (b) push-out test, (c) pull-out test, (d) insertional/removal torque test, (e) Periotest, and (e) resonance frequency analysis (RFA).

bone structures and then removed by applying a force parallel to the interface. The maximum load capability (or failure load) is defined as the maximum force on the force–displacement plot, and the interfacial stiffness is visualized as the slope of a tangent approximately at the linear region of the force–displacement curve before breakpoint (Brunski, et al. 2000, Lutolf, et al. 2003). Therefore, the general loading capacity of the interface (or interfacial shear strength) can be measured by dividing the maximum force by the area of implant in contact with the host bone(Berzins, et al. 1997). However, the push-out and pull-out tests are only applicable for non-threaded cylinder type implants, whereas most of clinically available fixtures are of threaded design, and their interfacial failures are solely dependent on shear stress without any consideration for either tensile or compressive stresses(Brunski, et al. 2000, Chang, et al. 2010)(Fig. 1b-c).

2.3 Removal torque analysis

Application of a reverse or unscrewing torque has also been proposed for the assessment of implant stability at the time of abutment connection(Sullivan, et al. 1996), however, implant surface in the process of osseointegration may fracture under the applied torque stress(Ivanoff, et al. 1997)(Fig.1d).

2.4 Percussion test

The test is carried out by a simple percussion with the handle of a dental instrument on the implant abutment and listening to the resulting sound. However, this method may be subjective according to the examiner and give inaccurate measurements for implants because of the high rigidity of implants and the lack of periodontal ligaments.

2.5 Insertion torque measurement

Insertion torque values have been used to measure the bone quality in various parts of the jaw during implant placement(O'Sullivan, et al. 2004). Insertion torque alone may be used as an independent stability measurement, but it may also act as a variable, affecting implant stability. In a different light, insertion torque is a mechanical parameter generally affected by surgical procedure, implant design and bone quality at implant site(Beer, et al. 2003). However, it cannot assess the secondary stability by new bone formation and remodeling around the implant. So it cannot collect longitudinal data to assess implant stability change after placement. Also, an increase in insertion torque may signify an increase in primary stability, but maximum insertion torque is produced by the pressure of implant neck on the dense cortical bone of the alveolus. Furthermore, it has been reported that if maximum insertion torque doesn't signify increased general bone density, it may indicate the insertion torque itself during tapping (Calandriello, et al. 2003)(Fig.1d).

2.6 Radiography

Radiography provides useful information for evaluating the quantity and quality of bone in the area for an implant before placing the fixture. It is also helpful in predicting implant stability by observing the process of osseointegration or peri-implant lesions. However, there is a limitation in image resolution and standardized X-rays are difficult to achieve due to the distortion of images, making quantitative measurements more challenging. In addition, it is difficult to perceive changes in the bone structures and morphology of the implant-bone interface unless over 30% bone loss occurs. Although the accuracy of the

diagnosis is low, radiography is the major method used clinically to evaluate osseointegration and implant stability because of its convenience. (Albrektsson, et al. 1986).

2.7 Periotest®

Periotest® (Siemens AG, Benshein, Germany) was originally devised by Dr. Schulte to measure tooth mobility(Fig.2). Teerlinck, et al.(1991) used this method to overcome destructive methods in measuring the implant stability. Periotest® evaluates the damping capacity of the periodontium. It is designed to identify the damping capacity and the stiffness of the natural tooth or implant by measuring the contact time of an electronically driven and electronically monitored rod after percussing the test surface. Periotest value(PTV) is marked from -8(low mobility) to +50(high mobility). PTV of -8 to -6 is considered good stability.

Periotest® can measure all surfaces such as the abutment or prosthesis, but the rod must make contact at a correct angle and distance. If the perpendicular contact angle is larger than 20 degrees, or if the parallel contact angle is larger than 4 degrees, the measured value is invalid. Also, the rod and the test surface must maintain 0.6-2.0mm distance and if the distance is over 5mm, the measured value may be insignificant. (Ito, et al. 2008, Schulte 1988). Periotest® has limited clinical use since it cannot measure the mesiodistal mobility and the position and angle of the rod affects the measured value. Also, it cannot detect the small changes in the implant-bone surface. The most failing point of this method is that the percussing force on the implant may deteriorate the stability in poor initial stability implants.

(a) (b)

Fig. 2. Periotest® (Siemens AG, Benshein, Germany) measures tooth mobility and implant stability by periotest value(PTV). (a) Periotest®, (B) Periotest®M.

2.8 Resonance Frequency Analysis(RFA)

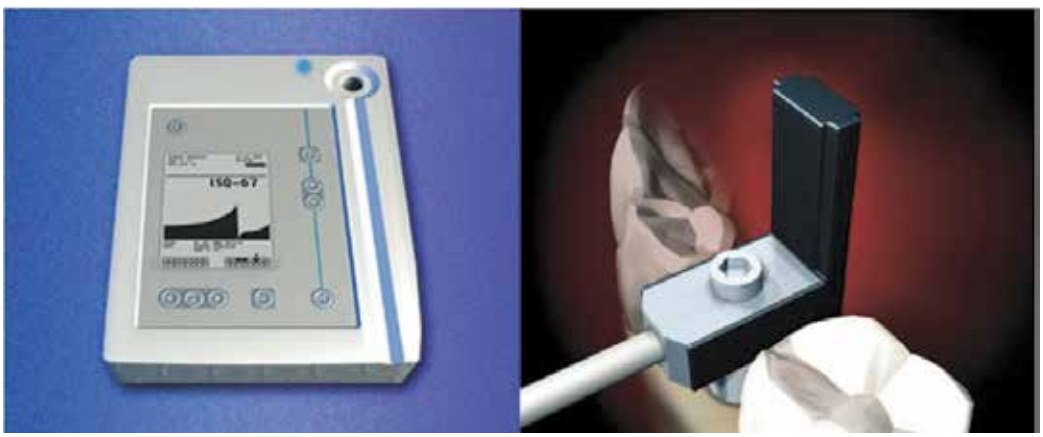
In 1998, Meredith suggested a non-invasive method of analyzing peri-implant bone by connecting an adapter to an implant in an animal study. The experimented resonance frequency analysis system was commercially produced as Osstell™ (Osstell AB, Göteborg, Sweden).

A measurement of Osstell™ is displayed as implant stability quotient(ISQ) from 1 to 100, where 100 signifies the highest implant stability. Osstell™ was later followed by Osstell™ Mentor, and Osstell™ ISQ.

3. RFA principle and application

3.1 Introduction

Meredith et al.(1996) reported the use of resonance frequency analyzer to evaluate implant stability by applying architectural engineering, and proved in early in vitro test the ability of the device in evaluating the stiffness change of the surface. RFA uses the principle of when a frequency of audibility range is repeatedly vibrated onto an implant, the stronger the bone-implant surface, resonance occurs in a higher frequency. The first commercial product of the resonance frequency analyzer(RFA) was Osstell™(Osstell AB, Göteborg, Sweden)(Fig.3), followed by Osstell™ Mentor and recently Osstell™ ISQ was introduced. Osstell™ uses electronic technology and other devices(Osstell™ Mentor, Osstell™ ISQ) use magnetic technology (Fig.5).



(a) (b)

Fig. 3. Pictures showing the first commercial products of resonance frequency analyzer. (a) the Osstell™ and (b) the application of the Osstell™ electronic transducer to the implant.(The figure and illustration are cited with permission from Osstell website, www.osstell.com, April, 2011)

3.2 Electronic technology resonance frequency analyzer(Osstell™)

The primary model Osstell™ produces alternating sine waves in a specific frequency range by uniform amplitude and makes the transducer connected to the implant or abutment vibrate under 1mm like an electronic tuning fork. A cantilever small beam is connected to the transducer and on this beam, 2 piezo-ceramic elements are attached. (Fig.3,4). One of them receives the signal and vibrates the transducer, and the other passes this vibration to the resonance frequency analyzer. Values on the monitor are displayed from 0-100 so that it can be conveniently used clinically. The value of 100 signify the highest stability state. Generally ISQ values for successfully integrated implants are reported from 57 to 82. These values can be displayed by graphs on the computer monitor or be expressed by values between 4500-8500Hz. The obtained output can be calculated by the equation below.

$$fn = \alpha \sqrt{\frac{EI}{\rho l^4}}$$

fn is the RF of the beam, l is the effective vibration length of the beam, E is the Young`s modulus, I is the moment of inertia, ρ is the mass, α the constant that increases as peri-implant bone density increases. Therefore, when osseointegration is achieved, RF increases since α value increases. 'l' signifies the length of implant above the bone. So as bone is resorbed, this value increases and thus RF decreases. In other words, ISQ is affected by the effective implant length, type of bone at implant site and bone density(Huang, et al. 2003, Huang, et al. 2003, Meredith, et al. 1996).

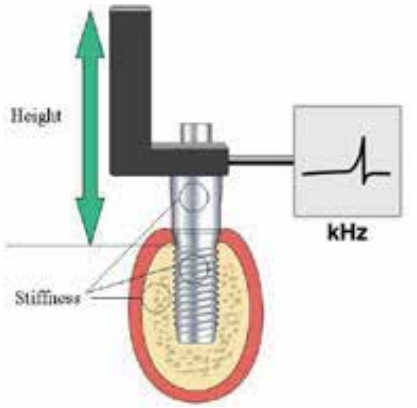


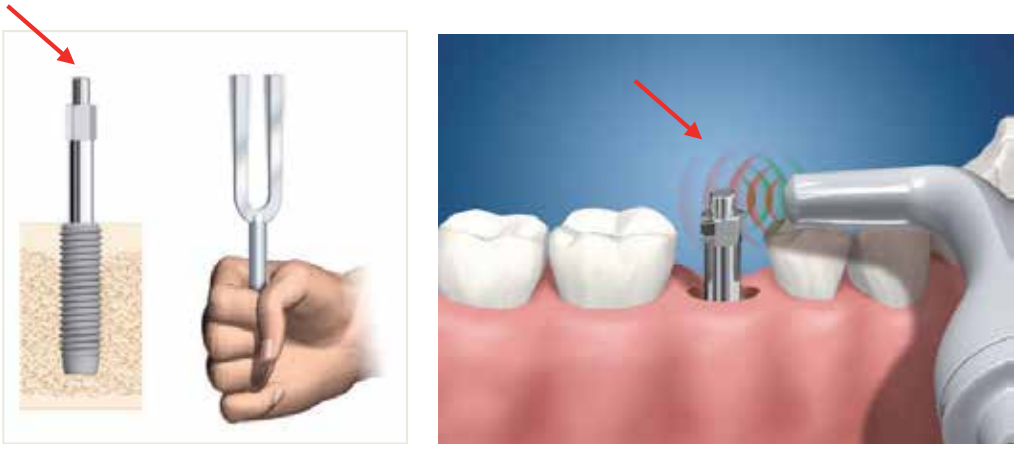
Fig. 4. Picture showing the principle of electronic resonance frequency analyzer. (The figure and illustration are cited from Osstell website, www.osstell.com, April, 2011)

3.3 Magnetic technology resonance frequency analyzer(Osstell™ Mentor, Osstell™ ISQ)

Resonance frequency between 3.5 KHz and 8.5 KHz formed from the magnetic field is converted into ISQ values by Osstell Mentor™(Fig. 5, 6). The transducer of Osstell Mentor™

(a) (b)

Fig. 5. Osstell Mentor™ and Osstell ISQ™ , both of devices measure ISQs by the magnetic technology. (The pictures are cited from Osstell website, www.osstell.com, April, 2011)



(a) (b)

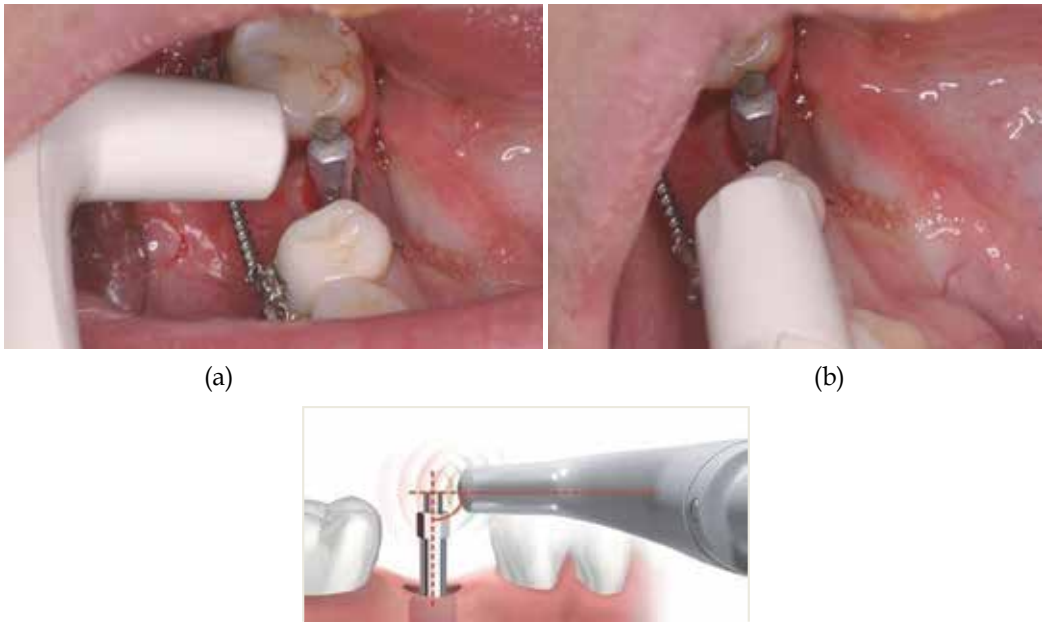
Fig. 6. Principle of the Osstell Mentor™. Magnetic peg(Smart peg™) works like a tuning fork. Red arrow is the Smart peg™. (The figure and illustration are cited from Osstell website, www.osstell.com, April, 2011)

has a magnetic peg on the top and is fixed to the implant fixture or abutment by a screw below. When magnetic resonance frequency is released from the probe, the magnetic peg is activated. The activated peg starts to vibrate, and the magnet induces electric volt into the probe coil and the electric volt is sampled by the magnetic resonance frequency analyzer (Fig. 6). The values are expressed as numbers between 1–100 in ISQ as Osstell™ (Valderrama, et al. 2007).

The device is relatively expensive, and each implant system requires the respective transducer for Osstell™ and magnetic peg for Osstell Mentor™. The restricted use of the transducer and the magnetic peg is a great disadvantage. Also, evaluation is impossible in a prosthesis state or when the magnetic peg is damaged or when in contact with the soft tissue. Therefore, when using Osstell Mentor™, the Smart peg™ must maintain a distance of approximately 1-3 mm, angle of 90 degrees, and 3 mm above the soft tissue, otherwise the measured value may be affected (Fig. 7). Valderrama et al.(2007) reported in a study experimenting the correlation between Osstell™ and Osstell Mentor™ that the two devices had high significant correlation.

3.4 Influencing factors of Implant Stability Quotient(ISQ)

In many literature, it has been reported that ISQ is affected by implant diameter, surface, form, bone contact ratio, implant site, implant system, surgical procedure, bone quality and bone height (Atsumi, et al. 2007). RFA is determined by the changes in the interface stiffness, and it is affected in three aspects. First, bone-implant surface stiffness affects RFA and it increases through bone healing and remodeling. Secondly, the stiffness of bone itself, and bone density as well as the ratio of cortical and cancellous bone affects RFA. Finally, the stiffness of implant components can acts as a variable and it is affected by the interlocking structures, and the composing elements of the materials. Bone and implant surface stiffness may be affected by using a small-diameter final drill, changes in surgical techniques such as



(a) (b)

(c)

Fig. 7. Application of magnetic RFA(Osstell™ Mentor) after immediate implant installation. The manufacturer recommends that the probe be held perpendicular to the alveolar crest(a) for the first measurement, and in line with the crest for the other measurement(b). And the Smart peg™ must maintain a distance of approximately 1-3 mm, angle of 90 degrees, and 3 mm above the soft tissue(c).

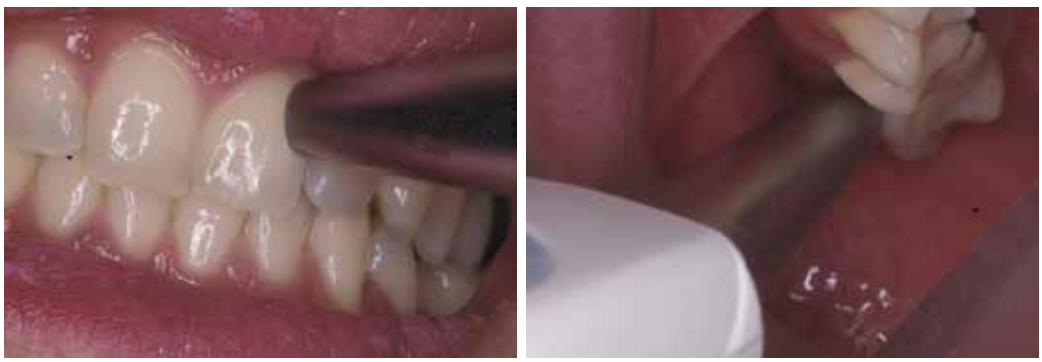
bone compaction technique, self-tapping design implants and wide tapered implants, but not by implant length. In a histomorphologic study, it was reported that the resonance frequency value is highly correlated with the bone-implant contact amount(Friberg, et al. 1999, Meredith, et al. 1997). There are reports showing a correlation between RFA and the histomorphometric analysis, and other reports claim that the correlation between the bone density and ISQ is not significant. Therefore RFA signifies the bone anchorage of implants but the relation of RFA and bone structure is not yet clear (Alsaadi, et al. 2007, Huwiler, et al. 2007, Rasmusson, et al. 1998, Zhou, et al. 2008). Such diverse results showed RFA value decreases during the first 2 weeks after implant placement, and this change can be related to early bone healing such as biological change and marginal alveolar bone resorption. Bone remodeling reduces primary bone contact and in the early stage after implant placement, the formation of bony callus and increasing lamellar bone in the cortical bone causes major changes in bone density. Thus, in the healing process, primary bone contact decreases and secondary bone contact increases (Barewal, et al. 2003, Zhou, et al. 2008). Also, the 3–dimensional implant-bone contact is displayed 2 dimensionally in the histological sample and BIC has possibility of inaccuracy to signify bone-implant contact (Perrotti, et al. 2010). The relationship of bone structure and RFA is not fully understood. Since primary stability is affected by bone volume or bone trabecula structure as well as cortical bone thickness and density, the effect of bone quality on implant stability cannot be explained by bone microstructure alone (Huwiler, et al. 2007).

4. Which device is more accurate to determine the stability of dental implants - recent literature review

There are two groups of non-invasice devices. One is the RFA analyzer group and the other is the mobility measuring device. The Osstell™ is the commercial name of the RFA analyzer group. This device has a cable which is linked a electronic transducer (Fig. 3). The later version of the Osstell™ is the Ossetell™ mentor which has no cable and uses of magnetic resonance frequency (Fig. 5). Periotest® is the commercial name of the mobility measuring device. Periotest® M is the newer device of the Periotest® and it is a wireless version (Fig. 2).

4.1 PTV and ISQ

Many studies have indicated the presence of correlation between PTVs(the values of Periotest®) and ISQ (the values of Osstell™ and Ossetell™ mentor). However, the correlation of implant stability and each value are still the controversial issue. Aparicio et al. (2006) presentd that the validity and relevance of both ISQ and PTVs for clinical use have to be questioned in their review article. Lachmann et al. (2006) compared Osstell™ and Periotest® by in vitro study and demonstrated that both methods are useful in the evaluation of implant stability but the Osstell™ was more precise than the Periotest® to determine the actual dental implant stability at peri-implant defects. Zix et al. (2008) studied with controlled clinical trial and concluded that Periotest® values appear to be more susceptible to clinical conditions and the Osstell™ instrument seemed to be more precise than the Periotest®. Winter et al.(2010) investigated the correlation between the two devices through the finite element study and demonstrated that Periotest® values had only good correlation with implant stability in case when there's no bone loss. Oh et al.(2009) reported that the Periotest® and Osstell™ Mentor were useful and comparably reliable, showing a strong association with each other in assessing implant stability in their experimental study. In summarizing the literature, it is generally accepted that the RFA is more accurate than the mobility measuring device, but the mobility measuring device is more convenient in clinical usage than RFA (Fig.8).



(a) (b)

Fig. 8. Application of Periotest® M. This device can measure the implant stability and mobility of natural teeth without special device, for example magnetic peg. (a) is the application of Periotest® M to natural tooth. (b) is the measurement of implant stability during follow-up period without implant crown removal.

4.2 Electronic resonance frequency and magnetic resonance frequency

Valderrama et al.(2007) performed clinical research using electronic- and magnetic-based devices on 34 non-submerged titanium dental implants in 17 patients and demonstrated that changes in implant stability measured with the magnetic device correlate well with those found with the electronic device. Both devices confirmed the initial decreases in implant stability that occur following placement and identified an increase in stability during the first 6 weeks of functional loading. Tozum et al.(2010) compared three devices which are RF with cable, RF wireless and wireless mobility measureing device using 30 dental implants in human dried cadaveric mandibles. The authors demonstrated that both RF with cable and RF wireless seem to be suitable to detect peri-implant bone loss around implants. But wireless mobility measureing device may not be suitable to detect the 1 mm peri-implant bone changes.

5. ISQ change pattern measured at different direction using magnetic RFA

Data from a conventional piezoelectric RFA are generally obtained with the transducer in the buccolingual position, because the shape of the transducer restricts its orientation when adjacent teeth remain. The measurement of the stiffness of the bone/implant complex in one direction by the use of piezoelectric RFA reflects the stability of an implant only partially, because implant–bone fusion occurs at 360° around a fixture and implant stability is a general reflection of this fusion. According to studies that used piezoelectric RFA, the ISQ of the mesiodistal(MD) measurement was 10 points higher than that of the buccolingual(BL) measurement(Fischer, et al. 2008, Veltri, et al. 2007). Unlike piezoelectric RFA, magnetic RFA(Mentor™: Ostell AB) is recommended to measure two ISQs, using the vibrations that occur in the directions of the higher and lower resonance frequency as a basis(Sennerby & Meredith 2008), because magnetic RFA can provide multi-directional measurements and it is known that the orientation of the transducer (mesiodistal or buccolingual) may affect the measurement of the implant stability quotient (ISQ). If the numerical difference of these two values is more than three ISQ units, both of them are displayed simultaneously. To ensure that both values are measured, the manufacturer of Mentor™ recommends that the probe be held perpendicular to the alveolar crest for one measurement, and in line with the crest for the other measurement. However, it is not known whether the ISQs estimated using Mentor™ vary with the direction of measurement in the same way as estimates measured using piezoelectric RFA. For this reason, the authors performed an randomized clinical trial to determine whether it is necessary to take measurements in both the mesiodistal(MD) and buccolingual(BL) directions in order to assess changes in bone–implant stiffness when such measurements are made using magnetic RFA.

5.1 Study design, methods and materials

A prospective clinical trial was completed, in a total of 53 patients, on 71 non-submerged dental implants that were inserted to replace the unilateral loss of mandibular molars. Two non-submerged implant systems with the same diameter (4.1mm), length (10mm), and collar height (2.8mm) were used in this clinical study. Standard Straumann® Dental Implants (Institut Straumann AG, Basel, Switzerland) were used for 32 of the implants. Osstem SSII Implants (Osstem Implants, Seoul, Republic of Korea) were used for the remaining 39 implants. Mentor™ (Ostell AB, Göteborg, Sweden) was used for to make magnetic RFA measurements. In addition, Type 4 Smartpeg™ (Osstell AB. Göteborg, Sweden) pegs were used during magnetic RFA. The ISQs were measured during the surgical procedure and at 4 and 10 weeks after surgery. Measurements were taken twice in

each direction: in the buccolingual direction from the buccal side (BL) and in the mesiodistal direction from the mesial side (MD). The mean of the two measurements in each direction was regarded as the representative ISQ of that direction. The higher and lower values of the buccolingual and mesiodistal ISQs were also classified separately. In other words, the ISQ of each implant was estimated using four measures at each time: the ISQ measured from the direction perpendicular to the alveolar crest on the BL; the ISQ from the direction parallel to the alveolar crest on the MD; the ISQ showing the higher value of the BL and MD (MX); and the ISQ showing the lower value of the BL and MD (MN). Discrepancies in ISQ were calculated by subtracting the BL from the MD in each period. The variation in ISQ was quantified by subtracting the MN from the MX during surgery; it was found to be the same as the absolute value of the ISQ discrepancy. The implants tested were classified into two groups: a group with variation in ISQ of three or more (3+Group) and a group with variation of less than 3 (3-Group).

5.2 Result of the study

During the surgical procedure, the ISQ discrepancies measured from 2 different directions were 0.36 to 1. Ten weeks later, the discrepancies had decreased to -0.14 to 0.42. Eight out of the 53 implants were classified in the 3+Group, accounting for 15.1% of the total(Table 1). The bone width at the insertion area was 6.89mm for the 3+Group and 6mm for the 3-Group (P=0.171). The average age of the 3+Group was 51.88 years, whereas that of the 3-Group was only 47.6 years. However, the difference was not statistically significant (P=0.398).

No differences were found between the BL and MD, but significant differences between MX and MN were observed at every measurement point for each implant system. The average BL during surgery showed a significant difference between the 3+Group and the 3-Group (P=0.002). No significant differences were observed in the MD values (P=0.177). The average MN during surgery showed a significant difference (P<0.001). In contrast, there were no significant differences in the MX values (P=0.417)(Table 2, 3). The ISQs were compared between the 3+Group and the 3-Group to determine whether there was a change in the values over time. A significant difference between the two groups was observed for the MN values (P=0.001). However, no significant differences were found for the MX values between the two groups (P=0.597). With respect to the BL and MD values, a significant difference was found between the two groups only for the BL value (P=0.001 for BL, P=0.392 for MD; Fig. 9).

5.3 Conclusion

The variation in ISQ obtained using magnetic RFA measurements from the two different directions was lower than that reported using piezoelectric RFA. The mean of the discrepancy in ISQ that was calculated from data obtained using magnetic RFA was <1 point. This showed that the discrepancy in ISQ was not skewed to the MD in such an extreme manner as the discrepancy of 10 points found using piezoelectric RFA. With this respect, two- directional measurement is not meaningful. However, our study demonstrated the possibility of observing a different pattern of change between the higher and lower values in a single implant. A significant difference was observed between the 3+Group and the 3-Group in the lower value (MN) of the change in ISQ during the initial healing period. This suggests that a longitudinal comparison of the higher and lower values may improve the evaluation of implant stability, in comparison with the use of a single directional measurement. This suggests that the follow-up observation of scale-based ISQ (lower and higher) values may detect a significant change in the ISQ pattern more readily than the direction-based observations (MD and BL).

Variables	ISQ variation		*P*-value*
	<3	≥3	
Implant based (N=71)			
Implant number	60	11	
Location			1
molar	30	6	
2nd molar	30	5	
Age (mean±SD)	47.00 ± 12.47	53.09 ± 10.27	0.123
Age			
10-50	33	3	0.111
>50	27	8	
Sex			
male	37	7	1
female	23	4	
Smoking			
Yes	26	4	0.75
No	34	7	
Width(mean±SD) †	6.93 ± 2.02	6.09 ± 0.30	0.12
Implant type			
Straumann	27	5	1
SSII	33	6	
Insertion depth (mean±SD) ‡			
Proximal	1.81 ± 0.56	1.85 ± 0.86	0.844
Distal	2.10 ± 0.59	1.91 ± 0.84	0.34
Participant based (N = 53)			
Participant number	45	8	
Location			
molar	20	4	0.771
2nd molar	25	4	
Age (mean±SD)			
Age			
10-50	24	3	0.486
>50	21	5	
Sex			
male	28	6	0.583
female	17	2	
Smoking			
Yes	17	3	0.99
No	28	5	
Width(mean±SD) †	6.89 ± 1.9	6 ± 0	0.171

Implant type			
Straumann	21	4	0.862
SSII	24	4	
Insertion depth (mean±SD) ‡			
Proximal	1.71 ± 0.53	2.03 ± 0.86	0.547
Distal	2.03 ± 0.6	2.13 ± 0.86	0.841

Data unit, except for continuous variables, are presented as the number. The units of age, width, and insertion depth are year, mm, respectively.
*P-values were calculated by a $\chi 2$-test for nominal variables, and Mann-Whitney test for continuous for continuous variables.
†Width was measured in the buccolingual direction using a microcompass, after implant insertion.
‡Insertion depth was checked by measuring the distance between the implant shoulders and the alveolar bone using a UNC periodontal probe.

Table 1. Comparison of demographic data between the two groups of patients with implants showing different levels of implant stability quotient (ISQ) variation during implant surgery (Cited from Park et al, 2010)

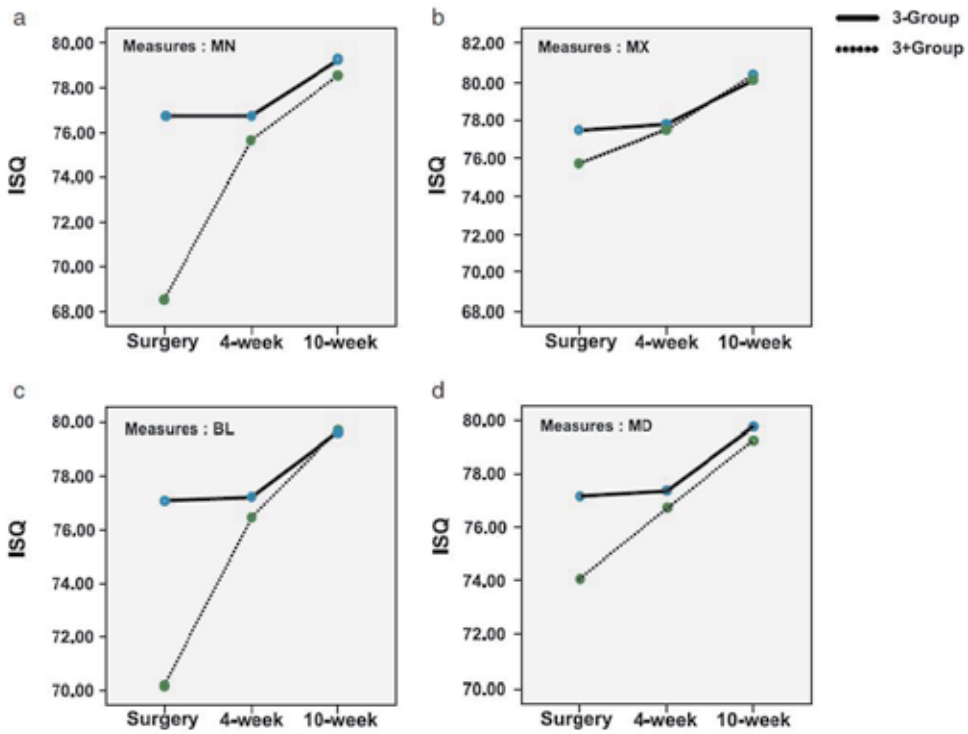


Fig. 9. The comparison of the pattern of change in the implant stability quotient (ISQs) obtained from the four measures from surgery to 10 weeks after surgery. 3+Group=the group with ISQ variation of 3 or more. 3-Group=the group with ISQ variation of < 3. (a) Pattern of change of minimum. (b) Pattern of change of maxilmum. (c)Pattern of change of buccoligual. (d) Pattern of change of mesiodistal.

	ISQ (mean ± SD)		ISQ (mean ± SD)	The difference of the paired data (mean ± SD)	***P***-value *
All implants (N=53)					
During surgery					
BL†	76.01 ± 6.57	MD‡	76.69 ± 6.26	0.71 ± 3.21	0.063
MX§	77.2 ± 6.13	MN ‖	75.51 ± 6.6	1.72 ± 2.79	<0.001
At post-operative week 4					
BL	77.09 ± 5.59	MD	77.28 ± 5.58	0.19 ± 1.82	0.469
MX	77.72 ± 5.52	MN	76.3 ± 5.6	1.11 ± 1.46	<0.001
At post-operative week 10					
BL	79.65 ± 3.98	MD	79.69 ±3.97	0.01 ± 1.76	0.671
MX	74.56 ± 6.19	MN	73.04 ± 6.2	1.58 ± 2.47	<0.001
Straumann (N=25)					
During surgery					
BL	73.28 ± 6.38	MD	74.32 ± 6.02	1.10 ± 2.72	0.056
MX	74.56 ± 6.19	MN	73.04 ± 6.2	1.58 ± 2.47	<0.001
At post-operative week 4					
BL	74.8 ± 4.52	MD	75.22 ± 4.28	0.42 ± 1.48	0.199
MX	75.54 ±4.23	MN	74.48 ±4.54	1.06 ± 1.1	<0.001
At post-operative week 10					
BL	78.1 ± 3.65	MD	78.34 ± 3.76	0.24 ± 1.98	0.732
MX	78.78 ± 3.51	MN	77.66 ± 3.8	1.12 ± 1.64	0.001
SSII (N=28)					
During surgery					
BL	78.45 ± 5.82	MD	78.8 ± 5.78	0.36 ± 3.6	0.523
MX	79.55 ± 5.17	MN	77.71 ± 6.24	4.84 ± 3.09	<0.001
At post-operative week 4					

BL	79.14 ± 5.72	MD	79.13 ± 6.02	-0.02 ± 2.07	0.861
MX	79.66 ± 5.86	MN	78.5 ± 5.87	1.16 ± 1.74	0.001
At post-operative week 10					
BL	81.04 ± 3.8	MD	80.89 ± 3.82	-0.14 ± 1.54	0.71
MX	81.43 ± 3.69	MN	80.5 ±3.88	0.93 ± 1.23	0.001

****P***- value was calculated using a Wilcoxon signed ranks test between BL and MD, or between MX and MN

†BL is the ISQ measured from the direction perpendicular to the alveolar crest at the buccal side

‡MD is the ISQ measured from the direction parallel to the alveolar crest at the mesial side

§MX is the ISQ of the direction that showed the higher value between BL and MD

‖ MN is the ISQ of the direction which show the lower value between BL and MD

Table 2. Comparison of four different measures of implant stability quotient (ISQ) (Cited from Park et al, 2010)

Period	Mode	ISQ Variation				***P***-value †
		< 3 (N=45) ISQ (mean ± SD)	***P***-value*	≥ 3 (N=8) ISQ (mean ± SD)	***P***-value*	
All implants (N=53)						
During surgery	BL	77.08 ± 5.97	0.567	70 ± 6.95	0.161	0.002
	MD	77.17 ± 5.8		73.94±8.48		0.177
	MX	77.48 ± 5.85	<0.001	75.56±7.97	0.012	0.417
	MN	76.78 ± 5.9		68.38±6		<0.001
At post-operative week 4	BL	77.23 ± 4.81	0.663	76.31±9.26	0.553	0.650
	MD	77.4 ± 4.95		76.63±8.75		0.722
	MX	77.78 ± 4.86	<0.001	77.38±8.81	0.018	0.862
	MN	76.79 ± 4.87		75.56±9.1		0.551
At post-operative week 10	BL	79.66 ± 3.99	0.471	79.63±4.14	0.553	0.639
	MD	79.78 ± 3.83		79.19±4.93		0.731
	MX	80.16 ± 3.81	<0.001	79.86±3.93	0.018	0.866
	MN	79.28 ± 3.97		78.5±4.8		0.645

****P***- value were calculated using a Wilcoxon signed ranks test between BL and MD, or between MX and MN in each group based on ISQ variation

† ***P***- value were calculated using a two-way analysis of variance between the two groups based on ISQ variation.

Table 3. Comparison of four different measures of implant stability quotient (ISQ) between the two implant groups based on the level of ISQ variation during implant surgery (Cited from Park et al, 2010)

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6

An Overview Regarding Contemporary Biomechanical Aspects on Immediate Loading Dental Implants

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1. Introduction

The use of dental implants for the treatment of partially or completely edentulous patients has become an effective therapy in the last years (Romeo et al., 2004). Therefore, the development of dental implants represents a remarkable advance in trends of Dentistry allowing to oral edentulous patients rehabilitation characterized by a high and long-term success.

Despite the great use of dental implants, many factors regarding its biomechanical aspects remain incompletely understood. According to Gross (2008), a preliminary consideration of the natural anatomy of the dentition, occlusion and alveolar support mechanisms would be helpful to provide a perspective for planning of implant supported restorations. Criteria as primary stabilization, bone quality, number, distribution, width, length and design of the dental implants, surface treatments, implant-abutment connection, and occlusion aspects must be also considered for the success of immediate, early or delayed loading dental implants (Casap et al., 2011).

In the delayed loading period, the implants are kept load free during the osseointegration period (varying from 3 to 6 months according to the insertion anatomic place and implant system requirements) and are rehabilitated afterward. In the early loading period, the rehabilitation of the implant is done during the first 3 months after the implantation, and according to Esposito et al. (2009), it is now recognized to generate harmful mechanical loading forces on the implants just at the time as the healing bone process has started and has not been finished yet.

In the immediate loading period, the waiting between implantation and loading is limited at a maximum of 48 hours, and the loading is only performed when good primary stability has been achieved. This procedure reduces the number of clinical steps and appears to allow a more comfortable and acceptable condition for the patients (Al-Omiri et al., 2005). Among the reasons for the immediate loading dental implants is the surgical trauma, which is minimized, in a one-step surgical procedure (Misch et al., 2004a). According to Misch et al. (2004a), the reduction of the surgical trauma in immediate loading procedures can be obtained by reducing heat during the surgical steps and reducing the stress on the bone-implant interface. The great advantage, besides avoiding a second surgical procedure, is the

possibility to carry the dental implants (provisionalization) immediately after the surgery or some brief period after it (Misch et al., 2004a, 2004b). Several *in vitro* and *in vivo* studies have observed similar success between immediate and/or delayed loading implants (Attard & Zarb, 2005; Becker et al., 1997; Brånemark et al., 1999; Chiapasco et al., 2001; Chow et al., 2001; Degidi & Piattelli, 2003; Degidi & Piattelli, 2005; Ericsson et al., 1994; Gatti et al., 2000; Misch & Wang, 2003; Misch et al., 2004a, 2004b; Morton et al., 2004; Nkenke et al., 2005; Schnitman et al., 1997). However, in order to achieve success in immediate loading techniques its required a proper planning prior to implantation and considerable coordination among the oral surgeon, the prosthodontist and the laboratory. And it's thus required the exactly intraoperative transfer of the previously planned. Furthermore, the patient is very often required to wait many hours after the implant surgery for the completion of the immediate prosthetic work in the laboratory and it´s installation.
Based on the above information, the aim of this Chapter was to accomplish an overview regarding contemporary biomechanical aspects on immediate loading dental implants.

2. Primary stabilization

Primary stabilization is influenced by the surgical procedures, implants design and bone quality and quantity. After dental implant insertion, bone responds to the local stimulus, thus propitiating its repair through properties of bone plasticity, resorption and apposition. A bone remodelation begins on the bone-implant interface, accelerated by the low intensity loads, which induce the bone cells stimulation (Kenney & Richards, 1998). The patient's diet has a major importance during the bone apposition and remodelation after the immediate loading procedures. Consequently, soft diet should be indicated during the initial period (3 to 4 months) of the healing process and bone deposition (Misch et al., 2004a, 2004b). Most of the immature bone tissues formed is substituted by lamellar bone 3 to 6 months after the surgical placement of the implants in the delayed loading procedures (Duyck et al., 2001). Therefore, the immediate loading dental implants not only can reduce the risks of development of fibrous tissues, but also can minimize the development of immature bone, promoting a faster maturation of the immature bone to lamellar bone (Duyck et al., 2001; Zubery et al., 1999). Load transfer depends on successful osseointegration, which is characterized as a direct structural and functional connection between the bone and the implant surface (Adell et al., 1981; Brånemark et al., 1977). Thus, increasing the bone-implant contact surface area, directly related to implant diameter and length, can improve the osseointegration of implant to bone and establish implant stability. According to Misch et al. (2004a, 2004b), the smaller the applied stress to the bone, the smaller will be its micro-deformation and an increased surface area on the bone-implant interface will be expected. Short and long-term histological studies have demonstrated that immediate loading implants do not necessarily result in excessive stress on the bone-implant interface (Piattelli et al., 1993).

3. Bone quality and quantity

The close relationship between the bone and the implant is the core of osseointegration. Occlusal overloading on poor-quality bone can be a crucial factor in implant success and longevity. Different bone density may be observed for each region of the jaws. The posterior regions of the jaws usually have less dense bone than the anterior regions (Misch et al.,

1999). Generally, the mandible has a denser and thicker cortical layer than the maxilla, with the cortical layer becoming thinner and more porous posteriorly. According to Morris et al. (2001), poor quality and quantity of surrounding bone was ranked as the most influential factor for reducing the success rate of dental implant treatments. Misch et al. (1999) stated that the density of the bone is directly proportional to the strength of the bone, with less density demonstrating strength reduction of 50% to 80% compared to higher density bone tissues. In addition, Goodacre et al. (2003) reported that dental implants loaded in lower density bone averaged 16% higher failure rates compared to more ideal bone quality. In a multicenter study by Weng et al. (2003), the posterior maxilla produced a 25% failure rate when short implants were used to support the prosthesis, and the implant failure occurred during the first 18 months of loading. Consequently, researchers have been unanimous for the indication of a larger number of implants for the rehabilitations of partially or completely edentulous maxillae. Therefore, the greater the number, the smaller will be the biomechanical risk. The design of the implants is more associated to the area of functional surface than to its size. Cylindrical implants without threads and with larger diameter possess smaller surface area in comparison to a screw implant of smaller diameter (Misch et al., 2004b). Consequently, implants with threads should be the most appropriate for the immediate loading procedures. This aspect will be focused in another section of this Chapter. Finally, following the recommendations of Attard & Zarb (2005), the posterior region of the jaws should be carefully evaluated for the indication of immediate loading implants. The cantilever elimination and the accomplishment of bilateral ferulization seem to be advantageous in order to reduce the stress concentrations on peri-implant bone.

4. Implant design

Several efforts have been focused to the knowledge and control of all factors that could enhance the osseointegration process, which includes those related to the implant design. The implant design refers to three-dimensional architecture of an implant system (Sykaras et al., 2000; Triplet et al., 2003), that is closely related to biological and biomechanical issues, especially those associated to the force transfer characteristics of implants (Geng et al., 2004; Siegele & Soltesz, 1989; Strong et al., 1998; Sykaras et al., 2000). Several aspects can be addressed in trends of implant design, but features related to the fixation shape, type of prosthetic interface and surface characteristics (surface topography and chemical composition) have been considerate the most important aspects within this context (Sykaras et al., 2000).

4.1 Dental implant shape

The Implant shape determines the surface area available for stress transfer and governs the initial stability of the fixation (Steigenga et al., 2003). Different kinds of implant shape designs have been described in the literature; however the root form implants have been dominating the implant market since it was developed. These dental implants are characterized by a body that works as a vertical bone column (Misch, 2008) and it can be presented as one or two-pieces implants (Jones & Cochran, 2006), solid or hollow, with a parallel, tapered/conical, or stepped shape/outline and a flat, round, or pointed apical end (Sykaras et al., 2000; Triplet et al., 2003).

4.1.1 Cylindrical vs tapered dental implants

Finite Element Analysis (FEA) and *in vivo* studies have demonstrated that taper implants are associated with advantages over cylindrical implants, including a greater initial stability (Lee et al., 2010) and the avoidance of "punching" stresses (Rieger et al., 1990). However, from a biomechanical perspective, studies have shown that cylindrical implants produced a more desirable stress profile than the conical shaped counterparts (Holmgren et al., 1998; Mailath et al., 1989; Siegele & Soltesz, 1989).

Within this context, recent studies have shown that in order to induce controlled compressive forces in the cortical bone layer during the implant insertion, a new hybrid self-tapping implant has been specifically designed for the use in critical quality bone, which combines the advantages of a conical implant with those of a cylindrical shape (Toyoshima et al., 2011).

4.1.2 One-piece vs two-pieces dental implants

Another category of implant design classify theses fixations as one-piece implant (non-submerged placement) which comprises the implant body and the soft tissue healing abutment manufactured as one piece, or two-pieces implants (submerged placement) that consist of an implant body and a separate abutment (Jones & Cochran, 2006). Regarding biomechanical issue, it was demonstrated that one and two-pieces implants have similar low force transmission characteristics under vertical loading (M.C. Cehreli et al., 2004) and since these stresses are extremely low, they do not seem to have any clinical relevance on the mechanical as well as the biomechanical outcomes (Pilliar et al., 1986; Szmukler-Moncler et al., 1998).

5. Dental implant prosthetic interface

The prosthetic interface represents the level in which the superstructure or the abutment connects to the implant body (Sykaras et al., 2000; Triplet et al., 2003). It is considered an important aspect of implant design since it can influence the force transmission mechanism by implant-prosthesis system (Bozkaya & Muftu, 2003; Geng et al., 2001) and the amount of bacterial invasion of the implant internal part (Tesmer et al., 2009). To date, both these factors are markedly implicated with the pathological bone loss around dental implants (Misch, 2008), which can compromise the maintenance of peri-implant aesthetic harmony or implant system stability.

The implant-abutment connection can be classified as external, which includes hexagonal, octagonal, and spline, with its interdigitating projections and slots, or internal that includes the morse-taper interface, the internal hexagon, and the internal octagon (Sykaras et al., 2000; Triplet et al., 2003). In general, morse-taper connections are associated with better outcomes regarding the maintenance of the peri-implant bone, since they have been associated with a lesser bacterial infiltration (Mangano et al., 2009) and a better force transmission mechanism by implant-prosthesis system (Merz et al., 2000), although other studies have found similar marginal bone levels and biological outcomes of different implant designs (Engquist et al., 2002; Heydenrijk et al., 2002).

As described previously, one limitation with the implant-suport rehabilitation relates to the marginal bone loss that still is seen in some implant systems. The probable factors are: a possible bacterial colonization located between implant and abutment (Goodacre et al., 2003) and/or a stress concentration at the neck of implants resulting from prosthesis

overloading leading to bone microfractures. In an attempt to reduce this stress concentration in the bone-implant interface, the companies put on the market different types of connections attached to the prosthetic abutment. From a biomechanical perspective, the major distinction among implant systems is the implant-abutment connection. Mechanical failures, such as loosening and/or fracture of occlusal screws, abutment screws or abutments, are related to the type of implant-abutment connection (Akca et al., 2003). When it comes to biomechanics, an internal conical joint design is mechanically more stable than an external hexagonal or butt-joint implant-abutment connection, which improves the clinical outcome (Merz et al., 2000).

In another words, the type of connection is important because it directly interfere in the prosthetic restoration, and the restoration must receive and transmit the masticatory loads to the implants in a controlled manner to avoid mechanical and biological failure after the osseointegration. When inadequate tensions occur in the bone-implant interface, bone resorption may occur in incompatible levels with the maintenance of osseointegration. There are already some experimental, numerical, and clinical studies evaluating the influence of implant-abutment connection on osseointegrated implants (Pessoa et al., 2010). For Hebel & Gajjar (1997), the success of implant-supported restoration and the health of surrounding tissues are related to the accuracy and fit between the components, stability at implant-abutment interface, and the resistance of this interface submitted to masticatory loads (Hebel & Gajjar, 1997). The stability at implant-abutment interface may be influenced by several factors, such as, connection type (M. Cehreli et al., 2004) and retention system (Pellizzer et al., 2010).

5.1 External hexagon

The initial purpose of external hexagon implants was to transmit torque during surgical placement. Afterwards, the external hexagon was also shown to work as an antirotational mechanism and to orient the abutment in single tooth prostheses (Davi et al., 2008). The biomechanical complications reported are loosening or fracturing of the abutment and prostheses screws (Merz et al., 2000). Therefore, the external hexagon connection continues to be comprehensively used (Figures 1, 2 and 3) and studied with the aim of improving the dimensional machining tolerances of the components (Schulte, 1994), and making this screwed junction more stable.

The external hexagon system has advantages such as (a) suitable for the two stage method, (b) an anti-rotation mechanism and retrievability and (c) compatibility among different systems. Possible disadvantages of the external hex are: (a) micro-movements because of the size of the hex, (b) higher centre of rotation that leads to lower resistance for rotational and lateral movements and (c) a micro gap leading to bone resorption. However, the weak-link to the fixture of the external hexagon configuration, is often referred as a fail-self mechanism for over-loading situations (Maeda et al., 2006).

Davi et al. (2008) evaluated the integrity of the external hexagon of an implant system with internal and external hexagons but with prosthetic connection through the external hexagon (internal torque) in comparison with that of an implant system with external hexagon with mount (external hexagon). They concluded that the internal torque implant system may be preferable in clinical situations where implant placement within a certain bone density could generate torques higher than 60 N.cm. After application of an 80 N.cm torque, the external hexagon did not support the torque, suffering deformation of its external hexagon. According to the authors, the fragility of the external hexagon of some systems can

compromise the future dental prosthesis if deformation of the hexagon vertices occurs due to the torque applied in the implant mount when the implant is placed. Greater rotation at the interface implant-abutment transfers stress to the implant components and to the bone, which could lead to screw loosening or fracturing, microfractures of bone, and loss of osseointegration.

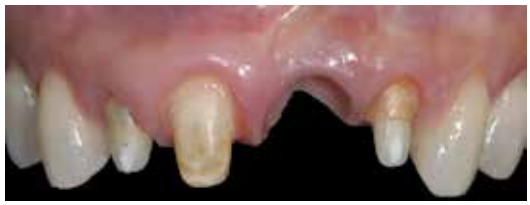

Fig. 1. Buccal view of a 3i external hexagon dental implant after provisionalization and soft tissue conditioning

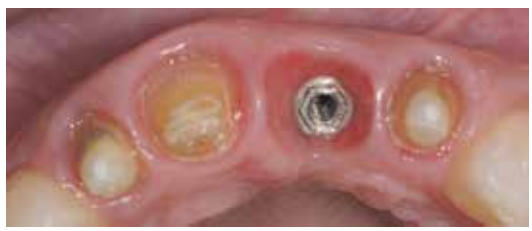

Fig. 2. Occlusal view of the 3i external hexagon dental implant

Fig. 3. Zirconia-based ceramic crowns after installation

5.2 Internal hexagon

One of the most important advances in the Implantology was the development of internal prosthetic connections, such as internal hexagon and morse-taper, in which excellent mechanical stability has been demonstrated *in vitro* (Merz et al., 2000). To ensure stability of the implants in long-term, science has turned its attention to improving the accuracy and passivity of prosthetic components, since it is unclear the level of mismatch between components that can affect the treatment success. Recently, some internal implant connections have appeared on the market, which are able to receive higher torques during surgical placement, with effective screw joint stability.

The internal hexagon system has advantages such as (a) ease in abutment connection, (b) suited for one stage implant installation, (c) higher stability and antirotation because of a wider area of connection and suited for single tooth restoration, (d) higher resistance to lateral loads because of the lower centre of rotation and (e) better force distribution; while its

disadvantages are (a) thinner lateral fixture wall at the connecting part and (b) difficulty in adjusting divergences in angles between fixtures (Maeda et al., 2006).
From a biomechanical point of view, the design of the internal hexagon implant establishes a greater hexagon retention depth and the more precise and safer antirotational components of the internal hexagon system reducing the stress at the neck of the implant and retention screw (Hunt et al., 2005; Krennmair et al., 2002). In a study conduced by da Silva et al. (2010) evaluating the influence of connector and implant design on implant-tooth-connected prostheses, when the internal hexagon implant was assessed in the three types of connection (rigid connection, semirigid connection and rigid connection with oclusal screw), it was observed that the stresses on it occurred more in the apical region in comparison with the external hexagon, probably because of the greater depth of union of the denture to implant, and that the internal hexagon presented better stress dissipation characteristics than the external hexagon design. According to Krennmair et al. (2002), transferring the fulcrum point from the neck of the implant (external hexagon) to close to the middle third of the implant (internal hexagon), as well as the greater denture retention depth in the internal hexagon implant, reduced the power arm in the face of biomechanical behavior, making the implant more stable, with less tendency to screw loosening of fracturing, and improving the dissipations of tensions.
Bone resorption around the implant neck or cervical area may be explained by many other factors, however, smaller stress at cervical area of the internal hexagon system might contribute to the bone preservation, while larger stress at tip area might be one of the risk factors for bone resorption or fixture fracture (Maeda et al., 2006). Maeda et al. (2006), in an attempt to clarify the difference in the stress distribution patterns between implants with external or internal-hexagon connection systems using *in vitro* models, suggested that fixtures with internal-hexagon showed widely spread force distribution down to the fixture tip compared with external hexagon ones.
Pellizzer et al. (2010) evaluated the stress distribution of different retention systems (screwed or cemented) associated to different prosthetic connections (external hexagon, internal hexagon and morse-taper) in 3-unit implant-supported fixed partial prostheses through photoelasticity, and concluded that the internal hexagon implant was more favorable according to the biomechanical standpoint and also that the oblique load increased stress in all systems and connections tested. They believed that the stability at the implant-abutment interface, with internal connections, exhibits better contacts between the surfaces of abutment and implant, which decreases the micromovements during loading. In their study, among the internal connections, the morse-taper indicated better stress distribution.

5.2.1 Morse-taper

While high incidences of mechanical complications were reported for external-hexagon implants (Binon, 1996; Merz et al., 2000), insignificant episodes of abutment loosening were reported for solid-screw morse-taper implants (Levine et al., 1999). A different type of internal connection, known as morse-taper, was developed in an attempt to solve some biomechanical problems that still occur with internal hexagons implants. The implants have a conical union between implant and abutment, and this bond strength is proportional to the force used to insert. Tapered interference fits provide a reliable connection method between the abutment and the implant (Bozkaya & Muftu, 2003) and can also withstand

prolonged lateral force applications (Merz et al., 2000). In the most common mechanical attachment method, a retaining-screw (abutment screw) is used to fix the abutment with respect to the implant. Another approach is to use a screw with a relatively large tapered end; the term taper integrated screwed-in (TIS) abutment is used to indicate an abutment, which uses simultaneously a screw and a tapered fit. A tapered interference fit (TIF) between the abutment and the implant is also used in some implant systems to provide the connection (Bozkaya & Muftu, 2005). For the systems using a screw, the connection between the implant and the abutment depends on the screw-preload, which is generated by applying a predetermined amount of torque during installation (Bozkaya & Muftu 2003). Designs in which the screw has a large tapered end essentially work like a tapered interference fit, and the screw threads do not appear to contribute to the connection; this mechanism relies on the large contact pressure and resulting frictional resistance, in the mating region of the implant–abutment interface, to provide a secure connection. In the morse-taper connection the bitting force acts in the direction of the abutment insertion, hence aids to secure the connection. This situation is in direct contrast to implants using screws where the biting force lowers the pretension in the screw (Bozkaya & Muftu, 2003).
Based on the previously information, it is clear that the morse-taper implant-abutment connection possesses higher mechanical behaviour than the external-hexagon (butt-joint) designs. In the external-hexagon implant design, the abutment screw alone is primarily responsible for maintaining the implant-abutment complex assembly under functional loads (Akca et al., 2003). Therefore, the axial preload of the abutment screw is a determining factor for the stability of the connection (Burguete et al., 1994). However, in the morse-taper connection, lateral loading is resisted mainly by the tapered design, which prevents the abutment from tilting (Akca et al., 2003). Because of the tapered design, a high normal pressure is maintained in the contact area, allowing stable retention of position by frictional forces (Merz et al., 2000). Taper joint connections with a conical seal, or Morse's taper, have advantages of better sealing capabilities in closing the micro-gap on top of those in an internal hexagon system (Maeda et al., 2006).
Regarding immediately loading implants, it was demonstrated that the implant-abutment connection design did not significantly influence the bone strain and the implant displacement. On the other hand, the Morse-taper connection presented superior abutment stability and the least stress concentration in the abutment screw, and the internal hexagon and external hexagon implants presented the lowest strain levels (Pessoa et al., 2010). Pieri et al. (2011) compared the clinical and radiographic outcomes of single implants immediately placed and restored with two different implant-abutment connections, prosthetic abutments with a Morse-taper connection and a platform switch (test group), and conventional abutments with an internal connection and a matching diameter (control group). No statistical significant differences were found between the two groups for periodontal parameters, marginal soft tissue level change, or papilla height, but greater marginal bone loss was observed at the control sites compared to the test sites. Although the control group demonstrated a slight increase in marginal bone loss compared to the test group, the peri-implant soft tissues were very stable with both types of implant-abutment connection after 12 months of loading.

5.3 Platform switching

According to Serrano-Sánchez et al. (2011), the platform switching effect was accidentally established in the 1980s and early 1990s when different dental implant manufacturers

introduced implants of larger diameter before producing the corresponding abutments of the same measures. Thus, it involves reducing the abutment diameter in comparison with the diameter of the dental implant. Sánchez reported that it is possible to use abutments with a diameter smaller than the implant body width, or alternatively an implant design can be used in which the neck diameter is increased with respect to the implant body width, like suggested by Calvo-Guirado et al. (2009). The contemporary literature is unanimous in affirm that the use of platform switching dental implants improves bone crest preservation, contributes to biological space reposition, and, therefore, is directly related to excellent aesthetic outcomes. Conversely, Sabet et al. (2009) reported that the platform switching should be not used in mandibular implant-mucosal support prostheses, since reduction of the diameter of the junction lessens the abutment resistance in response to occlusal loading applied in the posterior area of the overdentures.

6. Surface characteristics

The surface characteristics have been considerate by Albrektsson et al. (1981) as relevant factors that could influence the establishment of a reliable osseointegration. In fact, it was demonstrated that the surface properties could influence the healing dynamics around bone-interfacing implants (Lee et al., 2008). Within this context, topographic and chemical properties have been considerate the most relevant features related to surface characteristics since they play a major role in the biological events that follow implantation (Le Guéhennec et al., 2007).

6.1 Topographic properties

According to Stanford (2008) the evaluation of an implant surface refers to macroscopic and microscopic features that, when combined, are used to describe the surface topography, being considered a relevant issue, since it can produce orientation and guide locomotion of specific cell types and has the ability to directly affect cell shape and cell function (Brunette & Chehroudi, 1999; Chou et al., 1998; Qu et al., 1996).

6.1.1 Macroarchitecture

The main characteristics regarding the macroarchitecture include the presence or absence of threads as well its design which are considered important factors that could affects the osseointegration process (Vidyasagar & Apse, 2004), because they play an important role in load transfer from dental implant to the surrounding bone (Schenk & Buser, 1998), affecting the stress distribution and marginal bone resorption (Chun et al., 2002). Furthermore, threads are used to maximize the initial contact, improve stability (Sykaras et al., 2000; Triplet et al., 2003) and enlarge the implant surface area (Kong et al., 2008). According to Misch et al. (2006), the greater the number of threads, the greater will be the surface area, if all other factors are equal. On the other hand, the thread number may be more significant for the shorter implant in the posterior regions of the mouth with reduced bone density.
Regarding thread design, a sort of varying geometric pattern that determine the functional thread surface can be found relating to thread depth, thread pitch, thread helix angle, thread thickness and thread face angle (Misch, 2008). These two last geometric aspects determine the shape of the thread, which can be V-shape, reverse buttress or a square thread (Strong et al., 1998; Thakur, 1997) and this last one is associated to the highest contact area (Lee et al., 2008).

6.1.2 Microarchitecture

The surface microarchitecture of dental implants refers to the classification of the implant design based on the average surface roughness (Sa). According to Triplet et al. (2003) most of the papers have described the dental implants surface as smooth (Sa ≤ 1.0 μm) or rough (Sa > 1.0 μm), although other terms, such as porous, minimally rough (0.5–l.0 μm), intermediately rough (1–2.0 μm), and rough (2–3.0 μm) have also been proposed (Wennerberg et al., 1995).

a. Smooth surfaces

The original Brånemark implant (Nobel Biocare, Göteborg, Sweden) is a turned screw of minimal surface roughness (Sa between 0.5 and 1.0 μm) that represents the main example for smooth surfaces. Nowadays, these surfaces have not been indicated yet, since they are associated with several disadvantages, including: slower biological processes at the bone–implant interface (BIC) (Elias et al., 2008), poor mechanical integration with bone, since these surfaces provide no resistance to mechanical forces at the BIC, allowing epithelial down growth and are associated with deeper peri-implant pockets (Puleo, 2006).

b. Rough surfaces

The development of rough implant surfaces represents a great advance to solve the problems of smooth surfaces. In fact, rough surfaces typically result in better clinical outcomes, probably due to the advantages offered by these superficies, such as lesser crestal bone loss (Wiskott & Belser, 1999), faster rate and higher degree of bone formation (Abrahamsson et al., 2004), higher percentage of contact at the BIC (Suzuki et al., 1997), increased surface energy, improves matrix protein adsorption, bone cell migration and proliferation, and finally osseointegration (Dohan Ehrenfest et al., 2009).

On the other hand, surface roughness may lead to negative consequences due to the changes on surface microcomposition (M. Cehreli et al., 2004), such as increased risk of peri-implantitis, especially in high surface roughness (Albrektsson & Wennerberg, 2004), since rough surfaces acts in favor to plaque accumulation (van Steenberghe et al., 1999) and increased risk of ionic leakage, since greater surface roughness gives greater tissue-implant contact and hence ionic leakage (Albrektsson & Wennerberg, 2004).

The main clinical indication for using an implant with a rough surface includes areas with poor quality or volume of the host bone, since in these unfavorable clinical situations early and high bone-to-implant contact would be beneficial for allowing high levels of loading (Conner et al., 2003; Testori et al., 2001).

c. Porous surfaces

Some papers have described the Porous surface, which represents those with an extremely high Sa. These surfaces are characterized by pore size, pore shape, pore volume, pore depth and different from the rough surfaces due to the lack of sharp edges (Sykaras et al., 2000). It is evident that bone ingrowth into porous implant surfaces may result in improved osseointegration and mechanical stability by interlocking the surrounding bone tissue with the implant (Götz et al., 2004). These surfaces are produced when spherical powders of metallic or ceramic material become a coherent mass with the metallic core of the implant body (Sykaras et al., 2000, Triplet et al., 2003), being affected by the size of spherical particles, temperature and pressure conditions of the sintering chamber (Esposito et al., 1998).

6.2 Physicochemical properties

These properties usually refer to factors such as surface energy, charge and composition of the titanium implants (Albrektsson & Wennerberg, 2004; Puleo, 2006). These characteristics differ, depending on their bulk composition and surface treatments; affecting biological process including the protein adsorption and cell attachment (Le Guéhennec et al., 2007), as well largely determines the chemical stability/reactivity (Kasemo & Lausma, 1988).
The surface energy is a relevant issue, since affects directly the hydrophilicity of the surface. It is well know that highly hydrophilic surfaces (higher surface energy) seem more desirable than hydrophobic ones in view of their interactions with biological fluids, cells and tissues (Buser et al., 2004; Zhao et al., 2005).

7. Methods of surface modification

In order to improve the osseointegration of titanium dental implants, clinical efforts have been done to develop methods to provide an enhanced osseous stability through microsurface mediated events (Stanford, 2008) by the micro and nanoscale modifications of dental implant surface roughness and chemistry.
With surface treatment, it is possible to change the surface features of the titanium dental implant, such as chemical composition, energy level, morphology, topography and roughness (Upp et al., 2006). To date, several methods used to increase roughness, frequently tend to change the surface chemistry as well as texture (Puleo, 2006), such as Alkali and heat treatments (Lee et al., 2002).
For didactic reasons, only the main methods usually employed to modify surface properties will be discussed in detail in this Chapter and they can be classified as ablative (remove material from the surface) or additive (deposit material on implant surfaces) (M. Cehreli et al., 2004; Puleo, 2006).

7.1 Ablative methods

a. Grit blasting

This method consists in blasting the implants with hard ceramic particles, resulting in different surface roughnesses according to the ceramic particles sizes, time of blasting, pressure and distance from the source of particles to the implant surface (Sykaras et al., 2000; Triplet et al., 2003). Several ceramic particles have been used, such as alumina, titanium oxide and calcium phosphate particles (Le Guéhennec et al., 2007).

b. Acid etching

In this method the metallic implant is immersed into an acidic solution such as HCl, H_2SO_4, HNO_3 and HF (Le Guéhennec et al., 2007) which erodes the implant surface, creating pits of specific dimensions and shape that vary according to the concentration of the acidic solution, time, and temperature (Sykaras et al., 2000). Through acid etching it is possible to control the roughness, number, size and porous distribution on micrometer and nanometer scales (Elias et al., 2008).

c. Grit blasting followed by acid etching

This surface was produced by blasting implants with 250 to 500 mm corundum grit followed by acid etching in a hot solution of hydrochloric acid and sulfuric acid (Puleo, 2006) that have been developed by Institute Straumann (Basel, Switzerland) (Buser et al.,

1998). Sandblasting produces macro-roughness onto which acid etching superimposes micro-roughness (Cochran et al., 1998).

7.2 Additive methods

a. Plasma-spraying

Plasma spray coating is one of the most common methods for surface modification. This method consists in injecting both Ti or HA powders into plasma torch at high temperature (Le Guéhennec et al., 2007). Thickness depends on particle size, speed and time of impact, temperature, and distance from the nozzle tip to the implant surface area (Sykaras et al., 2000, Triplet et al., 2003).

It is relevant to state that by coating implants with hydroxyapatite (HA) both the roughness and surface chemistry are altered, resulting in an increased roughness with a dramatically change in surface chemistry from TiO_2 to a bone-like ceramic with the potential to chemically bonding to bone (Puleo, 2006). Furthermore, beyond plasma spray coating, other methods have been developed to coat metal implants, such as sputter-deposition, sol–gel coating, electrophoretic deposition or biomimetic precipitation (Le Guéhennec et al., 2007).

b. Anodization

This method produces modifications in the microstructure and the crystallinity of the titanium oxide layer (Sul et al., 2002) (Figures 4 to 9). It consists of preparing a porous oxide surface by potentiostatic or galvanostatic anodization of titanium in strong acids (H_2SO_4, H_3PO_4, HNO_3, HF) at high current density (200 A/m^2) or potential (100 V) (Le Guéhennec et al., 2007). The properties (thickness, microstructure, composition) of the oxide will depend on different process parameters such as electrolyte composition, anodic potential, current, temperature, and electrode geometry (Triplet et al., 2003).

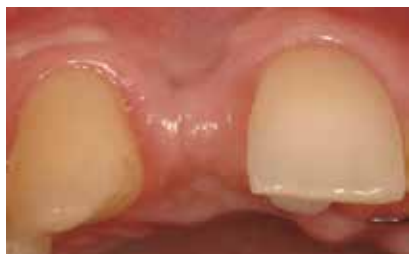

Fig. 4. Preoperative clinical aspect of the edentulous space

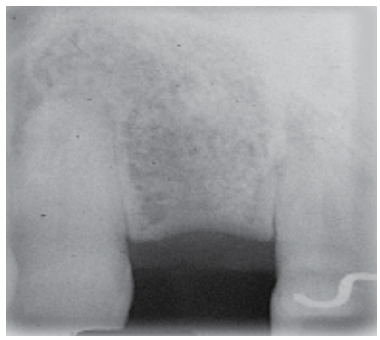

Fig. 5. Preoperative periapical radiographic

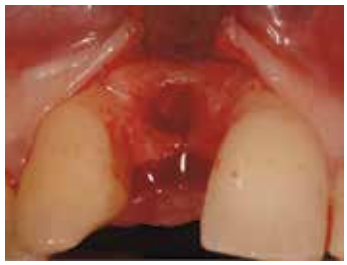

Fig. 6. Surgical approach to the alveolar bone

Fig. 7. Nobel Replace Select dental implant being positioned

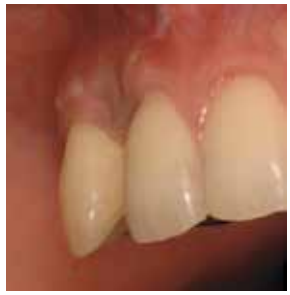

Fig. 8. Postoperative clinical aspect of the final prosthesis

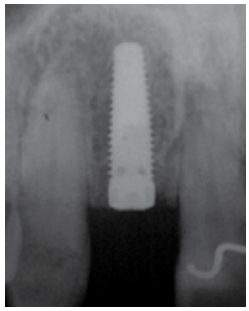

Fig. 9. Postoperative radiographic aspect of the dental implant

7.3 Incorporation of biologically active drugs into titanium dental implants

Modern trends associated with dental surface modification include the incorporation of several growth and differentiation factors either alone or combined as biocoatings of conventional implants. These factors include the bone morphogenetic proteins (BMPs), in particular BMP-2 and BMP-7 or osteogenic protein-1 (OP-1), and growth factors such as platelet-derived growth factor (PDGF), insulin-like growth factor (IGF), and transforming growth factor-beta 1 (TGF,-1) alone or combined with IGF-1, and TGF (Mavrogenis et al., 2009).

Other biological coatings that have been used to improve osseointegration of titanium implants include collagen and other extracellular matrix proteins such as fibronectin and vitronectin (Ku et al., 2005), and systemic administration of pharmacological agents such as ibandronate and human parathyroid hormone (Dayer et al., 2010).

8. Short implants

In a multicenter retrospective 6-year case series study, Misch et al. (2006) stated that there are three risk factors that increase stress and may explain why posterior short implants may have a higher failure rate compared to longer implants in the literature: 1) an increased crown height, 2) higher bite forces, and 3) bone density in the region. An increased crown height results in a vertical cantilever (Figure 10), in which the load transfer to the implant may be increased by 100% (Bidez et al., 1992). In order to reduce the stress at bone-implant interface the authors included 1) no cantilevers on the prostheses, 2) no angled forces to the posterior restorations, and 3) splinting multiple implants together. Splinted implants increase functional surface area of support whenever a load is applied to the prosthesis (Bidez et al., 1992). In addition, eliminating lateral contacts in mandibular excursions and cantilevers on the prosthesis helps to reduce forces on the implants. Increasing the implant number and splinting multiple implants in the prosthesis result in more functional area, in which the forces are applied and transferred. According to Gross (2008) studies after 1997 taking into account bone density and surface finish with microtexture versus machined co-variables, report comparable survival rates for short and standard length implants. These observations are corroborated by the study of Misch et al. (2006), in which, through employing properties of biomechanical stress reduction, high implant success rates in short implants of 7.0 and 9.0 mm can be predictably attained as reported in this and other studies.

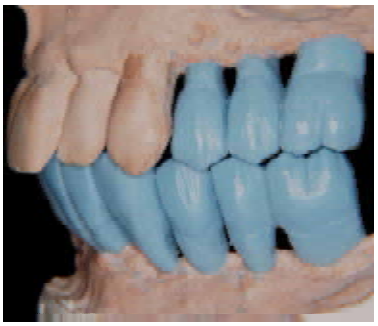

Fig. 10. Set-up wax of increased crowns height resulting in a vertical cantilever. Splinting must be considered

9. Guided dental implant surgery

Many methods to speed up the prosthetic stage have been devised in which devices could guide the surgeon on the implants placement, such as the Ohio State University Framework (Turkyilmaz et al., 2009) or the Novum System (Nobel Biocare, Göteborg, Sweden). However, these methods have not completely succeed because they solve a limited number of immediate planned loading cases because the failure in to feet individual anatomic variation.

The previous planning includes the patient complete anamnesis, the extra and intraoral examination in order to verify all anatomic and aesthetics components that are missing or should be improved. During the planning period conventional two-dimensional radiographs are necessary to evaluated available bone and the relationship between the implant insertion area and relevant anatomic structures, such as the inferior alveolar nerve and the maxillary sinus, and some templates representing the prosthetic setup could be made over these radiographs. However, this kind of preoperative planning neglects information about the third dimension of the patient´s anatomy.

Computer tomography has been providing medicine with some kind of three-dimensional anatomic information for at least thirty years, although for dentistry it was restricted to selected cases. At the last years the increasing availability, reduced radiation and lower costs of 3-D (three dimensional) imaging exams thanks to cone bean computer tomography development the 3-D implant planning is becoming more often used in dentistry and maxillo-facial surgery (Schneider et al., 2009). In conjunction with the 3-D tomography several manufactures developed computer software allowing virtual implant placement using the acquired digital data from the computed tomography (CT) scan (Mandelaris et al., 2010).

The transfer of the previously planned at the computer software according to the 3-D anatomic data scanned of the patients face, can be done by the use of stereolithographicsurgical guides created by computer-aided design and computer-aided manufacturing (CAD-CAM) technology or by "navigation" systems that use intra-operative optical tracking of the hand-piece position and guide the surgeon in real-time during the surgery providing visual feedback on a screen. The first one described is the more often used due to the inferior costs and because the high technology development required to use "navigations" systems are not available everywhere. Computer-aided implantation minimizes the error in implant positioning compared to conventional surgical guide implant placement and allows the provisory restoration to be manufactured prior to surgery (Yamada et al., 2011). Thereafter even the CAD-CAM technology provide the surgeon very precise information about the anatomy and the correct placement of the implants, so precise that allows the surgeon to perform flapless surgeries (Barnea et al., 2010; Patel, 2010).

The flapless surgery for placement of dental implants has some advantages such as the maintenance of the periosteum attachment and blood supply to the bone, avoids gingival profile modification following the contour of the surgical incision, reduces the postoperative edema, bleeding, pain and discomfort for the patients and clearly make the surgical time shorter (Abad-Gallegos et al., 2010; Azari & Nikzad, 2008). These advantages seem to increase the success rates of immediate loading, probably due to the blood supply preservation (Fortin et al., 2003; Malo et al., 2007). The flapless surgery is only possible with the use of surgical guides that should be precisely made; with this methodology it is always possible to avoid inadequate positioning of the implant and the unintentionally anatomic

structures contact with the implant surface. Remembering always that in this kind of surgery both the safety and success of treatment depend on the surgeon and prosthodontist accuracy. But despite many benefits described about the flapless implantation, this type of procedure could be perceived as a blind procedure due to the difficulty in evaluation alveolar bone contours and fenestrations or different angulations, setbacks that increases the chances of cortical plates perforation or fenestration when performed unassociated to the guided planning, however, the new 3-D computer guided planning technology made the implant insertion so precise that the setbacks of the flapless surgery were almost all vanished.

Some protocols for rehabilitation of completely edentulous jaws with flapless surgery and the placement of immediate fixed prostheses through computer guided surgery seems to be effective and predictable according to Puig (2010), besides with high potential for the patients acceptance, however, the author states that this techniques, for example the "all-on-four" and "all-on-six" protocols, could be sensitive to the experience of the surgeon and like all other surgical techniques its requires a learning curve from the surgeons who intend to perform they.

However, complications may occur during computer-guided surgery and the superstructure, sometimes, cannot be inserted immediately. Complications like insufficient primary implant stability or misfit of the restoration due to transfer mistakes, mistakes that can be justified due the mucosa anatomic alterations in flapless surgeries, unstable fixation of the surgical guide, imprecise impressions and incorrect pouring of the casts. Also the incorrect acquisition of tomographic image and processing could lead to errors (Almeida et al., 2010). Because of this some potentially complications, some author do recommend the application of guided surgery with flapless approach in cases with adequate bone volume and states that the guided technique can also be used in sites with insufficient bone volume, but a mucoperiosteal flap procedure is recommended (Fitzgerald et al., 2010).

The guided surgery has been indicated for complete and partial edentulism, for booth maxilla and mandibular bones. Thus many authors agree that the mainly advantage of this method is the use in the maxilla because of its anatomic peculiarities (Meloni et al., 2010; Vasak et al., 2011). Jung et al. (2009) revealed, after a systematic review including 29 different image guidance systems, a high mean implant survival rate of 96.6% after only 12 months of observation in different clinical indications.

There is no doubt that the computer guided surgery is a very advanced treatment and it's belong to the future of the implant treatment, although it seems to be a safe and predictable treatment, future long-term clinical data are necessary to identify the right clinical indications and to justify additional radiation doses, efforts and costs associated with this technique; because until now, despite all described advantages there is no evidence to suggest that computer guided surgery is superior to conventional procedures in terms of safety, outcomes, morbidity or yet success rates.

9.1 Surgical and prosthetic sequence

The virtual planning was first executed over the images acquired with the computerized tomography of the patient (Figures 11, 12 and 13), planning the implants position according to the desired teeth future positioning and to the existing bone support.

Afterwards the implant´s company makes the surgical guide based on the previous virtual planning done by the surgeon using the specific software that this company supplies for the surgeons (Figure 14).

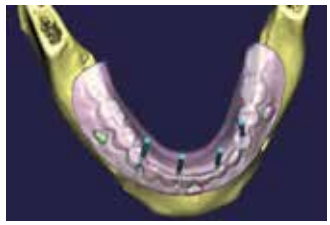

Fig. 11. Virtual planning occlusal view

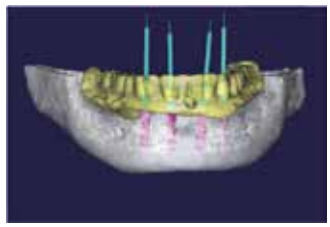

Fig. 12. Virtual planning frontal view

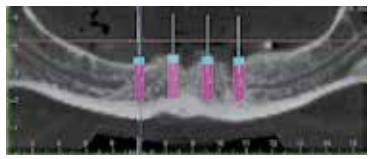

Fig. 13. Virtual planning on the panoramic view of the computerized tomography

Fig. 14. Surgical guide made by the implant system company

The preoperative frontal view of the patient's mouth can be seen in Figure 15. With the surgical guide in hands the surgeons shall performs the surgery, after the anesthetization the surgeons most secure the surgical guide by drilling three or four holes at the exactly spots and locking the guide with the proper devices (Figure 16).
After locking the surgical guide starts the drilling steps, following the exactly drill sequence designed by the implant company in order to make the implant insertion with the same inclinations that previously virtually planned (Figure 17). The implants were inserted by flapless surgery guided through the surgical guide (Figure 18). After the complete insertion, the prothetical abutments are locked over the implants (Figure 19) and the total prosthesis was installed (Figure 20).

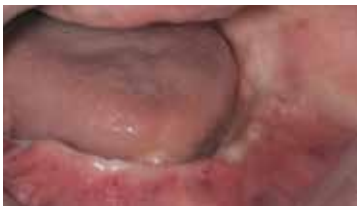

Fig. 15. Preoperative patient´s mouth view

Fig. 16. Surgical guide in place and locked

Fig. 17. Drilling steps according to the manufacturer´s orientation

Fig. 18. Implants insertion completed

Fig. 19. Removal of the surgical guide and abutment insertion

Fig. 20. Clinical case completed with the total inferior prosthesis installation in less than 24 hours (Courtesy of Prof. Dr. Valfrido Pereira Antonio Filho)

10. Occlusion aspects

Although the etiological factors underlying bone loss have not been fully established (Prosper et al., 2009), Canay & Akça (2009) stated that the main contributory factors of bone loss are occlusal overload and peri-implantitis. Current concepts are mixed regarding the peri-implant response to occlusal overload. Gross (2008) reported that a phenomenon of fatigue microtrauma has been proposed as the process of cervical and progressive bone loss as bone ''modeling'' due to excessive occlusal load. When the rate of fatigue microdamage exceeds the reparative rate, cervical bone is irreversibly lost. According to Kozlovsky et al. (2007), the overloading aggravated plaque-induced bone resorption, and increased bone loss of the dental implants. The decreasing of the functional surface of the dental crowns, the loads being directed to the long axis of the implants, the provisionalization and an adequate occlusal adjustment seem to favor the immediate loading implants result. In addition to poor bone quality, unfavorable force direction and concentration may increase failure rates of implants (Becktor et al., 2002; Chen et al., 2008). The question of splinting is also relevant to a discussion of occlusion as previously described. Some authors (Nokar et al., 2010; Zarone et al., 2003) advocated separation of mandibular superstructures in the midline (Figures 21 to 24) and cite mandibular flexure as a potential source of distal implant morbidity in full-arch restorations. However, additional studies about bone loss and prosthesis failure are necessary to confirm these findings.

Fig. 21. Initial clinical aspect

Gross (2008) suggested that the occlusion should be viewed as consisting of three basic elements: posterior support, occlusal vertical dimension (Figure 25) and eccentric or anterior guidance. The degree of vertical and horizontal overlap determines whether the anterior teeth disclude the posterior teeth in protrusion and whether the working side discludes the non-working side in latero-protrusive movements (anterior disclusion). Mutual protection is directly dependent on posterior support, in which the molars protect the anterior teeth during occlusion and the anterior teeth protect the posteriors in excursive movements. Gross also recommends to avoid creation of excursive guidance on single implant

Fig. 22. Cast after the impression of immediate placed dental implants

Fig. 23. Bar casted in two rigid segments, with a minimum separation in the anterior region

Fig. 24. Final aspect of the oral rehabilitation

restorations in order to prevent overloading to the prosthesis, abutment, implant and, therefore, to bone-implant interface. Cantilevers must be also avoided (Figure 26) or decreased (Figure 27) when possible. It must be remembered that the greater the bucco-lingual (Figure 28), mesial, distal or vertical cantilever, the greater will be the biomechanical failure risk. Finally, the decreasing of the functional surface of the crowns, the loads being directed to the long axis of the implants, the absence of cantilevers during the provisionalization and an adequate occlusal adjustment seem to favor the immediate loading implants results (Misch & Bidez, 1995).

Fig. 25. Occlusion vertical dimension determined by a Lucia's Jaw Interference Guide (JIG)

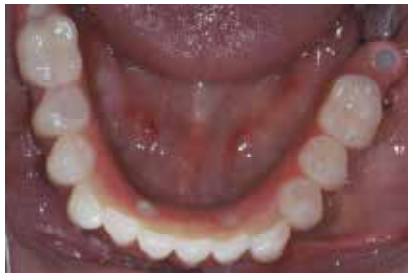

Fig. 26. Total implant-supported prosthesis with no cantilever

Fig. 27. Shortened dental arch concept reducing the length of the cantilever by using one premolar for each quadrant

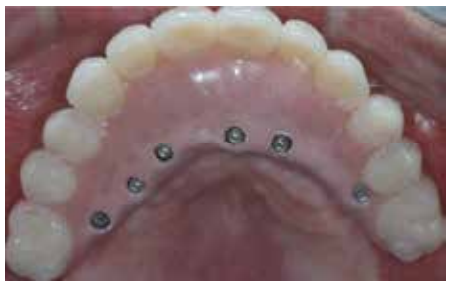

Fig. 28. Unsatisfactory implant-supported prosthesis. See the great bucco-lingual cantilever and the inadequate orientation of the teeth

11. Ferulization

A key factor for success or failure of dental implants is the manner in which stresses are transferred to bone-implant interface (Geng et al., 2001). Finite Element Analysis (FEA) is a useful tool for the determination of stresses and displacements in mechanical objects and materials, but is also frequently used in biological systems like in dentistry. Bevilacqua et al. (2008) reported that stress at the bone-implant interface increased with increasing single implant inclinations. Therefore, these authors demonstrated that vertical implants remain the first choice for single implants, given that stress transmitted to the bone-implant interface increases with increasing implant inclinations. On the other hand, different results were found in another study made by Bevilacqua et al. (2011), regarding the stress

distribution in maxillary implant-supported fixed dentures, in which tilted implants were used in fixed denture designs. In this study, tilted distal implants, rigidly splinted, decreased peri-implant bone stresses as compared to a vertical implant model with cantilevered segments. From the results of this investigation the authors concluded that the use of distal tilted implants results in a reduction in stresses in the peri-implant bone and in metal frameworks secondary to cantilever length reduction and implant length increase. Therefore, the concept of splinted arch seems to be very pertinent when immediate loading procedures are indicated for patients with extensive implant-supported prostheses and for edentulous patients. In addition, it seems to be quite evident the use of a larger number of implants and their splinting (if possible) when one-step surgical procedures are indicated (Attard & Zarb, 2005).

12. Parafunctional habits

Another relevant aspect that must be taken into account is the presence of parafunctional habits. Parafunctional habits may generate overloading and may contribute with up to 75% of the immediate loading implants failure. These non-functional habits may increase the looseness or fracture risk of the abutments and of the restorations (Mish et al., 2004b). According to Gross (2008), eccentric occlusal parafunction may generate extremely high and potentially destructive loads, sufficient to wear down the teeth, fracture crowns and roots, decement or break fixed partial dentures, dislodge or break abutment screws, fracture porcelain or superstructures, traumatize supporting bone and break implants. Thus, bruxism should be diagnosed and addressed as a complicating and additional risk factor. In agreement with some authors (Colomina, 2001; Misch et al., 2004a), when the parafunctional habits are not normalized, its presence may be an exclusion criterion for the immediate loading dental implants. Regardless the procedure (immediate, early or delayed) for the dental implants and prosthesis insertion, the use of a full-arch night splint may be beneficial in reducing potential overload from nocturnal parafunction. Despite the fact that some reviews show that bruxism has not been causally linked to supporting bone morbidity, its potential for creating complication in the superstructure and implant stack are very real (Gross, 2008).

Parafunction is a significant factor in the planning of excursive guidance and the creation of an occlusal scheme with abutment and bone support optimally designed to minimize the potentially destructive forces of bruxism (Gross, 2008). Therefore, flattening guiding inclines, increasing implant numbers and bone support, splinting multiple implants together, reducing occlusal vertical dimension to decrease crown-root ratio and minimizing functional occlusal surfaces and cupids without excessively compromising tooth shape should be also considered.

13. Conclusions

Physical and biomechanical procedures, such as splinting and appropriate occlusal adjustment, must be always followed in order to avoid the overloading risks and the stress on bone-implant interface.

Short implants, cantilevered segments and external hexagon connections may be associated with increased problems such as screw loosening, as well as screw, denture teeth, denture base, and framework fractures.

The treated surface dental implants and morse-taper implant-abutment connection possesses higher biomechanical behavior than the non-treated dental implants, and the conventional external and internal hexagon designs, respectively
Restorations should be planned on an articulator with a diagnostic wax set-up, and radiographic and surgical guides used when possible and necessary.
Computerized guidance systems may improve the accuracy of surgical procedures, especially in clinical situations in which the bone ridge and the anatomical relations are unfavorable.

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7

Load Transfer Along the Bone-Implant Interface and Its Effects on Bone Maintenance

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1. Introduction

The long term success of dental implant treatment relies on the proper stability of the implant within the host bone. This condition is achieved through osseointegration, which is characterized as a direct functional and structural connection between ingrown bone tissue and implant surface (Brånemark et al., 1977; Simmons et al., 2001). Osseointegration begins with rapid growth of random and unorganized woven bone around the implant, while a biomechanically favorable environment at the bone-implant interface develops (Leucht et al., 2007; Schenk & Buser, 1998). This initial bony structure is maintained by bone remodeling and bone adaptation, where woven bone is slowly replaced by more organized lamellar bone. Adaptation of bone morphology in response to functional loads continues throughout life (Schenk & Buser, 1998).

The load transfer from the implant to the host bone depends on the amount of bone surrounding the implant and in turn affects the success of treatment, by the load transfer from the implant to the host bone. X-ray imaging, computerized tomography (CT), and histomorphometric evaluation of the extracted implants provide insightful information about the quality and quantity of peri-implant bone. However, systematic evaluation of the mechanism of load transfer and its effect on peri-implant bone remodeling is difficult via aforementioned techniques, due to the cost and effort involved and due to the associated ethical concerns. Reliable computational models can be useful to predict the long term outcome of a dental implant treatment, and thus help with the decisions related to implant treatments and design. In this paper, a state of the art review of the computational models used in evaluating the biomechanics of dental implant systems is provided. The literature shows that load transfer along the bone-implant interface is not well understood, despite the fact that the bone loading starts along this interface.

Recently a systematic investigation of the effects of various parameters related to a dental implant's contour including the implant's diameter, body-length, collar length and slope, and the morphology of the external threads was carried out by Faegh and Müftü (2010). The variation of normal and shear stresses along the bone dental-implant interface was investigated. Here, in order to generalize the bone morphology an elliptical contour is used. The results are compared to a similar recent study in which the bone contour was drawn from a CT image of the incisor region (Faegh & Müftü, 2010).

1.1 Factors that influence the load transfer from implant systems to bone

Load transfer from the implant to the bone has been identified as one of the critical factors that determine the long term success of dental implant treatment (Duyck et al., 1997; Morris et al. 2001). Load transfer is influenced by several factors including: (i) the loading type, (ii) the length and diameter of implant, (iii) the implant shape, (iv) the structure of the implant surface, and (v) the bone quality (Duyck et al., 1997). A simple, analytical solution of the stress/strain distribution in the bone for an implant treatment scenario is not feasible, due to the complex geometry of the bone and the dental implant system. Photoelesticity (Farah et al., 1979; Kinni et al., 1987; Munir et al., 1975) and finite element analyses have been increasingly used in this field (Cook et al., 1980, 1982a, 1982b; Geng et al., 2001;) to analyze the stress distribution for different root form implant designs (Bozkaya et al., 2004; Hansson, 1999; Holmgren et al, 1998; Rieger, 1988; Rieger et al., 1989a, 1989b, 1990a, 1990b; Siegele & Soletz, 1989) prosthesis designs (Papavasiliou, et al. 1996a, 1996b; Stegaroiu et al. 1998a, 1998b) and for various clinical scenarios (Akça & İplikçioğlu, 2001; Canay et al., 1996; Gross & Laufer, 1997; İplikçioğlu & Akça, 2002; Meijer et al., 1994; Pierrisnard et al., 2002; Tuncelli et al., 1997; van Oosterwyck et al, 2002).

Over the years, numerous implant designs and clinical protocols emerged, sometimes dictated by market demands (Brunski, 1999). Currently, there are more than 50 implant designs available in the market. Research and development in the dental implant field led to significant progress in areas and applications that were previously limited. For example, implants can be successfully inserted in areas of reduced bone height and high functional load, such as the posterior segments of mandible and the maxilla. Moreover, advances in our understanding of the mechanobiology led to design of implant systems that can function immediately after insertion (Balshi & Wolfinger, 1997a; Brånemark et al., 1999; Brunski, 1999; Chow et al., 2001; Ericsson et al., 2000; Jaffin et al., 2000; Salama et al., 1995; Tarnow et al., 1997).

1.1.1 Bone-implant connection

One of the main drivers for different implant designs is to improve bone-to-implant connection. Osseointegeration, first described by Brånemark et al. (1977, 1985), defines the direct connection of bone and implant. Osseointegration involves chemical bonding of the tissue to the implant, as well as micro- and macro-level mechanical interlocking of the bone with the features on the implant surface. Chemical and morphological modifications of the outside surface of the implant material have been shown to enhance connection strength and reduce the healing time. To this end, bioactive ceramics such as hydroxyapatite have been used as coatings on the implant surface. Such coatings have been shown to improve bone-implant fixation through chemical bonding between the implant and the surrounding tissues. Surface morphology of implants can be modified in macro-level through the designs of external threads, undercuts and layers of wires, and in micro-level by increasing surface roughness.

Shape and chemistry of the bone-implant interface influence the stress distribution in the bone for different implant designs (Bidez et al., 1988; Hipp et al., 1985). Siegele and Soltesz (1989) modeled different bone-to-implant connection types by using frictional contact. Their work showed that high levels of bone stresses occur in the apex region of the implant if perfect osseointegration is assumed, whereas the high stress region occurs in the alveolar crest for frictional sliding contact condition. Similar results for the perfectly bonded interface have been reported by Weinstein et al. (1976).

Strength of bone fixation depends in part on the mechanical properties of the bone surrounding the implant. One common metric of bone quality is the bone density levels (Lekholm and Zarb, 1985). Whether the implant is surrounded by cortical bone or trabecular bone makes a significant difference in interfacial stresses (Borchers & Reichart, 1983; Lavernia et al., 1982). Lavernia et al. (1981) reported significant change in stress magnitude when bone properties are switched between trabecular and cortical. Kitoh et al. (1978) and Bozkaya et al. (2004) showed that the occlusal force applied to the implant is supported primarily by the cortical bone.

1.1.2 Implant-contour

The long term outcome of the implant treatment is influenced by the loading experienced by the bone, in several different respects. In general, excessive micro-motion of the bone-implant interface should be avoided, while providing adequate stimulation to promote healing and remodeling response (Brunski, 1999). The shape of the implant contour, and its local features have a considerable influence on bone healing and maintenance. Siegele and Soltesz (1989) compared the load transfer characteristics of five different implant shapes. Considered contours were cylindrical, conical, stepped, internally hollow cylindrical and externally threaded. They showed that under vertical load, lower stresses are induced in the bone with smoother implant shapes such as cylindrical, rather than implants with small radii of curvature such as the conical shape and implants with geometric discontinuities such as stepped implant contours. Under lateral loading, large stresses were observed in the apex area of the hollow cylindrical implant, and below the uppermost thread of the externally threaded implants. Holmgren et al. (1998) reported that the stepped implant design levels out the stress distribution better than a cylindrical design. Rieger et al. (1989a, 1990a, 1990b) investigated the effect of implant geometry and the elastic modulus of the implant materials on the stress distribution for different implant designs. A tapered design made of a material with high elastic modulus was concluded to be the most suitable design in their study. Weinstein et al. (1976) investigated a porous rooted dental implant and concluded that high bone-level stresses are induced near the apex of the implant in a model with continuously bonded interface. In their comparative evaluation of five commercially available implant systems, Bozkaya et al. (2004) showed that implant systems with internally sloping crestal modules are better at reducing the bone overload in the cortical bone, whereas systems with widening crestal-modules cause bone overload in compression. Kong et al. (2008) suggested that neck taper (collar slope) ranging from 64° to 70°and end (apex) fillet exceeding 0.8 mm result in the optimal stability of implant.

Siegele and Soltesz (1989) reported a high failure rate in the hollow cylindrical implants due to low primary stability. Moreover, the conical or shoulder-type implants distributed high stress level at the bone interface. Rounding off the corners of the implant was found to have a significant effect on reducing the stress (Siegele & Soltesz, 1989). Faegh and Müftü (2010) showed that cylindrical implants with no external threads induce low stresses along the bone-implant interface in the trabecular region, and indicated that this might lead to inadequate bone stimulation. Cylindrical implants are no longer recommended due to problems with osseointegration and high failure rates (Schenk & Buser, 1998).

Vaillancourt et al. (1995) investigated the possible causes of bone loss in the crestal bone surrounding both porous-coated implant and non-porous-coated regions of a partially coated implant designs. They reported that lower stress level was transferred to the crestal bone region in the case of partially-porous implant, where crestal bone loss was mostly

observed. They attributed this to disuse atrophy. A sufficient stress level of 1.6 MPa was reported to avoid bone loss resulting from disuse atrophy by histological studies.

1.1.2.1 Externally threaded implants

There are several advantages associated with externally threaded implants. Threads improve primary implant stability during the implant insertion (Misch, 1999b) and thus reduce micro-motion during the post insertion healing period until the stable osseointegration is established. This characteristic is of more importance in the regions of low bone density and in the submerged implant placement modality (Frandsen et al, 1984). In addition, applied (mastication) forces are diverted in normal and tangential directions to the faces of the thread and amplified in certain thread locations. This is beneficial in providing adequate loading for long term bone maintenance (Faegh & Müftü, 2010). Finally, bone growth between the threads provides the macro-level interlocking. There are different types of externally threaded implants available in the market, which vary in thread pitch, shape and depth. Since the morphology of screw threads plays an important role in the load transfer from dental implant to the surrounding bone (Frandsen et al, 1984), usage of different thread configurations for different bone qualities have been suggested (Misch, 1999a, 1999b; Misch et al., 1998, 1999, 2001).

In a finite element study carried out by Moser and Nentwig (1989), it was observed that using screw threads with an apically increasing screw thread depth reduces tension in the cervical area when implant was apically loaded. Similarly, Huang et al. (2010) suggested that external threads reduce the stress and sliding at the interface. Chun et al. (2002) reported that maximum effective stress in the cortical bone is higher in the plateau design as compared to the triangular or square thread designs. In another study carried out by Patra et al. (1998), tapered thread design implants were found to distribute higher stress levels in bone as compared to the parallel profile thread. Use of external threads on the implant body with some micro-scale roughness was reported to enhance osseointegration (Skalak, 1988). It was observed that inclined faces of threads allow for normal stress to be carried perpendicular to the interface. Transmission of shear stress can benefit from microasperities on the interface which work along each of the faces of a screw in a similar way that the screw threads work (Skalak, 1988). Faegh & Müftü (2010) carried out a systematic analysis of various implant designs with and without external threads. They showed that threads increase the interfacial stresses locally and could help in stimulating bone remodeling.

1.1.2.2 Implant diameter

Wider diameter implants provide increased implant-bone contact area, enable the engagement of the implant to the buccal and lingual (BL) faces of the bone, and have the ability to occupy the tooth socket especially in the posterior regions. These inherent characteristics of wide diameter implants significantly improve initial implant stability, which leads to the increase in likelihood of osseointegration (Langer et al., 1993; Renouard et al., 1999; Trauhlar et al., 1997). Wide diameter implants also provide higher mechanical strength to avoid implant fractures (Jarvis, 1996). Wide and short implants provide the advantage of avoiding sinus elevations and extensive bone augmentation procedures in regions of limited bone height due to the existence of alveolar nerve in the mandible and maxillary sinus in the maxilla, and potentially prevent the costs associated with bone grafting procedures (Blatz et al., 1998; Graves et al., 1994; Jarvis, 1996; Langer et al., 1993). Overall advantages of wide diameter implants include improved prosthetic stability,

reduced screw loosening, reduced incidents of implant fracture, and more optimal force distribution in qualitatively and quantitatively poor bone (Mahon et al., 2000).
Griffin et al. (2004) conducted a clinical study investigating the application of 6×8 mm hydroxyapatite coated screw retained implants in the mandibular and maxillary molar regions and reported a 100% success rate. They observed that significant stress concentration distributed to the crestal cortical bone, at the level of the first few threads and concluded that the use of long implants to provide a larger surface area for stress distribution is not necessary. Instead larger surface area provided by wide diameter implants was deemed to be better. On the other hand in a retrospective study conducted by Aparicio & Orozco (1998) the success rates of 5 mm- and 3.75 mm-diameter implants were reported to be similar in the maxilla, while higher success rate was observed for 3.75 implants in the mandible. They attributed the high failure rate in the mandible to the overheating during surgical bone drilling, excessive tightening force during implant placement, and variations of the remodeling response of the cortical bone caused by extensive drilling.
Geramy & Morgano (2004) conducted a finite element analysis comparing displacement of a standard diameter and a wide diameter implant under an occlusal load applied at the distobuccal cusp tip, and concluded that increasing the diameter of the implant will reduce both mesiodistal and buccolingual displacement of the implant system by approximately 50%. Davarpanah et al. (2001) evaluated the resistance to fracture and depth of insertion of wide diameter implants versus standard diameter implants. They found that wider diameter implants demonstrate more resistance to fracture than standard implants, which is attributed to increased surface area. Jarvis (1997) compared the 3.7 mm and 4.7 mm diameter implants and concluded that wider diameter implants decrease the induced load on the abutment screw which results in reducing implant fracture, and also the vibration of the implant that leads to loosening. Mahon et al. (2000) evaluated the stress distribution using implants with diameters 3.25, 3.75, 4, 5, and 6 mm under a load of 176 N applied 5 mm off axis. They observed that the mean stress level was highest for the 3.25 mm-diameter implant, and lowest for the 6 mm-diameter implant. High stress levels were located at the necks of the 3.25 mm implant which was consistent with the high deformation which occurred in these regions. They observed that stress level for 3.75, 4, and 5 mm diameter implants did not demonstrate large differences, however, 6 mm diameter implants showed the most reduction in the stress level. Due to this observation, they concluded that the implant diameter must be greater than a certain value in order to reduce the stress significantly. Li et al. (2011) suggested that implant with diameter greater than 4.0 mm and length longer than 12.0 mm is the optimal selection to treat tooth loss at the at locations with poor bone quality (ie. posterior mandible). Huang and Tsai (2003) reported that increasing the implant diameter and consequently the bone-implant contact area reduces stress concentration and results in improving implant stability. Chou et al. (2010) showed that the insertion depth and implant diameter affect the biomechanical response of bone, particularly between the plateaus of an implant. They indicated that the strain distribution can be optimized for long-term bone maintenance by adjusting the insertion depth for different levels of bone quality in the alveolar ridge.

1.1.2.3 Multiple implants

Using two narrow implants to support prosthesis in posterior regions has been an alternative solution to the wide diameter implant (Langer et al., 1993; Lazzara, 1994; Moscovitch, 2001). Balshi & Wolfinger, (1997b) stated that two implants maintain a more natural replacement of the missing tooth in position and direction, and allow for the preservation of the crestal bone. Mahon et al. (2000) and Trauhlar et al., (1997) stated that use of two implants also provides a

more appropriate support against buccolingual and mesiodistal bending, decreases the rotating forces around the implant axis, offers greater surface area and better biomechanical properties, and maintains prosthesis retrievability. However, there are some restrictions on using two narrow implants in the posterior regions. One of these is the cone space availability buccolingually and mesiodistally (Graves et al., 1994).

Geramy et al. (2004) compared the use of a wide diameter implant with the use of two implants and reported that use of two implants to support the restoration reduces the buccolingual displacement to the same level as the 5 mm-diameter implant. Stress distribution for both wide diameter implants and two implant design systems were compared by Balshi and Wolfinger (1997b), who concluded that the percentage of stress reduction was almost identical for both designs. In a study conducted by Bahat and Handelsman (1996), the failure rate of the 5 mm-diameter implants was 2.3% compared to the 1.6% failure rate of the double implants. They suggested using double implants to support restorations rather than a single implant in the molar regions, even though there were some disadvantages associated with using double implants, such as greater bone loss and higher prosthesis mobility. On the other hand, Sato et al. (2000) concluded that using double implants in molar areas does not always reduce loads on the implants however eliminates torque. They observed higher stress levels near the marginal ridge of the superstructure compared to stress field on the wide diameter implants.

1.2 Bone remodeling (cell interactions)

Unlike the bone growth or bone modeling which mostly occurs in the early age of skeletal development, bone remodeling is a process of continuous cellular activities to replace aged, injured and dead bone. Bone remodeling is a process that is composed of two consecutive, and interrelated physiological activities, namely bone resorption and bone formation. Remodeling is carried out by basic multicellular/bone metabolic units (BMUs). Normally, osteoclasts, which are responsible for resorption, are inhibited by osteoprotegerin (OPG), which is a protein secreted by osteoblasts as inhibitory signal (Carda et al., 2005). The osteoclastic resorption is signaled by the circulating parathyroid hormone and locally secreted receptor activator nuclear kappa-b ligand (RANKL), which binds to RANK receptors on the membrane of osteoclasts (Marx, 2007). In addition to OPG, osteoblasts also secrete RANKL so that the activation of osteoclasts and the amount of resorption are regulated.

When remodeling is activated, osteoclasts are first recruited to bone surface and start to excavate the bone by releasing hydrochloric acid to dissolve the inorganic matrix, and collagenases to break down the organic matrix (Marx, 2007). A tunnel with approximately 200 μm in diameter and 300 μm long is dug at the rate of 40 μm/day (Martin et al., 1998). Following the resorption, there is reversal phase before the initiation of formation. A cylindrical space in the tunnel can be observed and the length of this region varies with the lag between the resorption and formation.

During bone resorption, some bone morphogenic proteins and insulin-like growth factors are released as active cytokines (growth and differentiation factors), which induce the differentiation of stem cells into osteoblasts (Marx, 2007). Bone formation is conducted by the osteoblasts, which refill the space with unmineralized bone matrix, osteoid, at a rate of about 1-2 μm/day (Martin et al., 1998). As the osteoblastic activity continues, a tunnel with 40-50 μm in diameter called Haversian canal is left for the transportation of the nutrients to bone cells. Finally, the bone matrix deposited by osteoblasts is mineralized and turns into Haversian system, osteon. Osteoclastic activity restores to quiescent condition under the influence of osteoblasts, and bone is maintained until the aging or diseased bone triggers the secretion of RANKL by osteoblasts (Marx, 2007).

1.2.1 Theoretical models of bone remodeling

Wolff (1892, 1986) observed that internal structure and density of bone depends on the load that it carries. It is generally well established that this functional adaptation is the result of the BMU activity as described above, which is triggered by some mechanical stimulus that BMUs can sense. Several theoretical models were formulated in order to quantitatively describe the functional adaptation of the bone (Hart, 2001). These models assume that a mechanical control signal (remodeling stimulus) governs the bone density regulation, and the BMU has the capability to respond to the changes in this signal. A biomechanical equilibrium or homeostatic state is assumed, so that bone remodeling is only triggered when the control signal deviates from this equilibrium state. Remodeling activity continues until the biomechanical equilibrium is restored and new bone morphology is established. This approach neglects the effects of hormonal, genetic and metabolic factors on bone regulation.

1.2.1.1 Mechanostat hypothesis

Frost proposed the mechanostat, which is a non-linear switch, to explain his experimental observations of bone remodeling (Frost, 1987, 2003). He used strain as the mechanical control signal, and divided the remodeling response to four different regimes. Each regime, which he called "window," is separated by threshold strains levels. These minimum strain levels were called minimum effective strain (MES). The disuse window (DW) is the lowest strain regime. If the bone is exposed to strain levels in DW for a prolonged duration, Frost's hypothesis states that decrease in bone mass will occur. Adapted window (AW) is where bone strength is naturally accepted to sustain the strain level caused by normal daily activities. Increased strain level to the mild overload window (MOW) promotes increase of bone mass. However, further increase of strain will lead to the pathologic overload window (POW) and generate internal micro damage that cannot be repaired by normal cell activities. The following relation gives a compact representation of the mechanostat hypothesis in terms of the MES:

$$\text{Bone tissue response} = \begin{cases} \text{DW}: \text{ reduced bone mass}; & \text{strain} < \text{MESr} \\ \text{AW}: \text{ constant bone mass}; & \text{MESr} < \text{strain} < \text{MESm} \\ \text{MOW}: \text{increased bone mass}; & \text{MESm} < \text{strain} < \text{MESp} \\ \text{POW}: \text{ bone damage}; & \text{MESp} < \text{strain} \end{cases} \tag{1}$$

where MESr is the threshold of disuse remodeling; MESm is the modeling threshold; and MESp is the pathologic threshold. Note that what type of strain measure to be used in this theory was not precisely stated.

1.2.1.2 Bone remodeling base on strain energy density

Huiskes et al. (1987) suggested strain energy density U as the remodeling stimulus, and they proposed that the change of bone's elastic modulus (E) can be described as,

$$\frac{dE}{dt} = \begin{cases} C_e\left(U - (1+s)U_n\right); & U > (1+s)U_n \\ 0; & (1-s)U_n \le U \le (1+s)U_n \\ C_e\left(U - (1-s)U_n\right); & U < (1-s)U_n \end{cases} \tag{2}$$

where C_e is a remodeling constant, U is the strain energy density of bone due to loading, U_n is the homeostatic equilibrium strain energy density, and s is the fraction of U_n indicating the width of lazy zone, where no net change of elastic modulus takes place. The lazy zone and the AW appear to describe the same phenomena where the bone's elastic modulus does not depend on the remodeling stimulus, in other words it is in equilibrium.
Weinans et al. (1992) proposed a remodeling stimulus (S) that depends on, not only the strain energy density, but, but also on the bone density ρ , and on different types of loadings as follows,

$$S = \frac{1}{n}\sum_{i=1}^{n}\left(\frac{U_i}{\rho}\right) \tag{3}$$

where n is the total number of load types (i) that induce strain energy density (U_i). The density change was expresses as,

$$\frac{d\rho}{dt} = \begin{cases} A_1\left(S-(1+s)K\right)^2; & S > (1+s)K \\ 0; & (1-s)K \le S \le (1+s)K \\ A_2\left(S-(1-s)K\right)^3; & S < (1-s)K \end{cases} \tag{4}$$

where A_1 and A_2 are remodeling constant, s is the width of lazy zone, K is the homeostatic stimulus for remodeling equilibrium. The exponents of bone formation and bone resorption are set to be 2 and 3, respectively, to simulate that resorption is a faster process than formation.

1.2.1.3 Bone remodeling based on daily effective stress

Carter et al. (1987) stated that a minimum amount of daily remodeling stimulus is required for bone maintenance (Carter et al., 1987; Beaupré et al., 1990). This daily remodeling stimulus (Ψ_b) characterizing the magnitude and cycles of loads is defined as,

$$\Psi_b = \left(\sum_{day} n_i \bar{\sigma}_i^{m}\right)^{1/m} \tag{5}$$

where n_i is the number of cycles of load type i, and m is an empirical constant to weight the relative importance of stress magnitude and number of load cycles, and $\bar{\sigma}_i$ is the continuum level effective stress, which is defined as,

$$\bar{\sigma}_i = \sqrt{2EU} \tag{6}$$

where E is the continuum average elastic modulus and U is the strain energy density. The velocity of surface remodeling in response to the daily remodeling stimulus was formulated as follows,

$$\dot{r} = \begin{cases} C_1\left(\Psi_b - \Psi_{bAS}\right) + \left(C_1 - C_2\right)w_1; & \Psi_b - \Psi_{bAS} < -w_1 \\ C_2\left(\Psi_b - \Psi_{bAS}\right); & -w_1 \le \Psi_b - \Psi_{bAS} < 0 \\ C_3\left(\Psi_b - \Psi_{bAS}\right); & 0 \le \Psi_b - \Psi_{bAS} \le w_2 \\ C_4\left(\Psi_b - \Psi_{bAS}\right) + \left(C_3 - C_4\right)w_2; & \Psi_b - \Psi_{bAS} > w_2 \end{cases} \tag{7}$$

where Ψ_{bAS} is the attractor stimulus for remodeling equilibrium, C_1 – C_4 are rate constants, and w_1 and w_2 are the boundaries of the normal activity region. Biologically, bone remodeling only occurs at the bone surface so the remodeling potential depends on the amount of available bone surface. Bone specific surface is used to quantify available bone surface for remodeling in bulk bone. The relation between the rate of density change and the rate of surface change can be expressed as,

$$\dot{\rho} = kS_v\rho_t\dot{r} \tag{8}$$

where k is the fraction of local area, which is actively remodeling, S_v is the bone-specific surface, which is determined according to apparent bone density (Martin, 1984), and ρ_t is the density of the fully mineralized tissue.

1.2.2 Modeling dental implant induced bone remodeling

Numerous clinical and histologic studies have been carried out to understand osseointegration in order to improve dental implant designs, surfaces and surgical protocols. Developing mathematical models of dental bone remodeling can help uncover biomechanical factors controlling short and long term survivability of implant treatments. Mathematical models mentioned previously were originally developed to study the phenomenon of bone adaptation to functional loads in long bone. However, simulations of bone remodeling in other bone regions such as acetabulum, proximal tibia, metacarpal, calcaneus and mandible (Carter & Beaupré, 2001; Pérez et al., 2010; Reina et al., 2007) have been reported. These long bone remodeling theories were used to study the bone remodeling, as a result of biomechanical alteration of the equilibrium state in the jaw bone due to use of dental implants (Lin et al., 2009a). Long term bone maintenance following fixed partial denture treatment was simulated by Field et al. (2010). A qualitative validation was reported by comparing the prediction of dental implant induced mandibular bone remodeling to clinical follow-up x-ray images over 48 months (Lin D. et al. 2010). Marginal bone loss is a common problem following dental implantation. Crupi et al. (2004), Li et al. (2007) and Lin C.-L. et al (2010) investigated the biomechanical causes of marginal bone loss by adding an overload bone loss criteria to remodeling equations. Lian et al. (2010) examined the effect of initial bone implant contact percentage on long term peri-implant bone remodeling and showed that 58-60% bone implant contact state develops at the equilibrium state no matter what initial contact percentage was assumed. Chou et al. (2011), investigated the effects of bone grafts in peri-implant bone remodeling in fresh extraction sockets and predicted that graft materials that are relatively stiff and that have high equilibrium stimulus values are likely to result in increased bone loss in the long term. In addition to studying clinical scenarios, factors influencing peri-implant bone remodeling is also of great interest to implant designers. A functionally graded dental implant, where the material composition varies from hydroxyapatite at the implant apex to titanium at the implant collar, was suggested. Lin et al. (2009b) predicted that the bone density can increase for implants made of functionally graded materials, but the initial stability of implant can be compromised due to the excessive vertical displacement due to the overall reduction in implant stiffness.

In Section 3, the strain energy density based remodeling theory (Section 1.2.1.2) is adopted to investigate the effects of various dental implant designs on bone remodeling. Equation (4) is first solved by the forward Euler time integration method, which gives,

$$\rho^{j+1} = \begin{cases} \rho^j + A_1\left(S^j - (1+s)K\right)^2 \Delta t; & S^j > (1+s)K \\ 0; & (1-s)K \le S^j \le (1+s)K \\ \rho^j + A_2\left(S^j - (1-s)K\right)^3 \Delta t; & S^j < (1-s)K \end{cases} \tag{9}$$

where j is the integration time step. Parameters A_1, A_2 and Δt can be treated as a single constant. To implement these formulations into finite element analysis, bone density must be related to material properties. The general relation of density and linear isotropic elasticity is,

$$E = C\rho^d \tag{10}$$

(Carter & Hayes, 1977), where E is the elastic modulus of bone. Empirical parameters C and d are set to be 3.79 and 3, respectively. The minimum modulus is 1 kPa. The maximum modulus is taken as 13 GPa, which corresponded to a density of 1.508 g/cm^3.

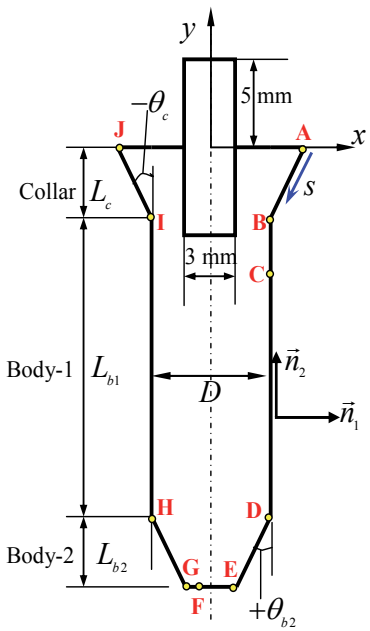


Fig. 1. The definitions of the parameters used to identify the contour of a generic dental implant.

2. Load transfer along the bone-implant interface

In order to investigate the nature of load transfer along the bone implant interface, a comprehensive parametric study of different implant designs was carried out. A generic implant with adjustable contour features, much like Faegh and Müftü (2010), was used. The normal and shear stress components, σ_{11} and σ_{12} acting normal and parallel to the implant surface, respectively, (Figure 1) were computed and plotted along the s-coordinate axis

placed on the bone implant interface. Note that s = 0 represents the buccal-side and it is also marked as point-A, whereas point-J is the end of the interface path.

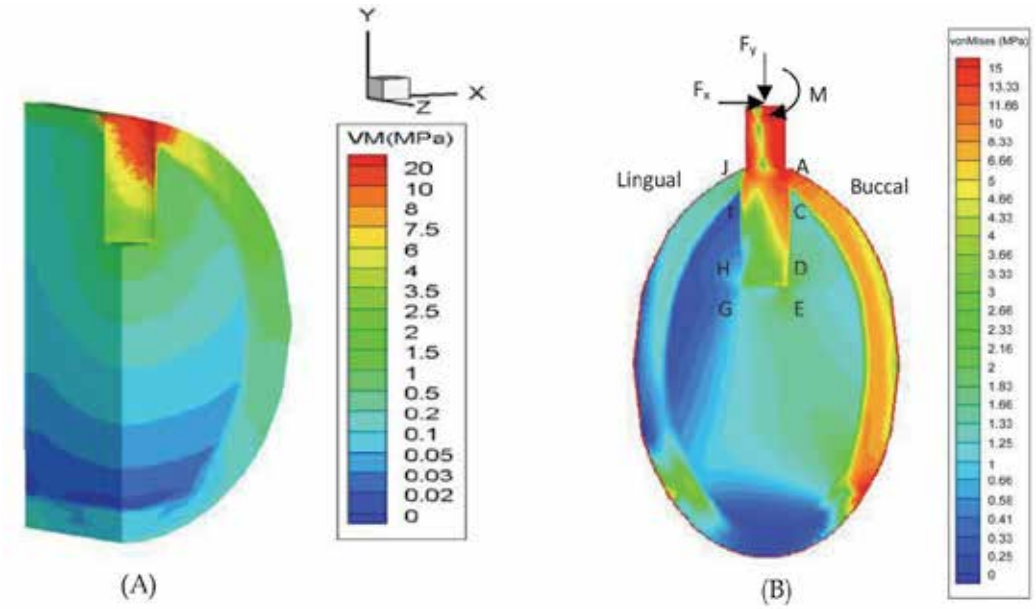


Fig. 2. von Mises stress distribtution in (A) the 3D model, (B) the 2D model.

2.1 Methods

Four main regions were designated to define implant geometry as the *collar, body*-1, *body*-2, and *apex* regions. The effects of the length, L_c, and slope, θ_c, of the collar region, the length, L_{b1}, and the diameter, D, of the body-1 region and the length, L_{b2}, and the slope, θ_{b2}, of the body-2 region were investigated. The apex was modeled to be flat. Faegh and Müftü (2010) investigated the effects of four common external thread shapes. The values they used were chosen according to the commercially available dental implants. Here we only report on the effect of a triangular thread shape, as the results and conclusions are similar. The thread geometry is defined by using three parameters. These are the *thread pitch*, p_t, the *thread depth* h_t, and the *thread slope* θ_t. The thread depth was h_t = 0.32 mm and the thread pitch was p_t = $L_{b1}/7$ in this study.

The implant-abutment connection was assumed to be monolithic; and, all of the components, (implant, abutment, cortical bone, and trabecular bone) were assumed to be perfectly bonded along their individual interfaces. The (x, y) coordinate system was placed at the center of the superior surface of the implant, as shown in Figure1 and the locations of the key points (A – J) on implant geometry, were programmed to be variable. In order to eliminate effects of bone morphology, which vary in individual jaws, the external geometry of bone was simplified as an ellipse. The major and minor axes of the bone model were idealized as 30 and 18 mm respectively, and a cortical layer of 2 mm was assumed.

Finite Element Method (FEM) was used and the system was modeled in ANSYS ver. 11 (Canonsburg, PA, USA). The analysis was carried out in 2D plane-strain. However, a 3D analysis was conducted to verify the level of validity of the 2D analysis. In 3D, the bone was modeled as an elliptical cylinder. The model was gradually meshed by creating extra

regions around the implant with very high mesh density as in Faegh and Müftü (2010). 3D and 2D models were meshed with the structural solid elements, SOLID 185 and PLANE 42 of ANSYS respectively. An occlusal load of 113 N was applied at the center of abutment with the direction of 11 degrees with respect to the main axis, and a moment of 90 N.mm to mimic the biting force on the prosthesis. The elastic moduli of the implant system (Ti), the cortical bone, and the trabecular bone were set to 113, 13 and 1 GPa, respectively (Rieger et al., 1989a; Steinemann, 1996).

2.2 Results

Distribution of the von Mises stress in the bone, as predicted by 2D and 3D analyses, is presented in Figure 2, for a smooth faced implant with the dimensions θ_c = -10 degrees, L_c = 1 mm, L_{b1} = 5 mm, L_{b2} = 3 mm, θ_{b2} = 5 mm, D = 3.3 mm. This figure shows a reasonably similar stress distribution both in magnitude and trend. Close inspection of this figure also shows that: (i) Highest von Mises stress levels are observed on the buccal side of the cortical bone, and on the superior region of implant and abutment system; (ii) In general, the trabecular bone bears relatively low levels of stress compared to cortical bone; and, (iii) Higher von Mises stress is observed near the bone implant interface. Differences in the details of the 2D and 3D stress contours are due to the boundary conditions. In the 3D analysis, the bone was restricted at the distal ends, whereas in the 2D analysis the restriction is near the inferior periphery. This results in some distinct variations in regions away from the implant, as shown in the figure.

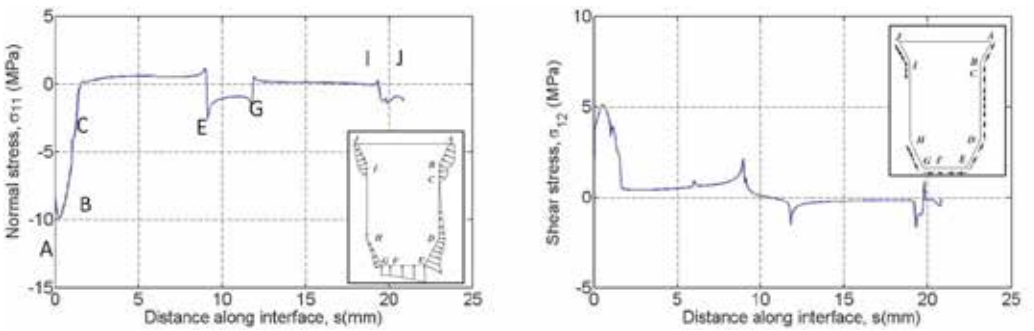
The effect of external thread shape on the von Mises stress distribution is presented for a smooth faced-implant and an externally threaded implant in Figure 3. The general contour parameters of these two cases are described above. This figure shows the load transfer along the bone-implant interface, via the normal σ_{11} and shear σ_{12} stresses. For the smooth (threadless) implant the normal stress σ_{11} is primarily compressive along the collar region and the apex of the implant, but it is small and tensile along the smooth faces of the body-1 and -2 regions. Jumps and stress concentrations are observed at the locations with abrupt changes in geometry and material properties. The collar region on the lingual side is seen to experience roughly $1/10^{th}$ of the compressive stress experienced on the buccal side. Variation of the normal σ_{11} and shear σ_{12} stresses along the bone-implant interface for the externally threaded implant is presented in Figure 3B. It is observed that the interfacial normal and shear stresses increase around the external threads. In particular, on the first thread of the buccal side, where the thread is engaged with the cortical bone, a significant σ_{11} stress peak is observed. On the other hand, the general behavior of σ_{11} and σ_{12}, between the two implant types shows that the overall load transfer characteristics in the bone-implant interface are similar. It appears that at a local level the externally threaded implant is able to transfer higher loads to the tarbecular region. This can have significant effects on long term bone maintenance. Effects of different thread shapes are presented by Faegh & Müftü (2010).

The effects of different implant contours are investigated by changing the implant design parameters (θ_c, L_c, L_{b1}, L_{b2}, θ_{b2}, D) systematically (Table 1). Analysis of the interfacial stresses showed that the parameters that have the highest impact on the stress magnitude are the implant diameter D, the collar parameters θ_c and L_c, and the length of the body-1 region L_{b1}. The effects of these four parameters are summarized in Figure 4. Note that this analysis was carried out for smooth (threadless) implants. Figure 4 gives the maximum normal and shear stress values transferred to the bone. Incidentally all of the maximum values are found in the collar region of the buccal side. The results presented in Figure 4 are summarized as follows:

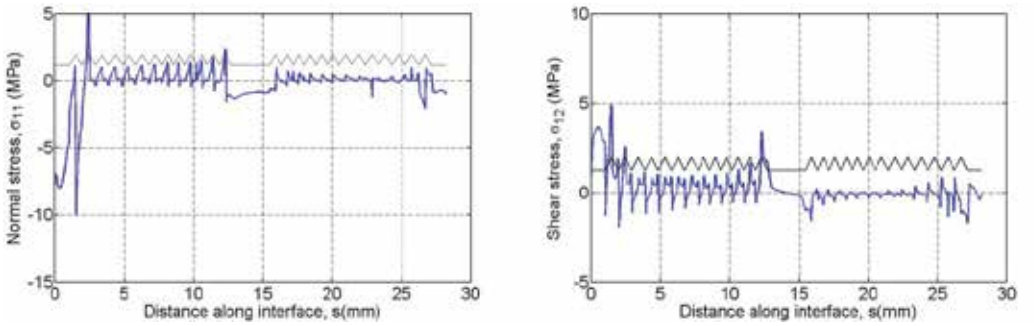
- For implants with larger diameter D the largest normal σ_{11} and shear stress σ_{12} transferred to the bone is reduced (Figures 4A-C).
- Increasingly negative collar slope (θ_c) causes the maximum normal stress transferred to the bone to increase, but it causes the maximum shear stress to decrease (Figure 4A).
- Increasing the length (L_c) of the collar and length (L_{b1}) of the body-1 regions cause the maximum normal stress and the maximum shear stress transferred to the bone to decrease (Figures 4B,C).

Length of Collar, L_c (mm)	1, 2
Angle of Collar, θ_c (degrees)	-10, -5, 0, 5, 10
Length of body-1, L_{b1} (mm)	4, 5, 6
Diameter of body-1, D (mm)	3.3, 3.5, 4
Length of body-2, L_{b2} (mm)	3, 4
Angle of body-2, θ_{b2} (degrees)	5, 10

Table 1. Implant dimensions that were varied in this work. See Figure 1 for the definitions of these variables. Note that θ_c as drawn in this figure is defined to be a negative angle, whereas θ_{b2} is defined to be positive.

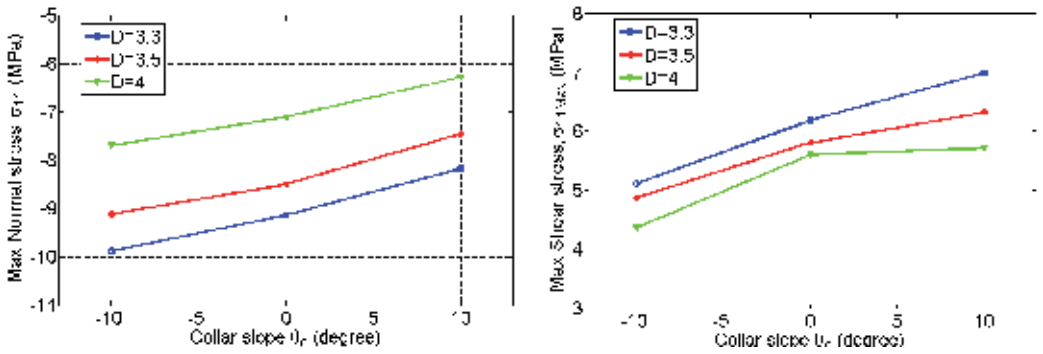


(A) σ_{11} and σ_{12} for smooth faced implant

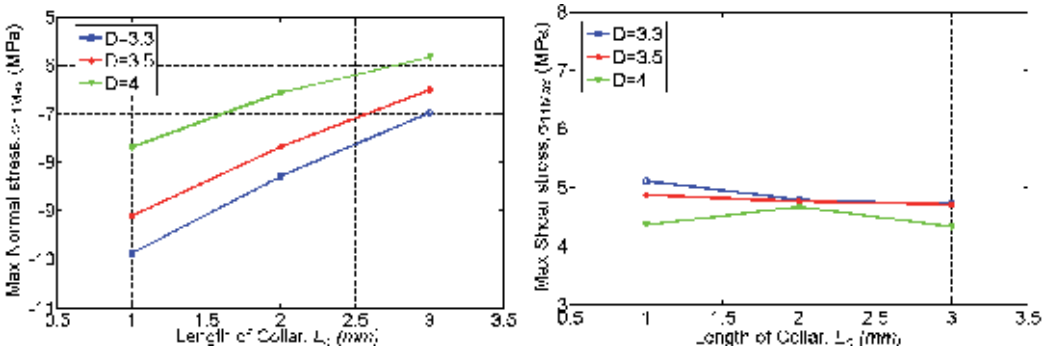


(B) σ_{11} and σ_{12} for externally threaded implant

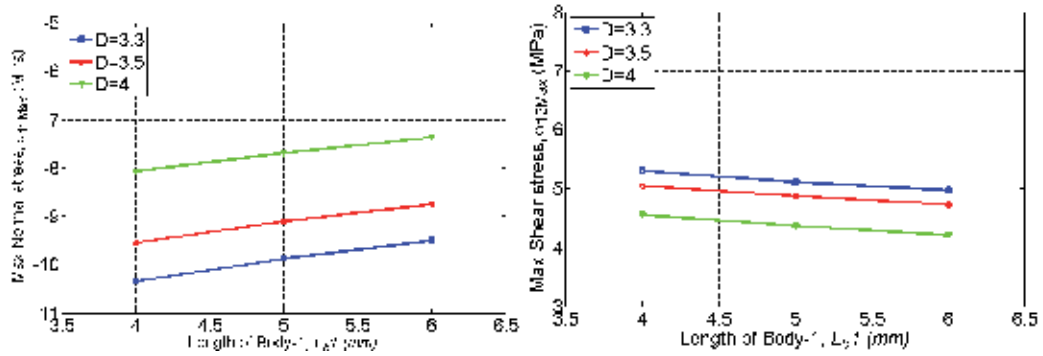
Fig. 3. Normal and shear stresses along the interface for an implant with (A) no-external thread, and (B) triangular external thread. The other parameters of the implants are as follows: θ_c = -10 degrees, L_c = 1 mm and L_{b1} = 5 mm, L_{b2} = 3 mm, θ_{b2} = 5 degrees, D = 3.3 mm.



(A) Effect of θ_c



(B) Effect of L_c



(C) Effect of L_{b1}

Fig. 4. Maximum normal and shear stress components σ_{11}, σ_{12} along the bone-implant interface with respect to contour parameter (A) collar slope, θ_c, (B) length of collar, L_c, (C) length of body-1, L_{b1}.

3. Simulation of dental implant induced bone remodeling

3.1 Methods

Bone remodeling around implant systems was modeled by using the remodeling theory presented by Huiskes and co-workers. Finite element method was used to assess the strain

energy density in loading. Equations (9) and (10) were programmed into ANSYS. Two separate analyses are presented. The first one is a 2D plane strain analysis of bone remodeling originally presented by Chou et al. (2008), and the second one is a 3D analysis of bone remodeling by Chou et al. (2011). In the 2D analysis, the external bone contour of the mandible was obtained from a slice of CT scans at the premolar region in the buccal-lingual plane. A layer of cortical bone with a thickness of 1 mm was assigned. Elastic modulus and Poisson's ratio of this cortical layer are 13 GPa and 0.3, respectively. Dental implant systems considered were assumed to be made of titanium alloy (Ti-6Al-4V). Elastic modulus and Poisson's ratio are 113.8 GPa and 0.3 (Misch & Bidez, 1999), respectively. Quadrilateral elements were used to mesh the implant bone complex, and the bottom of mandible was constrained as shown in Figure 5. Occlusion was modeled as a concentrated force, F_o = 100 N, applied on the abutment in the buccal-lingual plane at 11° with respect to vertical axis (Chou et al., 2008). In addition, a uniform pressure (P_{mf} = 500 kPa) was assumed on the outer periphery of cortical bone to simulate the effect of mandibular flexure during jaw movement. Remodeling algorithm was applied only to the trabecular region, which was initially assumed to have a uniform density of 0.808 g/cm^3 corresponding to an elastic modulus of 2 GPa. Poisson's ratio was taken as 0.3. Remodeling parameters in Equation (9) were K = 25 J/kg, s = 0.65 and $A_i\Delta t = 5\times10^{-3}$ for i = 1, 2.

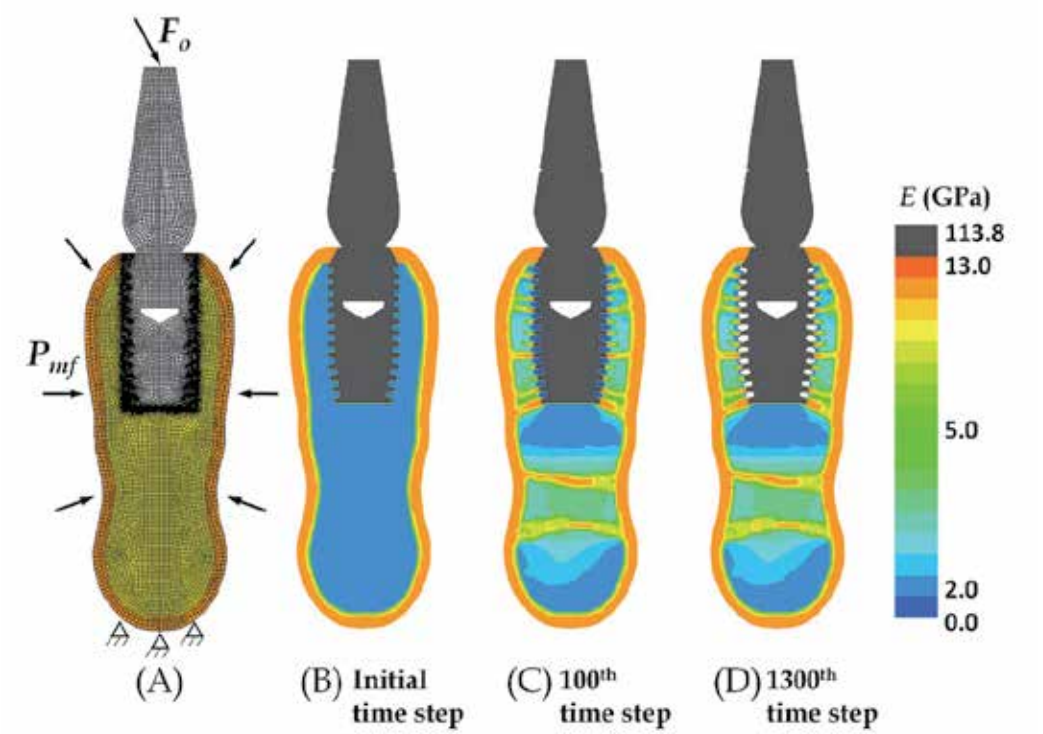


Fig. 5. (A) Two dimensional finite element mesh and loading conditions. Fine mesh is assigned at the bone implant interface. Elastic modulus distribution at (B) initial time step, (C) 100th time step, and (D) 1300th time step (Chou et al, 2008). (Printed with permission from Elsevier Limited).

3.2 Results and discussion

The transient change in the bone's elastic modulus at time steps 1, 100 and 1,300 is presented in Figure 5. This figure shows that the bone density, and hence the elastic modulus, changes gradually form a uniform initial state to a non-uniform state that is reflective of the local loading conditions. It is seen that high modulus bone is developed in the first 100 time steps, and no significant update takes place afterward. It is also observed that the tips of the external threads promote high density bone (high elastic modulus) but the area between the threads experience some bone resorption in the later stages of remodeling. As the Huiskes' model of bone remodeling doesn't have an effective means to handle actual time and loading rates, the time steps in this figure have arbitrary units. Nevertheless, one can see that bone density redistribution takes place quickly, but stays stable for prolonged loading.

Effects of four different implant contours on trabecular bone remodeling are presented in Figure 6. Three smooth faced implants systems and one externally threaded implant system are considered. Details of the geometrical differences are given in the figure. Cylindrical implant with the flat apex (Figure 6A) results in the largest amount of bone loss. The cylindrical implant with the rounded apex (Figure 6B) causes a similar response, albeit with less bone loss. The root form implant (Figure 6C) further reduces this bone loss region with the narrow apex design. For these three smooth faced implants, high density trabecular bone develops near the apical corners, and some high density struts emerging from the implant body are found in Figures 6A-6C. The main bodies of these implants fail to stimulate the bone sufficiently to induce significant bone remodeling. A study carried out by Watzak et al. (2005) in baboons investigates the effects of surface features such as threads and chemical modifications to the surface also show similar results. Note the lack of tarbecular bone under the flat apex of the implant in Figure 6A. Watzak et al. (2005) also indicate that signs of bone remodeling at the surface of cylindrical implant were absent.

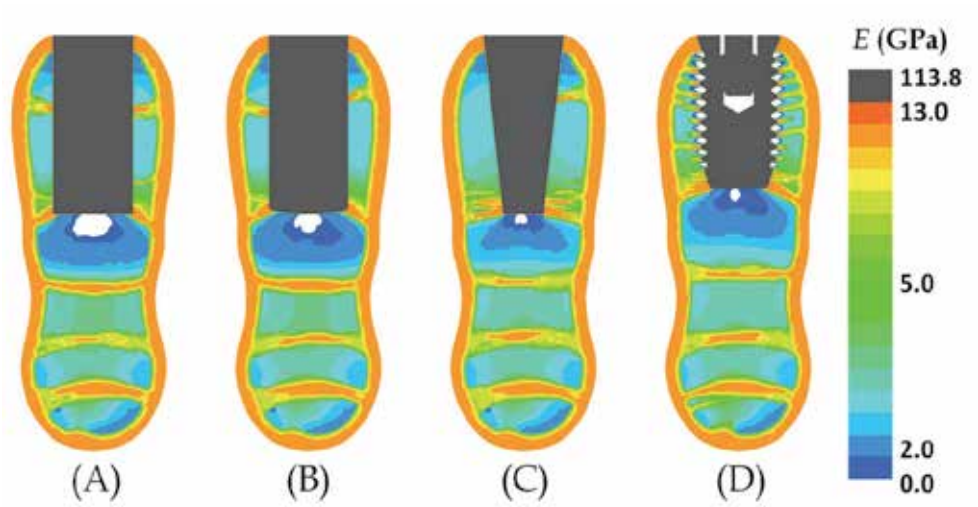


Fig. 6. Elastic modulus distribution predicted around a (A) cylindrical implant, a (B) cylindrical implant with rounded apex, a (C) root from implant and a (D) threaded implant. (Chou et al., 2008). (Printed with permission from Elsevier Limited).

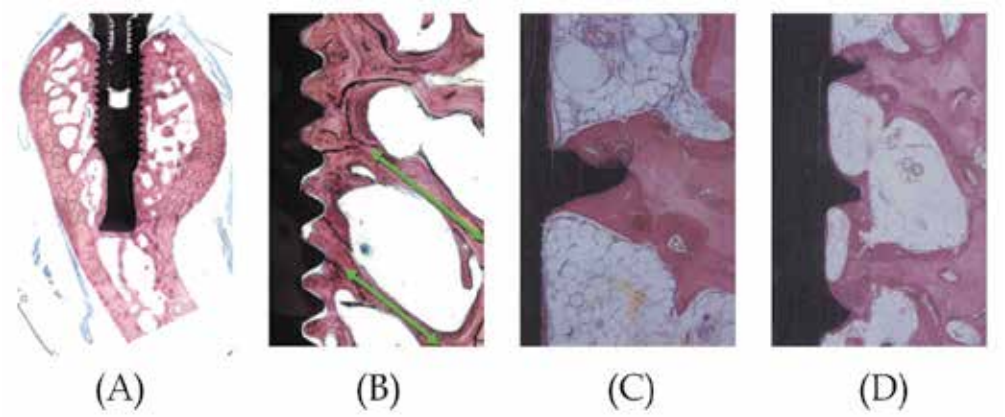


Fig. 7. Histologic studies show (A) bone remodeling around dental implant (Watzak et al., 2005), (B) trabeculae like dense struts at implant surface (Watzak et al., 2005), (C) and (D) bone growth around implant threads (Schenk & Buser, 1998). (Printed with permission from John Wiley and Sons.)

The predictions for the externally threaded implants (Figures 5D and 6D) are significantly different from smooth faced implants. In the case of threaded design, development of high density bone around the threads is evident. Similar remodeling patterns were reported in the histologic observations of Watzak et al. (2005) in Figures 7A and 7B, and those of Schenk & Buser (1998) in Figures 7C and 7D. Note that while Figures 7B-7D show bone density increase around the threads some resorption is also observed between the threads in Figures 7C and 7D similar to our simulations.

In the study presented above, the homeostatic stimulus, K, was assumed to be constant. Although satisfying results were predicted by this simplification, it implies that bone remodels toward a spatially homogenous biomechanical field, despite the fact that the biological environment (i.e. the cells and the nutrients) varies among bone sites. In order to address this issue, we used a site dependant homeostatic stimulus, $K(x,y,z)$ in a 3D analysis of bone remodeling around a dental implant. This approach was also used by Huiskes et al. (1992) and Weinans, et al. (1993) to simulate bone remodeling around hip prostheses. In addition, we hypothesize that the site specific homeostatic stimulus must be similar to that induced by a natural tooth in its supporting bone. Therefore, the site-specific K value was computed, first for a model with a natural tooth that is shown in Figure 8A. These K values were subsequently used for predicting the bone remodeling around a dental implant system. Details are presented by Chou et al. (2011).

A three-dimensional mandibular segment was constructed from the CT-scan of the premolar region of the mandible. Same material properties and occlusal load, as above, were applied to the finite element models of bone tooth and bone implant prosthesis complexes shown in Figure 8. The elastic modulus of the tooth and the prosthesis were taken as 20 GPa and 80 GPa, respectively; and the Poisson's ratios were assumed to be 0.3. Similar to clinical practice, the interstitial gap created by the incongruence of dental implant with extraction socket is filled with a (virtual) bone graft in the finite element model. The elastic modulus of the graft was set to be the same as trabecular bone. The mandible segment was constrained in all directions on the distal buccal-lingual plane, and symmetry boundary condition was applied to the mesial buccal-lingual plane shown in Figure 8.

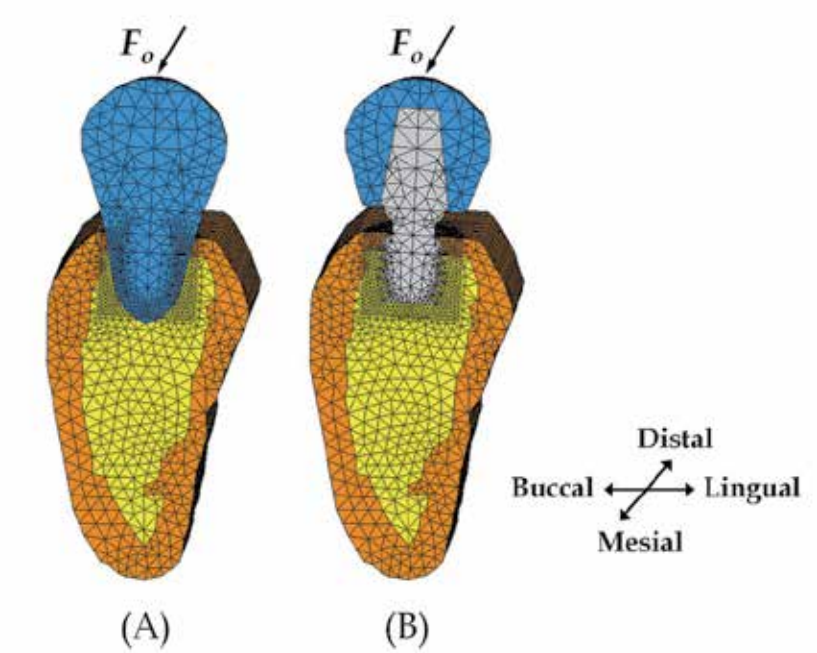


Fig. 8. Finite element models of (A) bone tooth and (B) bone implant prosthesis complexes. A concentrated force F_o is used to simulate occlusion.

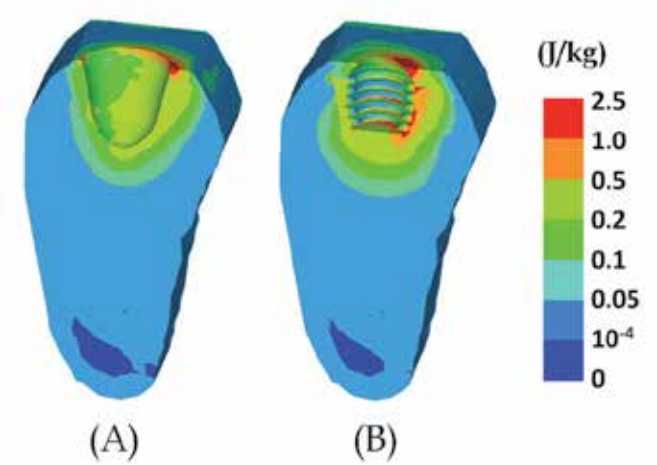


Fig. 9. (A) Homeostatic stimuli distribution in bone induced by tooth. (B) Remodeling stimuli distribution in bone induced by dental implant prior to bone remodeling (Initial time step).

The site dependant homeostatic stimuli K was based on the strain energy per unit bone mass, induced by the occlusal force acting on the natural tooth. Next, homeostatic stimuli in the graft region had to be assumed. This assumption was based on the stimulus levels near the tooth. Therefore, a constant value K_g = 0.25 J/kg was used to represent the homeostatic stimulus of the bone graft. This parameter is treated as the potential of bone graft to induce

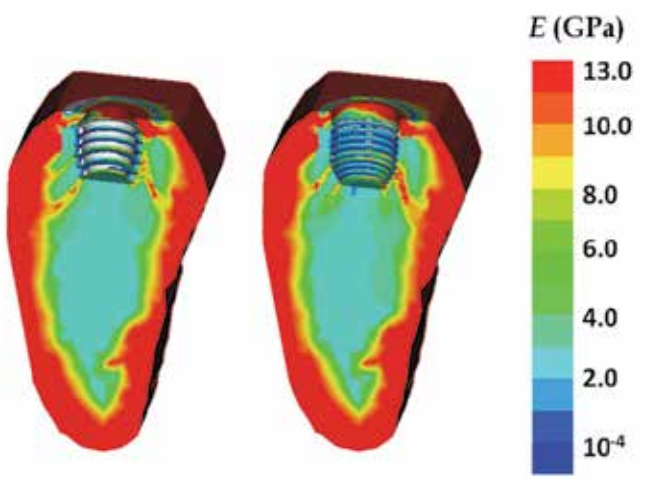


Fig. 10. Elastic modulus distribution predicted around two different implant designs at remodeling equilibrium.

bone remodeling (Chou et al., 2011). Figure 9A shows the computed site specific *K* distribution, and Figure 9B shows the initial remodeling stimuli *S* distribution around the implant It is seen that the variations of the homeostatic stimuli *K*. It is seen that the homeostatic stimuli *K* and the remodeling stimulus *S* are localized around the tooth and the dental implant. In fact, it can be stated that a certain degree of biomimetic match has been obtained in this case. For implants with longer body-1 and body-2 regions, the remodeling stimulus is markedly different than that of the tooth (Chou et al., 2011).

Figure 10 shows the elastic modulus distribution at remodeling equilibrium for two wide-diameter, short implants with different thread profiles. Trabeculae like dense bone struts develop at the implant surface and extend toward cortical layer. Implant threads show same characteristics as in 2D analysis; bone apposition occurs at the thread tips, and the regions between the implant threads are prone to bone resorption. The predicted results also demonstrate that bone remodeling is a localized event, and it decays with increasing distance away from implant surface. A histologic study by Coelho et al. (2009) reported high levels of osteoactivity taking place near the implant surface. This can be observed in the predictions in Figure 10.

4. Summary and conclusions

Dental implants provide an attractive alternative to classical prosthodontic techniques in the treatment of edentulism. It has been shown clinically that the bone loss after tooth extraction is reversed by the placement of dental implant, since the first human study reported by Brånemark et al. (1977). The mechanical loads exerted by occlusion are transferred into jawbone through the dental implant, and can potentially affect the bone remodeling according to Wolff's law (Wolff, 1892). Therefore, it is critical to develop a sound understanding of the load transfer mechanism from the implant to the bone. It is equally important, to supply a dental implant with critical chemical and contour features on its surface. If the ideal load transfer characteristics can be identified, it may be possible to improve the osseointegration.

A systematic analysis of the load transfer along the bone-implant interface was carried out by using finite element analysis. Various implant systems were designed by changing their contour parameters. Among all design parameters, the diameter, the collar slope, the collar length and the length of the implant were found to be the most influential parameters to the interfacial variations of the normal and shear stresses. Maximum normal and shear stresses were found to occur on the buccal side of the cortical bone, as in many other studies. It was shown that both maximum normal and shear stress values can be reduced by either widening the implant diameter, or increasing the lengths of the collar and body regions. Varying the slope of the collar from negative to positive was found to increase the maximum normal stress, but to reduce the maximum shear stress transferred along the interface. The effects of the external threads were also investigated. It was seen that the general interfacial load transfer behavior doesn't change with respect to smooth faced implants, but locally the interfacial stresses are elevated around the threads. A bone remodeling algorithm was implemented to analyze the bone maintenance characteristics of smooth faced and threaded implants. This showed poor bone maintenance around smooth faced implants. On the other hand, significant remodeling and densification was predicted around threaded implants. It was shown that the thread tips promote the development of dense bone. Total bone resorption was predicted in the areas between the threads. Similar remodeling phenomenon around implant threads was reported in histologic studies by Schenk & Buser (1998) and Watzak et al. (2005). It appears that adequately high interfacial stresses are introduced by using externally threaded implants.

This study contributes to our understanding of the complex problem of load transfer mechanism in the bone-dental implant interface and the subsequent peri-implant bone remodeling. Despite the interesting conclusions drawn from the results, the computational predictions are still limited by the assumptions and simplifications of loading, geometry and material properties made in this study.

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8

Stress Distribution on Edentulous Mandible and Maxilla Rehabilitated by Full-Arch Techniques: A Comparative 3D Finite-Element Approach

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1. Introduction

Many surgical protocols and guidelines are actually available in clinical practice for rehabilitating edentulous patients (Bocklage, 2002; Ganeles et al., 2001). They generally differ for number, type, and positioning of implants that support the full-arch prostheses. Moreover, each technique is characterized by a specific healing period and exhibits a success rate strongly affected by individual morphological and biological conditions (Drago, 1992). The actual clinical trend is to reduce both the number of implants and the healing period by employing threaded devices based on novel design concepts, advanced materials, and enhanced surgical procedures. In this context, the immediate-loading techniques, firstly introduced in Seventies, have been recently rediscovered. They usually allow a functional rehabilitation of edentulous arches in a single surgical session, resulting in promising aesthetic and functional results.
Clinical practice confirms that rehabilitation systems based on osseointegrated implants mainly fail because of bone weakening or loss at the peri-implant region rather than as a result of the mechanical failure of the load-bearing prosthetic structure (*e.g.*, Eckert & Wollan, 1998; Lekholm et al., 1999; Piattelli et al., 1996; Romeo et al., 2002; Roos-Jansåker et al., 2006; Tonetti, 1999; Weyant, 2003). Furthermore, the failure rate is generally higher for implants in posterior region than in the anterior (Drago, 1992; Romeo et al., 2002; Roos-Jansåker et al., 2006; Tonetti, 1999; Weyant, 2003), and in maxilla rather than in mandible (Eckert & Wollan, 1998; Lekholm et al., 1999; Piattelli et al., 1996). These evidences, especially in edentulous patients, are strictly related to the poor bone quality and quantity in molar regions, as well as to the different bone density between upper and lower jaws (Devlin et al., 1998). Possible reconstructive alternatives in atrophic cases could be considered (*e.g.*, Keller et al., 1987; Tatum, 1986), but these practices are often characterized by postoperative discomfort, questionable predictability, and surgical complexity (Al-Nawas et al., 2004; Chung et al., 2007). In light of previous considerations and since the presence of sinuses (in maxilla) and mental foramina (in mandible), nowadays full-arch restorations are mainly obtained by placing implants in the anterior region, generally resulting in the use of long cantilevered prostheses.

As pointed out in several researches (*e.g.*, Sertgöz & Güvener, 1996; Shackleton et al., 1994; White et al., 1994), high values of cantilever can be directly associated with high overloading risks. Overloads, generally induced by a shortcoming in load transfer mechanisms under functional forces, lead to possible high stress concentrations at the bone-implant interface, producing in turn possible physiologically-not-admissible strains that activate biological bone resorption (Carter et al., 1996; Guo, 2001; Irving, 1970). As a consequence, cratering phenomena (namely, bone resorption at the implant necks) usually occur, strictly depending on implant geometry and positioning (Baggi et al., 2008a). Recent clinical evidences have showed that such an effect can be minimized by employing microstructured devices subcrestally placed and characterized by a connection diameter of the abutment narrower than the implant collar. These concepts are generally referred to as platform switching (Lazzara & Porter, 2006; Lòpez-Marì et al., 2009; Maeda et al., 2007).

With the aim to reduce cantilever and to obtain a conservative and rational solution for optimizing load transfer mechanisms on the available bone, systems based on tilted implants have been recently proposed (Aparicio et al., 2001; Calandriello & Tomatis, 2005; Capelli et al., 2007; Del Fabbro et al., 2010; Krekmanov et al., 2000; Testori et al., 2008), as well as the possibility to employ short implants in molar regions could be considered (Renouard & Nisand, 2005).

Actually, two of the most used systems for the full-arch immediate-loading rehabilitation of upper and lower edentulous jaws are based on the "Allon4" and "SynCone" concepts (Eccellente et al., 2010; Ferreira et al., 2010; Romanos, 2004). Both systems employ threaded implants usually placed in the anterior region, and allow the functional and aesthetic rehabilitation of 12-14 teeth per arch. The "Allon4" protocol is based on two vertical mesial implants and two tilted distal implants, whose abutments are rigidly fixed to the prosthetic bar. Tilted distal implants are usually distally-angled with respect to the vertical direction of about 30-45 degrees, enabling the use of short cantilevered prostheses. Nevertheless, since in this case implants are crestally positioned, significant cratering effects are generally induced after a healing and functioning period. On the contrary, when "SynCone" protocol is applied, both mesial and distal endosseous implants are conceived on the basis of the platform-switching concepts and are vertically placed. Accordingly, a significant reduction of the crestal bone loss at the implant necks is expected, but a longer cantilever is generally needed for full-arch restorations. In this case the prosthetic denture is retained by telescopic crowns, allowing for excellent three-dimensional immobilization, defined release force, flexibility of design, and optimum access for oral hygiene (Bayer et al., 2009; Wostmann et al., 2007; 2008).

In order to overcome drawbacks of previous rehabilitation systems as well as to account for their advantages, a novel approach is herein proposed and analyzed. It assumes that the prosthetic bar is supported by four vertical implants, designed and positioned in agreement with platform-switching concepts. Two implants are placed in the anterior region and are fully consistent with the SynCone protocol, whereas lateral implants are placed in the posterior molar regions, enabling a significant cantilever reduction (up to zero, if it is possible). Nevertheless, due to the usual quality and quantity of the posterior bone, such a positioning needs the use of short implants (mini implants) similar to those employed in clinical orthodontic or skeletal applications, and sometimes applied in prosthetic dentistry for single-tooth rehabilitations (Baggi et al., 2008a;b; Papadopoulos & Tarawneh, 2007; Renouard & Nisand, 2005).

Clinical effectiveness and reliability of Allon4 and SynCone techniques have been focused in a number of recent studies, showing results of both experimental *in-vivo* tests and follow-up analyses (Degidi & Piattelli, 2005; Ferreira et al., 2010; Khatami & Smith, 2008; Malò et al., 2005; Portmann & Glauser, 2006; Puig, 2010), whereas significant and conclusive clinical evidences are not available for full-arch rehabilitations that combine the use of posterior mini implants and platform-switching concepts.
Nevertheless, clinical *in-vivo* approaches and follow-up analyses usually furnish *a posteriori* indications of functional performance and osseointegration evolution associated with a given rehabilitative protocol. On the contrary, the control *a priori* of design parameters affecting both load transfer mechanisms and possible overloading risks should arise from parametric approaches able to identify stress and strain distributions induced by functional loads. Such a *modus operandi* should allow to obtain clear biomechanical evidences towards the choice of the best treatment in a given clinical scenario, as well as to optimize durability and effectiveness of a specific rehabilitative solution, minimizing patient discomfort and complex clinical procedures.
Stress and strain fields at bone-implant interfaces are affected by a number of biomechanical factors (loading type, material and geometrical properties of both implant and biological *situ*, clinical procedures, Brunski (1997); Mailath-Pokorny & Solar (1996)) and their assessment via *in-vivo* techniques is almost unreliable and ineffective in usual clinical practice (Begg et al., 2009; Clelland et al., 1993). Moreover, the high complexity and the multifield coupling characterizing the bone-implant system generally prevent the use of closed-form approaches. Therefore, numerical methods can be fruitfully employed. In the last years the finite-element method has been widely applied in many fields of dentistry in order to analyze the influence of both mechanical and biological factors, as well as for improving clinical treatments and surgical protocols (*e.g.*, Baggi et al., 2008a;b; Chun et al., 2006; Kitagawa et al., 2005; Maceri et al., 2007; 2009; Petrie & Williams, 2005; Van Staden et al., 2006). In this context, some recent numerical studies have compared the bone-implant mechanical interactions induced by distally-tilted and vertical implants, as well as numerical simulations based on simple geometrical models of Allon4 applications have been carried out (Bellini, 2009; Bonnet et al., 2009; Carvalho Silva et al., 2010; Zampelis et al., 2007). Nevertheless, the numerical analysis of full-arch rehabilitative techniques by using refined three-dimensional models can be still considered at an early stage and then as an actual and open important task.
In this paper the stress-based performances of full-arch rehabiltations supported by four implants and based on the previously-introduced concepts are addressed, by proposing and discussing many numerical results obtained through a three-dimensional finite-element approach. A general numerical method, able to analyze parametrically 3D patient-based models of restored jaws, was developed and applied for comparing three different techniques (namely, Allon4, SynCone-based, and mini-implant-based) when used in both edentulous maxilla and mandible. Load transmission mechanisms and possible bone overloading risks were quantitatively characterized by linearly elastic simulations, considering different functional loads as well as accounting for a detailed and realistic description of both morphological and mechanical aspects.

2. Materials and methods

The following three rehabilitative approaches for the treatment of completely edentulous arches were analyzed and compared:

	ℓ [mm]	d [mm]	p [mm]	t [mm]	L_1 [mm]	L_2 [mm]	c [mm]
SC	9.5 (9.5)	3.5	0.9	0.45	12.0 [16.0]	29.0 [31.0]	15.0
A4	11.0 (15.0)	3.75	0.6	0.2	12.0 [16.0]	35.0 [38.0]	5.0
ZC	9.5 (5.0)	3.5	0.6	0.3	12.0 [16.0]	37.0 [45.0]	0.0

Table 1. Values employed for the main geometrical parameters defining implants and rehabilitative techniques analyzed in this study (SC: SynCone-based, A4: Allon4, ZC: Zero Cantilever). Values of L_1 and L_2 in square brackets refer to mandible model (otherwise in maxilla), and values of ℓ in round brackets refer to distal (posterior in ZC) implants (otherwise mesial). The notation refers to Figs. 1 and 2

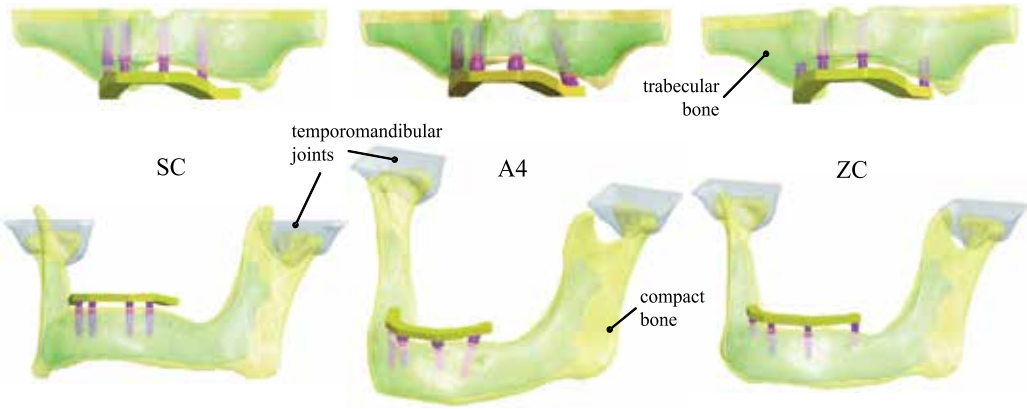
- Allon4 (denoted as A4). Full-arch rehabilitations were obtained by four commercially available Nobel Biocare implants (Nobel Biocare AB, Göteborg, Sweden) crestally positioned in the anterior jaw region. Two vertical implants (*i.e.*, with the implant axis orthogonal to the occlusal plane) were placed in the middle part of the anterior jaw region (mesial implants), and two tilted implants in the lateral one (distal implants).
- SynCone-based (denoted as SC). Full-arch rehabilitations were obtained by four (two mesial and two distal) commercially-available Ankylos implants (Dentsply Friadent, Mannheim, Germany), subcrestally and vertically placed in the anterior jaw region.
- Zero Cantilever (denoted as ZC). Full-arch rehabilitations were obtained by: two commercially-available Ankylos implants, placed in the mesial region as in SC; two vertical non-conventional short implants (mini implants, not commercially available), characterized by the Ankylos geometry, and subcrestally placed in the posterior molar region in order to minimize the cantilever.

2.1 Computational models

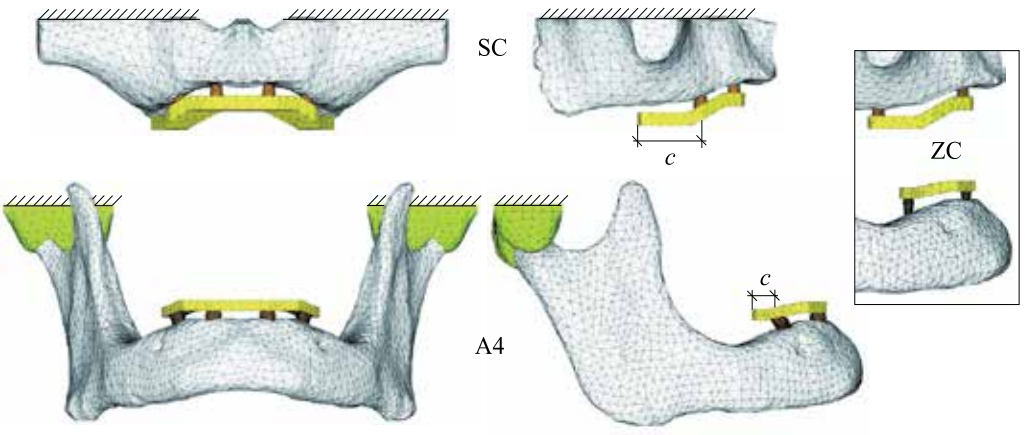
A trapezoidal thread for all the implants as well as abutments that allow a suitable implant-bar connection were modelled. Abutments of Nobel Biocare implants (in A4) were assumed to be different in vertical and tilted devices, and rigidly connected to the prosthetic bar. Abutments of Ankylos implants (long and short, that is in SC and ZC) were consistent with the platform-switching concepts, and the abutment-bar connection was thought to be achieved by telescopic crowns. In agreement with both commercial availability and clinical practice, numerical models were built up (see Fig. 1) by considering implants whose main geometrical properties are summarized in Table 1.

Implant models were fitted into the computational models of the upper and lower edentulous bone arches (maxilla and mandible). These latter were obtained by disregarding gingival soft tissues and distinguishing between trabecular (inner regions) and cortical (outer layers) bone. The mandible was modelled by considering the complete arch, and temporomandibular joints were accounted for by describing the articular discs as two layer-wise volumes. The maxilla was modelled by reproducing the maxillary process up to the anterior-nasal-spine level, resulting delimited in the upper region by two planar cutting surfaces (Fig. 1).

With the aim to perform significant comparisons, axes of vertical mesial implants were identically positioned for a given jaw in all the three approaches, and implant lengths were chosen such that the in-bone depth was the same, except for the posterior short implants in ZC. Distal implants in A4 were assumed to be distally-tilted at a 30-degree angle in the plane orthogonal to the buccal-lingual direction, and positioned such that their in-bone ends belong



(a) Solid models

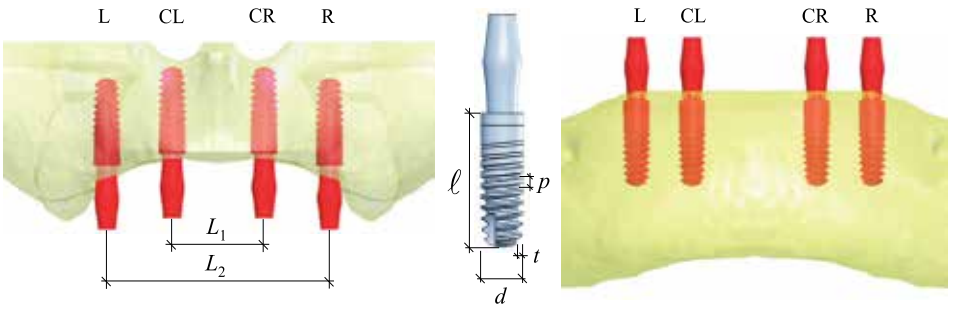


(b) Mesh details

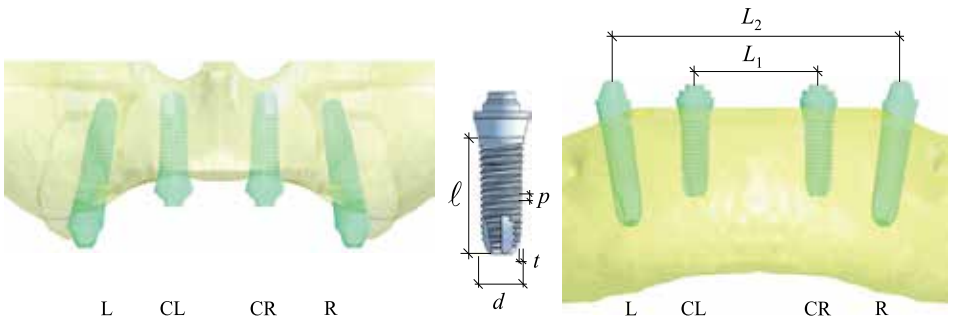
Fig. 1. Three-dimensional computational models for mandible and maxilla equipped with three different rehabilitative devices: SynCone-based (SC), Allon4 (A4) and Zero Cantilever (ZC). As a notation rule, c denotes the cantilever length

to the vertical axes of the SC's distal implants (Fig. 2). Accordingly, a cantilever scheme 5 mm long for A4 and 15 mm for SC arose (Fig. 1 and Table 1). For what concerns ZC, posterior mini implants were placed so that a zero cantilever length was obtained. Due to the different bone morphology in lower and upper jaws and in agreement with general clinical guidelines, distances among implants in mandible and maxilla were assumed to be different (Fig. 2 and Table 1).

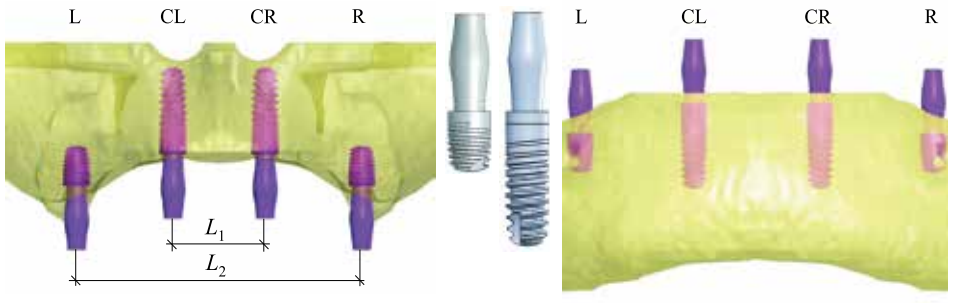
The prosthetic bar was modelled by considering a pseudo-parabolic middle-line geometry that followed the bone morphology. Implant abutments and bar shape were arranged to ensure that the distance between bar and bone was about 5 mm. The bar, slightly different in shape for mandible and maxilla, was 3 mm thick, 5 mm depth, and its linear length in the occlusal plane was 65.8 mm. It is worth pointing out that the bar's mechanical response was behind the scope of the present study and then the bar modeling has been performed with the only purpose to allow a suitable loading transfer towards the implant-bone coupled system.



(a) SynCone-based technique (SC) employing Ankylos implants



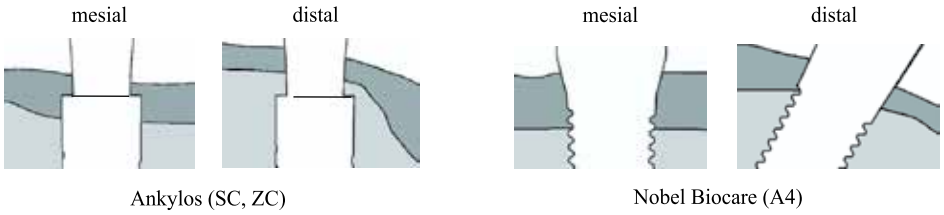
(b) Allon4 technique (A4) employing Nobel Biocare implants



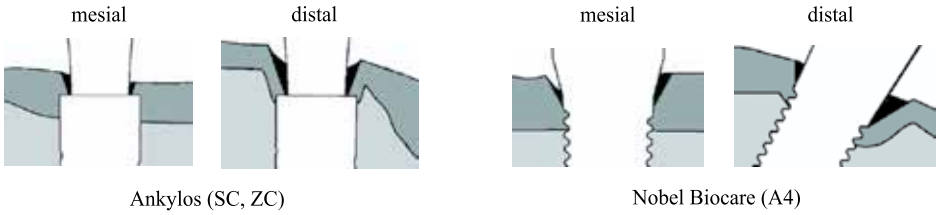
(c) Zero-Cantilever technique (ZC) employing Ankylos implants and Ankylos-type mini implants

Fig. 2. Implant positioning in both edentulous maxilla (on the left) and mandible (on the right). ℓ: implant length; d: implant maximum diameter; p: average thread pitch; t: average thread depth; L_1: distance between mesial implants; L_2: distance between distal implants; L: left implant; CL: central-left implant; CR: central-right implant; R: right implant

In order to describe realistically the physiological structure of the cortical bone arising around a functioning implant after a healing period, different peri-implant crestal bone geometries were modelled, depending on both implant shape and positioning. Starting from the local bone configurations and the virtual implant positioning, Fig. 3 sketches



(a) Virtual implant positioning



(b) Peri-implant post-healing geometry

Fig. 3. Geometrical modeling of the post-healing crestal bone morphology in functioning implants. Comparison with the local bone configurations obtained after the virtual implant positioning

as the peri-implant bone geometries were arranged in order to match well-established clinical evidences associated with crestal bone loss and remodeling at the implant necks (Abboud et al., 2005; Degidi et al., 2009; Shin et al., 2006). Accordingly, for Nobel Biocare devices the peri-implant cortical geometries were modelled such that the first coil was always in contact with the compact bone layer, and a cratering morphology with a mean crestal bone loss of about 45% in thickness was considered. In the case of Ankylos implants (short and long), since the platform-switching configuration and subcrestal positioning, a lower crestal bone loss (assumed to be about 20% in thickness), and a bone layer apposition (about 0.3 mm thick) were modelled.

Three-dimensional models of implants and prosthetic bar were developed by using a parametric CAD software (SolidWorks 9; Dassault Systems, Concord, Massachusetts). Detailed solid models of mandible and maxilla were built up from patient-based computed tomography images, and morphological parameters were evaluated by using a commercial tool (Mimics 10.1; Materialise Dental NV, Leuven, Belgium). All 3D volumes were arranged by using the CAD software, generating as an output the models fully compatible with a commercial finite-element code (Ansys 11.0; Ansys Inc, Canonsburg, Pa). The latter was used for merging all parts, as well as for generating and solving the discrete numerical models. Computational meshes were obtained by employing ten-node tetrahedral elements based on a classical pure displacement formulation, with quadratic shape functions and three degrees of freedom per node (Zienkiewicz & Taylor, 2005).

As a result of a preliminary convergence analysis, the mean value of the mesh size was set equal to about 1 mm far away from the bone-implant interfaces, and to about 0.1 mm at the peri-implant regions (Fig. 1). In this way, good accuracy and admissible computing effort were obtained, with an expected relative error for the displacement-based numerical solutions less than 0.1% at the peri-implant regions and less than 2% elsewhere (Baggi et al., 2008b;

	SynCone (SC)		Allon4 (A4)		Zero Cantilever (ZC)	
	Mandible	Maxilla	Mandible	Maxilla	Mandible	Maxilla
Nodes	235,465	281,279	263,354	258,780	251,780	254,113
Elements	431,561	449,287	421,220	448,254	432,974	468,423

Table 2. Number of elements and nodes characterizing present convergent finite-element models

Material	Region	E [GPa]	ν
Titanium Alloy[a,b]	Implants	114.0	0.34
Gold Alloy[a,b]	Prosthetic bar	105.0	0.23
Cancellous bone[c,d]	Mandible	1.0	0.3
	Maxilla	0.5	0.3
Cortical Bone[c,d]	Mandible and maxilla	13.7	0.3
Soft tissue[e]	Articular discs (in mandible)	0.006	0.4

[a] Lemon & Dietsh-Misch (2007)
[b] Baggi et al. (2008b)
[c] Natali et al. (2003)
[d] Baggi et al. (2008a)
[e] Beek et al. (2000)

Table 3. Elastic constants adopted in finite-element analyses (E: Young modulus, ν: Poisson ratio)

Zienkiewicz & Zhu, 1987; Zienkiewicz & Taylor, 2005). Table 2 summarizes the number of elements and nodes characterizing the convergent discrete models employed in this study.

2.2 Material properties

Dry material models approximated the biological tissues (that is, bone and articular discs), neglecting any effect of fluid-solid interactions. Materials were assumed to be characterized by a linearly elastic isotropic behavior, and all material volumes were considered as homogeneous. Referring to well-established approaches available in literature (Baggi et al., 2008a;b; Beek et al., 2000; Lemon & Dietsh-Misch, 2007; Natali et al., 2003), Table 3 summarizes the elastic properties adopted in this study.
It is worth pointing out that, according with the classification of Lekholm & Zarb (1985), material properties considered for mandibular tissues approximate a quality-II bone, whereas maxillary trabecular bone was assumed to be less dense than mandible's, resulting in a smaller value of the Young modulus (Beek et al., 2000).

2.3 Loading and Boundary Conditions

Finite-element analyses were carried out considering three different static loading scenarios (Fig. 4):

- Full mouth biting (denoted as Load 1), defined as a uniformly distributed intrusive vertical load acting upon the free surface of the prosthetic bar, with a resultant value of 300 N.

- Cantilever load (Load 2), defined as a distal concentrated load applied at the end of the right cantilever, and angled with reference to the vertical axis. It consists in an intrusive vertical component of 250 N and in an horizontal one (along the buccal-lingual direction) of 100 N.
- Frontal load (Load 3), defined as a concentrated load applied at the midspan of the bar portion between mesial implants, consisting in an intrusive vertical component of 250 N and in an horizontal one (along the buccal-lingual direction) of 100 N.

Muscular forces were disregarded in the case of the maxillary arch and were included in the mandible model. In agreement with Trainor et al. (1995), forces relevant to masseter, temporalis and internal pterygoideus muscles were taken into account, by assuming uniformly distributed loads on the corresponding physiological surfaces (Fig. 5). With reference to the Cartesian frame introduced in Fig. 5 and depending on the loading type, components of the resultant muscular forces produced by these distributions were summarized in Table 4.
For what concerns boundary conditions, complete osseous integration between implants and bone was modelled, resulting in the continuity of displacements at the implant-bone interfaces. Furthermore, displacement functions were assumed to be continuous at all possible interfaces among contiguous volumes. The overall arch models equipped with rehabilitative devices were constrained by preventing any displacement component of every node belonging to the upper surfaces of the layer-wise articular discs in mandible and to the virtual cutting surfaces in maxilla (see Fig. 1).

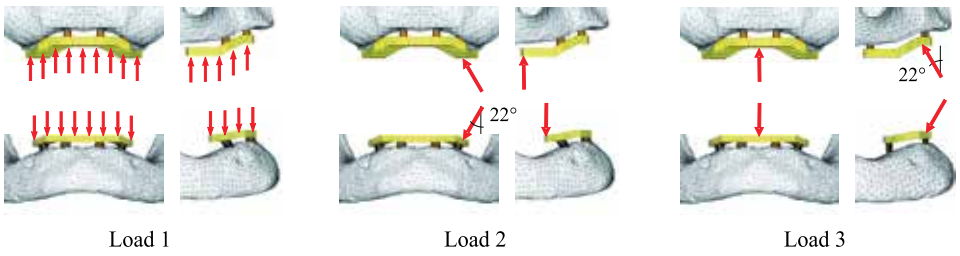


Fig. 4. Loading conditions. Load 1: full mouth biting. Load 2: cantilever load. Load 3: frontal load

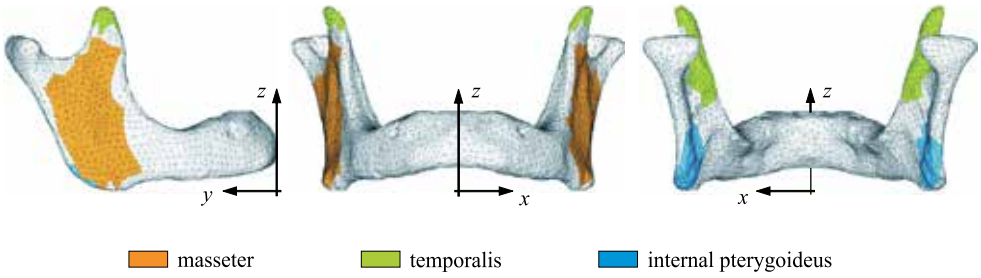


Fig. 5. Physiological surfaces on mandible model where muscular force distributions were assumed to be uniformly applied

	Masseter			Temporalis			Pterygoideus		
Comp.	x	y	z	x	y	z	x	y	z
Load	[N]	[N]	[N]	[N]	[N]	[N]	[N]	[N]	[N]
1	20.0	-31.8	82.8	9.7	19.4	77.8	-20.6	-12.5	35.7
	(-20.0)	(-31.8)	(82.8)	(-9.7)	(19.4)	(77.8)	(20.6)	(-12.5)	35.7
2	20.0	-31.8	82.8	9.7	19.4	77.8	-20.6	-12.5	35.7
	(-13.2)	(-21.0)	(54.6)	(-8.2)	(16.3)	(65.3)	(13.9)	(-8.4)	(24.1)
3	20.9	-33.3	86.6	16.8	33.5	134.1	-19.0	-11.4	32.8
	(-20.9)	(-33.3)	(86.6)	(16.8)	(33.5)	(134.1)	(19.0)	(-11.4)	(32.8)

Table 4. Components of the resultant muscular forces acting upon the mandible model, referred to the Cartesian frame introduced in Fig. 5 and to the loading cases under investigation. Values in (respectively, not in) parentheses indicate force components acting upon the corresponding physiological surfaces at $x > 0$ (respectively, $x < 0$)

2.4 Stress measures, risk indicators, and loading partition index

The models of lower and upper jaws treated by the previously-introduced techniques were numerically analyzed and, in order to furnish risk measures of critical bone overloading as well as performance indications on load transfer features, comparisons were performed evaluating stress distributions on both cancellous and compact bone at the peri-implant regions. In agreement with well-established studies (Baggi et al., 2008a;b; Bellini, 2009; Bonnet et al., 2009; Carvalho Silva et al., 2010; Chun et al., 2006; Kitagawa et al., 2005; Petrie & Williams, 2005; Van Staden et al., 2006; Zampelis et al., 2007), the Von Mises equivalent stress σ_{VM} (always positive in sign) was used as a global stress indicator for characterizing the load transfer mechanisms, whereas principal stresses were employed as local risk measures of the bone-implant interfacial physiological failure and/or of the resorption process activation. Accordingly, by assuming the ultimate bone strength as a physiological limit, local overloading at the cortical bone occurs in compression when the maximum compressive principal stress (σ_C) exceeds 170-190 MPa in modulus, and in tension when the maximum tensile principal stress (σ_T) exceeds 100-130 MPa, as well as local overloading at the trabecular bone occurs when σ_T and/or $\|\sigma_C\|$ exceeds 5 MPa (Guo, 2001; Natali et al., 2003), symbol $\|\sigma_C\|$ denoting the modulus of σ_C.

For each implant mean and peak values of σ_{VM}, σ_C, and σ_T were computed at both trabecular (Σ_t) and compact (Σ_c) peri-implant control volumes, defined by considering bone layers about 1 mm thick surrounding the implants (Baggi et al., 2008b). Stress solutions obtained by 3D finite-element simulations were post-processed through a custom-made procedure, employing as an input some geometric and topological data (namely, nodal coordinates and elements lying in bone-implant interfacial control volumes Σ_t and Σ_c), as well as stress solutions at the Gauss integration points.

In order to analyze quantitatively the loading partition mechanisms in rehabilitative approaches herein investigated, a meaningful performance index was also introduced, denoted in the following as partition ratio. In detail, under an assigned load and for a given bone arch, the partition ratio at the peri-implant bone region r of the implant $\mathcal{I}$ and related to the technique $\mathcal{T}$ was defined as:

$$P_r^{(\mathcal{I},\mathcal{T})} = \frac{(\bar{\sigma}_{VM})_r^{(\mathcal{I},\mathcal{T})}}{(\bar{\sigma}_{VM})_r^{\max}} \tag{1}$$

$(\sigma_{VM})_r$ denoting the average value of the Von Mises stress distribution in Σ_r (with $r = t, c$), and $(\bar{\sigma}_{VM})_r^{\max}$ indicating the maximum value of $(\bar{\sigma}_{VM})_r$ computed for all implants in all rehabilitative techniques, that is

$$(\bar{\sigma}_{VM})_r^{(\mathcal{I},\mathcal{T})} = \frac{1}{(\Sigma_r)^{(\mathcal{I},\mathcal{T})}} \int_{(\Sigma_r)^{(\mathcal{I},\mathcal{T})}} \sigma_{VM}^{(\mathcal{T})} \, d\Sigma \tag{2}$$

$$(\bar{\sigma}_{VM})_r^{\max} = \max_{\mathcal{T}} \left\{ \max_{\mathcal{I}} \left\{ (\bar{\sigma}_{VM})_r^{(\mathcal{I},\mathcal{T})} \right\} \right\} \tag{3}$$

where, in agreement with the notation rules introduced in Fig. 2, $\mathcal{I}$ = L, CL, CR, R and $\mathcal{T}$ = SC, A4, ZC.

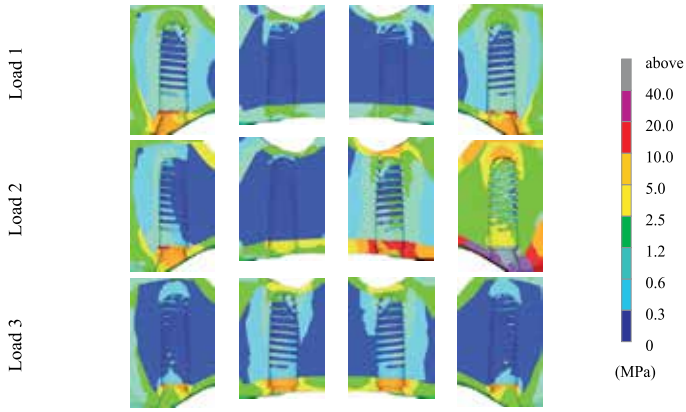
Therefore, a prosthetic treatment on a given jaw and for an assigned load can be retained to exhibit load transmission performance better than another one if the corresponding values of P are more uniformly distributed among the supporting implants. Furthermore, small values of P can be retained to furnish a first indication of low overloading risks. Nevertheless, since the Von Mises stress measure does not allow to trace a distinction between tensile and compressive local stresses, more effective and straight evidences on possible overloads were obtained by analyzing stress measures σ_C and σ_T (Baggi et al., 2008a;b).

3. Results

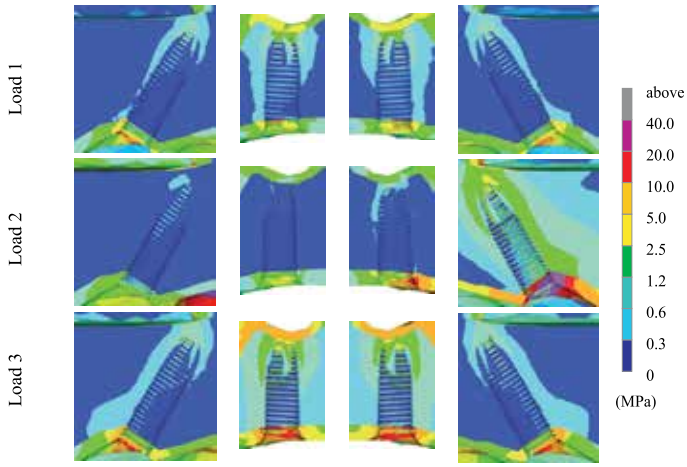
The main findings obtained by numerical simulations are proposed and discussed in the following. Figures 6 and 7 show the Von Mises stress distributions at the peri-implant bone regions in maxilla and mandible, respectively, for the three rehabilitation techniques previously introduced and considering different loads. For a given implant, numerical results have been plotted in the plane containing the implant axis and orthogonal to the buccal-lingual direction. Moreover, in order to obtain significant comparisons, the same contour legend has been employed in all cases. In Fig. 8 values of the partition ratio P, computed in both upper (Fig. 8a) and lower (Fig. 8b) jaw, and for cortical (P_c) and trabecular (P_t) bone regions, are plotted and compared. Finally, Figs. 9 and 10 depict mean (bars) and peak (lines) values of the principal stress measures σ_C and σ_T, computed at each peri-implant cortical (Σ_c, Fig. 9) and trabecular (Σ_t, Fig. 10) bone region of maxilla and mandible.

All the numerical simulations clearly highlighted that stress concentration areas were located at the cortical bone around the implant necks, and that the right cantilever load (namely, Load 2) was the most severe, resulting in the highest values of stresses (both Von Mises and principal measures) at the right peri-implant bone.

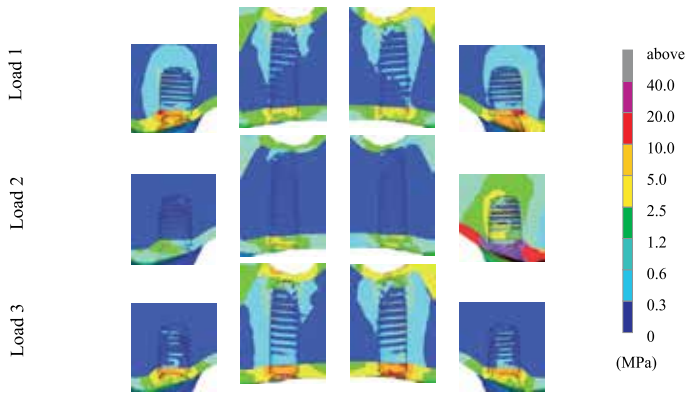
For what concerns the comparison between conventional techniques (namely, A4 and SC), Von Mises stress patterns induced by A4-based restorations in both lower and upper jaw were more homogeneous and characterized by smaller stress values than SC, except in the maxillary rehabilitation under the frontal load (Load 3). Such an evidence is fully confirmed by analyzing the values of the partition index P. In fact, for all loading conditions in mandible and for full mouth biting and cantilever load in maxilla, A4 produced more uniform distributions of P among the implants (*i.e.*, better load transmission mechanisms) than SC. On the contrary, when the frontal load was applied on the upper jaw, differences among the values of P at mesial and distal implants were greater in A4 rather than in SC. In mandible, the greatest differences in P between A4 and SC were experienced at the right implant under the Load 2 (P_{A4} was smaller than P_{SC} of about 18% in cortical bone, and 60% in trabecular), and at the distal implants in the case of Load 1 and Load 3 (P_{A4} was smaller than P_{SC} of



(a) SynCone-based rehabilitation (SC)

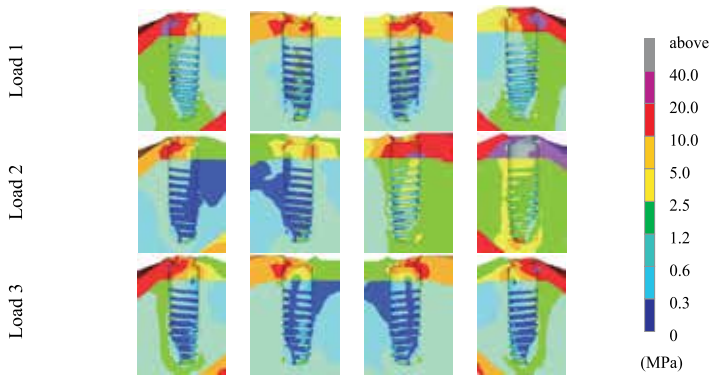


(b) Allon4 rehabilitation (A4)

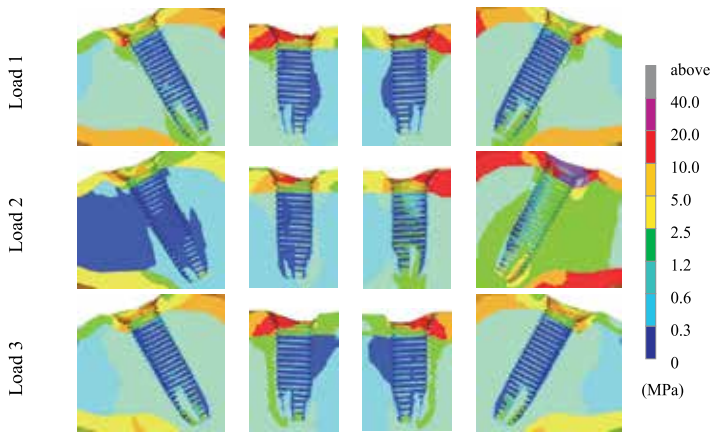


(c) Zero-Cantilever rehabilitation (ZC)

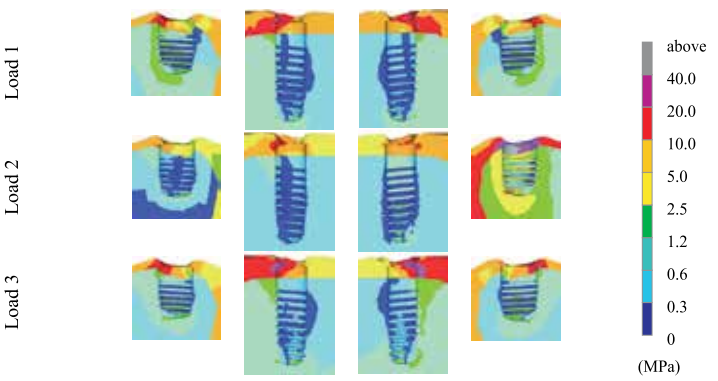
Fig. 6. Von Mises stress contours at each peri-implant bone region in maxilla, referred to the plane containing implant axis and orthogonal to the buccal-lingual direction



(a) SynCone-based rehabilitation (SC)

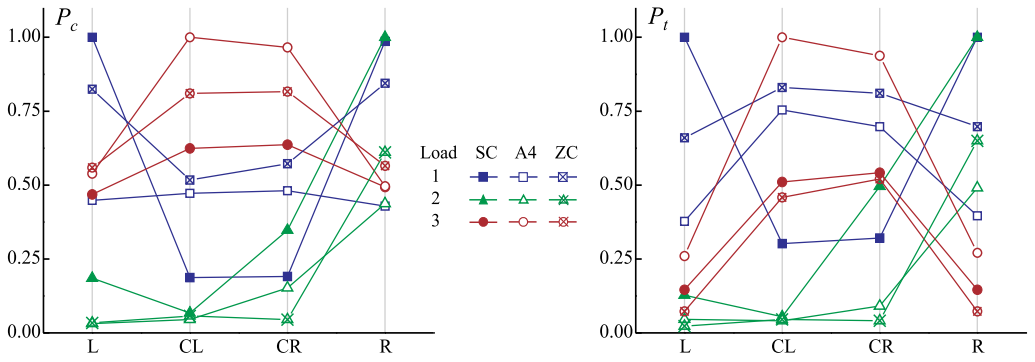


(b) Allon4 rehabilitation (A4)

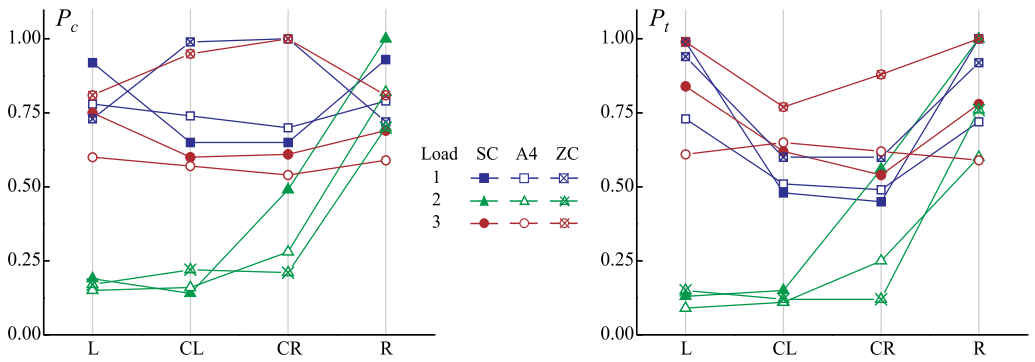


(c) Zero-Cantilever rehabilitation (ZC)

Fig. 7. Von Mises stress contours at each peri-implant bone region in mandible, referred to the plane containing implant axis and orthogonal to the buccal-lingual direction



(a) Maxilla



(b) Mandible

Fig. 8. Loading partition ratio at cortical (P_c, on the left) and trabecular (P_t, on the right) bone for SynCone-based (SC, filled symbols), Allon4-based (A4, unfilled symbols), and Zero Cantilever (ZC, cross symbols) rehabilitations, in upper (a) and lower (b) jaw under different loads (Load 1: full mouth biting, blue symbols; Load 2: cantilever load, green symbols; Load 3: frontal load, red symbols; L: left implant; CL: central-left implant; CR: central right implant; R: right implant)

about 15-22% in cortical bone, and about 30% in trabecular). In maxilla and for Load 2, the greatest differences in P were again at the right implant (P_{A4} was smaller than P_{SC} of about 56% in cortical bone, and 51% in trabecular), whereas a different behavior with respect to the mandible was proved under Load 1 and Load 3. In detail, for a full-mouth-biting load applied on the SC-based restoration, distal implants transferred the greatest amount of the load (mesial P_{SC} was smaller than the distal's of about 70-80%), whereas with A4 the load was more uniformly distributed, resulting in greater contributions acting upon the mesial implants (distal P_{A4} was smaller than the mesial's of about 5-10% in cortical bone, and 45-50% in cancellous). On the contrary, for Load 3 acting on the maxillary jaw the system A4 exhibited the worst performance, resulting in values of both P_c and P_t higher and less homogeneous (*e.g.*, the difference between mesial and distal values of $(P_c)_{SC}$ was smaller than $(P_c)_{A4}$ of

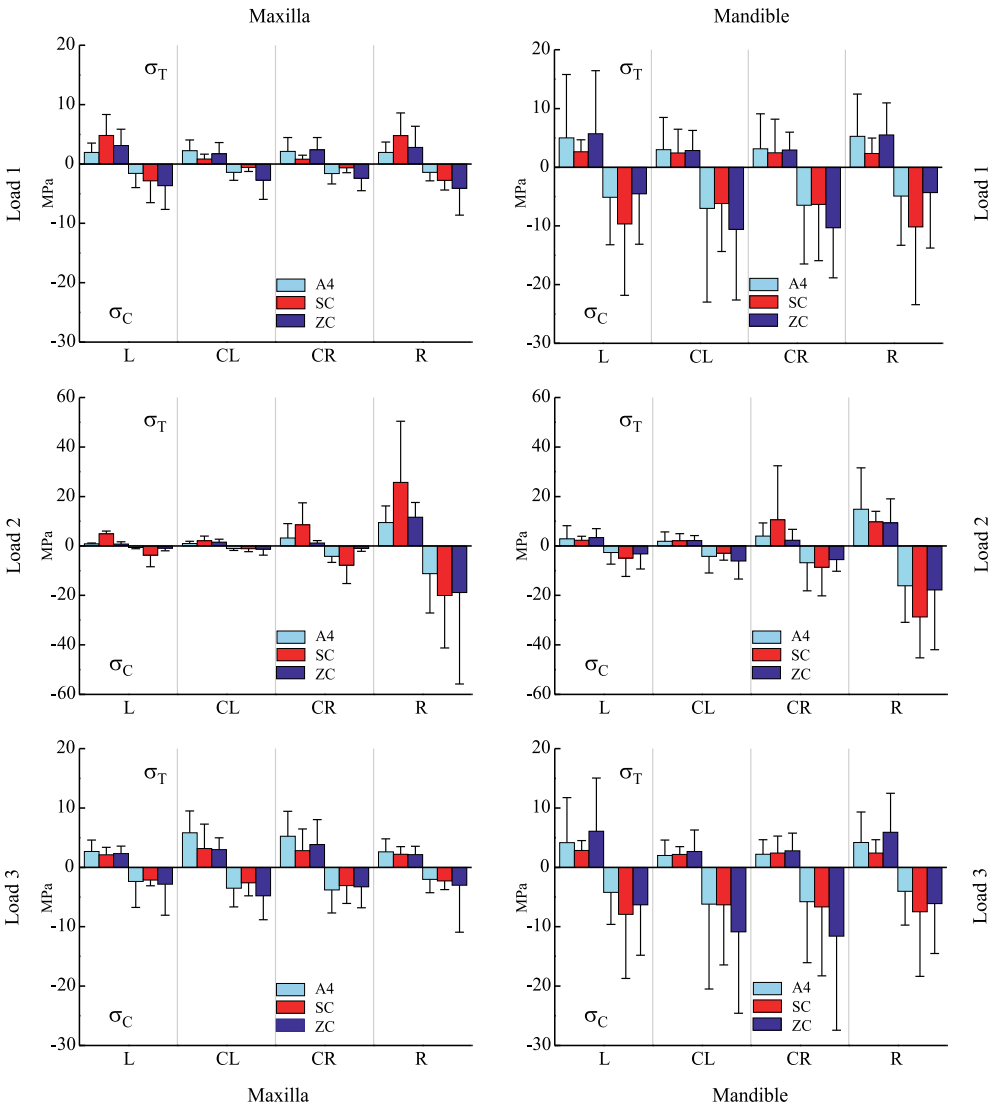


Fig. 9. Principal stress measures (σ_C compressive and σ_T tensile) at the cortical bone-implant interfaces for implants in A4 (Allon4, light blue bars), SC (SynCone-based, red bars), and ZC (Zero Cantilever, violet bars) restorations, in maxilla (on the left) and mandible (on the right). Average (bars) and peak (lines) values (L: left implant; CL: central-left implant; CR: central-right implant; R: right implant)

about 50-60%, with the highest values of $(P_c)_{SC}$ –at the mesial implants– smaller than those of $(P_c)_{A4}$ of about 40-50%).

As regards the non-conventional Zero-Cantilever approach (ZC), it produced Von Mises stress patterns at the peri-implant bone regions very similar in both values and homogeneity levels to those obtained with A4. Moreover, the use of Ankylos-type mini implants at the posterior molar regions allowed to achieve loading partition mechanisms almost comparable (sometimes better, as for Load 2 in mandible) with those obtained through both A4 and SC. In

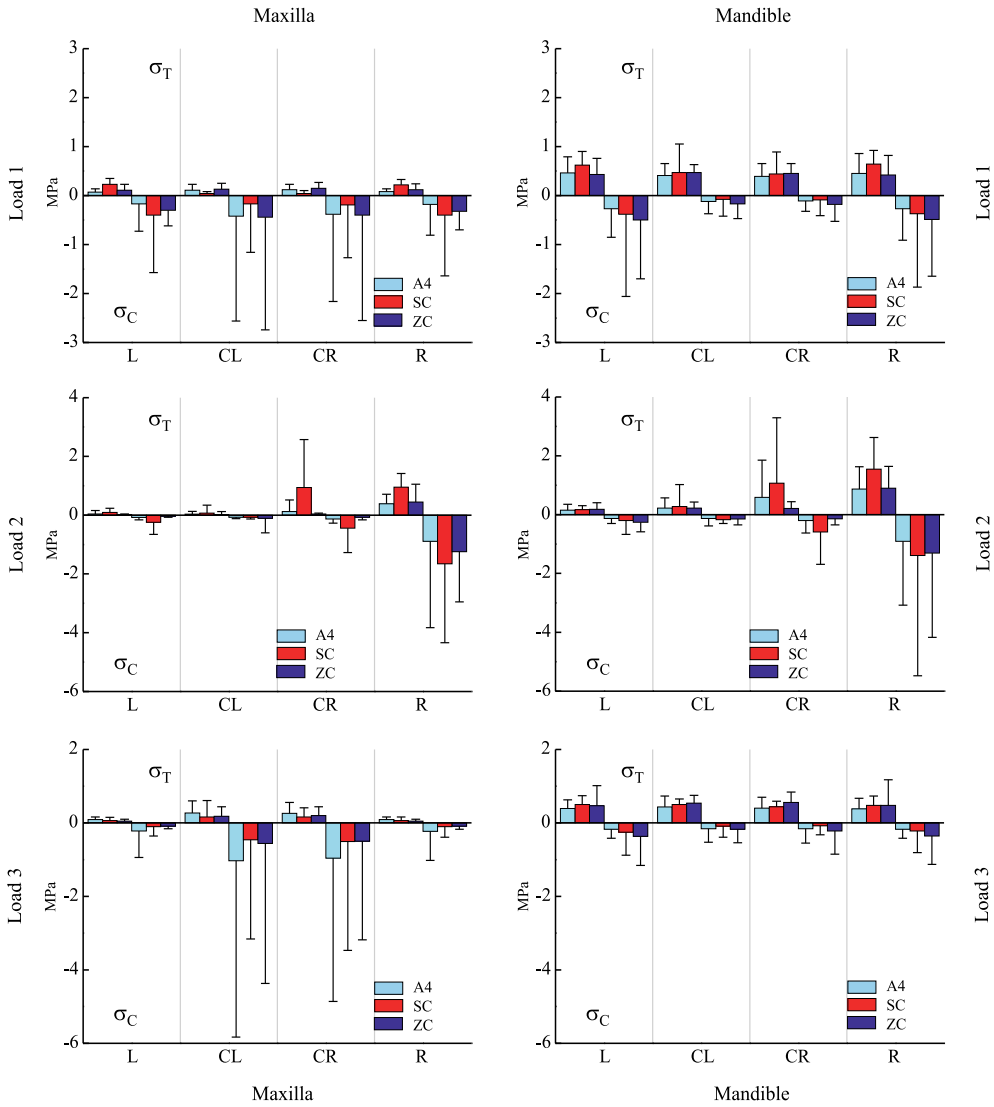


Fig. 10. Principal stress measures (σ_C compressive and σ_T tensile) at the trabecular bone-implant interfaces for implants in A4 (Allon4, light blue bars), SC (SynCone-based, red bars), and ZC (Zero Cantilever, violet bars) restorations, in maxilla (on the left) and mandible (on the right). Average (bars) and peak (lines) values (L: left implant; CL: central-left implant; CR: central-right implant; R: right implant)

edentulous maxilla treated by ZC, posterior short implants transferred the greatest amount of the full-mouth-biting load (mesial P_c was smaller than the distal's of about 50-60%), whereas the frontal load mainly moved towards the bone through the mesial implants (distal P_c was smaller than the mesial's of about 40%). In mandible rehabilitated through the ZC system, both Load 1 and Load 3 were significantly transferred by mesial implants (distal P_c was smaller than the mesial's of about 20%), with transmission mechanisms quite similar to those

induced by A4 and SC in maxilla under Load 3, and with values of mesial P_c slightly higher (about 25%) than those obtained with SC and A4.
Since the different transmission features exhibited by the three techniques when applied in maxilla and mandible, different patterns of the principal stress measures were induced. Under Load 1 and Load 3 and in cortical bone, tensile and compressive stress measures in mandible were greater than in maxilla, whereas they were almost similar for Load 2. Opposite evidences were highlighted at the trabecular peri-implant regions. Moreover, A4 generally produced peaks and mean values of the compressive stresses in distal cortical bone (both mandibular and maxillary) smaller (up to 40-50%) with respect to SC and comparable with ZC. On the contrary, under Load 1 and Load 3, A4 gave rise to values of $\|\sigma_C\|$ at the mesial trabecular peri-implant regions in maxilla higher (up to 90-100% with respect to SC) than those induced by the other techniques. Furthermore, the tilted implants in A4 induced at the crestal bone regions values of the tensile stress σ_T higher (up to 180-200%) than SC and of the same order of magnitude with respect to ZC, especially in mandible.
Physiological limits previously introduced were never reached in cortical bone. On the contrary, the bone strength value for cancellous bone (about 5 MPa) was slightly exceeded in compression for A4 and SC: at the A4's mesial implants in maxilla under the frontal load, and at the SC's right implant in mandible under the cantilever load.

4. Discussion

Proposed numerical results, obtained via three-dimensional finite-element analyses, clearly proved that the four-implant-supported full-arch prostheses based on Allon4 (A4) and SynCone (SC) concepts exhibit very different stress-based biomechanical behavior, as well as different loading transmission characteristics when applied in maxillary and mandibular jaw. Such an evidence was confirmed also in the case of a novel non-conventional approach, based on the use of short implants placed at the posterior molar regions (Zero Cantilever, ZC), in order to minimize the cantilever length. Numerical investigations accounted for functioning implants by modeling crestal bone loss after a healing and loading period. The temporomandibular joints and the loading-dependent muscle-bone static interactions were also modelled in mandible.
Simulation results highlighted that the local bone-implant biomechanical interactions as well as the overall performance of the rehabilitative techniques were mainly dependent on: cantilever length, implant design concepts and crestal positioning (highly affecting the bone-loss level at the implant necks), implant tilt and mutual distances between implant axes, patient-dependent morphology and mechanical properties of bone tissues. Moreover, mutual effects of cantilever and crestal bone geometry were proved to be strongly related to the type of both load and jaw.
In the case of a full-mouth-biting load (Load 1), the influence of the cantilever length was prevailing and the use of distal tilted long implants in A4 (Nobel Biocare implants) or posterior vertical short implants in ZC (Ankylos type) induced smaller overloading risks (mainly in compression) and more uniform stress distributions on bone than the distal vertical implants employed in SC (Ankylos). On the contrary, as a consequence of the reduced level of crestal bone loss induced by the Ankylos devices in SC, mesial implants exhibited opposite comparative results. It is worth pointing out that, although mesial implants in ZC were the same as in SC, they induced compressive stress performance almost comparable with A4. In fact, due to the use of short posterior implants and since the values of L_2 (namely, the distance between the distal implants, see Table 1 and Fig. 2), basic statics allows to show that benefits

associated with platform switching were partially compensated by the different loading partition of ZC, resulting in load components transmitted through the ZC's mesial implants higher with respect to SC (see Fig. 8). Due to the different bone quality and morphology, the greatest overloading risks under Load 1 were computed at the cortical bone-implant interfaces in mandible (for distal implants) and at the trabecular bone in maxilla (for mesial implants), both in compression. Maxillary stress peaks at the trabecular peri-implant regions, as experienced also for the frontal load (Load 3), can be mainly associated to the bone morphology. In fact, due to the thin cancellous layer separating implants and cortical bone at the nasal cavity, high mesial compressive states were generated near the in-bone implant ends (see Fig. 6). This effect reduced when the SC system was employed, because of the more favourable loading partition mechanisms in mesial region with respect to both A4 and ZC (see Fig. 8a).

Under the cantilever load (Load 2), that was proved to be the most dangerous and unbalanced condition, the main influence on the stress-based performance was again related to the cantilever length. Accordingly, the use of tilted implants in A4, reducing the cantilever, allowed to obtain also in this case a loading partition better than SC and smaller risks of bone overload (mainly in compression). Good partition features were also computed for ZC but, since the short length of the posterior implants, compressive stresses at the cortical bone were greater then those of both A4 and SC (although within physiological limits).

As a matter of fact, Load 1 and Load 2 activated the implant-to-bone transfer of mainly intrusive loading components, as directly proportional to the overall load acting upon the bar. In the first case, all implants were involved in such a transfer mechanism and distal implants transferred load components directly depending on the cantilever length as well as on the values of L_1 and L_2 (see Table 1). In the second case (cantilever load), only one or at most two implants were mainly acted upon by an intrusive component (namely, the right implant and at most the mesial-right one, Fig. 8), whereas implants on the opposite side (on the left) were practically unloaded. A frontal load (Load 3) did not activate cantilever mechanisms. Therefore, main effects can be associated to platform switching and implant positioning. In this case the highest stress peaks were computed at the cortical bone in mandible and at the cancellous bone in maxilla. Under the frontal load, the transfer characteristics of the conventional approaches (A4 and SC) were proved to be strongly different in lower and upper arches, A4 resulting better in mandible and worse in maxilla than SC. On the contrary, the loading partition achieved by the non-conventional ZC system was weakly affected by the jaw type, resulting better than A4 in maxilla and the worst in mandible. These evidences can be strictly related to the distances between mesial and distal implants (namely, L_1 and L_2, Fig. 2), that depend on both treatment type and jaw morphology. In fact, when an intrusive force component acted upon the prosthetic bar at the middle of the central span (Load 3), the load was statically transferred towards the bone mainly by intrusive actions upon the mesial implants and by extrusive upon the distal ones. In agreement with basic statics, when L_1 reduced (passing from mandibular to maxillary applications) intrusive forces acting upon the mesial implants increased and distal extrusive ones reduced, modifying the loading partition performance. Moreover, when the difference $(L_2 - L_1)$ increased (*e.g.*, passing from SC to A4, or from A4 to ZC) distal extrusive actions further reduced, producing an additional contribution towards a non-homogeneous loading partition.

As presented results have proved, tilted implants in A4 or short posterior implants in ZC may induce tensile stresses greater than SC at the cortical bone, mainly in mandible because of the crestal bone morphology. Nevertheless, the localization of bone areas subjected to these

traction states was strongly dependent on the loading type. In fact, when mainly intrusive components loaded tilted distal or posterior short implants (namely, Load 1 and Load 2), prevailing compressive states were induced at the distal side of the cortical bone-implant interface and prevailing bone tractions appeared at the opposite side. Conversely, when mainly extrusive loading components were considered on tilted or posterior implants (Load 3), tractions were essentially localized at the distal side of the peri-implant cortical region and compressive stresses arose at the mesial side.

Proposed numerical findings confirm that a rehabilitative full-arch technique should be chosen and/or designed by bearing in mind that the loading transmission features and the risks of bone resporption activation are strongly affected by cantilever configurations, as well as by morphological and mechanical bone properties. In detail, in agreement with many clinical (Aparicio et al., 2001; Calandriello & Tomatis, 2005; Capelli et al., 2007; Del Fabbro et al., 2010; Krekmanov et al., 2000; Malò et al., 2005; Sertgöz & Güvener, 1996; Shackleton et al., 1994; Testori et al., 2008; White et al., 1994), photoelastic (Begg et al., 2009), and numerical (Bellini, 2009; Bonnet et al., 2009; Carvalho Silva et al., 2010; Zampelis et al., 2007) evidences, an higher distal cantilever length has been proved to induce higher and dangerous stress concentrations on bone, mainly at the distal peri-implant regions. Therefore, proposed results confirm that the biomechanical rationale related to the use of tilted distal implants is effective for reducing cantilever mechanisms and generally for inducing more favourable load transmission characteristics. Nevertheless, as a complementary and novel indication, present results have clearly proved that tilted implants can produce high tensile stress concentrations at distal peri-implant regions, inducing high risks of an ineffective osseous integration process and of local bone damage (bone is most resistant against compressive stress and 30% less against the tensile actions, Guo (2001)). The localization at the cortical bone-implant interfaces of these traction states was proved to be strongly dependent on the loading type. In agreement with previous researches (Baggi et al., 2008b; Begg et al., 2009; Carvalho Silva et al., 2010; Chun et al., 2006; Clelland et al., 1993; Petrie & Williams, 2005; Van Staden et al., 2006), present numerical simulations have also confirmed that possible bone overloads can affect cortical regions around the implant necks, mainly in compression. In addition, present numerical findings have shown that for implants mesially placed in maxillary arch, overloading risks in trabecular bone are mainly depending on jaw morphology and they proportionally increase with the in-bone implant depth. Moreover, in agreement with numerical results proposed by Maeda et al. (2007) and by Baggi et al. (2008a;b), the biomechanical stress-based performance of a rehabilitative technique and its long-term effectiveness can be significantly improved, especially for loads that does not induce significant cantilever effects (as for purely frontal loads), if crestal bone loss is effectively counteracted. As a further novel contribution, proposed numerical analyses have showed that the use of non-conventional short implants based on platform switching concepts and vertically placed in the posterior region, allow both to vanish cantilever length and to obtain stress distributions and loading transmission features fully comparable (sometimes better) than the Allon4-based conventional technique. Accordingly, such an approach can be retained as an effective alternative to the actual clinical protocols, although it could be enhanced by choosing suitable values of parameters L_1 and L_2, consistent with patient-specific bone morphology and allowing for optimal bone-implant biomechanical interactions.

It is worth pointing out that, in a number of recent numerical researches the influence of crestal bone loss in functioning implants, of detailed geometrical modeling for lower and upper jaws, as well as of muscle-bone static interactions and temporomandibular

articulation have been disregarded (*e.g.*, Baggi et al., 2008b; Bellini, 2009; Bonnet et al., 2009; Carvalho Silva et al., 2010; Chun et al., 2006; Kitagawa et al., 2005; Maeda et al., 2007; Petrie & Williams, 2005; Van Staden et al., 2006; Zampelis et al., 2007). In the present study, although different crestal bone loss configurations were considered, the ideal condition of a complete osseous integration between implants and bone was assumed. Furthermore, stress analyses were performed by assuming static loads and, in agreement with modeling approaches available in literature (Lekholm & Zarb, 1985; Trainor et al., 1995), by including temporomandibular joints and muscular forces on mandible. As far as the mechanical behavior of bone is concerned, living tissues were modelled as isotropic linearly elastic materials, distinguishing two homogeneous material volumes describing the trabecular and cortical regions. These assumptions do not exactly represent actual clinical scenarios because of: possible osseointegration defects; different loading distributions due to patient-dependent functional and aesthetics prosthetic elements; much more complex and time-dependent both functional forces and muscular effects; anisotropic, non-homogeneous, non-linear and inelastic response of living tissues. Nevertheless, in agreement with a number of well-established numerical results (*e.g.*, Baggi et al., 2008a;b; Beek et al., 2000; Bellini, 2009; Bonnet et al., 2009; Carvalho Silva et al., 2010; Chun et al., 2006; Kitagawa et al., 2005; Maeda et al., 2007; Petrie & Williams, 2005; Sertgöz & Güvener, 1996; Trainor et al., 1995; Van Staden et al., 2006; White et al., 1994; Zampelis et al., 2007), the present assumptions can be considered as effective and consistent in a computational sense, in order to deduce significant and clinically useful indications. Accordingly, proposed fully three-dimensional simulation approach can be considered as an accurate and effective tool for stress-based comparative assessment of full-arch rehabilitations.
With the aim to enhance the present finite-element formulation, next studies will be devoted to model the bone as a non-linearly anisotropic, viscous and non-homogeneous regenerative tissue, that responds to stress by resorption or regeneration under time-dependent muscular and external loads.

5. Concluding remarks

Within the limitations of this study, proposed three-dimensional finite-element simulations proved that the "Allon4" and "SynCone"-based full-arch rehabilitative systems, supported by four endosseous implants, induced load transmission mechanisms and bone overloading risks highly different when mandibular and maxillary applications were compared. Simulation results were obtained through detailed numerical models of both lower and upper jaw, and were analyzed by introducing meaningful performance indexes and local stress measures. The coupled influences of several biomechanical factors were clearly highlighted, indicating that the prevailing effects are related to the cantilever length, the implant design concepts and positioning, the bone morphology and its mechanical properties. Stress concentrations occurred in compression at the implant necks and, depending on implant length and jaw morphology, at the in-bone implant ends. The reduction of the distal cantilever by employing tilted implants (Allon4 system) allowed to enhance the loading distribution and to reduce the risks of bone resorption activation at the distal peri-implant regions. Nevertheless, tilted distal implants induced on cortical bone and for all loads analyzed in this study higher tensile stresses than vertical distal implants, producing higher risks of non-effective crestal osseous integration and of bone damage. The localization of these traction states was proved to be mainly dependent on the loading type, and their intensity was greatly affected by crestal bone quantity and quality. When implants based on a platform-switching configuration

and subcrestal positioning were considered (Ankylos implants in SynCone-based system), since the reduced level of crestal bone loss, more favourable and homogeneous stress distributions were computed at the implant necks and at the trabecular bone, such an effect resulting prevailing for mesial implants and when the load did not significantly activate cantilever transmission mechanisms. Therefore, although both systems seemed to ensure stress levels physiologically admissible in both mandibular and maxillary rehabilitations, proposed numerical results clearly indicated that each technique has both benefits and drawbacks, essentially as a result of mutual coupling between cantilever mechanisms and cratering effects.

Finally, in this study the possible use of a non-conventional full-arch rehabilitative system, based on four vertical implants consistent with platform switching concepts, has been also investigated. Following such an approach, two commercially-available mesial implants are combined with two non-conventional short implants placed at the posterior molar regions. In this way cantilever length is minimized (up to zero, if the patient-dependent bone quality and quantity in that region permit it) and, since also the platform-switching effects, both transmission mechanisms and overloading risks can result comparable or better than other well-established conventional techniques. Accordingly, such an approach can be surely considered as an effective and reliable clinical alternative to available actual protocols.

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Part 3

Computer-Aided Implant Dentistry and Digital Imaging

9

State-of-the-Art Technology in Implant Dentistry: CAD/CAM

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1. Introduction

Implant dentistry has come a long way since 1982 when Per-Ingvar Branemark first presented his work on osseointegration of endosseous dental implants (Branemark & Albrektsson, 1982). In the last three decades, the use of dental implants has increased exponentially (Friberg B & Jemt T, 2010; Turkyilmaz et al., 2010). Initially, very few specialists were trained in surgical placement and subsequent restoration. As the treatment became more predictable, the benefits of therapy became evident. The tremendous demand for implants has fueled a rapid expansion of the market. Presently, general dentists and multiple specialists offer implants as a solution to partial and complete edentulism. The field is evolving and expanding, from surgical techniques to types of restorations available. Whereas early implant restorations were primarily indicated for rehabilitation of function, increasing consideration is being placed on esthetics in modern implant dentistry.

1.1 Role of CAD/CAM in dental technology

Presently, there is a trend toward decreasing numbers of dental laboratory technicians in the United States. The number of dental technology programs in the U.S. has decreased by half since 1990 (Christensen, 2005). Conventional implant restorations are time and labor intensive, due to the multiple steps in fabrication, such as casting and fitting. Simultaneously, there is an increasing demand for efficient treatment that can be completed in minimal time— the "drive-thru" mentality of modern society. Fortunately, technology has kept up with this demand, and the application of CAD/CAM in implant dentistry is a promising solution (Valente et al., 2009; Van Assche et al., 2010).

Computer-aided design and computer-aided manufacturing (CAD/CAM) is being utilized in many fields besides dentistry. In the manufacturing industry, rapid prototyping using SLA modeling, which is a crisp, highly detailed CAM method, is used to produce prototypes (Jacobs, 1992; Ozan et al., 2009). Frequent applications of SLA technology are highly detailed and accurate medical models, master patterns for casting and even soft tissue facial prostheses. Several authors have suggested that CAD/CAM may improve the accuracy of dental implant planning and placement (Sarment, 2003; Tardieu, 2003; Van Assche et al., 2010; Arisan et al.,2010; Mandelaris et al., 2010). An extension of this application is the ability to prefabricate dental prosthesis prior to the implant surgery.

1.2 Range of implant-supported restorations

Dental implants can support many types of dental restorations, ranging from a single tooth to a full-arch fixed bridge. The prosthetic design must take into consideration many factors, including number of teeth to be replaced, biomechnical considerations regarding how many implants are necessary to support the restoration, functional considerations such as the occlusal scheme and opposing dentition or restoration, and relative cost of the restorative materials. Implant based restorations can be either fixed or removable, depending on the patient's desires, ability to perform adequate hygiene, and whether adequate support can be achieved by the implants alone, without additional support of the soft tissue. The final prosthetic design must account for all the individual patient variables, take into consideration the best available evidence regarding long-term prognosis, and ideally meet the patient's expectations for both esthetics and function.

1.3 Edentulism and role of implant-based restorations

Considering the range or restorations available, implants can serve the greatest utility when considering complete dentures. Conventional dentures have significant functional limitations when compared to natural teeth. Masticatory performance of people wearing complete dentures is less than 20% of those with natural dentition (Kapur & Soman, 1964). Patients commonly report pain, areas of discomfort, poor denture stability and difficulties eating as reasons for dissatisfaction with conventional dentures (Allen & McMillan, 2003). However, there are many clinical factors that may affect the overall function and patient satisfaction with conventional complete dentures, such as residual ridge height, salivary flow, and technical quality of the dentures (Turkyilmaz et al., 2010). It is therefore essential that a thorough clinical examination of the patient and any existing prostheses be coupled with a detailed patient interview about masticatory performance of the existing prostheses and impact on quality of life. This information is vital to proper treatment planning and consideration of one of the many possible implant-based restorations including a two-implant overdenture with ball or locator attachments, a bar overdenture supported by two or four implants, or a completely implant supported fixed hybrid denture.

Many authors have investigated the impact of implant supported dentures compared to conventional dentures. A clinical study by Awad et. al.(2003), included 104 edentulous adults, aged 35 to 65 years. Patients were randomly assigned to one of two groups that received either a mandibular conventional denture or a two-implant bar overdenture. Patients rated their general satisfaction and specific factors of both their previous dentures, as well as their new prosthesis at 2 months post-delivery. Oral health-related quality of life was also evaluated pre- and post-treatment. The mean general satisfaction of the implant-overdenture group was significantly higher than the conventional denture group. The implant-overdenture group also rated comfort, stability, and ease of chewing better than the conventional group. The conclusion of this study was that a mandibular implant-supported overdenture opposing a maxillary complete denture was more satisfactory than conventional dentures.

Heydecke et al.(2005), studies the impact of mandibular two-implant overdentures compared to conventional complete dentures on leisure and sexual activities. This study of 102 patients found social activity was improved with implant-supported overdentures compared to conventional dentures. Implant-supported dentures including either complete overdentures or a hybrid prosthesis significantly improve the quality of life for edentulous patients compared with conventional complete removable complete dentures.

It is true that people are keeping their teeth longer than in the past. Measures such as oral hygiene, access to care and water fluoridation are having a positive impact on oral health in this country. The decrease in percentage of edentulous adults over the past 20 years has prompted some educators to propose that complete dentures be removed from the dental curriculum (Turkyilmaz et al., 2010). However, it appears that the decrease in rates of edentulism among older adults is insufficient to offset the growing US population.
Several trends are apparent when relating the US Census data from 1991-2020. The population projections from the 1996 Statistical Abstracts of the United States illustrate these trends. The total adult population will increase significantly from 187,020,000 to 245,139,000 people. The number of adults aged from 55 to 74 years will increase by 86%. The number of adults aged 75 and older will increase by 61%. Thus the US population of older adults will grow dramatically over the next 12 years. Estimated decreases in the percentage of edentulism for maxillary and mandibular arches for each age group of 10% for year 2000, 20% for year 2010, and 30% for year 2020 (Weintraub & Burt, 1985). Even if a decrease in edentulism is assumed, an increase in the actual number of adults will result in an increase in the number of dentures needed over the next 12 years. Actually, the 2010 US Census reported 308,745,538 residents, which indicates a significant increase compared to the predicted number (245,139,000).
We can conclude that there will be a significant need for denture therapy, and that implant dentistry has the potential to dramatically improve the quality of life for those edentulous patients. Further, a range of treatment is available for improving the function, from two-implant overdenture with mechanical attachments to a fully fixed-detachable hybrid prosthesis.

1.4 Patient demand and knowledge regarding implant therapy

The number of implants placed has been increasing significantly each year, (about 18% in the USA) (Turkyilmaz et al., 2010). Improved implant surfaces and surgical techniques have led to a marked increase in predictability. This has resulted in a tremendous demand. The demand for implant therapy has fueled growth of the industry, and now many clinicians offer implant therapy, not just specialists. Problems with implants have been raising as more clinicians who do not have advanced training and skills have been involved in implant placement. Unfortunately, little quantitative data regarding implant complications related to level of training are available.
Consecutive surveys of the Australian population showed that patient awareness of implant dentistry is increasing (Pommer et al., 2011). Most patient's trust their general dentist for information regarding implant therapy, while one quarter turn to the media. Overall, the level of knowledge is satisfactory. The exception is patient's unrealistic expectations. Patient's demand for high-quality restorations has increased, and the majority felt that practice of implant dentistry should be limited to specialists.
Similar trends regarding increasing patient awareness in the United States have been observed. However, due to the increasing prevalence of direct marketing, more patients are relying on media and internet sources for information regarding implant therapy. Advertisement has contributed to patient's unrealistic expectations regarding treatment times, and led to significant confusion regarding the range of treatment options available. Few resources are available to assist patient's in understanding of the variety of implant restorations along with the advantages and disadvantages of each.

1.5 Success criteria for implant therapy

Objective evaluation of the treatment outcome is paramount in order to ensure predictability and excellent long-term prognosis. The first criteria for success were proposed by Albrektsson et. al., in 1986. However, success and failure lie at opposite ends of a spectrum. In order to better elucidate the actual condition of an implant, not just it's presence in the mouth, the Health Scale for Dental Implants was developed (Misch et al., 2008). This scale consists of four categories: success with optimum health, satisfactory survival, compromised survival, and failure. The clinical indices evaluated in this scale include pain, mobility, radiographic bone loss, probing depths, and peri-implant disease. Optimum health is defined as the absence of pain or tenderness on function, zero mobility, less than 2 mm of radiographic bone loss from time of placement, and no history of exudate. At the other end of the spectrum is absolute or clinical failure, in which any of the following are present: pain on function, mobility, radiographic bone loss greater than 1/2 the length of the implant, uncontrolled exudate, or the implant is no longer in the mouth.

1.6 Treatment planning for implant-based restorations

The first phase of implant dentistry is planning. It is insufficient to identify an edentulous space, or missing tooth, and simply initiate surgery. First, a diagnostic wax-up of the proposed tooth form and ideal location must be achieved. From this, a radiographic guide is fabricated that simulates the wax-up. Next, diagnostic imaging must be done in order to determine the alveolar bone available for implant placement. Traditional radiographs including periapical films and panoramic films are helpful, but limited in application due their two dimensional nature and potential distortion. In 1972, the invention of computed tomography revolutionized medical and dental imaging. It became possible to obtain 3-dimensional digital images, thus an accurate assessment of the height and width of alveolar bone available for implant placement.

This 3-dimensional image is the basis of establishing the treatment plan. It allows a practitioner to identify potential implant sites, measure the height and width of the available bone, and the necessary restorative space for the planned prosthesis and the components. If bone grafting, such as sinus augmentation, is necessary in order to position implants properly for a given prosthetic design, the necessary procedures can be incorporated into the treatment plan. Basically, this 3-dimensional image gives both the clinician and the patient a better idea of the limitations that will be encountered at the time of surgery, ensuring better predictability of both the surgery and the final prosthetic outcome.

2. CAD/CAM technology- surgical guides

CAD/CAM technology takes implant planning a step further, and enables fabrication of a surgical guide (Figure 1). The surgical guide directs the surgeon in the exact location and angulation to place the implant. There is a growing number of software programs that allow viewing and analysis of the 3D images and subsequent fabrication of a surgical guide.

In the youth of implant dentistry, the treatment was surgically driven, meaning that the implant was placed according to the bone available at the time of surgery. This approach eventually proved erroneous, because many implants were placed in locations and angulations that made them difficult or impossible to restore. The evolution of the field has led to a restoratively-driven approach, where the restorative dentist communicates the desired position and angulation via a surgical guide. Conventional surgical guides, however, have some significant limitations.

Fig. 1. Example of CAD/CAM surgical guide for implant placement.

2.1 Surgical guides for implant placement

Computer-assisted planning and use of CAM surgical guides dramatically increases the accuracy of implant placement, which directly improves the outcome of the final restoration. These surgical guides help the surgeon avoid vital structures, and may decrease the length of the surgery. Furthermore, it assures the restorative dentist and dental technician a functional, esthetic, and predictable outcome. Equally important, CAD/CAM design and fabrication of guides improves the patient's experience with implants. CAD/CAM allows the possibility of flapless surgery, which entails less bleeding, less swelling, decreased healing time and post-operative pain (Fortin et al., 2006).

There are three broad categories of surgical guides: conventional, SLA fabricated, and cast-fabricated. Conventional implies it was the method employed prior to CAD/CAM, but with the rapid evolution of the field, the term conventional is unclear, and encompasses a large variety of techniques. One specific conventional technique for surgical guide fabrication entails fabricating a scanning template or radiographic guide, usually tooth-borne. Then, according to the findings of the CBCT, identifying reference points that allow orientation of the radiographic guide on a surveyor table in conjunction with a drill press to create the pilot hole that will guide the surgeon. This technique, since it is the opposite of digital, is coined "analog".

The major distinction between the two types of CAD/CAM surgical guides lies in the fabrication. SLA guides are purely CAD/CAM, whereas cast-fabricated are initially made on a stone model, then a computerized version of the surveyor and drill press create the pilot holes based on the digitally planned implant placement. Each has its advantages and disadvantages. The SLA process leaves topographic seams, which may not fit the occlusal

and axial anatomy of a tooth. If the surgical guide does not fit precisely and accurately, the surgical result may be compromised. A surgical guide that is fabricated on a stone model, however, can be tried in intra-orally and verified prior to the CBCT scan and subsequent conversion into a surgical guide.

Fig. 2. A tooth-supported CAD/CAM surgical guide on the cast.

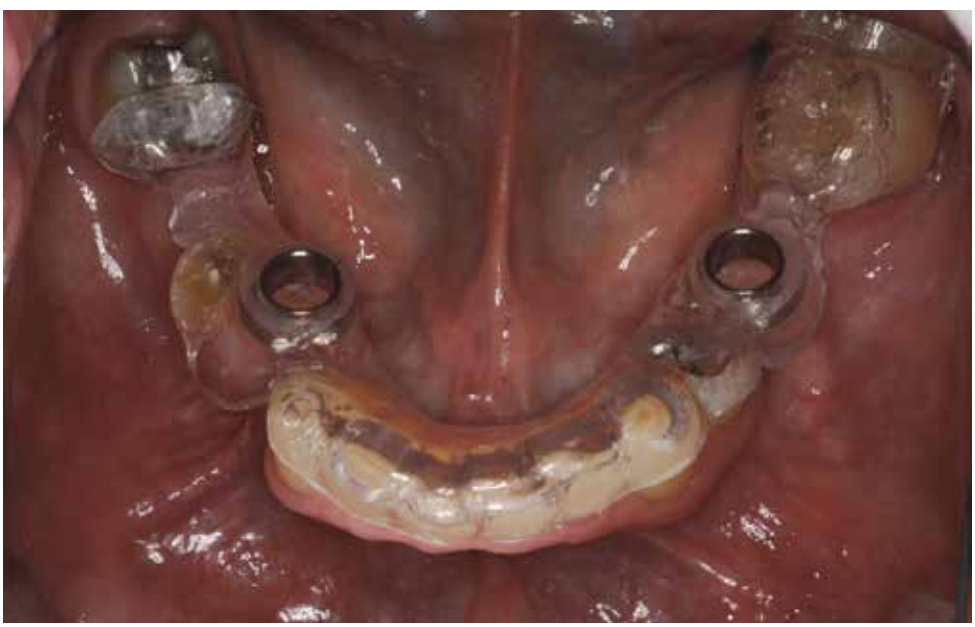

Fig. 3. A tooth-supported CAD/CAM surgical guide seated on the teeth.

2.2 Type of support for implant surgical guides

Surgical guides can also be classified according to the type of support: bone, mucosa, tooth (Figures 2,3), or combination tooth-mucosa. The choice of which type of support depends on many factors, such as the number of teeth remaining in the arch, whether the mandibular or maxillary arch is being treated, and the anatomy of the edentulous or partially edentulous ridge. Teeth offer a very stable support for a surgical guide, but the complex topography of the occlusal surface may make increase the time required to fit the surgical guide to the mouth. Soft tissue, is by definition compressible and displaceable to varying degrees. Extra measures must be taken to ensure that a mucosa-supported surgical guide is positioned accurately to ensure surgical success.

2.3 Software for implant planning and surgical guide fabrication

Presently, there are a multitude of software programs for virtual placement of implants and subsequent fabrication of surgical guides. The most well-known are Procera from Nobel Biocare and Simplant by Materialise, but many more have recently been introduced to the market. Each software platform varies in the types of guides available and which implant system it is compatible with. Procera NobelGuide includes mucosa and tooth based guides and is strictly compatible with Nobel Biocare implants. Simplant offers bone, tooth, or mucosa based guides and is can be employed with virtually any implant system. Each software presents it's own limitations and challenges; cost is also a consideration for the clinician. All of the current software programs are based on algorithms for medical CT, not CBCT, which may influence interpretation of the data. In addition, the corresponding surgical kit for each implant system may or may not offer depth control, which will ultimately influence the surgical outcome.

2.4 Accuracy of guided implant surgery

The accuracy of CAD/CAM surgical guides has been investigated with in vitro, human cadaver, and clinical studies. The available research supports the hypothesis that guided surgery is accurate, with certain limitations. Ersoy et. al.(2008), placed 94 implants using SLA surgical guides generated from CT. CT images were obtained with radiographic templates in place, and implants were placed virtually. SLA surgical guides including bone-based, mucosa-support, and tooth-support were then fabricated and used for implant surgery. Following implant placement, a new CT scan was taken. Special software was employed to overlay the planned placement with the post-surgical outcome, matching anatomical markers. This allows analysis of the outcome in three dimensions. The mean linear deviation was 1.22 ± 0.85 mm at the implant neck and 1.51 ± 1 mm at the implant apex. In general, a greater distance between simulated and actual implants was observed at the implant apex than at the implant neck. The mean angular deviation in long axis between the planned and placed implants was 4.9 ± 2.36 degrees.

Careful consideration must be given to the mean error, versus actual error for an individual patient. In the previous study, the mean angular deviation was 4.9 degrees, but the actual error for one patient was 9 degrees. Depending on the available height and width of the alveolus, this error could result in dehiscence of the bone and eventual failure of the implant.

In vitro studies such as Besimo et al. (2005), aimed to determine the magnitude of error in transferring the planned position of implants from CT scans to a surgical guide. The deviation between the positions of the apex of the proposed implants in cross-sectional CT images and on the corresponding study cast was measured in 77 prospective sites in five maxillae and nine mandibles. The transfer error was 0.6 ± 0.4 mm in the maxilla and 0.3 ± 0.4 mm in the mandible. However, they concluded that the transfer errors found in their study were not clinically relevant as their study was an in vitro study. They also stated that other factors involved in transferring positional and angular measurements from CT images to the surgical area may result in greater errors.

Little evidence is available regarding the accuracy of guided surgery compared to conventional implant placement, using the analog technique for guide fabrication. Sarment et al.(2003), placed 50 implants into five epoxy edentulous mandibles. Each epoxy mandible received five implants in each side. On the right side, five implants were placed using a conventional surgical guide (control side), while on the left side, five implant were placed using a stereolithographic surgical guide (test side). They found a statistically significant improvement in all measurements when SLA surgical guides were used compared to conventional guides and suggested that the clinical significance of this result may be relevant when multiple parallel distant implants are placed, and where the degree of accuracy is critical to obtain a single prosthetic path of insertion. They also reported, when the control surgical guide was used, the center of the osteotomy was 1.5 ± 0.7 mm away from the center of the planned implant at coronal end and 2.1 ± 0.97 mm at the apex. When the test appliance was used, these distances were 0.9 ± 0.5 mm at the implant head and 1 ± 0.6 mm at the apex.

The available evidence suggests that CAD/CAM surgical guides are relatively accurate, but more research is needed in this area. Better data on the possible error will ultimately improve clinical judgement and case selection. This could potentially reduce or even eliminate error.

2.5 Guidelines for CAD/CAM guided surgery

Currently there are no published guidelines regarding indications for flapless surgery versus a conventional open-flap surgery. It is clear from Sarment's study (2003) that the use of a CAD/CAM guide can increase the accuracy of implant placement, and when used in an open-flap surgery, the surgeon has the capacity to intercept potential error by visualizing the bone and implant directly. Thus, in an open-flap surgery, CAD/CAM surgical guides are superior to conventional guides.

The decision of whether to perform a flapless surgery depends on many factors. Patient comfort, decreased healing time, maintenance of blood supply, and decreased surgical time are all advantages of flapless surgery. The accuracy of implant placement required depends in large part on the type of restoration planned. For example, an implant-overdenture has a medium level of accuracy necessary, in that linear and angular deviations can be accommodated by the attachment system. A fixed restoration, on the other hand, has a significantly lower degree of freedom, and may indicate CAD/CAM guided surgery in order to maximize the precision of implant placement.

The type of template support is also an important consideration. Flapless surgery can be accomplished with a tooth-born guide, a tooth-tissue born guide, or a purely tissue-

supported guide. The number of teeth, condition of the tissue, and morphology of the residual ridge will all affect the overall stability of the guide and the accuracy of placement, which directly impact the accuracy of implant placement. A good rule of thumb for an edentulous arch is if the denture has reasonable stability and resistance to lateral dislodging forces, a tissue-supported surgical guide will have the same degree of stability. In general, a maxillary denture is more stable than a mandibular denture. In addition, the opposing dentition or prosthesis can aid in predictable placement which will increase the accuracy.

It is reasonable to incorporate the mean accuracy of guided systems into a set of guidelines, particularly for flapless surgery. For example, if the average linear deviation is 1.22-1.51 mm, and 1 mm of bone is necessary buccal and lingual to the implant, one can conclude that the alveolar ridge must be wide enough to accommodate both the implant and the potential error. This window of safety may vary based on the stability of surgical guide, which relates back to the type of support and the stability of the scanned template from which the surgical guide is patterned. Establishing guidelines based on the available is imperative, but ultimately clinical judgement must be the final determinate.

Immediate loading and pre-fabricated provisional restorations are other advantages of CAD/CAM surgical guides. By using a CAD/CAM surgical guide, a pre-fabricated provisional restoration can be delievered immediately after implant placement, which increases the patients' self-confidence dramatically. The pictures of one of our patients using NobelGuide and a maxillary provisonal restoration (screw-retained fixed dental prosthesis) have been presented below (Figures 4-13).

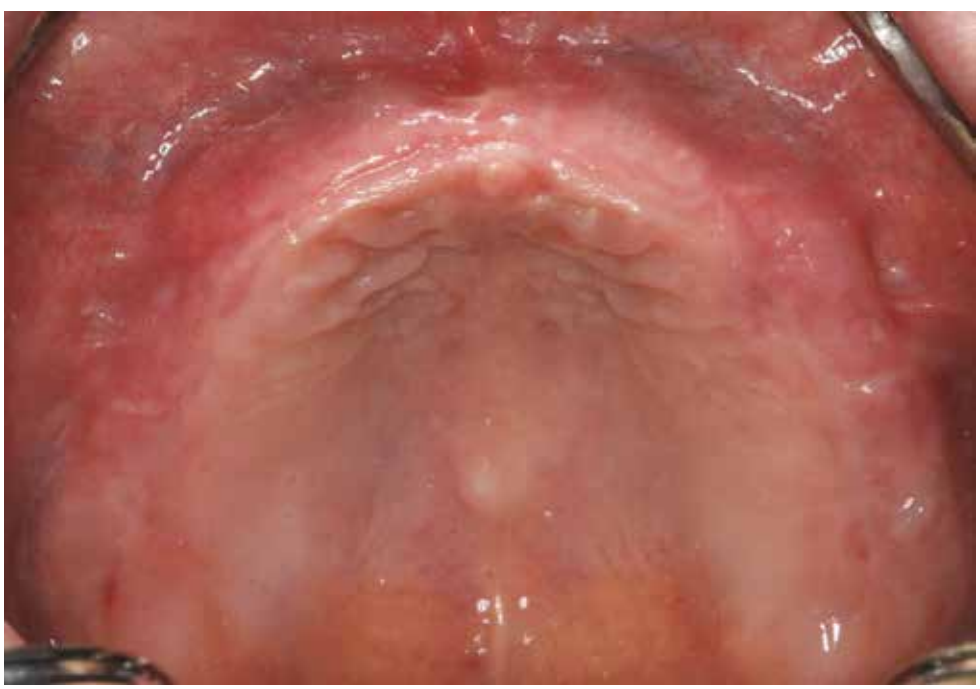

Fig. 4. Occlusal view of edentulous maxilla.

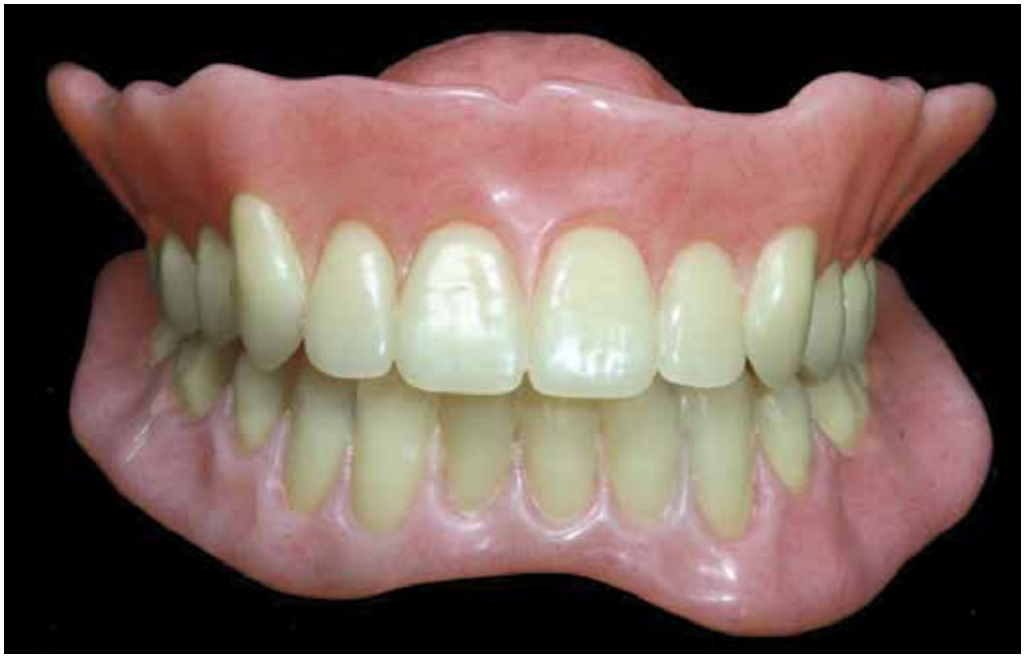

Fig. 5. Implant diagnostic dentures to serve as radiographic template for implant planning and surgical guide fabrication.

Fig. 6. NobelGuide: steriolithographic surgical guide for flapless implant placement.

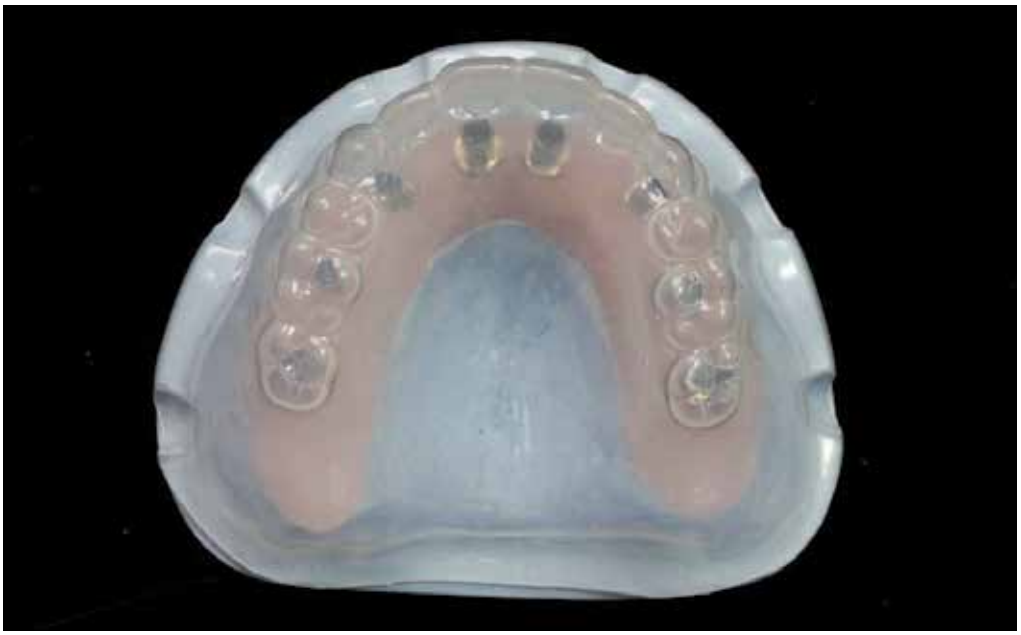

Fig. 7. Pre-surgical fabrication of cast with implant analogs, temporary abutments, and clear matrix of diagnostic tooth arrangement.

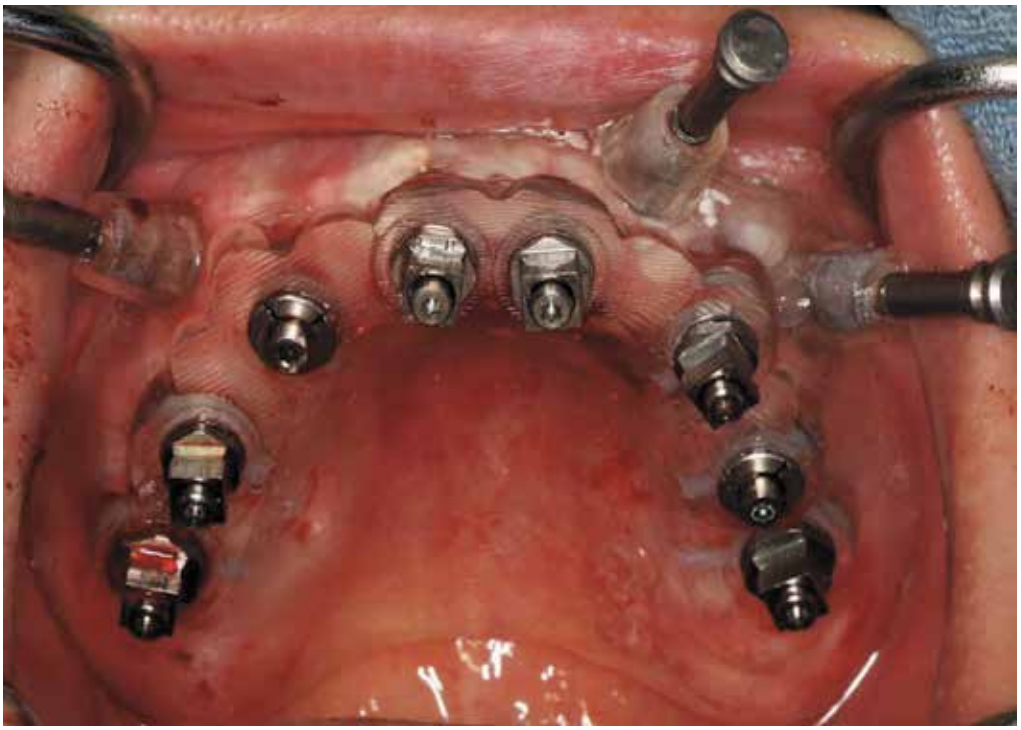

Fig. 8. NobelGuide and fixation pins at time of surgery.

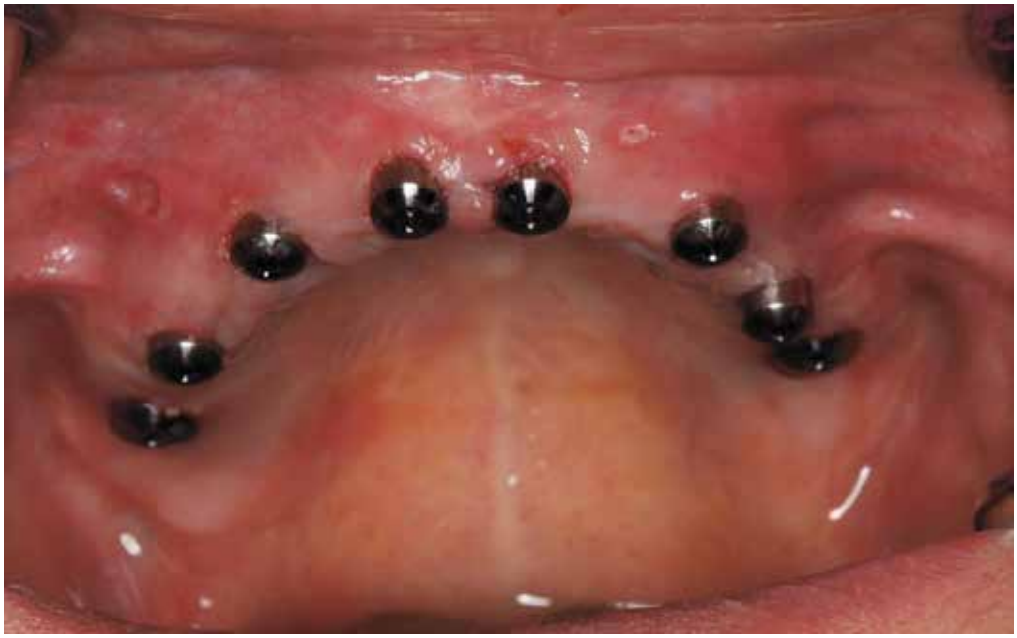

Fig. 9. Immediately post-op following flapless guided implant placement using NobelGuide.

Fig. 10. Diagnostic denture converted into immediate fixed provisional for immediate loading.

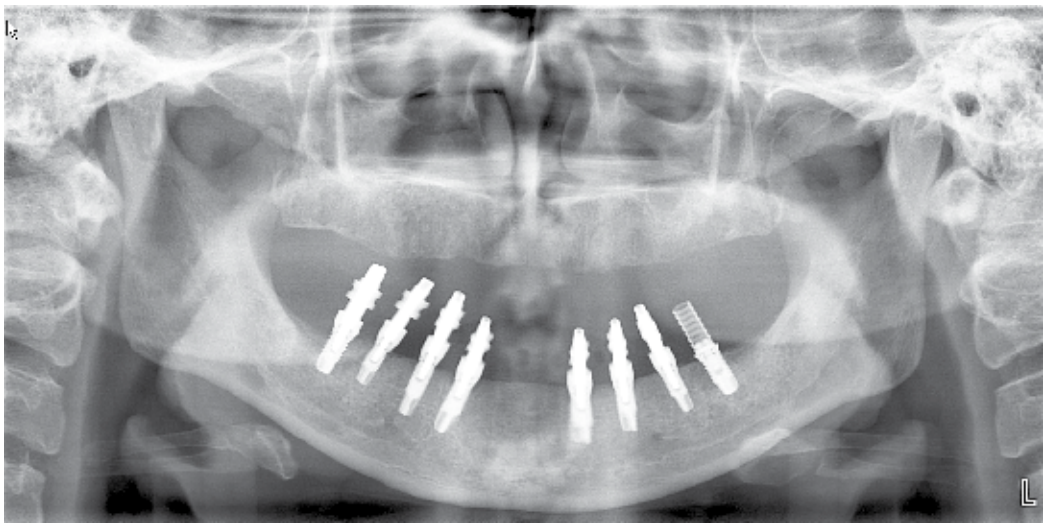

Fig. 11. Pre-operative panoramic image of edentulous maxilla.

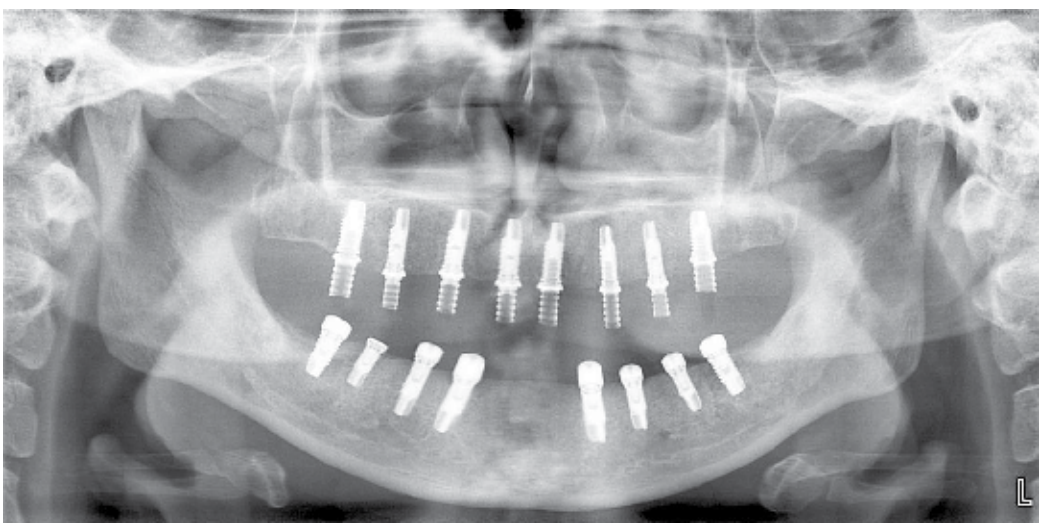

Fig. 12. Post-operative panoramic image following guided implant placement and immediate provisionalization.

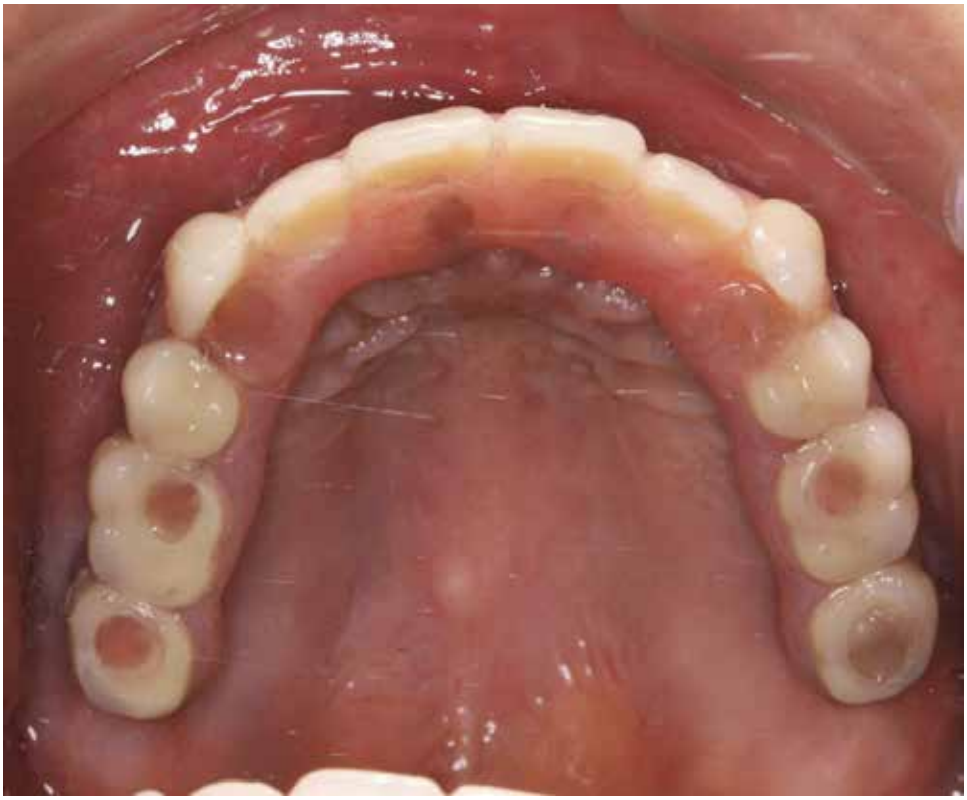

Fig. 13. Occlusal view of immediately loaded maxillary implants.

3. CAD/CAM technology- bars & frameworks

CAD/CAM technology has significantly improved the restorative aspects of implant dentistry as well. Implant restorations can be supported or retained by individual attachments, splinted with a bar for an overdenture, or splinted by a framework that supports a fixed restoration such as a hybrid. Prior to CAD/CAM, bars and frameworks had to be cast from gold alloy.

3.1 Conventional framework fabrication

Traditional castings have a major limitation inherent in the process, which is distortion of the casting with increasing size of the pattern (Takahashi & Gunne, 2003; Al-Fadda et al., 2007). Osseointegrated implants lack a periodontal ligament, thus tolerance of fit is greatly reduced when comparing tooth-supported cast restorations to implant-supported restorations. Single and two implant restorations can be cast within this tolerance, because the distortion is limited based on size. Full arch restorations, however, are difficult to cast successfully. Over the years, a multitude of casting corrective procedures have been employed, including sectioning and soldering, laser welding, and electric discharge machining.

CAD/CAM fabrication of bars and frameworks has resulted in elimination of distortion, better fit, fewer fabrication steps, and faster turn-around (Ortorp & Jemt, 2000; Takahashi &

Gunne, 2003; Al-Fadda et al., 2007). The workflow for creating a CAD/CAM bar starts with an accurate impression and model including the implant analogs. The model containing the implant analogs is then scanned, and then the CAD portion begins. Currently, bars and frameworks can be milled from titanium or zirconium. Titanium is abundant on Earth and offers a significant cost savings relative to gold.

3.2 Prosthetic designs and space allocation

There are several prosthetics designs with dental implants (Figure 14). Overdentures, whether supported by a conventional cast gold bar or a CAD/CAM titanium bar, are space intensive, due to the multiple components involved. Careful planning is necessary to ensure that the implants are placed in the correct position, and there is adequate restorative space for the soft tissue, the implant-supported bar, attachment system, overcasting or prosthetic framework, artificial teeth and pink acrylic base.

The exact amount of restorative space depends on the specific prosthetic design and the restorative materials employed. The issue of space allocation can be addressed in the planning stage for implant placement, utilizing the scan template in order to calculate the distance between the alveolar crest and the occlusal surface. Some authors have advocated 8-12 mm of crown-height space for fixed restorations and greater than 12 mm for removable prostheses (Misch et al., 2005). More specific recommendations based on the specific prosthetic design are 6-8 mm for single implant crown, 8-12 mm for locator retained overdentures, 10-14 mm for acrylic hybrid restoration, and 12-14 mm for a bar-supported overdenture. In actuality, the various prosthetic components exist in three-dimensions, thus linear measurements can only serve as guidelines to ensure adequate restorative space.

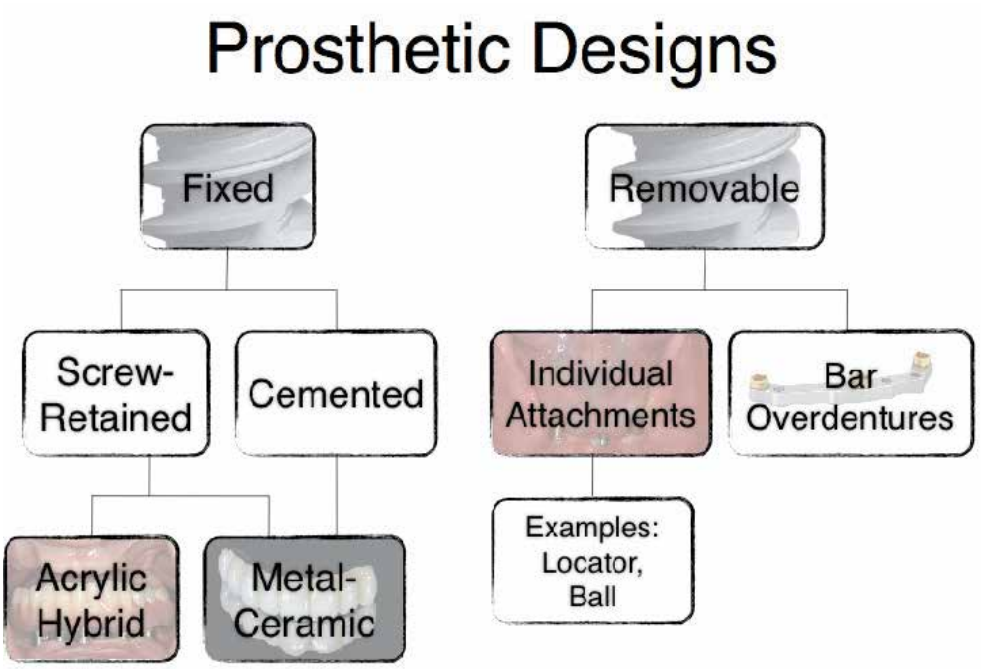

Fig. 14. Classification of prosthetic designs.

Many of the newer software platforms are incorporating virtual abutments so that components can be pre-selected and ordered at the same time as the surgical guide.
Prosthetic design is also influenced by material compatibility. Certain materials are conducive to CAD/CAM while others are not. Titanium and zirconia are well suited for CAM techniques, whereas gold is not. Conversely, porcelain systems developed for gold alloys have been used for many years with a high degree of success, whereas the newer porcelain systems developed for veneering titanium and zirconia lack long term clinical data. For example, a 6 year follow-up on porcelain fused to titanium fixed dental prostheses revealed that titanium PFMs had a 84% survival after six years, compared to a 98% survival for gold alloy PFMs (Walter et al.,1999). As porcelain systems continue to be improved, the applicability of CAD/CAM in implant dentistry will increase.

3.3 Passive fit

Critical to the long term success of implant based restorations is careful consideration of the biomechanics involved. Following osseointegration and placement of a final restoration, both functional and parafunctional loads can be transfered to the implants that may affect remodeling of the bone-implant interface. In the case of splinted implant restorations, it is possible that the restoration itself may transmit strain to the bone-implant interface. Ideally, the restoration would fit passively on the supporting implants, thus minimizing strain and the concomitant biological response.
The concept of passive fit was considered even in early applications of implant-based restorations. The original Branemark design consisted of five implants placed in the anterior mandible, a cast framework supported by five standard abutments and acrylic resin teeth and gingiva processed onto the framework (Figure 15). Branemark considered passive fit to exist when the gap between the framework and the abutment was 10 microns (Abduo et al., 2010). Several authors have proposed definitions of passive fit, however all definitions are theoretical, and difficult to assess clinically.
It has been suggested that absolute passive fit cannot be achieved, nor is there concrete evidence that passive fit ensures the long term prognosis of the implants and restoration (Sahin & Cehreli, 2001). It is, however, reasonable to expect fewer mechanical complications, such as screw loosening and porcelain fracture, when the components fit more accurately. The concept of clinically acceptable fit incorporates the goal of minimizing both biologic complications and mechanical complications. Clinically acceptable fit in combination with control over the occlusal forces is a practical approach to ensuring success of the implants and the restoration.
Framework fit can be assessed by a variety of methods. Clinical methods for assessing framework fit include finger pressure, visual inspection, radiographs, tactile sensation, Sheffield test, disclosing materials, and the screw resistance test (Abduo et al., 2010). Each method has both advantages, disadvantages, and relative accuracy. In general, the intra-oral methods such as visual inspection, finger pressure, and disclosing agents are of limited value with subgingival margins. The screw resistance test (Jorneus et al., 1992) is based on the thread pitch of the original gold prosthetic screws, thus has limited application to newer systems and alloys. The Sheffield test, also known as the single screw test, combined with radiographic evaluation, is an efficient technique, especially for long span frameworks. If a single screw placed in a distal abutment does not create a vertical gap on the opposite end of the framework, the framework is said to have clinically acceptable fit.

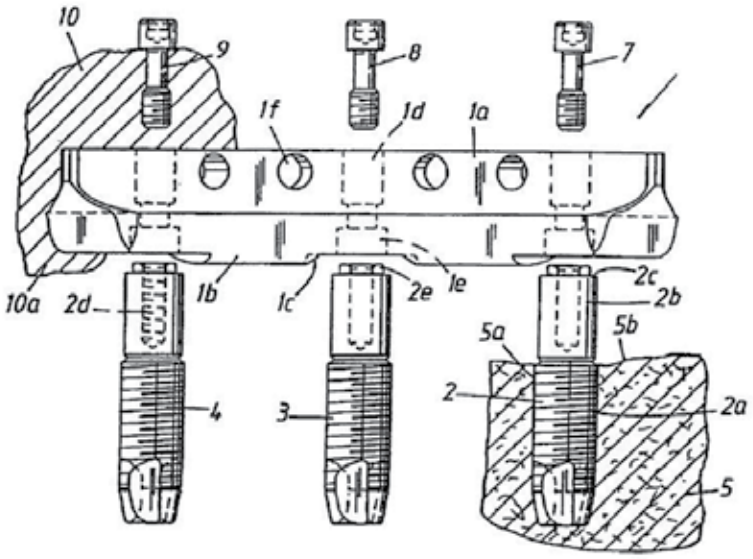

Fig. 15. Illustration of Branemark's original design for restoration of the completely edentulous mandible. (1) Cast gold framework. (2b) Standard Abutment. (2d) Abutment screw. (4) Implant fixture. (9) Prosthetic Screw. (10) Acrylic teeth and gingiva.

Multiple in vitro methods to assess framework fit can be utilized to compare the relative accuracy of various methods of fabrication. In vitro methods include photoelastic, strain gauge analysis, finite element analysis, microscopic, photogrammetric, and coordinate measuring machine (Abduo et al., 2010). These methods can be qualitative, quantitative, 2-dimensional or 3-dimensional. For example, strain gauge analysis is both quantitative and 2-dimensional, yet depends on the location of the strain gauge, and the ability of the material to mimic natural tissues. At this time, none of the available methods for assessing accuracy of fit have been validated with clinically relevant parameters.

3.4 CAD/CAM Framework and bar fabrication

CAD/CAM applications have surged in the market over recent years. There are now multiple commercial sources that can produce purely CAD/CAM bars and frameworks, or copy-milled CAM structures for implant prostheses. Procera from Nobel Biocare, CAMStructure from Biomet 3i, and Vericore from Whip Mix are just a few examples. Most companies offer stock designs such as a Dolder bar or Hader bar that can be masked on a virtual master cast of the implant analogs and soft tissue contour. The stock design is then contoured to the arch form, and modifications can be made to idealize the bar design. A second scan of the wax denture can be overlaid in order to allocate adequate space for attachments and adequate thickness of the resin denture base. For ceramic frameworks, a scan of the full-contour wax-up can be matched to the virtual master cast, and a virtual cutback can be performed to allow adequate thickness for veneering porcelain. By using CAD/CAM frameworks, fixed partial (Figures 16-24) or full-arch (Figures 25-38) dental prostheses can be fabricated.

For more complicated designs, a resin pattern of the desired framework can be scanned and the structure can be CAMed via a process known as copy-milling. Zirkonzahn, for example,

utilizes a optical scanner with computerized 5-axis copy-milling technology that allows fabrication of highly detailed zirconia frameworks.

Fig. 16. Procera copy-milled titanium framework from Nobel Biocare.

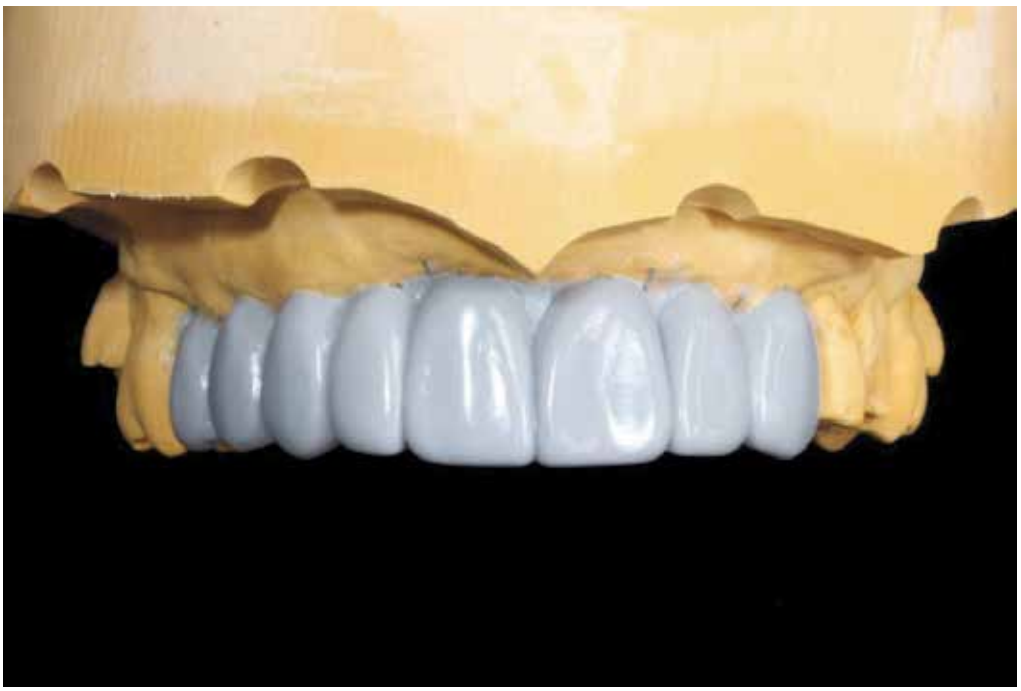

Fig. 17. Diagnostic wax-up for planning implant placement, prosthetic design, and space allocation.

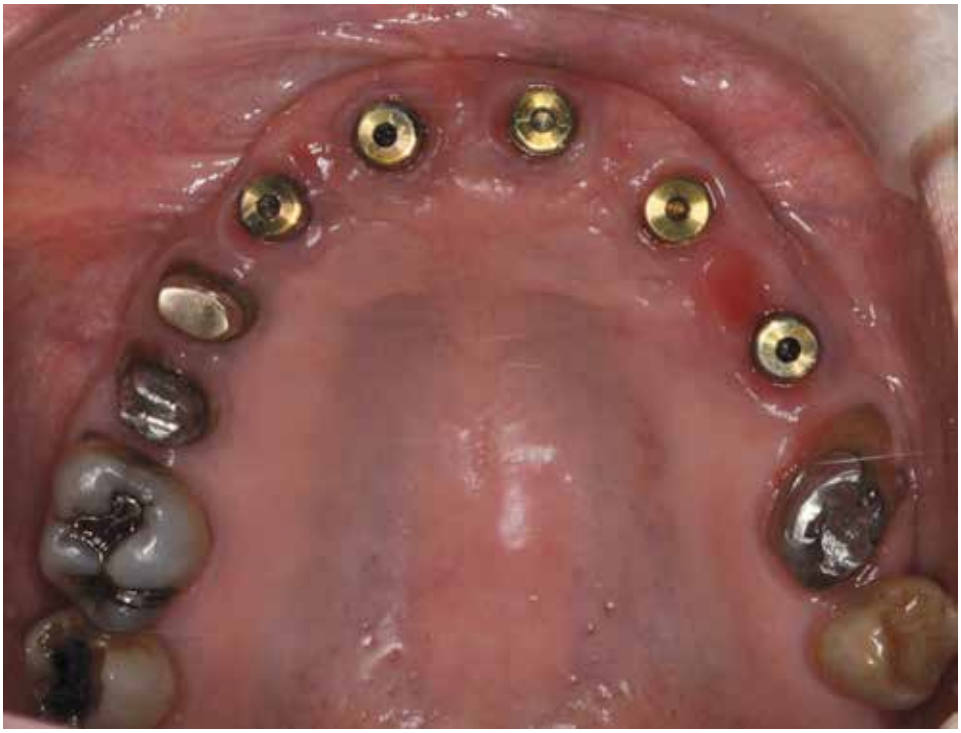

Fig. 18. Occlusal view of implants with healing abutments and tooth preparations.

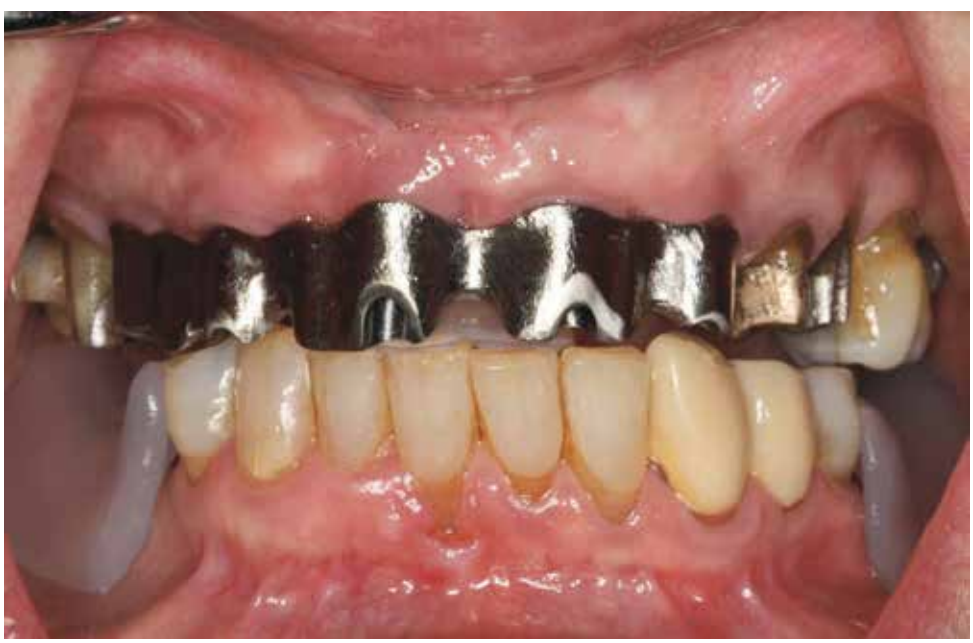

Fig. 19. Nobel Procera copy-milled titanium framework at time of try-in and making inter-occlusal records.

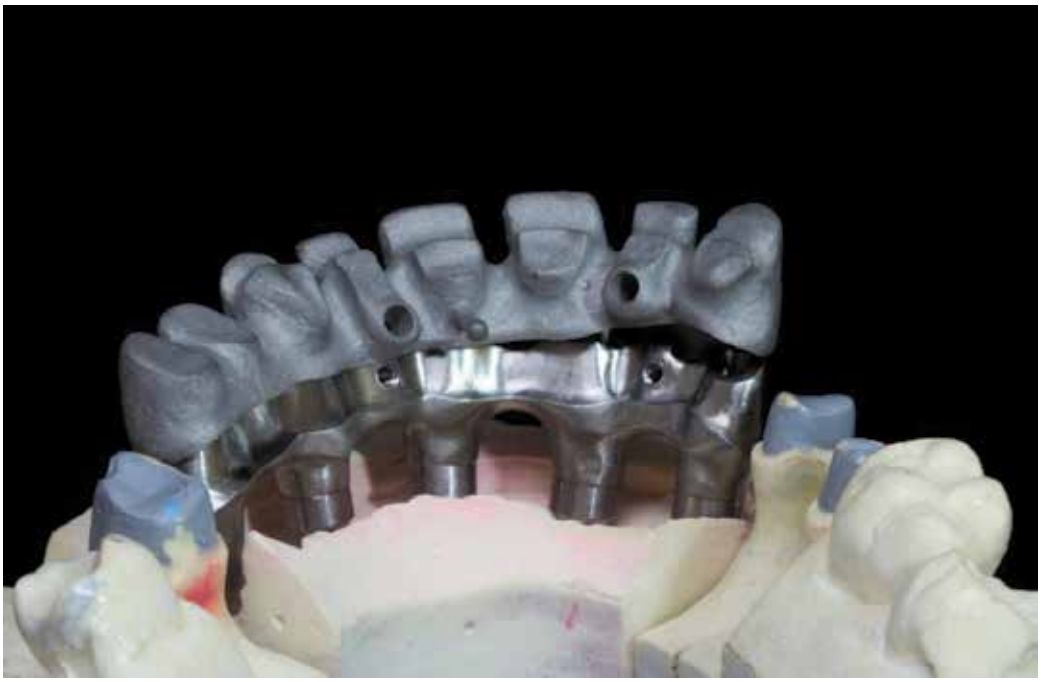

Fig. 20. Procera titanium framework with cast high-noble superstructure.

Fig. 21. Cast high-noble superstructure after porcelain application and firing.

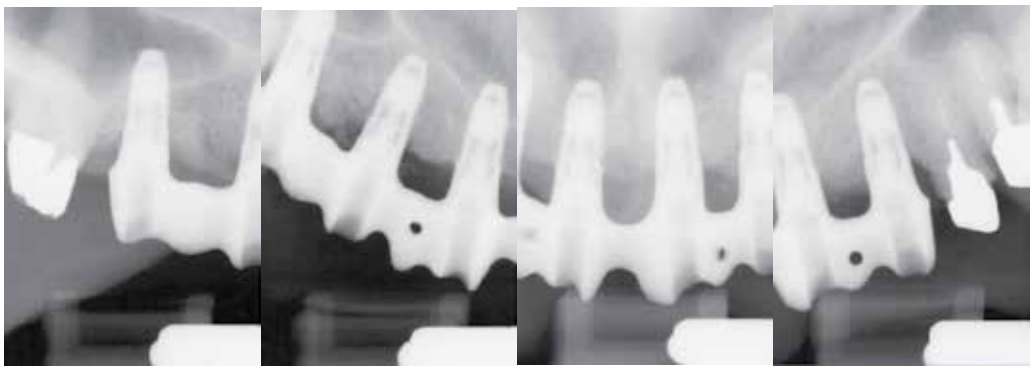

Fig. 22. Radiographic verification of framework fit prior to placement of superstructure.

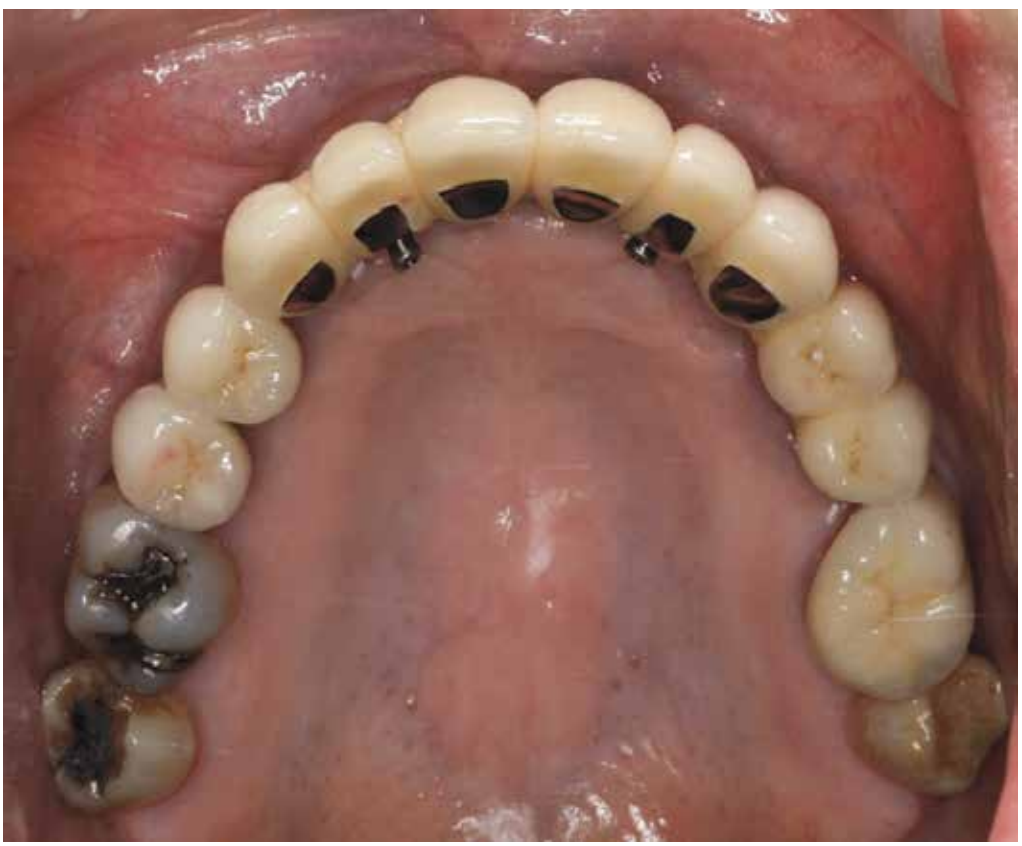

Fig. 23. Occlusal view of lingual set screws retaining metal-ceramic superstructure to CAM framework.

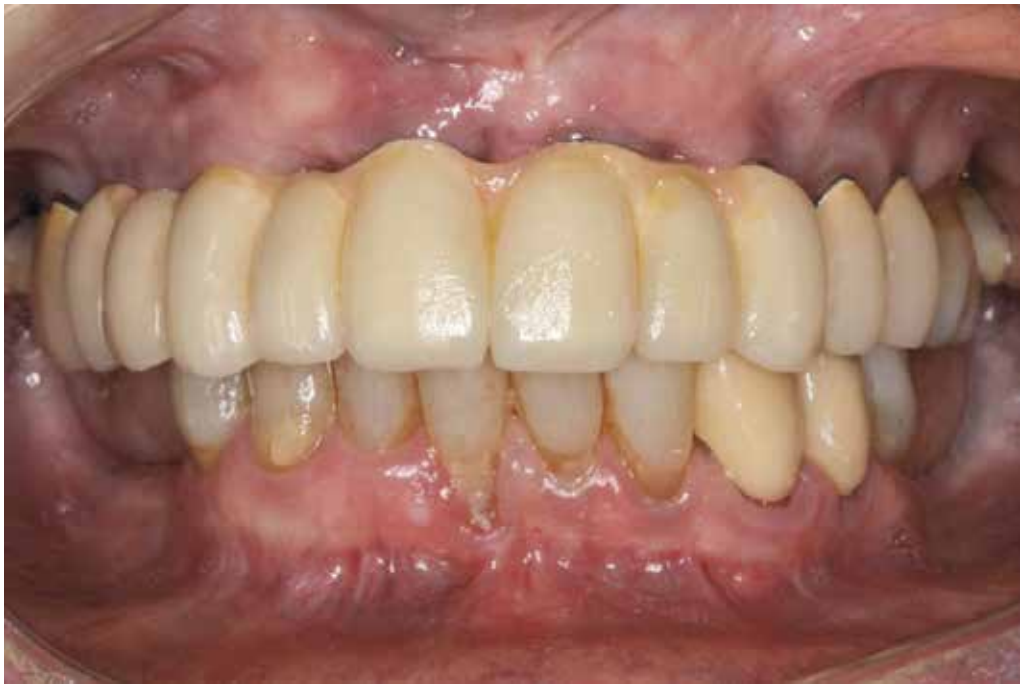

Fig. 24. Frontal view of completed prosthesis.

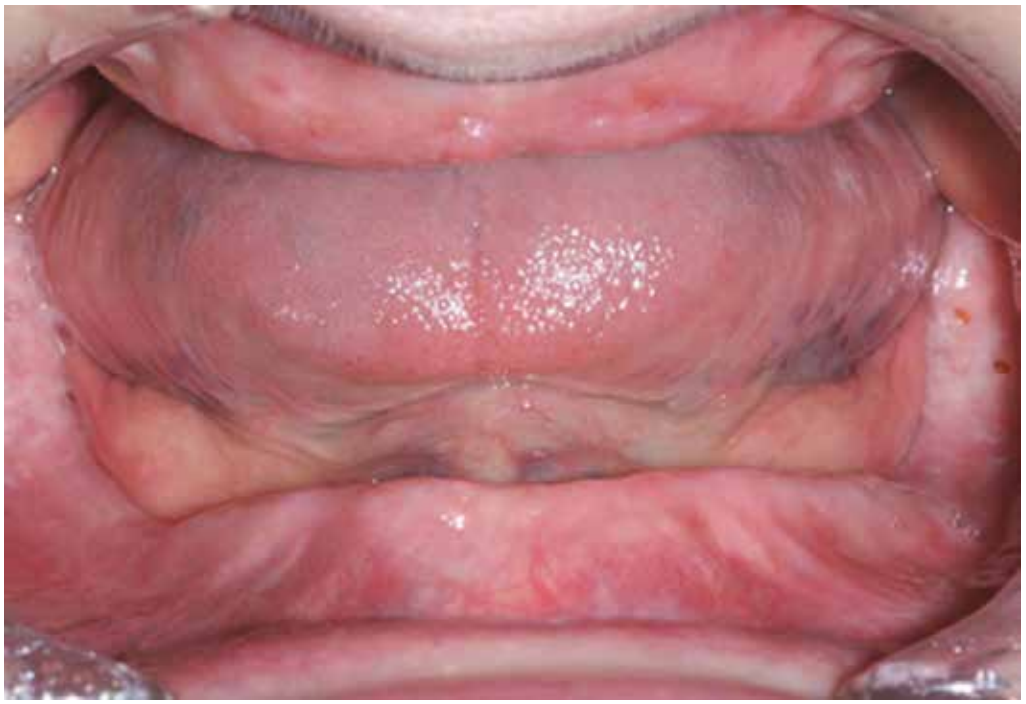

Fig. 25. Intra-oral view of an edentulous patient.

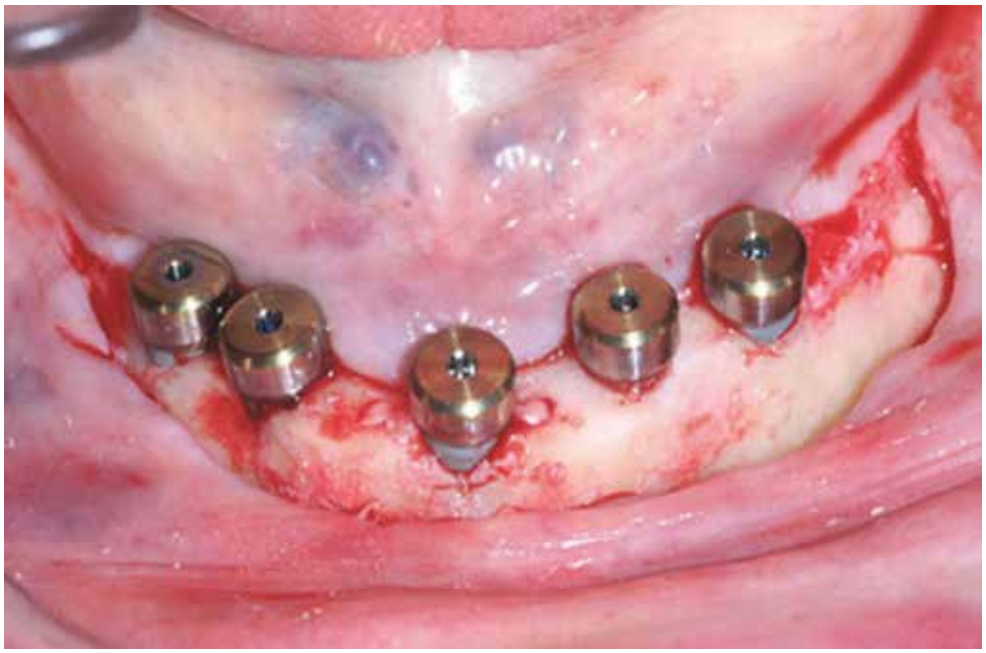

Fig. 26. Clinical view of the five healing abutments on the implants seated immediately after the implant placement.

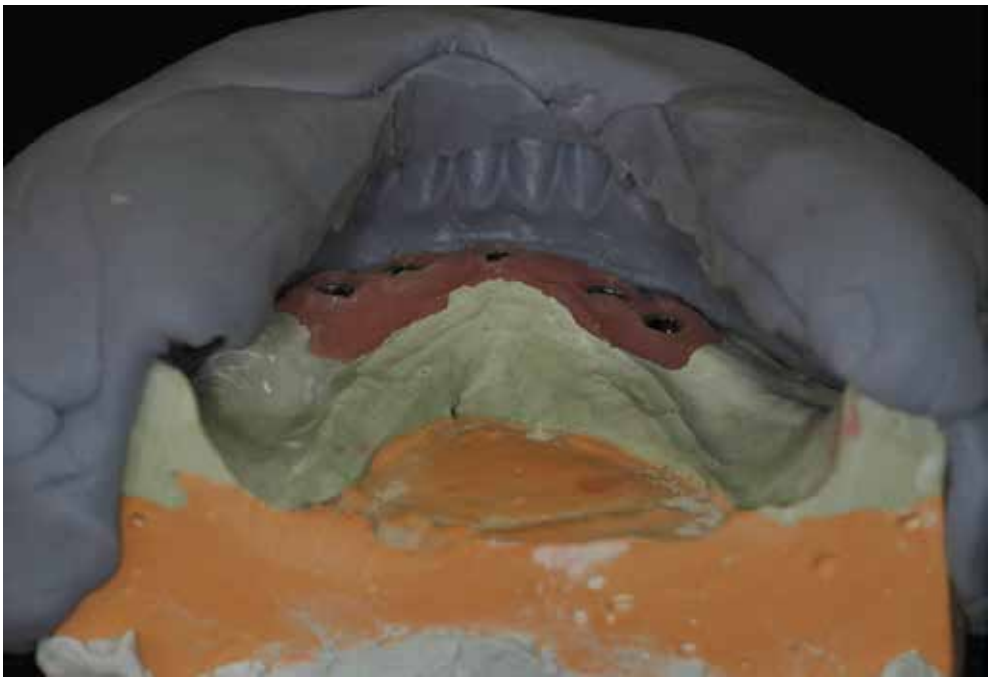

Fig. 27. The lingual view of the mandibular definitive cast with the tooth index, showing the room for the framework.

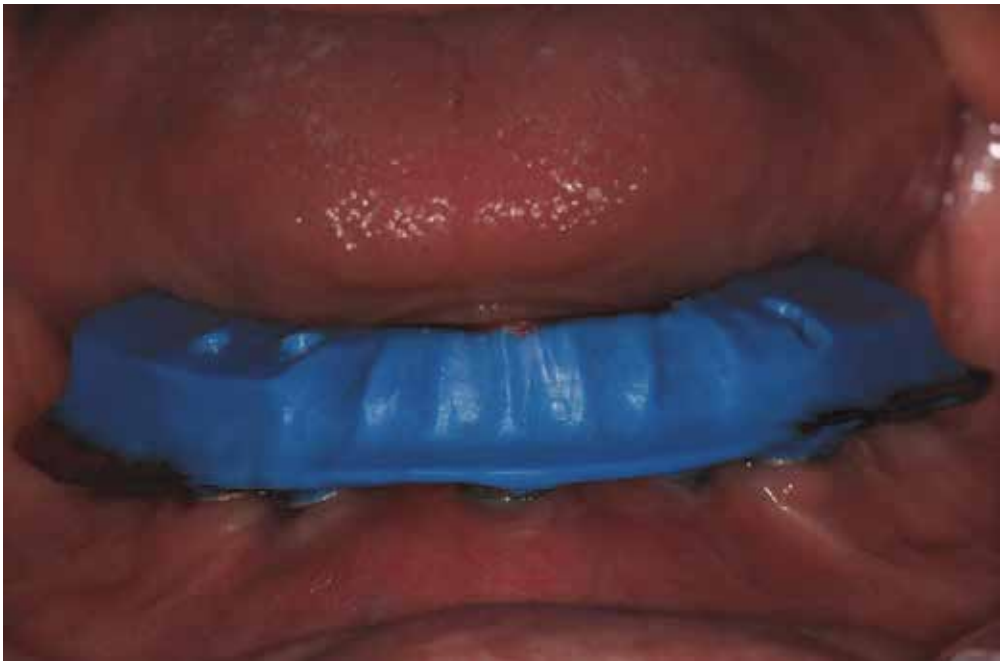

Fig. 28. The fit of the mandibular wax pattern was verified clinically.

Fig. 29. The scanning process of the implant replicas on the mandibular definitive cast in order to determine the position of the implant platforms using NobelProcera scanner.

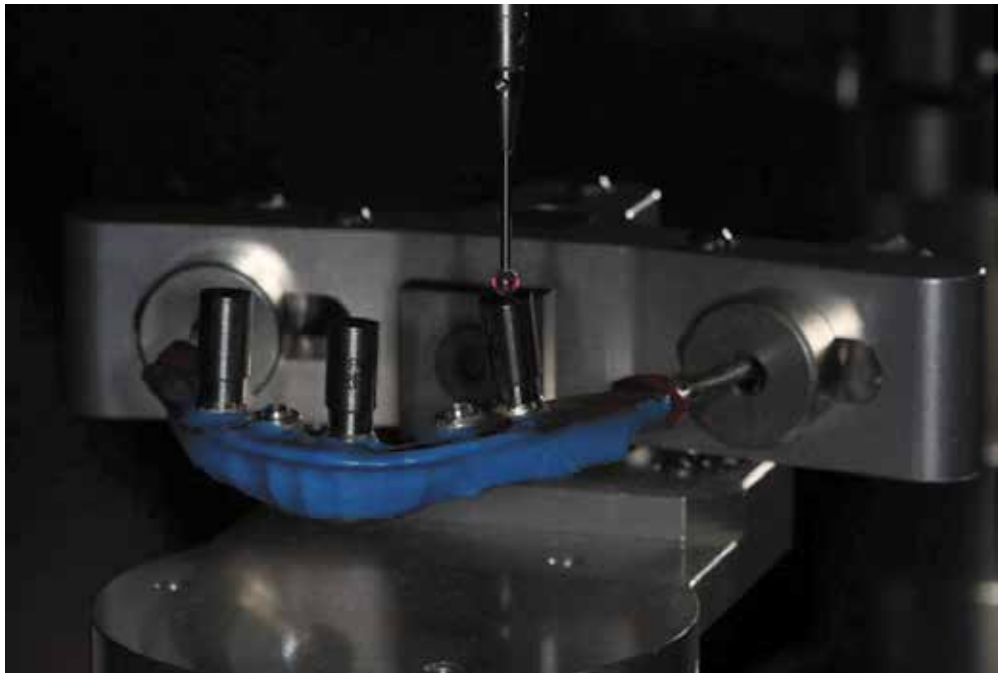

Fig. 30. The scanning process of the implant replicas in the mandibular wax pattern in order to determine the position of the implant platforms using NobelProcera scanner.

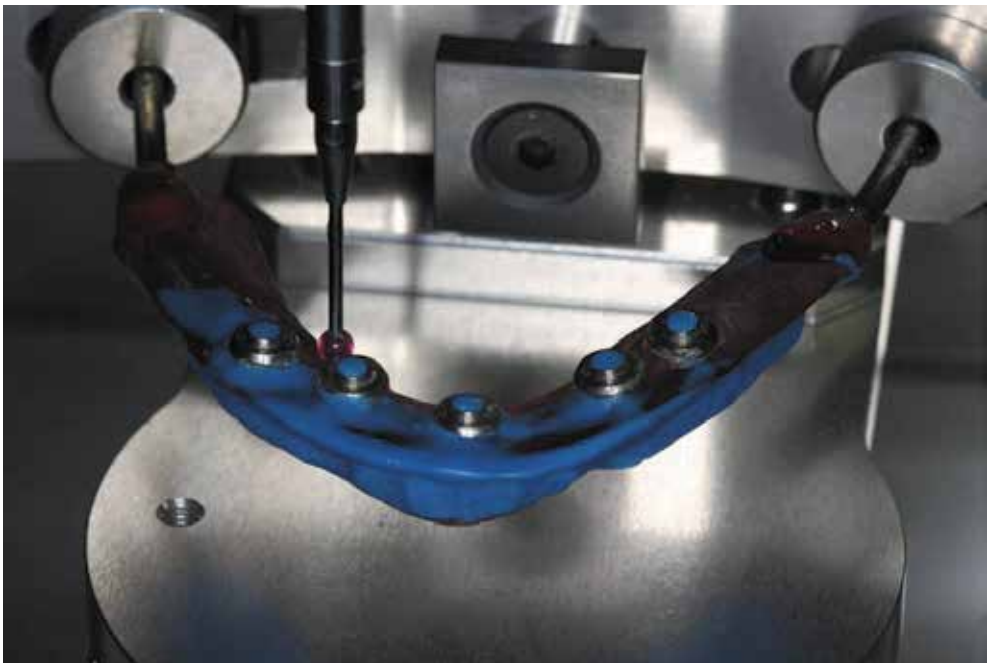

Fig. 31. The scanning process of the gingival surface of the mandibular wax pattern using NobelProcera scanner.

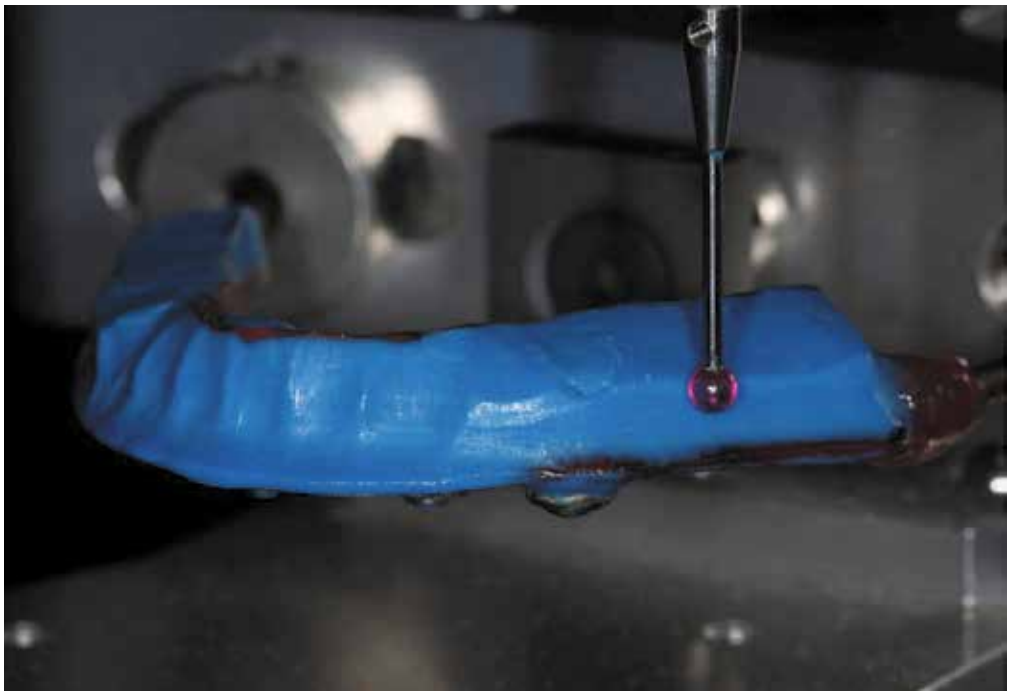

Fig. 32. The scanning process of the occlusal surface of the mandibular wax pattern using NobelProcera scanner.

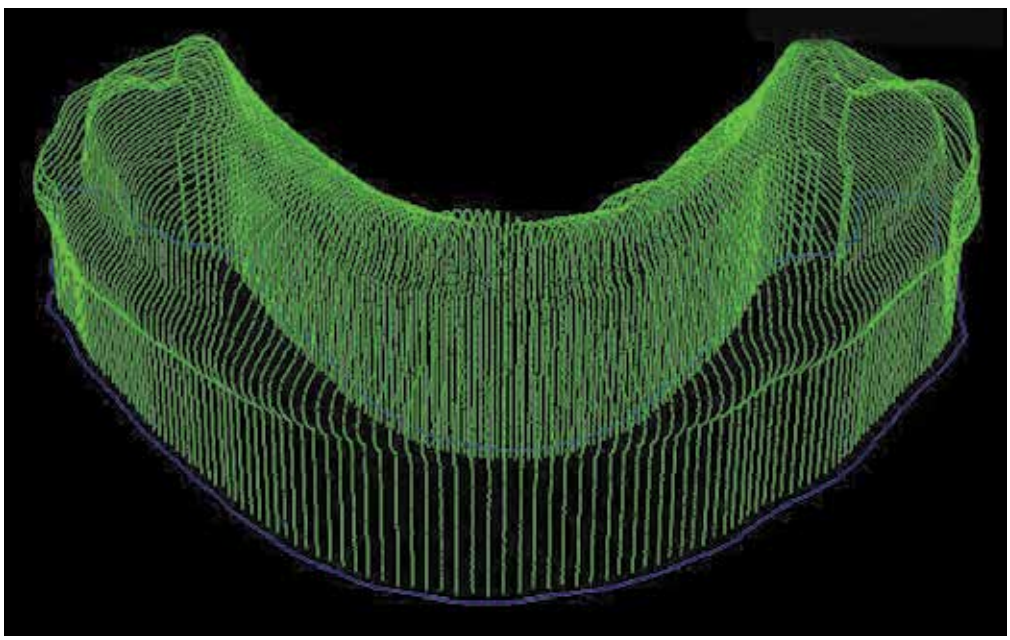

Fig. 33. The design of the occlucal surface of the mandibular framework using NobelProcera scanner.

Fig. 34. The final design of the mandibular framework using NobelProcera scanner.

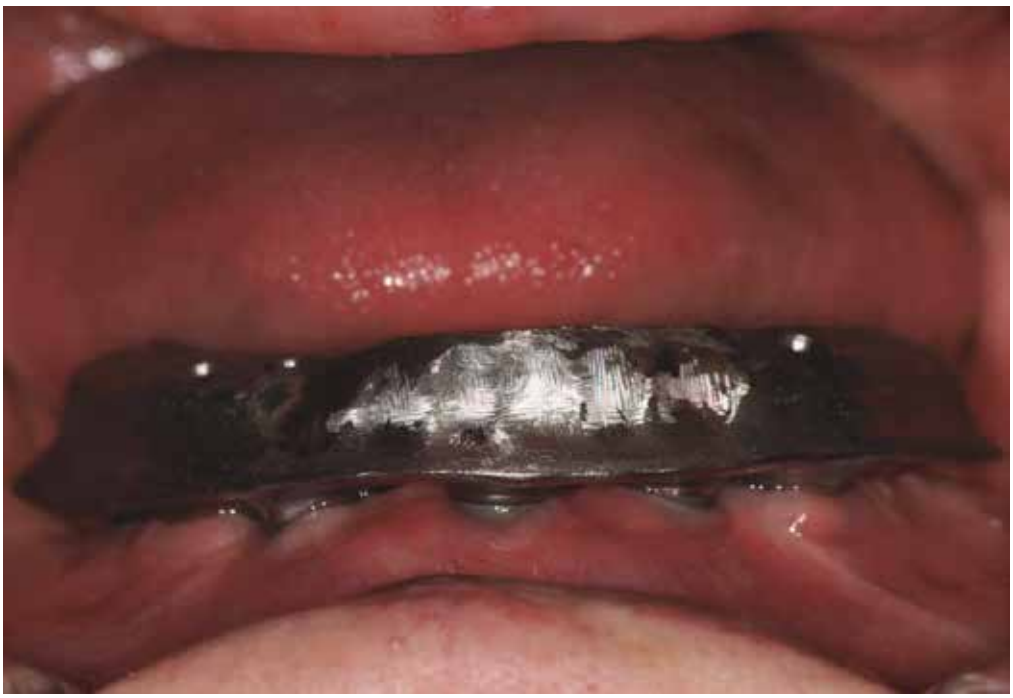

Fig. 35. Clinical fit of the final mandibular framework fabricated was verified.

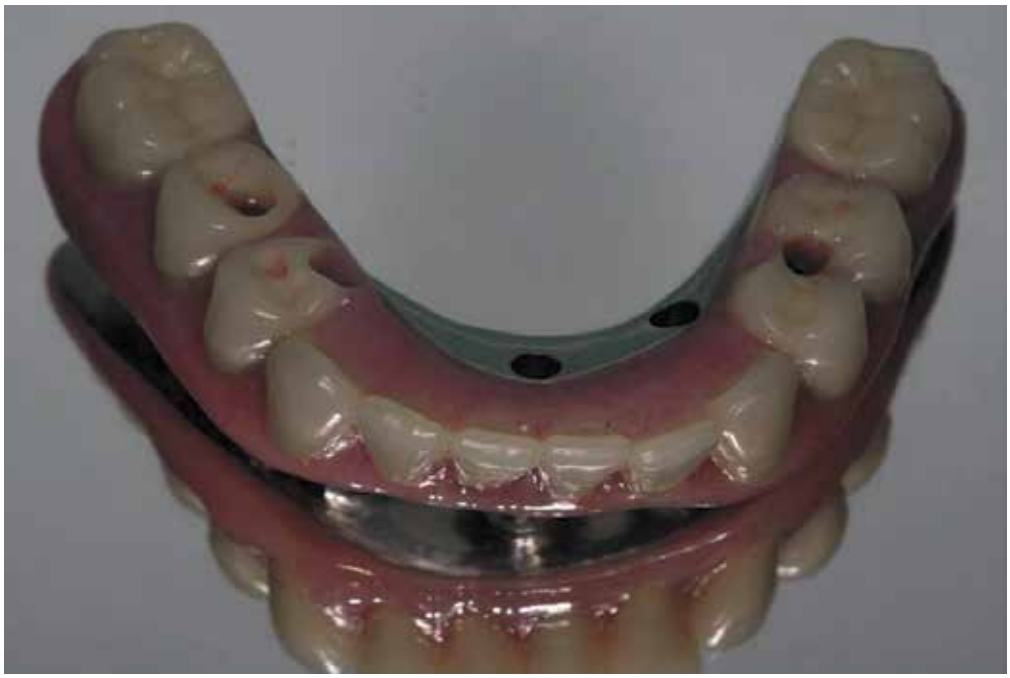

Fig. 36. The implant-supported screw-retained fixed dental prosthesis after processed.

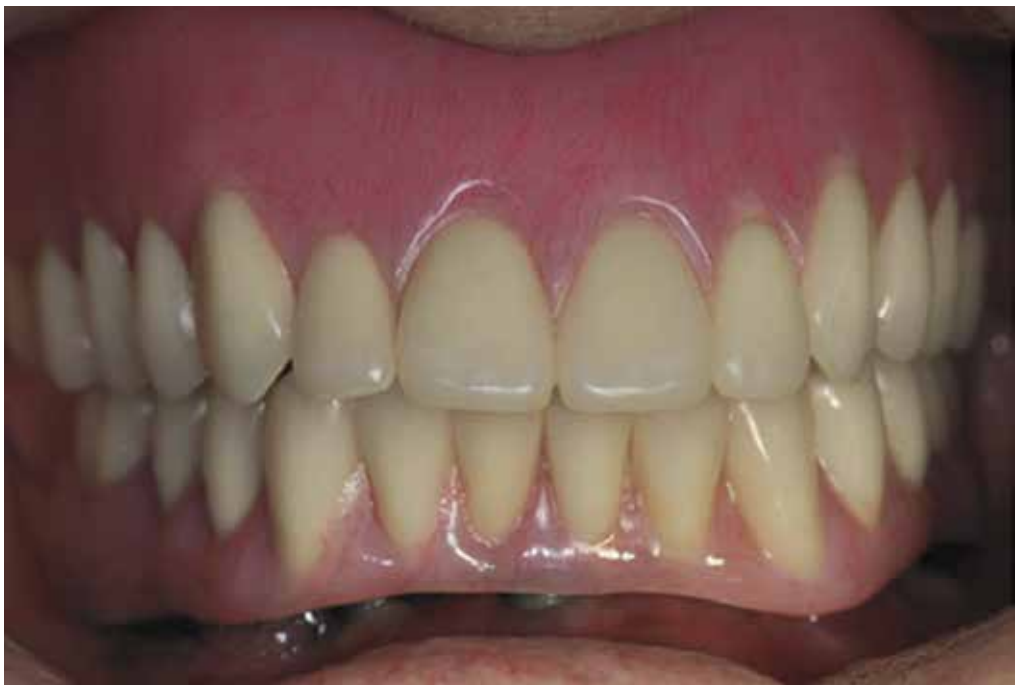

Fig. 37. Clinical view of both maxillary complete denture and mandibular implant-supported screw-retained fixed dental prosthesis.

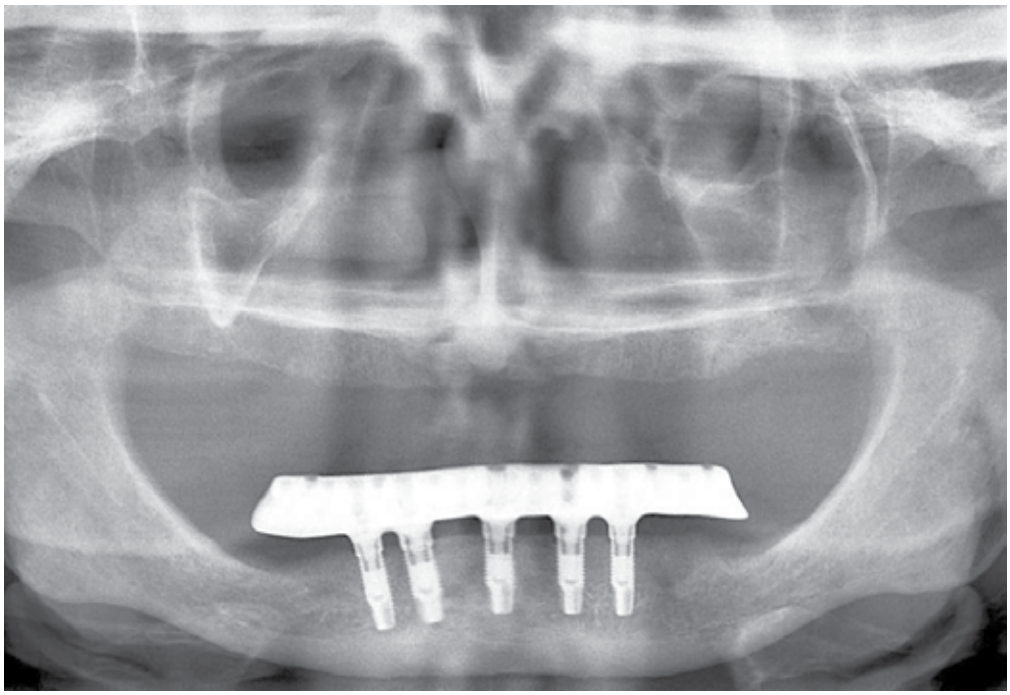

Fig. 38. Panoramic radiograph of the patient a year after the implant placement.

3.5 Comparison of fabrication techniques

An abundance of literature supports the improved accuracy of CAD/CAM over traditional casting, even when corrective procedures are included. A recent publication by Drago et al. (2010), evaluated volumetric misfit of CAM and cast 5-implant frameworks fabricated in three different laboratories. Thirty implant level impressions with verified implant indices were made from one master cast with five intra-foraminal mandibular implants. Fifteen verified master casts were scanned and CAD/CAM frameworks were fabricated. Another fifteen verified master casts served as the base for attachment of UCLA abutments and resin pattern fabrication for casting procedures. A volumetric analysis of fit based on single screw test and "best fit" of individual frameworks to respective master cast revealed that the CAD/CAM frameworks were significantly more accurate than the cast frameworks.

An earlier study by Riedy et al.(1997), showed similar results when comparing one piece cast frameworks to Procera CAD/CAM frameworks. They also found that sectioning and laser welding cast frameworks significantly improved the overall fit. These results are consistent with other studies comparing conventional casting to CAD/CAM techniques (Al-Fadda et al., 2007). Given the significant improvement of fit and decrease in laboratory time, CAD/CAM bars and frameworks, particularly for overdentures and hybrids, will soon be the standard.

4. Conclusion

CAD/CAM technology has revolutionized the field of implant dentistry. CAD/CAM surgical guides have greatly improved the predictability of implant surgery. CAD/CAM

bars and framework have proven more accurate, less expensive, and less time-consuming to produce. All of this results in improved experience for the patient, decreased treatment time, and greater accessibility.

The future of dentistry is quickly approaching. Digital impression systems and CAMed models for tooth born restorations are rapidly expanding in the market. Virtual tooth libraries allow CAD/CAM of both provisional and final tooth-born restorations. Numerous implant companies have already designed abutments for compatibility with digital impression systems. Just on the horizon is virtual articulation and virtual tooth arrangement, thus completing the virtual relm of dental technology. It is clear that CAD/CAM technology has transformed all aspects of dentistry, not just implant dentistry.

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10

Digital Engineering of Bio-Adaptable Dental Implants

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1. Introduction

Dental implants are the most integral part of modern dentistry (Brånemark, et al., 1969); they provide a permanent and effective solution for a wide range of dental complications and diseases (Tatum, 1988). The prominence of dental implantology is demonstrated by the increase of the number of dental implants used in the U.S. by ten folds from 1983 to 2002, leading to an increase in production capital from $19 million (1983) to $150 million (2002), with a projected yearly growth of 9.4% over the following few years (NIH, 1988; MRG, 2003) According to a report submitted by Merrill Lynch in 2007, the world dental industry is estimated around $2.2 billion (Jüngling, et al., 2006).

From a technological and clinical advancement stand-point, the field of dental implantology has rapidly expanded since its introduction in the late 60s' by Branemark (Spiekermann, et al., 1995). With the introduction of more complex and capable technologies in design, manufacturing, and testing, the dental implant converged to its dominant design of the three-piece assembly (rootform, abutment, and abutment screw) due to incremental changes driven by clinical research and feedback from patient monitoring and the attached trends of success and failure. The prominent design was also crystallized with an attached implant insertion protocol and corresponding pre- and post- implantation routines. The protocol includes biological, functional, and biomechanical assessments, which results into the formulation of different implantation factors such as implant position, amount of available alveolar bone, soft tissue biotype and morphology, implant design and material, abutment, and permanent crown (Sadan, et al., 2004; Poggio, et al., 2002; Touati, et al., 1999). An implantation requirement of great importance is the one devised by Brånemark and Breine et al. (1969), which suggests the countersinking of the implant below the level of crestal bone, while maintaining a soft tissue enclosure for 3-6 months, enforcing a non-loading period before a second-stage surgery would be required in order to uncover the implant and place the abutment and the permanent dental prosthesis. This loading prevention period was discussed in several subsequent studies, where it was concluded that the amount of motion provoked at the implant/alveolar bone interface in early stages of implantation strongly affects the implantations success. Pilliar et al. (1986) states that successful bone

integration is only possible in the case of micromotion, not macromotion, suggesting a threshold of 100 μm of micromotion would induce fibrous repair instead of osseointegration (Pilliar, 1991). A finding that was also discussed by Brunski et al. (1993) who considered that displacements of 150 μm to 500 μm are excessive micromotion that would disrupt the process of osteogenesis jeopardizing the implantation's success. Such thresholds prove to be dependent on surface and design characteristics; e.g. porosity (Szmuckler-Moncler, et al., 1998).

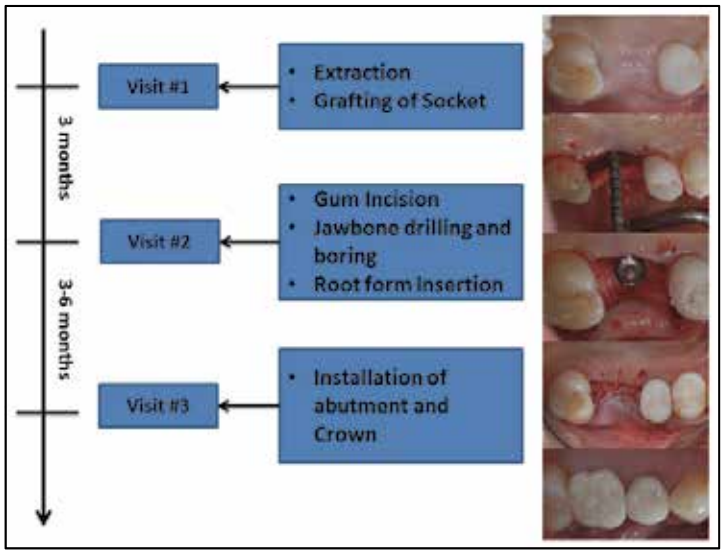

Fig. 1. Traditional post-extraction implantation protocol of a first molar

One area of traditional implantology that is of interest in the current Chapter is the replacement of a decaying unrepairable multi-root posterior dentition. While the survival rates of current implants can reach 95% (Buser, et al., 2002), this is only restricted to anterior single root dentitions. Fig. 1 exhibits a timeline of a traditional replacement of a first molar; it starts with an initial visit to the dentist, where the decaying dentition is extracted and the socket produced is packed with grafting material and enclosed for a healing period reaching 3 months. The second visit includes the surgical insertion of the implant, which is preceded by soft tissue incision, drilling, and boring of the jawbone in preparation of the insertion of the rootform. After insertion, the gum incision is enclosed in order to enforce the aforementioned non-loading period of 3-6 months. The third visit includes the discovery of the rootform and a subsequent installation of the abutment and the permanent dental prosthetic. In summary, the process spans over a period of 6-9 months costing three dentist visits, and a considerable period of incomplete esthetics or function.

In addition to the clinical complications that are imposed by the replacement of a decaying multi-root tooth, when comparing the dental implant to the organ in consideration (natural dentition), several discrepancies are eminent from the functional and physical perspective. In contrast to other load-bearing endosseous implants where a function is being replaced; e.g. hip joint replacement, or knee joint replacement a dental implant is replacing a complete organ which constitutes of a plurality of functions which drastically affect the well-being of a patient. One general discrepancy is the difference in micromotion provided by a dental implant, when

compared to natural teeth. A summary is portrayed in Table 1, extracted from (Misch, 2008), where a difference in functionality between natural dentition and dental implants is prominent due to a lack of initial movement (micromotion) in the latter.

Type of Movement	*Natural Tooth*	*Dental Implant*
Vertical Clinical Mobility	0 μm (Misch, 2008)	0 μm (Misch, 2008)
Initial Vertical Movement	28 μm (Parfitt, 1960)	2-3 μm (Sekine, et al., 1986)
Horizontal tooth mobility	56-108 μm (Rudd, et al., 1964)	<73 μm (Sekine, et al., 1986)

Table 1. Comparison of micromotion found in a natural tooth and a dental implant

Another important incongruity between a dentition and the device replacing it is the mismatch in elasticity between the biomaterial (Ti6Al4V 110 GPa (Collin, 1984)) and the surrounding alveolar bone (3-20 GPa (Abe et al., 1996)). A common complication in endosseous implants, the elasticity mismatch causes "stress shielding" which results in disuse bone atrophy manifesting in crestal bone loss in the case of dental implants and a higher risk of implant loosening (Vaillancourt, et al., 1996). In addition to a mismatch in mechanical properties, a mismatch in geometrical aspects is more pronounced in the case of posterior dentition. In a manual published by Zimmer Inc. (Zimmer Dental, n.d.), the average surface area of natural dentition was shown to vary from 154 mm^2 in the case of a mandibular central dentition, to 433 mm^2 in the case of a mandibular first molar. In contrast to a traditional implant that can reach a textured surface of only 310 mm^2.

The multi-component aspect of the traditional design of a dental implant provokes certain impediments that relate to three modes of deterioration which were investigated by Williams (1977): Stress Corrosion Cracking, Galvanic Corrosion, and fretting Corrosion. The latter is mostly pronounced at the abutment/rootform interface and it causes fatigue loading failure.

All the mentioned deviations in physical aspects and functionalities when comparing the modern dental implant to the organ that it replaces lead to a series of shortcomings which seems to be more pronounced in the case of posterior teeth; with the complex implantation surgery and the divergent functionality of the traditional medical device. Accordingly, a series of innovations were suggested over the past few years in order to overcome the mentioned shortcomings, while employing emerging technologies in design, data acquisition and manufacturing. Discussed in the next section, the prior art of new concepts of dental implants, which lead to the crystallization of the concept of bio-adaptable implant that is discussed in the current Chapter.

2. Prior art

Due to the different complications that aroused from traditional dental implantology, several alternative rationales were addressed along the years, which deal with shortcomings found in the function of dental implants, and the prescribed insertion protocol. Hodosh et al. (1969) introduced the concept of root-analogous implants, which enables insertion right after extraction. Some in-vivo testing proved root-analogous dental implant to provide some initial success, however portrayed poor success results (48%) 9 months after implantation (Kohal, et al., 1997), rendering the concept as unattractive. More recent work done by Pirker et al. (2008), employs CAD/CAM techniques to produce root-analogous zirconia implants with macro-retention on the surface. A main improvement is the reduction of the implant

size where it comes in contact with the brittle crestal bone, which was one main factors affecting the poor success rates of older versions of the concept.

Fig. 2 displays a few patents that provide alternative concepts of dental implants. Uckleman et al. (2004), introduced the use of laser-based additive manufacturing for the production of a customized abutment, which when coated produces the dental prosthesis. Hayashi et al. (2009), provided a similar concept of using additive manufacturing, where an abutment is produced on top of an abutment screw; hence, reducing the assembly of the implant to two components (in contrast to the traditional three-piece assembly). Rubbert et al. (2005) proposed the use of intraoral scanning for diagnostics and treatment pre-planning purposes, in addition to producing patient-specific dental devices. Mount et al. (2008), patented the concept of a root-mimicking dental implant that exhibits macro-retentions on the surface.

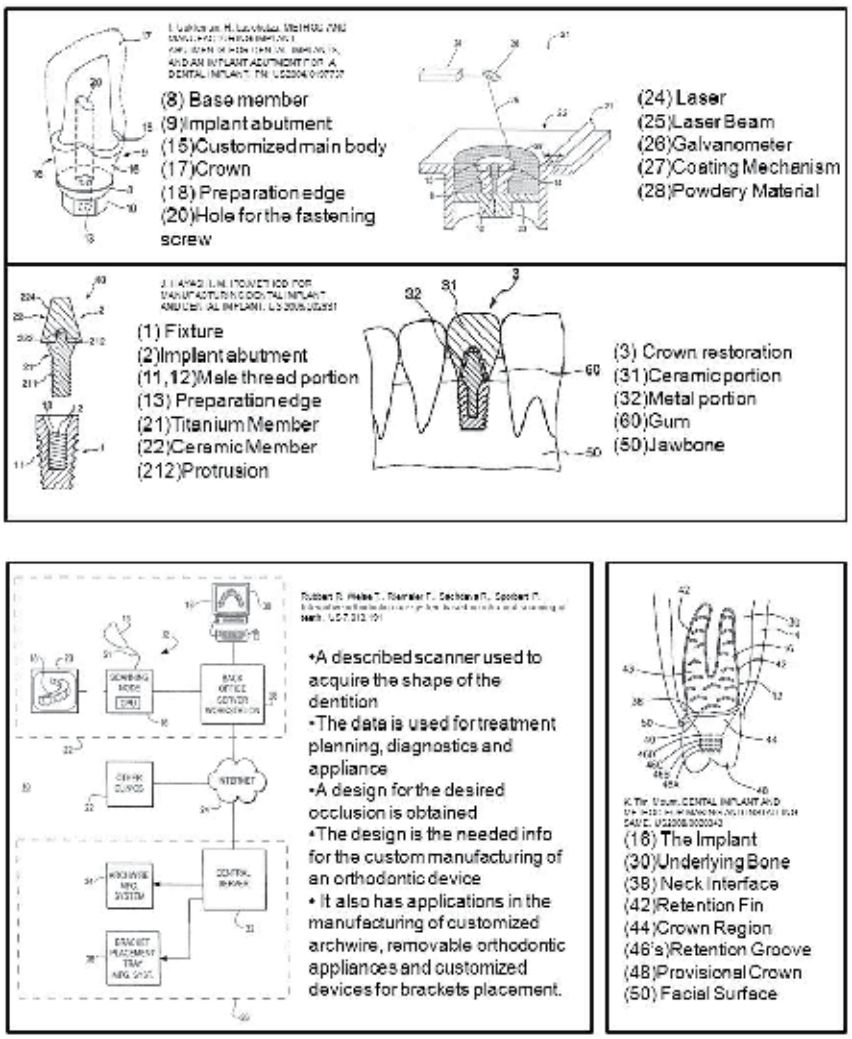

Fig. 2. Different dental implant rationales illustrated by their corresponding patents

An attractive design aspect, which provides a wide range of interest, is the use of porosity on the surface of the implant. In fact, porosity has been proven to improve clinical success by increasing the surface of the contact area (Geng, et al., 2001). In addition, a favorable osteo-blast reaction to the pores is also proven by (Xiropaidis, et al., 2005). One theory suggests that pores provide favorable mechanical conditions for bone growth, which was proven by finite element analysis (Cook, et al., 1982). In addition to porous coatings on the surface, dental implants that are built out of porous materials are also introduced by either additive manufacturing (Laoui, et al., 2006) or the by machining metal foams (NRC, 2005).
Dental implants with damping mechanisms also have been extensively addressed by several concepts, which are believed to provide better load transfer from the bite to the surrounding alveolar bone. Kraut et al. (1993), introduced intra-mobile damping, which employs polyoxymethylene connections, which is found in commercially available IMZ implants (Kanth, 1971; Kirsch, 1983). Patents provided by Ford (1999) and Wagher (1995) also introduced concepts of force distributing, and elastic implants respectively. Despite the several benefits expected from damping capabilities, the mobile aspect of the medical devices introduces failure concerns and maintenance requirement to ensure proper functioning.

3. Rationale of bio-adaptable dental implant

Singularities found in the biomedical field are as frequent as in any biological environment. Every patient has his own characteristics of jawbone density and geometrical aspects of teeth and surrounding biomass. The field of implantology has been limited to certain standards that were adopted due to design and manufacturing limitations. With the advent of digital engineering and its capabilities of designing and producing performance-specific customized parts in a time- and cost-efficient manner, the need of standardized sizes can be eliminated. In contrast of fitting patients' characteristics by means of intrusive and traumatic surgical practices, the implant can be tailored and customized to fit the patient in the least intrusive manner, maximizing benefits and minimizing healthcare cost, which has a positive impact on patient satisfaction and quality of life.
Digital engineering can be defined as the art of using extensive computational power to contribute and ameliorate endeavors in design, manufacturing, and testing. Accordingly, the field unrestrictedly includes: imaging technologies, image processing techniques, reverse engineering, additive manufacturing, and numerical simulation.
The work portrayed in the current chapter discusses the use of the various techniques that constitute digital engineering to design and manufacture a bio-adaptable dental implant that provides high levels of compliance to user-defined needs while abiding to design and functional constraints.

4. Concept

The concept of bio-adaptable dental implants was initially introduced as a customized root-mimicking dental implant (Chahine, et al., 2008; Chahine, et al., 2010). By taking advantage of modern computed tomography (CT) techniques and the subsequent analysis capabilities of the scan data and the generation of three-dimensional computer models, in addition to additive manufacturing (AM) and its ability of producing application-specific parts, a cost and time effective track of designing and producing customized dental implants was devised. A more elaborate approach is discussed in the current section, where the ability of AM to produce highly complex structures is taken to its full extent.

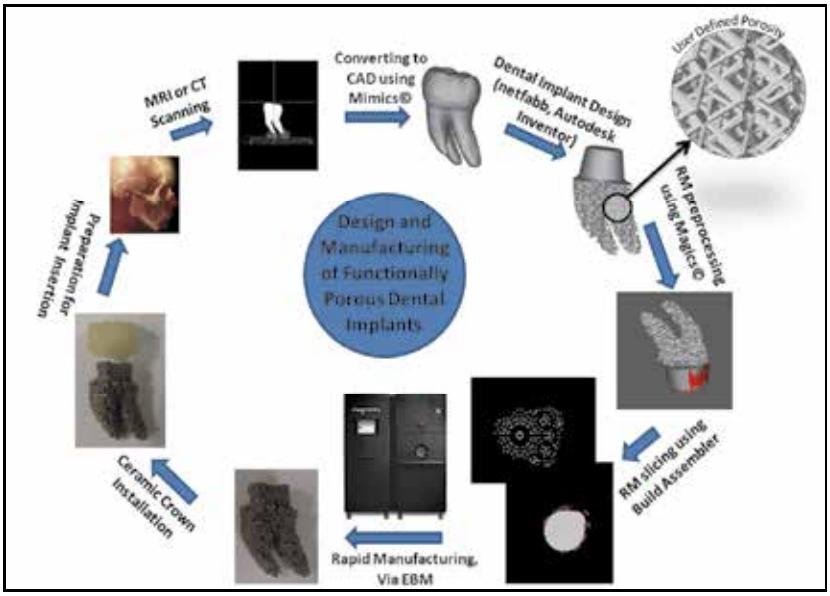

Fig. 3. Design and production of a bio-adaptable dental implant

The main application of the current concept deals with treating decaying posterior teeth by means of immediate implantation after extraction. Fig. 3 displays the design and manufacturing track of a bio-adaptable dental implant. A CT scan of a patient's dentition to be replaced is sufficient to provide enough geometrical data to produce a CAD model of the organ. The model is subsequently used to generate a root-mimicking design along with two main design characteristics: functionally graded porosity (FGP) and advanced abutment design (AAD) which will be discussed in more detail in a subsequent section. The design is then prepared for AM and manufactured. The implant undergoes post-manufacturing processing steps before being sent to the dentist's office before extraction. The lead-time of the entire process is in the range of 24 to 48 hours, enabling the production of the medical device in a time- and cost-efficient manner. Fig. 4 devises the concept of a service center for dental implants, where a the need of several dental clinics treating several patients' needs can be addressed by a single service center by bundling all the different patient-specific dental implants in the building envelope of an AM machine. The development of specialized software to generate bio-adaptable dental implant designs complying with patients' specifics can drastically reduce the already short lead time.

From a clinical concept point of view, the insertion protocol of a bio-adaptable dental implant provides several advantages when compared to the traditional approach. As displayed in Fig. 5, the implantation is executed in one dental visit in contrast to the three-visit protocol discussed earlier. The bio-adaptable implant is customized according to every patient and clinical situation; resultantly it provides optimal function and superior esthetics when compared to stock manufactured implants. In the case where CT scan banks are available, the implant can be ready upon the initial dental visit of the patient where the dentist can atraumatically remove the damaged tooth and insert the implant with minimal to no site preparation. Minimizing trauma will provide with faster healing of the surrounding bone (Misch, et al., 2005). In addition, the immediate placement can provide immediate esthetics and function.

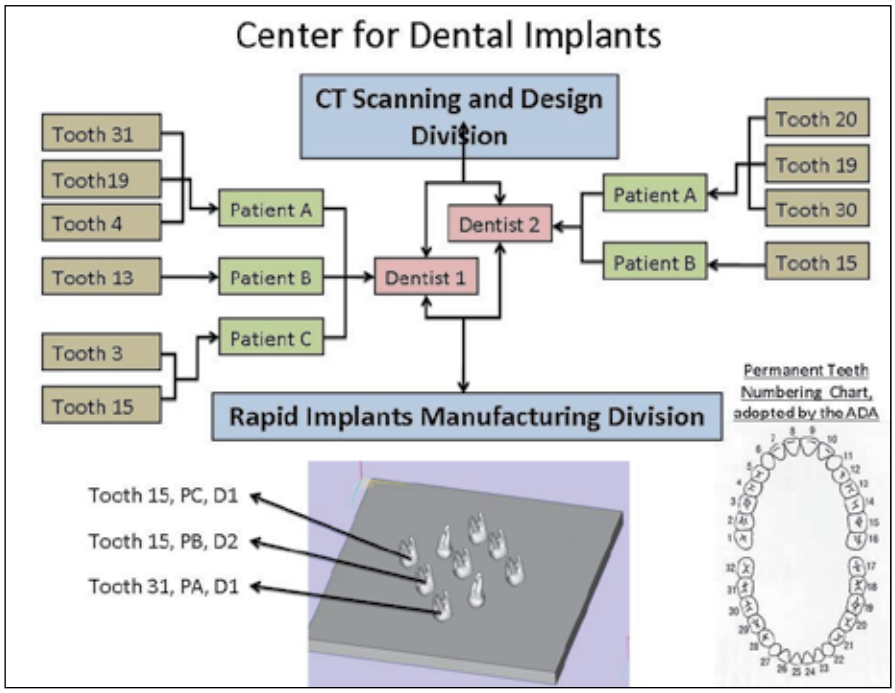

Fig. 4. Mass production Concept of a bio-adaptable dental implant

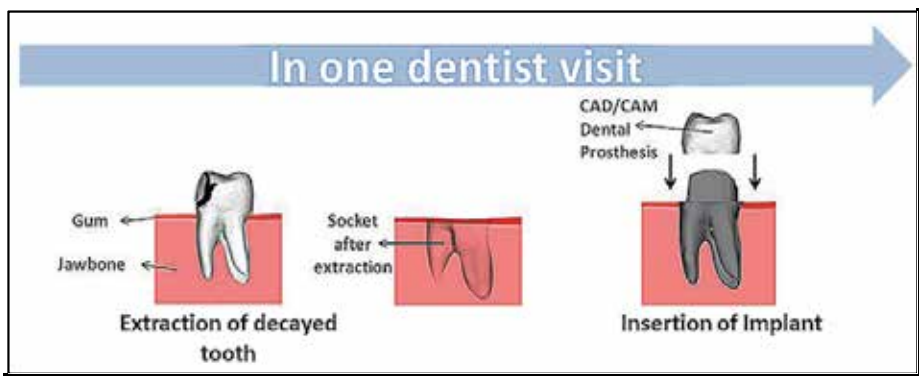

Fig. 5. Clinical concept of a bio-adaptable dental implant as a root-mimicking concept

5. Design and functionality

With the advent of scan analysis techniques and software, surgical pre-planning offers surgeons the ability to visualize and predict the surgical outcome (Stocker, et al., 1992). By analyzing the imaging data obtained from computed tomography (CT) or magnetic resonance imaging (MRI), geometrical models of different organs can be generated and used for a wide range of potential numerical simulation of thermal, bi-mechanical, and biological response. Fig. 6 displays a partial geometry of a patient's jaw that was extracted by CT scan analysis using Mimics®, software developed by Materialise (Leuven, Belgium), where

grayscale analysis is employed at every image to separate the different biomaterials (cortical bone, alveolar bone, dentition, periodontal ligament) and produce CAD models of the different bio-components. The first mandibular model displayed in the aforementioned Figure is designated as the dentition to be replaced. Accordingly it is used as the geometrical reference to which a bio-adaptable dental implant would comply.

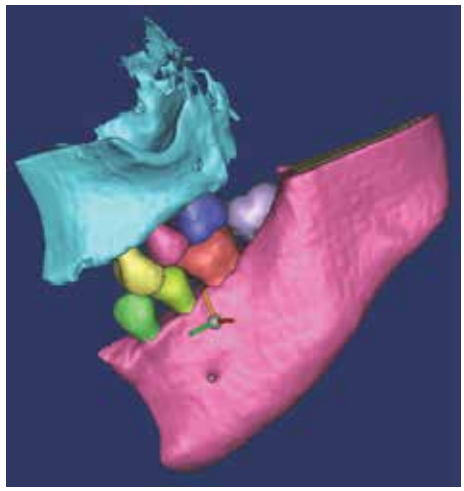

Fig. 6. Geometry of a patient's partial jaw extracted by means of CT analysis

In addition to detecting the geometry of various elements of the bio-environment, grayscale analysis also enables the detection of the anisotropic material properties of the different components. By mapping the grayscale distribution within a component, a distribution of the local material properties can be generated; e.g. elasticity and density. This contributes to a more realistic representation of the domain of interest.

As mentioned earlier, the main functional discrepancy between a dental implant and a dentition is the lack of micromotion, which is also referred to as initial movement. The main reason for the difference is the absence of a periodontal ligament at the implant/bone interface, which surrounds a natural dentition. Actually, a successful implantation is closely dependent on the osseointegration of the surrounding bone, and its mechanical and functional adhesion to the alloplastic material; i.e. the biomaterial. Despite a successful initial retention which can be enforced by macro-topologies at the surface, a long term implantation requires a successful bone reaction on the micro-level. Due to the direct bonding between the rootform area and the surrounding bone, the only approach that can enable crown movement in different directions involves imposing an elastic connection between the dental prosthesis and the anchored rootform.

Fig. 7 displays a preliminary design concept where either a fully porous abutment or an elastic interface can be designed in order to provide the relative micromotion of the crown. A more elaborate concept is shown in Fig. 8, where a thin featured abutment might provide enough flexing to induce micromotion. In contrast to intra-mobile dental implants that are commercially available, the current design approach deviates from the multi-component assembly and converges towards a one-piece dental implant which provides a wide set of functionalities which are provided by locally varying the mechanical properties of the implant.

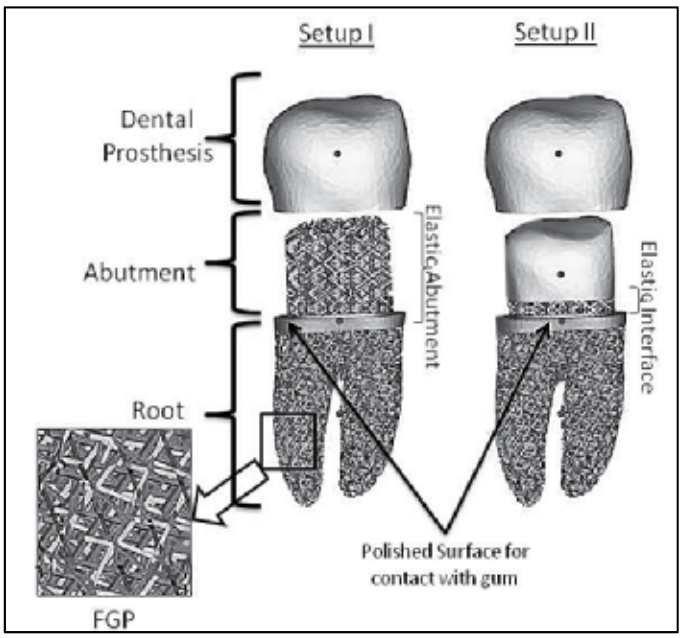

Fig. 7. Rendering of the FGP and AAD design aspects of a bio-adaptable dental implant

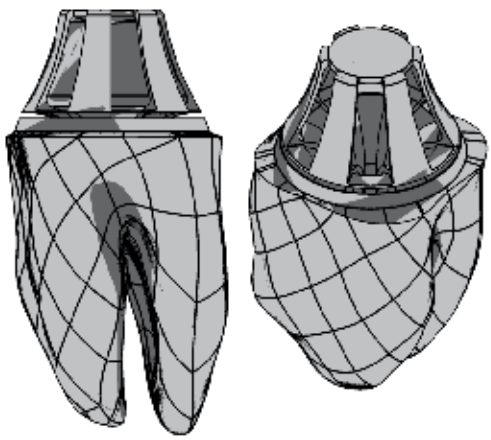

Fig. 8. A rendering of an AAD example

Fig. 9 displays a design example where the abutment rests on an elastic interface that exhibits a porosity corresponding to a desired elasticity. Under loading, the crown will exhibit more elastic behavior in contrast to the conventional case where it is directly anchored to the implant body.

One complication that can be imposed by the current approach of having open gaps in the abutment area is the risk of bacterial infection. A proposed solution involves injecting the cavity by medical polyethylene terephthalate, commonly known by the commercial brand Dacron® which is used in heart valves and internal sutures (Metzger, n.d.). Other candidate materials include medical silicone and polyoxymethylene.

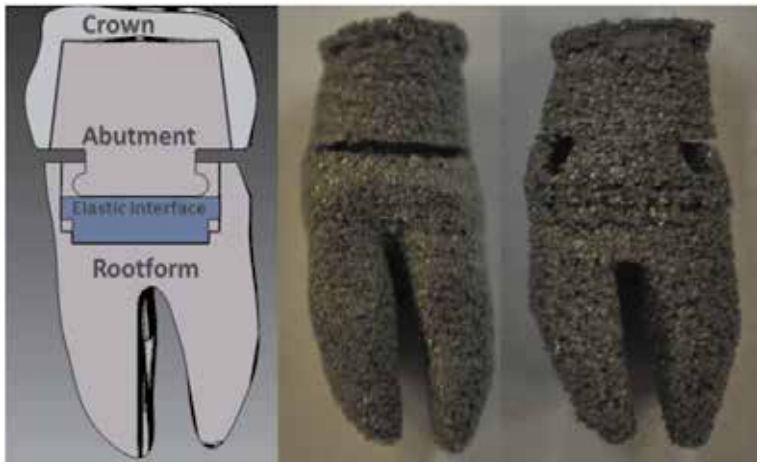

Fig. 9. Bio-adaptable dental implant with AAD (left), built by EBM® (middle), cross-section of the build (right)

The micromotion provided by the AAD, contributes towards a more natural function of the implant, rendering it an improved tooth-replacement. It promotes a more natural bite feel, and an enhanced interaction with the surrounding teeth. In addition, it enables the implementation of fixed bridging supported by a combination of an implant and a tooth, which is traditionally endangered by the discrepancy of the amount of micromotion exhibited by the tooth and the implant. However, perhaps the most prominent advantage of the AAD is minimizing the amount of micromotion transferred from the bite load to the connecting interface between the implant and the surrounding bone, especially in the early stages of implantation where excessive micromotion at the rootform leads to fibrous encapsulation.

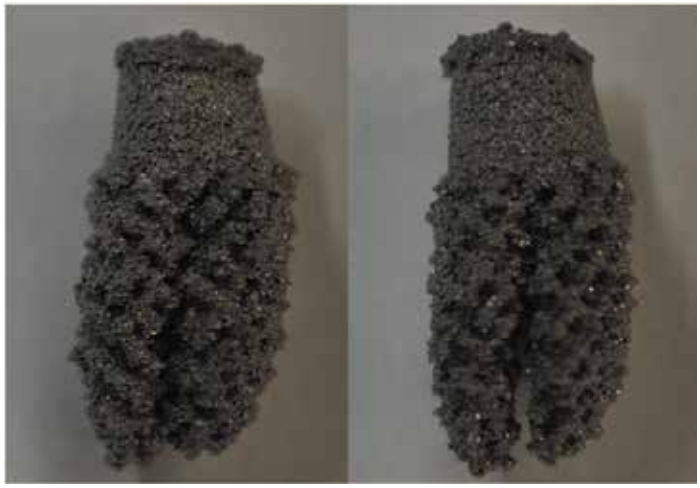

Fig. 10. Two bio-adaptable dental implants with porous rootform built by EBM®

FGP deals with locally varying the geometrical aspects of porosity, inducing locally varying mechanical, physical, and biological properties. FGP is applied at the rootform area of a bio-adaptable dental implant (See Fig. 10) provoking two levels of bone response: a macro-level,

and a micro-level. The latter relates to the reaction of bone cells to the micro-topology of the implant's surface. According to Hulbert et al. (1970), a 100 μm pore induces bone ingrowth, while a pore that is larger than 150 μm leads to an osteon formation. Work done by Simmons et al. (1999) discusses how mineralization rates are higher in porous surface when compared to a plasma sprayed texture, which is related to a favorable localized mechanical conditions in the pores. FEM analysis conducted by the same group (Simmons, et al., 2001) proves less severe volumetric and distortional tissue strains at the pores located at the interface of the implant, which provided favorable bone mineralization conditions according to Carter's tissue differentiation law (Carter, et al., 1998). Consequently, a porous surface contributes towards a biological union between the implant and the surrounding bone, leading to a longer lasting and stronger fixation. In fact, studies have shown that metal implants with a rough surface require a larger removal torque when compared to polished implants (Cohen, 1961).
The macro-level of bone response relates to the effect of osseointegration due to the stress induced in the bone. One main function of dental implant is to ensure the compressive bite-load transfer to the surrounding bone, which contributes to maintaining healthy bone levels in the jaw, in contrast to dentures which lead to alveolar ridge resorption. The optimal range of stress in the surrounding bone can be enforced by the development of FGP compliant to the loading conditions and the mechanical properties of the surrounding biomass.
Finally, one important function promoted by the bio-adaptable implant is the preservation of the stress pattern in the surrounding bone, due to the geometrical mimicking of the root of the initial dentition. This fact also reduces the need for orientation adjustments, due to the inert orientation provided by the socket, which otherwise would be calculated by the dentist and provided by a drill guide in the case of traditional implantation.

6. FEM as a design tool

Finite element method (FEM) is a numerical simulation which is used to solve problems in the physical domains of solid mechanics, heat transfer, fluid dynamics, and electromagnetism. Its main functioning deals with solving discretized equations that govern thermal, mechanical, and flow phenomena. During the 1970's, when FEM was initially introduced, it was mostly used in the aerospace industry. Since then, the fields of application have been drastically expanded.
Overviews provided by DeTolla et al. (2000) and Geng et al. (2001) discuss the application of FEM in the field of dental implantology. Compared to in-vivo and in-vitro testing, FEM provides a cost and time effective solution to predicting the clinical outcome of an implantation that is governed by specific variables. Extensive FEM work can be found in the literature that covers the effect of placement and inclination (Akça, et al., 2001; Canay, et al., 1996; Watanabe, et al., 2003), thread design (Eraslan, et al., 2010), implant dimensions (Himmlová, et al., 2004; İplikçioğlu, et al., 2002), occlusal loading position (Eskitascioglu, et al., 2004), and biomaterial (Stegaroiu, et al., 1998) on the surrounding biomasses and organs; i.e. jawbone, periodontal ligament, and neighboring dentition (Ishigaki, et al., 2003; Nagasao, et al., 2002; Nagasao, et al., 2003; Borchers, et al., 1983; Widera, et al., 1976; Akpinar, et al., 2000).
The main approach of implementing FEM into the design of a bio-adaptable dental implant, deals with tailoring the mechanical properties of different elements of the medical device, in order to comply with certain conditions and constraints that are imposed by the implantation. An example is displayed and discussed in the current section.

Fig. 11. FEM model, load, and constraints of a bio-adaptable dental implant

The schematic of Figure 11 displays a geometrical model that constitutes of a bio-adaptable dental implant with a solid rootform and elastic interface (See Figure 9) and the surrounding bio-elements; cortical bone, and cancellous bone. The bottom surface is constrained, while a vertical bite load is being applied on the implant. ANSYS® Workbench is used to solve for the stress and strain distribution along the geometrical domain. By employing the DesignXplorer® module provided by the software, the range of different outcomes can be evaluated, depending on user-set variable inputs. In this example the elasticity of the elastic layer is varied between 1-50 GPa, with a bite load ranging from 50-500 N. The plotted outcome is the maximum occlusal displacement of the crown, which related to the micromotion expected to be achieved by implementing AAD in a bio-adaptable dental implant. Figure 12 displays a 3D distribution of the micromotion vs. the two aforementioned inputs. As expected, a lower elasticity and higher bite load produce a higher level of micromotion in the occlusal direction. The range of micromotion that is produced by different combinations of inputs spans from 0.66 to 45.7 microns.
Referring to Table 1, a vertical initial movement of a natural tooth is 28 μm. By evaluating the patient's bite load range, an optimal elasticity of the elastic interface can be selected providing a range of micromotion analogous to that of a natural tooth.

7. Conclusion

The current chapter displayed a detailed description of the novel concept of bio-adaptable dental implants, and the expected clinical and functional advantages that it provides. It employs numerical information obtained from CT scans to produce an implant that provides maximum compliance to patient-specific geometrical and biomechanical constraints, while producing optimized functionality. Design aspects, such as FGP and AAD that display a local tailoring of mechanical properties, take full advantage of additive manufacturing's capability of producing parts with complex geometries. Potential advantages provided by the new concept include:

- Immediate restoration of function and esthetics
- Reduced treatment time
- No to minimally invasive site preparation

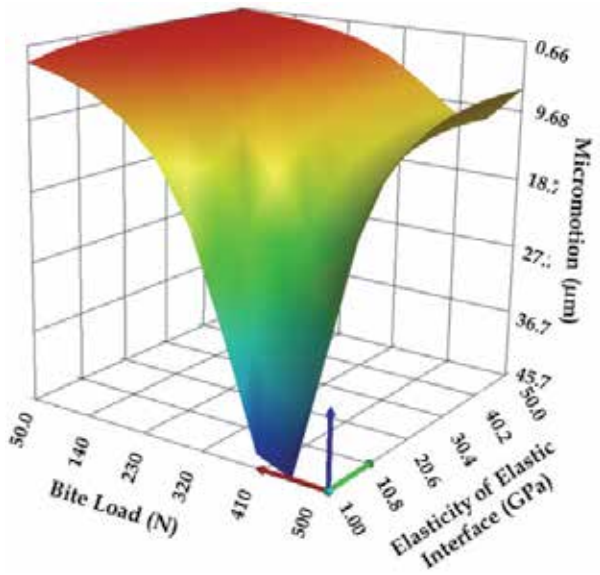

Fig. 12. DOE result of the maximum amount of occlusal micromotion produced by various levels of bite loads and elasticity of the elastic interface

- Better bite feel due to micromotion capabilities
- Enhanced bone response
- Improved patient satisfaction, and quality of life
- Reduced health care cost

The work portrayed discusses a new direction in implantology, where the implant matches the patient, instead of the contrary. This is only possible due to the advent of digital engineering, and the ability of producing customized medical device in a cost and time efficient manner, rendering it economically attractive.

Future work includes in-vivo testing of bio-adaptable dental implants, which depending on the preliminary findings might lead to clinical testing. In addition, with the progression in CT scan and additive manufacturing resolution, more defined features can be designed and produced, and compliance can be achieve at a higher degree.

8. Acknowledgements

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11

Dental Implant Imaging: How CT Scan Became a Help to Surgery

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1. Introduction

Imaging has always been an important part of dental implant procedures from its beginning.
Radiologists and dentists always worked together in the dental implant field, where imaging takes a major place. Year after year, their respective roles have changed, as we shall see further.
At the beginning, dentists performed imaging. Originally dental panoramic X-ray was prescribed for first screening checkup (Abrahams, 1990, 1993).
Of course the emergence of CT scan at the end of the seventies revolutionizes data collection (Bränemark, 1995, Albrektsson & Johansson, 2001), dentists had quickly understood dentascan's interest. They didn't have access to heavy medical imaging tools without radiologists. They lost the monopoly of imaging management.
These radiologists took place at the heart of radiation risk assessment, and played a major role in image generation and distribution. So collaboration between radiologists and dentists came out. Each actor's role was well-defined. Radiologist controls radiological source and imaging data management, dentist handles implant plan.
But development of dedicated software modifies habits. In fact it enables dentists recovery and utilization of imaging data. Radiologist sometimes becomes service provider, dentist managing by himself images and data.
More recently, in the last five years, a revolution is occurring with the availability of "cone beam" CT machines (Rouas et al., 2006, 2007) in dental offices and directly in dental surgery enables dentists to manage all the stages, from diagnosis, choice of imaging technique, generation and distribution of imaging data, implant planning, to surgical step. Nowadays radiologist takes place as a specialist in dental imaging, that pays attention to up-to-date and evolution of dental implant techniques.
After a fast reminder of the place of CT scan in dental implant diagnosis, this chapter takes an interest in imaging software, developed for surgical help.
The three principal softwares created for dental implant planification are called Simplant, Nobel Guide, and Robodent. They are mainly designed for surgical act.

2. Help to diagnosis (Cavézian et al., 2006)

2.1 Dental panoramic X-ray

This radiography shows at one sight lower and upper jawbone overall.
It's bringing to light missing teeth of course, but also radicular lesion, radicular granuloma, dental fillings extrusion, calcifications, demineralization, bone lesions, included tooth (Liu, 2006). It often shows maxillary canal. But this imaging does not allow dentist to take measurements, indeed it is a flat projection of curved surface. It is just a first screening checkup. However this technique is sufficient to reject implant plan because of substantial demineralization.

2.2 Denta-scanner

It is a very accurate method of jawbone's exploration. It enables dentists to obtain morphological analysis of implant site and bone structure. The initial acquisition gives millimetric slices in axial plan with high resolution. Acquisition volume is parallel to occlusal plan, which is located on a profil scout-view of the face (Muppararu, 2004).
Denta-scanner multiplanar reconstructions from axial millimetric acquisition observe perpendicular plan to maxillary or mandibular arch, but also follow panoramic plan (flat projection of curved surface) (Cazevian&Pasquet, 2008). They give different measurements as bone cortical thickness, and dental space (Cazevian et al., 1995, Chiarelli et al., 2010). There are some artifacts, caused by amalgam or metallic prosthesis.

2.3 Cone beam CT

It consists in a new device family using cone-shaped X-ray emission. It enables multiplanar reconstructions of dento-maxillary sphere (Hauret et al., 2009). The device includes X-ray source which emits cone-shaped beam with constant width. X-ray run through body to explore and finish the course on a flat detector (Hintze, 2007). This system generates a single 360 or 180 degrees rotational movement around the head of the patient. A short X-ray pulse is released each degree, giving 360 (or 180) images (Patel et al., 2007). Because of cone-shaped beam, the rotation of this complex is sufficient to give raw data, without patient's translation (Cazévian et al., 2006).
Several technical differences occur according to manufacturer:

- detection system,
- exploration field of view ,
- combination with panoramic X-ray,
- acquisition duration,
- voxel's size,
- metallic artifacts.

2.4 Purposes

The purpose of pre-implant check up to the present was to locate the implant site, to determine quantitatively and qualitatively the bone volume of implant place and to detect an anatomical obstacle. We only remind principles.
The quantitative evaluation of bone volume requires three measures and sizes:

- height to mandibular canal in mandibular level and to lower bone cortical of maxillary sinus or nasal cavity in maxillary level,

- width in vestibulo-lingual level,
- length in mesio-distal level.

Qualitative analysis of bone volume using:

- subjective specification : cortical thickness, alveolar bone density,
- objective specification: densitometry and different methods using Hounsfield unit measures, but at the present time no method is recognized (fig. 1).

The implant place has to be marked by axe and guide (fig. 2).

At last imaging has to look for anatomical obstacle restricting bone volume:

- in maxillary level: maxillary sinus or nasal cavity bottom, nasopalatine canal, dorsal palatal artery,
- in mandibulary level: above all mandibular canal,
- included tooth, tumor, inflammatory or infectious lesion.

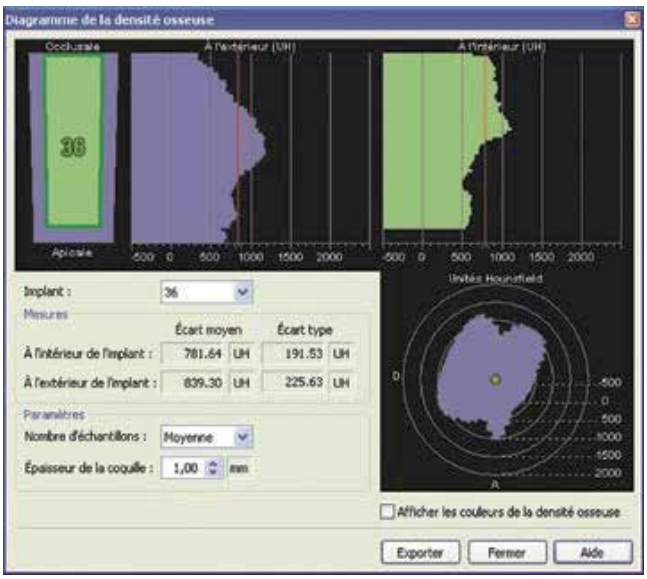

Fig. 1. Bone density around implant measurement according to Mirsch classification.

3. Help to surgery

Recent years much software for implant planification and navigation are developed. Meticulous protocol is needed to computered implant planning whichever software is choosen (Verstreken et al., 1996, 1998). The two principal softwares created for dental implant planification are called Simplant and Nobelguide, they are mainly designed for surgical act, and a work tool to show dental surgeon the way in implant installation called Robodent (Treil et al., 2009). These different examples should illustrate this topic.

3.1 Simplant

Study begins by making articulated models (Corcos, 2007). Then a wax setting simulates the final dental prosthesis and allows surgeon to visualize technical constraints. He visualizes imperatives implementation of implant prosthesis. Then the radiological guide derived from prosthetic model can be achieved (fig. 2). Either radio-opaque commercial false teeth are

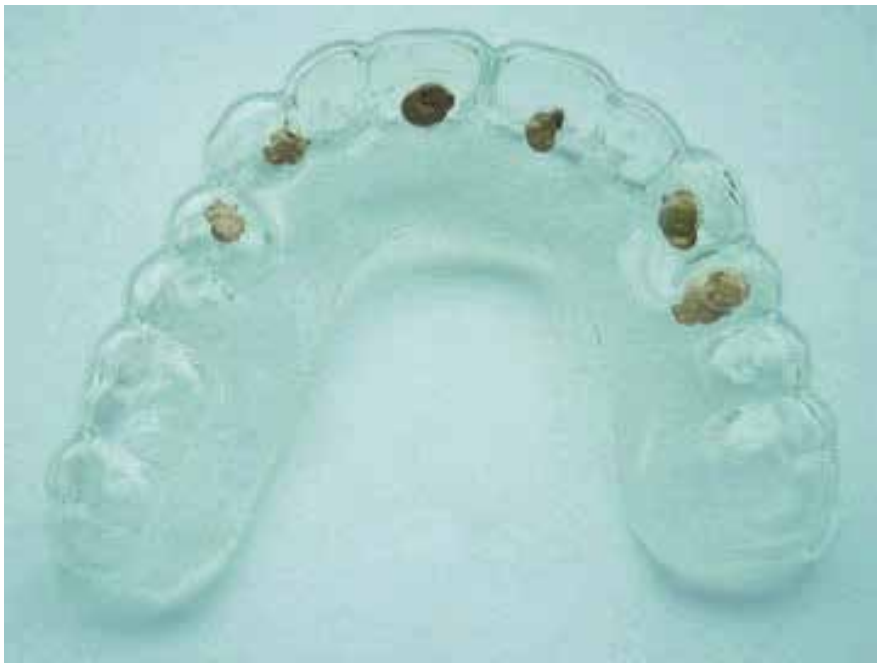

Fig. 2. Example of radiological guide with gutta percha radio-opaque spots.

inserted or baryum sulfate balls are included in wax (fig. 3 and 4). While different baryum sulfate concentrations are adjusted, we can precisely differentiate and individualize masks of different density. A cylindral cavity focused on occlusal tooth's side and emerging from cervical side makes the main tooth axis visible (fig. 4).

3.1.1 CT scan

Patients wear the radiological guide during the CT scan acquisition. Dental arches must not be in contact together, in order to make the CT scan data processing easily. Radiologist has to take care of:

- stability and well-positioning radiological guide, with control of accommodation or adjustment with mucous membrane,
- determination of axial plane that is parallel to the teeth occlusal area,
- visibility of teeth occlusal area, that has to be full visible.

3.1.2 Implant planification

Several points have to be controlled by dentist:

- check CT scan accuracy,
- location of axial emergence on incisal side or occlusal face,
- put the implant on a lateral view,
- set up guide anchor cotters,
- check on implants parallelism, confirmed on 3D view (fig. 3 and 4),
- check bone fenestrations,
- check on bone density,
- place an order of surgical guide.

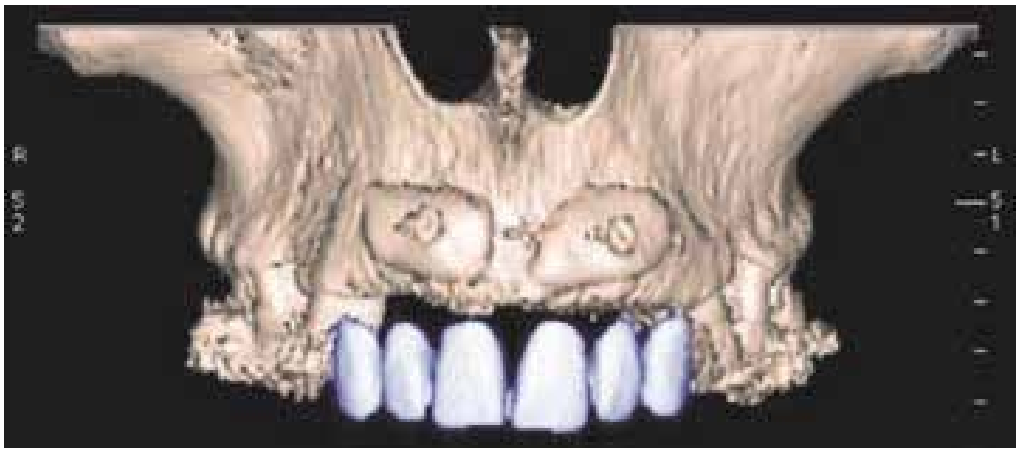

Fig. 3. Example of radiological guide with false teeth, on tridimensional reconstruction.

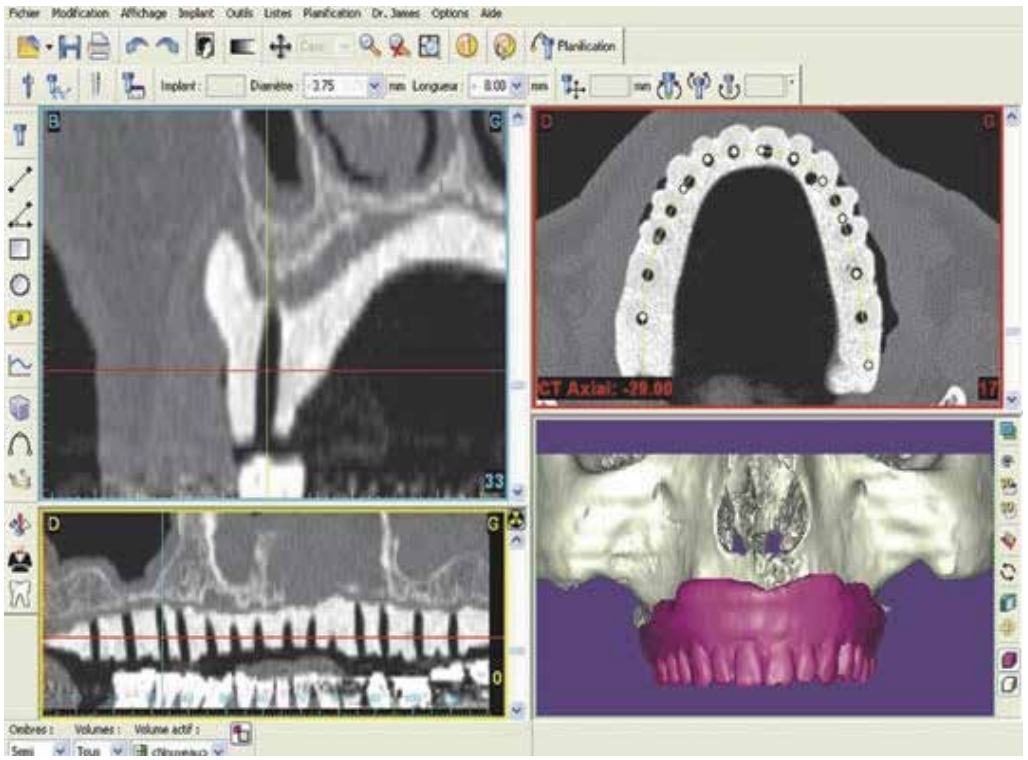

Fig. 4. Example of Simplant planification of upper jawbone.

3.1.3 Surgical time

Then after planification and dentist's control, time comes for surgical act.

The surgical guide is achieved by a stereo-lithographic system: a pure and initially clear wax hardens by laser action. This guide is aimed to laboratory technical expert, used to make a plaster model with implants duplication in order to fabricate temporary prosthesis.

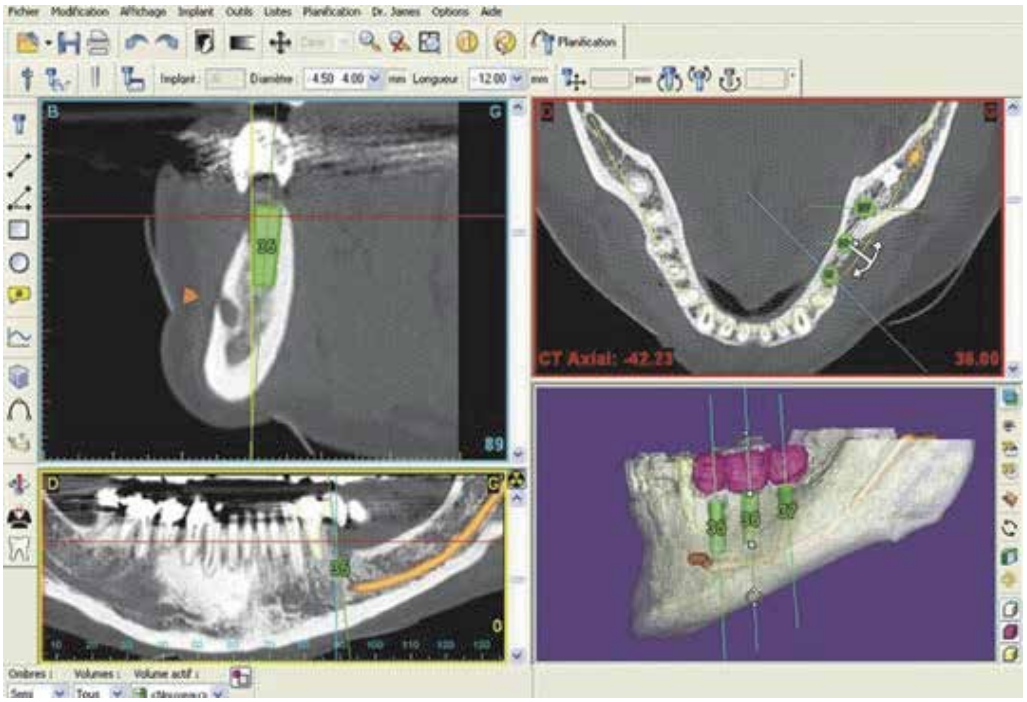

Fig. 5. Simplant planification. Implants simulation with implants parallelism.

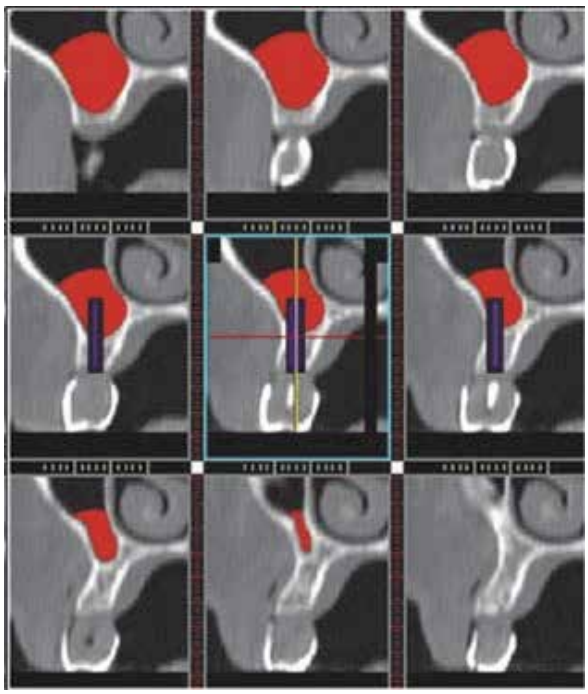

Fig. 6. Example of bone volume evaluation with implants simulation.

Simplant software allows surgeon to make a dental guide with bone or mucous support. That simplifies surgery, and enables surgery without incision reducing surgical length and post-operative complications.
Detailed precision with accuracy to within one millimeter is essential:

- maximal horizontal deviation to 0.6 mm,
- maximal vertical deviation to 0.9 mm,
- maximal angulation deviation to 6.1.

This technique allows immediate loading.
Simplant software enables dentist to mark anatomical pieces (fig. 5) and bone volume evaluation to "sinus lift" (fig. 6), choice among all existing implants, and choice of adjusted pillar.

3.2 Nobelguide

Nobelguide is the same concept as Simplant one, including five steps (Van Steenberghe et al., 2002, Vaida et al., 2007). This concept should be illustrated by an example, of this mandibule toothless man (fig. 7).

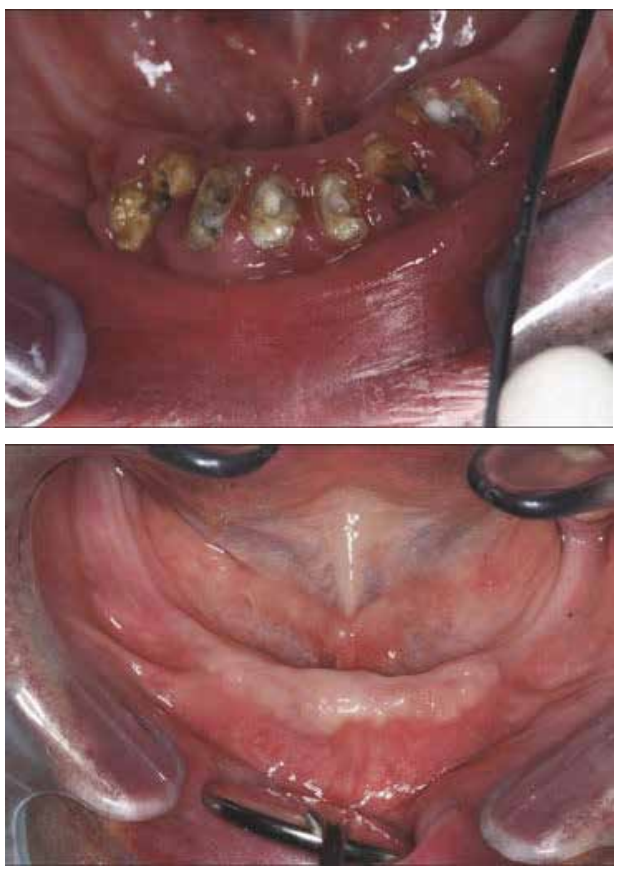

Fig. 7. Prosthesis plan NobelGuide in a toothless man mandibule
7-a: outstanding dental of tooth root
7-b: healing after dental extraction.

3.2.1 Temporary prosthesis

It is a very important step in planification, aesthetic assembly and occlusal plan are the same for the definitive prosthesis. Prosthesis efficient stability is very important and seeked throughout the procedure. This temporary prosthesis is mostly used as radiological guide. It is most often made in radio-transparent acrylic resin with eight to twelve balls of radio-opaque small-diameter gutta percha (1.5 mm) (fig. 8 and 9). These balls are placed on vestibular and lingual side of prosthesis on different occlusal plans.

Fig. 8. Temporary prosthesis made in radio-transparent acrylic resin with radio-opaque gutta percha balls.

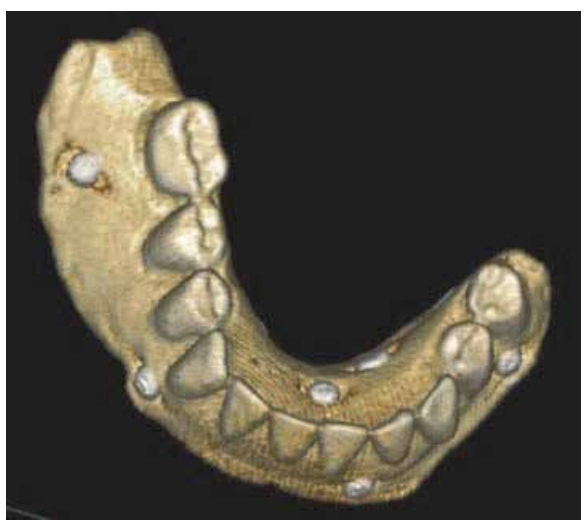

Fig. 9. Three dimensional CT scan reconstruction of temporary prosthesis with gutta percha balls.

3.2.2 Occlusal positioning index

Prosthesis should be well-positioned in mouth and above all stable. Its position compared to antagonist teeth is registered with a specific material for occlusal registration. This material must be rigid, radio-opaque or not (fig. 10) (for example polysiloxan vinyl).

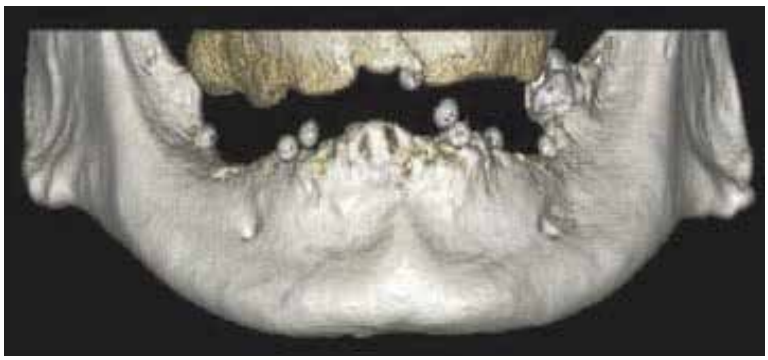

Fig. 10. Three dimensional reconstruction of radio-opaque positioning index between upper jawbone and temporary prosthesis.

3.2.3 CT scan

A double CT scan acquisition is needed to obtain a reliable account of bone on the one side and radiographic guide on the other side.

Gutta percha balls included on radiological guide are essential marks to merge accurately the two CT scans.

The first CT scan is acquired on patient bearing radiological guide stabilized and by occlusal index well-positioned. It brings to us important information about bone detail and gutta percha balls positioning through detailed data. The acquisition always follows parallelism of occlusal plan, covering lower or upper jawbone and part of antagonists teeth (fig. 11 and 12).

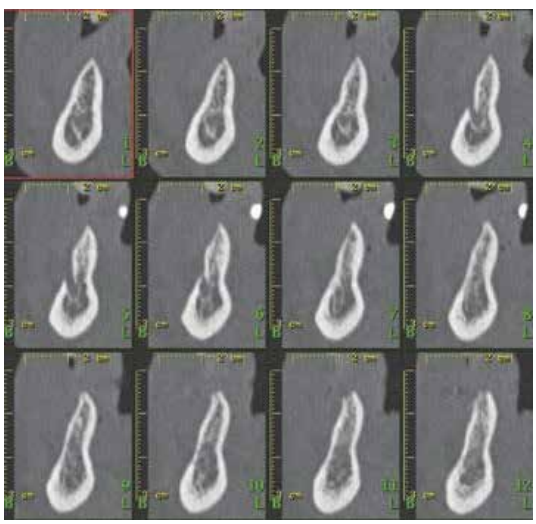

Fig. 11. Bone reconstruction as denta-scanner showing sharpened alveolar ridge.

Second CT scan is acquired with only radiologic guide, without occlusion. That gives very detailed informations about radiologic guide and gutta percha marks. This acquisition must be precisely realized in the same conditions as the previous one (fig. 9 and 13).

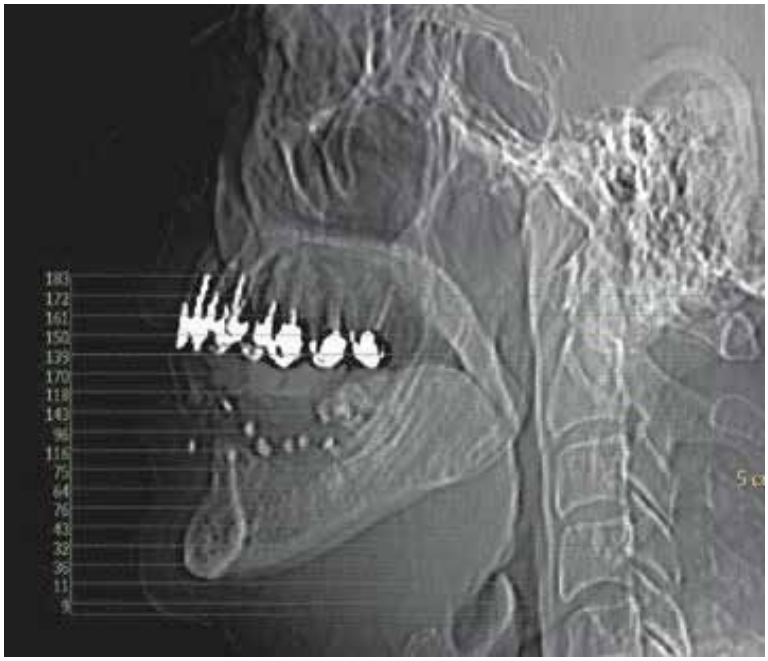

Fig. 12. Profil scout-view of the face and acquisition volume that is parallel to occlusal plan. Gutta percha balls are visible.

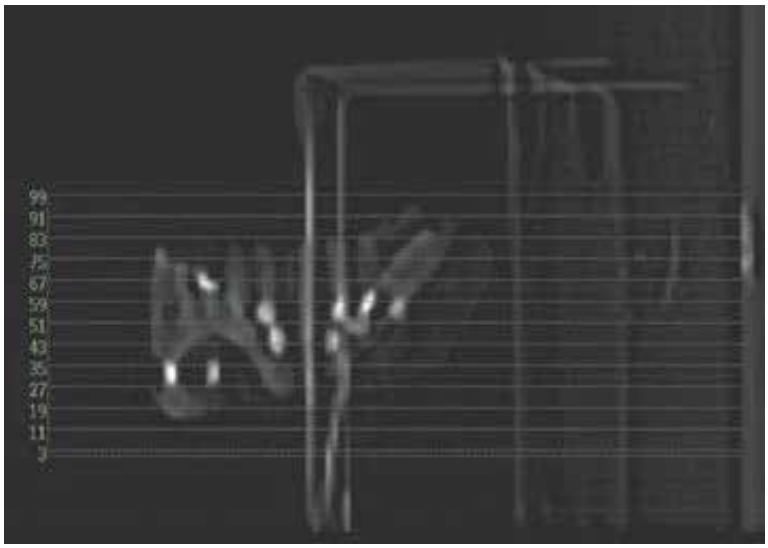

Fig. 13. Profil scout-view of temporary prosthesis in its stand. Same acquisition volume as patient CT scan.

3.2.4 Planification

Software enables practitioner to position radiologic guide on alveolar bone and as the same time to keep carefully a gap for mucous layer, and to position virtually dental implants (fig. 14 to 16).

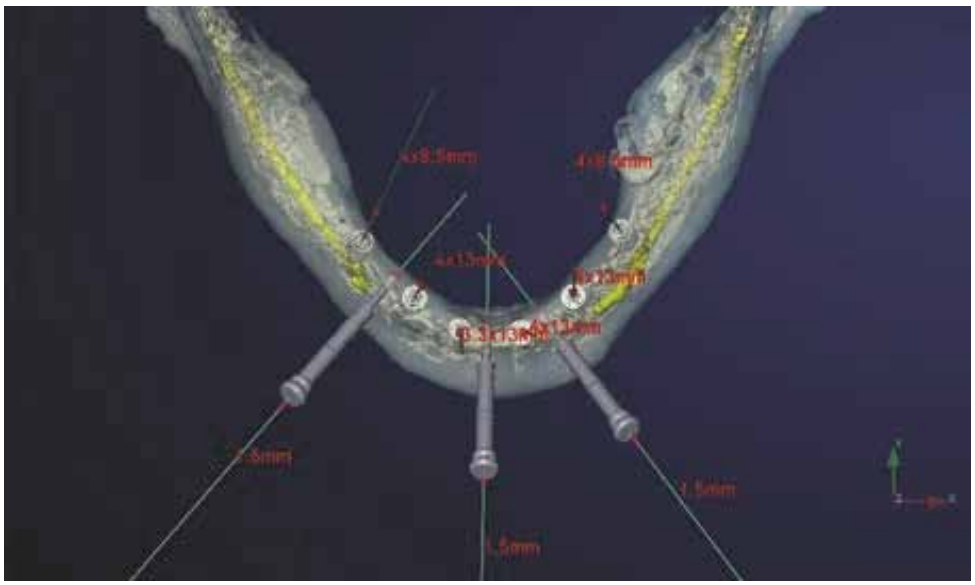

Fig. 14. 3D planification image of lower jawbone in axial incidence showing stabilization cotter and implants.

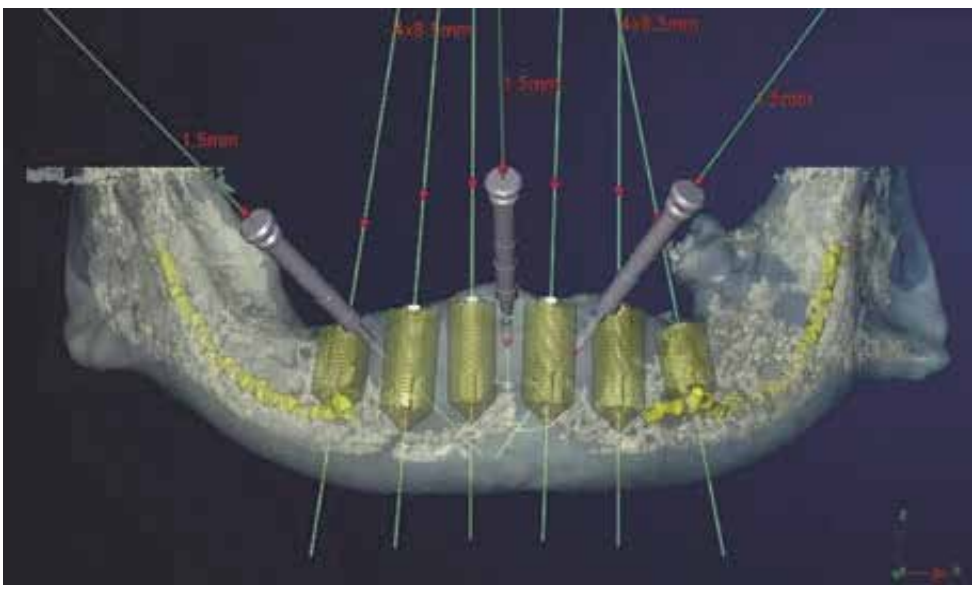

Fig. 15. 3D planification image of lower jawbone in frontal incidence showing stabilization cotter and implants.

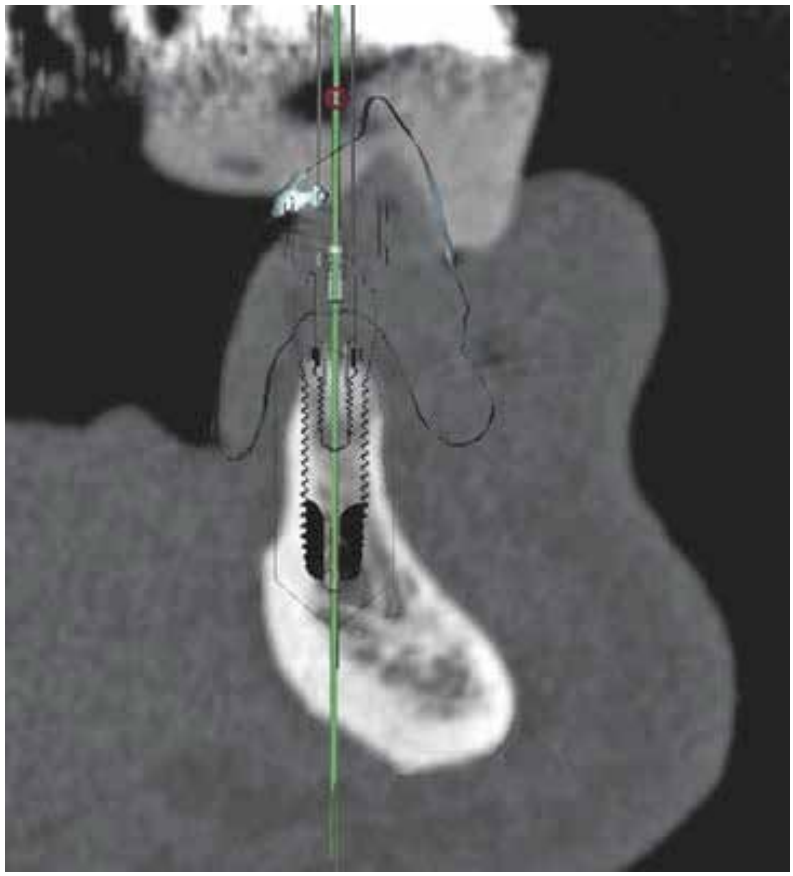

Fig. 16. Reconstruction as denta-scanner: positioning occlusal index, temporary prosthesis and mucous layer.

3.2.5 Surgical guide

Planification enables to manufacture surgical guide by scanner technique (fig. 17). It is radiological guide replica converted to allow drilling and setting up of implants. Surgical guide replaces toothprint for prosthesis laboratory, to cast the framework model.

Nobelguide concept helps to computerization of implants planification according to initial prosthetic project, to manufacturing of surgical guide and prosthesis before to put down implants. Surgical guide manufacturing should be provided at the same time as prosthesis conception. Guide conception and its stability guarantee a setting up corresponding to planification. Its initial stability when practitioner installs prosthesis in mouth depends on occlusion bite and cotter introduction in preoperative period (fig. 18 and 19). These cotters must go through surgical guide in vestibular region in wax extensions thick enough to avoid guide's wrist over drilling. Then these extensions must be apical enough so that cotters' shaft be horizontal, and to realize bone's insertion outside the anatomical hurdles.

Fig. 17. Occlusal view of surgical guide: drilling orifices, stabilization cotter and implants direction.

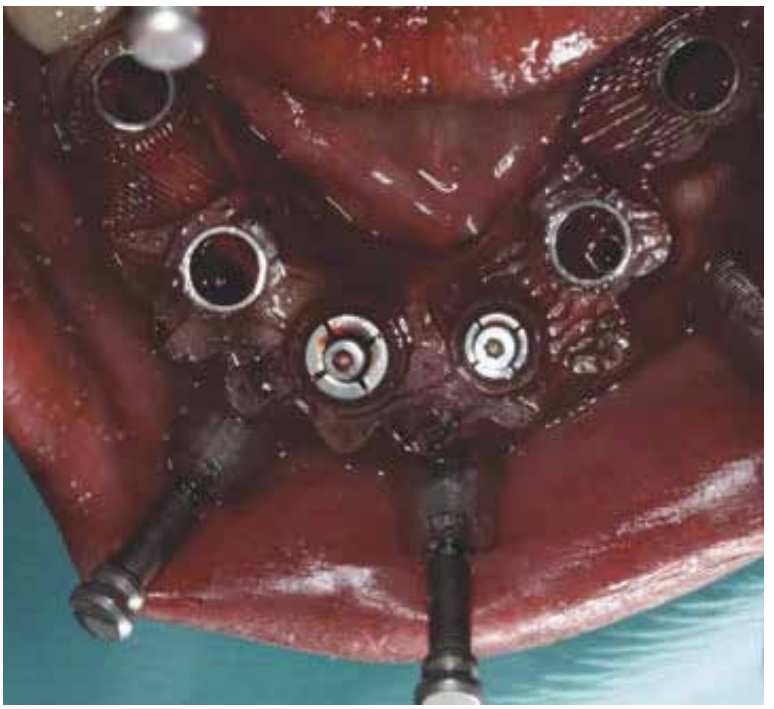

Fig. 18. Peroperative occlusal view with surgical guide and cotter, and firsts implants.

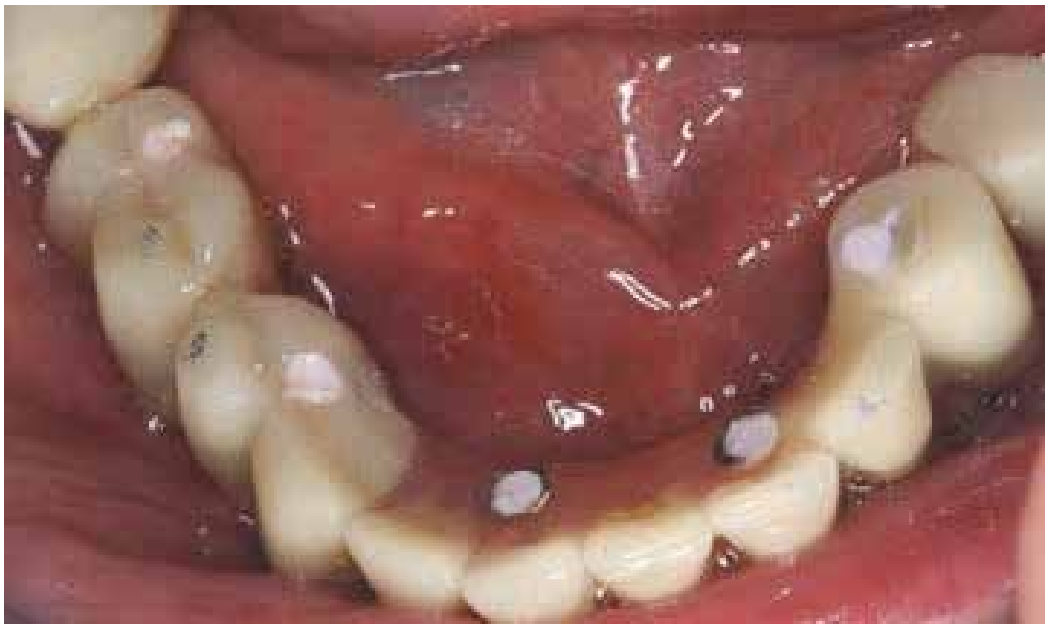

Fig. 19. Occlusal view at the end of surgical act, the prosthesis is putted down.

3.3 Robodent

Softwares such as Nobelguide or Simplant give way to undeniable surgical help, particularly for surgical step (Penel et al., 2007, Miller&Bier, 2006, Ewers, 2005, Casap, 2006). But it requires a rigourous procedure and laboratory time to transfer all the data of pre-implant check-up. New tools recently appear that leads surgeon's hand while implants installation, these tools are already used in neuro-surgery, maxilla-facial surgery and otorhinolaryngology. Softwares enable a real-time interface between pre-implant plan and rotating instrumentation for implant site.

In addition the surgical tool named Robodent is a navigational instrument. Surgeon can also follow the drills progress on line in comparison to contiguous anatomical structures.

It pilots the surgeon's hand while he drills the bone. Optical tracer is fixated on wax prosthesis, as well as on the drill. Then their motion is captured by a camera and worked out with three-way correlation. The more advanced systems use to optical tracers. Optical tracers, passive (ceramic balls) or active (LED) according to system (fig.20 a) secured with dental arch. Then their motion is captured by a camera and worked out with three-way correlation. It is a real-time tool to follow the drill in anatomical pieces (fig. 20 b).

Prosthetic analysis happens as usual. A diagnostic wax model is made for functional and aesthetic necessities. Radiological guide as a gutter, secured with facial arch contenting radiological marks is adapted to dental arch (fig. 21). This guide should serve as a support for location system in surgical navigation. The CT scan is acquired with this system on dental arch. A temporary removable prosthesis should be used for toothless jaw; it has to be secure and motionless meanwhile.

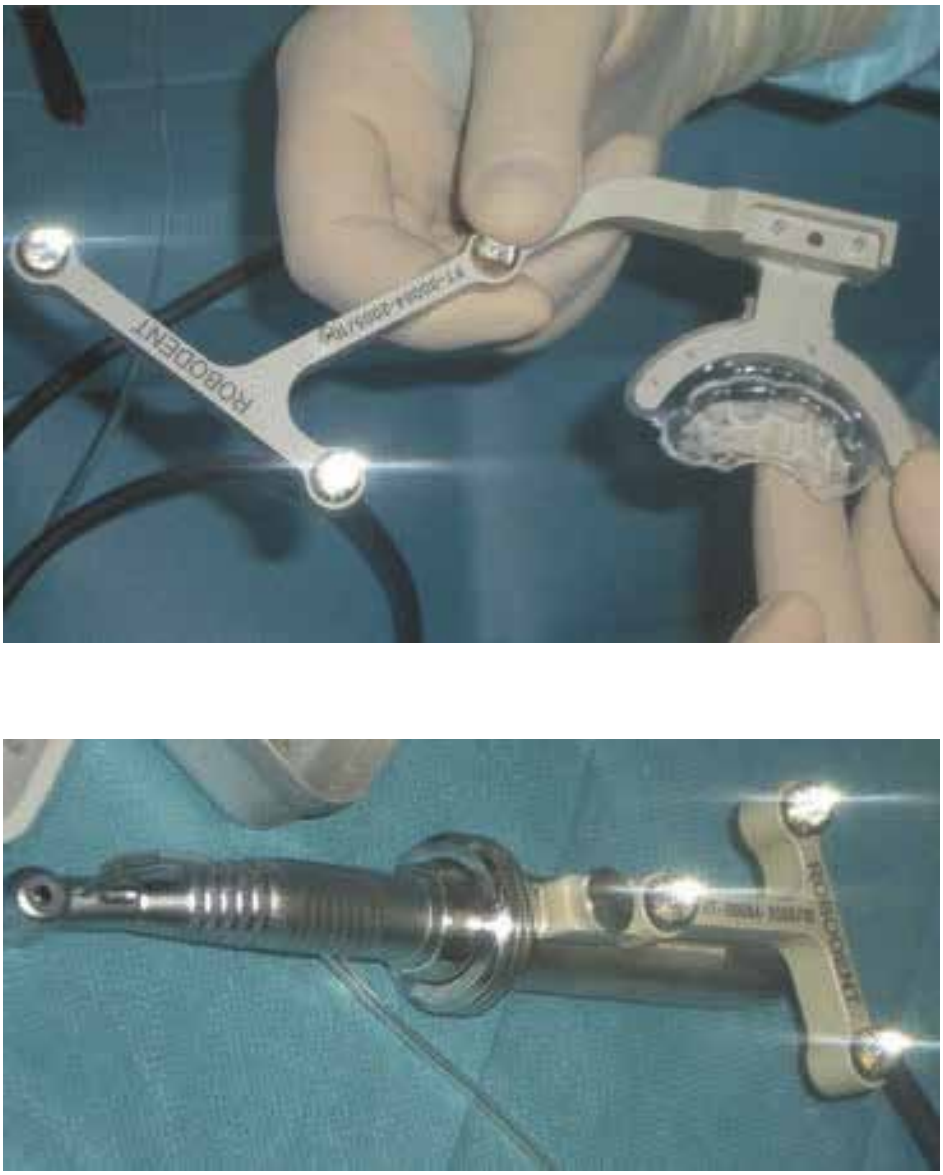

Fig. 20. a and b: Robodent: radiological guide and the extremity of drill present optical marks to give the spatial position.

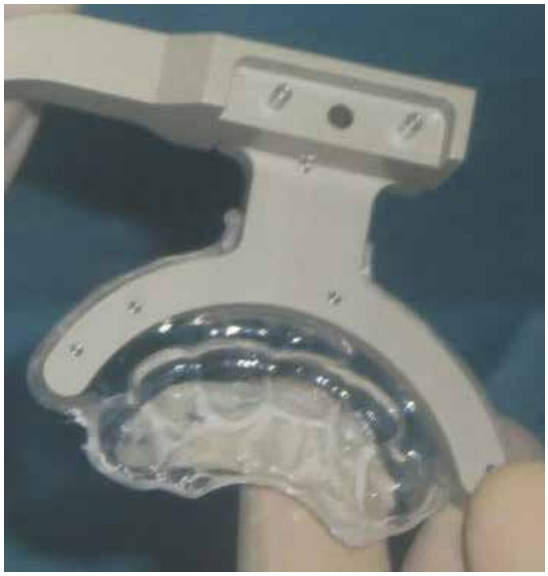

Fig. 21. Radiological guide secured with facial arch contenting radiological marks.

A CD is burned with CT images in DICOM format, given to dentist. He validates the choice of anatomic sites for implants with analyze and planification software (fig. 22).

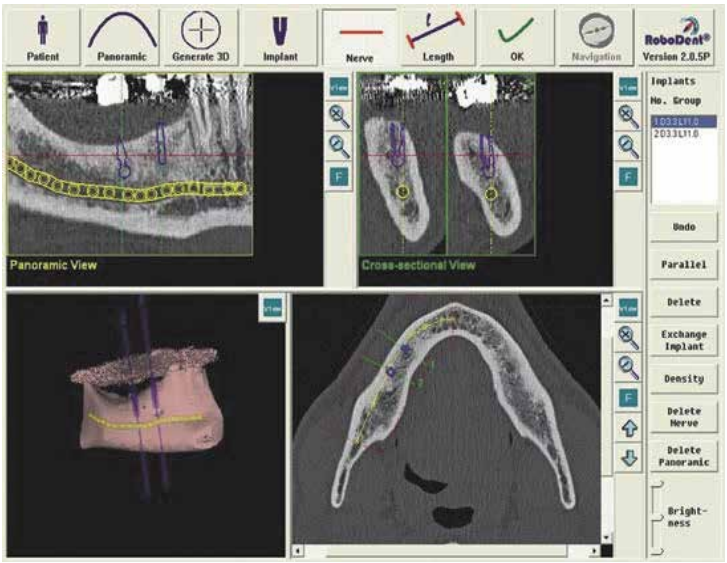

Fig. 22. Example of planification at upper jawbone level. 2D and 3D reconstructions as dentascanner. Implants simulations are made. Mandibular canal marked.

These accurate tools enable dentist to simulate whole implant plan. Two- or three-dimensional representations of implant make surgical plan easier. Furthermore this global approach enables patient to understand surgical act and to give enlightened consent. It represents a very good tool for communication with patient.

Surgical operation happens in a standard way, but surgical area and rotary instrumentation are adapted (fig. 23).

Fig. 23. The surgeon should adapt his surgical technique and controls the trajectory on the screen.

Patient's dental arch and drill carry marks, a camera check their spatial position in order to enable respective motion following. Computer calculates this position and transcribes drill coordinates in bone structures on the screen real time. Control device gives surgeons visual tracking with a sight and audible alarm (fig. 24). Sonorous alert gives constantly position control of shaft and drill depth. Accuracy and measures reliability are remarkable: 0.1 mm for linear deviation, 0.3° for angular deviation. However surgeon should acquire experience with guides' obstruction. He must also position himself to avoid crossing with optical follow-up.

Fig. 24. Control panel of point of impact and drill angulation, the drill is represented as a sight with audible alarm.

4. Conclusions

These technologies represent a real and very interesting progress.
As a conclusion, we can see that dental imaging has a major role in implant techniques, with noticeable precision and reliability in pre-implantal planification and surgical help.
If practitioner purely respects implant plan process, these technologies supply very accurate and repeatable data in user-friendly and intuitive environment. It gives security in surgical act by using positioning guides, also in drilling with drill-stop. It enables instant prosthesis' loading. Surgeon should focus on surgery accuracy and improve aesthetic and functional results. He should be able to increase aesthetic and functional results, broadening medical indications.
At present, these technologies are reserved to very experienced practitioners and surgeons and require a significant work to analyze each case and to prepare laboratory models.
At last, these systems bring competitive communication's tools for patient and prosthodontist. These tools are essential in diagnostic stage as well as surgical act. We see that dentists can manage all steps of the proceeding. What role can we assign to radiologist? What role can we assign to dentist? This problem is proper to every specialized medical field with imaging development. For radiologists, we stress upon the necessity of being attuned to these dental innovations.

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12

Computer-Guided Implantology

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1. Introduction

Anatomically planned and functionally optimal implant placement has long been a major goal of implant dentistry (Drago, 1994.; Garber & Belser, 1995). Many surgical procedures are necessary to the optimal placement of the implant. Thus, it would be of great clinical advantage for patients to have dental implants placed flapless and immediately loaded with prosthesis, delivered just after surgery. Post-operative morbidity and treatment times could be reduced significantly (Cannizzaro et al., 2008; Meloni et al., 2010). Thereby the growing interest for flapless surgery in conjunction with immediate loading of the edentulous patients has led to the development of software programs that allow treatment planning, fabrication of a surgical template, as well as the production of a prosthesis that can be secure to the patient immediately after the placement of the implants (Fuster-Torres et al., 2009).

However, the accurate diagnostic is the main factor for the treatment success. The edentulous patients generally have resorption when they loose their teeth.

The resorption can be related to bone loss and bone loss associated with the soft tissue. The type of resorption is decisive to determine the kind of fixed implant supported prosthesis. Patients who lost soft tissue and underlying supporting bone in addition to teeth may be considered to have a composite defect. To evaluate the relative amount of soft tissue deficiency, it is suggested to utilize a denture or denture set-up in wax that has been confirmed for proper tooth position, border extension, and relationship between the arcs (Bedrossian et al., 2008). So, an appropriate selection of the type of prosthesis is fundamental in the beginning of the treatment planing using implants.

There are two main objectives of computer-aided design (CAD), computer-aided machining (CAM): guided dental implant placement and restoration. The first allow the precise planning of implant positions on computed tomography scans, and the second is to generate an accurate surgical guide that permits the surgeon to place implants precisely into planned positions allowing the immediate prosthesis placement (Fuster-Torres et al., 2003).

Thus the objective of this chapter is to discuss the indications, contraindications, protocol preparation, maintenance problems and postoperative-guided in implantology.

2. Guided surgery

The use of software associated with digital images, acquired from computerized tomography, it is a new trend in dentistry. The CAD/CAM technologies associated with stereolithography provide to the professional tools to improve the planning and the rehabilitation with more security.

The use of software combined with three-dimensional images obtained by computerized tomography enables the professional to evaluate the optical density, to measure the bone thickness and, therefore, to choose the implant size and its appropriate positioning in the arch (Spin-Neto et al. 2011).

The guided surgery is a highly accurate in implantology. By this technique, the extensive amount of information obtained in a virtual planning is transferred for the surgical field by means of surgical guides manufactured in stereolithography (Parel & Triplett, 2004). Later, the advantages and limitation of the surgical guide will be discuss.

2.1 Indications

The guided surgery is indicated both for total edentulous patients (Casap et al., 2005 ;Van Steenberghe et al., 2004) as for partially edentulous patients (Fortin et al. 2003; Kupeyan et al., 2006; Marchack, 2007; Serry et al., 2007).

The guided surgery is counter-indicated for patients with reduced mouth opening that jeopardizes positioning of surgical instruments on the guide (Almeida et al., 2010).

This technique has several advantages compared to the conventional open flap surgery. These are the preservation of the vital anatomical structures, minimal invasive surgery, faster and simpler technique and leads to less discomfort to the patient after the surgery (Kupeyan et al., 2006; Van Steenberghe et al., 2004; Becker et al., 2005; Widmann et al., 2010) as well as lower risk of infection. However, due to the use of a range of sophisticated technology and specialized instrumentals, the guided surgery technique has a higher cost compared to the conventional surgery. In addition, some authors reports that the surgical guide can be unstable for completely edentulous patient mainly when only remaining soft tissue is present. (Bedrossian, 2007; Holst et al., 2004).

2.2 Technique

Before the tomography, some steps are necessary to assist the planning, as a specific clinical exam. In this session, it is important to evaluate the existing prosthesis of the patient, relationship between the arches, the dental oclusal pattern and the inter maxillary distance. An initial clinical exam is accomplished to evaluate the relationship among the arches, the oclusal pattern and the inter maxillary distance.

For the total edentulous patients, it is fabricated the total prosthesis with appropriate vertical dimension of occlusion (Figure 1). After that, the prosthesis should be duplicated to facilitate the tomography guide construction. To associate the edentulous arches to the tomographic guide at the software the radiopaque marks of barium sulfate are made in the guide near the canine or molar region (Figure 2). The relationship of the maxillary and mandibular arches is registered using condensation silicone.

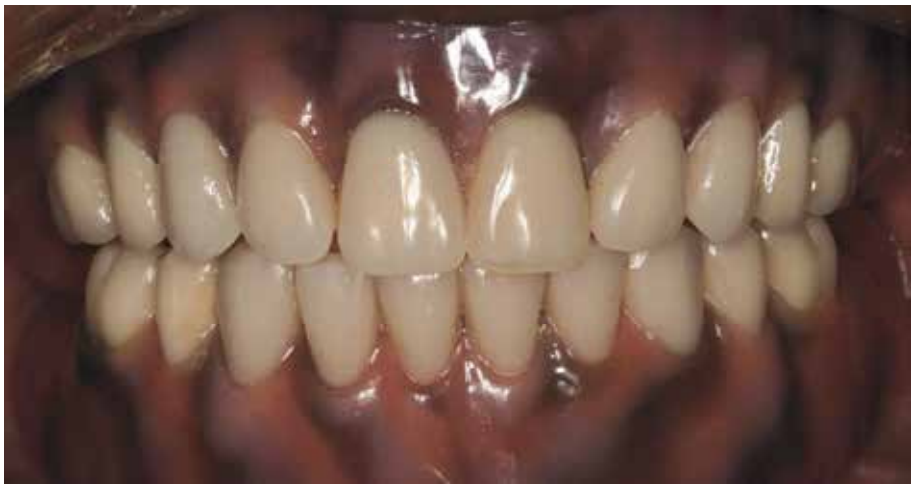

Fig. 1. Total prosthesis with appropriate vertical dimension of occlusion.

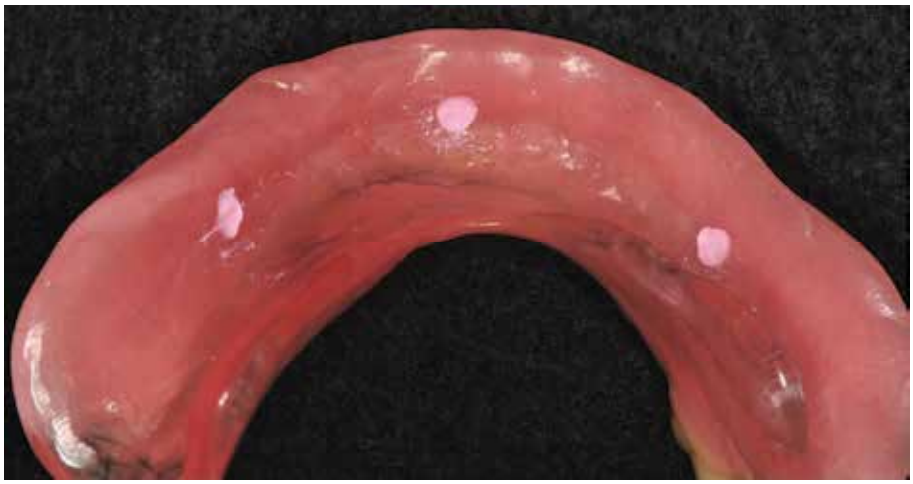

Fig. 2. Tomographic guide with radiopaque marks.

Virtual planning:

The virtual planning has two steps in the computed tomography (CT): the double scanning technique of the patient (Widmann et al., 2007) with both tomographic guide in position and the CT of the guide alone to superimpose the images later in the software. During the CT the complete denture should have adequate positioning in relation to the antagonist arch and the anatomy of the soft tissues. The patient can be asked to use an adhesive to improve stabilization of the denture during the scanning (Almeida et al., 2010). Afterwards, the CT is transformed in 3D images with DICOM extension. It is necessary conversion to a planning guide software, as DentalSlice® (Bioparts, prototipagem biomédica, São Paulo, Brazil).

At this moment, the virtual planning can be made into the software by the prosthodontics and surgery professionals. They can choose the best three-dimensional position of each

implant based in the quantity and quality of bone and at emergence profile of the artificial teeth represented by the image of the guide. Wherever possible, it is recommended to plan the posterior implant more distant to the anterior in order to reduce the cantilever. (Figure 3).

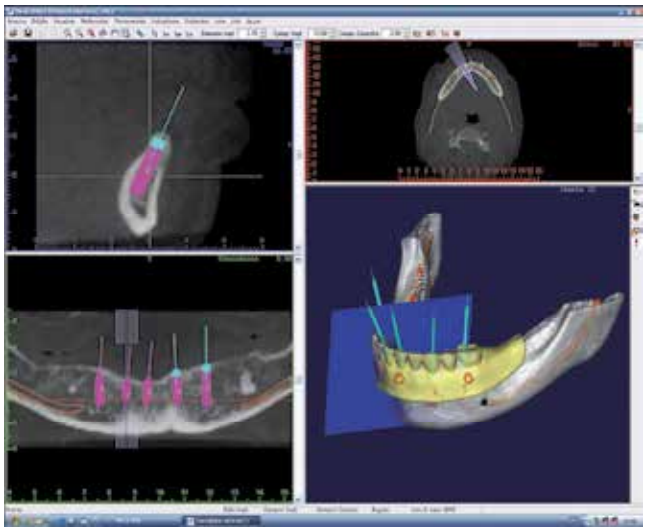

Fig. 3. Virtual planning of the surgery in the DentalSlice Software (Bioparts, Brazil).

Technique description:

After the prototyping and the guide confection, the guide is tested to verify the adequate position to the edentulous area and the dental position. The guide should touch the edentulous area being passive and avoiding ischemic areas (Figure 4).

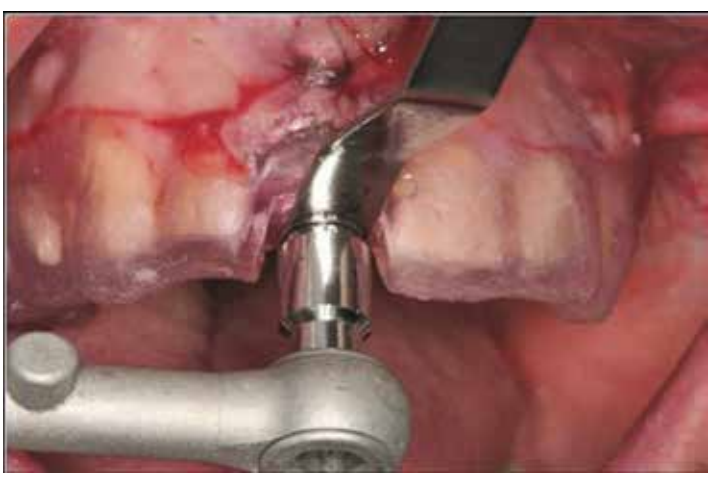

Fig. 4. Surgical guide for partially edentulous patient.

The drill guide inside the guide is important to assist the direction of the surgical drill during perforation to avoid lateral deviations (Valente et al., 2009) (Figure 5).
The guides should be sterilized according to the manufacturer indications.

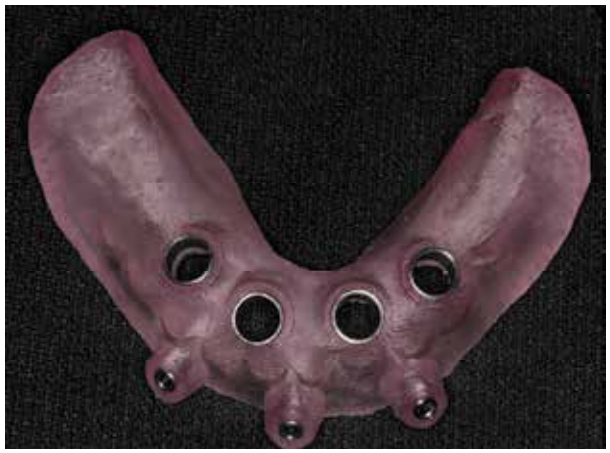

Fig. 5. Mandible surgical guide.

At the moment of the surgery, the first step is the distant local anesthesia because the region can develop edema areas and prevent the guide adaptation.
Later, the guide is stabilized at the planned dental occlusion using the silicone and the retaining pins are screwed at the buccal region to stabilize the guide in the correct position (Figure 6).

Fig. 6. Surgical guide stabilization at the planned dental occlusion.

Afterwards, the mucous membrane can be removed bellow the drill guide by punch (Figure 7). The perforations should respect the progressive sequence of drills with their guides corresponding to the diameter of the drill to be used (Slice-guide, Conexão Sistema de Prótese Ltda, Arujá, SP).
The sequence of drill was used with its respective guide with intermittent movement and abundant irrigation to avoid heating of the bone tissue. The speed of the drill can vary from 400 to 800 rpm, depending on the bone quality. The long length of the drill is a limitation of this technique for reduced mouth opening.
After the drill perforations, it is recommended to start the installation of the implants by the intermediary positions ones to avoid the guide displacement (Figure 8).

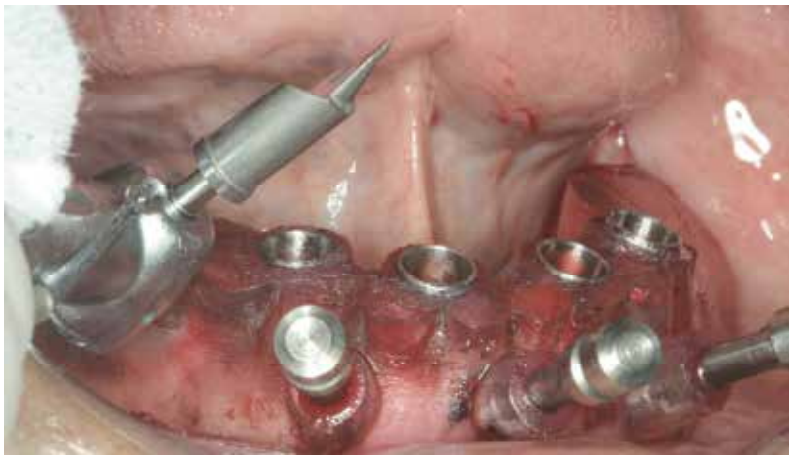

Fig. 7. Punch used to remove the mucous membrane bellow the drill guide.

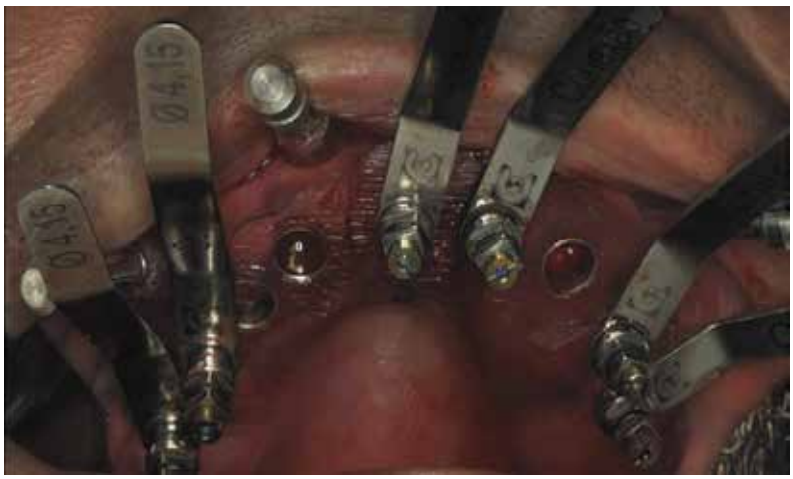

Fig. 8. Placement of implants.

When the last implant is installed, all screws and the palate fixation are removed together with the guide (Figure 9).
For the placement of an immediate prosthesis, all implants should have an appropriate primary stability, in other words, an initial torque around 40N.cm.
There are two options for prosthesis confection: prosthesis fabricated before the implants installation surgery or prosthesis fabricated after the surgery.

2.3 Manufacturing of the prosthesis

Prosthesis fabricated after the guided surgery:

Firstly, the impression cooping are attached to the implant and the surgical guide is positioned (Figure 10). Thereafter, the impression cooping are conected with auto polimerized resin (Pattern Resin LS; GC America, Alsip, Ill) to record the implant position (Figure 11).

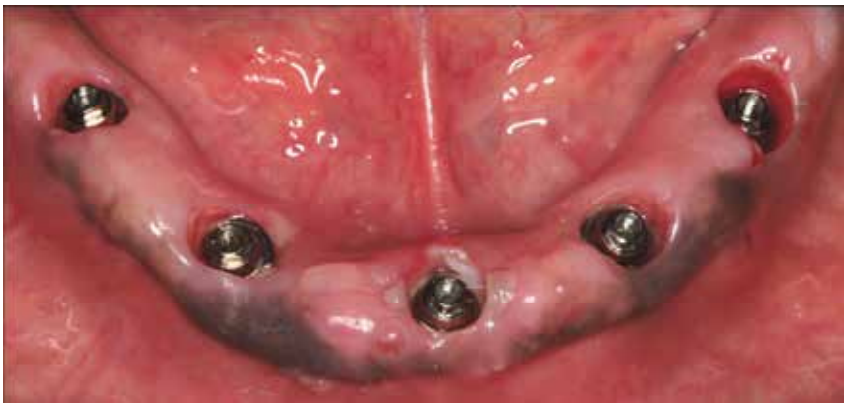

Fig. 9. Final aspect of the soft tissue after the surgical guide been removed.

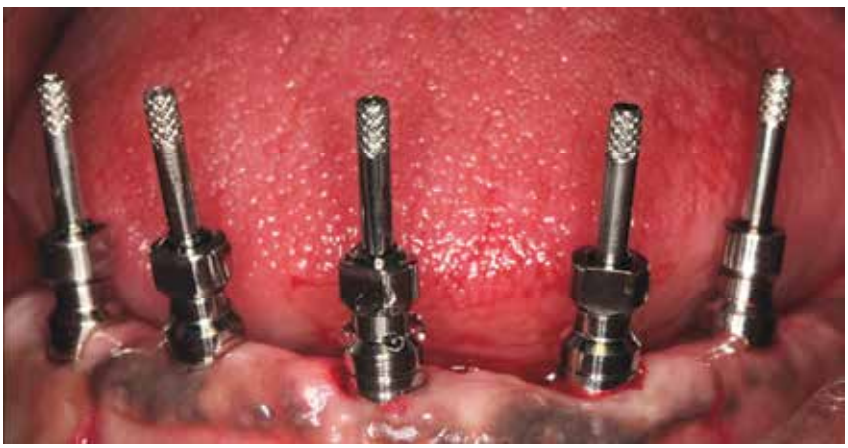

Fig. 10. Impression cooping attached at the implants.

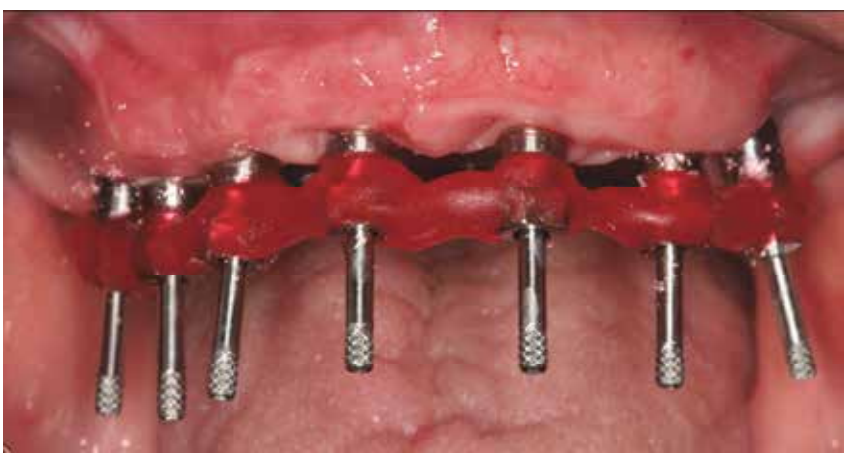

Fig. 11. Impression cooping connected with autopolymerized acrylic resin (Patter Resin LS) to record the implant position

Impression cooping are carried out in both arches using the same surgical guide and condensation silicone (Zetaplus/Oranwash; Zhermack, Rovigo, Italy) (Figure 12). Then, the analogs are attached to the transfer copings before dental stone pouring. In laboratorial phase, the implant superstructure and the teeth in wax are positioned on a base of light-polymerized resin on the working cast (Margonar et al., 2010a). The implant superstructure is attached to the implant to verify the passive fit (Figure 13). Later, the teeth in wax on the base of light-polymerized resin are tested on the superstructure (Sterngold ImplaMed, São Paulo, Brazil) during the same clinical session (Margonar et al., 2010a) (Figure 14).
On the second day, the immediate implant-supported fixed dentures are inserted and the occlusion is evaluated in order to favor the force distribution (Figure 15). The appropriate three-dimensional positioning of the implants was verified by panoramic radiography and computed tomography and that can preview the success of the treatment (Figure 16 and 17).

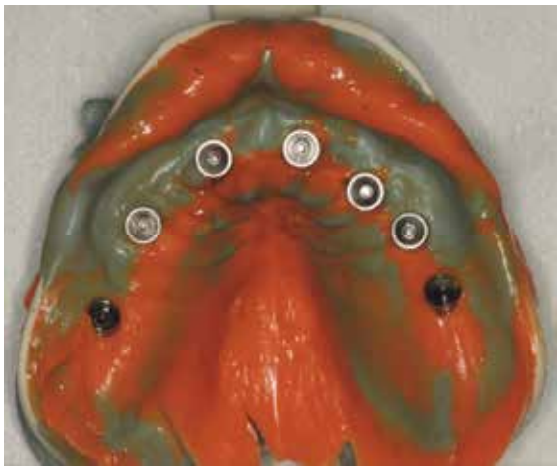

Fig. 12. Mold obtained.

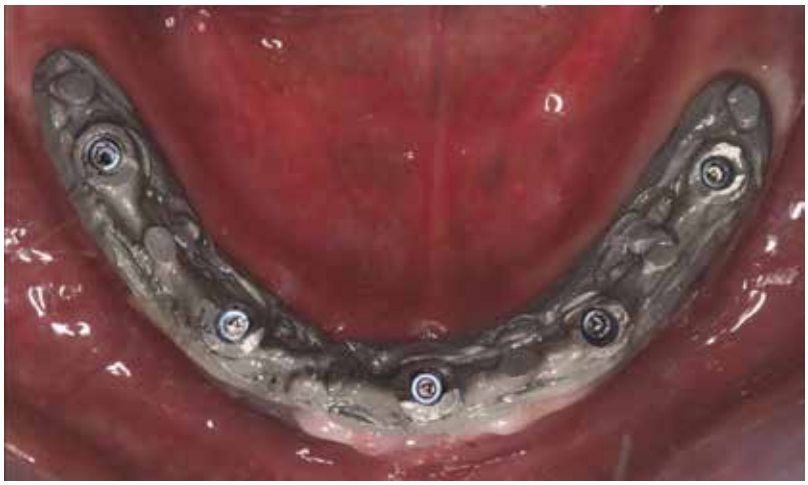

Fig. 13. The implant superstructure attached to the implant to verify the passive fit.

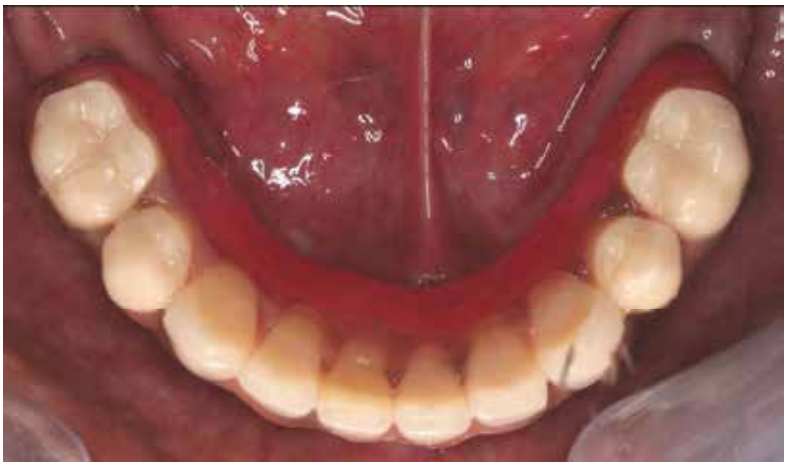

Fig. 14. Teeth in wax on the light-polymerized resin plate.

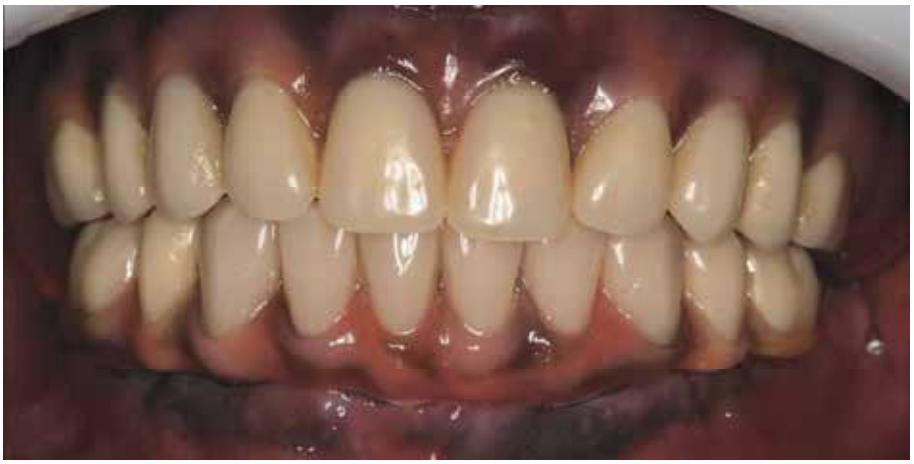

Fig. 15. Final view of the immediate implant-supported fixed denture installed.

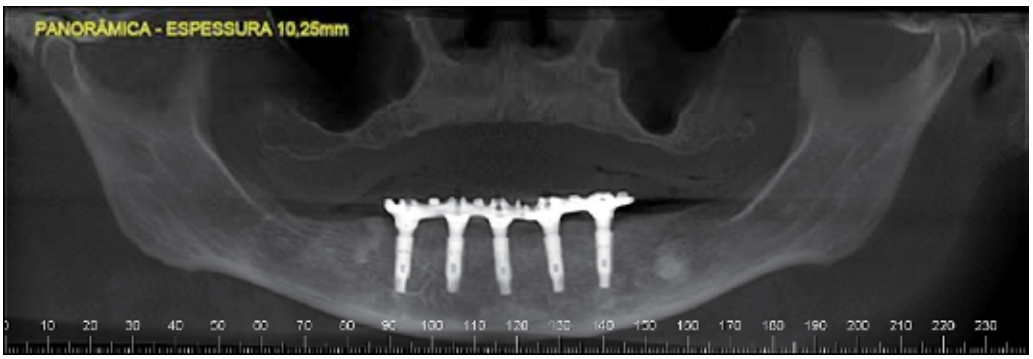

Fig. 16. Panoramic radiography showing the appropriate positioning of the implants.

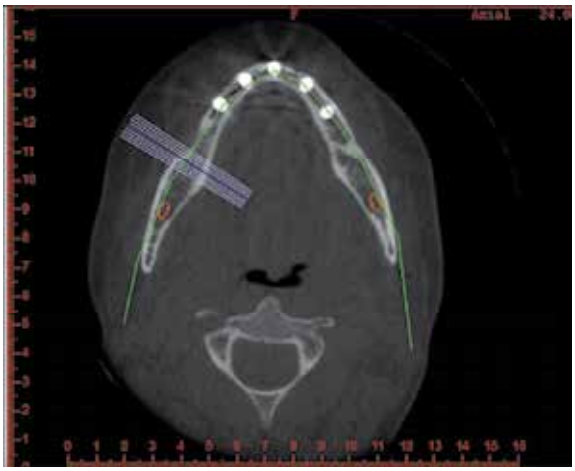

Fig. 17. Computed tomography showing the appropriate three-dimensional positioning of the implants.

Prosthesis fabricated before the guided surgery:

Some techniques have been cited in the literature for the fabrication of prosthesis before the guided surgery. These techniques use the passive cementation. One of them uses the Nobel Biocare system. In this technique the surgical guide is used to make a master model, the abutments are selected, and then the titanium cylinders are placed onto the abutments for the bridge manufacture, that is immediately secured to the implants, installed by the guided surgery (Bedrossian et al., 2008).
Another technique is the technique of the cemented cylinder (Siirilä et al. 1988; López, 1995). In this technique the components installation in the mouth is done after the guided surgery. They are selected previously with torque from 20 to 32N.cm. It is accomplished the molding of the components for the fabrication of an index. And it is made the cementation of the cylinders inside the prosthesis in agreement with the index. Then, it is made the cementation of the prosthesis in the mouth (Siirilä et al. 1988; López, 1995).

2.3 Complications

The complications in guided surgery can be divided in early complications and late complications:
Early complications: lack of primary stability (Yong & Moy, 2008), loosening of prosthesis screw (Young & Moy, 2008), slight genial tumefaction (Gillot et al., 2010), difficulty in speech and bilateral cheek occlusion (Young & Moy, 2008), jugal hematoma (Gillot et al., 2010) and heating of tissues (Figure 18).
Margonar et al., 2010b, evaluated bone tissue heating and the wear drills after repeated osteotomies for implants, simulating the guided surgery technique and comparing it with the classical technique. According to that study, the heating of the bone tissue due to the guide surgery technique was higher when compared with the conventional open flap surgery during the preparation of the surgical site, but both techniques have not reached the threshold temperature that causes immediate necrosis.
Late complications: persistent pain (Gillot et al., 2010), gingival recession (Yong & Mo, 2008), osseointegration loss (Yong & Moy, 2008). The success rate ranges from 83 to 100% (Canizzaro et al., 2008; Komiyama et al., 2008; Schneider et al., 2009; Van Steenberghe et al., 2005).

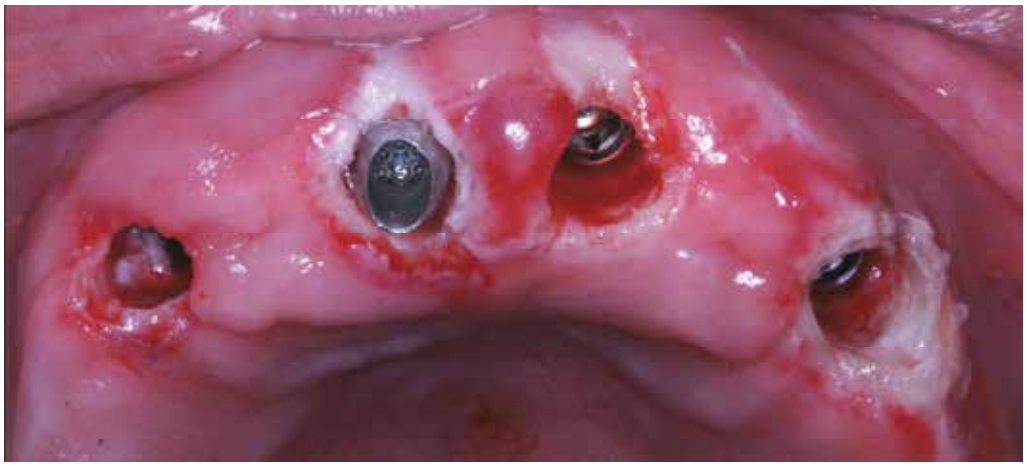

Fig. 18. Soft tissue with necrotic aspect due to heating in the region.

2.4 Mistakes in guided surgery

The computer-guided surgery has a sequence from the diagnostic stage to the prosthetic, and mistakes may occur in different stages. The most common mistakes found in the literature are as follows:

1. Mistake on acquisition of tomographic image or incorrect processing (mean of error <0.5 mm) (Reddy et al., 1994; Valent et al., 2009).
2. Deviation of 0.1 a 0.2 mm on fabrication of the surgical guide (Valent et al., 2009; Van Steenberghe et al., 2002.)
3. Inaccurate fixation of the guide resulting in displacement during perforation (Valent et al., 2009).
4. Mechanical errors caused by angulation of the drills during perforation that may cause lateral deviations (Valent et al., 2009).
5. Changed positioning of surgical instruments due to reduced mouth opening (Valent et al., 2009).
6. Human mistakes as not using the whole length of the drill during perforation (Valent et al., 2009).

3. Conclusion

The guided surgery is an excellent option of treatment for patients with satisfactory bone quantity for implant insertion. The guided surgery can be indicated for complete and partially edentulous arches in the maxilla and/or mandible.

When properly prescribed and monitoring, the virtual planning and the guide surgery are excellent tools used in implantology to perform surgical procedures with more safety, confort and predictability to the patient.

4. Acknowledgment

The authors gratefully acknowledge "Conexão Sistemas de Próteses Ltda" for supplying the implants, "DVI: Diagnóstico Volumétrico por Imagem" for providing the tomographies and "BIOPARTS: prototipagem biomédica" for supplying prototyping used in this study.

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13

Intuitive Surgical Navigation System for Dental Implantology by Using Retinal Imaging Display

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1. Introduction

As dental implants have become an established treatment, their application to aggressive cases with insufficient quantity and quality of bone has increased. To perform safe and precise surgery, overcoming these difficulties, computer-assisted systems have been developed (Jabero et al., 2006). There are two major classes of these systems, that is, a computer-guided (static) system (Schneider et al., 2009) and a computer-navigated (dynamic) system (Jung et al., 2009). The computer-guided system such as SimPlant software and SurgiGuide (Materialize Dental Inc., USA), NobelGuide (Nobel Biocare Management AG, Sweden), and 10DR (10DR JAPAN Co., Ltd., Japan) are a surgical template based system which can simulate an optimal implant location, angle, direction, depth and size pre-operatively. Our system, BoneNavi (Bionic Inc., Japan), has also been developed to simulate implant placement and the surgical template fabrication for dental implant surgery (Ohtani et al., 2009) and applied in more than 200 clinical cases in Japan (Sohmura et al., 2009). On the other hand, the computer-navigated system such as IGI system (Image Navigation Ltd., USA) offers freehand implant navigation empowered by highly accurate motion tracking technology that tracks the positions of the dental drill and patient throughout the surgery (Casap et al., 2004). It has also already been applied in clinical cases (Casap et al., 2005 & 2008). Advantages and disadvantages of the computer-guided system and the computer-navigated system are shown in Table 1.

Unlike an open chest surgery and an open abdominal surgery, looking away from the oral cavity (narrow space (Fig.1)) intra-operatively involve a risk of operation errors in case of a dental implant surgery. However, with conventional systems, surgeons have to manipulate instruments in the patient's oral cavity while watching a surgical monitor as shown in Fig.2(a) and they feel anxious during operations.

To overcome this problem, we have been developed a novel surgical navigation system by combining the retinal imaging display (RID) and the augmented reality (AR) techniques

	Advantages	Disadvantages
Computer-guided system	General familiarity High degree of precision	Difficulties in cases of poor edentulous ridge form or loose teeth
Computer-navigated system	Modifiable surgical plan intra-operatively	Complications and difficulties for mounting markers on patiens or hand-piece

Table 1. Comparison between advantages and disadvantages of the computer-guided system and the computer-navigated system

(Azuma, 1997) that can directly overlay pre-operative simulation images onto the real view of the surgeon (Yamaguchi et al., 2009) as shown in Fig. 2 (b). In the last few decades, AR techniques have been applied in wide areas such as medical treatment (Peters et al., 2006) and education (Dede, 2009; Thomas, 2010). Moreover, various possibilities are still expected (Buxton et al., 2008). However, only few attempts have so far been made at an application in dentistry (Birkfellner et al., 1999) because of challenging field by means of image registration accuracy. It is because I believe that our system lead to progress in future dentistry that I have written this chapter.

Fig. 1. Scene of dental implant surgical operation in narrow space of patient's oral cavity

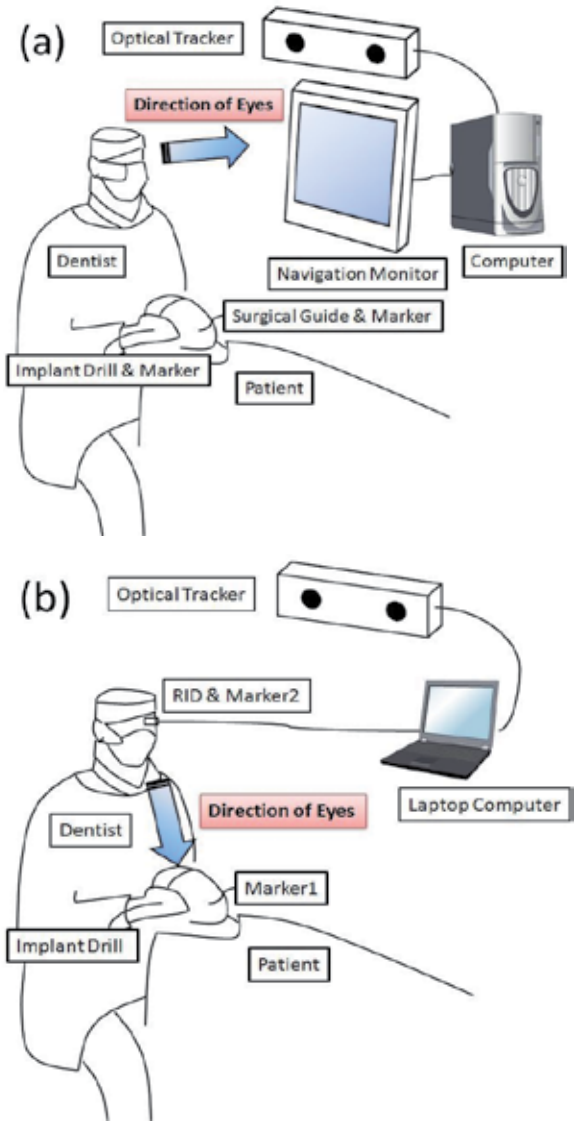

Fig. 2. Schematic illustrations of a surgical navigation system for dental implantology. (a) Conventional approach: A direction of eyes of a dentist is directed to a navigation monitor. (b) Our approach: The direction of eyes of the dentist is directed to an oral cavity of a patient.

2. Materials and methods

2.1 System configurations

As shown in Fig. 3 system configurations, our system consists of a retinal imaging display (Prototype of RID (RID), Brother Industries, Ltd., Japan), an optical tracker (Micron Tracker 2 Sx60 (MT2), Claron Technology Inc., USA), and a laptop computer (Thinkpad X32, IBM, Japan). The RID have an image projection technology that focuses light, of an intensity

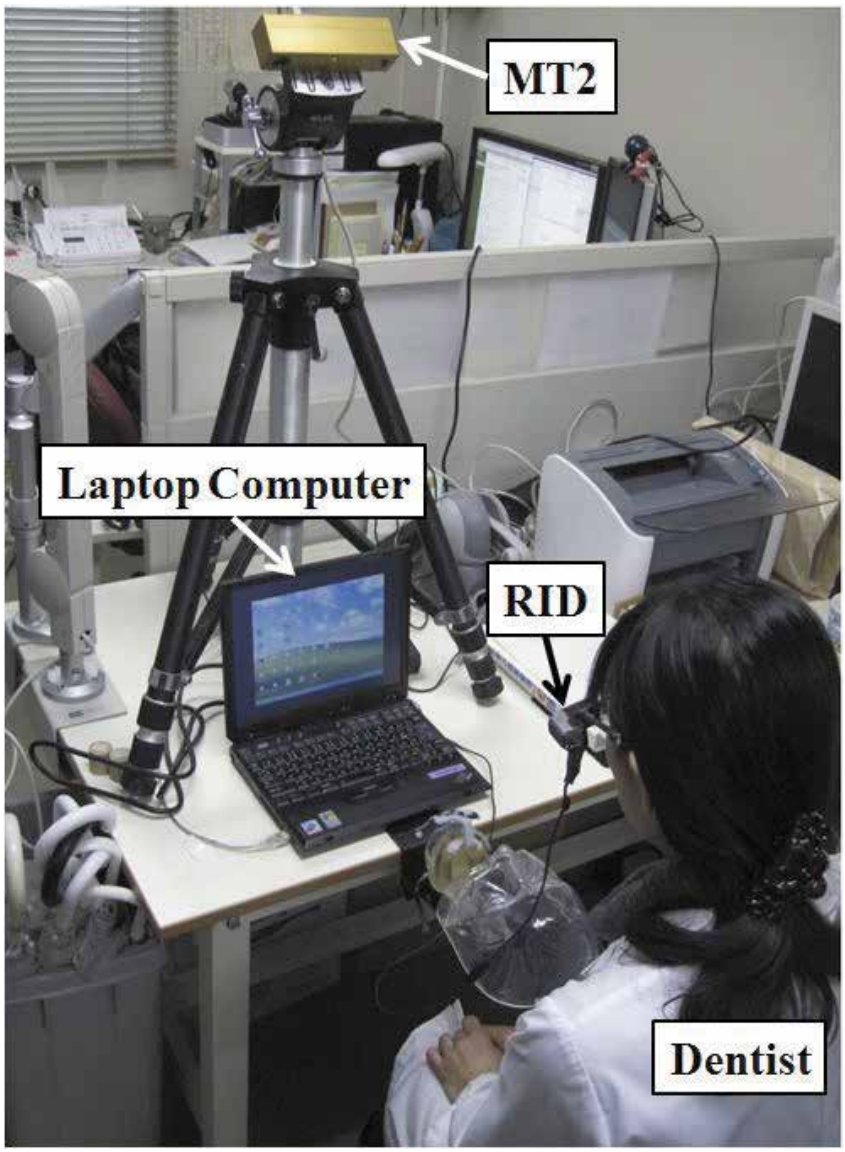

Fig. 3. System configurations

harmless to the eyes, onto the retina and then moves the light at high speed to create after images. This technology differs from an optical see-through head mounted display and a half mirror in respect of projection principle for eyes and has many advantages for dentists. Dentists can intuitively confirm an ideal implant placement without an uncomfortable feeling. And, dentist's view is not interrupt by lenses such as glasses. Moreover, dentist can view private images and personal data of patients away from being viewed by others intra-operatively. To track a position and a pose of marked patient's oral cavity, computer vision technologies are implemented on MT2 instead of conventional optical tracker by using infrared light emission. Thus, MT2 is a cost-effective and high accurate (jitter for moving target is less than 70 micron) optical tracker. A laptop PC receive signals from RID and MT2 and calculate a translate matrix for real-time image overlay.

2.2 Pre-operative procedures

1. To measure the position and orientation of a marker 1, the marker 1 is placed onto a partially edentulous model.
2. A placement position of dental implants for the scanned images is simulated by CAD software (FreeFormModeling, SensAble Technologies, Inc., USA) and the three-dimensional simulation image is generated as a computer graphics (CG). At this time, a translation matrix ${}^{implant}_{marker1}\mathbf{D}$ from the marker 1 to implants is recorded.
3. A translation matrix ${}^{eye}_{marker2}\mathbf{A}$ to dentist's eye from the RID with a marker 2 attached thereto is calculated. By using the marker 1 for calibration, the ${}^{eye}_{marker2}\mathbf{A}$ is calculated from three-dimensional positions on the RID coordinate system and its corresponding two-dimensional positions on the dentist's eye coordinate system (Kato et al., 1999).

2.3 Intra-operative procedures

1. Translation matrixes ${}^{marker1}_{tracker}\mathbf{D}$ and ${}^{marker2}_{tracker}\mathbf{D}$ are measured by the MT2 in real-time intra-operatively.
2. A translation matrix ${}^{eye}_{implant}\mathbf{P}$ is calculated from simulated dental implant CG image to the dentist's eye as per a following equation (1). Finally, the CG image is projected onto the dentist's view,

$$ {}^{eye}_{implant}\mathbf{P} = {}^{marker1}_{implant}\mathbf{D}\,{}^{tracker}_{marker1}\mathbf{D}\,{}^{marker2}_{tracker}\mathbf{D}\,{}^{eye}_{marker2}\mathbf{A} \tag{1} $$

where, ${}^{marker1}_{implant}\mathbf{D} = {}^{implant}_{marker1}\mathbf{D}^{-1}$ and ${}^{tracker}_{marker1}\mathbf{D} = {}^{marker1}_{tracker}\mathbf{D}^{-1}$.

2.4 Design of markers and partially edentulous model

CAD models of the marker 1 and the marker 2 were designed by the CAD software (Fig. 4). A partially edentulous model was scanned by three-dimensional measurement system (Rexcan scanner, Solutionix Corp., Korea). The marker 1, the marker 2, and the partially edentulous model were fabricated by rapid-prototyping machines (Connex500 (two-color process) and EDEN260 (one-color process), Objet Geometries Ltd., Israel). In clinical case, the marker 1 will be placed inside oral cavity of the patient. As shown in Fig.4 and Fig.5, the markers consist of three faces. Sizes of all faces were set to 26 × 21 mm. Both two faces were tilted to a center marker. Its tilt angle was 30 degree. Unlike a white and a black color, a grey and a black color were adopted to improve a contrast ratio for MT2. Both the marker 1 and

the marker 2 have different patterns. Fig. 6 shows a pre-operative simulation result including five implant models and simplified models of a mandibular canal which was extracted from a CT data by using a volume rendering software (VG Studio Max 2.0, Volume Graphics GmbH, Germany).

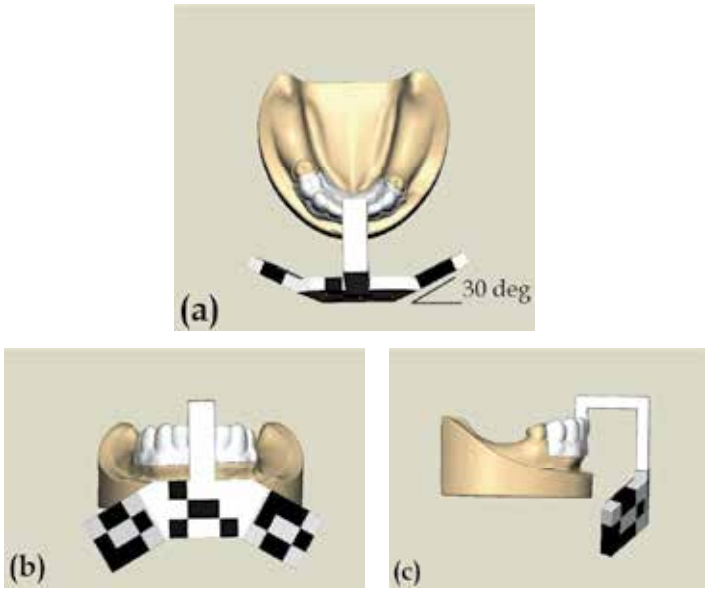

Fig. 4. The CAD model of the marker 1 and the scanned model of the partially edentulous model: (a) top view, (b) front view, (c) lateral view

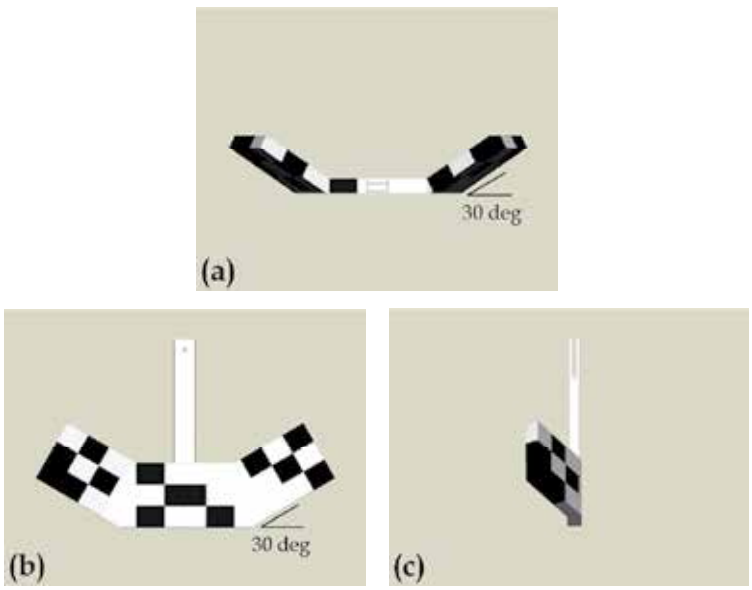

Fig. 5. The CAD model of marker 2: (a) top view, (b) front view, (c) lateral view

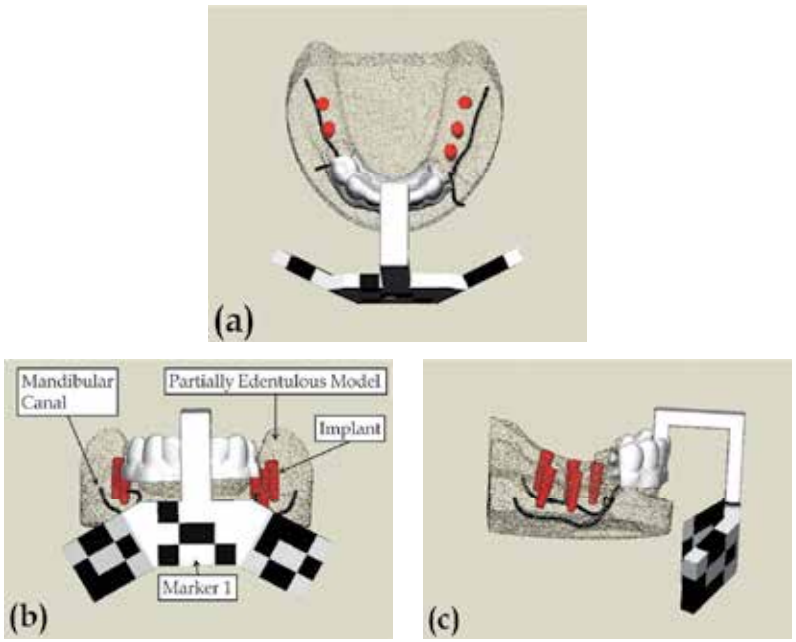

Fig. 6. Pre-operative simulation result: (a) top view, (b) front view, (c) lateral view

2.5 Calculations of ${}^{eye}_{implant}\mathbf{P}$

2.5.1 DLT (Direct Linear Transformation)

Direct linear transformation is a gold standard calibration method (Hartley, R. & Zisserman, A., 2003). By using the marker 1 for calibration, A translation matrix ${}^{eye}_{marker2}\mathbf{A}$ was calculated from three-dimensional positions on the RID coordinate system $\mathbf{p}(x,y,z)$ and its corresponding two-dimensional positions on the dentist's eye coordinate system $\mathbf{P}(X_C,Y_C)$. A transform relationship between a RID coordinate value $\mathbf{p}$ and a dentist's eye coordinate value $\mathbf{P}$ was represented as per a following equation (2).

$$[H_C X_C, H_C Y_C, H_C] = [x,y,z,1]\begin{bmatrix} C_{11} & C_{21} & C_{31} \\ C_{12} & C_{22} & C_{32} \\ C_{13} & C_{23} & C_{33} \\ C_{14} & C_{24} & C_{34} \end{bmatrix} \tag{2}$$

These twelve parameters represent constant values such as a relative position, an orientation, and a focal length. A translation matrix C calls camera parmeters. The camera parameters were calculated by collecting some three-dimensional positions on the RID coordinate system $\mathbf{p}_i(x_i,y_i,z_i)$ and its corresponding two-dimensional positions on the dentist's eye coordinate system $\mathbf{P}_i(X_{Ci},Y_{Ci})$. Once a coordinate value x_1,y_1,z_1 of a three-dimensional position $\mathbf{p}_1$ on the RID coordinate system and its corresponding coordinate value X_{C1},Y_{C1} of a two-dimensional position $\mathbf{P}_1$ on the dentist's eye coordinate system was determined, an equation (3) was derived from the equation (2).

$$\begin{aligned} C_{11}x_1 + C_{12}y_1 + C_{13}z_1 + C_{14} - C_{31}x_1X_{C1} - C_{32}y_1X_{C1} - C_{33}z_1X_{C1} = C_{34}X_{C1} \\ C_{21}x_1 + C_{22}y_1 + C_{23}z_1 + C_{24} - C_{31}x_1Y_{C1} - C_{32}y_1Y_{C1} - C_{32}z_1Y_{C1} = C_{34}Y_{C1} \end{aligned} \tag{3}$$

Six noncoplaner fiducial points were required for calculation of twelve parameters $C_{11} \cdots C_{34}$ because we have two equations once a fiducial point. Actually, a least square method was applied for accurate calculations by using over six fiducial points. In this chapter, we collected fifteen fiducial points for the calculation. Here, we just have to collect a relative (not absolute) coordinate value of $\mathbf{p}_i$ (a distance between each point and an orientation) on the RID coordinate system. If a set of n > 6 fiducial points were given, an equation (4) was derived. There is no problem either C_{34} or H_C are set to a value of constant because a scaling was determined by both parameter. Therefore, we assume that the C_{34} in the camera parameters equal to 1.

$$\mathbf{AC} = \mathbf{R} \tag{4}$$

where

$$\mathbf{A} = \begin{bmatrix} x_1 & y_1 & z_1 & 1 & 0 & 0 & 0 & 0 & -x_1X_{C1} & -y_1X_{C1} & -z_1X_{C1} \\ 0 & 0 & 0 & 0 & x_1 & y_1 & z_1 & 1 & -x_1Y_{C1} & -y_1Y_{C1} & -z_1Y_{C1} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ x_n & y_n & z_n & 1 & 0 & 0 & 0 & 0 & -x_nX_{Cn} & -y_nX_{Cn} & -z_nX_{Cn} \\ 0 & 0 & 0 & 0 & x_n & y_n & z_n & 1 & -x_nY_{Cn} & -y_nY_{Cn} & -z_nY_{Cn} \end{bmatrix}, \tag{5}$$

$$\mathbf{C} = \begin{bmatrix} C_{11} \\ C_{12} \\ C_{13} \\ \vdots \\ C_{32} \\ C_{33} \end{bmatrix}, \mathbf{R} = \begin{bmatrix} X_{C1} \\ Y_{C1} \\ \vdots \\ X_{Cn} \\ Y_{Cn} \end{bmatrix}. \tag{6}$$

If n fiducial points were given, translation matrixies $\mathbf{A}$, $\mathbf{C}$ and $\mathbf{R}$ are represent as $2n \times 11$, 11×1 and $2n \times 1$ respectively. In cases where n > 6 fiducial points including measurement errors were given, each value of $\mathbf{C}$ could not be calculate because of mathematically impossible problem. Consequently, a task is to find the matrix $\mathbf{C}$ that minimizes a norm $\|\mathbf{AC} - \mathbf{R}\|$. In the case of a determination of the camera parameters, eleven unknown parameters $\mathbf{C_{11}} \cdots \mathbf{C_{33}}$ were given and a number of equations is $2n$ (a number of fiducial points = n), that is, the impossible problem $\mathbf{AC} = \mathbf{R}$ was solved by means of a least square solution. Its solution $\langle \mathbf{C} \rangle$ was derived as an equation (7).

$$\mathbf{A}^{\mathrm{T}}\mathbf{A}\langle \mathbf{C} \rangle = \mathbf{A}^{\mathrm{T}}\mathbf{R} \tag{7}$$

2.5.2 LMedS (Least Median Square)

Our system was operated not only by researchers in engineering and engineers but also dentists without technical knowledge. Therefore, our system was expected that anyone could perform an image overlay easily in not only laboratories but also operating rooms. In

conventional system, we adopted a least square method which is best used in statistical methods to calculate a projection matrix. The least square method which determine parameters by minimizing a sum of square of fitting errors is used as a general calibration method. However, an unchanged application of the least square method is not enough. In case of including exception values, the projection matrix which is estimated by the least square method could not be trusted. If the exception values could be automatically eliminated by fitting a model to a major part in data set, parameters in the major part will be able to estimated accurately. To solve this problem, we introduce a least median square (LMedS) method as a typical robust statistics. A method and an algorithm are as follows. A least square criterion is

$$LMS = \min \sum_i \varepsilon_i^2. \tag{8}$$

A LMedS criterion is

$$LMedS = \min med\varepsilon_i^2 \tag{9}$$

where med means median. In case that the least square criterion, a solution is affected by one big exception value. However, even if a half of all data set were exception values, the solution of the LMedS criterion is not affected. Thus, the LMedS criterion is suitable for this situation.

Step 1. n click of a mouse for an origin position of the marker 1 on the view through the RID, varing location of the marker 1. By this task, n set of three-dimensional points on the marker 1 coordinate system and its corresponding two-dimensional points on the dentist eye's coordinate system are collected. By selection F points from n set of corresponding points, candidates of the projection matrix are calculated by the calibration using the least square method.

Step 2. Calculate error values of the candidate of solution as following equation.

$$err^2 = med\left(\left(X_{Ci} - \overline{X}_{Ci}\right)^2 + \left(Y_{Ci} - \overline{Y}_{Ci}\right)^2\right) \tag{10}$$

where $\left(X_{Ci}, Y_{Ci}\right)$ is two-dimensional coordinate value correspoinding to ith origin of the marker 1 on the dentist eye's coordinate system and $\left(\overline{X}_{Ci}, \overline{Y}_{Ci}\right)$ is reprojected two-dimensional coordinate value which is calculated by the candidate of solution. $med\left(f(i)\right)$ represent a median of $f(i)$ in all i.

Step 3. Repeat Step 1 and Step 2 q times. F correspoinding points that minimizing err^2 in equation (10) are calculated as following equation (11). Then, camera parameters which is calculated by F corresponding points are selected. A required repitation time in this algorithm can be determined considering a probability that exception values are not included in at least one sample in q random samplings. Let ε be a ratio of exception value in all data. This probability is represented as following equation (11).

$$P = 1 - \left\{1 - \left(1 - \varepsilon\right)^F\right\}^q \tag{11}$$

For instance, the number of random samplings in $\varepsilon = 0.3, F = 3$ is $q = 11$. In other words, this means the number of random samplings is over eleven. In our system, $F = 10, n = 15, \varepsilon = 0.3, P = 0.99$ are adopted emprically.

Next, we shall focus on a measurement range. Let A be a measurable range of both the marker 1 and the marker 2 on the MT2 coordinate system. Let B be a measurable range of the marker 2 on the RID corrdinate system. A measurable range of our system represent $A \bigcap B$. Within this measurable range, the calibration is available.

3. Results and discussions

Fig. 7 (a) shows fabricated models of the marker 1 and the partially edentulous model. Fig. 7 (b) shows the marker 2 attached to the RID. Few systematic errors are expected because both markers were fabricated together. Moreover, a stable intra-operative navigation is achieved even if any one of a pattern of the makers which consists of multiple patterns is hide out in surgical instruments.

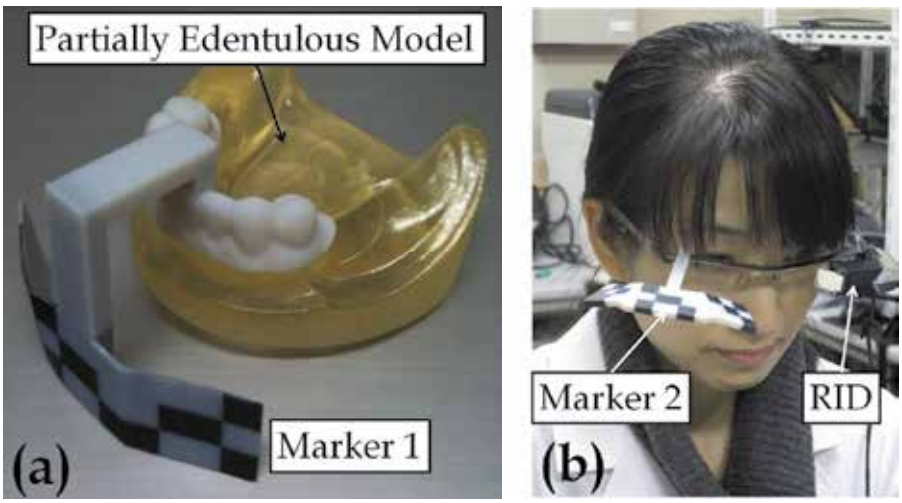

Fig. 7. Fabricated models: (a) The marker 1 and the partially edentulous model, (b) The marker 2 attached to the RID

We adjusted a contrast ratio of colours using the markers on the grounds that the contrast ratio of a grey and black (GB) colour is 20 times higher than that of a white and black (WB) colour. Fig. 8 shows an adjustment result of the contrast ratio. Fig. 8 (a) shows a condition of no spot light in case of a combination with the white and the black colour. Fig. 8 (b) shows the condition of a spotlight in case of a combination with WB. Fig. 8 (c) shows the condition of the spotlight in case of the combination with the grey and the black colour. In the condition of Fig. 8 (b), the WB marker was not measurable because of halation cause the spotlight. However, as shown in Fig. 8 (c), the GB marker was measurable under the condition of the spotlight. Accordingly, we adopt the GB marker around the marker 1 attached to patient's oral cavity with the spotlight and the WB marker 2 around the RID with an environmental light.

As shown in Fig. 9, a measurable range of a new marker was about 2.6 times higher than that of a conventional marker. A tilt angle was set to opposite direction between the marker

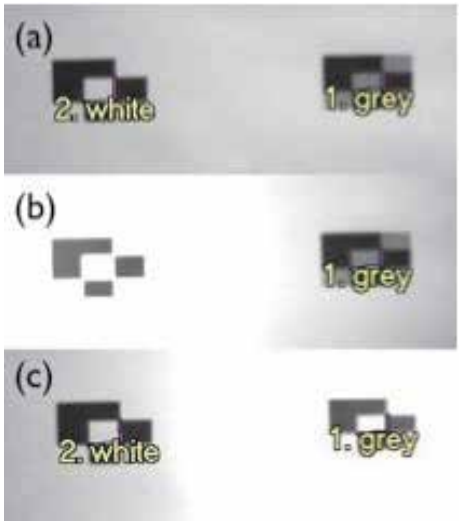

Fig. 8. Adjustment result of contrast ratio. Left marker is combined with a white and black colour (WB). Right marker is combined with a grey and black colour (GB). (a) No spot light, (b) WB marker with spot light, (c) GB marker with spot light

1 and the marker 2 to prevent a false recognition. Fig. 10 shows reprojection errors between the DLT and the LMedS method. An average and a standard deviation of the reprojection errors in the LMedS method indicated decreasing trend in comparison with the DLT method. One of the reasons for the reprojection errors in the LMedS method is dentist's hand movement while sampling. As we have mentioned before, the sampling is performed manually by clicking a mouse in our system. Therefore, some errors may be observed cause dentist's hand movement. So, there is room for further investigatioin about the sampling. And, it must be notice that calibration will be required again in case that a movement of dentist's own misalign relationship between the RID and the dentists.
Fig. 11 and Fig. 12 show real-time image overlay results on the conventional head mounted display and the RID respectively. As shown in Fig. 12 (a) and (b), an image overlay result through the RID was crucially clear view in comparison with that of a conventional head-mounted display (Fig. 11 (a) and (b)). To take Fig. 11 and Fig. 12, we used an off-the-shelf USB camera in place of dentist's eye. Therefore, actual view was better because of direct overlay onto dentist's retina in case of the RID.

4. Conclusion

We proposed the dental implant surgical navigation system by combining the AR technology and the RID and its image overlay procedure, and our procedure proved to be performed as a real-time image overlay. By implementation of the LMedS method, more robust calibration was achieved. Further development of the markers will be planned to decrease the reprojection errors by using the other markers including known sampling points fixed on patient's oral cavity. To achieve clinical applications of this system, evaluation of a fiducial registration error (FRE) and a target registration error (TRE) (Fitzpatrick et al., 1998) and the procedure by real CT data is in progress.

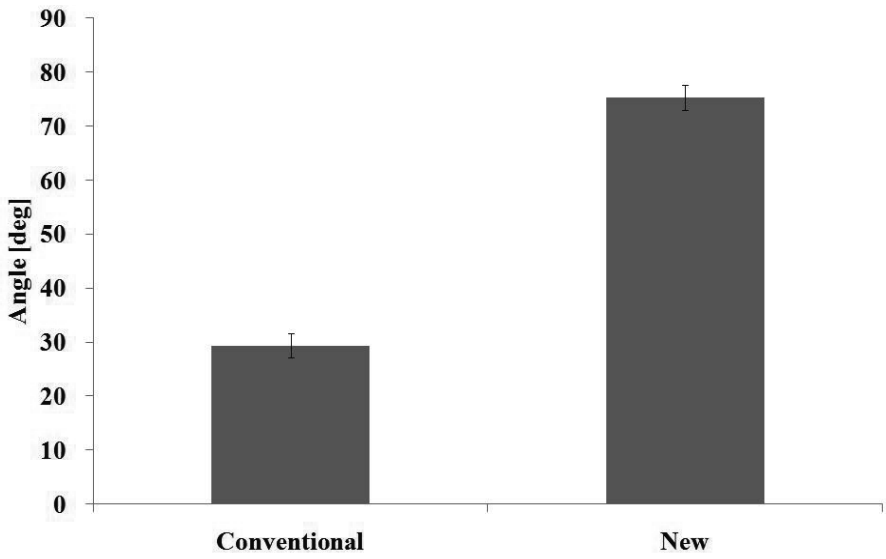

Fig. 9. Comparison with conventional and new measurable range

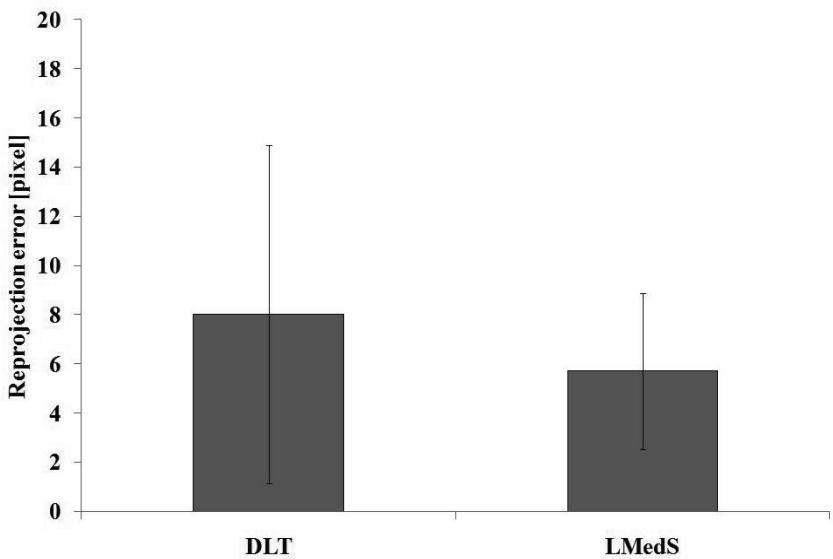

Fig. 10. Comparison with reprojection errors of the DLT method (Yamaguchi et al., 2009) and the LMedS method

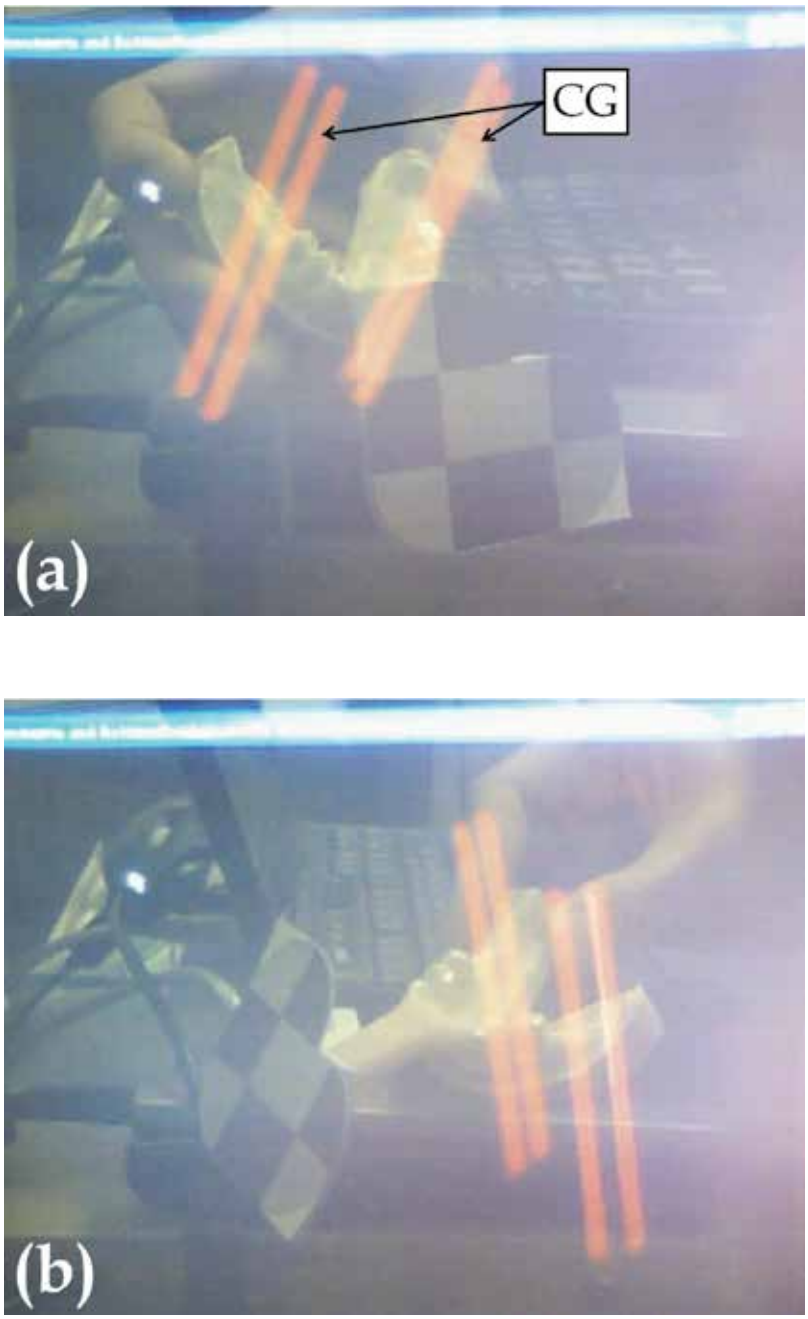

Fig. 11. Real-time image overlay result on the conventional head mounted display: (a) scene 1, (b) scene 2

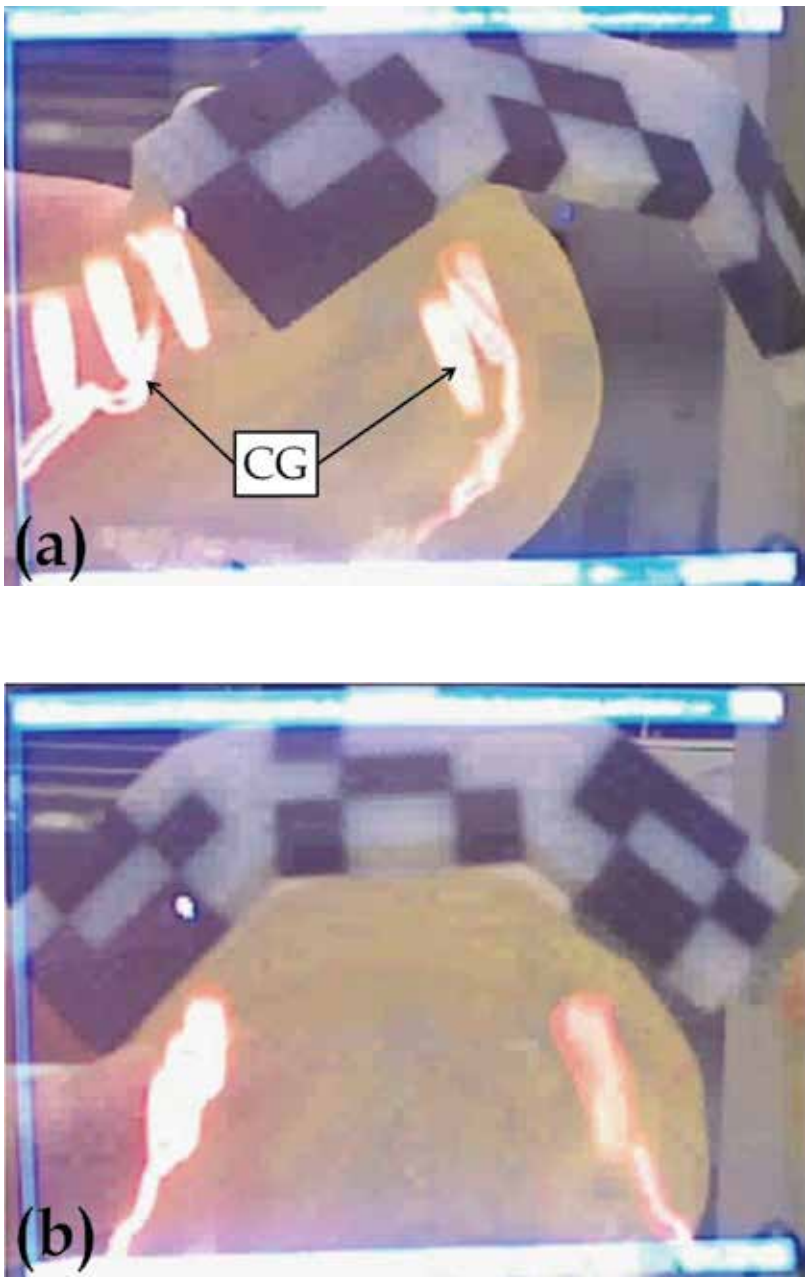

Fig. 12. Real-time image overlay result on the RID: (a) scene 1, (b) scene 2

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Part 4

Clinical Applications of Implants

14

Factors Affecting the Success of Dental Implants

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1. Introduction

Dental implants are fully placed in the bone in order to replace the natural root of the tooth and allow the installation of a dental prosthesis. The implant has gained importance with the work of Professor Per Ingvar Brånemark, who studied the microcirculation in bone tissue. Brånemark used stainless steel optical chambers to investigate the anatomy and physiology of tissue injury. The chamber was inserted in rabbit and dog legs. In some experiments the chamber structure of stainless steel was replaced by titanium. At the end of the experiments, Prof Brånemark observed that the titanium chamber was firmly attached to the bone (Brånemark et al., 1964). In fact, the titanium chamber could not remove from the surrounding bone once it had healed. Histological studies showed complete integration of titanium with the bone. After this chance observation, Brånemark developed a new concept of osseointegration which led to dental implants. The use of titanium-based dental implants in humans begun in 1965.

Dental implant technology was improved in recent years, providing patients with unparalleled levels of effectiveness, convenience, and affordability. This is one of the main reasons why so many dentists recommend dental implants as their preferred method to replace missing teeth. Titanium dental implants can offer many benefits. Because they present osseointegration with the jawbone, they are more stable than dentures. Patients with dental implants may be able to talk and eat more easily because they do not face the risk of their dentures dislodging. Dentures require replacement when the gum tissue shrinks and changes the fit; implants are not affected by this problem. The maintenance and hygiene of dental implants are easier than with dentures. Another reason for continued growth of the global market for dental implants is that dental implants offer an effective treatment for edentulism and because of the rising demand for cosmetic dentistry worldwide across all age groups.

The conventional clinical protocol proposed by Brånemark (Brånemark, 1990) for placement of dental implants involves two phases. The first is the placement of the implant in a surgical cavity prepared in the bone. The protocol recommends a healing period for tissue reorganization. The waiting time for healing to occur depends on bone quality and the region in which the implant was performed and was estimated by Brånemark as between 3 months to 6 months. The second phase of treatment is the prosthesis placement. With this technique, all natural teeth can be replaced, restoring function and aesthetics to the patient.

The conventional protocol can be changed so that insertion of the implant and prosthesis placement can be made in a single step. In this case, the protocol is called immediately loading. The dentistry has an interest in reducing the healing time after surgery and loading the implants with oral forces safely. To meet this expectation one must consider that the body has a minimum time to perform the reactions that lead to osseointegration. In order to shorten the healing time, the strategy is to alter the biocompatibility of titanium implant surfaces, modifying the surgical technique and changing the implant design.

Despite the influence of the implant shape on the primary stability and the distribution of oral loads, there is no standardization of implant design. As shown in figure 1, there are dental implants on the market with different shapes. The cylindrical screw threaded implants are the most commonly used. Based on biomechanics and clinical observations, it was found that tapered implants have a higher compression capacity than cylindrical ones. During insertion the tapered implant induces compression stresses on the bone and increases the implant primary stability. However, the tapered implant is not suitable for all applications.

In an attempt to increase the success rate of implants, some researchers used the control of surface properties to select the type of cell that interact with the implant. It is known that osteoblastic cells adhere more quickly to rough surfaces of titanium than to smooth surfaces (Zhu et al., 2004; Puleo & Bizios, 1992). Despite the advances in prosthodontic, the explanation of the influence of the implant surface on osseointegration remains incomplete. The new surfaces improve the success of implants in patients with low bone quality and quantity. However, there is still an unexplained loss of implants.

Several papers in the literature (Wennerberg, 1998; Tete et al., 2008; Suzuki et al. 2009; Stadlinger et al. 2008; Richards, 1996) describe the importance of titanium surface properties in implant osseointegration. These works studied the morphology, topography, roughness, chemical composition, surface energy, surface energy, surface composition, chemical potential, residual stress, the existence of impurities, thickness of titanium oxide film and the presence of metallic and nonmetallic compounds on the surface. The mentioned factors influence the concentration of cells involved in osseointegration. The importance of this work is the fact that by controlling the surface one can reduce the healing time of the implant and the bone-implant interface has enough mechanical strength to withstand the forces in the oral environment (Schucker et al., 2006).

Fig. 1. Available dental implants with different design. (Courtesy of Conexão Sistemas e Prótese Company, Brazil).

As discussed below in detail, besides biomechanics, the shape and dimensions of the implant, the quality and quantity of the bone, the surgical technique and the loading conditions (load intensity, direction of the forces involved) influence the stability of the implants and the maintenance of osseointegration.

2. Biocompatibility

The modern concept of biocompatibility involves, not only compatibility of the material with the tissue but its ability to perform a specific function. The response to specific individual materials could vary from one application site to another. Therefore, biocompatibility is defined only for a determined application. For example, the biomaterial used in intraocular lenses is not adequate for dental implants, although both show biological compatibility. In practice, there is no material that is biocompatible for all applications. Thus biocompatibility could not solely be dependent on the material properties (physical, chemical, mechanical) but also had to be defined by the situation in which the material is used (Williams, 2008).

The requirement for biocompatibility in a medical device intended for long term contact with the tissues of the human body is that the material does no harm to the tissues, and this presupposes chemical and biological inertness. However, in the case of dental implants, there is a need for osseointegration, which implies in a need for specific and direct interactions between biomaterials and tissue components.

The main factors influencing the biocompatibility of biomaterials are chemical composition, mechanical properties, electrical charge and surface features. The biocompatibility of materials used in dental implants is evaluated by studying the reaction between the implant and the bone. The reaction between the implant and the soft tissue is also important. The region where the implant is in contact with the soft tissue is responsible establishing a kind of seal that isolates implant and the bone from the mouth environment.

The analysis of the biocompatibility of biomaterials is accomplished by testing *in vitro* and complemented with tests *in vivo*. Tests *in vitro* involve cell culture, characterization of the chemical composition of surfaces, identification of the types of oxides and crystalline structures, determination of the thickness of the oxide layer, and quantification of resistance in mechanical loading conditions and dynamic resistance corrosion. The implant stability, surface roughness and surface wettability are also important.

The implant tests *in vivo* are done in animals, especially mice, rabbits, dogs, sheep and pigs. The last testing stage involves analysis of human clinical trials. In tests *in vivo*, after implant removal from the animal, the samples are analyzed by microscopy to determine the tissue quality around the implant. In such tests certain types of tissue reaction have been repeatedly observed. Another important test is the interface implant-bone mechanical resistance after osseointegration of the implant. This measurement is indirectly determined by measuring the minimum torque required to remove the implant.

Tests *in vivo* are done to evaluate the corrosion resistance and the breakdown between toxicity, hijacking (non-vascular tissue and thick in contact with the implant, the absence of pathological cells) and inertia (vascularized tissue and loose connective tissue). It is known that a relationship exists between the material toxic reaction and a high corrosion rate. Co, Cu, Ni and V give rise to increased degradation in this order, and the degree of toxicity is increased in the same order. Metals that have corrosion passivation, i.e., high resistance to corrosion, do not trigger a negative response of tissues. This behavior is observed with Pt,

Ta, Nb, Zr and Ti. It is possible to identify a correlation between biocompatibility, chemical stability and biological performance.
Corrosion resistance, degradation and the corrosion products released are important parameters for materials selection. Morais et al. (Morais et al., 2009) evaluated the concentration of Ti, Al, and V in rabbit tissues (kidney, liver, and lung) after 1 week, 4 weeks, and 12 weeks of placement in the tibiae of Ti-6Al-4V orthodontic mini-implants. Various amounts of Ti, Al, and V were detectable (figure 2), confirming diffusion of Ti, Al and V from orthodontic mini-implants, with accumulation in remote organs (kidney, liver, and lung). Each metallic element had a different release behavior as a function of time. However, it is not enough to know which chemical elements are released; it is also important to analyze their influence on biocompatibility. Despite the tendency of metallic ion release with the Ti alloy, the measurable amounts of metals (Ti, Al, and V) released from Ti-6Al-4V orthodontic mini-implants in rabbits' tissues were significantly below the average dietary intake of these elements through food and drink and did not reach toxic concentrations.

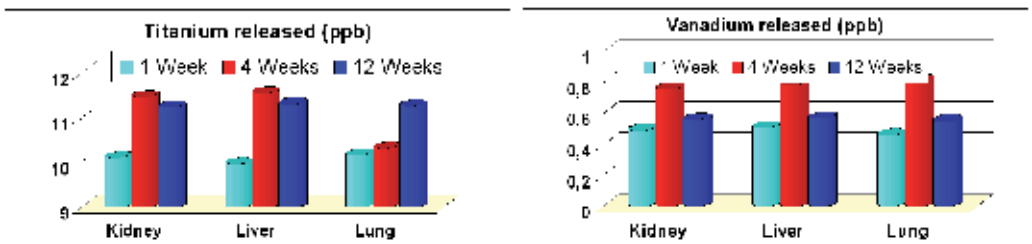

Fig. 2. Levels of metallic ions released from orthodontic Ti-6Al-4V mini-implants inserted in rabbits. (A) Ti (ppb). (B) V (ppb). Adapted from Morais et al. (Morais et al., 2009)

The analysis of biocompatibility becomes more complex when one considers that a low corrosion rate is not sufficient to ensure compatibility between the implant and the host tissue. Despite the fact that the corrosion resistance of stainless steel is about 300 times greater than that of Mg, many steel alloys release nickel, that, depending on the patient, can be highly toxic. A similar behavior problem is observed in Cr-Co alloys (Williams, 2008). The amount of some chemicals that are released in the body is a determinant factor of material biocompatibility. There is evidence that there is correlation between the intrinsic toxicity of the ions and their ability to bind macromolecules. It is thus necessary to study the ability of the products of corrosion of metals to react with host proteins to form a potentially toxic metal-protein, and to analyze the stability of compounds formed during the release of corrosion products. A high corrosion resistance does not ensure biocompatibility; the tissue reaction depends on the concentration and toxicity of the corrosion products.
The materials that ensure osseointegration are cp titanium, tantalum and niobium. Most companies employ cp titanium. Implants made of Ti-6%Al-4%V must be submitted to a surface treatment to exhibit osseointegration.

3. Tissue and dental implant interactions

Dental implants withstand oral loading because they have mechanical interlocking, fibro-osseous retention and osseointegration. The mechanical retention is not dependent on the

implant material. Dental implants are primarily anchored in bone by means of mechanical interlocking. For dental implants with a screw shape, axial loading is transmitted to the bone via threads. The factors that affect mechanical interlocking are associated to the implant shape, surface irregularities and roughness, holes and grooves, screw thread type and the number of threads.

The term "fibro-osseous retention" or "fibrointegration" is applied to cases where the implant is attached to the bone by connective tissue. The "fibrointegration" concept is that there is a soft tissue interface surrounding an implant or a dense collagen tissue between implant and bone, whereas the term osseointegration in optical microscopy analysis refers to the physical contact between new bone and the implant, without the interposition of connective tissue.

Osseointegration was defined as a phenomenon where intimate contact between bone and biomaterials occurs at the optical microscopy level, enabling surgical implants to replace load-bearing organs restoring their form and function (Albrektsson et al., 1981). In the case of osseointegrated implants, when there is no fibrous capsule, high resolution microscopic results shows an afibrillar interfacial zone at the bone-implant interface; mineralized tissue generally does not directly touch the biomaterial. The interfacial layer is rich in noncollagenous proteins as well as certain plasma proteins. Titanium-newbone interface presents a thin layer with proteoglycans and glycoproteins. Some researchers have suggested that this interfacial zone provides a mechanism for bonding between hard tissue and cp Ti (Dee, 2002a).

The cellular interactions at the surface of cp Ti implants occur through the weak forces of van der Waals and hydrogen bonds. The first exhibit a binding energy of only 10 kcal/mol, due to molecular electric dipoles. The hydrogen bonds have energy of 1.10 kcal/mol. The strong binding forces, both covalent and ionic, with a binding energy of 10-100 kcal/mol, depend on the microstructural characteristics of the surface at atomic scale. These connections occur at defects such as cations, anions and impurity atoms. The placement of dental implant results in blood leakage, homeostasis, and fibrin blood cot formation at the tissue-bone interface (Cooper, 2003). The first cells to appear on a biomaterial surface during blood contact (adsorption), coagulation, and fibrinolytic phases are blood cells, i.e., platelets, monocytes, and polymorphonuclear granulocytes followed by erythrocytes. Immediately after insertion of dental implants in the surgical alveolus, reactions occur with the host tissues.

Bioactive materials (glass ceramics and hydroxyapatite) induce specific biological reactions on the surface, resulting in the formation of a union between implant and host. These biomaterials form strong bonds with the adjacent tissue. They promote a connection with the bone tissue through bridges of calcium and phosphorus. Titanium does not fit into this classification because it has a titanium oxide layer, which is inert when in contact with the tissue. The micromechanism responsible for connection with the bone depends on specific surface chemical properties.

As Albrektsson et al. (Albrektsson et al., 1982) commercially pure (cp) titanium implants were shown to establish very close contacts with bone, without any interposed cellular layers. There was only a thin (20-40 nm) interfacial collagen-free layer of ground substance, i.e. macromolecules consisting of proteoglycans and glucose aminoglycans attached to a backbone of hyaluronic acid. Such observations, supported by other morphological and functional studies, indicated that cp. titanium was excellently tolerated by the tissues. Johansson et al. (Johansson, 1990) examined the interface between bone and cp Ti implants and found a layer of proteoglycans about 20 nm thick and then, at a distance of about 100 nm, heavily mineralized collagen fibers. Between the two layers, were identified fibrin and no organized mineral deposits.

The oxidized surface of metals on an aqueous environment has a hydroxyl layer. Free metal ions can dissociate the water molecules and saturate or camouflage their positive charge with negatively charged hydroxyl ions. In the case of titanium oxide, for each dissociation of a molecule of water are produced two hydroxyl groups, which are differently positioned on the surface and produce an acid and a base in the neighboring area. These forms act as bipolar or amphoteric that can attract and bind with other molecules. An important feature of the amphoteric materials is the value of their point of zero charge measured by the pH. At point zero, the positive and negative charges on the surface are balanced. The equilibrium point for the titanium oxide is a pH around 6.2. Some amino acids are bipolar and can react as acids (because of the carboxyl groups) or as bases (because of amino groups). These hybrids are ideal for chemical absorption and form a double bond with amphoteric hydroxylated titanium oxide.
Results of a study by Suzuki et al. (Suzuki et al., 2009) supports the suggestion that the implant surface treatment positively influenced the early bone healing, resulting in the presence of lamellar bone morphology due to primary remodeling in the woven bone/vascular rich network observed at the bone surrounding.

4. Osseointegration

It is well known that success in implant dentistry depends on several parameters that may improve considering both biologic and mechanical criteria. To explain the micromechanisms involved in osseointegration is necessary to know concepts of biology, physiology, anatomy, surgery and tissue regeneration. Osseointegration is observed in several areas, including not only dental implants, but also maxillofacial implants, replacement of damaged joints and placement of artificial limbs.
Osseointegration was defined by Brånemark as the direct connection of living bone with the surface of an implant subjected to a functional load. This definition has been modified over the years. Among the important requirements for osseointegration are the existence of a biocompatible surface, the presence of alveolar bone in the potential recipient sites and no traumatic surgery.
To Brånemark et al, the phenomenon of osseointegration is due to new bone formation in close contact with the implant. To achieve this end, protocols were developed, since several parameters have to be defined, from the choice of the metal to the placement and preservation of the prosthesis. Thus, osseointegration depends on the material used in the implant, the machining conditions, the surface finish, the type of bone that receives the implant, the surgical technique, design of the prosthesis and the patient care.
Among the surgical factors that influence osseointegration, implant bed preparation is of critical importance. Drilling the implant bed not only causes mechanical damage to the bone but also increases the temperature of the bone directly adjacent to the implant surface. Mechanical and thermal damage to the tissue surrounding the implant during drilling can have a destructive effect on the initial state of the cavity housing the implant (Anitua et al., 2007).
Necrosis occurs when the temperature exceeds 47 ^{o}C for 1 min. Therefore, care must be taken to avoid thermal bone injury during the procedure. External irrigation at room temperature can provide sufficient cooling during drilling and keep the temperature below the critical value of 47 ^{o}C. Lower temperature saline was shown to be more effective in cooling the bone, and irrigation of the site should be continued between the drilling steps

(Sener et al., 2009). Other factors affect heat generation during drilling, such as the drilling speed and force.

Bioactive materials bond to bone tissue through bridges of calcium and phosphorus. On the other hand, the chemical bond between non-coated titanium implants and living tissue occurs through weak van der Waals and hydrogen bonds.

The van der Waals forces (polarization and molecular electric dipoles) have bond energy of about 10 kcal/mol. The hydrogen bonds have energy of 1.10 kcal/mol. Covalent and ionic bonds have energy of the order of 10-100 kcal/mol. The types of connections between the implant and the body depend on the microstructural characteristics of the surface on atomic scale. These connections occur at defects such as cations, anions and impurity atoms. The chemical composition of oxide, density and grain boundary impurities exert great influence on the occurrence of strong bonds.

Osseointegration is a biological concept which involves the incorporation of a foreign body to the living bone (host) with fixation and stability when subjected to functional loads. In order for dental implant osseointegration to occur, there must be an adherence of the cells to the surface of the biomaterial. The implant surface characteristics can modulate the adsorption of proteins, lipids, sugar, and ions present in the tissue fluids. Attachment to a surface is a critical first step in cell response because it determine which cells will populate the surface and how many (Boyan et al., 2001). In vitro tests with osteoblastic cells showed that when cell adhesion occurs, the cells change shape and spread. In this phase, reorganization of cytoskeletal proteins occurs. At points of contact between cells and biomaterials there is an exchange of information between cells and the extracellular matrix, leading to activation of specific genes and remodeling. As the chemical composition of biomaterial induces different reactions of the cells, the surface properties of biomaterials induce different reaction mechanisms (Anselme & Bigerelle, 2005). Both the morphology and the surface roughness of biomaterials influence proliferation, differentiation, extracellular matrix synthesis, production of local factors and even cell shape (Jayaraman et al., 2004)

The tests for implant removal by torsion indicate that there is a strong bond between the titanium implant and the bone. In the analysis of implants removed from animals it can be observed that there is a considerable amount of bone attached to the surface of the implant. This is an indication that osseointegration occurred.

Histologically, the identification of osseointegration is by the presence of regenerated bone at the implant-bone interface. The structure of the contact region can be analyzed in detail by means of electron microscopy and microanalysis. Histological preparations are suitable for this purpose. Several studies have found that there is a contact zone between implant and bone after placement. In these works it was possible to identify the presence of titanium atoms in the tissues surrounding the site of the alveoli. There was also the presence of lamellar bone with lacunae characteristics. Microanalysis and mapping of chemical elements in the region around the implant with microprobe indicated the presence of titanium, calcium and phosphorus. By this technique it is possible to verify that the relative intensities of Ca and P are constant, indicating that the bone is completely mineralized. Semiquantitative analysis in the region of the implant-bone interface shows the presence of chemical elements constituting the bone at a distance of 0.5 μm. These results show that the micromechanics of osseointegration is at the molecular level.

The tissue contact with the osseointegrated implant is the result of a process of new bone growth that involves continuous modeling and remodeling. Thus, it is important to

understand that integration of bone with the implant is a dynamic process. The formation and stability of new bone about the implant is a combination of resorption and bone apposition. The balance between these processes is affected by various types of stimuli, including biomechanical forces in the dental prosthesis and the potential presence of inflammation (mucositis and peri-implantitis).

5. Influence of movement on the osseointegration

Despite the results obtained in studies to elucidate various aspects of osseointegration, there are doubts as to the actual micromechanisms involved in the formation of the union between bone and titanium, especially regarding the necessity of mechanical stimulation to induce bone connection.

After installation, the dental implants should provide initial mechanical stability to prevent movement. Movement between an implant surface and hard tissue causes fibrous capsule formation around the implant. Clinically, encapsulation is prevalent with stainless steel, alumina, zirconia and rarely seen with cp Ti implants without movement.

In fact, previous studies in animals reported a threshold of micromotion between 50 and 100 mm, above which micromotion induces bone resorption at the interface, thus producing fibrosis around endosseous implants (Soballe et al., 1993; Szmukler-Moncler et al. 2000).

Implant stability depends on direct mechanical connection between implant surface and the surrounding bone and can be divided into primary, secondary and tertiary stability. The stability obtained immediately after insertion of a dental implant is called primary stability. The stability obtained after osseointegration is named secondary stability. The tertiary stability is the maintenance of osseointegration. Primary implant stability is considered to play an essential role in successful osseointegration. It depends on bone quality and quantity, implant geometry and the site preparation technique.

Primary implant stability can be remarkably decreased in “low quality bone” (Beer et al., 2003). There are no conclusive studies of the minimum primary stability that ensures osseointegration. Clinical results indicate that when the dental implant insertion torque is higher than 40 N.cm, the success rate increases. Implant insertion and prosthesis installation in the same surgery procedure is called immediate/early function of dental implants. Immediate loading is today a commonly used term in the dental field and indicates the possibility of applying an occlusal load to dental implants earlier than the traditional healing period of 3 to 6 months. However, the applied load is often reduced or even absent; therefore, it is more correct to use the term “immediate/early function” rather than “immediate/early loading.” Moreover, the subdivision between “immediate function” (when the prosthesis is applied within hours from the implant insertion) and “early function” (when the prosthesis is applied earlier than the traditional period of 3 to 6 months) has been accepted (Bogaerde et al., 2010).

6. Importance of titanium oxide layer in osseointegration

Although titanium is used extensively in the manufacture of dental implants since the early 1970's, there are still doubts about the mechanisms involved in its biological response.

Titanium spontaneously forms a very thin oxide film on its surface. This passive film protects titanium against corrosion attack or degradation in a wide range of harsh or aggressive environmental conditions. The biocompatibility of titanium as an implant

material is attributed to surface oxides spontaneously formed in air and/or physiological fluids (Williams, 1981).

During machining of titanium, absorption of O_2 molecules occurs. After about 10 nanoseconds, the molecules dissociate and a monolayer of atomic oxygen is deposited. This oxygen reacts with titanium to form a titanium oxide film with a thickness between 50 and 100 Å (5 a 10 nm). This film, which forms spontaneously at ambient temperature and pressure, is called native oxide. Titanium oxide films can also be artificially grown by heating, acid etching and electrolytic oxidation also known as anodizing.

Titanium oxide films with thicknesses up to 800 nm can be formed by anodizing. At the body pH, the stable form of titanium oxide is TiO_2. After the implant has remained in place for some time, its surface becomes covered with plasma protein, especially fibronectin and vitronectin.

Some researchers studied the titanium oxide films on dental implant surfaces, measuring properties such as the crystalline structure, composition and thickness of the film. These studies showed that healing around titanium implants occurs through a gradual process of mineralization, i.e., osseointegration involves mechanisms that do not start at the implant surface (Larsson et al., 1996). Moreover, during healing, which occurs in a few days and remodeling, which requires weeks or even years, the biological processes that occur at the interface affect the properties of the initial oxide layer. The thickness of the oxide layer increases with time and incorporates ions of Ca, P and S from the physiological environment.

The surface properties of implants, such as morphology, roughness, thickness of the oxide layer, impurity level and types of oxide depend on the treatment to which the material was submitted. These surface properties have a significant effect on new bone formation.

After machining and cleaning, commercial dental implants are submitted to a surface treatment in order to attain the desired roughness and an adequate thickness of the titanium oxide film. It is important to remember that contact between the implant and the body established through a titanium oxide film; there is no contact between metallic titanium and the body.

The main difficulty for studying the influence of titanium oxide on osseointegration lies in isolating the variables that characterize the surface and analyze then one at a time. For instance, in a specific study it is necessary to change only the type of oxide layer (crystalline structure) while maintaining the same roughness and thickness; in a second study, it is necessary to change only the roughness and so on.

Larsson et al. (Larsson et al., 1996) investigated the bone formation around titanium implants with varied surface morphologies (machined, electropolished and electropolished followed by anodizing). The results showed that after one week a thin layer of bone covered with osteoid from the endosteum has been observed around the implants. After seven weeks the amount of bone around electropolished implant surfaces is lower than for anodized and machined machined implants with grooves between 1 and 10 μm. Anodic oxidation of the electropolished surfaces, which produced areas of increased roughness and a thicker surface oxide, had an enhancing effect on the rate of bone formation. Electropolished implants have less bone formation around the implant due to a lower surface roughness and the presence of a thin oxide layer. This behavior can be attributed to the fact that osteoblast cells adhere and spread more easily on rough surfaces than on smooth ones. They concluded that both surface topography on the submicrometer scale and oxide thickness influence the bone response to titanium.

Since host cells interact with adsorbed proteins and not with the material itself, the types and states of adsorbed proteins are critical determinants of cells responses to implanted

biomaterials. Albumin, fibrinogen and immunoglobulin predominate on many blood and tissue contact biomaterial (Tang & Hu, 2005). But blood has over 150 proteins. On the basis of mass transport considerations, more abundant proteins and proteins with the highest diffusion coefficient will be first to arrive at the surface. The most abundant proteins are albumin (40 mg/mL), IgG (15 (mg/mL), α_1–Antitrypsin (3 mg/mL), fibrinonogen (3 mg/mL). Because of its highest concentration and diffusion coefficient (6.1×10^{-7} cm^2/s), albumin dominates initial interaction with surface. Fibrinogen can dominate the surface because of greater affinity, even though its rate of arrival is more than 100 times less than that of albumin (Dee et al., 2002b).

In the past, implants coated with hydroxyapatite (HA) were widely used. They are no longer used due to the huge number of periimplantitis observed. However, HA-coated implants had a larger amount of bone overlying the surface compared to uncoated implants. In these implants the number of gaps between the HA coating and bone was lower and the formation of mineralized nodules was more pronounced.

7. Interaction of cells with the biomaterial surface

Any material placed in the body will cause a biological response, and the implants interact with the body environment through their surface. Consequently, the study of the properties of the outmost layer of a dental implant is critically important in the analysis of both the biological response to the implant and the titanium responses to the physiological environment.

With insertion of the biomaterial in the human body and contact with the material with the body fluids (BF), multiple events are triggered. In the past, it was believed that identification of a foreign body by the cells led to defensive strategies and inflammatory reactions that resulted in encapsulation of the biomaterial to isolate it from the body. Currently, it is known that through material selection, processing and surface coating, it is possible to obtain the desired cell response. One can favor the adsorption and absorption of a specific type of cell or even prevent the adhesion of organic material. For example, the surface of coronary stents must have properties that prevent cell adhesion. Moreover, the surface of dental implants must allow the adsorption of specific proteins to trigger the mechanisms involved in osseointegration.

As soon as an implant is inserted, adsorption of cells on the surface of the foreign body begins. The cells activate mechanisms to identify the chemical composition of the material and induce different reactions. Cell react differently to bioinert, bioactive and bioreactive materials (Wolner et al., 2006). In the case of bioinert materials (stainless steel, Co-Cr alloy, zirconia, alumina, nylon, etc.) the body induces the formation of a capsule of fibrous tissue surrounding the biomaterial. Bioactive materials (titanium, niobium and tantalum), on the other hand, induce mechanisms that lead to osseointegration. For bioreative biomaterials (hydroxyapatite, calcium phosphate, bioglass), ionic changes occur in the body and the biomaterial is resorbed.

When a bioactive implant is inserted into bone, its surface is modified by ions and proteins. The increased surface energy may alter plasma proteins adsorbed to the surface and activate cell membrane receptors. The process of coagulation is triggered and platelet activation initiates an inflammatory response by recruiting neutrophils and monocytes to the wound area. Platelet-derived cytokines such as IGF, TGF-ß and PDGF enhance the osteogenic response and bone formation by stimulating the migration and proliferation of osteogenic

cells, which differentiate into osteoblasts and eventually produce bone matrix. Thus, the cascade of events induced by the activation of platelets, including the release of chemotactic and mitogenic factors, increased production of thrombin and the recruitment and activation of neutrophils and monocytes may explain the faster bone repair around surfaces of different chemical composition (Togashi et al., 2007; Kikuchia, 2005).

New technologies and new materials have emerged based on these concepts (Kashiwagi et al., 2009; Li et al., 2008). The new biomaterials are developed with the aim of presenting biocompatibility for a specific application. Unfortunately, sometimes the foreign material inserted into the human body does not induce the desire response. In some cases, the physiological reactions are deleterious. Better understanding and control of material properties can eliminate or minimize the critical reactions and allow the advancement of technology of biomaterials. One of the critical responses to foreign materials is directly related to the interaction between the material surface and adsorption proteins (Le Duc & Wang, 2006).

In the body fluid (BF) there are ions in solution as well as lipids, carbohydrates and proteins that can be adsorbed on the biomaterial surface. The biomaterials are selected to obtain a specific response necessary for certain applications (Niinomi, 2002). In this process, proteins play an important role to induce the desired response.

After the initial reaction of proteins with the foreign body a physiological response occur, following by a sequence of events leading to acceptance or rejection of the material. These responses involve the recruitment of several cell types that are present at the interface of the material and perform activities such as extracelular matrix remodeling (Thull, 2002). In the case of dental implants, recruitment of cells, that leads to implant encapsulation, is not desirable. Proper implant surface preparation, adequate loading conditions and control of micromovements are essential and decisive to avoid formation of fibrous tissue in the bone-implant interface. The use of commercially pure titanium is no guarantee of osseointegration.

Based on the concepts presented, it is concluded that the surface properties of implants are extremely important for controlling the reactions that lead to improved performance and osseointegration of the implant. Among the properties of the implant surface that influence the attraction, repulsion, adsorption and absorption of proteins and cells as well as on osseointegration are roughness, wettability, electrical charge, chemical composition, surface energy, residual stresses and morphology.

The wettability of a liquid is defined as the contact angle between droplets of the liquid in thermal equilibrium on a horizontal surface. Depending on the type of surface and liquid the droplet may take a variety of shapes as illustrated in figure 3. The wetting angle θ is given by the angle between the interface of the droplet and the horizontal surface. The liquid is seemed wetting when $90 < \theta < 180$ degrees and non-wetting when $0 < \theta < 90$. When $\theta = 180$ degrees corresponds to perfect wetting and the drop spreads forming a film on the surface. Figure 4 shows hydrophilic dental implant surface.

Fig. 3. Wetting ability of material surface. Hydrophilic surface (left), normal hydrophilic surface (middle) and hydrophobic surface (right).

Cell adhesion involves short term events such as physicochemical linkages between cells and substrates and long term events leading to the regulation of cell expression involving extracellular proteins, cell membrane proteins and cytoskeleton proteins (Anselme, 2000). The chemical composition and microstructure of a surface can regulate the adsorption of components present in the extracellular fluid. It is known that rough and chemically activated surfaces provide the ideal conditions for direct protein adsorption and alter the adsorption of fibronectin and albumin due to modifications in their ionic state. These mechanisms are important for implant osseointegration.

Fig. 4. Vulcano Actives™ dental implant showing its high hydrophilic surface.

Adhesion is a basic cellular process that directly influences cell growth, differentiation and migration, as well as morphogenesis and healing. The extracellular matrix (ECM) elaborated by cells constitutes a regulator of cell adhesion and differentiation and contributes to the mechanical properties of the tissue. These regulatory effects of ECM are mediated through transmembrane proteins specialized in cell substrate adhesion. These cell surface receptors are called integrins, which are αβ heterodimeric proteins. The αβ association is essential for integrins to bind to their ligand and determines the specific ligand binding (a ligand is an ion or molecule that binds to a central metal atom to form a coordination complex. The bonding between metal and ligand generally involves formal donation of one or more of the ligand electron pairs. The nature of metal-ligand bonding can range from covalent to ionic). Some integrins are able to bind several ligands, α3β1 is a laminin, collagen, fibronectin, and, enctatin receptor (Verrier et al., 2002). All these mechanisms depend on the surface properties of the biomaterial.

The arrangement of atoms in the surface of metals is different from the atomic arrangement in the bulk and makes is more receptive to adsorption of atoms and molecules from the environment. The reactions between the environment and the biomaterial surface increases when the energy per unit area at the metal surface increases.

Titanium, having a high energy surface, will easily adsorb O_2 molecules, which dissociate and form titanium oxide in a few milliseconds. Therefore, even in the implants without surface treatment, there is no body contact with metallic titanium, but only with a layer of titanium oxide. Therefore, for the biocompatibility of commercially pure Ti implants, the properties of the oxide layer are more important than those of the metal.

The thickness of the protein coating on the surface of the implants depends on the surface energy of the material. Histological observations made on implants with high surface energy indicated that they have layers of proteins with greater thickness than those with

low energy, revealing that cellular activity varies with the surface energy. When implants with low surface energy were mechanically separated from the capsule tissue and inspected under a microscope, it was found that most of the surface did not have tissue. In implants with low surface energy, the cells remain with an almost spherical shape, lose their attachment and can easily be separated from one another. The globular appearance of these cells allowed identifying them histological as fibroblasts. The globular appearance of the cells is associated with poor cell growth, but is not related to the normal activity of fibroblasts in the healing process.

In order to study the biocompatibility of materials and the extent of osseointegration, one needs quantitative and qualitative information on the surface energy of the implants, since it affects the interactions between biomaterial surfaces with proteins, cells and bacteria. Different cell types use different mechanisms when attaching to different surfaces and, as a rule, cells do not interact with the surface directly, but via proteins secreted by the cells and adsorbed by the surface, forming a distinct layer. Adhesive compounds such as fibronectin and vitronectin are present in the serum adsorbed on the substrate and adhesion is in fact an interaction with these compounds. This interaction is of the type ligand-receptor because the cells have specialized receptors (integrins) through which they identify the adsorbed adhesive proteins-ligands. Guided by the substrate surface properties, conformational alterations of the adsorbed proteins possibly change their biological behavior. In this context, the initial cellular interactions depend on surface physicochemical properties such as wettability, charge, heterogeneity, topography, roughness and the presence of functional groups (Vladkova, 2010)

The direct biochemical interactions between the surface of titanium implants and tissue molecules are short range; the predominant type of chemical bonds is the weak forces of van der Waals and hydrogen bonds such as polarization and molecular electric dipoles. The surface energy is directly proportional to the tendency to adsorb molecules. The general rule is that materials with a surface tension between 20 and 30 dynes/cm^2 exhibit a low adsorption. Materials with surface tension values above this range are more adsorptive.

The sessile drop technique is a method used for the characterization of solid surface energies, and in some cases, aspects of liquid surface energies. The main premise of the method is that by placing a droplet of liquid with a known surface energy, the shape of the drop, specifically the contact angle (figure 3), and the known surface energy of the liquid are the parameters which can be used to calculate the surface energy of the solid sample.

The Owens/Wendt theory (Owens et al., 1969) divides the surface energy into two components: surface energy due to dispersive interactions and surface energy due to polar interactions. The no dispersive or polar component arises from electrostatic interactions, metallic bonding forces, hydrogen bonding and dipole interactions. The dispersive or no polar component has its origin in interactions between molecules and covalent bonds. These two components can be calculated as t he ratio of the contact angles with surfaces with known properties and the contact angles with the surface under investigation.

There is a relationship between critical surface tension and biocompatibility. The surface energy model includes contributions from the solid phase (implant) and the liquid phase (blood) to the physiological results. The basic premise is that the driving force for protein adsorption is the surface free energy. Thus, proteins are not strongly absorbed in a surface with low interfacial free energy and remain in solution. In the case of dental implants, the properties of the liquid phase can be changed by drugs to activate tissue mechanisms that facilitate adherence. The use of drugs and an adequate preparation of the implant surface are seen as complementary methods to improve osseointegration.

Materials with a high surface energy adsorb macromolecules more easily, have a higher number of favorable sites for cell adhesion, and facilitate the growth of layers that stimulate cell binding. In order to improve osseointegration, it is desirable that the strength of the non-dispersive component of the surface tension be as low as possible, while the dispersive component remains high.

8. Types of dental implants

There is not a consensus among researchers as to the best surface roughness and even the shape of the implants. As shown in figure 1, there are a number of types of dental implants available. The same manufacturer produces implants with different shapes and surfaces. It is common knowledge that the geometric shape of the implant should be chosen in such a way to provide the largest bone-implant contact area in order to improve osseointegration decrease the stress concentration close to cervical area.

Commercial dental implants can be divided into groups according to shape, type of connection to the prosthetic component, surface treatment and roughness.

a. Shape (figure 5): cylindrical, conical, hybrid;
b. Type of connection (figure 6): external hexagon, internal hexagon, Morse taper, dodecagon;
c. Surface treatment (figure 7): acid etching, sandblasting, anodizing, coated by plasma sprays, nanoparticles deposition, laser treatment,
d. Surface roughness: macroroughness (figure 7D and 6E), microroughness (figure 7A), nanoroughness

In an attempt to improve the interaction between bone and implant, increase the surface area, improve the distribution of forces to the bone and achieve a better primary stability, various implants shapes were developed. Screw-shaped dental implants dominate the dentistry market. The screw shape provides a large contact area between implant and bone, increases primary stability, reduces the shear stress in the bone-implant interface, reduces the stress concentration in the cervical region and relieves stress concentration. The thread profile is characterized by the depth, pitch, flank angle, the top radius of curvature, and the straight part at the bottom of the thread. The rounded thread top relieves stress concentration and reduces the stress on the bone. However, there is no recommendation or standardization for the screw of dental implants. During bone repair, it is important that implant micromotions do not submit the tissues to any kind of trauma. Destabilization of the bone-implant interface leads to the interposition of fibrous tissue on its surface and prevents osseointegration.

Implants with large thread steps increase bone-implant interface shear stresses which should be avoided because bones have a lower strength to shear than to tension and compression.

Fig. 5. Dental implants design. (Courtesy of Conexão Sistemas e Prótese, Brazil).

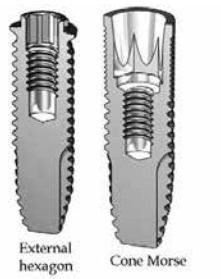

Fig. 6. Dental implant with external hexagon and internal Morse taper. (Courtesy of Conexão Sistemas e Prótese)

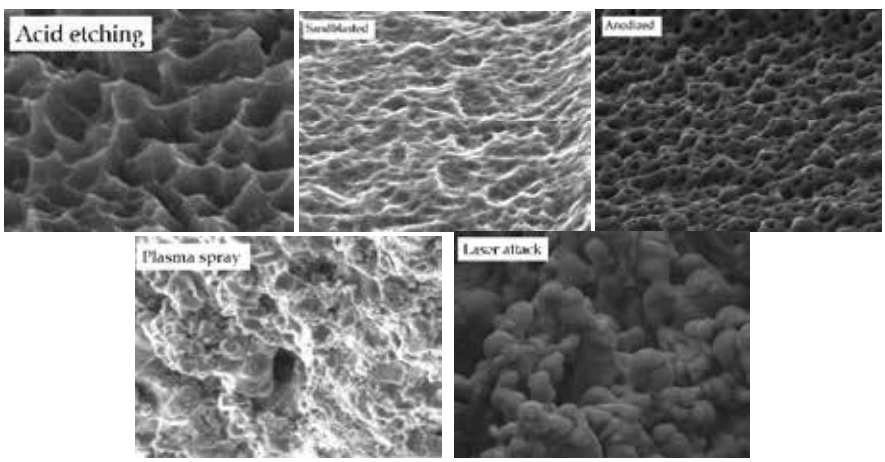

Fig. 7. Surface morphologies of available titanium dental implant. (A) Acid etching. (B) Sandblasting. (C) Anodizing. (D) Coated with TiO_2 by plasma spray. (E) Laser treatment.

By varying the profile of fillets of tapered threads is possible to increase the surface area of the conical implant relative to cylindrical implants with the same diameter and length (table 1). Implant thread fillets are not standardized. The fillet can be triangular, square, V-shaped, rounded or trapezoidal (figure 8).

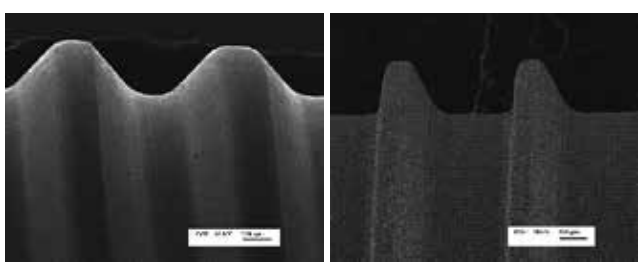

Fig. 8. Profiles of fillets. Cylindrical implant (left) and conical implant (right).

Initially, prostheses were composed of seven parts: implant, intermediate, intermediate screw, abutment, abutment screw, bolt retainer and prosthesis. However, clinical experience has shown that the larger the number of components, the greater the possibility of failure.

Currently, cemented prostheses are composed of four elements: implant, abutment, abutment screw fixation and prosthetic crown. Screwed prostheses are made of implant, abutment, abutment screw, crown and screw crown. These sets require a strict control of manufacturing and design to ensure that the chewing forces are properly transferred to the host. There is an apparent lack of consensus as to the implant shape that provides the best performance. For some, the choice of a threaded cylindrical implant takes into account the prevalence of compressive stresses in relation to shear; the choice of a cylindrical implant maximizes the importance of maximum resistance to shear stress.

Length (mm)	Cylindrical	Conical
8.5	217.57	-
10.0	252.55	283.69
11.5	283.52	311.76
13.0	316.92	343.44
15	360.18	383.51

Table 1. Influence of dental implant design on the surface area. Implant diameter equal to 5.0 mm.

With respect to length and diameter, the implants are marketed with different dimensions, in order to take into account different clinical treatment. Dental implants with cylindrical threads are commercially available with diameters between 3.25 and 6.0 mm and lengths between 5 and 18 mm. For implants with similar surface treatments, the larger the size, the greater the resistance to removal of the implant after osseointegration. The choice of implant size is determined by the available space, bone quality and implant bed. Based on the characteristics and volume of available bone in the region of surgery, the professional defines the type, shape and size of the implant to be used.

Among the different parts of the implants, the dimensions of the cervical region deserve the most attention. About 12% of connections show loosening of the abutment screw during the first year of use due to lack of stability. To minimize this problem, many implants are designed with an external or internal hexagon. However, only changes in the design of implants are not sufficient to eliminate the problem; one must examine the dimensional tolerances of the implants, the interchangeability of parts and the couplings between parts. Binon (Binon, 1998) found that the lack of fit between implant and prosthesis causes instability of the joints connecting the system. In other words, a difference between the dimensions of the implant hexagon and hexagon connection impairs the system stability Therefore, one should take special attention to dimensional tolerances of the implants and connections, which depend on factors related to part manufacturing, surgery planning and execution and the implant quality.

9. Roughness

The importance of implant surface topography for successful osseointegration was first pointed out by Albrektsson et al. (Albrektsson et al., 1981). More recent studies have confirmed that the surface roughness of implants affects osseointegration and the mechanical stability of dental implants (Werner et al., 2009; Zhu et al., 2004; Puleo, 1992;

Wennerberg et al., 1998a) . Several mechanisms involved in osseointegration depend on surface morphology, since the cells react differently in contact with smooth surfaces and rough surfaces. Fibroblasts and epithelial cells adhere more strongly to smooth surfaces and the ability of osteoblast proliferation and collagen synthesis is greater in surface with moderate roughness (Wennerberg et al., 1998b; Cochran et al., 1998). Despite the importance of roughness in osseointegration, there is no standard for the roughness of dental implants.
The surface of dental implants is greatly influenced by the action of the cutting tool. Elements such as tool shape, speed, feed, and cutting fluid can be varied to affect the surface topography. Other factors affecting the surface are the instability of the cutting tool due to chatter or imbalance in the grinding wheel, and errors in the machine tool guideway (Morton, 1994).
Machined dental implants have a pattern of grooves from the manufacturing process that can be detrimental for osseointegration (figure 9). To improve osseointegration it is important that the surface treatment creates the right kind of defects. Depending on size, surface topography can be defined in terms of surface roughness, waviness and form (Figure 10). For dental implants, roughness is the most important feature.

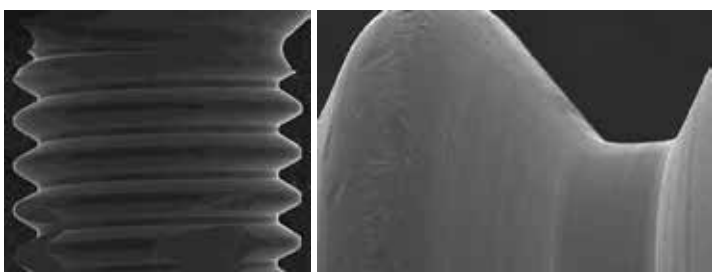

Fig. 9. Surface morphology of machined dental implant, showing the grooves left by the manufacturing tools.

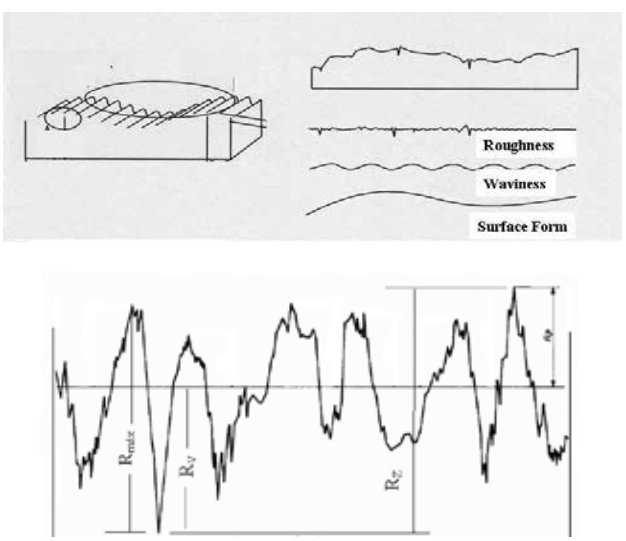

Fig. 10. Sketch representing the surface topography and roughness parameters.

Surface roughness is the primary component of texture and refers to high frequency irregularities. In the case of dental implants, surface roughness consists of fine imperfections on the order of micrometer (μm) due to the cutting process (figure 9) or due to a surface treatment (figure 7). In machined implants, roughness is closely related to the cutting tool and consists of a regular pattern of shallow grooves.
Surface waviness refers to the secondary component of texture upon which roughness is superimposed. It is as a series of regular deviations of approximately sinusoidal shape and a size on the order of millimeters. It is attributed to the deformations and vibrations of the machine and the part during manufacturing.
Surface form is some irregularity the general shape of the surface, neglecting roughness and waviness, which is frequently caused by errors in the machine tool guideway and deformations due to stress patterns in the component.
Since the basic types of surface geometry are caused by different factors and tend to have different relationships to the performance of the component, it is usual to consider them separately during analysis. In general, if control of dental implant performance related to surface topography is required, roughness is main parameter to be analyzed.
For effective analysis of surface roughness, the profile is evaluated according to internationally recognized mathematical formulas called parameters (ISO 468: Surface roughness parameters. ISO 4287: Surface texture: Profile method, terms, definitions and surface texture parameters. ISO 4288: Surface texture: Profile method, rules and procedures for the assessment of surface texture. ISO 8785: Surface imperfections, terms, definitions and parameters. BS 1134-1: Assessment of surface texture, methods and instrumentation. BS EN ISO 3274: Geometric product specifications (GPS). Surface texture and profile method. ASME B46.1: Surface texture: surface roughness, waviness, and lay). The purpose of using a parameter is to resort to a number that can characterize a certain aspect of the surface and hence eliminate the need for subjective operator assessment. Since it is not possible to characterize a surface completely with a single parameter, a combination of parameters is normally used.
Despite the importance of surface roughness on osseointegration of dental implants, there are no standards to measure the roughness of the implants. The procedure adopted has been to adopt the same parameters used in engineering. Moreover, previous studies of the subject (Wennerberg 1996; Elias et al., 2008) analyze only a few parameters and offer no conclusive explanation of the influence of each roughness parameter on osseointegration.
Roughness measurements are performed using mechanical or electronic devices, such as a style instrument called profiler. The use of a contact roughness meter (mechanical) has several limitations, including the fact that the values of peak heights and depths of valleys are limited by the tip shape. The most common non-contact technique uses a laser beam. It is also possible to evaluate the surface roughness by atomic force microscopy; however, this technique is limited to a small region of the specimen.
Surface roughness is characterized by small protrusions (peaks) and holes (valleys) on the surface in relation to a reference plane. The parameters used to quantify this roughness are determined in two dimensions (2D) or three-dimensional (3D). The letter "R" is used for parameters related to roughness and the letter "S" for parameters related to the surface profile. The measured parameters can be divided into three groups:

a. Spaciousness parameters are measures of the height of the irregularities or vertical deviations on the surface. They are determined by the peak heights and depths of

valleys, or both, regardless of the spacing between the irregularities along the surface (R_a, R_q, R_z, R_{sk}, R_{ku}, R_t, S_a, S_q, S_z, S_{sk}, S_{ku}, S_t, R_p, R_v, R_c, R_m).

b. Spacing parameters are determined by the distance between irregularities along the surface (Sm and Scx)
c. Hybrid parameters describe a combination of the amplitude and spacing of surface irregularities (S_{qd} and S_{dr}).

Roughness average (R_a), the most common1y used roughness parameter, is defined as the mean height of the roughness profile. Its main drawback is the fact that different profiles may have the same Ra and differ significantly in performance. Another averaging parameter, R_q, defined as the root mean square of the roughness profile, is more sensitive to surface variations. After a surface treatment of the implant, it may be more adequate to specify the maximum roughness height, R_{max}, or the peak-to-valley height, R_z, rather than use the mean height given by R_a. The R_{max} parameter measures the highest and lowest points of the profile. There are doubts as to whether the variations in the heights of surface irregularities are more important than the distance between them, or what the best combination of these factors for osseointegration is.

The definitions of the main roughness parameter are:

- R_a (average roughness): R_a is average value of the amplitudes in relation to a reference line. This parameter quantifies the average vertical distance between the five highest peaks and five major valleys.
- R_q or R_{ms} (root mean square roughness): R_q is the square root of the squares of the amplitudes in relation to the midline. The squaring of the values of irregularity increases the effect of the irregularities that deviate markedly from the average.
- R_z (average partial roughness): R_z is the arithmetic mean of five values of the partial roughness Z_i. The partial roughness Z_i is defined as the sum of the absolute values of the ordinates of the points of greatest deviations (above and below the midline) existing within a sampling length. Graphically, this represents the height between the maximum and minimum points of the profile within the sampling length.
- R_{max} (maximum roughness). R_{max} is the largest value of partial roughness Z_i along the measurement path. Another parameter similar to R_{max} for measuring surface roughness is R_y, defined as the maximum distance between the highest peak and the largest valley within the sampling length.
- R_t (total depth). R_t is the vertical distance between highest peak and the deepest valley.
- R_{3z} (average roughness of the third peak). In each module are plotted the distances between the third highest peak and the third deepest valley. R_{3z} is the height of this peak plus the depth of the valley.

Other amplitude parameters are:

- R_{sk}: asymmetry factor (skewness);
- R_{ku}: flattening profile (kurtosis);
- R_p or Z_p: maximum height of the highest peak of surface roughness, situated above the midline.
- R_v or Z_v: depth profile of the largest valley
- R_c: average height of the profile elements
- R_{om}: depth of the deepest valley
- S_m: mean distance between furrows or average distance between peaks
- R_{Sm}: average width of the profile elements

- PC: number of peaks per unit length

The mean values of some roughness parameters for a titanium surface are displayed in Table 1. After surface treatment, significant changes are observed in the roughness parameters that affect the cell-surface interaction, as measured by implant removal torque. Multiple comparisons Tukey's HSD tests have shown a statistically significant difference in R_a after surface treatment. The machined surface has grooves, which increase roughness. The surface area (A_1 and A_2 in Table 2) was larger after sandblasting and anodizing; statistically significant differences were found between these groups and the others (Elias et al., 2008).

Group	R_a (µm)	R_q (µm)	R_z (µm)	R_{max} (µm)	R_{pkx} (µm)	A_1 (µm²)	A_2 (µm²)
Machined	0.65±0.11	0.81±0.17	6.09±0.37	7.76 ± 1.37	21.6±0.41	24.71 ± 5.42	70.66±16.20
Acid	0.51±0.10	0.71±0.07	5.09±0.46	6.78 ± 1.33	1.77±0.37	34.76 ± 7.35	103.86±14.80
Blasted	0.75±0.05	0.98±0.04	5.55±0,21	12.44 ± 9.7	6.75±0.76	99.75± 6.76	190.13± 4.90
Anodized	0.87±0.14	1.12±0.18	5.14±0.69	19.84±2.13	16.71±2.47	97.67±11.43	215.37± 1.67

Table 2. Mean value ± SD of titanium cylinder surface roughness parameters.

A previous study (Links et al., 1998) pointed out the importance of the surface topography of implants on the regulation of the osteoblast physiology. For instance, on smooth surfaces osteoblasts seem to have decreased adhesion, but proliferate at a high extent. On rougher surfaces they seem to adhere further, proliferate at a low extent and show an increased protein secretion, resembling a more differentiated phenotype. However, if the peaks of the surface topography are too high or the distance between them is too great, the cells may be essentially dealing with smooth surfaces.

Also important is the osteoblast attachment, which is affected by surface treatment. Menezes et al. (Menezes et al., 2003) analyzed osteoblast adhesion onto titanium implant acid etched (HNO3) for 20 seconds (Group 1), 60 seconds (Group 2) and 90 seconds (Group 3). They observed a tendency of increase in cell attachment as the surface becomes rougher. Figure 11 shows the influence of osteoblast attachment onto surface acid etched during different time.

Data concerning cell attachment reveal a tendency of smooth surfaces to be a poorer substrate for osteoblast attachment when compared to rougher ones. (Eriksson et al., 2001) demonstrated that leukocyte adhesion on rough titanium surfaces is higher as well as its expression of adhesion receptors when compared to smooth counterparts. This could also occur with osteoblasts onto titanium surfaces.

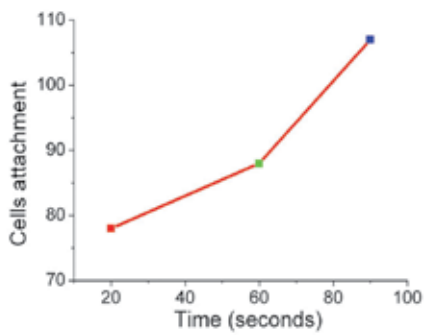

Fig. 11. Osteoblast cell attachment on titanium surfaces acid etched after 20, 40 and 60 seconds. (Adapted from Menezes et al., 2003)

The fact that osteoblasts on smoother surfaces exhibited a lengthened shape may be reflecting the grooves on the surface formed by the machining tolls (figure 12) Cells tend to grow along the grooves where those are seen. In consequence, if the grooves of the surface are arranged parallel to each other, cells become arranged in the same way. Osteoblasts also tend to spread over large areas in smooth surfaces. Thus, a rectangular shape and an arrangement in a continuous monolayer are expected to occur. Menezes et al. (Menezes, 2003) conclude in their work that smooth implant surfaces are poorer substrates for osteoblast attachment. Also, differentiation of the cells surrounding the implant should be the primary concern as long as a calcified bone around the implant is wanted.

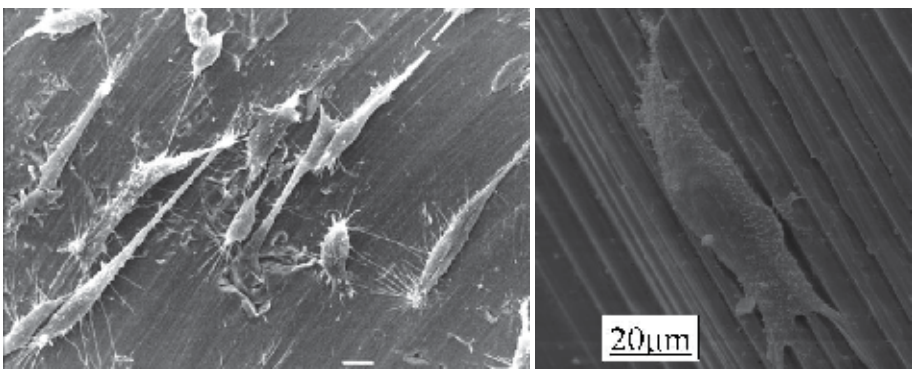

Fig. 12. Osteoblast cells growing along the grooves. (Menezes et al. 2003)

10. Influence of the implant surface on primary stability

Javed and Romanos (Javed & Romanos, 2010) evaluated the role of primary stability for successful of immediate loading (IL) of dental implants. This analysis is important because a fundamental prerequisite for implant success is substantial primary stability at the time of insertion and following loading of the implant. It may be considered as the unifying principle behind the need for adequate bone volume and density, longer or wider implants, and the 3–6-month delay recommended before implants are placed in function. A poor primary stability is one of the major causes of implant failure.

Although establishment of a good primary stability has been the primary focus during implant placement, there are numerous other factors that may contribute to the initial retention of the implant. Therefore, it is critical to maintain the integrity of the peri-implant tissues since bone resorption takes place with or without implant placement in the fresh extraction site. Specifically, for immediately loaded implants, the role of the primary implant stability with the surrounding, mature bone seems to be crucial for long term success.

Studies have shown that surface topography and roughness positively influence the healing process by promoting favorable cellular responses and cell surface interactions. Implant surface characteristics have also been shown to influence primary stability (Santos et al., 2009). Rough surfaces are considered to enhance primary stability as they present a larger surface area and allow a firmer mechanical link to the surrounding tissues (Romanos et al., 2002). Figure 13 shows the influence of surface finishing on dental implant primary stability.

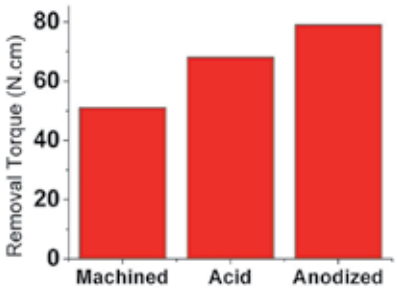

Fig. 13. Effect of the implant surface treatment on the insertion torque (N.cm). (adapted from Santos et al., 2009)

The primary stability of an implant fixture at the time of placement is often estimated by judging the presence of any mobility. In clinical work, primary stability can be evaluated either by the mobility from percussing an implant with a blunt instrument such as a mirror handle. The follow up of the implants can be estimated by devices such as Periotest, Periometer, resonance frequency analysis (RFA) and placement torque. Some factors affect the implant's primary stability, including the bone density, the implant design, the surgical technique, the insertion torque, and the instrumentation protocol. Among these parameters, the insertion torque has not yet been sufficiently analyzed. The insertion torque is a function of the implant surface treatment, design, and screw-thread geometry.

Santos et al. (Santos et al., 2009) analyzed the influence of dental implant surface on primary stability. Their results showed that the maximum torque to insert the implant depends on the friction coefficient between the implant surface and the placement wall, implant design, implant thread geometry and surface treatment.

For the same finishing surface, the differences in insertion torques reflect different implant geometries. The torque to install a conical implant is larger than the torque to install a cylindrical implant (figure 14). This difference can be attributed to the different thread geometry. Figure 8 and 15 show the cylindrical and the conical implants threads geometries. The screw threads are different in cylindrical and conical implants. The thread geometry of the conical implant increases the implant surface area in contact with the host tissue. The reduction in pitch of the conical implant thread increases its contact area as compared to the cylindrical implant. The conical implant has a larger area than the cylindrical implant (table 1). As surface area increases, the friction surface between the implant and the site wall increases, demanding a larger insertion torque.

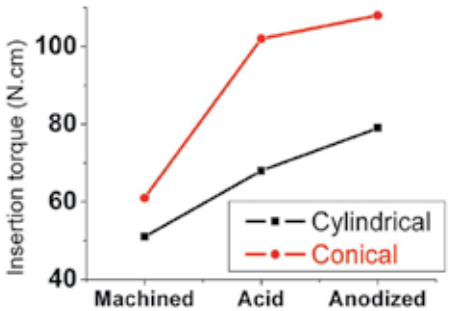

Fig. 14. Effect of the dental implant design and surface treatment on the insertion torque (N.cm). (adapted from Santos et al., 2009).

The implants submitted to a surface treatment presented a higher roughness and higher friction coefficient than the machined one. The implant that required the smaller insertion torque was the machined one, which possesses a smooth surface compared to the acid-etched or anodized samples. The insertion torque for the acid-etched implant was significantly different from the anodized implant.

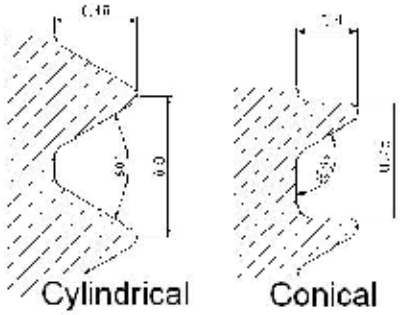

Fig. 15. Thread geometries of implants with cylindrical and conical design.

Javed et al. (Javed et al., 2011) reviewed the influence of surface morphology on the primary stability of dental implants. They conclude that rough-surfaced implants have significantly higher success rates compared with dental implants with smooth surfaces. Although the results in the literature show a direct relationship between surface roughness and overall implant stability, the influence of surface roughness on primary stability remained undetermined. Therefore, it is important to differentiate the initial implant stability gained from surface topographical features from that gained by the BIC.

11. Wettability

Dental implant surface wettability influences the degree of contact with the physiological environment. Highly hydrophilic surfaces seem more desirable than hydrophobic ones in view of their interactions with biological fluids, cells and tissues. Complete moistening and distribution of a liquid on a surface indicates high surface energy, biocompatibility and hydrophilicity of a material. Measurement of the contact angle of a liquid is one way to quantify the surface free energy of solids or the ability of the liquid to wet the solid. When the contact angle is greater than 90 degrees the surface is hydrophobic, as opposed to less than 90 degrees, when the surface is hydrophilic.

When a drop is placed in contact with the surface of a solid, there is interaction between the atoms of the liquid, the solid and the surrounding air. This interaction is observed in form of an attractive force between the atoms of the three materials. The greater the interaction between the surface and the liquid, the greater is the flattening of the drop (figure 3).

Baier and Meyer (Baier & Meier, 1988) related the critical surface tension between implants and biocompatibility. According to these authors, materials with high surface free energy adsorb more easily and have a higher number of favorable sites to allow connections to the cells. The general rule is that materials with a surface tension between 20 and 30 dynes/cm ^{2} exhibit low adhesion and materials with surface tension above this range have better results for osseointegration.

Baier (Baier & Meier, 1988) observed the effect of surface energy of titanium in bioactivity and found that the thickness of the protein that forms on the surface of the implants after 10 days of deployment depends on the surface energy. Histological observations made on implants with high surface energy indicated that they have layers of proteins with greater thickness than those with low energy. The cellular activity varies with the surface energy of the sample. When implants with low surface energy were mechanically separated from the capsule tissue and analyzed under a microscope, it was found that soft tissues occurred in most of the surface. It was observed that the host tissue in contact with implant with low surface energy has cells with globular appearance, almost spherical, that can easily be separated. The globular appearance of these cells identified them as fibroblasts and is associated with poor cell growth, but is not related to the normal activity of fibroblasts in the healing process.

Elias et al. (Elias et al., 2008) analyzed the influence of the dental implant surface treatment on contact angle and on removal torque (Table 3). The results showed that the surface treatment changes the surface wettability. The implants with treated surfaces showed greater roughness, higher friction coefficient, lower contact angle and demanded a larger insertion torque than machined implants. The contact angle of NaCl (highest hydrophilic liquid tested) with the anodized surface had the smallest value. No statistically significant difference ($P < 0.05$) in the contact angle between blood and any titanium surface was observed, except between blood and the anodized surface.

	Mean value ± SD contact angle (degree)				Removal Torque (N.cm)
Implant Treatment	**Water**	**DMSO**	**NaCl**	**Blood**	
Machined	85.20 ± 3.55	72.4 ± 2.3	51.6 ± 1.8	66.4 ± 0.5	57.0 ± 18.6
Acid etched	96.24 ± 9.20	68.7 ± 2.5	44.4 ± 1.6	61.6 ± 0.7	75.45 ± 10.5
Sandblasted	79.86 ± 4.85	52.5 ± 2.6	43.0 ± 0.9	61.8 ± 0.1	72.15 ± 14.9
Anodized	47.25 ± 2.94	38.3 ± 2.1	25.3 ± 1.3	55.5 ± 0.3	83.15 ± 12.7

Table 3. Mean value ± SD contact angle of treated titanium surfaces and dental implant removal torque from rabbit.

12. Influence of bone

Theoretically, for implants with the same dimensions, the choice of surface finishing is based on the type of bone that will receive the implant. Lekholm and Zarb (Lekholm & Zarb, 1985) classified the types of bones based on the quality of cortical bone and trabecular bone density. According to them, the bones can be classified as type D1, D2, D3 and D4.

The D1 bone has dense cortical and trabecular bone. Clinically, the D1 bone has little bleeding during surgery, indicating a slight vascularization. Because it is a harder bone, one should take extra care during the preparation of the implant insertion site to prevent overheating. Localized heating prevents the initial necrosis, which can be prolonged by ischemia caused by compression of the implant on the walls of the bone, keeping the contact area of bone in a state of compression. Implants with a length of 10 mm can be used.

The D2 has satisfactory cortical bone and a less dense and vascularized trabecular bone. In D2 bone there is lots blood in contact with the implant surface and initial stability is good. The implant should be at least 12 mm length and is required that at least 50% of the surface keeps the initial contact with the bone.

The cortical and trabecular in D3 bone is less dense than D2 and lower mechanical strength. Clinically, it is a brittle bone, with cortical and trabecular fragile little dense, which can often lead to poor initial anchor the implant.
The D4 bone has cortical papyracea (slender), slightly mineralized trabecula and has low mechanical strength. This type is very fragile, leading to a delicate surgical procedure to achieve initial implant anchorage.
Normally, the bone is of type D1 and D2 in the region between the mental foramen in the mandible and anterior maxilla. The bone type D3 can be found in the region of upper premolars and lower type D4 and will always be found in the molar region of mandible and maxilla.
For bone D1 and D2 can indicate machined dental implants without surface treatment. For the bone type D3 and D4 must be employed treated implant surface, which has higher contact area than machined and can improve the mechanisms involved in osseointegration. For the D3 and D4 bone type should always choose implants with surface treatment Misch (Misch, 2008) suggested for the D4 bone the use of implants larger than 12 mm and the largest diameter possible. The cavity preparation must be done very carefully, since due to low mechanical strength of bone, small lateral movements can easily move the slope of the planned implant.

13. Influence of surface morphology on implant osseointegration

Although titanium is used extensively as a biomaterial, there are still doubts about the procedure to obtain the best biological response. When analyzing the importance of the surface of the implant osseointegration to occur, one should separate the discussion of the influence of implant shape (design) and surface morphology. In shape analysis consider the dimensions of the implant (length, diameter, thickness), shape (barrel shape, cylindrical, conical and hybrid), type of threads (triangular, square, trapezoidal, rounded, microthread), height of fillets of threads, the thread angle, thread pitch and implant-prosthesis connection type (extern hexagon, internal connection in the form of a hexagon, cone Morse, star grip). These parameters influence the primary stability, the distribution of forces and mechanical properties of the implant. As for surface morphology should be analyzed macro and nanomicroestructure as well as the homogeneity of the surface, the chemical and physical properties.
Several researchers (Wennerberg et al., 1998; Hayakawas et al., 2000; Kokubo et al., 1999) examined the influence of surface properties of titanium implants on bone apposition into surface and the results showed that the biological response depends on the morphology, surface composition and titanium oxides on the implant surface in contact with the physiological environment. These results are important because the dentistry selects the roughness of the implant according to the surgical protocol, site of insertion, quality and quantity of available bone.
The surface properties of implants such as morphology, roughness, thickness of the oxide layer, impurity level and types of oxides depend on the surface treatment process. The difficulty in analyzing the influence of these parameters is the current inability to change only one parameter at a time keeping the others unchanged. For example, it is not feasible to modify only the titanium oxide crystalline structure or chemical composition, without change the oxide thickness.
During insertion of the implants immediately after the surface comes in contact with blood, a protein cover the implant surface. Titanium in contact with the physiological environment

absorbs molecules from the plasma, as so absorb factor I, factor III, Ig G and C1q. A few seconds after inserting the implant can find polymorphonuclear granulocytes and platelets adhered on its surface. Then there is the adhesion of mature granular leukocytes, neutrophils, basophils and acidophilus. The granulocytes polymorphonuclear leukocytes are the first recruited by the titanium surface exposed to contact with blood. Depending on the surface preparation is no difference in the absorption and reaction of cells exposed to titanium by contact with human blood (Werner et al., 2009; Puleo &Bizios, 1992; Kasiwagi et al., 2009; Novak et al., 2009; Eriksson et al., 2001). The adhesion of monocytes (mononuclear leukocytes of intense phagocytic activity, representing 3-7% of circulating blood leukocytes) is sensitive to variations in the thickness of the titanium oxide layer (Eriksson et al., 2001). Polymorphonuclear granulocytes are more dependent on surface roughness of the implant. Macrophages prefer areas with lower roughness.

A few months after insertion, the implants with treated surface have a higher amount of bone overlying the surface than machined implants with lower roughness. Possibly, the success depends on the speed of osteogenesis around the implant, ie, early osteoblast adhesion on implant surface. Despite this finding, it is unclear how the implant surface promotes or inhibits osteogenesis. The behavior of cells is dependent on the interaction of action and triggering activity of the cells and molecules (Henessy et al., 2009).

Cells have mechano-receptor properties that can identify whether or not the surface has features appropriate to begin the process of differentiation and bone matrix. The proteins attached on the surface of the implants induce adsorption and pre-osteoblastic cells. Research results show that the surface treatments affect the interfacial forces, wettability, roughness, energy and adsorption capacity of the molecules that recognize osteoblasts (Eriksson et al., 2001). Biomaterials in contact with the biological environment suffer dynamic changes in their surface properties, involving a cascade of reactions at the interface between the environment and biomaterial, forming a "conditioning film" that modulates the responses cellular (Puleo & Bizios, 1992). The wettability and surface energy influence on the adsorption of proteins and increase focal adhesions of osteoblasts on the surface of implant (Kashiwagi et al., 2009).

14. Surface treatment of implants

Numerous surface modification approaches have been developed for all classes of dental implants to modulate biological responses and improve the osseointegration and primary stability. Study of the surface treatment of dental implants is multidisciplinary, involving researchers from Materials Science, Mechanical Engineering, Mathematics, Computer Science, Dentistry, Surgery, Biophysics and Veterinary Medicine. The involvement of professionals from various fields and diverse knowledge facilitates the work, the analysis of results and development of new shapes and surfaces for the implants. Research results show that despite of the high success (95 to 98%) of titanium dental implants, it is necessary to analyze the surface characteristics of the implant with respect to surface finishing, physical properties, chemical composition, residual stress, morphology, microstructure and type of oxide (Henessy et al., 2009). A finishing deficiency of the implant can jeopardize the success of surgery, especially when there are contaminants from the manufacturing process, presence of burrs and stress concentration that compromises the mechanical performance of the implant during loading.

The success of dental implants will not occur when the implant surface morphology does not present features that allow adhesion and cell growth. The problem is increased by the presence of contaminants, mainly alumina particles used in the blast, which are toxic and lead to apoptosis. The deleterious effect of the existence of machining chips or holes in the surface of the implants refers to the possibility of these defects releases during implant insertion into the cavity and compromise the osseointegration. The process of machining and processing further determine the surface properties of implants, especially the electronic structure, crystalline oxide, chemical composition, mechanical and chemical properties.

The primary stability depends on the shape and surface morphology of implant. The secondary stability depends mainly on the implant surface. The differences among surfaces of available dental implants are the roughness, chemical composition, surface energy, chemical potential, the segregation of hydrides and nitrides, work hardening, the presence of metallic and nonmetallic, existence of impurities resulting from the manufacture or handling, type titanium oxide, crystal structure and oxide thickness of the oxide layer. This is important since the proteins interact with the oxides of the implant surface and the interaction depends on these parameters.

Surface roughness of dental implants can be analyzed in three orders of magnitude: macroscopic, microscopic and nanoroughness. Each size of the roughness provides contacts with different cells and biological molecules and is responsible for the intensity and types of biological bonding. A priori, it is expected that the increased surface area of the implant, increase the number of sites to bind to cells, facilitates tissue growth and increase the mechanical stability. However, this is not a general rule. Fibroblasts avoid rough surfaces and accumulate in the smooth surface. In contrast, macrophages exhibit rugophily behavior, or prefer to attach to rough surfaces. The epithelial cells are more attracted to rough surfaces than for smooth. Osteoblast cells adhere more easily on rough surfaces like those found on commercial implants with treated surfaces than in machined (Jayaraman et al., 2004; Le Duc & Wang, 2006; Thull, 2002; Lim et al., 2004).

The chemical composition of the surface determines the stability and reactivity of the implant, which shall consist solely of titanium oxide. Although there are no conclusive studies of the influence of impurities on the surface of the implants, the surface should contain the lowest possible levels of contamination. The surface energy and the existence of residual stresses after sandblasting modify the reactivity of the surface. Implant with coating has a complete different behavior. The coating modifies the behavior of cells and cascade reactions.

The surface morphology of dental implants is modified by chemical, mechanical and electrochemical treatments. By treating the surface of implants is possible to reduce the healing and loading time after surgery, accelerate growth and bone maturation, to increase the primary stability and to ensure the successful application in bone with less quality and quantity. There are many variables, combinations of parameters related to the implant surface treatment and factors that influence osseointegration (material, implant shape, implant surface, bone quality and quantity, surgical technique and loading condition).

The companies adopt a variety of techniques for surface treatment of commercial implants. By treating the surface of implants, it is possible to increase the stability, the wettability, the contact between implant and bone, the strength of the bone-implant interface and the success of treatment in patients seen as critical. Furthermore, it is possible to improve the retention of tissue, stimulate the healing process and reduce the loading time.

The choice of the methodology to be used in surface treatment is initiated by selecting the desired roughness, since the procedures for macroroughness, microroughness and

nanoroughness are different. The current trend is to obtain hybrid surfaces, i.e., a morphology with micro- and nanoroughness. In some cases, the chemical composition of the implant surface is changed with addition of calcium, phosphorus and fluoride (Ellingsen et al. 2004). The precise role of surface chemistry and topography on the early events in dental implant osseointegration remain poorly understood.
For study purposes, the surface modification of dental implants shown in figure 7 and 9 can be divided in the followings classes:

a. machined surface (untreated surface);
b. plasma spray;
c. laser treatment;
d. acid etching;
e. sandblasting and sandblasting followed by acid etching;
f. anodizing;
g. deposition of nanoparticles by physical or chemical methods.

14.1 Implants with untreated surface (as machined)

Implants with untreated surface (machined) were the first to be used, but are seldom employed nowadays After manufacturing, these implants are subjected to cleaning, decontamination, passivation, and sterilization. The implants without surface treatment are inappropriately called "smooth". The term "smooth" is inadequate, since scanning electron microscopy shows that the surface of these implants has tool marks from the machining process (figure 9).
The disadvantage regarding to the morphology of untreated implants is the fact that osteoblastic cells are rugophilic – that is, they are prone to grow along the grooves existing on the surface, as shown in figure 12. This characteristic requires a longer healing time between surgery and implant loading. The use of these implants follows a protocol suggested by Brånemark: 3–6-month healing or waiting time prior to loading. Owing to morphological characteristics and lower resistance to removal torque (Table 1), machined dental implants are becoming commercially unavailable.

14.2 Surface treatment with plasma spray and laser

Two alternative surface treatments are laser ablation and plasma spraying the surface with a ceramic. After both treatments the implant surface has a large roughness (figure 7), which can be characterized as an area under macroroughnesss. The macroroughnesss influence the primary stability and mechanical fixation of bone formation but does not alter the behavior of cells during the period of osseointegration.
Gaggl et al. (Gaggl et al., 2000) cited that (i) surfaces of laser-treated Ti implants showed a high purity with appropriate roughness for good osseointegration, and (ii) the laser-treated Ti had regular patterns of micropores with interval of 10-12 μm, diameter of 25 μm, and depth of 20 μm.
Cho and Jung (Cho & Jung, 2003) evaluated the significance of different surface textures by comparison of the removal forces for laser-treated and machined titanium screw 8 weeks after the installation in rabbit tibia. They observed that laser treatment created a deep and regular honey-comb pattern with small pore, while machined treatment created the typical microscopically grooved and relatively smooth surface characteristic. In the laser surface, the distance between the pore was 10–12 μm. Eight weeks after implant placement, the

average removal torque was 23.58 ± 3.71Ncm for the machined implants, 62.57 ± 10.44Ncm for the laser-treated implants.
The micropores in laser treated implants, evaluated by Gaggl et al. (Gaggl et al., 2000) and by Cho and Jung (Cho & Jung, 2003), do not improve osseointegration. Figure 16 shows the morphology of an implant surface treated with a laser. The surface exhibits macroroughness at low magnification, whereas melting structures can be observed at high magnification. At higher magnification, a laser-treated surface is smoother than acid etching. The best implant surface has microroughness and nanoroughness.

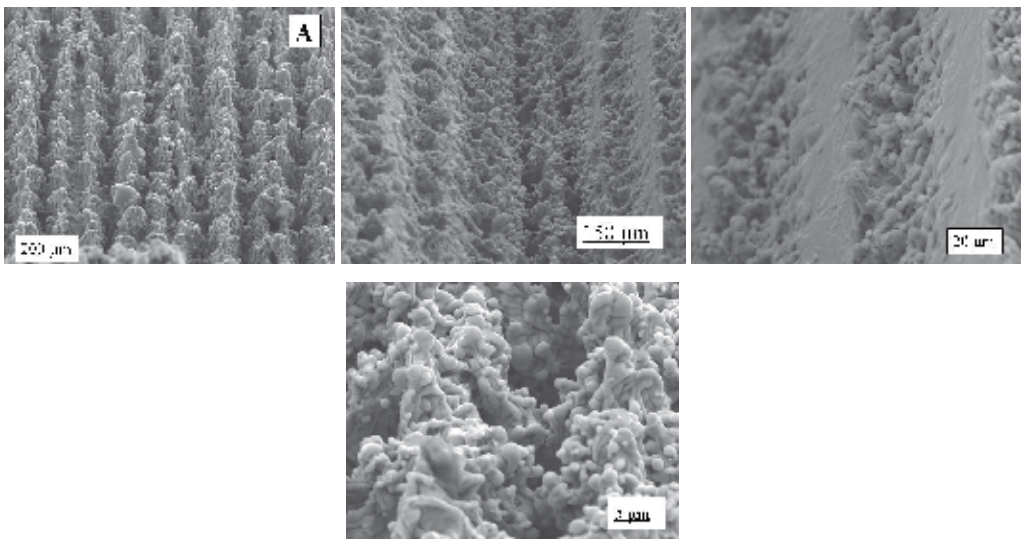

Fig. 16. Surface morphology of titanium after laser treatment. The surface has macroroughness and at high magnification shows melting structure.

Cordioli et al. (Cordioli et al., 2000) reported that average removal torque value was 25.28 N·cm for the machined implants, 26.85 N·cm for the grit-blasted implants, 29.57 N·cm for the plasma-sprayed implants, and 40.85 N·cm for the acid-etched implants under similar conditions. Their results showed that removal torque value of plasma-sprayed implants has approximately the same value of machined or grit-blasted implants.
Plasma spraying and laser treatments are no longer being used, because of the resulting macrorugosities. It is expected that surface characteristics exhibit biological influence during implant installation and interaction with cells by modifying the mechanisms involved in cell adsorption and differentiation.
The osseointegration of dental implants with plasma-sprayed HA is faster than for uncoated implants. However, studies have shown that these coatings may be partially dissolved/resorbed after long periods in use (Sun et al., 2001). [. In addition, the HA coating is chemically unstable and bonds weakly to the implant surface.
Considering the potential of the association between laser ablation and smaller scale HA coatings to create a stable and bioactive surface on titanium dental implants, Faeda *et al.* (Faeda et al., 2009) analyzed the effects of a surface treatment by laser-ablation (neodymium-doped yttrium aluminum garnet [Nd:YAG]) and, later, thin deposition of HA particles by a chemical process. They compared the removal torque of implants treated with

laser followed by acid etching, implants with only laser-ablation and implants with machined surface (MS). After 4, 8 and 12 weeks of healing, the removal torque was measured. Average removal torque in each period was 23.3, 24.0 and 33.9 N·cm for MS, 33.0, 39.9 and 54.6 N·cm for laser modified surface (LMS), and 55.4, 63.7 and 64.0 N·cm for HA (Figure 21). The difference was statistically significant ($p < 0.05$) between the LMS-MS and HA-MS surfaces for all evaluation periods, and between LMS-HA for 4 and 8 weeks of healing. The surface characterization showed a deep, rough and regular topography provided by the laser conditioning that was followed by the HA coating. They conclude that the implants with laser surface modification associated with HA biomimetic coating can shorten the implant healing period by the increase of bone implant interaction during the first 2 months after implant placement.

Although the use of hydroxyapatite-coated endosseous implants in the treatment of dental patients has been established, their clinical predictability remains controversial. A number of clinical and basic studies evaluating the effect of HA coating have been reported. Concerns regarding microbiological susceptibility, resorption, fatigue, and fracture in long-term application have been pointed out. Clinical studies suggest that HA-coated implants have short-term survival rates (ranging from 6 months to 6 years) that are comparable to short-term survival rates of titanium implants (Biesbrock & Edgerton, 1995). In conclusion, the clinician needs to take into consideration the enhanced bacterial susceptibility of HA coatings compared with titanium implants. In addition, the clinician needs to consider the possible failure of HA coatings as a result of coating-substrate interfacial fracture (Ong & Chan, 2000). Dental implants with titanium or hydroxyapatite coating produced by plasma spray are in disuse.

Among commercially available dental implants coated with hydroxyapatite using the plasma spraying technique one can cite the Bonelike® (Biomet 3i, USA) and Calcitek (Sulzer Calcitek Inc., USA)

14.3 Surface treatment with acid

The acid etched dental implant surface presents a superficial morphology that varies with the treatment conditions (acid, chemical composition percentage, etching time and temperature treatment). Through acid etching, it is possible to control the roughness, number, size and porous distribution on micrometer and nanometer scales.

Every manufacturer has its own acid etching method regarding concentration, time and temperature for treating implant surfaces. In general, acid treatment is performed by immersing the implants into solutions of HCl + H2SO4, HF + HNO3 and HNO3. After acid attack, the implant is again immersed into an aqueous solution of HNO3 for passivation of titanium oxide and formation of a stable oxide layer (Elias & Meirelles, 2010). An example of the morphology of an acid-etched surface of a commercially available implant is shown in figure 17.

Acid treatments provide homogeneous roughness, increased active surface area and improve cells adhesion. The morphology of the implant surface shown in figure 16 is isotropic and exhibits micro-cavities with defined edges. This type of surface not only facilitates retention of osteogenic cells, but also allows them to migrate towards the implant surface. Implants having surface morphology similar to that shown in figure 16 induce fibrin retention, favor adsorption of fibronectin and improve the osseointegration (Brunette, 2001; Braceras et al. 2009).

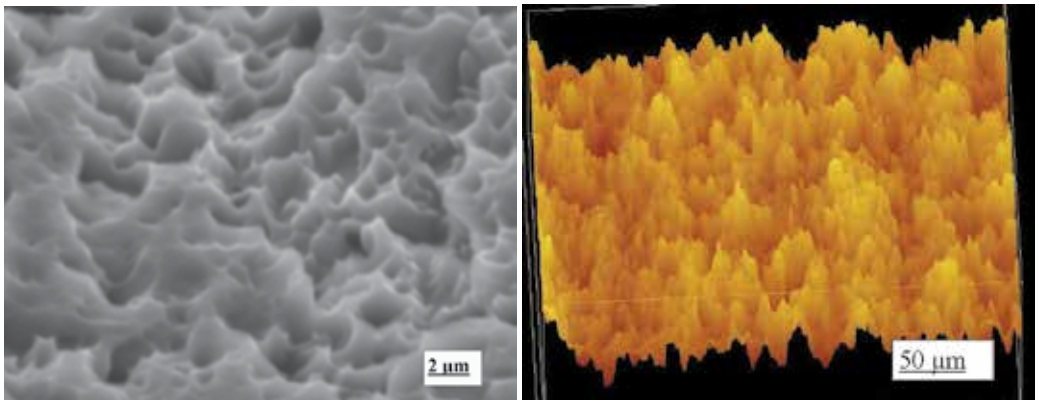

Fig. 17. Surface morphology of dental implant Master Porous™ acid etched, showing microporous.

As Table 3 and figure 14 show, the removal torque of acid etched implants is higher than that of machined implants, which means that the osseointegration mechanisms are faster in acid treated implants than machined implants

Among the commercially available acid-treated implants, one can cite the Master Porous System® (Conexão Sistema de Próteses, Brazil), Osseotite™ (Biomet 3i, USA), Friadenty Plus® (Friadent GmbH, Germany), Defcon TSA® (Impladent SL, Spain) and BlackFix® (TitaniumFix, Brazil).

Wennerberg (Wennerberg et al., 2003) analized some samples of the Osseotite™ implants and measured the roughness surface parameters. They showed that the Tioblast™ has S_a = 0.94 µm, S_{cx} = 11.68 and S_{dr} increased.

14.4 Sandblasting surface treatment

When the implant is blasted with silicon oxide (silica), aluminum oxide (alumina), titanium oxide (rutile), hydroxyapatite and calcium phophate, the implant surface suffers plastic microdeformation. The sandblasting process induces the formation of a fine superficial layer with residual stress. Part of the kinetic energy of the particles is stored in the form of crystal defects, such as dislocations, twins and grain boundaries, and these modifications increase the material surface energy. The superficial layer with residual compressive stress increases the material's fatigue resistance (Askeland, 2006). The residual stress values obtained from blasting procedures depend on both hardness and particles size distribution. The influence of residual stress has not been analyzed in the field of dental implants.

The influence of surface roughness on bone formation on titanium-blasted surfaces was evaluated by Wennerbeg et al. (Wennerbeg et al., 1995). The samples were blasted with Al2O3 particles. After surface preparation, the samples were passivated, washed with distilled water and dried. The results from animal experiments showed higher values for removal torque and bone-to-implant contact for samples blasted with 25 µm and 75 µm sized particles compared with those machined or blasted with 250-µm particles.

The blasting procedure allows control of the size of microcavities. After the grit blasting procedure some particles may be encrusted on the implant surface, which is a contamination (figure 18). The particle must be removed with ultrasonic bath and acid etching.

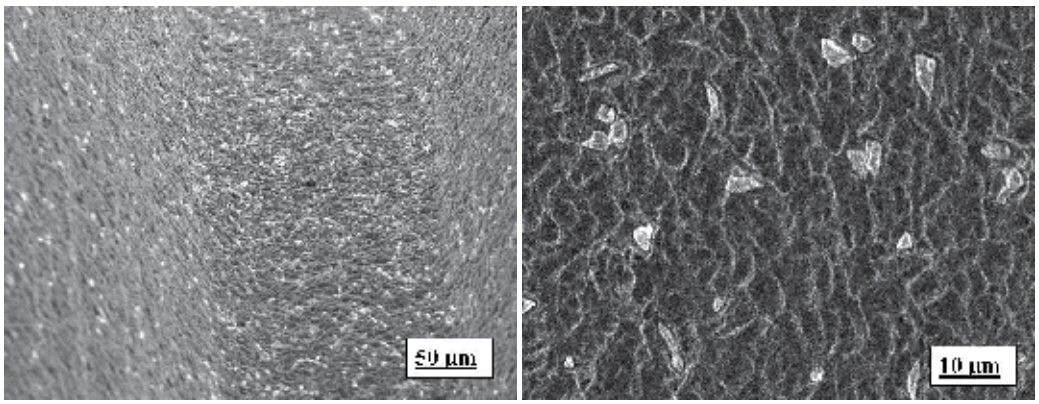

Fig. 18. Particles of alumina (left) and titanium oxide (right) encrusted on the sandblasted implant surface.

Sandblasting with TiO2 is also adopted in the production of implants Tioblast™ (Astra Tech Implant System, Sweden) and TitaniumFix BlackFix (TitaniumFix Implant, Brazil). Tioblast™ is gritblasted with 25-µm titanium oxide particles, which create small pits of predetermined size and shape. Another example of sandblasted implant is Bicon (Bicon LLC, Boston, MA) which is alumina-blasted/acid-etched titanium alloy substrate.
Wennerberg (Wennerbeg et al., 2003) evaluated the Tioblast™ implant. Their results showed this implant has S_a = 1.07 µm, S_{cx} = 10.11 µm and the surface parameter S_{dr} increased 29%.
Another procedure to implant surface treatment is acid etching after blasting. Acid treatment after blasting removes some atomic layers of the titanium surface deformed by the blasting procedure, but part of the residual strain remains at the implant surface.
Available implants SLA™ (Sand-blasted, Large grit, Acid-etched) from Straumann (Straumann ITI, Germany) are sandblasted and acid etched. Alumina particles in the size range 25–50 µm are used to sandblast the SLA™ implant. Sandblasting is followed by an acid etch in hot HCl/H2SO4 acid solution. These processes create micropits superimposed on the rough-blasted surface. Jarmar et al. measured the roughness on SLA™ and found it to be 1.98 ± 0.08 µm (Jarmar et al., 2008). Another way Wennerberg et al. (Wennerbeg et al., 2003) verified that SLA™ implant has Sa = 1.42 µm, waviness parameter S_{cx} = 16.60 µm and the surface parameter S_{dr} increased 33%.

14.5 Surface treatment with fluoride

It is known that fluoride ions have osteopromoting capacity leading to increased calcification of the bone. One of the characteristics of fluoride is its biphasic nature. Fluoride produces beneficial effects when used in low concentrations and toxic effects if used in high concentrations. In therapeutic doses, it is capable of causing mass increase of cortical and trabecular bone. If used in excessive doses, it can lead to bone deficient in collagen cross-links and with increased solubility. With high doses of fluoride, the tensile mechanical properties of the bone are reduced.
Fluoride increases proliferation and differentiation of osteoblasts (Cooper et al., 2006). Ion modification of the topographically enhanced c.p. titanium surface can affect bone formation by modulation of cellular activities at relatively early stages in wound healing at the implant surface. Fluoride increases the alkaline phosphatase activity and increases collagen synthesis.

According to Cooper et al. (Cooper et al., 2006) in vitro evaluation of hMSC (human mesenchymal stem cells) differentiation along the osteoblastic lineage demonstrated that fluoride ion modification of the TiO2 grit-blasted surface led to greater osteoblastic differentiation by adherent hMSCs. This conclusion is most strongly supported by the assessment of BSP expression showing greater expression on all fluoride ion-modified surfaces. The increased BSP expression observed in hMSCs cultured on fluoride ion-modified c.p. titanium was consistent. Whenever the fluoride surface ion content was greater than 5.0 ion % on the 25 μm grit-blasted surface, BSP expression increased (4 fold when compared to densitometric scanning versus Actin) and when fluoride surface ion content was greater than 1.0 ion%, BSP increased 1.6 fold. BSP expression is required for osteoblastic differentiation and mineralization in culture and is temporally associated with the onset of osteoid mineralization in vitro.

Human osteoblastic cells grown on the fluorapatite-collagen composites exhibited significantly higher proliferation and differentiation (according to alkaline phosphatase activity) than those on the hydroxyapatite-collagen composite and the investigators attributed this effect to fluoride release from the fluorapatite containing composite. In addition to direct effects of fluoride ions with osteoblastic cells or indirect fluoride ion effects on protein adsorption and subsequent cell adhesion, another possible indirect effect of fluoride at the c.p. titanium surface could be calcium phosphate precipitation that could influence local calcium concentrations and cell behavior. Ionic modification could alter the array of adhesive proteins adsorbed to the implant surface that could further affect cell and tissue interactions.

There is a relationship between cellular response and the concentration of F-ions (Cooper et al., 2006). For concentrations from 25 to 200 ngF-/mL, i.e., up to the threshold of toxicity, there is a linear increase of intracellular calcium. If the concentration is raised from 500 to 1000 ngF-/mL, the intracellular calcium falls to a level lower than for concentrations in the 100 ngF-/mL range. The cellular effects mentioned occur for short times of exposure to fluoride ions.

Berglundh et al. (Berglundh et al., 2007) studied the early stages of osseointegration to implants with a fluoride-modified surface. Six mongrel dogs, about 1-year old, were used. All mandibular premolars and the first mandibular molars were extracted. Three months later, mucoperiosteal flaps were elevated in one side of the mandible and six sites were identified for implant placement. The control implants (MicroThreadt) had a TiOblast™ surface, while the test implants (OsseoSpeed™) had a fluoride-modified TiOblast™ surface. The results showed that the amount of new bone that formed in the voids within the first 2 weeks of healing was larger at fluoride-modified implants (test) than at TiOblast™ (control) implants. It was further observed that the amount of bone-to-implant contact that had been established after 2 weeks in the macro-threaded portion of the implant was significantly larger at the test implants than at the controls. They suggested that the fluoride-modified implant surface promotes osseointegration in the early phase of healing following implant installation.

The OsseoSpeed™ (Astra Tech AB, Sweden) dental implant surface is fluoride-modified (hydrofluoric acid-treated surface). The implant surface is blasted and later etched with diluted hydrofluoric acid, which slightly reduces the high peaks. The final surface structure has an isotropic roughness – that is, there is no preferred direction of the surface irregularities (Ellingsen et al., 2004). During the blasting procedure, the surface roughness is increased. The OsseoSpeed surface has Sa = 0.91 ± 0.14 μm and the TiOblast™ surface has Sa = 1.12 ± 0.24 μm. The hydrofluoric acid treatment does not only change the microstructure,

but also the surface chemistry. According to Ellingsen (Ellingsssen, 1995) the surface fluoride incorporated in the oxide acts as a precipitation site for calcium and phosphorus, and also allows covalent bonding to the phosphate to create fluoridated HA and fluorapatite.

14.6 Anodizing surface treatment and crystalline oxide structure

One of the methods used to treat the surface of implants is increasing the thickness and change the crystalline structure of the titanium oxide layer on the surface by anodizing.
Anodizing is an electrochemical process where the implant is immersed in an electrolyte while a current is applied, which will make the implant the anode in an electric cell. Commercial dental implants, such as TiUnite™ (NobelBiocare, Switzland) and Vulcano Actives™ (Conexão Sistemas de Prótese, Brazil), are anozided. The electrolyte and the current used in the implants treatment process create a porous surface structure (figure 19).

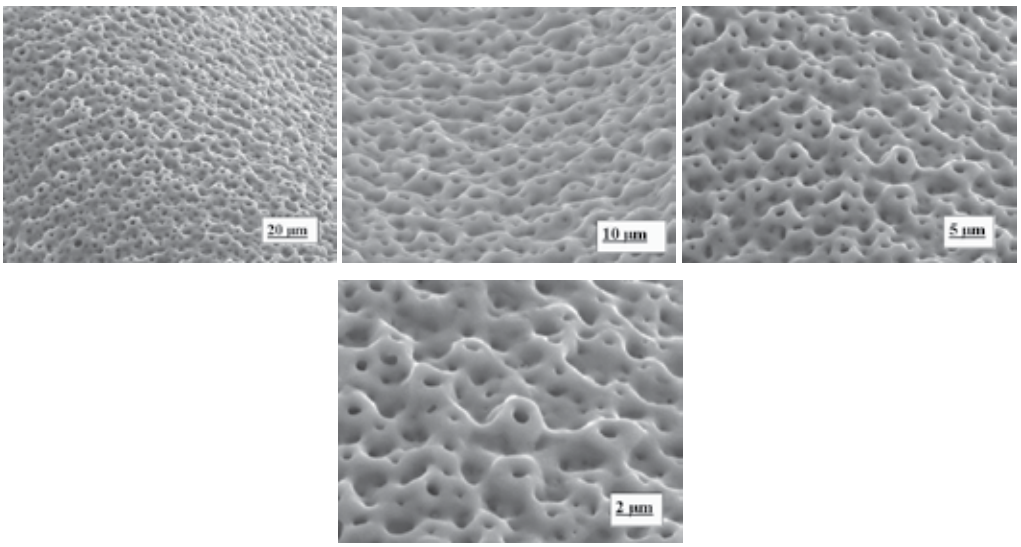

Fig. 19. Anodized dental implant surface, showing volcano shaped saliencies

As Oshida et al. (Oshida et al., 2010) oxides formed on Ti materials are varied with a general form; TiOX (1 < x < 2). Depending on x values, there are five different crystalline oxides; i.e., (1) cubic TiO (ao = 4.24 Å), (2) hexagonal Ti2O3 (ao = 5.37 Å, α = 56°48′), (3) tetragonal TiO2 (anatase) (ao = 3.78Å, co = 9.50 Å), (4) tetragonal TiO2 (rutile) (ao = 4.58 Å, co = 2.98 Å), and (5) orthorhombic TiO2 (brookite) (ao = 9.17 Å, bo = 5.43 Å, co = 5.13 Å). Besides these, there are (6) non-stoichiometric oxide (when x is not integral), and (7) amorphous oxides. It is widely believed that, among these oxides, only rutile and anatase type oxides are stable at normal conditions. Of interest, choice for rutile formation or anatase formation depends on the acidity of used electrolyte. The rutile and anatase type oxides exibit different physical properties – interms of surface tension (Lim et al., 2001) prepared various surface conditions on pure titanium and measured surface contact angles, surface electrochemical potential and roughness. It was found that the surface covered with only rutile type TiO2 was hydrophobic, whereas that covered with a mixture of rutile and anatase type of oxides showed hydrophilicity.

Rutile and anatase titanium oxide are the most important oxide structures for osseointegration of implants. In addition to the increase in oxide layer thickness, the titanium oxide film obtained from electrochemical anodizing incorporates calcium and phosphorus as a heritage from the electrolyte. The surface has more than 7% phosphorus in the oxide layer, the highest percentage of amorphous hydroxides compared with other implants assessed by x-ray photoelectron spectroscopy (XPS). As a result, the titanium oxide existing on the implant surface shows changes in its morphology and crystal structure (Busquim et al., 2009).
Busquim et al. (Busquim et al., 2009) analyzed with x-ray diffraction, Raman and XPS the surface of anodized implant. They found that a predominance of anatase forms on anodized surfaces compared with MS, where the rutile crystal is predominant figure 20).

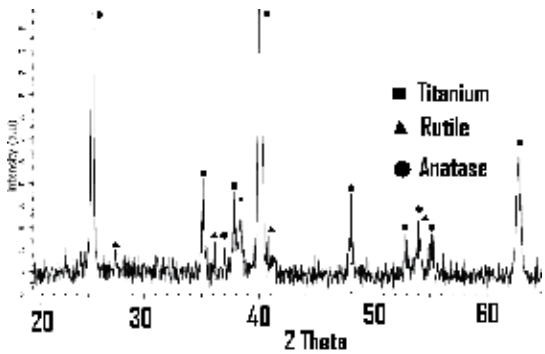

Fig. 20. X-ray diffraction pattern of the anodized titanium surface showing the presence of titanium oxides with crystalline structure in the form of rutile and anatase (dental implant Vulcano Actives™).

The anodized surface implant has a higher polarity compared with that of acid-treated samples, which causes adsorption of water and molecules. Adsorption of these molecules creates an electric field along the oxide thickness. This electric field induces titanium oxidation and, at the same time, the oxide layer thickness increases, thus decreasing both potential difference and the driving force for dissolution (Sul et al., 2006). In this way, taking into account that surface structure as well as morphology are correlated with wettability, changes in their properties affect adsorption of proteins needed for cell adhesion on the implant surface. Consequently, the performance of a given treated surface depends on the biological response of the implants used.
Depending on the anodizing parameters (potential, electrolyte chemical concentration, temperature), the solid oxide layer can be either compact or nanotubular (nanoporous). Figure 18 shows that the oxidized dental implant surface morphology has volcano shaped saliencies.
The TiO2 film obtained by electrochemical anodizing incorporates P and Ca ions from the electrolyte, which alters the final properties of titanium oxide (Elias & Meirelles, 2010). Experiments in cell cultures have shown that incorporated calcium ions on the implant surface increase the adhesion of human bone cells to the implant, when compared to unmodified titanium implants and implants with incorporated phosphate ions (Fröjd et al., 2008; Feng et al., 2004; Nayab et al., 2005). Also, the release of alkaline phosphatase from osteoblasts during bone formation has been found to be increased (Feng et al., 2004). The expected effect of the added calcium ions is a more rapid initiation of bone mineralization,

because of the attraction of bone matrix proteins. The calcium ions may also function as binding sites for initial mineral crystal growth when they bond with phosphate ions in the extracellular body fluid (Ohtsu et al., 2007).

The characterization of the anodized implant surface by X-ray diffraction, Raman and XPS show that the surface of anodized implants shows a predominance of anatase. On machined implant surface the main oxide is rutile (Figure 11) with hydrophobicity. The sandblasted and acid etched implants surfaces OsseoSpeed™, Osseotite™, and SLA™ have rutile too, but their surface morphologies are different of machined implant. The anodized implant Vulcano Actives™ (Conexão Sistemas e Prótese, Brazil) and TiUnite™ (Nobel Biocare, Sweden) have rutile and anatase on the surface (figure 19).

The tissue healing process around anodized or acid etched implants, inserted in bone sites with and without defects, is quicker than in machined implants. Gurgel el al. (Gurgel et al., 2008) analyzed the efficiency of anodized implants. They used dog, and 3 months after teeth extraction, they produced defects measuring 5 mm high and 4 mm wide. After this they inserted the implants. The animals were sacrificed 3 months after the implant insertion. The researchers found that the percentages of bone-to-implant contact (BIC) and bone density (BD) of anodized implants were 57.03 ± 21.86% and 40.86 ± 22.73%, whereas machined implants had 37.39 ± 23.33% and 3.52 ± 4.87%, respectively.

Sul *et al.* (Sul et al., 2006) compared mechanical strength and osseous-conductivity of anodized implants containing magnesium, TiUnite™ (anodized) and Osseotite™ (double acid attack). The implants were inserted into rabbit tibia, and 3–6 weeks later removal torques and the percentage of bone-to-implant contact were measured. Figure 21 shows the experimental results. Magnesium implants demonstrated significantly greater removal torque values and more quantity of new bone formation than Osseotite™ at 3 and 6 weeks. Magnesium implants also showed higher removal torque values at 3 weeks and new bone formation at 6 weeks than TiUnite. The results indicate that surface chemistry facilitated more rapid and stronger osseointegration of the magnesium implants. This suggests potential advantages of magnesium implants for reducing high implant failure rates in the early post implantation stage and in compromised bone, making it possible to shorten bone healing time from surgery to functional loading, and enhancing the possibility of immediate/early loading.

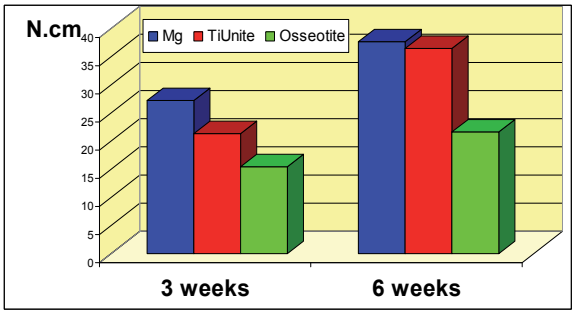

Fig. 21. Torque for removal (N.cm) and percentage of bone contact with implant surface Mg, TiUnite™ and Osseotite™. (Adapted from Sul et al. (Sul et al., 2006).

The anodized surface implant has a higher polarity compared with that of acid-treated samples, which causes adsorption of water and molecules. Adsorption of these molecules

creates an electric field along the oxide thickness. This electric field induces titanium oxidation and, at the same time, the oxide layer thickness increases, thus decreasing both potential difference and the driving force for dissolution (Sul et al., 2006).
In this way, taking into account that surface structure as well as morphology are correlated with wettability, changes in their properties affect adsorption of proteins needed for cell adhesion on the implant surface. Consequently, the performance of a given treated surface depends on the biological response of the implants used.
Fröjd et al. (Fröjd et al., 20008) evaluated the bone response to an oxidized titanium implant (Ox) and a calcium-incorporated oxidized titanium implant (Ca). A blasted with 75 μm Al2O3 particles titanium implant (Bl) was used as control. The implants were topographically characterized using an optical interferometer and placed: one in each distal femoral metaphysis and two in each proximal tibial metaphysis in rabbits. The rabbits were killed 12 weeks after implant insertion. Topographical evaluation revealed three different surfaces: average height deviation (Sa, μm) values for Ca:Ox:Bl implants were 0.3:0.6:0.9, developed surface area ratios (%) 17:44:31. The Ca implants had a significantly denser surface, as represented by the parameter Sds, with 208 $\pm$ 24 sumsummits/μm^2; the Ox implants had a mean value of 136 $\pm$ 9 sumsummits/$\mu m^2$and the Bl implants 118 $\pm$ 9 sumsummits/μm^2. The core fluid retention index values were 1.33:1.33:1.38 in Ca, Ox and Bl implant, respectivaly. The mean percentages of bone contact to the implants placed in the tibia (Ca:Ox:Bl) were 47:30:34 and to the implants placed in the femur (Ca:Ox) 32:20. The mean percentages of surrounding bone area for the implants placed in the tibia were 40:47:37 and for the implants placed in the femur 43:46. A significant increase in bone contact was found for smooth (Sa <0.5 μm) but more densely peaked calcium-incorporated oxidized implants when compared to slightly rougher (Sa = 0.5-1.0 μm) oxidized or blasted implants.

14.7 Nanoroughness

Yang et al. (Yang et al., 2009) produced through the electrochemical anodizing treatment a mixed nano/submicron-scale TiO2 network layer (lateral pore size: 20–160 nm) on polished Ti surface. Results showed that a nano/submicron-scale TiO2 network layer with a lateral pore size of 20–160nm could be rapidly produced on Ti surface through electrochemical anodizing treatment. This TiO2 network layer significantly enhanced the whole blood coagulation and human bone marrow stem cell .
Webster *et al.* evaluated osteoblast adhesion *in vitro* on alumina and titania discs prepared by compacting powders with different sized particles onto the surface (Webster et al., 1999). The discs were sintered at different temperatures to obtain different nanoroughness parameters. Higher osteoblast adhesion was observed on both alumina and titania discs with increased mean root square deviation (Sq) and larger surface area. Additionally, discs prepared with an identical method consisting of Ti, Ti6Al4 and CoCrMo was tested. As previously reported on alumina and titania discs, increased osteoblast adhesion was found on the discs from the different groups with increased mean root square deviation (Webster & Ejiorf, 2004). Webster *et al.* investigated osteoblast adhesion and concentration of different proteins adsorbed on alumina, titania and HA, with different nanoroughnesses (Webster et al. 2000). Once again, the osteoblast adhesion was greater on the discs that exhibited increased nanoroughness, independently of the surface chemistry. Protein adsorption revealed a greater amount of vitronectin associated with increased osteoblast adhesion on the rougher discs. Osteoblast proliferation and alkaline phosphatase synthesis on these

surfaces was evaluated in another study from the same group; alkaline phosphatase synthesis was higher after 21 and 28 days on the discs with increased nanoroughness values. De Oliveira and Nanci (Oliveira & Nanci, 2004) cultured bone rat calvaria cells on titanium discs etched with H2SO4 and H2O2. They observed that the acid-etched surface revealed nanopits, whereas the control failed to show such features, although the surface roughness was not numerically evaluated. The results indicated an overexpression of osteopontin and bone sialoprotein, both intra- and extra-cellularly, on cells seeded on the nano-modified group. In addition, a higher proportion of cells with peripheral cytoplasmic distribution of osteopontin were observed as early as 6 h.

Larlsson *et al.* evaluated turned plus anodized, electropolished, and electropolished plus anodized implants on a rabbit model after 1–6 weeks (Larsson et al., 1996). After 6 weeks, the electropolished implants showed decreased bone formation compared with the rougher implants. In an identical study, similar implants were investigated after 7–12 weeks of healing (Larsson et al., 1994 After 7 weeks, the results were similar to the previous study, which indicated higher bone formation to implants with increased surface roughness values (anodized) compared with the smooth implants (electropolished). After 12 weeks, the values for the rough implants were steady and the values for the electropolished implants increased to approximately the same level as that found for the rougher implants. Long-term evaluation of these implants for 1 year did not reveal any difference in bone formation (Larsson et al., 1997). It is concluded by *in vitro* and *in vivo* experiments that cell activity and bone healing may be optimized by modulating surface roughness on the nanometer level of resolution.

15. Conclusion

The success in implant dentistry depends on several parameters that may improve considering both biologic and mechanical criteria. Given below are some conclusions which show factors affecting the success of dental implants treatment.

- Although titanium is used extensively as a biomaterial, there are still doubts about the procedure to obtain the best biological response. Special relevance is the study of commercially pure titanium dental implant osseointegration.
- The strategy to improve dental implant osseointegration is to alter the biocompatibility of titanium implant surfaces, modifying the surgical technique and changing the implant design.
- The study of the interaction of cells with implant surface is a field of high topical interest and the detailed knowledge of these interactions can be used as the basis for the development of new surface treatments.
- Topographic characteristics, roughness, energy, and chemical composition modify cell growth and change cell function at the initial stages of osseointegration.
- Numerous surface modification approaches have been developed in order to improve commercially pure titanium dental implant osseointegration, to increase the primary stability and, in order to shorten the healing time.
- The surface properties of implants such as morphology, roughness, thickness of the oxide layer, chemical composition, impurity level and types of oxides depend on the surface treatment process.

- The titanium dental implant surface morphology was modified by chemical and electrochemical treatment. Most of these surfaces have been analyzed by *in vivo* and *in vitro* studies, showing that the surface characteristics of the dental implants influence cell activity, which modifies the differentiation, proliferation, differentiation, and formation of extracellular matrix.
- The results show that the acid etching, sandblasting and electrochemical implant surface treatments are better than plasma spray or laser treatment. But, there is not a consensus among researchers as to the best surface and even the shape of the implants.
- The dental implant primary stability depends on the shape and surface morphology. The secondary stability depends mainly on the implant surface. The torque to install a conical implant is larger than the torque to install a cylindrical implant.
- The implants submitted to a surface treatment have a higher roughness, higher friction coefficient and higher primary stability than the machined one.
- There is need for research to improve the description of the interaction of cells with the implant surfaces, as well as analysis of the influence of different parameters in the interaction with proteins, stimulation of bone formation, use of individualized therapy and able to submit response differentiated for patients considered critical.

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Soft Tissue Biology and Management in Implant Dentistry

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1. Introduction

Implant Dentistry has been the fastest growing treatment modality in dentistry for the past 20 years. The success in using dental implant to support dental restorations and reconstructions has been underpinned by the predictable formation of a bone-to-titanium interface (osseointegration) after the insertion of a titanium implant into the human jaw bone. As a result, the titanium implant becomes a rigid extension of the jaw and can be utilised as a stable foundation to support dental restorations and enable normal function of mastication to be carried out by the patient in comfort over long periods of time. The longevity of the dental implant treatment is therefore dependent upon the stability of the bone-to-implant interface. This interface is a dynamic situation subject to the influence of bone metabolism and turnover as well as bone remodelling according to functional demand. It is therefore reasonable to assume that successful implant treatment and implant supported prostheses can be maintained over long periods of time in the absence of bone metabolic diseases or disturbance.

The reporting of peri-implantitis as a significant threat to implant survival in the jaw bone (Roos Jansåker, Lindahl et al. 2006; Lindhe and Meyle 2008) has dramatically changed our perception of the expected trouble-free service life of dental implants in patients, particularly in those who have had a history of periodontal disease in the past. It also brought into focus a number of known risk factors associated with the bacteria-related breakdown of osseointegration and raised concerns about how best to address these risks. It is now apparent that maintaining a competent seal of the "gingival cuff" surrounding dental implants or abutments has an important role to play in achieving long term complication-free service of dental implant restorations/reconstructions(Berglundh, Lindhe et al. 1991). This Chapter will review all relevant biological and clinical aspects of our current knowledge of the peri-implant gingival tissue and the management of this tissue to achieve long term clinical success of implant treatment.

In the anterior aesthetic zone, the restorative dentist is often faced with a challenge to restore not only the missing teeth but also the missing volume of gingival tissue surrounding them. In augmented implant sites, the recreated volume of gingival tissue must have a healthy appearance and be in harmony with the gingival tissue surrounding adjacent teeth. Furthermore, this tissue should be stable and remain unchanged in volume and appearance over time. This demand in aesthetic outcome for dental treatment in the anterior region is

often at odds with the known biological events in soft tissue healing and remodelling after surgical wounding. In clinical practice, it is therefore critically important for the dentist to understand all the biological events associated with wound healing and to have the knowledge and skill to perform procedures of augmentation that are evidence based. Equally important, the patient should be encouraged to have only "realistic" expectation in terms of aesthetic outcome in any dental reconstruction in the anterior region. This Chapter will also review some surgical procedures that had been shown to yield reliable results.

2. Biological basis for soft tissue healing around dental implants

2.1 Gingival shrinkage around dental implants

During the healing phase following implant placement surgery (stage 1 surgery) or the trans-mucosal surgery for abutment connection (stage 2 surgery), the soft tissue re-organises itself according to the new environment (namely, surrounding a metallic implant). Noting the histologic observation made by Berglundh (Berglundh, Lindhe et al. 1991)and other investigator groups (regarding the orientation of the collagen fibre groups in the peri-implant gingival tissue) it is easy to appreciate why the peri-implant gingival tissue appears to shrink during the early stage of wound healing. The longitudinal arrangement of the major collagen fibre groups amplifes the process of collagen fibril contraction (as part of collagen maturation) in the vertical direction. Clinically, this process is observed as marginal gingiva shrinkage. In the anterior aesthetic zone, the amount of gingival shrinkage can be crucial to the success or failure of a case. Therefore when planning such a case, it is important to take into account the position and structural integrity of the labial bone wall which forms form the support base for the labial gingiva.

2.2 Peri-implant soft tissue seal

In a dog study(Berglundh, Lindhe et al. 1991), Berglundh and co-workers compared the similarities in the peri-implant soft tissue to that of the gingival tissue around teeth. In both cases, the soft tissue consisted of a junctional epithelium component and a connective tissue component. In both situations, the epithelium adhered to the tooth or titanium surface in similar fashion. However, in the connective tissue compartment there were notable differences. The peri-implant tissue had a higher fibre content (and hence a lower cellular content) than that of gingiva around teeth. In addition, the collagen fibres were arranged parallel to the titanium surface(Çomut, Weber et al. 2001) in contrast to that of the gingiva which tended to be arranged perpendicular to the cementum surface of the tooth root with other fibre groups arranged in various patterns elsewhere in the marginal gingiva. Some of these fibres had previously been observed to be inserted and embedded into the cementum layer forming Sharpey's fibers(Garant and Cho 1979). Because the study animals were subjected to plaque control regime for 8 weeks prior to sacrifice, there was little or no inflammatory cell infiltrates observed in either the gingiva or peri-implant tissues. The authors thus concluded that a satisfactory seal had been formed around the implant/abutment and that this seal was capable of maintaining tissue health (provided plaque control is practiced).

Since the time when the Berglundh's group described the pattern of collagen fibre bundles running parallel along the titanium surface (Berglundh, Lindhe et al. 1991), others had reported various fibre bundles organized in different fashions either obliquely to the titanium surface or circumferential to it(Buser, Weber et al. 1992; Ruggeri, Franchi et al.

1994; Piattelli, Scarano et al. 1997; Çomut, Weber et al. 2001; Schupbach and Glauser 2007). The precise significance of these observations was unclear. There were speculations that these fibre groups fulfil structural support and defensive role of the peri-implant soft tissue. In one recent report, controversial claims were made that "functionally" oriented fibre bundles were found lying perpendicular to the TiUnite surface of Branemark implants(Rocci, Martignoni et al. 2003). The significance of this finding was also not clear as no follow up study was done. Nevertheless, implants with roughened surface (up to the collar) are now available for clinical use, on the basis that such implant design could enable faster osseointegration and allow the formation of a durable soft-tissue cuff even on roughened titanium surface. This concept has not received general support among dental practitioners partly because of the lack of good clinical data to support its use, and partly because of concern about the potential for accelerated loss of osseointegration should this roughened surface becomes uncovered and exposed to the oral environment(Cosyn, Sabzevar et al. 2007).

This anatomical feature of soft tissue around titanium implant was found to be consistent for titanium surfaces irrespective of the type of implant system used(Abrahamsson, Berglundh et al. 1996). Furthermore, the surface roughness of the titanium had no bearing on the adherence of the soft tissue(Abrahamsson, Zitzmann et al. 2002). Neither was the clinical protocol used in implant placement (one-stage as versus 2 stages protocol)(Abrahamsson, Berglundh et al. 1999). Despite these observations, the clinical performance of this seal in protecting against bacterial ingression and thus peri-implant infection remained untested. Indirect evidence from human clinical studies which generally reported very low incidence of peri-implantitis and peri-implant mucositis suggested that indeed, the soft tissue cuff around titanium implant/abutment could provide comparable protection as gingiva around teeth. The importance of this physical seal notwithstanding, for long term peri-implant health, the presence of bacteria, bacterial plaque and biofilm will also need to be kept at a minimum. It is therefore crucial that restorations supported by implants should have built-in access channels or space for hygiene practice, and the patient should be educated in an effective method of plaque control. The failure to do so are seen too frequently as heavy plaque and calculus build-up around dental constructions as well as abutment or even implant surfaces when significant gingival recession has uncovered these implant components.

2.3 The keratinized gingival zone

The controversy about the need for a keratinized (attached) gingival zone around implant supported restorations is an interesting one. Based on the data from long term implant success and implant survival studies, there appeared to be little or no difference in the success rate for implants to be placed in oral mucosa zone or keratinized gingival zone(Jemt, Chai et al. ; Brånemark, Svensson et al. 1995; Lindquist, Carlsson et al. 1996; Buser, Mericske stern et al. 1997; Mericske-Stern 1998). It was therefore argued that there was no convincing evidence to support the clinical obsession of placing dental implants in keratinized gingival zone only or to re-create this soft tissue band after implant placement(Carmichael, Apse et al. 1989). In a recent systemic review, Esposito and colleagues concluded that there was insufficient evidence to suggest any surgical technique or approach was superior to another although they did note that flapless approach tended to result in less post-operative discomfort and pain. They also found no case to recommend that increasing the "keratinized tissue" band around dental implants as a preferred method of tissue management(Esposito, Murray-Curtis et al. 2007). Nevertheless, the common clinical

observation of frequent plaque accumulation associated with mobile mucosal tissue around implant restorations and the subsequent soft tissue inflammation (and hence patient complaints) often lead to the demand for clinical intervention (figure 1). Clearly, the amount of peri-implant mucosal tissue movement during function is influenced by a number of physical variables and is difficult to measure. Until there is a reliable and accurate way of clinically assessing soft tissue movement during function, for many clinicians there is a case for routinely providing a keratinized gingival band around implant restorations in order to facilitate plaque control and hence reduce the incidence of plaque-related peri-implant disease. In a recent publication in the International Journal of Oral & Maxillofacial Implants, in a Current Issues Forum, the editor posted the question "To minimize complications, is it essential that implant abutments be surrounded by keratinized tissue?"(Krygier, Glick et al.). The consensus of opinions expressed by the authors participating in this debate was in general, supportive of the clinical practice of providing a keratinized gingival band around implant restorations where possible and practical. Another recent study reported a 5-year observation provided further data to support that keratinized gingival band of > 2 mm promotes better gingival health around dental implant/restorations(Schrott, Jimenez et al. 2009). In a systemic review, Cairo and others concluded that in some clinical situations soft tissue augmentation is warranted(Cairo, Pagliaro et al. 2008). A more recent review also concluded that "the functional need for attached gingiva around implants has not been established but its aesthetic value has been widely accepted.(Mehta and Lim 2010)

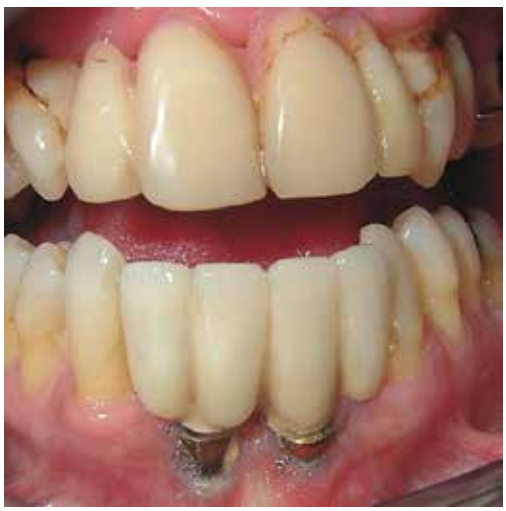

Fig. 1. Common situation encountered where poor oral hygiene resulted in the breakdown of mucosal tissue around implant/abutment.

2.4 Peri-implant tissue thickness and biological width

The dimension of the soft tissue attachment to the implant/abutment surface was considered important for the maintenance of peri-implant health and for the overall aesthetics of the final restoration. For many years, the concept of a biological width was used to explain the clinical observation of a constant dimension of dento-gingival junction around teeth and dental restorations(Gargiulo, Wentz et al. 1961). Berglundh and Lindhe demonstrated that in a dog model, similar constancy of gingival dimension was observed in

peri-implant tissue as well(Berglundh and Lindhe 1996). In an elegant experiment, the authors showed that by surgically reducing the thickness of the gingival flap prior to suturing, a corresponding crestal bone remodelling will subsequently occur allowing for the re-establishment of the "biological width" of the peri-implant soft tissue to its original dimension at the expense of reduced crestal bone height. This situation is analogous to the surgical procedure used in " crown lengthening" on natural teeth –an attempt to surgically position the gingival margin more apically and thus allow for an increased restorative space either for aesthetic reasons or for increasing the ferrule of coronal structure to improve on the retention of the planned restoration. This finding had great clinical implications because it provided a rationale for the careful placement of the soft tissue at the "correct" and stable position for the final peri-implant tissue finish. It also explained, at least in part, why it was important to maintain the alveolar crest in order to support the over-lying soft tissue.
Further studies comparing one-stage and two-stage procedures (submerged versus non-submerged) (Buser, Weber et al. 1992; Weber, Buser et al. 1996), loaded or unloaded non-submerged implants (Cochran, Hermann et al. 1997), different implant systems (Abrahamsson, Berglundh et al. 1996), different material surfaces (Arvidson, Fartash et al. 1996) and different level of placement of the implant-abutment junction (micro-gap) (Hermann, Cochran et al. 2001) failed to demonstrate any difference in peri-implant tissue dimension (thickness) under these variable conditions. Taken together, these observations confirmed that the concept of biological width of the gingiva around natural teeth was equally applicable to peri-implant soft tissues. These data further validated the need for a suitable implant design that allow for optimal soft-tissue attachment in order to achieve good soft tissue stability. It also provided a useful reminder to the clinicians that careful attention should be paid to the soft tissue finish when planning implant treatment cases.

2.5 The 3-dimensional relationship between alveolar bone and the overlying gingiva

If the biological width concept does indeed accurately describe the natural phenomenon of the inter-dependency of these two tissues (alveolar bone and gingiva), a corollary of the biological width concept would then state that a fixed thickness of gingiva will follow the position and contour of the underlying alveolar bone crest. Indeed, clinical observation of the remodelling of alveolar ridge, such as that following tooth extraction, does appear to confirm this concept. It is therefore important that when planning an implant placement in an extraction site, the dentist is able to predict and anticipate where the remodelled bone will be in future, and hence where the gingival margin will lie in relation to the dental restoration supported by the implant(Khoury and Happe 2000; Grunder, Gracis et al. 2005). Unfortunately, it is not always possible to accurately predict the extent of bone resorption during the remodelling process. In an animal model, Araujo and colleagues described in detail the pattern of alveolar remodelling following tooth extraction(Araujo and Lindhe 2005) and following implant placement(Araújo, Sukekava et al. 2005). Cumulative clinical experience suggests that bulky alveolar process (thick biotype) shows greater dimensional stability during remodelling compared with less bulky alveolar process (thin biotype). It was theorised that in thick biotype, the presence of lamina bone adjacent to the outer cortical plate of the alveolus provides the foundation for metabolic support of the cortical bone, and hence its stability and sustainability. In thin biotype, where the lamina bone is scarce or absent, the cortical bone is subjected to rapid resorption by osteoclastic type cells present in the healing bone wound (such as an extraction socket). Although the relationship between bone repair and the host genotype is not entirely clear at the moment, the above theory does

go some way in explaining the clinical observation in alveolar ridge remodelling following tooth extraction.

2.6 Does the presence of implant help to preserve bone?

The placement of a dental implant in a fresh extraction socket (immediate placement) does not appear to interrupt the healing process of the socket wound(Botticelli, Berglundh et al. 2004; Araújo, Sukekava et al. 2005; Araújo, Sukekava et al. 2006; Araujo, Wennstrom et al. 2006). It is therefore, possible to extract a tooth (or teeth) and place dental implants in the same visit. The proponents and supporters of this clinical protocol of immediate implant placement have argued that the presence of a dental implant helps to preserve the height of the surrounding bone. Animal studies and human clinical studies have not yield evidence to support this notion(Wyatt and Zarb 2002; Covani, Cornelini et al. 2003; Covani, Bortolaia et al. 2004). In a single-tooth implant situation, the stability of the interseptal bone appears to be influenced by the periodontal ligament level of the adjacent teeth, rather than the level of bone-titanium interface. The labial bone plate is not supported by any neighbouring teeth and therefore can undergo rapid resorption and remodelling once its "host tooth" has been extracted. In patients with thin biotype, a rapid remodelling and disappearance of the labial bone crest can often result in disastrous clinical outcome where implants were placed immediately into extraction sockets. It is now clear that this clinical technique can yield unpredictable results and therefore should be attempted only with great caution. Drawing from our current understanding of the sequence of biological events in bone repair after tooth extraction, and in particular, the remodelling of the labial bone plate, it is not surprising to find that many immediately placed implants in the aesthetic zone ended up with disastrous results.

3. Managing the soft tissue around implants

3.1 Implant placement in the "correct" anatomical position

Based on our understanding of the constancy of gingival tissue thickness overlying alveolar bone surrounding teeth or dental implants and our knowledge of the healing behaviour of peri-implant soft tissue after wounding, it is possible to estimate the "final position" of the healed tissue around restorations placed on dental implants. The ability of the clinician to accurately forecast the final position of the healed tissue will underpin the long term success of any implant restoration (figures 2a and 2b). On the other hand, unrealistic expectation of reconstituting lost tissues by placing gingival tissue a greater distance from the underlying alveolar bone, such as in the case when the implant is placed apically relative to the adjacent teeth, will inevitably lead to future complications. This scenario can arise when the implanted site has been compromised by previous extraction or exposed to infection of long standing. In these situations, bone augmentation should be considered as part of the treatment plan if a stable soft tissue result is to be achieved. (Figure 3 a and b)

3.2 Important considerations during case planning

During the treatment planning stage of dental implant treatment, special attention should be given to assessing the proposed implant site as well as other systemic factors that may influence the performance and survival of the implant. Implant site assessment should include:

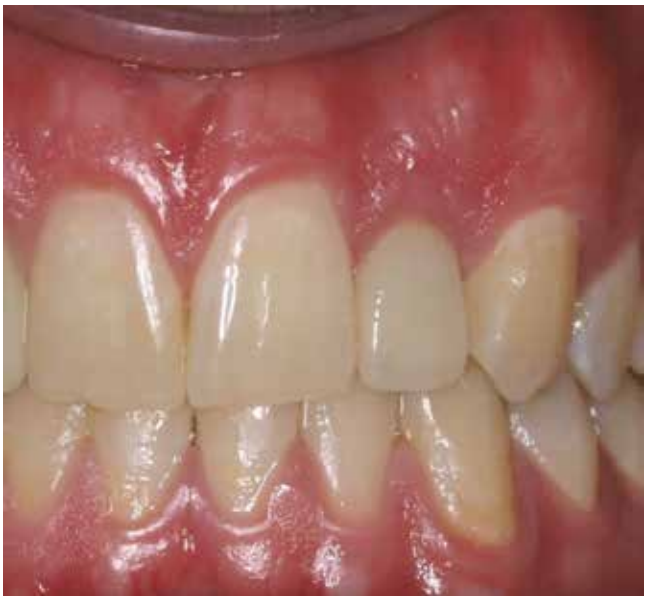

Fig. 2a. Stable gingival position with adequate bone support

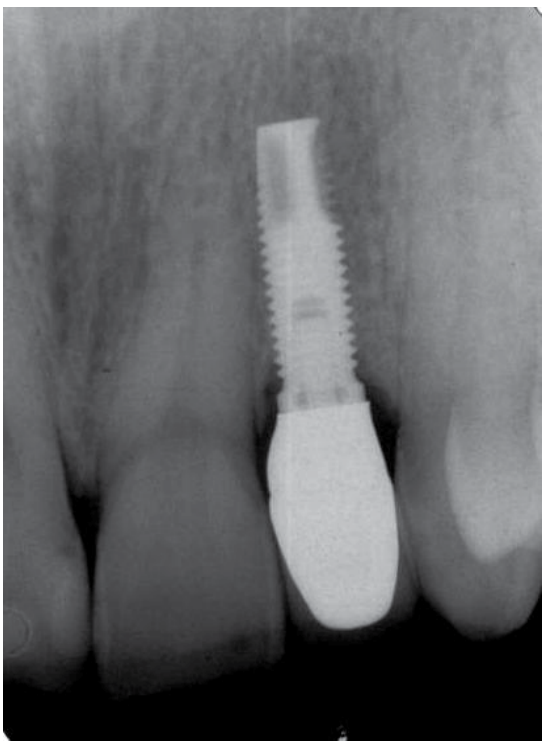

Fig. 2b. Radiograph showing the position of the dental implant relative to the adjacent teeth

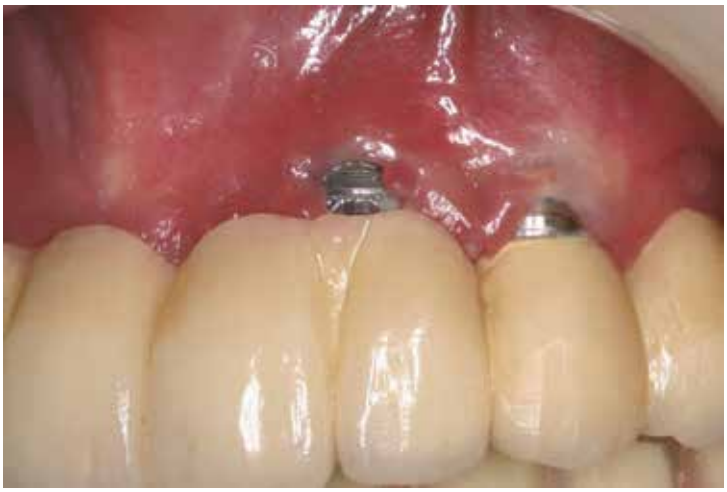

Fig. 3a. Gingival recession due to missing bone underneath

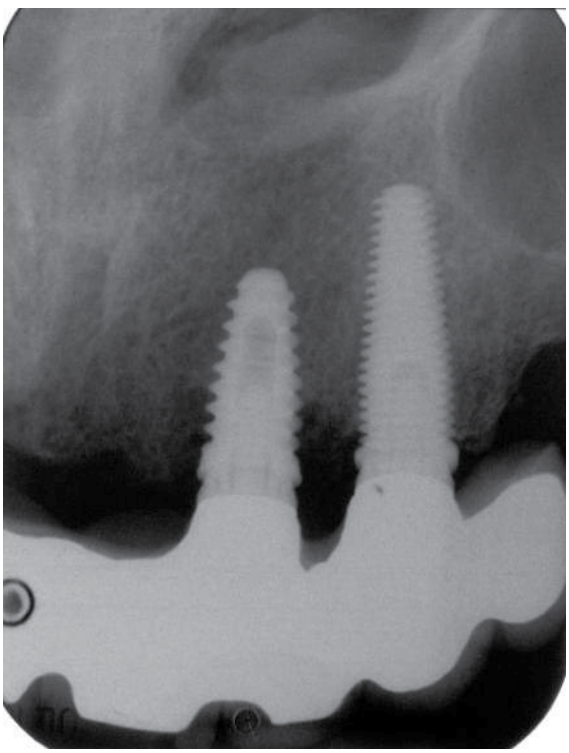

Fig. 3b. Radiograph of the same patient in figure 2a

- Checking for pre-existing pathology – such as chronic and persistent granulomatous lesions associated with the extracted tooth, non-healing abscesses, dentigerous cysts etc
- Evaluating the anatomical defect at the site – such as extreme ridge resorption following extraction
- Determining the biotype of the patient especially when the treatment site is in the aesthetic zone
- Deciding on the appropriate time for the implant placement in relation to the time of extraction

The systemic factors that require special attention are the important "risk factors" associated with implant complications and failures such as past history of periodontal disease and a smoking habit.

3.3 Surgical techniques

There had been numerous publications in the dental literature describing various surgical techniques suitable for augmenting the implant sites. Most of these procedures aim at adding bulk and thickness to the soft tissue surrounding dental implant restorations. Others aim at increasing the width of the attached gingival band surrounding these restorations. The interchangeable use of the term "keratinized gingiva" and "attached gingiva " had led to some confusion among dentists. From the current data available, there is no conclusive evidence to suggest that keratinized gingiva is essential in maintaining health of the peri-implant soft tissue(Carmichael, Apse et al. 1989). Paradoxically, most clinicians comment that attached gingiva around implant restorations will provide longer term stability and comfort and acceptance by the patient(Cairo, Pagliaro et al. 2008; Schrott, Jimenez et al. 2009). It may well be that the "immobilisation" of the soft tissue band is important for oral hygiene maintenance and stability and health of the tissue, and not so much the type of epithelial cells covering this soft tissue band.

By far the most popular surgical technique for augmenting the soft tissue at implant sites utilises autogenous graft from the same patient either in the form of subepithelial gingival graft (connective tissue graft)(Langer and Langer 1985) or gingival graft (free gingival graft)(Miller Jr 1982; Miller Jr 1985; Miller Jr 1993). These grafts are usually harvested from the palatal vault of the same patient and transferred to the recipient site. In the aesthetic zone it is usually necessary to provide a band of keratinized gingiva in order to harmonise with those surrounding the adjacent natural teeth. Under this circumstance, a connective tissue graft with a collar of epithelium attached will achieve the desired result. (Figure 4)

In a systemic review of surgical procedures for soft tissue augmentation, all autogenous tissue graft procedures were found to be effective in increasing tissue volume. No one technique was found to be superior to others (Thoma, Beni et al. 2009). It would therefore appear that treatment success is not a function of the choice of a surgical technique and the choice of a specific surgical technique is not as important as the adherence to sound biologic principles (such as those listed earlier in this chapter) if good clinical outcome is to be achieved.

4. Future research

The advancement in implant dentistry in the past 20 years has been rapid. Studies in the biological sciences have provided us with a clearer understanding of the wound healing events following tooth extraction as well as following dental implant placement in the

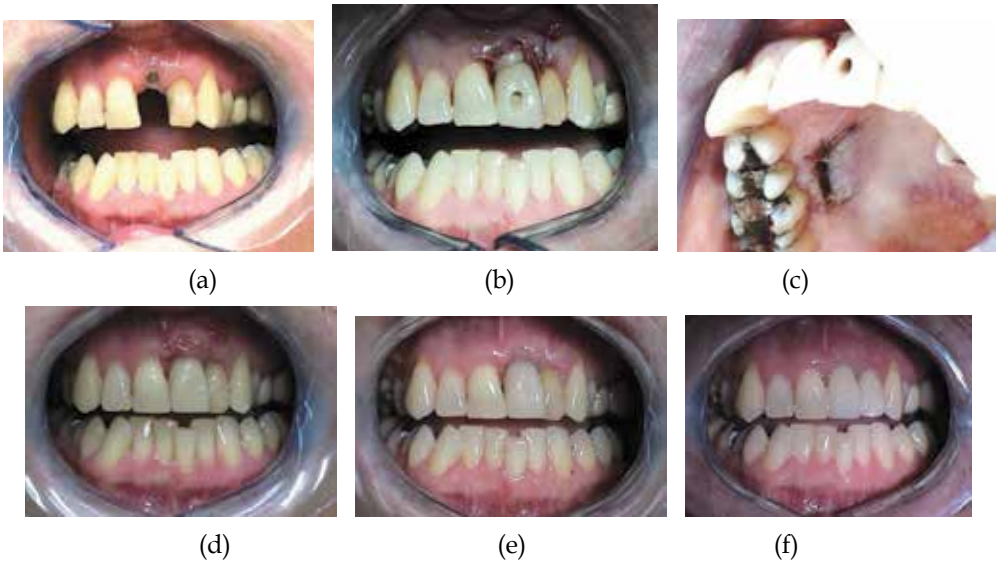

Fig. 4. Connective tissue grafting was used to repair tissue deficit as a result of implant mal-positioning. a) positioning of dental implant (too labially placed and too palatally angled) and showing a lack of labial gingiva; b) connective tissue graft placed at the time when the temporary crown was issued; c) donor site on the palatal vault where the graft tissue was harvested from; d) healing at 1 week; e) at 1 month and f) at 1 year.

human jaws. This in turn drove the implant industry to seek to improve on the surface characteristics of implants to enhance early healing. The introduction of the "roughened" surface did show reduced time for osseointegration and establish clinical stability to enable earlier loading. However, the concept of immediate implant placement after extraction had not demonstrated universal success mainly due to bone remodelling complications. The research in "biological factors" to enhance the speed and quality of osseointegration has shown some promise and is continuing. The release into the market place of two dental implants with "bioactive" surface has not met with resounding success.(Cooper, Zhou et al. 2006; Schwarz, Herten et al. 2007; Junker, Dimakis et al. 2009). Clearly, the industry-driven effort in improving the engineering aspect of implant development will continue at a rapid pace. On the other hand, we have not made as much progress in the biological advances in the clinical science of implant therapy. We have used biomechanical refinement on the engineering of implant to cope with "softer" bone, such as implant thread design, implant body design, and implant surface design. To date, we have not explored the possibility of modifying the bony trabecular pattern and density in order to change a "type 4 bone" to a "type 3 bone", or from a "type 3 bone" to a "type 2 bone" etc. Equally important, we have not harnessed the adaptive property of living bone to respond to the presence of a loaded dental implant nor have we attempted to influence the metabolic activity of bone tissue to ensure that the dynamics of the osseointegration interface is maintained throughout the life of the implant. Last, but not the least, we have not paid enough attention to the complication of peri-implantitis – how to prevent it, how to treat it and how to repair the defect it creates. Future research in these two important areas of biology and clinical practice is urgently needed.

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16

Crestal Bone Level Alterations in Implant Therapy

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1. Introduction

Tooth restorations using implant-supported prostheses for functional and esthetic rehabilitation of patients has become an established and widely used treatment modality in modern dentistry. Preservation of peri-implant bone is one important factor for success. The quantity and quality of the bone surrounding an implant not only affect implant osseointegration, but also influence the shape and contour of the overlying soft tissues, which are important for the esthetic outcome of treatment. Therefore, assessment of peri-implant marginal bone levels has become an integral part of the evaluation of the implant patient. Different evaluation protocols and success criteria based on marginal bone level changes have been described in the literature. Radiographic techniques including panoramic tomography and intra-oral radiography using long cone parallelling techniques have been widely used to monitor marginal bone levels at implants and diagnose interproximal bone loss (Kullman et al. 2007). Here the distance from a fixed reference point (e.g. implant shoulder or implant–abutment junction) to the inter-proximal bone level is recorded at baseline and monitored longitudinally. In numerous studies baseline radiographs are taken at the time of prosthesis installation, where any marginal bone level changes which occurred at the period between implant installation and prosthesis installation are not taken into account. While a panoramic tomograph allows the entire implant to be visualized limitations including image resolution and distortion are well known (Åkesson et al. 1993, De Smet et al. 2002). Further limitations of conventional radiography include the inability to monitor facial and lingual/palatal bone levels, low sensitivity in the detection of early bone changes and the underestimation of bone loss (Brägger et al. 1988, De Smet et al. 2002). Recently, multi-slice computer tomography (CT) and cone beam volume imaging have been used in implant dentistry offering the advantage that osseous structures can be represented in three planes, true to scale and without overlay or distortion (Mengel et al. 2006).

2. The effect of surgical protocols on crestal bone level alteration

The evolution of implant dentistry has lead to treatment protocols and approaches that differ substantially to the ones that utilized at the initial stages of implantology. Treatment modifications on stages of implant surgery, load timing and implant placement in grafted sockets have been introduced and utilized extensively the two last decades. In addition factors related to treatment planning such as inter-implant, tooth-implant distances and

supra-crestal, crestal and subcrestal placement of the implant-abutment interface can have effects on crestal bone level alterations around implants.

2.1 One versus two-stage implant surgery

One stage implant surgery refers to placement of a healing abutment following implant installation that remains transmucosally and exposed to the oral cavity following replacement of the mucoperiosteal flaps (Figure 1). In contrast, during two-stage implant surgery a cover screw is placed following implant installation and the implant is completely submerged following suturing of the flaps. Three to six months later the implant is uncovered with a second surgical procedure and a healing abutment is placed allowing the peri-implant mucosa to heal.

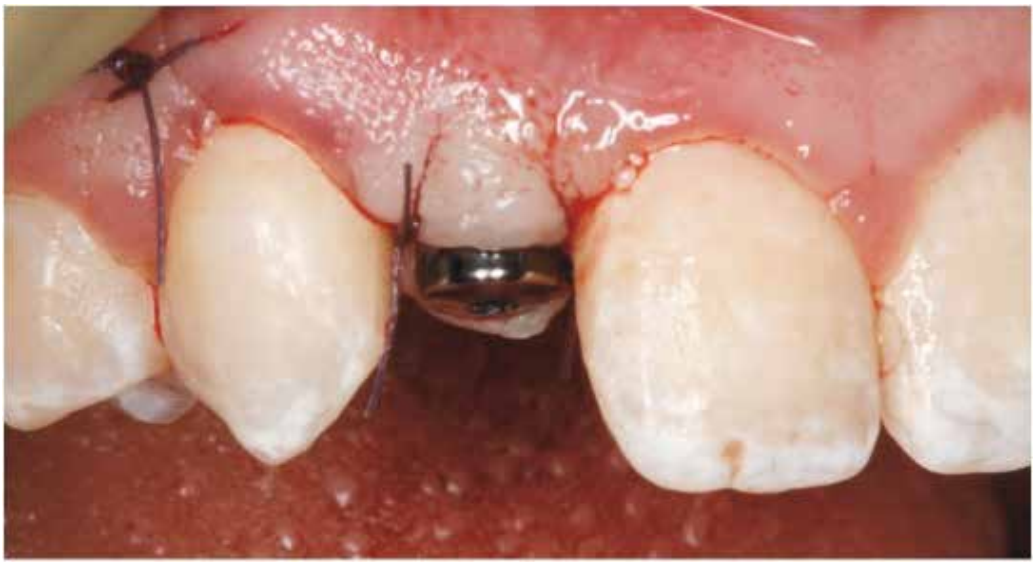

Fig. 1. Healing abutment remains transmucosal at the one-stage implant surgery

The effect of one-stage and two-stage implant surgery on peri-implant mucosa and crestal bone level changes have been evaluated in both experimental and clinical studies. Abrahamsson et al. 1996 in an animal study compared the morphology and the composition of the transmucosal tissue for 3 different implant systems (Astra Tech, Brånemark, Straumann), using either a two-stage (Astra Tech, Brånemark) or one-stage technique (Straumann) over a six-month period. The epithelial and connective tissue components had similar dimensions and composition. All 3 groups exhibited bone loss of around 0.5 mm, the epithelium height was around 2 mm (slight variation among groups, 1.6-2.3 mm) and the connective tissue was roughly 1 mm. The connective tissue consisted of 86% collagen and 8% fibroblasts, where the collagen fibers were parallel to the surface of the implant. These histological observations suggested that the soft tissue seal has the same characteristics using these implants systems. Similarly, in a following study (Abrahamsson et al. 1999) no histological and radiographical differences were found between implants of one system (Astra Tech) placed with different installation techniques (one-stage vs two-stage).

Although there is a large number of clinical studies and reports for implants placed with one-stage or two-stage surgical techniques, there are few studies which directly compare

these two techniques. Åstrand et al. 2004 in a split-mouth clinical study compared implants placed with one-stage (ITI, TPS solid screws) and two-stage (Brånemark) surgical technique supporting maxillary screw-retained fixed partial dentures for 3 years. No statistically significant differences were found between the implants studied (regarding bone level changes and survival rates), except for the frequency of periimplantitis, which was higher for the ITI implants. Similar findings were reported in another clinical study comparing implants placed with one-stage (ITI, TPS hollow screws) and two-stage surgical technique (Brånemark) supporting mandibular fixed partial dentures over a 3 year time period (Momberg et al. 2001). After 3 years, the cumulative success rates were 97.9% and 96.8% for the Brånemark and ITI systems, respectively. Kemppainen et al. 1997 with a parallel group design study compared Astra Tech implants placed with a two-stage surgical technique versus ITI hollow cylinders placed with a one-stage surgical technique for single tooth replacement for 1 year. Again, there were no statistically significant differences in failures and marginal bone level changes between the implant systems and surgical protocols after 1 year of function (mean marginal bone loss was 0.13 mm for Astra Tech implants and 0.11 mm for ITI implants).

It appears that using one-or two-stage surgical techniques have no clinically significant effect on success, survival rates and marginal bone levels. However, one has to consider that the one-stage technique has less morbidity for the patients since it involves a single surgical procedure, but the two-stage surgery might offers greater potential for soft tissue management.

2.2 Load timing and marginal bone level changes

Healing associated with oral endosseous titanium implants is based on osseointegration or 'functional ankylosis' (Brånemark et al. 1969). It has been advocated that after implant placement, surgical sites should be undisturbed for at least 3-6 months to allow uneventful wound healing, thereby enhancing osseointegration between the implant and the bone (Adell et al. 1981). The rational behind this approach is that implant micro-movements caused by functional forces during wound healing may induce fibrous tissue formation rather than bone contact, leading to clinical failure (Adell et al. 1981). Micromovements of more than 100μm were reported to be sufficient to jeopardize healing with direct bone to implant contact (Brunski 1993).

Interestingly, several experimental studies have shown that immediate loading of endosseous titanium implants will not necessarily lead to fibrous tissue healing (Henry et al. 1997, Piattelli et al. 1997, 1998, Romanos et al. 2001, Nkenke et al. 2001, 2003). In fact some data have demonstrated that early loading increased bone to implant contact when compared to unloaded controls (Piattelli et al.1998, Romanos et al. 2001). In addition several clinical studies investigating the efficacy of immediate loading protocols (Esposito et al. 2009, Nkenke et al. 2006, Weber et al. 2009) suggested that immediate loading of endosseous implants might be a realistic protocol in various jawbone regions. However, from the available clinical studies it is not possible to draw definitive conclusions regarding exclusion and inclusion criteria for immediate loading, threshold values for implant stability that permit immediate loading, nor bone quality needed for immediate loading. Moreover, evaluations of implants subjected to immediate loading have been reported mainly on the basis of implant survival without mentioning marginal bone level changes. Evaluation of marginal bone level changes around implants subjected to immediate loading is more

frequently reported for single tooth replacements rather for fixed and complete partial dentures.

The definition of immediate functional loading which was suggested in Consensus Conference Meetings (Aparicio et al. 2003, Cochran et al. 2004) relate to an implant-supported restoration, which is placed in occlusion with the opposing dentition within 48 h from implant placement. In this context, a critical evaluation of publications in the field of single-tooth replacement is required. Thus, despite the use of an immediate or early-cemented crown restoration on an implant, functional loading was applied after an additional period of healing in several studies (Ericsson et al. 2000, Chaushu et al. 2001, Andersen et al. 2002, Malo et al. 2003, Norton 2004, Ottoni et al. 2005). There are a few studies on immediate functional loading of implants used for single-tooth replacement (Calandriello et al. 2003a, 2003b, Cannizzaro & Leone 2003, Glauser et al. 2003, Lindeboom et al. 2006). The majority of these studies were prospective cohort studies and included between 20 and 50 subjects/implants. Cannizzaro & Leone 2003 compared 23 single-tooth implants that were subjected to immediate loading along with 24 implants whose loading was delayed. No implants were lost in the test and control groups at the 2 year follow-up. The radiographic examination revealed that 91.3% of the test implants and 87.5% of the controls showed a marginal bone loss of 1 mm, while 8.7% of the test group and 12.5% of the controls demonstrated marginal bone loss that varied between 1 and 2 mm. Thus, the percentage of implants that had 1 mm of marginal bone loss was higher in the control group than in the test groups. Calandriello et al. 2003a evaluated 20 implants used for single-tooth rehabilitation which were exposed to immediate loading. At the 12-month re-examination, no implants were lost and the mean marginal bone loss was 1.22 mm. In a subsequent prospective multicenter trial, Calandriello et al. 2003b evaluated immediate functional loading of implants used in single-tooth replacement in the molar segments of the mandible. The survival rate recorded at 6 months was 100%, and the overall marginal bone loss was 1.0 mm. Glauser et al. 2003 analyzed 20 implants used for single-tooth replacement with immediate functional loading. No implant loss was recorded at the 12-month evaluation and the mean marginal bone loss was 1.2 mm.

Koutouzis et al. 2011 evaluated the outcome of immediately loaded implants placed with the osteotome technique for single tooth replacements over a 12-month period. Twenty patients in need of oral prosthetic rehabilitation that included single implant placement in the anterior-premolar position participated in this prospective trial. A modified implant installation procedure with an under preparation of the implant bed using the osteotome technique and immediate loading of the implant was performed (Figure 2). Out of the 22 implants placed in 20 patients one implant failed to integrate (4.5%) and was therefore removed 3 months following implant installation. The mean marginal bone loss from the time of implant placement to the 6-month examination was 0.08 mm, while 0.19 mm loss was observed from the time of implant placement to the12-month examination. The amount of marginal bone loss reported in this study was smaller compared to immediate loaded single implants placed with a conventional site preparation (Calandriello et al. 2003a,2003b, Glauser et al. 2003).

In conclusion the current literature suggests that immediate loading does not promote marginal bone loss for implants replacing single teeth. Importantly the majority of marginal bone level changes occur during the first 3-6 months of loading with no significant alterations thereafter.

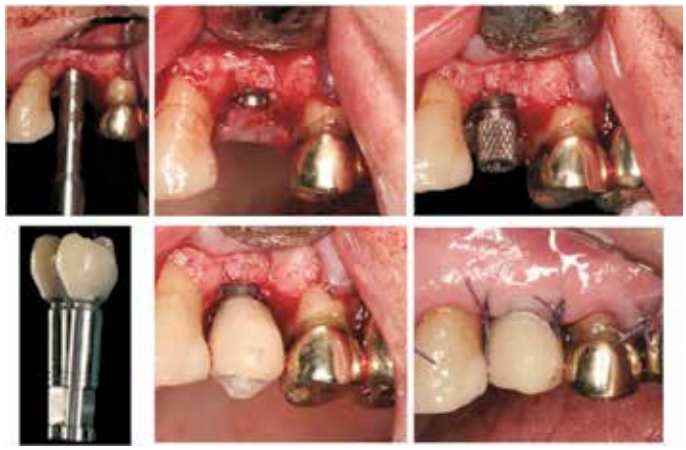

Fig. 2. Implant placement with the osteotome technique and immediately loaded

2.3 Marginal bone level changes around implants placed in grafted sockets.

Following tooth extraction, bone modeling and remodeling characterize the healing of the extraction socket (Carlsson et al. 1967, Araujo & Lindhe 2005) where a reduction in both the height and the width of the alveolar ridge can occur (Pietrokovski & Massler 1967, Johnson 1969, Schropp et al 2003). In an attempt to preserve alveolar bone and to optimize implant installation, several materials have been used to augment the residual extraction socket.

In experimental animal studies, it was demonstrated that several of the biomaterials used were incorporated in newly formed bone, maintained as inactive fillers and slowly resorbed during host tissue remodeling (Araujo et al. 2001, Carmagnola et al. 2002, Cardaropoli et al. 2005). Multiple human histological studies evaluating socket preservation procedures have also described the presence of residual biomaterials for various healing periods (Becker et al. 1998, Artzi et al. 2000, 2001, Iasella et al. 2003, Carmagnola et al. 2003). It was reported that the implanted particles were entrapped in dense connective tissue and thus, potentially interfere with normal extraction healing. This was further exemplified in two human clinical and histologic studies (Becker et al. 1996, 1998) where it was reported that extraction sockets filled with demineralized freeze-dried bone allograft (DFDBA) or freeze-dried bone allograft (FDBA) resulted in retention of graft particles in the fibrous connective tissue and interfered with the healing of the extraction socket. Similar findings were observed by Carmagnola et al. 2003 where extraction sockets were filled with deproteinized bone xenograft (DBX). The authors of this study reported that healing was comprised by increased amount of connective tissue and small amounts of newly formed bone surrounding the graft particles. Conversely, other studies have reported more favorable histologic outcomes for extraction sockets filled with DFDBA, bioactive glass and DBX (Iasella et al. 2003, Froum et al. 2002, Barone et al. 2008).

Several clinical studies (Artzi et al. 2000, 2001, Iasella et al. 2003, Lekovic et al. 1997,1998, Nevins et al. 2006) utilizing biomaterials to augment socket healing have reported smaller changes in ridge dimensions compared to non-grafted controls thus enhancing the possibility of implant installation in adequate bone volume and in desired positions. However, these studies do not describe implant survival nor implant success rates following the socket preservation procedures. In a systematic review (Fiorellini & Nevins 2003) evaluating dental implant survival rates, the authors concluded that implant survival was

similar between implants placed in native bone and implants placed in sites previously treated with ridge augmentation and preservation techniques. Notably, none of the 13 studies included in the analysis reported on survival rates of implants placed following socket preservation techniques.

There is limited information regarding crestal bone level alterations for implants placed in sockets preserved with various biomaterials. A recent study (Koutouzis et al. 2010) retrospectively compared bone level changes around implants placed in post extraction sockets augmented with DFDBA to implants placed in native bone (Figure 3). The overall survival rate from baseline to the last follow-up visit was 100% for both groups. The mean marginal bone loss was a mean of 0.15 mm for both groups at the 12 month follow-up. There were no significant differences regarding the percentage of implants and implant surfaces demonstrating marginal bone loss.

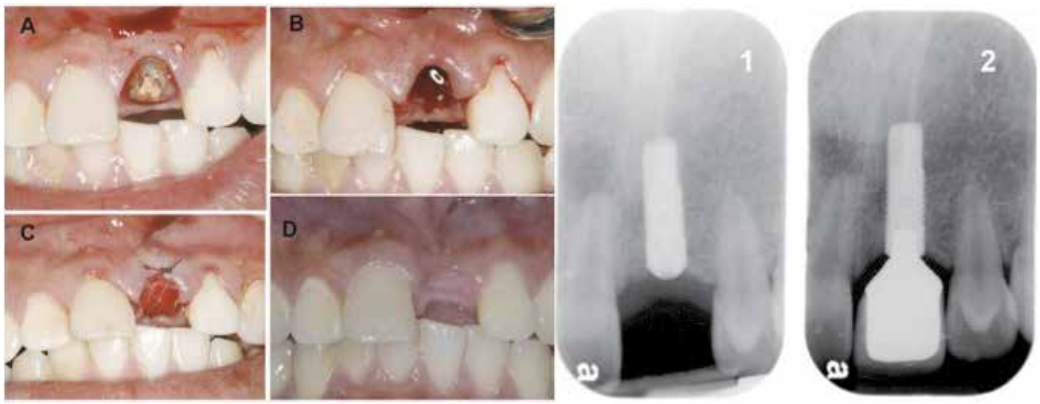

Fig. 3. Clinical photos of tooth #9 A) prior to extraction, B)immediately following extraction, C) following DFDBA and collagen membrane placement, D) 4 months following extraction. Radiographs of implant at the same site 1) at implant installation and 2) one year following implant installation.

In conclusion grafting extraction sockets with various types of biomaterials has a beneficial effect on preserving the dimensions of the edentulous ridge. Although there is variation in histologic findings from animal and human studies regarding the composition of the sites that healed following grafting procedures. This variation may reflect differences in the potential of different grafted materials to regenerate extraction sockets, differences in surgical techniques, the use of barrier membranes and/or differences in healing time. Although there are reports showing that implant survival is similar between implants placed in native bone and implants placed in sites previously treated with ridge augmentation and preservation techniques there is very limited information regarding marginal bone level changes around those implants. From the results of one study it can be concluded that implants placed in post extraction sockets augmented with DFDBA exhibited minimal amount of marginal bone loss, similar to implants placed in native bone.

2.4 The effect of tooth-implant and inter-implant distances on marginal bone level changes

Studies on Brånemark implants placed adjacent to teeth revealed that the inter-unit distance is a risk factor to consider with respect to marginal bone loss at the adjacent tooth (Esposito

et al. 1993, Andersson et al. 1998, Thilander et al. 2001). In these studies there was a large variation in bone loss between subjects and that the recorded bone loss differed significantly between anterior and posterior tooth regions. Furthermore, from radiographic examinations of young individuals who received their single implant therapy during adolescent, Thilander et al. 2001 reported 1.4-2.2 mm bone loss between crown cementation and 10-year follow-up at adjacent teeth to single implants placed in incisors position. On the other hand, Esposito et al. 1993 found that the increased bone loss at adjacent teeth was confined to the time period before loading and that no increase in bone loss was detected following the period of functional loading. The latter finding is supported by data from Cardaropoli et al. 2003 and Chang et al. 2010 showing a lack of a relationship between the inter-unit distance and longitudinal marginal bone loss at the proximal tooth surface next to an implant. The later study evaluated implants with a micro-threaded conical portion (Astra Tech).

The horizontal distance between two implants may have an influence on the maintenance of the proximal bone crest level (Figure 4). It was shown in experimental and clinical studies that the inter-implant bone crest level shifted apically when the inter-implant distance decreased. Based on observations made in a cross-sectional study, Tarnow et al. 2000 accredited the more apically located position of the bone crest between implants with less than 3mm of inter-implant distance to the lateral component of the vertical bone loss to the first thread that is common at implants with an external hex design. The proposed explanation, however, was not supported by a 3-year longitudinal study of the same type of implants (Cardaropoli et al. 2003), in which multivariate analysis failed to identify lateral bone loss as a significant factor for longitudinal reduction of the inter-implant bone crest level. Furthermore, animal studies revealed no significant difference in mid-proximal bone crest resorption in relation to the horizontal distance between implants designed with a Morse cone connection and platform switching (Novaes et al. 2006 a & b, de Oliveira et al. 2006). It has been claimed, based on observations of implants placed in the tibia of rabbits, that closely placed implants may favor bone growth between implants (Hatley et al. 2001). However, whether maintenance of the mid-proximal bone crest level may be related to the design of the implant-abutment interface needs to be documented in longitudinal studies.

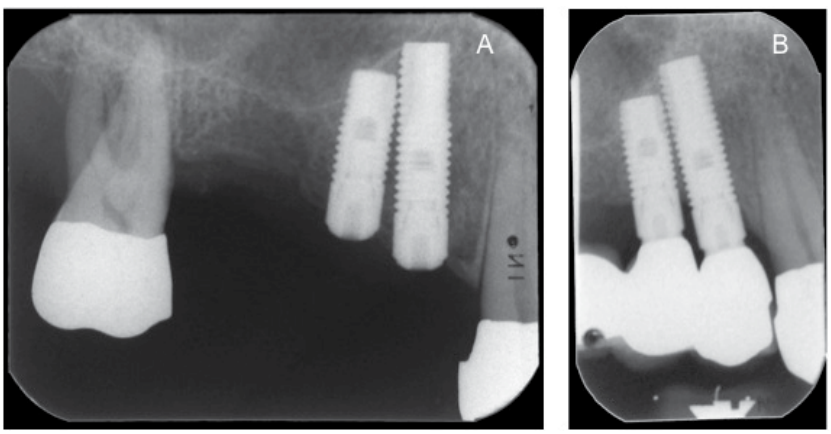

Fig. 4. Radiographs of implants at #4 and #5 position placed with an inter-implant distance less than 3mm. Note the marginal bone loss between implant installation (A) and prosthesis delivery (B).

Taken together one can conclude that the marginal bone level at teeth adjacent to single implants with a micro-threaded conical portion is not influenced by the horizontal and vertical tooth-implant distances. However, this statement cannot be supported for implants with an external-hex design. Loss in height of the mid-proximal bone crest in the inter-implant areas is influenced by the bone loss at the two bordering implants and the horizontal inter-unit distance, although no such relationship is evident for the proximal area between an implant and the adjacent tooth.

2.4 Position of the fixture/abutment interface in relation to the alveolar crest and marginal bone level changes

The location of the fixture/abutment interface (FAI) can be placed in various positions in relation to the alveolar crest (crestal, supracrestal, subcrestal) (Figure 5). The location of the FAI can be of major importance when the goal is to construct aesthetic restorations. Placement of the FAI in a more apical position can create an ideal emergence profile for the prosthetic construction (Buser & von Arx 2000).

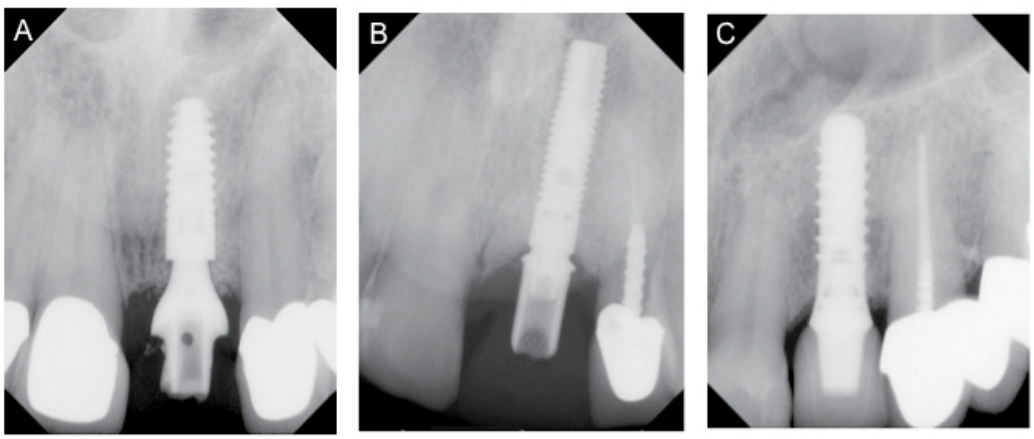

Fig. 5. Radiographs of implants placed with the FAI at A)subcrestal, B)crestal, C)supracrestal in relation to the alveolar crest

Subcrestal position of the FAI has been reported to have a negative influence on marginal bone level changes in a few animal studies (Jung et al. 2008, Hermann et al. 2000, Todescan et al. 2002, Pontes et al. 2008). In an experimental study in dogs Hermann et al. 2000 reported that placement of two-part implants with the FAI 1 mm below the crestal bone resulted in pronounced crestal bone loss following 6 months of healing. In this study the authors used custom-made implants with a FAI micro-gap of 50 μm. Similarly, Jung et al. 2008 reported that the greatest amount of bone loss occurred in implants placed with the FAI 1mm below the bone crest compared to implants placed with FAI 1mm above or at the level of the bone crest. In this study, implants with non-matching implant abutment diameters were utilized. However, the amount of crestal bone loss was smaller compared to that found in the study by Hermann et al. 2000. In a similar animal experiment, Todescan et al. 2002 evaluated the healing around implants (Brånemark System) that were placed either 1 mm above, level with or 1 mm below the crestal bone. Here it was reported that the first marginal bone to implant contact was located between 1.6 mm and 2.5 mm apical to the FAI

with the shortest implant contact distance associated with implants that were placed in the subcrestal position. Similar findings have been reported by Pontes et al. 2008 where they placed implants with the FAI at the bone crest, 1 mm and 2 mm apical to this position. Following 4 months of healing all implant groups had the first bone to implant contact apical to the FAI. None of these animal studies reported bone formation above the FAI when implants are placed in a subcrestal position. In contrast to the previously described studies, few animal experiments (Welander et al. 2009, Weng et al. 2008) have reported a more favorable outcomes for implants in a subcrestal position with bone formation close to or even above the FAI. Welander et al 2009 observed osseointegration coronal to the FAI when placing implants with the FAI 2 mm subcrestally. The test implants in this study had a surface modification extending to the implant margin that included the shoulder part of the implant and a conical interface between the abutment and the implant. Similar findings were reported by Weng et al. 2008, showing that implants with subcrestal position presented bone growth onto the implant shoulder in nearly all histological sections. Implants utilized in this study contained a reduced abutment diameter in relation to the fixture diameter, a Morse taper implant-abutment connection, and a microstructured surface treatment which included the cervical collar and extended onto the implant shoulder.

The effects of altered vertical implant positioning in patients were reported by Hämmerle et al. 1996. Here one-stage transmucosal implants were placed with the border between the rough/smooth surface 1 mm subcrestally. This group of implants was compared to implants placed according to the manufacturer' s recommendation with the rough/smooth border positioned precisely at the alveolar crest. The implants in the subcrestal group lost a mean of 2.26 mm of clinical bone height during the first 12 months, and the control implants lost 1.02 mm during the same time period. The authors concluded that subcrestal placement of implants with smooth/polished collars should not be recommended.

There is limited information from clinical studies for subcrestal placement of two-part implants. In a recent case series Donovan et al. 2010 reported that subcrestal placement of dental implants with microstructured surface treatment extending onto the implant shoulder and with reduced abutment diameter resulted in minimal marginal loss of hard tissues (0.11 mm). In addition, mineralized hard tissue on the implant shoulder was demonstrated in 69% of the implants after a mean follow-up time of 14 months. However, in this study grafting of the remaining osseous wound defect between the bone crest and the coronal aspect of the fixture was performed subsequent to implant placement. A subsequent study (Koutouzis et al. 2011) reported on the same patient population and evaluated the effect of bone grafting of the defect between the bone crest and the coronal aspect of the implant for implants with reduced abutment diameters placed non-submerged and in subcrestal positions (Figure 6).

Records of 50 consecutive patients treated with subcrestally placed dental implants grafted with a xenograft (Group A) and 50 consecutive patients with subcrestally placed dental implants without any grafting material (Group B) were reviewed. The mean marginal loss of hard tissues was 0.11 ± 0.30 mm for Group A and 0.08 ± 0.22 mm for Group B. Sixty nine percent of the implants in Group A and 77% of the implants in Group B demonstrated hard tissue on the implant platform. There were no statistical significant differences between the groups regarding marginal peri-implant hard tissue loss. Thus grafting of the remaining osseous wound defect between the bone crest and the coronal aspect of the implant has no effect on marginal peri-implant hard tissue changes (Figure 7).

Fig. 6. Implant with a Morse taper implant-abutment connection and a microstructured surface treatment including the cervical collar and extending onto the implant shoulder.

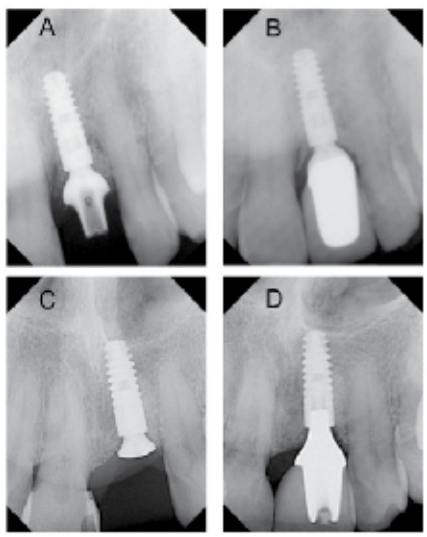

Fig. 7. Radiographs of an implant at #9 site of a patient in Group A: A) at implant installation and B) 12 months following implant installation and of a patient in Group B: C) at implant installation and C) 16 months following implant installation.

Taken together it seems that the location of the FAI can have an effect on marginal bone level changes depending on the type of implant system used. Even though one-stage transmucosal implants exhibit stable peri-implant bone levels when the FAI is located supracrestal and the border between rough and smooth surface is located at the alveolar crest it seems that placement of the border between the rough and smooth surface below the bone crest can lead to marginal bone loss and it is not recommended. Placement of the FAI in subcrestal position has been documented to have positive effect on marginal bone levels for implants with reduced abutment diameter in relation to the fixture diameter, a Morse

taper implant-abutment connection and a microstructured surface treatment which includes the cervical collar and extends onto the implant shoulder.

3. The effect of fixture-abutment interface (FAI) design on marginal bone level changes

Early bacterial colonization of implant surfaces and peri-implant tissues can occur within minutes after implant installation (Fürst et al. 2007). When a prosthetic abutment is connected to a fixture, a microgap is created between the components. Microorganisms may grow into this fixture-abutment interface microgap (Quirynen et al. 1993, 2006, Callan et al. 2005) and establish a bacterial reservoir resulting in an area of inflamed soft tissue facing the fixture-abutment junction (Ericsson et al.1995). The presence of an FAI microgap in close relation to bone may thus have a role in the development of peri-implant inflammation and bone loss (Persson et al. 1996, Herman et al. 1997, 2001, King et al. 2002, Piatelli et al. 2003). Prevention of microbial leakage at the fixture-abutment interface is a major challenge in the construction of two-piece implant systems in order to minimize inflammatory reactions and to maximize peri-implant bone stability.

Microbial penetrations along the internal part of dental implants have been reported in some in vitro studies utilizing implants with different fixture-abutment interface geometries devoid of mechanical loading (Quirynen et al. 1994, Jansen et al. 1997, Tesmer et al. 2009, Aloise et al. 2010). For instance, Quirynen et al. 1994 demonstrated that when fixtures with an external hex design and abutments were assembled and installed in a liquid blood medium inoculated with oral microorganisms, bacterial invasion of the fixture-abutment interface microgap was detected. Similarly, Jansen et al. 1997 reported microbial leakage of thirteen different implant-abutment combinations using *E.coli* as indicator bacteria. Among the different implant-abutment combinations an implant with an internal connection and a silicon washer demonstrated the fewest cases of leakage. Tesmer et al. 2009 evaluated the potential risk for invasion of *A. actinomycetemcomitans* and *P. gingivalis* at the fixture-abutment interface of implants with Morse-taper internal connection. Fixtures and abutments were assembled and allowed to incubate in a bacterial solution of *A. actinomycetemcomitans* and *P. gingivalis* for five days. They reported that three of the ten implants evaluated developed one colony-forming unit (CFU) for *A. actinomycetemcomitans*, whereas zero of ten samples developed CFUs for *P. gingivalis.* Similar results have been reported from Aloise et al. for implants with Morse-taper internal connection. In this experiment they utilize a different evaluation method were the internal part of the implants were inoculated with *S.Sanguinis* and then implants connected to the respective abutments. Following total immersion of 10 implants with Morse-taper internal connection in a sterile solution for 14 days, only two implants showed evidence of bacterial leakage.

There is limited information from in vitro studies evaluating microbial contamination of the fixture-abutment interface microgap under loading conditions. Steinebrunner et al. 2005 used a 2-axis chewing simulator to apply a 120N force for a total of 1200000 cycles. They reported statistically significant differences between five implant systems with respect to number of chewing cycles and bacterial leakage. Specifically, implants with a tri-channel internal connection showed bacterial leakage at significantly higher numbers of chewing cycles compared to implants with external hex, implants with internal connection and a silicon washer, and implants with internal hex with friction fit connection. Koutouzis et al. 2010 utilized an in vitro dynamic loading model to assess the potential risk for invasion of

oral micro-organisms into the fixture-abutment interface microgap of dental implants with different fixture-abutment connection characteristics. In this experiment twenty-eight implants were divided into two groups (n=14/group) based on their microgap dynamics. Group 1 was comprised of fixtures with internal Morse-taper connection that connected to standard abutments. Group 2 was comprised of implants with a four-groove conical internal connection that connected to multi-base abutments (Figure 8). The specimens were immersed in a bacterial solution of *Escherichia coli* and loaded with 500,000 cycles of 15 N in a wear simulator. Following disconnection of fixtures and abutments, microbial samples were taken from the threaded portion of the abutment, plated and cultured under appropriate conditions. The difference between loosening and tightening torque value was also measured. One of the 14 samples in Group 1 and 12/14 of samples in Group 2 developed multiple colony forming units (CFU) for *E.coli*. Implants in Group 1 exhibited an increase in torque value in contrast to implants in Group 2 that exhibited a decrease. This study indicated that differences in implant design may affect the potential risk for invasion of oral micro-organisms into the FAI microgap under dynamic loading conditions.

The effects of FAI design on marginal bone level changes have been analyzed in several animal studies that have been also reported results on the effect of the position of the FAI. Those studies have been discussed extensively in a previous section of this chapter. In

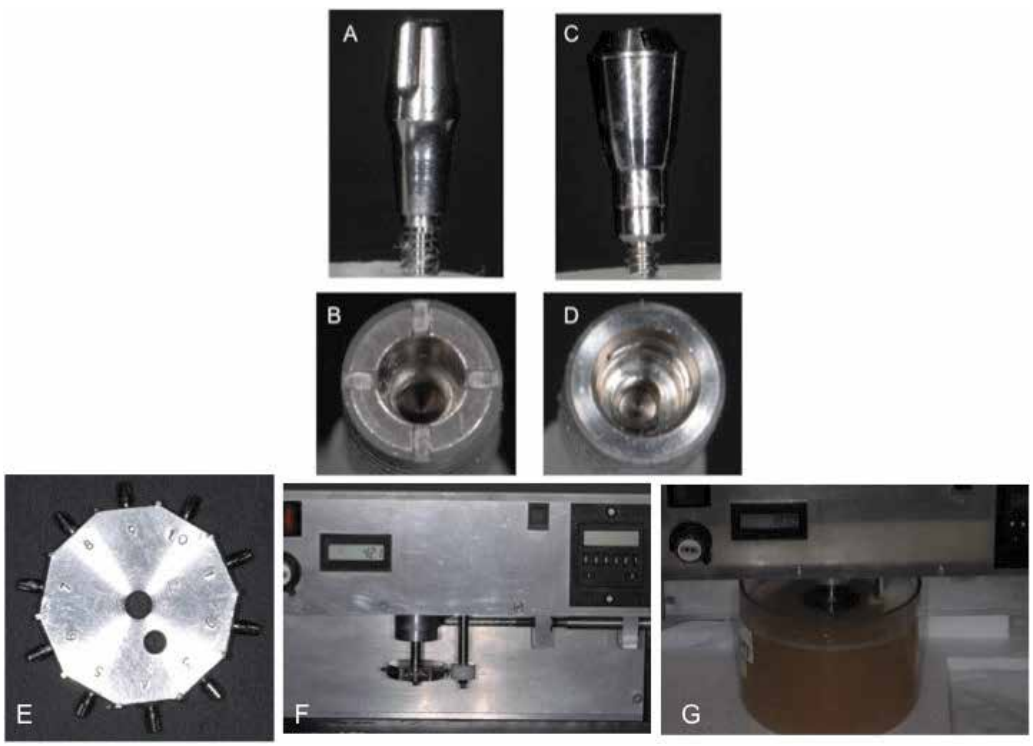

Fig. 8. A) Standard straight abutment of Group 1. B) Implant with internal Morse-taper connection of Group 1. C) Multibase abutment of Group 2. D) Implant with a four-groove conical internal connection of Group 2. E) Specimen wheel with implants and abutments of Group 1. F) Specimen and Agonist wheels. G) Specimen and Agonist wheels immersed in the bacterial solution.

summary it seems that the design and location of the FAI can have an effect on marginal bone level changes. Placement of the FAI in subcrestal position has been documented to have positive effect on marginal one level only for implants with reduced abutment diameter in relation to the fixture diameter, a Morse taper implant-abutment connection and a microstructured surface treatment which included the cervical collar and extended onto the implant shoulder.

The results of animal studies on the effect of FAI design on marginal bone level changes have been confirmed in clinical studies. Based on observations of the performance of implants with an external hex connection Albrektsson et al. 1986 observed 1mm peri-implant bone loss during the first year of function, followed by an annual loss <0.2mm after the first year in service as a criteria for implant success. Albrektsson & Isidor 1993 also proposed criterion for implant success where they suggested an average peri-implant marginal bone loss of less than 1.5 mm the first year after insertion of the prosthesis and less than 0.2 mm annual bone loss after that as a standard for successful therapy. However more current studies utilizing two-piece implant systems with an altered horizontal relationship between the fixture diameter and the abutment diameter, report minimal marginal peri-implant bone loss (Wennström et al. 2004, 2005, Norton 2006). The positive effect of this design known as platform shifting is explained by an increased distance of the FAI from the crestal bone creating an establishment of increased biologic width reducing the risk of inflammatory induced bone loss in cases of peri-implant submucosal bacterial colonization. In a 5-year prospective study Wennström et al. 2005 reported mean bone level changes from the time of crown placement to the first year follow up of 0.02 mm measured on implant level. Norton et al. 2006 reported an average of marginal bone loss of 0.65 mm from implant therapy in 54 patients where the implants had been in function for 37 months. In further clinical studies (Koutouzis & Wennström 2007, Koutouzis et al. 2010) utilizing dental implants with an altered horizontal relationship between the fixture diameter and the abutment diameter minimal marginal bone level changes have been observed even in conditions where the FAI were placed subcrestally.

Taken together the results of in-vitro studies show that differences in implant design may affect the potential risk for invasion of oral micro-organisms into the FAI under non-loading and dynamic loading conditions. Implants with internal Morse-taper connection have the highest potential to prevent bacterial contamination of the FAI interface. The results from animal studies demonstrate that implants with reduced abutment diameter in relation to the fixture diameter, a Morse taper implant-abutment connection and a microstructured surface treatment which included the cervical collar and extended onto the implant shoulder can maintain stable peri-implant bone levels even when the FAI is placed in a subcrestal position. These results are in line with clinical studies showing that implants with reduced abutment diameter in relation to the fixture diameter and a Morse taper implant-abutment connection exhibit less marginal bone loss compared to implants with an external hex connection at least at the earlier stages of healing (the interval of implant installation to prosthesis installation).

4. The effect of loading on marginal bone level changes

It has been suggested that biomechanical overload is one of the major determinants for late implant failure (Esposito et al. 1998a). The biomechanical aspects of the relation between the

applied load, the supporting capacity of the prosthesis, implant and characteristics of the alveolar bone seem to be essential for the long-term outcome of the treatment.
Based on investigations of biomechanics in the implant-supported fixed prosthesis, two main types of loading of the anchorage unit were suggested to be considered: (i) axial force and (ii) bending moment (Rangert et al 1989). The axial force was suggested as most favourable as it distributes stress more evenly through the implant, while the bending moment exerts stress gradients in the implant as well in the bone. Bending moment can be produced from axially applied forces when a cantilever extension is used, but non-axial applied forces can also induce bending movement. The extent of the bending moment is dependent on the distance from the point of occlusal contact to the abutment-fixture junction, which forms the lever arm for the bending moment induced by the non-axial force.

4.1 Laboratory and animal studies

Laboratory tests utilizing finite element analysis demonstrated that, when applying lateral or oblique loads, the highest stress concentration occurs at the marginal part of the implant (Borchers & Reichart 1983; Clelland et al. 1993, 1995; Papavasiliou et al. 1996; Holmes & Loftus 1997; Kitamura et al. 2004). With regard to the biological effects of such stress concentrations, however, animal experiments revealed conflicting results. Barbier & Schepers 1997 studied the effect of axial and non-axial loading conditions induced by either a bilaterally supported fixed partial dentures (FPDs) or a cantilever FPD on two implants. Based on the histological observations, non-axial loading for 7 weeks gave rise to a more dynamic remodeling of the surrounding cortical and trabecular bone tissue. Therefore, the authors extrapolated that a longer experimental period of loading could have resulted in marginal bone loss. Similarly, using a rabbit tibia model, Duyck et al. 2001 reported that dynamic excessive loads perpendicular to the implant axis caused crater-like bone loss around the marginal part of the implant. The hypothesis that excessive dynamic load can trigger bone resorption through the induction of micro-damage in the bone may also be supported by observations made by Isidor (1996, 1997), who demonstrated that excessive occlusal load in a lateral direction caused implant failure due to loss of osseointegration in five out of eight implants during an 18-month observation period. However, it was also observed that the bone crest remained at a position close to the margin of the implant without signs of triangular-shaped bone craters. The latter observation corroborates findings made in several other experimental studies (Hürzeler et al. 1998; Miyata et al. 1998; Gotfredsen et al. 2001a, 2001b, 2001c, 2002; Heitz-Mayfield et al.2004) which demonstrated no detrimental effect on the marginal bone following excessive loading. In the most recent of these studies (Heitz-Mayfield et al. 2004), the effect of excessive oblique load on osseointegration of implants placed in beagle dogs was examined. Single crowns in supraocclusion with the opposing maxillary teeth were connected in one side of the mandible, while no crowns were placed on the implants in the contra-lateral side. The authors reported that no differences were found in clinical, radiographic or histological parameters between implants in supra-occlusion and unloaded controls after the 8-month experimental period.
In summary, it is obvious that conflicting results with regard to the effect of various loading conditions have been reported from animal experiments. The majority of the studies involving unfavourable loading conditions failed to confirm that excessive loading will cause marginal bone loss and/or loss of osseointegration.

4.2 Clinical studies

Limited clinical data are available in the literature regarding the possible influence of loading characteristics, such as magnitude and direction, on the marginal bone stability around implants. The assessment of the loading characteristics has been performed mainly through factors related to patient characteristics (parafunctional activity, bite force), prosthesis characteristics (cantilever length, height of the suprastructure, material of the suprastructure) and implant location characteristics (position in relation to occlusal level). In the interpretation of the available data one has to consider the difficult task to quantify the magnitude and direction of bite forces applied by the patient in relation to the biomechanical capability of the bone as well as the lack of appropriate controls.

Quirynen et al. 1992 reported that excessive marginal bone loss (more than 1 mm) after the first year of loading and/or fixture loss correlated well with the presence of overload due a lack of anterior contact, the presence of parafunctional activity and osseointegrated full fixed prostheses in both jaws. The data were generated from 84 patients having fixed total dentures in one or both jaws or overdentures. These participants had been selected from a group of 467 consecutive treated patients. However, the retrospective nature of the study with a very heterogeneous material and a large range in follow-up time may limit the validity of the findings. Parafunctional activity and bite force in relation to marginal bone loss was evaluated in a series of studies (Lindquist et al. 1988, 1996) involving patients with mandibular fixed total dentures. Using data from 3-6 years of follow-up Lindquist et al. 1988 reported that both poor oral hygiene and tooth clenching were associated with marginal bone loss. Smoking habits were not assessed in this report. Interestingly, analyzing data from 12-15 years of follow-up of the same cohort, Lindquist et al. 1996 reported that smoking and poor oral hygiene had a significant influence on marginal bone loss, and that factors such as maximal bite force and tooth clenching were of minor importance.

Studies in humans have documented an increase in vertical loading as a result of inclusion of cantilever extension. Falk et al. 1989 studied naturally occurring axially directed forces on implants supporting cross arch mandibular prostheses with bilateral posterior two-unit cantilevers. The authors found that 70% of the forces were placed on the cantilevers and 30% on the fixture-supported segment of the prostheses. Limited data have been reported regarding the possible influence of prosthesis related factors such as cantilever extension on marginal bone stability around implants. Lindquist et al. 1988 reported that seven patients with long cantilevers (>15 mm) showed more bone loss than 6 patients with short cantilevers (<15 mm). However the difference was small (0.95 mm vs 0.61 mm) and only observed in the medial fixture sites. The authors analysed the same material after 15 years of follow-up (Lindquist et al. 1996) and found that the length of the cantilever segment was of minor importance but that smoking and oral hygiene had significant effects on the amount of peri-implant bone resorption. Naert et al. 1992 reported data derived from examinations of 103 complete fixed total dentures in 91 patients. The authors concluded that after 3-years of follow-up the length of the cantilever extension did not have a significant influence on the rate of marginal bone loss around the supporting implants.

The clinical studies referred to (Lindquist et al. 1988, 1996, Naert et al. 1992) indicate that cantilever extensions might not jeopardize the stability of peri-implant bone level in a complete fixed total denture situation. However, these reports do not provide information whether in an FPD, supported by a few implants, the load exerted on the cantilever extension may cause undue bone loss.

Romeo et al. 2003 studied the effect of cantilever extension on the prognosis of fixed partial dentures and marginal peri-implant bone stability. The overall cumulative implant survival rate was 97% for an observation period of 1-7 years. Slightly greater bone loss was reported for implants close to the cantilever compared to implants more distant to the cantilever (0.82 mm vs 0.69 mm). The authors also reported that for every 1 mm increase of cantilever length there was a 0.099 mm increase in bone resorption around the fixture closest to the cantilever extension. In a retrospective study, Wennström et al. 2004 assessed whether the inclusion of a cantilever extension increased the amount of marginal bone loss at fixed partial dentures (FPDs) over a 5-year period of functional loading. The cohort comprised of 45 periodontally treated and well maintained partially dentate patients. Comparison between FPDs with and without cantilever extension was performed at FPD, implant and surface level and revealed no statistical significant differences at any level, but that jaw of treatment and smoking had a significant influence on peri-implant bone level change on the FPD level.

The influence of the height of the supra-structure on marginal bone loss has also been evaluated (Naert et al. 2001, Wennström et al. 2004). Naert et al. 2001 in a multivariate analysis of potential factors influencing marginal bone loss around implants supporting FPDs reported that long abutments significantly increased the amount of bone loss in the first 6 months, but not thereafter. Wennström et al. 2004 on the other hand found that the height of the supra-structure failed to significantly influence bone loss on the FPD level but had an effect on the most posterior implant in the FPD. In this context it should be noted that the mean height of the supra-structure was significantly greater for patients having FPDs with cantilever extension as well as for fixed partial dentures placed in the maxilla than in the mandible.

Clinical trials designed to evaluate the potential influence of oblique loading direction in relation to the implant axis on peri-implant bone stability are few. Aparicio et al. 2001 reported data derived from examinations of 29 maxillary FPDs in 25 patients supported by 101 Brånemark implants, 59 inserted in an axial and 42 in a tilted direction. No significant difference in marginal bone level change between tilted and axial positioned implants could be observed over the 5 years of follow-up. This finding is in large supported by observations made by Krekmanov et al. 2000 and Calandriello &Tomatis 2005. Balshi et al. 1997 evaluated in a 3-year study the performance of angulated abutments used to compensate for a non-ideal implant inclination, where no increase in failure rates with the use of angulated abutments was observed. In a more recent study Koutouzis & Wennström 2007 retrospectively analyzed the potential influence of implant inclination on marginal bone loss at freestanding, implant-supported, fixed partial dentures (FPDs) over a 5-year period of functional loading. The cohort was comprised of 38 periodontally treated, partially dentate patients with a total of 42 free-standing FPDs supported by implants of the Astra Tech System. Mesio-distal inclination of the implants in relation to a vertical axis perpendicular to the occlusal plane was measured with a protractor on standardized photographs of the master cast (Figure 9).

The two tail quartiles of the distribution of the implants with regard to the implant inclination were defined as axial-positioned (mean 2.41°; range 0 ° –4.1 °) and non-axial positioned implants (mean 17.11 °; range 11 ° –30.1 °), respectively. For FPDs supported by two implants, both the mesial–distal and buccal–lingual inter-implant inclination was measured. The 5-year mean bone level change amounted to 0.4mm (SD 0.97) for the axial and 0.5mm (0.95) for non-axial-positioned implants (P>0.05). For the FPDs supported by

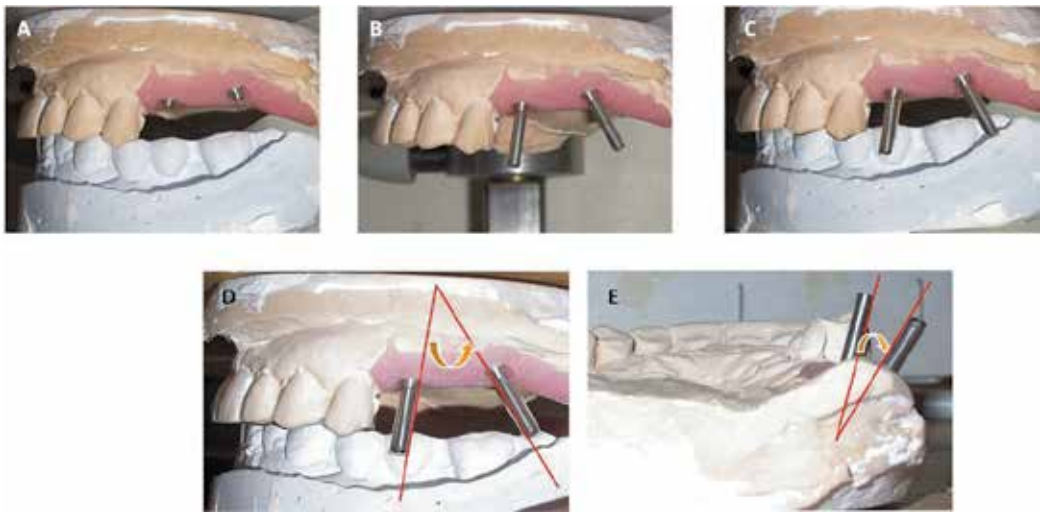

Fig. 9. Illustrations describing the photographic process for performing implant inclination measurements. (A) upper and lower casts in occlusion, (B) upper cast with guide pins abutment pick-up in place and (C) the final image produced by superimposing image b on image a, (D) mesio-distal inter-implant inclination measurements and (E) bucco-lingual inter-implant inclination measurements.

two implants, the mean inter-implant inclination was 9.21° in the mesial–distal direction and 6.71 ° in the buccal–lingual direction. Correlation analysis revealed lack of statistically significant correlation between inter-implant inclination (mesial–distal and buccal–lingual) and the 5-year bone level change. This study failed to support the hypothesis that implant inclination has an effect on peri-implant bone loss.

In conclusion, the findings of this 5-year study involving moderately tilted implants, as well as those reported by others who have clinically investigated the influence of more extreme non-axial loading on peri-implant bone level stability at implants of different design and surface texture (Balshi et al. 1997; Krekmanov et al. 2000; Aparicio et al. 2001; Calandriello & Tomatis 2005), indicate that a tilted position of the implant does not render an increased risk for bone loss during functional loading.

There are several aspects to consider when evaluating the outcomes of the clinical studies on the effect on loading parameters on marginal bone level changes including the retrospective nature of the majority of the studies, the lack of appropriate controls and the difficult task to quantify the magnitude and direction of bite forces. Within the limitations of the literature one can conclude that excessive loading forces and implant/prosthesis characteristics that can contribute to unfavourable loading conditions such as cantilever units, height of the prosthesis and angulation of the dental implants have limited effect on marginal bone level changes over time.

5. The effect of patient related factors

Patient selection is a fundamental part of the dental implant treatment plan. Patient related factors such as oral hygiene, smoking, diabetes, susceptibility to periodontal diseases and type of peri-implant mucosa have been evaluated in the literature with respect to their effect on the degree of marginal bone level changes. In addition peri-implantitis has been

identified as a major etiologic factor for marginal bone level changes and recent studies have explored epidemiological aspects of this condition.

5.1 Oral hygiene

In a prospective clinical study, Lindquist et al. 1997 reported an association between poor oral hygiene and peri-implant bone loss after 10-years of follow-up. Poor oral hygiene had a greater influence on marginal bone loss in smokers than non-smokers. For patients with poor oral hygiene, smokers had nearly three times the amount of bone loss than non-smokers. Ferreira et al. 2006 in a study analyzing risk variables in a Brazilian population, reported that presence of plaque and periodontal BOP at >30% of sites were associated with increased risk of peri-implant mucositis and peri-implantitis. The association between the full-mouth plaque score and peri-implantitis was dose dependent.

5.2 Smoking

The effect of cigarette smoking on the peri-implant soft and hard tissues has been documented in a number of studies. Strietzel et al. 2007 published a systematic review with meta-analysis, including 35 papers, to investigate if smoking interferes with the prognosis of implants, with and without augmentation procedures. The authors reported that smoking is a significant risk factor for failure of dental implant therapy and augmentation procedures accompanying implantations. This systematic review also included studies reporting on the influence of smoking on peri-implant marginal bone changes. Multiple studies have demonstrated a significant increase in peri-implant marginal bone loss in smokers compared with non-smokers (Haas et al. 1996, Lindquist et al. 1996, 1997, Carlsson et al. 2000, Feloutzis et al. 2003, Karoussis et al. 2004, Penarrocha et al. 2004, Wennström et al. 2004, Galindo- Moreno et al. 2005, Nitzan et al. 2005, Schwartz-Arad et al. 2005). Additional studies which have addressed risk indicators associated with peri-implant disease report a significant association of smoking with peri-implant mucositis, marginal bone loss and peri-implantitis (Roos-Jansåker et al. 2006a, Fransson et al. 2008). Chung et al. 2007 reported, significantly more bone loss in smokers in a retrospective study of 69 patients, including seven smokers followed between 3 and 24 years. Similarly, Deluca et. Al (DeLuca & Zarb 2006) showed that peri-implant bone loss was associated with a positive smoking history using a long-term retrospective study.

5.3 History of periodontitis

Tooth restorations using implant-supported prostheses for rehabilitation of patients who have experienced loss of teeth due to periodontitis has become an established and widely used treatment modality in modern dentistry (Figure 10).

A pertinent question in relation to implant therapy in patients susceptible to periodontal disease is whether this group of patients may also demonstrate an elevated risk for peri-implant tissue infections and subsequent marginal loss of hard and soft tissues. Only limited data are available on the outcomes of implant therapy in periodontitis-susceptible patients. In one study of 75 patients, Ellegaard et al. 1997 presented follow-up data (varying from 3 to 84 months) where the patients after initial periodontal treatment received prosthetic reconstructions supported by implants. The authors indicated that periodontally compromised patients can be successfully treated with dental implants. Nevins & Langer 1995 reported an overall implant survival rate of about 97% in a 1–8-year follow-up study of 59 patients whose periodontal disease had been categorized as refractory.

Fig. 10. #9 extracted due to loss of periodontal support and development of periodontal abscess and replaced with a dental implant

Less favorable outcomes of implant treatment in periodontal patients was reported by Brocard et al. 2000. In this multicentre study over a 5-year period the overall cumulative implant survival rate was reported to be 95% (success rate 94%) but implants placed in patients previously treated for periodontal disease showed a success rate of only 89%.
In a systematic review of prospective and retrospective cohort studies with at least a 5-year follow-up comparing the outcomes of implant treatments in partially edentulous individuals with periodontitis-associated and non-periodontitis-associated tooth loss, Schou et al. 2006 identified two studies one with 5-year follow-up (Hardt et al. 2002) and an other with 10-year follow-up (Karoussis et al. 2003). In these two studies a combined total of 121 implants were placed in 33 patients with previous tooth loss due to periodontitis and 183 implants were placed in 70 patients with non-periodontitis associated tooth loss. The endurance of the supra structures after 5 years was not significantly different when comparing these two groups. In addition, the survival rate of the implants was not significantly different, but a significantly increased peri-implant marginal bone loss was observed in patients with previous tooth loss due to periodontitis. Peri-implantitis, defined as probing depths of 5 mm or more, bleeding on probing, and radiographic signs of marginal bone loss was a more common finding in individuals with a periodontitis background than in individuals where the teeth before the implant treatment were extracted for other reasons.
All together these data indicate a potential risk for marginal bone loss in patients susceptible to periodontal disease.

5.3 Diabetes

While the association between diabetes and implant loss has been addressed in systematic reviews by Kotsovilis et al. 2006 and Mombelli & Cionca 2006 there is limited information describing the effect of diabetes on marginal bone level changes. Ferreira et al. 2006 in a recent cross-sectional study including 212 non-smoking subjects in a Brazilian population

investigated the presence of risk variables for peri-implant infection. At the time of examination, all implants had been in function between 6 months and 5 years. Glycemic data at the time of implant surgery were gathered from participant medical records. For all subjects diagnosed with diabetes at the time of surgery as well as for those who reported having the disease at the time of evaluation, a new exam was requested. Diabetes mellitus was diagnosed if an individual had fasting blood sugar >126 mg/dl or had been taking anti diabetic medicine over the past 2 weeks. The prevalence of peri-implant mucositis and peri-implantitis were 64.6% and 8.9%, respectively. The prevalence of periodontitis in these subjects was 14.2%. In multivariate analyses, the risk variables associated with increased odds for having peri-implant disease included: gender, plaque scores, and periodontal BOP. In addition presence of periodontitis and diabetes were statistically associated with greater risk of peri-implantitis. The results showed that poor metabolic control in subjects with diabetes was associated with peri-implantitis (Ferreira et al. 2006).

5.4 Presence of keratinized mucosa

It has been suggested that the presence or absence of keratinized mucosa may alter the resistance of peri-implant region to plaque-induced tissue destruction. In fact Warrer et al 1995 using an animal model reported that the absence of keratinized mucosa around dental endosseous implants increases the susceptibility of the peri-implant region to plaque-induced tissue destruction.

There is a limited number of clinical studies evaluating the influence of keratinized mucosa on marginal bone level changes. Mericske-Stern et al. 1994 followed for 5 years 66 ITI implants placed in the mandible of 33 edentulous elderly patients. The implants served as overdenture anchorage. Approximately 50% of the implants had been installed into the lining of the mucosa. The peri-implant mucosal tissue was maintained healthy during the whole observation period, and no or minimal loss of attachment was observed. Wennström et al. 1994 evaluated the soft tissue conditions at implants in relation to the width of masticatory mucosa. The results showed that 24% of the sites were lacking masticatory mucosa, and an additional 13% of the implants had a width of less than 2 mm. Mobility of the facial marginal soft tissue (i.e., lack of an attached portion of masticatory mucosa) was observed at 61% of all implants. No differences in the clinical parameters examined were found between sites with and without an "adequate" width of masticatory mucosa. Multiple regression analyses revealed that neither the width of masticatory mucosa nor the mobility of the border tissue had a significant influence on (i) the standard of plaque control or (ii) the health condition of the peri-implant mucosa, as determined by bleeding on probing. Hence, the study failed to support the concept that the lack of an attached portion of masticatory mucosa may jeopardize the maintenance of soft tissue health around dental implants.

Bengazi et al 1996 evaluated alterations in the position of the peri-implant soft tissue margin, occurring during a 2-year period after insertion of fixed prostheses. Apical displacement of the soft tissue margin mainly took place during the first 6 months of observation. Lingual sites in the mandible showed the most pronounced soft tissue recession, decrease of probing depth, and decrease of width of masticatory mucosa. The statistical analysis revealed that lack of masticatory mucosa and mobility of the peri-implant soft tissue at time of bridge installation were poor predictors of soft tissue recession occurring during the 2 years of follow-up. It was suggested that the recession of the peri-implant soft tissue margin might be the result of a remodelling of the soft tissue in order to establish "appropriate biological dimensions" of the peri-implant soft tissue barrier (i.e., the

required dimension of epithelial-connective tissue attachment in relation to the faciolingual thickness of the supracrestal soft tissue). The role of keratinized mucosa in peri- implant disease was studied by Roos- Jansåker et al. (2006b) who examined 218 patients treated with titanium implants. A multivariate analysis of potential explanatory variables for peri-implant mucositis and peri-implantitis was made, where no association between the absence of keratinized peri-implant mucosa and peri-implant disease was found.
From animal experiments there is limited evidence demonstrating differences regarding the soft tissue seal between masticatory and lining mucosa. Evidence from longitudinal retrospective and prospective clinical trials shows that, with adequate plaque control, there is no difference in the prognosis for maintaining a healthy functioning soft tissue seal as judged by clinical measures.

5.5 Peri-implant disease and epidemiology

Peri-implant disease is a collective term for inflammatory reactions in the tissues surrounding an implant (Zitzmann & Berglundh 2008). Peri-implant mucositis is used to describe the presence of inflammation in the mucosa at an implant with no signs of loss of supporting bone. Peri-implantitis in addition to inflammation in the mucosa is characterized by loss of supporting bone. Detection of inflammation in the peri-implant mucosa requires the use of periodontal probing to identify bleeding and/or suppuration. For the assessment of peri-implantitis detection of marginal bone loss in radiographs is also needed (Figure 11). It is important though to distinguish between bone remodelling that occurs early after implant installation and the loss of supporting bone that may be detected at implants during function.

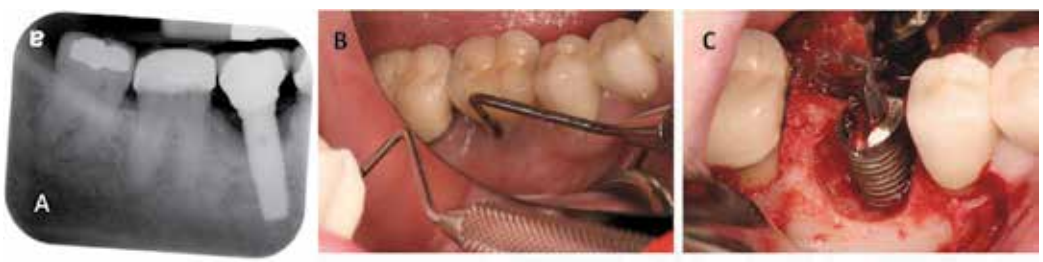

Fig. 11. Crater-form bone loss on radiographs (A) and clinical (C) and deep pocket with BoP and suppuration are the main characteristics of peri-implantitis lesions

Zitzmann & Berglundh 2008 performed a literature review in order to describe the prevalence of peri-implant diseases. Cross-sectional and longitudinal studies on implant-treated subjects with implants exhibiting a function time of at least 5 years were considered. The prevalence of peri-implant mucosa was evaluated in two studies (Roos-Jansåker et al. 2006 and Frannson et al. 2008). Roos-Jansåker et al. 2006 reported that peri-implant mucositis (BoP and no bone loss) occurred in about 79% of the subjects and 50% of the implants. In the study by Fransson et al. 2008, BoP was found in >90% of the implants without a history of bone loss. The prevalence of peri-implantitis was addressed in five publications that represented three subject samples with average function times of 9–11 years (Karoussis et al. 2004a, Brägger et al. 2005, Fransson et al. 2005, 2008, Roos-Jansåker et al. 2006). Peri-implantitis was found in 28% and ≥56% of subjects and in 12% and 43% of implant sites, respectively.

From the data available it seems that peri-implant disease is a very common problem although it is unfortunately addressed in very few studies. Careful selection of patients, effective recall program and early diagnosis are key factors for successful long term results.

6. Conclusions

Implant therapy success is dependent on other factors apart from successful osseointegration, where preservation of peri-implant bone is one of them. Marginal bone level changes are multi-factorial and only with careful considerations of the biological principles of the peri-implant soft and hard tissues, as well as the appropriate selection of implant type and position, can a functional and esthetic treatment result be achieved.

From the surgical factors that have been reviewed there is substantial evidence to support that using one-or two-stage surgical procedures have no clinically significant effect on success, survival rates and marginal bone levels. In addition several studies have shown that immediate loading does not promote marginal bone loss for implants replacing single teeth and that the majority of marginal bone level changes may occur during the first 3-6 months of loading with no significant alterations thereafter. However, no recommendations regarding patient inclusion, exclusion criteria, surgical techniques and implant characteristics can be made from the reviewed studies for immediate loading protocols.

Grafting of extraction sockets is beneficial in terms of limiting the dimensional changes of the alveolar ridge following tooth/teeth extraction. Several biomaterial and surgical techniques have been described, but no substantial evidence exists in order to support a specific technique as the most efficient. In addition there is variability on the histologic findings which may be a reflection of differences between biomaterials, surgical techniques and stages of healing. Although it is difficult to directly compare biomaterials among studies utilizing histologic evaluation, the majority of the grafting materials are osteoconductive and particles are always found in biopsies following different time intervals. Information that is commonly lacking from many histologic studies is the proportion of the particles that are in contact with new vital bone or embedded in loose connective tissue. Despite the fact that are several reports on the survival of implants placed in grafted sockets there is very limited information regarding marginal bone level changes. One study reporting on implants placed in sockets grafted with DFDBA showed minimal amount of marginal bone loss, similar to implants placed in native bone. It is obvious that more studies are needed in order to evaluate the benefit of grafting extraction sockets and the long term effect on implant survival.

Implant positioning is a major part of implant treatment planning and should be based on careful evaluation of each individual case. Implant position can have an effect on marginal bone level changes depending on the type of implant design used. Several studies have shown that the marginal bone level at teeth adjacent to single implants with a micro-threaded conical portion is not influenced by the horizontal and vertical tooth-implant distances. However, this statement cannot be supported for implants with an external-hex design. Loss in height of the mid-proximal bone crest in the inter-implant areas is influenced by the bone loss at the two bordering implants and the horizontal inter-unit distance, while no such relationship is evident for proximal areas between implant and tooth. While this statement has been based and confirmed from studies using implants with an external hex-design it still remains controversial for implants with different internal connection designs.

Implant positioning also refers to the location of the FAI in relation to the alveolar crest (depth of implant placement). The majority of the available implant system manufacturers recommend placement of the FAI at the level of the alveolar crest (crestal) or above that level (supracrestal), depending on the design of the implant system. In clinical reality though, it is not uncommon that part of the FAI has to be placed in a subcrestal position due to anatomic variations of the implant sites. In addition placement of the FAI in a more apical position can create an ideal emergence profile for the prosthetic construction. In addition, the location of the FAI can have an effect on marginal bone level changes depending on the type of implant system used. Placement of the FAI in subcrestal position has been documented to have positive effect on marginal bone level for implants with reduced abutment diameter in relation to the fixture diameter, a Morse taper implant-abutment connection and a microstructured surface treatment including the cervical collar and extending onto the implant shoulder. The main explanation for why this FAI design favors preservation of marginal bone levels even in the subcrestal locations is the prevention of the microbial leakage into the internal part of the implant and the lack of abutment micro-movement during functional loading. Despite the positive findings of subcrestal implant placement it still remains unknown the ideal depth of the FAI in relation to the alveolar crest.

The effect of loading on marginal bone level changes has been a matter of controversy over the years. Most of the data supporting a positive effect of loading on peri-implant bone loss is coming from laboratory studies that do not take into consideration the biologic response of the bone and are poorly mimicking the biologic reality. Although many animal and clinical studies exist supporting that factors contributing to excessive loading are not related to the marginal bone level changes, there are still basic biomechanic principles which are still valuable on the long term success of implant therapy.

Apart from surgical factors and factors related to the implant design, patient selection is a fundamental part of the dental implant treatment plan. Studies suggest that there is a positive effect of poor oral hygiene with marginal bone loss and this relationship is dose depended. This observation stresses out the importance of supportive periodontal therapy for dental implant candidates. Similar findings have been reported for smoking, history of periodontal disease and uncontrolled diabetes.

At last it is apparent that peri-implant disease is not only a clinical reality but also is very common, specifically in populations that do not receive regular supportive periodontal care. Treatment of peri-implant disease although it seems to be possible it might be invasive and can lead to compromised functional and esthetic outcomes. In addition there are several aspects of the treatment of peri-implant disease that there are not adequately studied and understood. With the continuous introduction of implants with novel characteristics it will be very difficult to evaluate the effect of those innovations in the development and treatment of peri-implant disease. Thus, prevention of peri-implant disease by an appropriate supportive periodontal care program is essential for the long term success of implant therapy.

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17

Bone Biology for Implant Dentistry in Atrophic Alveolar Ridge - Theory and Practice

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1. Introduction

It's a common experience for dental clinicians to note that the edentulous alveolar ridges always become atrophic as time goes by. It was late in the 19th century that Doctor Wolff first mentioned that form follows function (Wolf, 1892, as cited in Bilezikian et al., 2002). He described the individual capacity of morphological adaptation to a specific function as an "ontological adaptation" against the gravity through a daily locomotion or other daily mechanical duties (Fig.1-a). As a dentist I may illustrate the "dental compensation" in an Angle's class III malocclusion as a morphological adaptation to a masticatory function (Fig. 1-b), which itself is an example of the Wolff's "ontological adaptation."

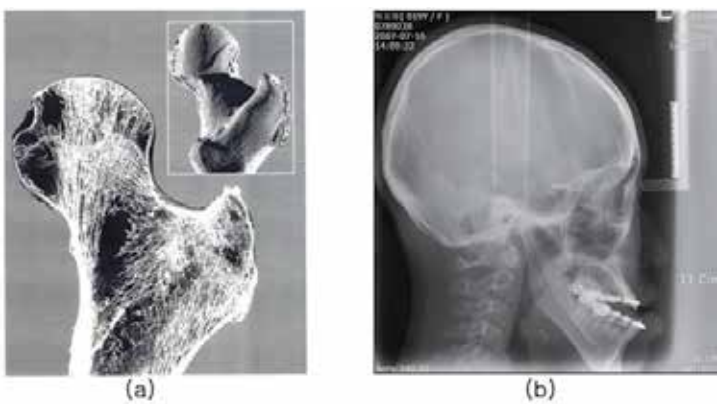

Fig. 1. Form as determined by function.
(a) As an orthopaedic surgeon, Dr. Wolff mentioned ontological adaptation on observing the morphological adaptation against gravity. The trabecular pattern of the trochanter reflects the functional loading against gravity through a daily locomotion or other daily mechanical duties.
(b) As dentists, we may exemplify the dental compensation as Dr. Wolff's ontological adaptation. Upper incisors are labially tipped in accordance to everyday masticatory function.

There's a tendency for Angle's class II patients to have new symptoms of temporomandibular disorder (TMD) after orthognathic surgery. In contrast, there's no definite relationship of Angle's class III patients to postoperative development of TMD. It was deduced that altered biomechanical situation after orthognathic surgery was the

causative factor for the new TMD symptoms in Angle's class II patients after orthognathic surgery (De Clercq et al., 1995). De Clercq compared the trabecular bone pattern of the Angle's class II and III patients to show that those of the former usually have less compact trabecular pattern than those of the latter. He conceived that this natural sparse trabecular pattern of the Angle's class II patients was brought about by the less functional loading subject to the mandibular condyle during mastication. And it was the increased masticatory stress after changed biomechanical circumstances that, in his opinion, was related to the newly-developed TMD after orthognathic surgery. It's a good example of the observation that "form follows function."

The author intended this chapter into two parts; the matter of why in the basic aspect and the matter of what to do for the clinician's perspective. First I will address the matter of why. Why does the unloaded bone go atrophic? Not exactly can we answer this question yet but current opinion pertaining to this problem will not only encourage current clinical treatment such as the principle of orthodontic tooth movement, but also implicate the future development of treatment outcome such as the complete regeneration of the alveolar bone loss of the periodontal pathologic origin. Next part will be on clinical aspect to assist in improving the implant site. Current treatment rationale, principles, and techniques for site improvement will be discussed with emphasis on autogenous bone graft using bone blocks. Additionally I will address the treatment strategy for the edentulous maxillary posterior alveolar ridge which is of main concern to many dental practitioners planning implant treatment in this troublesome region.

2. Why does the unloaded bone go atrophic?

2.1 Mechanotransduction

Solutions to the problem of atrophic alveolar bone begin with understanding why unloaded bone goes atrophic. Nobody can exactly depict why alveolar ridge goes atrophic after extraction of teeth. Efforts have been made to elucidate the scientific basis for the observation that the integrity of the skeletal tissue has something to do with mechanical usage. Frost has evolved the concept of the mechanostat (Frost, 1996) which he himself proposed as a new paradigm of understanding the mechanical-usage-dedicated message traffic routes between the skeletal tissue and the circumstances in which it is tuned. He argued the mechano-biologic negative feedback mechanisms would adjust skeletal architecture under the control of a subject's mechanical usage (Fig. 2).

Nowadays the secret of skeletal adaptation is more and more unveiling since around the opening of the 21st century. Doctor Burger hypothesized mechanotransduction as a main cause of the skeletal adaptation to a given functional loads (Burger & Klein-Nulend, 1999). She suggested that strain-derived fluid flow transduces the strain information to stimulate bone metabolism as a cellular response to a given load by the annular porosity produced by the osteocytes and their lacuno-canalicular hollow (Fig. 3). Osteocyte, the most abundant cell in our skeletal tissue was at first known as just a terminal stage cell of the osteoblastic lineage. But evidences are accumulating concerning its role as orchestrating skeletal adaptation to given functional loads. Orchestration of the cellular function is presumed earlier to be performed by the osteocytic syncitium through gap junctions (Moss, 1997). Evolving technology of current molecular biology has revealed many aspects of scientific evidences for this sophisticated orchestration of the skeletal tissue.

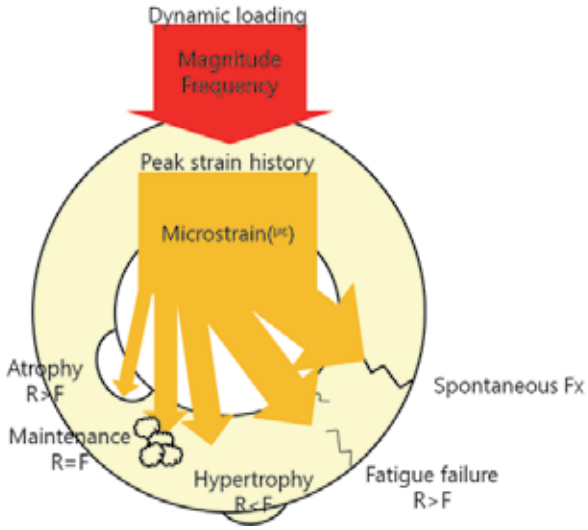

Fig. 2. The concept of the mechanostat.
Mechanostat hypothesis by Frost is schematically presented. Skeletal tissue has its loading history by dynamic loading which is remembered as a microstrain.
(1) If the strain is too small value, resorption dominates formation of bone tissue and the bone goes atrophic.
(2) If the strain is adequate, resorption balances formation and the bone maintains its volume.
(3) If the strain is adequately high value, formation at last dominates resorption and the bone goes hypertrophic.
(4) If the strain value is high by the overloading outreaching the range of physiological limitation, the strain is accumulated in the bone tissue causing microdamage leading to fatigue failure.
(5) Finally, if the strain value over the limit of yield strength the bone goes spontaneous fracture.

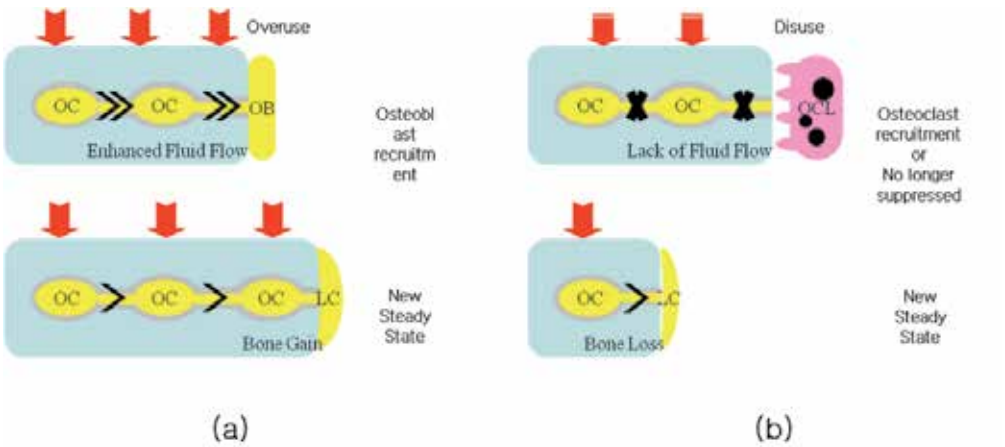

Fig. 3. Schematic diagram of mechanotransduction.
Mechanical information indicating the change of the external loading (red block arrows) is transduced by the strain-derived fluid flow (thin black arrowheads) to deliver biological information for the surrounding osteocytes to initiate bone metabolism for either (a) bone gain (overuse hypertrophy), or (b) bone loss (disuse atrophy). OC, osteocyte; OB, osteoblast; LC, bone lining cell; OCL, osteoclast.

2.1.1 Gap junction

Gap junction is the connection of the 2 hemichannels of each neighbouring cells which permits nanomolecular exchange of these cells. Hemichannel, in other words connexon is composed of six connexins switching from closed to open state depending upon the external stimulation (Fig. 4-1). Fluid shear stress stimulates cell to increase the production of connexin, an amino acid sequence that has 4 transmembrane domains with its two terminals in the cytoplasm (Fig. 4-2). Freely floating on the lipid bilayer, the connexons are able to dock with hemichannels of adjacent cells forming gap junctions (Fig.4-3). Gap junction is known to be restrictively permissive to intercellular mediators such as nitric oxide, Ca^{2+}, and prostaglandin (PG) E_2 (Bakker et al., 2001; Jørgensen et al., 2003; Siller-Jackson et al., 2008) or secondary messenger such as cAMP, IP_3 or cADP ribose (Civitelli, 2008). Connexons can work even without coupling with apposing connexons letting the PG E_2 or ATP out of the cell in response to mechanical stimulation (Cherian et al., 2005). External mechanical stimulus is thought to increase the connexin production, which will promote exchange of the biochemical information through the formation of new gap junctions (Cheng et al., 2001).

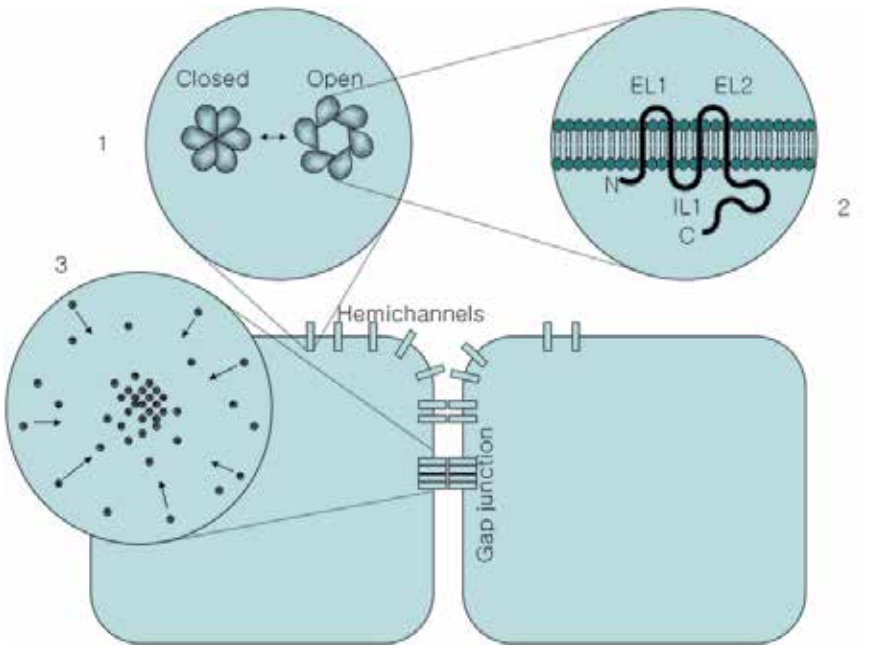

Fig. 4. Schematic diagram of the gap junction and hemichannel.
Hemichannels are selectively permissive pore of nanomolecular size staying free on the cell surface or docking with a hemichannel at sites of cell-cell contact to form a gap junction channel. Gap junction channels may cluster to form a gap junction plaque. 1: En face view of the hemichannels which are at a steady-state between two conformational states (open and closed). 2: Connexin topology at the plasma membrane. 3: En face view of a growing gap junction plaque.

2.1.2 Ionic mechanotransduction

The main mechanical stimulus which evokes mechanotransduction in bone cells is shear stress caused by the fluid flow. Stretch-activated channels open their gate in response to

external mechanical stimuli via this shear stress caused by fluid flow. The net results are increase of the intracellular concentration of the divalent ionic molecules such as calcium ion. These calcium ions are propagated to the neighbouring cells via the gap junctions, which is called slow intercellular calcium waves. On the other hand, intercellular calcium waves can occur by activation of purinergic receptors by extracellular nucleotides, resulting in fast intercellular calcium waves. Ionic mechanotransduction is through both of these mechanisms in human bone cells (Jørgensen et al., 2003). Activation of G-proteins also induces fluid-induced PG E_2 production in osteoblasts (Reich et al., 1997). As a kind of intercellular mediators of bone cells, PG E_2 mediates bone anabolic effect via prostaglandin receptor EP_4 (Machwate et al., 2001).

2.1.3 Mechanical mechanotransduction

Other than ionic mechanotransduction, hypothetical genomic control mechanism was postulated involving transmembrane protein integrins (Huang et al., 2004). Integrins are thought to form focal adhesions against the extracellular matrix to sense the external mechanical loading. Transduced mechanical signals are relayed to the nucleus mechanically via nuclear junctions. Thus genomic activity in response to external mechanical stimuli is postulated to encourage biochemical change in mechanical cellular devices, which is called mechanical mechanotransduction. Cell-cell junctions can also be mechanically involved to inform the signal to the neighbouring cells. But there is no direct evidence supporting this hypothesis until now.

2.1.4 Established model for cell mechanotransduction

Mechanical adaptation is one of the determining factors for regulating bone mass along with calcium and sex steroids (Harada and Rodan, 2003). Many efforts in the area of the molecular biologic cell study have revealed the details of mechanotransduction in all areas of the biological sciences. We now have a schematic depiction on mechanotransduction in cellular level (Jaalouk and Lammerding, 2009) although it is still lacking much (Fig 5). Up to now, mechanotransductive pathways are known to be activated via stretch-activated ion channels, G-protein coupled receptors, and transmembrane protein integrins which sense the shear stresses caused by the extracellular fluid flows. This mechanotransduction model is currently evolving according to cutting-edge knowledge lead by prominent molecular biological work.

2.2 Dynamic alveolar bone

Bone is a dynamic tissue as a kind of supporting structure for our body. Systemically controlled under the influence of calcium and phosphate metabolism, it is under tight control of local physical influence sensitive to surrounding mechanical conditions (Harada & Rodan, 2003). Alveolar bone, the most labile structure of the 4 periodontium, is more active in bone metabolism as much as 10 times that of the long bones, which makes the alveolar bone more sensitive to external mechanical stimuli.

Bisphosphonate is one of the anti-osteoporotic drugs on worldwide sales nowadays. One of the most widely used bisphosphonate is Fosamax and a newer drug, Fosamax Plus D, which had worldwide sales of more than $23.8 billion from 1999 to 2009, according to IMS Health, a health information company that tracks drug sales (Singer, 2010). Since the first report (Marx, 2003), bisphosphonate-related osteonecrosis of the jaw (BRONJ) has been a matter of

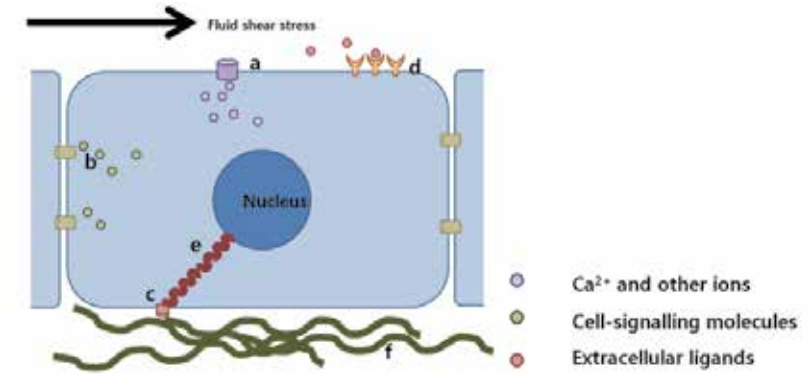

Fig. 5. Schematic depiction of mechanotransduction
a. Stretch-activated ion channels in the plasma membrane. b. Gap junctions for nanomolecular exchanges. c. Extracellular matrix (ECM)–cell focal adhesions to probe their environments. d. Cell surface receptors for autocrine and paracrine signalling molecules which are altered by compression of the intercellular space. Additionally, changes in G-protein-coupled receptors, lipid fluidity and even mitochondrial activity have been proposed as mechanosensors. e. The nucleus itself as proposed to be a mechanosensor. f. Mechanotransductive signalling outside the cell as given by force-induced unfolding of ECM proteins, such as fibronectin.

debate. Its pathogenesis is also still obscure but there is some clue. Osteonecrosis of the jawbone is caused not only by bisphosphonate but also by Denosumab, a monoclonal antibody to osteoclastogenetic factor, RANKL (Aghaloo et al., 2010; Taylor, et al., 2010). Upon this observation, pathogenesis of BRONJ is presumed to be delayed bone turnover resulting from osteoclastic inactivation. The jawbone is the only bone to be necrotised among the whole skeletal system that is complicated by the anti-osteoporotic bisphosphonate drugs, which is known as a BRONJ. Detailed information on BRONJ will be addressed elsewhere in this book.

2.3 Bone remodelling and sclerostin

Sensitive bone reaction is performed by the bone remodelling procedure encompassing bone resorption by osteoclast and bone redeposition by osteoblast. Microdamage to the bone tissue accumulates by mechanical overloading, and causes osteoclastic resorption of the damaged bone tissue. After osteoblastic transition which is marked by switching from bone resorption to formation, functional bone adaptation to a given loading is completed. One of the most dramatic advances in the study of the osteocyte is its orchestrating function on the bone remodelling procedure, the key protein of which is the recently discovered sclerostin.
Sclerostin is a gene product of the SOST and secreted by the osteocytes into the extracellular matrix reaching a steady concentration gradient. As a functioning glycoprotein it inhibits the osteoblast development and bone formation via Wnt signalling pathway (van Bezooijen et al., 2007). Adequate concentration gradient of the sclerostin enables the maintenance of the normal bone mass responding to a given functional loading. Adequate mechanical stimulation increases bone mass via a downregulation of the osteocytic production of the sclerostin. Irritable overloading affords the osteocytes focal microdamage, which renders reduced concentration of the sclerostin around the focal damage site. Soon the recruitment of the osteoclastic lineage cells is commenced to resorb the focal site, followed by the influx of osteoblastic precursor cells to build a new bone tissue. Generally bone remodelling is accomplished according to the change of local mechanical stress.

3. What can I do for atrophic bone to be prepared for dental implant?

3.1 Characteristics of the bone tissue

Bone is a distinctive tissue in that it undergoes regeneration rather than a repair procedure in the healing process after surgical trauma. The result is that it is always replaced by the same parenchymal structure, i.e. bone, and not by the scar tissue formation. The most important aspect for the adequate regeneration process is the close contact and rigid fixation of the graft bone to the recipient bed. We will discuss the aspect of wound healing of the skeletal tissue in the implications from the fracture healing (See 3.3)

Developmentally there are two types of bone formation, intramembranous and intracartilagenous ossification, with the resultant two types of bone tissues, membranous and endochondral bone, respectively. Cranial bone underwent progressive evolutionary adaptation to be composed of neurocranium and viscerocranium (Park, 2005). The combination of these two classification systems yield four types of cranial bone; membranous neurocranium, cartilaginous neurocranium, membranous viscerocranium, cartilaginous viscerocranium (MacKinnon & Morris, 1990) (Fig. 6). Alveolar bone belongs to membranous viscerocranium and has different developmental origin from iliac bone which belongs to endochondral bone. It is my clinical experience that donor bone block from the mandibular ramus is rather hard and difficult to manage in drilling and fixating with screws on the recipient bone bed in alveolar bone reconstruction. But the clinical result after bone graft is fairly good without so much resorption. Contrast to it, iliac bone block relatively offers little difficulty in surgical manipulation with some degree of bone resorption after alveolar bone reconstruction procedure.

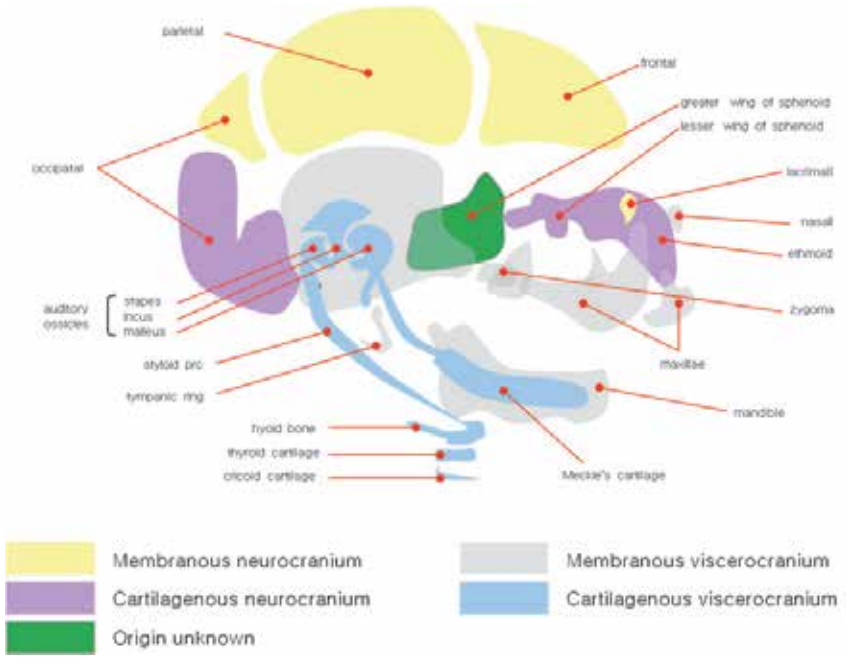

Fig. 6. Head and neck bone tissue.

Cranial bone is classified into four types; membranous neurocranium, cartilaginous neurocranium, membranous viscerocranium, cartilaginous viscerocranium.

3.2 What is going on in there?

Contrasted to the previous issue, an atrophic alveolar bone which is a matter of why, selection of the bone augmentation method is a matter of choice. Adequate selection of the graft material is based upon correct understanding of the biology pertaining to bone graft. Regeneration after bone graft is well studied in autogenous bone graft, which is the gold standard of the bone grafting procedures. Free-graft bone must be replaced with new bone of the recipient site origin, which is called osteoconduction. It functions as a scaffold for osteoprogenitor cells to reside in, and adequate remodelling process is essential because timely activation of osteoclastic function must be preceded before full blown osteoblastic cells begin to build new bone tissue. In addition to osteoconduction, osteoinduction is also an important mechanism of autogenous bone graft repair. Bone morphogenetic protein (BMP) is a potent skeletal mesodermal inducer, which blocks all the other pathways from mesenchymal stem cell but to the osteoblastic commitment. Bone formation can also be accomplished by the bone cell of donor origin, which is called osteogenesis. This is the predominant mechanism for new bone growth in vascularised bone grafts.

3.3 Implications from the fracture healing

Management principle of the bony injuries is close contact of the fractured segments and undisturbed healing without movement or infection (Lavery, 1994). So the most important aspect of the fracture healing is firm immobilization after adequate reduction and the same rule applies to bone graft.

3.3.1 Direct healing

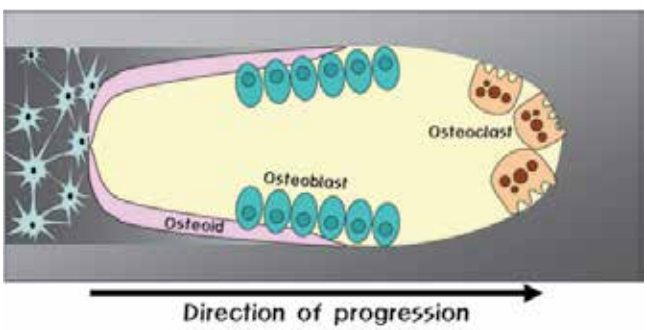

Fig. 7. Schematic diagram of basic multicellular unit (BMU).
Histologically the BMU consists of 1) osteoclastic front or osteogenic front, 2) reversal phase mononucleocytes, 3) osteoblastic layer. It is observed in the Haversian system of the cortical bone which is under the physiological loading such as the masticatory function. The osteoblasts are exclusively intraosseous Haversian system osteoblasts reacting to the load.

3.3.1.1 Contact healing

Contact healing occurs when the fracture segments are held firm within the interfragmental distance of 100 ㎛ (Shapiro, 2008). Histologically it is mediated mainly by the intraosseous Haversian system osteoblasts (Fig. 7). Bone repair occurs bridging the minimal gap with osteoprogenitor cells crossing in the same direction of the Haversian system. It seems like that the osteoclastic front feels no barrier on its way across the gap. (Fig. 8).

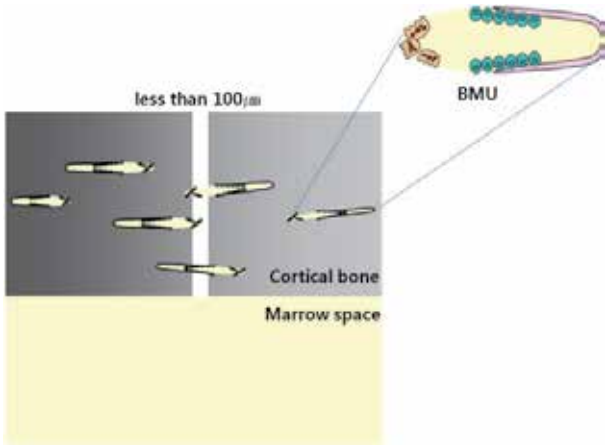

Fig. 8. Schematic diagram of the contact healing.
When the fracture segments are held firm within the interfragmental distance of 100 ㎛, the shape of the osteones in the cortical bone does not change when crossing the fracture or osteotomy. The direction of the lamellar bone is parallel to the long axis of the bone from osteoprogenitor cells in the Haversian longitudinal vessels.

3.3.1.2 Gap healing

If the fracture is reduced and rigidly fixated but the gap is over 100 ㎛, it goes gap healing procedure. Reduced segments are stable but the distance is too far for the Haversian longitudinal osteogenic front to cross. New bone begins to form in the marrow laid to the pre-existing rim of lamellar cortical bone at right angles to the long axis of the bone. After the gap is filled with this mechanism, the osteogenic fronts of the original pre-existing fracture segments find their ways to cross the filled gap (Fig 9).

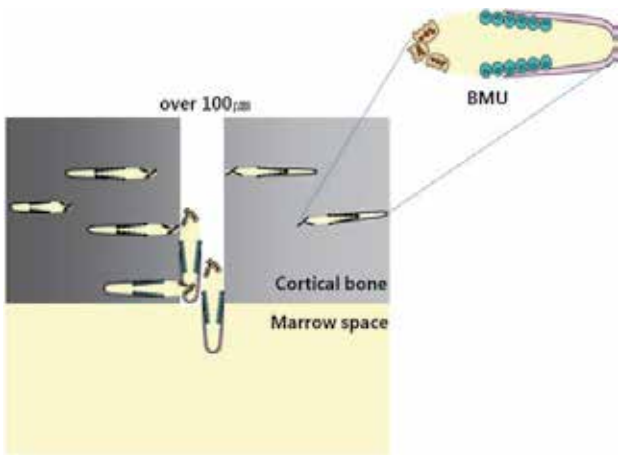

Fig. 9. Schematic diagram of the gap healing.
When the interfragmental distance is over 100 ㎛ under the stable rigid fixation, gap healing commences. Osteoprogenitor cells from Haversian longitudinal vessels cannot cross the gap anymore, and instead those of bone marrow origin will creep on the segmental surfaces to fill the gap at right angles to the long axis of the bone. At last osteoclastic cutting cone from the original cortex begins to cross the filled gap to realign the lamellar bone parallel to the longitudinal axis.

3.3.2 Indirect healing

Failed anatomic repositioning or mobility across the fracture gap gives rise to indirect healing. Indirect healing occurs by callus formation followed by cartilage formation. Initial hematoma under hypoxic circumstances is gradually replaced by the granulation tissue, which in turn forms a fibrocartilagenous callus in the condition of hydrostatic pressure. With minimal strength but having the tolerance to the deforming forces in the interfragmentary zone, granulation tissue helps attenuate interfragmentary movement. Decreased interfragmentary movement in tern aids laydown of the fibrous tissue. Stabilised bone segments further permits fibrocartilagenous callus to form. Bridging the gap across the fracture segments the callus shades into the bone tissue.

The type of force healing bone experiences determines the tissue type the healing bone will be. It's a general agreement that the tensile force favours intramembranous ossification, while compressive stress encourages the pluripotent mesenchymal cells into chondrocytes. Continuous hydrostatic compression incurs cartilage formation whereas intermittent compressive stress gives intracartilagenous ossification (Carter et al., 1998).

3.4 Healing process after bone graft

3.4.1 Initial phase

At the beginning of the bone graft healing, cells with bone forming potential must be recruited to the graft site to construct a new bone tissue. This is done in two weeks after bone graft, which is called the initial phase. It is the most important period although there is no actual bone formation because the osteoblast can lay down mineralized tissue only in their adjacent area.

3.4.2 Phase 1 bone regeneration

Actual mineralization ensues following 4 weeks in which period new bone is formed as a woven bone type. There is no orientation of bone trabeculae irrespective of surrounding mechanical stress. Designated as a phase 1 bone regeneration, it is finished by 6 weeks after the bone grafting, followed by mechanical stress-sensitive period, phase 2 bone regeneration.

3.4.3 Phase 2 bone regeneration

It reaches a peak around 3 to 4 months after bone grafting when bone remodelling occurs in accordance with the mechanical demand. Functional loading guides the existing woven bone into a lamellar type of new bone which is suitable for supporting the mechanical stress within a functional range.

Bone remodelling differs from bone modelling seen in skeletal growth period, in which the bone resorption and formation are accomplished independently in concert with bone growth. On the contrary, the osteoclastic and osteoblastic effects are coupled tightly in bone remodelling which is well demonstrated histologically in the temporary anatomical structure, basic multicellular unit (BMU) (Frost, 1963, as cited in Robling et al., 2006)(Fig. 7). The time with which the BMU travels through tissue space is called sigma (σ). In human cortical bone, it would take approximately 120 days to complete one σ, consisting of roughly 3weeks of osteoclastic phase, 10days of reversal phase, and 3months of osteoblastic phase (Robling et al., 2006).

3.5 Autogenous block bone graft in alveolar defect of height and/or width problems

Edentulous alveolar ridges must be prepared for dental implant treatment. Autogenous bone block can be harvested from diverse sites (Fig. 10) which have their own advantages and disadvantages. Small defects such as those caused by periodontitis can be prepared using small bone blocks from intraoral donor origin. Two intraoral sites are outstanding; the external oblique ridge-ramal area of mandible, and the chin cortex. Of these, I prefer an external oblique ridge-ramal bone, for approaching to chin bone possibly risks the incisive branches of the mental nerve, which is very annoying. Large defects over the basal bone as a result of radical resection of the large head and neck tumours or major trauma can be rehabilitated with reconstructive surgery with extraoral large donor bone block such as iliac bone or fibula. I prefer iliac free bone graft but free vascularised osteocutaneous fibular graft can also be of use.

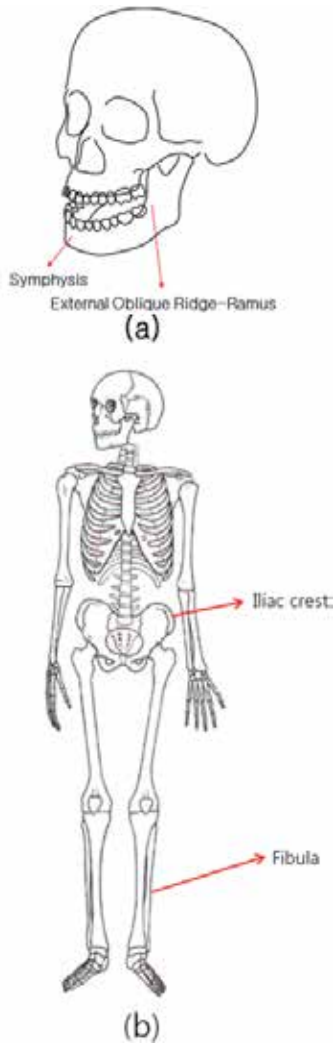

Fig. 10. Favoured donor sites for autogenous alveolar bone reconstruction with bone block.
Many parts can be donor site for autogenous alveolar bone reconstruction but the author favours these arrow-indicated sites; (a) intraoral, and (b) extraoral donor sites.

3.5.1 Reconstruction with external oblique ridge-ramal bone block

Fifty six years old female patient resorted to our clinic with the chief complaint of lost anterior upper teeth. Her problem was not only the lost dentition, but also the lost alveolar ridge revealed as in Fig. 11-a. External oblique ridge-ramal area of the mandible was selected as a donor site and harvested for augmentation of the depressed alveolar bone as in Fig. 11-b. Harvested bone was placed and secured in the recipient site as in a Fig. 11-c and waited 4 months for dental implant fixture installation. Immediate before fixture installation we evaluated the bone graft area with CT scan, which revealed good integration of the graft (Fig. 11-d).

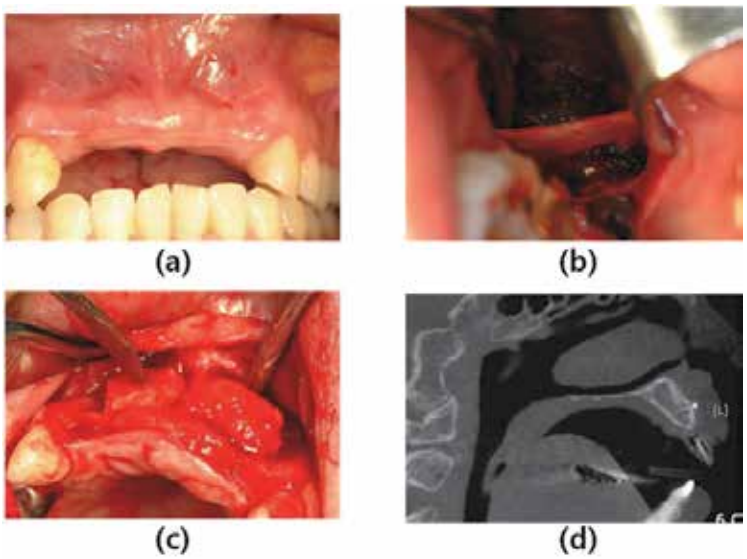

Fig. 11. Alveolar bone augmentation with ramal bone block.
(a) Preoperative figure shows depressed anterior maxillary wall due to lost alveolar bone accompanying loss of maxillary anterior 4 teeth.
(b) As an augmentation source for donor bone, both external oblique ridge-ramal area of the mandible were approached and 2 pieces of bone blocks were harvested.
(c) Harvested bones were well adapted in the depressed recipient area which were fixated with adequate miniscrews.
(d) Graft area was evaluated with CT scan four months after the graft procedure, which showed adequate healing ready for installation of the dental implant fixtures. One of miniscrews was evident on this CT slice.

After instillation of local anesthetics with 2% lidocaine and 1:100,000 epinephrine, previously augmented site was approached, which showed acceptable augmentation as in Fig. 11-e. Fixation screws were retrieved before dental implant fixtures were installed as in Fig. 11-f, and zirconia abutments were used because the aesthetic consideration was important in maxillary anterior region (Fig. 11-g). Clinical appearance after the completion of final prosthesis was good as in Fig. 11-h although slight loss of interdental papilla was observed.

3.5.2 Reconstruction with chin bone block

This 56 years old male patient was diagnosed as total maxillary insufficiency precipitated by long duration of periodontal diseases (Fig.12-a). Implant was planned for implant-

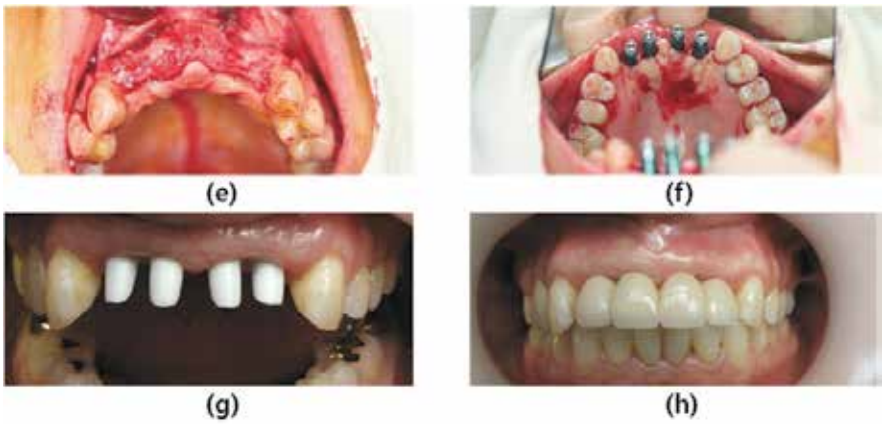

Fig. 11. (continued). Alveolar bone augmentation with ramal bone block.
(e) Maxillary anterior area of the same patient was re-entered 4 months later to find acceptable appearance of the graft site for implant fixture installation.
(f) Fixtures were installed after retrieval of the fixation screws.
(g) Zirconia abutment was selected for cosmetic consideration.
(h) Minimal aesthetic problem was detected after final prosthodontic rehabilitation.

supported overdenture and total height- and width problem was identified (Fig. 12-b). Ideally iliac bone graft was recommended but the patient refused general anesthesia and finally multiple event of minor augmentation procedure under local anesthesia was accepted as an alternative method. Insufficient alveolar bone was recovered with bilateral sinus graft and lateral wall augmentation along with anterior subapical block bone augmentation. Fig. 12-c shows insufficient anterior maxillary wall inadequate for dental implantation. Both mandibular ramal bone blocks were utilised as the donor for both lateral maxillary wall augmentation, and still we need another bone block for anterior maxillary alveolar ridge. In spite of the possible numbness after donor bone harvesting, chin bone was unavoidable choice (Fig. 12-d). Along with autogenous bone block, allogenic bone powder was accepted for filling the gap between the graft and recipient bed (Fig. 12-e). Fig. 12-f shows clinical picture after successful dental implantation 4 months after the bone graft.

3.5.3 Reconstruction with free iliac bone block

Initial diagnostic panoramic view of forty nine years old male with severe chronic periodontitis showed many hopeless teeth on maxillary anterior and right posterior areas (Fig. 13-a). After scheduled periodontal treatment with extraction of many hopeless teeth diagnostic CT scan revealed compromised areas of the maxillae on the anterior (Fig. 13-b) and right posterior region (Fig. 13-c).
Free iliac bone graft was done under general anesthesia, in which operation inner medial cortical bone was harvested with cancellous bone and marrows leaving the outer cortical bone intact (Fig. 13-d). Maxillary alveolar bone was augmented with harvested cortical block for future dental implant treatment (Fig. 13-e). Prosthodontic treatment was done with excellent treatment outcome as in Fig. 13-f and g.

3.5.4 Microsurgical reconstruction with free vascularised fibular bone

Young man resorted to our clinic with the chief complaint of painless lower facial swelling and preoperative panoramic findings revealed multiple radiolucencies all around the mandible

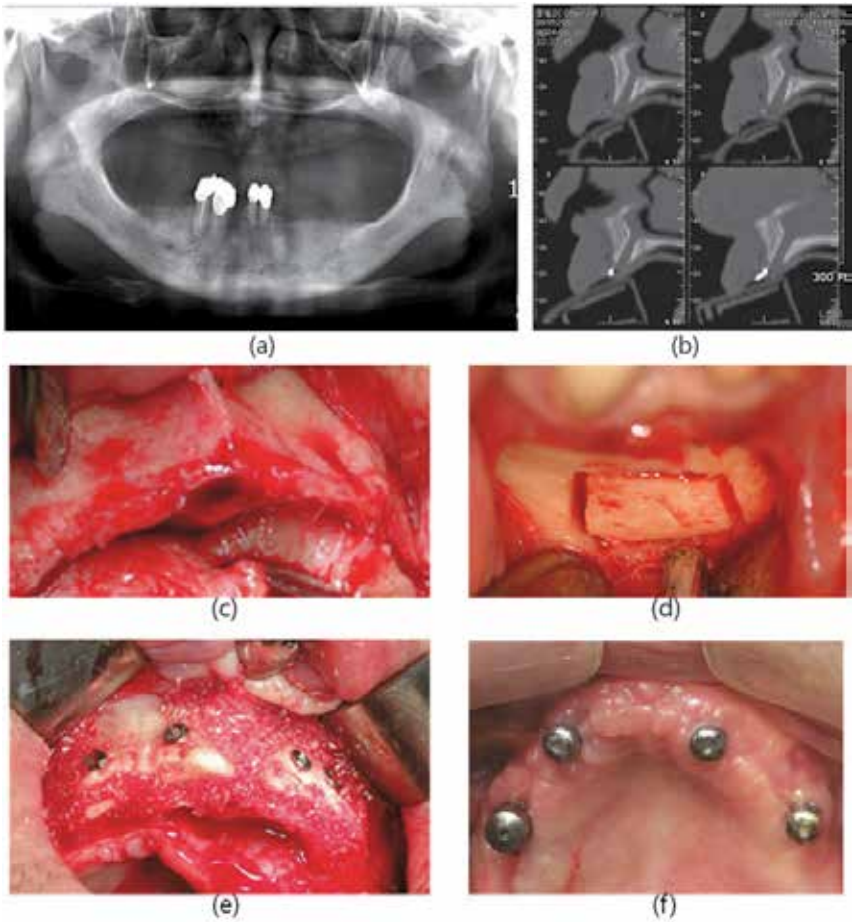

Fig. 12. Alveolar bone augmentation with chin bone block on anterior maxillary defect.
(a) General bone resorption is identified on preoperative panoramic view.
(b) Dentascan on anterior maxillary region revealed large space for nasopalatine neurovascular bundle and poor bone bed for dental implant.
(c) Reflection of the flap revealed thin alveolar process on the anterior maxillary edentulous area. Note large nasopalatine foramen hindering fixture installation on #11 and #21 site.
(d) Dense labial cortex of the chin bone was found after careful dissection, which was harvested for augmentation of the thin anterior maxillary alveolar process.
(e) Bone blocks from the chin cortex were fixated with miniscrews and the remaining gaps were filled with commercially available allogeinic bone powder.
(f) Four fixtures were installed 4 months after the bone graft on the strategic sites.

(Fig. 14-a). Biopsy of the lesion confirmed the diagnosis of ameloblastoma and the mandible was extensively removed using segmental resection ranging total body area anterior to both antegonial notches. Mandibular reconstruction plate was utilised immediately as a bridging plate for the maintenance of the mandibular continuity. Six months later when no evidence of recurrence was confirmed, free vascularised fibular reconstruction was done with microsurgical technique utilising peroneal artery as a feeding artery (Fig. 14-b). Four months later when successful reconstruction was identified (Fig 14-c), six fixtures were installed (Fig. 14-d), followed by hybrid type overdenture treatment (Fig. 14-e).

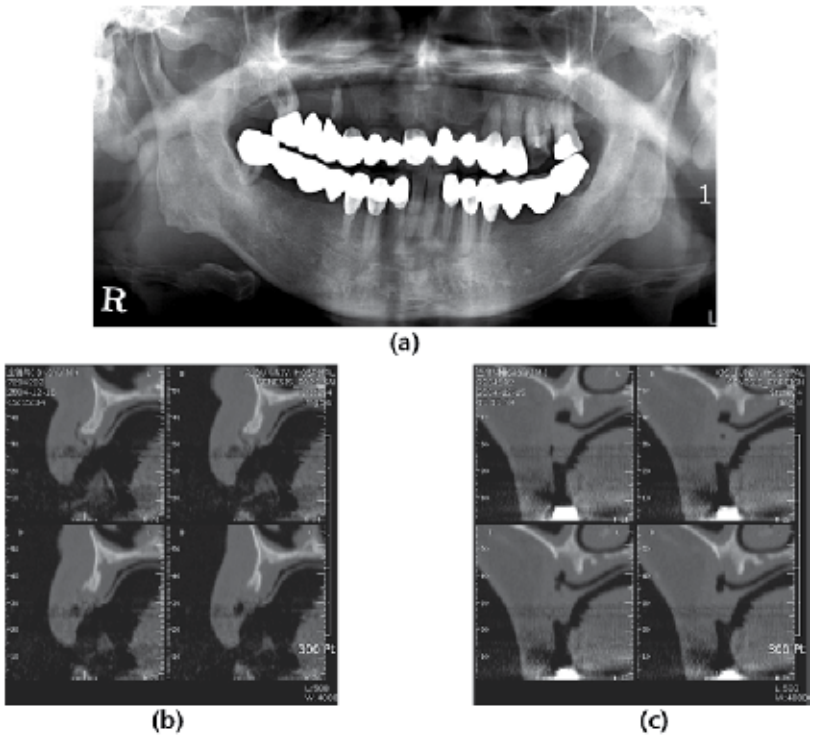

Fig. 13. Alveolar bone augmentation and additional maxillary basal bone reconstruction with free iliac bone block-Preoperative diagnostic imaging.
(a) Severe periodontal disease were evident in preoperative panoramic view in which all maxillary anterior teeth and maxillary right posterior teeth were scheduled to be extracted and periodontally treated with surgical intervention.
(b) Diagnostic CT scanning was inevitable after extraction of all poor teeth and scheduled periodontal surgery was finished, where width problem was evident in anterior maxillary region.
(c) CT also revealed both width and height problems in right maxillary region.

3.6 Treatment strategy for the edentulous maxillary posterior alveolar ridge

Dental implantation on the atrophic posterior maxillary alveolar ridge is always challenging because both quantity and quality of the bone are poor in this area. Maxillary posterior alveolus exhibits poor bone quality, for anatomically maxillae consists almost of cancellous bone and biomechanically posterior teeth are subject to three times more occlusal forces than anterior teeth. Usually the quality of the bone in this region is classified as D3 or D4 in Misch's classification which is composed of fine trabecular bone with thin cortical bone or even finer trabecular bone with almost no cortical bone (Misch, 1990, as cited in Misch, 2008). The amount of available alveolar bone is usually deficient because of the dual resorption inside and outside of the sinus floor, because of pneumatisation and alveolar resorption, respectively. Frequently this area needs bone augmentation to allow an implant-supported prosthesis.

Alabama implant meeting held at Birmingham in 1976 was the first meeting that Tatum presented a surgical technique involving the maxillary sinus (Tatum, 1986). It was several years later that the first publication on this technique was reported by Boyne and James

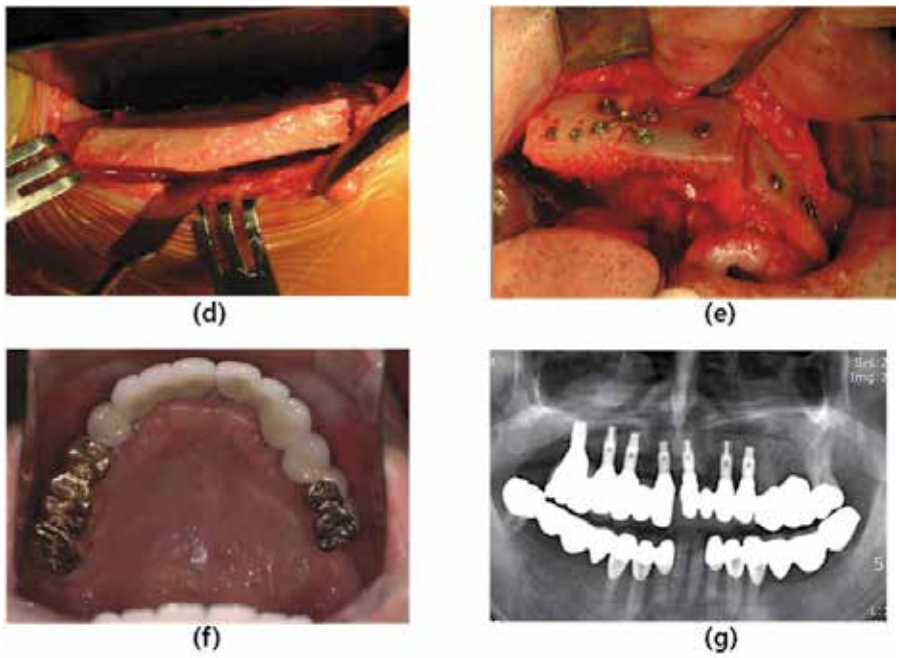

Fig. 13. (continued). Alveolar bone augmentation and additional maxillary basal bone reconstruction with free iliac bone block-Operative procedures and postoperative results.
(d) Harvesting of the free iliac bone. Cancellous bone and marrows along with inner medial cortex were harvested leaving the outer cortical bone intact for reduction of postoperative complication.
(e) Insufficient maxillary alveolar bone was augmented with the harvested iliac bone.
(f) Complete prosthodontic rehabilitation was possible after dental implant fixture was osseointegrated to successfully augmented graft bone.
(g) Panoramic view taken after the completion of the dental implant treatment.

(Boyne & James, 1980). They introduced infracture technique with upper hinge in the lateral wall of the maxilla. Consensus meeting on sinus surgery held in 1996 at Babson College, Willesley City, MA was remarkable in that it was the first meeting that reaches an agreement on terminology on the sinus surgery for dental implantation. Sinus augmentation is generally considered a good method for edentulous maxillary posterior alveolar bone to allow an implant-supported prosthesis. Some modifications are available involving hydraulic elevation of the sinus floor via crestal approach (Vitkov et al., 2006) or outfracture of the lateral maxillary window (Lee, 2010).

Evaluation of bone graft is based on the clinical evidence of fixture survival and functioning final prosthesis. However strict criteria for success are based upon the histological evidence of a microscopic activity conducted by vital bone tissue. It can be evidenced by bone remodelling, which means the viable osteoclast and osteoblast is available by the bone grafting procedures. It is therefore one of the criteria for bone graft materials to be incorporated in the bone remodelling procedure. The determinant factor for success of sinus bone graft however is known to be not related to the kind of a graft bone but to the remaining alveolar bone height. Actually many graft materials used in the sinus floor augmentation demonstrate an acceptable success rate irrespective of their nature. It is because that the sinus cavity is compartmentalised and has a natural housing for the graft materials to be stabilized, which is a specific anatomical advantage of the sinus cavity.

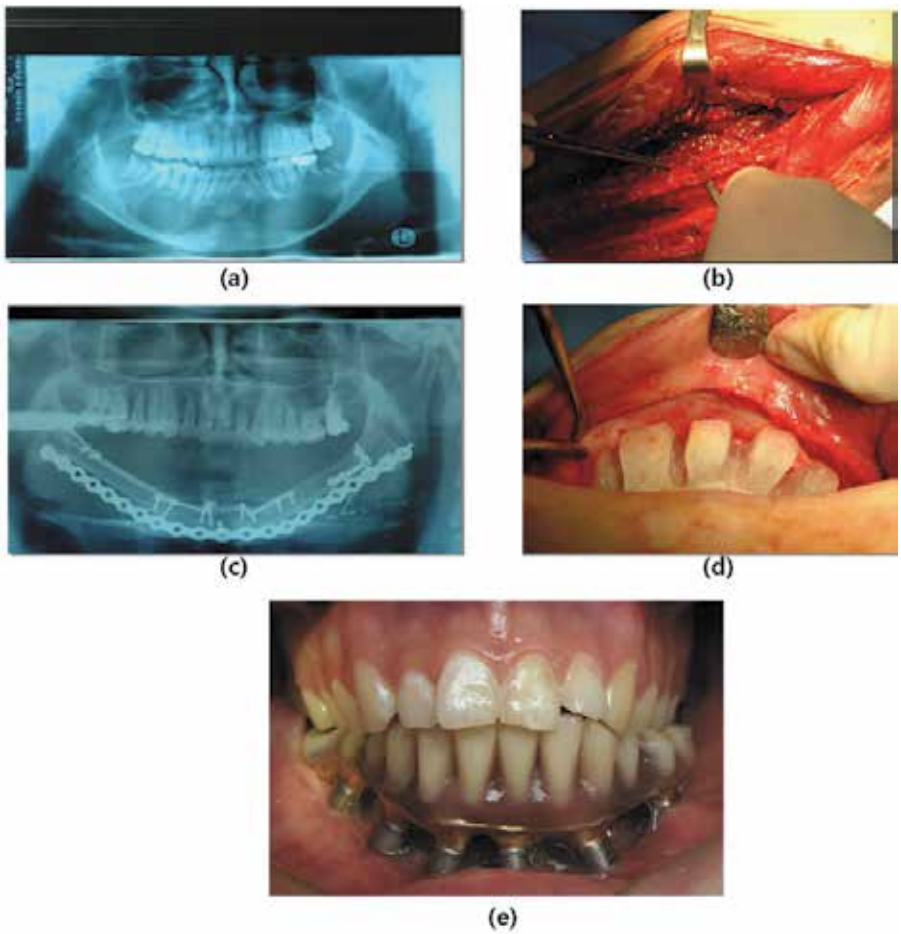

Fig. 14. Mandibular reconstruction utilising microvascular free fibular graft.
Preoperative panoramic view showing multiple large radiolucencies all around the mandibular body area (a), which was segmentally resected for radical treatment diagnosed as multicystic ameloblastoma. Confirming no evidence of recurrence at 6 months later, patient's fibula was utilised as in (b) for reconstruction of the basal part of the mandibular body. Four months later when stable reconstruction was identified (c), dental implant fixtures were installed on strategic positions in the fibula as in (d). This fibula was only for the basal part of the mandible and the final denture was designed as a hybrid type as in (e) to facilitate the oral hygiene procedures.

3.6.1 Outfracture osteotomy sinus graft technique for posterior maxillary edentulous ridge concomitant with dental implantation.

The original method of Tatum first presented in the Alabama implant meeting (Tatum, 1986) adopted a trapdoor design which involved inward opening of the lateral bony window with a top hinge. It was a methodological revolution for it was a pushing back the frontiers of a prosthodontic treatment by surgical measure. But it has its own limitations in anatomical considerations in cases with a sinus septum or a thick lateral sinus wall in the operation field. These limitations were overcome by modifying window opening method form inward to outward direction. Outfracture osteotomy sinus graft technique was introduced utilising

readaptation of the outfractured bony window segment after sinus floor augmentation (Lee, 2010). It involves routine window opening on the lateral maxillary wall as in Fig. 15-a. Completion of the outfracture of the bony window segment (Fig. 15-b) is followed by the elevation of the Schneiderian membrane and floor augmentation using the space created by the membrane elevation (Fig. 15-c). Outfractured bony segment was placed back into the original position and secured without any screws or plates (Fig. 15-d). The success rate with the outfracture osteotomy sinus graft technique was reported as 97.2 % in 113 cases through August 2004 to July 2009 in Department of Dentistry, Ajou University Hospital (Song, 2009).

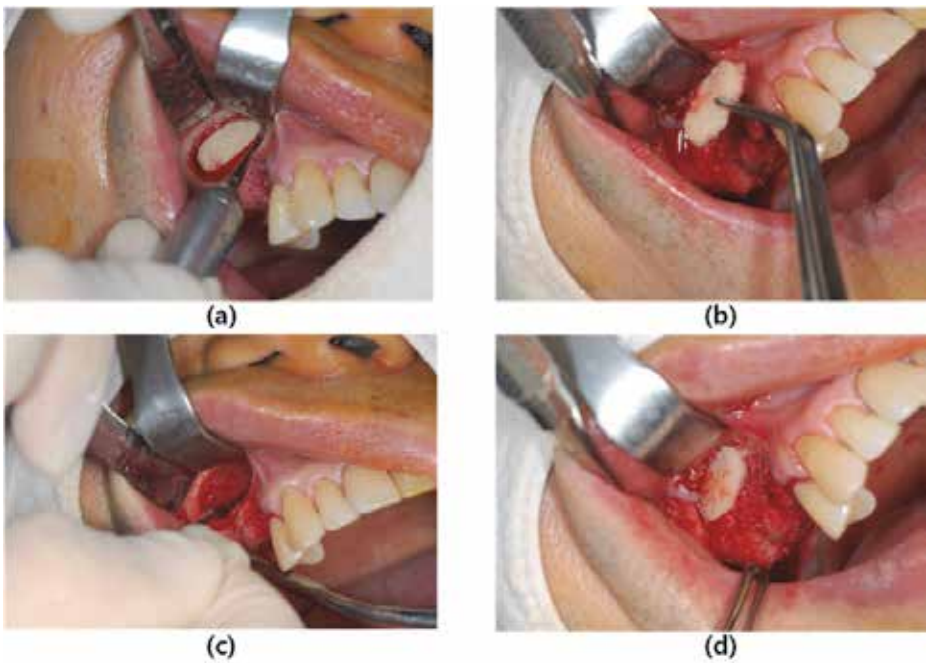

Fig. 15. Outfracture osteotomy sinus graft technique.
(a) Osteotomy of the lateral maxillary wall is done as routine.
(b) Outfractured bony window is shown, which is to be preserved in normal saline solution during Schneiderian membrane elevation.
(c) Schneiderian membrane is elevated via bony aperture created by the osteotomy.
(d) Repositioned bony segment is secured without a screw or plate.
Courtesy by Lee JK in J Oral Maxillofac Surg 68:1639-1641 (2010).

3.6.2 Dental implant treatment in severely compromised posterior maxillary edentulous ridges

Fifty nine years old female resorted to our clinic with a chief complaint of chewing difficulty owing to complete loss of teeth. Several years of ill-fitting denture was very annoying to her and doing without this ill-fitting denture inevitably caused her severe alveolar resorption. She agreed with mandibular removable denture but insisted on fixed type maxillary prosthesis. Prosthesis design for the mandible was an implant supported overdenture but maxillary alveolar bone must be augmented for dental implant treatment. Anterior maxillary wall was planed to be augmented with external oblique ridge-ramal bone block

from both sides of the mandible. Both maxillary sinuses were examined with dental CT showing that double resorption inner and outer sides of the sinus floor due to pneumatisation and alveolar bone resorption, respectively (Fig. 16-a and b). The CT showed resultant minimal alveolar bone heights with maximum thickness of 2 mm in these areas. Maxillary sinus floor augmentation was done utilising outfracture osteotomy sinus graft technique (Fig. 16-c and d) on both sides. She was very satisfied with maxillary fixed-type prosthesis along with removable-type mandibular overdenture (Fig. 16-e). Radiographic finding after final prosthodontic treatment demonstrated excellent treatment results Fig. 16-f).

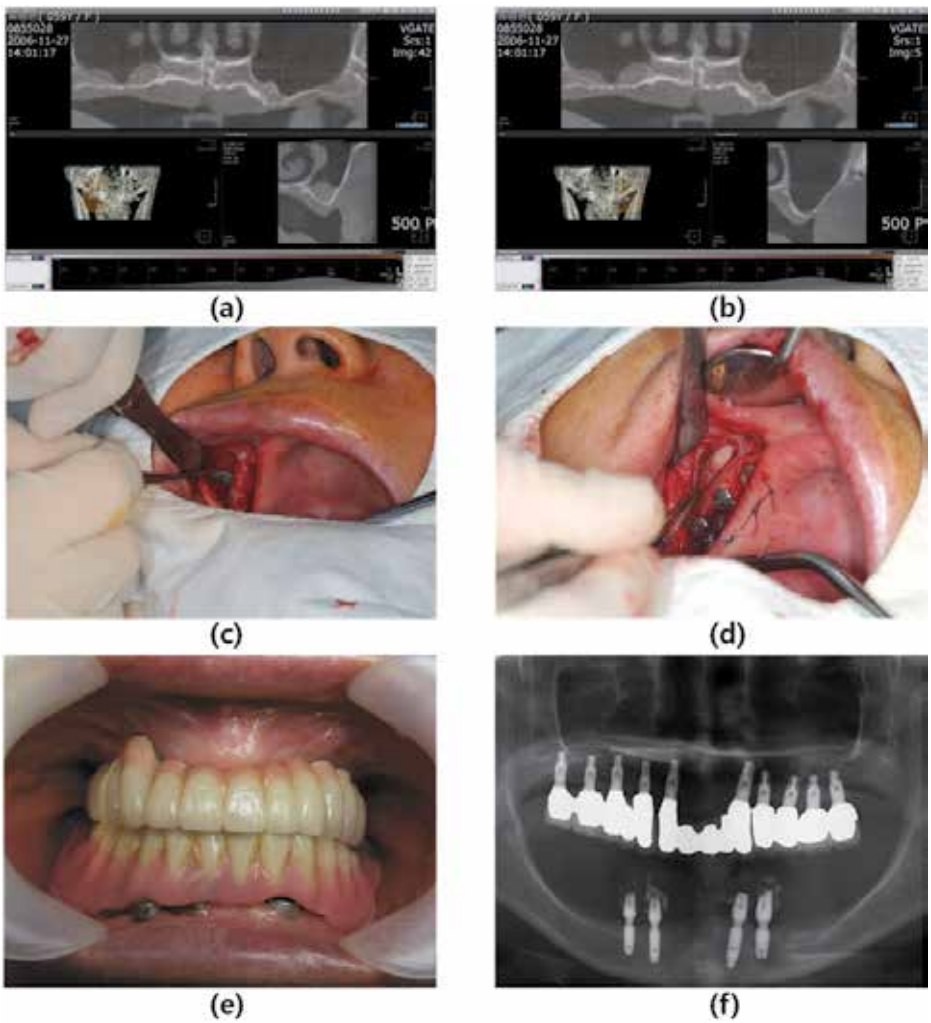

Fig. 16. Sinus graft and dental implant treatment with fixed type bridges.
Preoperative CT showed severe pneumatisation and alveolar bone loss leaving only thin cortex of 2 mm thickness or less on both sides of the floor of the maxillary sinus (a and b). Sinus graft utilising outfracture osteotomy technique was done on right maxillary antrum (c and d). The same procedure was repeated on the contralateral sides later. Clinical photograph (e) and panoramic radiograph (f) of final prosthesis showed good function without any complication.

4. Conclusion

Treatment strategy for the dental implant-supported prosthesis in atrophic edentulous alveolar ridge is one of the most difficult tasks for dental clinicians. As a rule, autogenous bone is a gold standard of bone graft and has rated better treatment score than any other types of bone. Clinically available autogenous donor bone was exemplified by respective clinical cases with the theoretical background based upon the basic bone biology. In severe cases such as the defect involving not only an alveolar bone but also a basal part of the jaw bone, harvesting a donor bone was not a minor oral surgery anymore requiring microsurgical techniques under general anaesthesia. But the sinus floor augmentation was possible under local anaesthesia even in the severe cases with the remaining floor thickness only 2 mm or less (Fig. 16).

Dental implant treatment is a powerful option in the treatment choice for edentulous ridge and is now replacing many parts of the traditional prosthodontic treatment. In general losing teeth is accompanied by atrophic alveolar ridge, which compels dentists into complete understanding of the biology of bone augmentation to maximize the benefit of the patients. Ever accumulating medical information and technologies have been increasing the quality of life of many patients. Although still obscure many aspects of the biology of the bone grafting; i.e. the matter of choice, are nowadays being elucidated with molecular biological advancement. What is more, what makes the edentulous bone atrophic; i.e. the matter of why, is unveiling its secret through unwearying enthusiasm of the many brilliant scientists. Having a long way to go, we're still on the road.

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18

An Important Dilemma in Treatment Planning: Implant or Endodontic Therapy?

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1. Introduction

One of the goals of a successful traditional dental practice has been the preservation and rehabilitation of a patient's natural dentition. Endodontic treatment has played a key role in the retention and restoration of teeth affected by pulp and/or periapical pathosis. In earlier times, diseased teeth would invariably be extracted. The improvements in modern endodontic techniques for conventional and later re-treatment and periradicular surgery has allowed for the retention of a number of teeth that would have been extracted in the past. Currently, the extraction of natural teeth has generally been considered undesirable and as a treatment choice of last resort when there are financial considerations and limited restorative options (John et al., 2007; Morris et al., 2009).

The development of osseointegrated implants has offered even more choices for dental practitioners and their patients in prosthetic rehabilitation for compromised teeth that require extraction. However, the choice of whether to retain a compromised tooth and restore it or to remove and possibly replace it is still unclear and presents as a common dilemma in restorative dentistry. In general, clinical decisions could become consistent and straightforward, if they are informed by unequivocal evidence, are supported by clear and accepted guidelines, and lead to recommended actions that are universally acceptable to patients and care providers (Pennington et al., 2009). However, especially in dental practice, a few decisions are not always so clear-cut. Although the traditional viewpoint is to retain teeth for as long as possible, this viewpoint has been challenged by emerging trends in implant dentistry, with implant replacements being touted as being equal to or even superior to the preservation of natural teeth.

In many cases, the choices are obvious. If a tooth is intact, there is no question that the endodontic treatment should be done, provided that the dentist has the skills required to do a satisfactory job. However, the choice of treatment for particularly compromised teeth may not be clear-cut in many situations. It must be realized that not only is the choice of the treatment controversial, but also the criteria for defining a tooth as "compromised" are controversial and subject to differences in interpretation. To discuss treatment of compromised teeth, a compromised tooth must be clearly defined and differentiated from a tooth with "end-stage" failure (Iqbal & Kim, 2008). An "end-stage" tooth is defined by Iqbal & Kim (2008) as a tooth with a pathologic state or structural deficiency that cannot be successfully repaired with reconstructive therapies, including root canal treatment and retreatment, and that continues to exhibit progressive pathologic changes and clinical

dysfunction. In end-stage tooth failure, the treatment choices are obvious. However, the abundance of treatment alternatives for compromised teeth has caused dentists to make variable treatment recommendations for the teeth in the same and/or similar clinical situations. In particular, with implant dentistry rapidly gaining acceptance, the choice to retain a diseased and/or compromised tooth by root canal therapy or to extract the tooth and replace it with an implant-supported crown has become controversial and is still argued by opinion leaders and experts in both fields in the dental literature (Heffernan et al., 2003; Glickman, 2003; von Arx, 2005; Ruskin et al., 2005; Trope, 2005; Felton, 2005).

Nowadays, implant-supported prostheses have become the gold standard for the treatment of total or partial edentulism in most clinical scenarios (Avila et al., 2009). As a result, many practitioners have considered an implant-supported prosthesis as an alternative to the preservation of the natural dentition. This interest in implant dentistry has affected the treatment planning of not only end-stage teeth but also compromised teeth that may be more frequently extracted in favor of an implant placement. In truth, implants may be a better therapeutic alternative than performing more extensive conservative procedures in an attempt to save or maintain a compromised tooth. Nevertheless, an inadequate indication for implantation may result in the sacrifice of many sound salvageable teeth. Therefore, when the decision of whether to preserve a compromised tooth or to extract it and place an implant has to be made, a variety of factors (e.g., survival rates of endodontic treatment versus implant placement; patient's expectations, perception of treatment, and health conditions; time; financial status; esthetics; and clinician's proficiency and clinical background) should be considered.

2. Factors influencing treatment planning

2.1 Survival rates

One of the most-often debated components of this implant or endodontics dilemma is whether endodontic treatment and restoration can compete with a dental implant-borne prosthesis in terms of survival rates and success. Survival rates of endodontic treatment and implant placement are generally taken into account while choosing whether to extract or retain a compromised tooth. Both outcome measures for survival in the endodontic and implant literature are the same: retention of the tooth within the mouth (Iqbal & Kim, 2007). In fact, it is important to keep in mind the fact that implant-based therapy and endodontic treatment are very different therapeutic options, given the variety of factors that can independently affect the diagnosis and outcomes of both modalities (White et al., 2006). One of the primary reasons for the variability of reported outcomes is the inconsistent definition of success in the evaluation criteria. Success in endodontics is very different from success for implants. The endodontic studies have applied strict definitions of success based on clinical and/or radiographic criteria (i.e., absence of apical radiolucency, looseness, and reduction in size of radiolucency) (Ng et al., 2007), while implant studies have considered an implant to be successful if it is functional and present in the mouth without definite signs of absolute failure, such as peri-implant radiolucency or implant mobility (Doyle et al., 2006). The use of lenient success criteria in implant studies may translate to higher success rates, whereas the stringent criteria used in root canal studies may lead to lower success rates (Watson et al., 1999; Johnson & Persson, 2001; Wennström et al., 2005, Doyle et al., 2006). Furthermore, operator differences exist between the two treatment modalities in the literature as well (Blicher et al., 2008). Implant studies generally report procedures completed by specialists, while many endodontic studies involve work performed by

students or general dentist (Cheung, 2002; Salehrabi & Rotstein 2004; Alley et al., 2004; White et al., 2006; Cohn, 2005; Trope, 2005). The average survival rate of teeth that are endodontically treated by a general dentist is ~89.7% after 5 years; if the treatment is performed by a specialist, the survival rate increases to 98.1% (Alley et al., 2004). This difference underscores how specialty training can affect success outcomes. There are also fundamental differences in the oral environments of patients receiving either endodontic treatment or implant therapy. Implants tend to be placed in the context of good oral health, whereas endodontic treatment usually is performed in the presence of active disease (Spangberg, 2006; Iqbal & Kim, 2007). Obviously, some standardization is needed to make a more informed and appropriate comparisons between the two treatment modalities (Blicher et al., 2008).

Stockhausen et al. (2011) investigated whether general dentists can appreciate the differences in the outcome measures between the implant and the endodontic literature and reported that a majority of respondents were unaware that a difference in criteria for success exists between the endodontic and implant literature.

Despite the fact that it might not be appropriate to compare endodontic treatment with implant placement due to the varying outcome measures and prognostic indicators in the literature (John et al., 2007), selecting the optimal treatment plan for each patient requires a critical comparison of the reported outcomes of these treatment modalities. While making a decision between endodontic treatment and implants, long-term success is still an important factor that must be considered by both dentist and patient, especially because a dental implant is an invasive procedure and involves the extraction of teeth.

A retrospective cross-sectional comparison of the initial nonsurgical endodontic treatment and single-tooth implants showed that endodontic and implant therapies resulted in an identical number of failures, and the implant group experienced a much greater incidence of post-operative complications (e.g., prosthetic repairs) (Doyle et al., 2006). When comparable criteria are applied to the outcome, survival rates of endodontic treatment and implant placement are found to be similar (John et al., 2007). Depending on the results of a meta-analysis study, Iqbal & Kim (2007) reported that the outcomes for the two treatments were equivalent and that the decision to treat a compromised tooth endodontically or replace it with an implant must be based on factors other than treatment outcome. Consequently, because outcomes are similar with either treatment, it may be advised that the decisions should be based on other factors related to the tooth, the patient, and the clinician, such as the patient's informed decision concerning restorability, costs associated with the procedures, esthetics, potential adverse outcomes, and ethical factors.

In general, endodontic treatment that is done for the first time in a particular tooth has a higher long-term tooth survival rate (Imura et al., 2007). Also, the absence of periapical lesions, or the presence of smaller ones, has a better prognosis than larger lesions in terms of the success of endodontic treatment (Stoll et al., 2005). If an endodontically treated tooth presents persistent symptoms, retreatment of the affected tooth is a suitable option. Nevertheless, re-treatment of failed endodontic therapy is often complex. These procedures, in addition to being time-consuming and expensive, expose the patient to a significant decrease in the long-term predictability of any planned restoration(s) as valuable tooth structure has been lost leading to decreased structural integrity (Ruskin et al., 2005). In short, in cases where re-treated root canals are performed, the survival rates are substantially lower. However, these rates are slightly lower than those for implant-supported, single-tooth restorations (Noack et al., 1999; Ratner, 2001).

Apical surgeries are considered as other options in the case of root canal treatment failure where re-treatment is not indicated (Nair, 1999). With respect to apical surgeries, apicoectomies have a success rate of 74% and a survival rate of 91% (Wang et al., 2004). A systematic review reported that the success rate of endodontic surgery (64.2%) was significantly greater than the resurgery percentage of success (35.7%) (Peterson & Gutmann, 2001). However, apicoectomies do not always preclude the need for dental implants. In addition, buccal fenestrations created to gain access to the periapical area may not heal with an intact buccal plate of bone. Therefore, these procedures may compromise an implant site and precipitate the need for additional bone grafting when an implant is needed (Greenstein et al., 2008). Although there are differences in studies, a recent review of the literature concluded that endodontic treatment is the best option in many cases; however, dental implants provide a good alternative in certain cases in which the prognosis of maintaining the tooth is questionable or poor (Iqbal & Kim, 2008).

2.2 Patient factors

With patients considering endodontic treatment or implant placement, the clinician should perform a complete informed-consent protocol, which includes a discussion of alternatives for care, the advantages and disadvantages of each option, the costs of each option and what will happen if nothing is done (Christensen, 1999; Graskemper, 2005; Sippy, 2006). Patient-specific factors influence the most appropriate treatment option. For example, when designing a dental treatment plan, a patient's expectations may bear more important than the clinical factors. Friedman & Mor (2004) presented a scenario where a patient was asked if he wished to retain his hand after having sustained a complicated wrist fracture or would proceed to amputation and replacement with a functional prosthetic limb. Clearly, the patient would most likely choose to save his hand even if function and comfort were reduced. Therefore, the expectations of the patients have to be clearly identified and should be taken into account while making a decision for the treatment plan. If an extraction is indicated for a tooth after the initial clinical examination, but the patient wants to save it, the decision can be made to save the tooth; however, the patient should be informed about the possible consequences and potential risks associated with this decision (Avila et al., 2009).

Patients' perceptions of the psychological and physiological trauma related to each therapy may affect their decision. Many patients fear both the endodontic therapy and even the mere thought of any surgery because of the peri- or post-treatment pain. However, it should be considered that the pain experienced after endodontic treatment and implant surgery fell within the guidelines for adequate control of peri-operative pain (Iqbal & Kim, 2008). Other factors that should be considered include the dental history, the cultural implications of the tooth loss, and the quality of life that such treatment would produce (Bader, 2001, 2002; Tang & Naylor, 2005; Torabinejad & Goodacre, 2006; White et al., 2006; Cohn, 2005; Christensen, 2006).

The patient's age is a distinct factor to be considered while making an initial treatment plan. In young people, implants are contraindicated until the growth phase is completed because the fixture will ankylose, resulting in infraocclusion (Brugnolo et al., 1996). Infraocclusion may cause changes in the gingival architecture around the implant, with esthetic implications (Cohn, 2005). However, endodontic treatment can be applied to patients in every age group. If the patient's age does not permit a permanent prosthesis or implant because of incomplete skeletal development, endodontic treatment can be advantageous for

patients in their adolescent or childhood period by maintaining the height of the alveolar bone and allowing for the provision of an esthetically acceptable permanent restoration at a later age (Cobankara & Ungor, 2007; Ferrazzano et al., 2010). In addition, it must be kept in mind that significant bone loss can be observed in younger patients receiving implant treatment by the time they reach old age (Bowles et al., 2010).

Knowledge of patient-related risk factors may assist the clinician in proper case-selection and treatment planning. For example, the patient's health condition is also an important factor when deciding between implant and endodontic therapy. Diabetes mellitus is often accompanied with systemic adverse sequelae, such as wound healing alterations, which may affect the osseointegration of dental implants or healing of periapical lesions. In one study, patients with diabetes showed a reduced likelihood of endodontic success, especially in cases with preoperative periradicular lesions (Fouad & Burleson, 2003). In a matched case-control study, Doyle et al. (2007) noted that the outcomes for single-tooth implants and restored endodontically treated teeth were not significantly affected by diabetes; however, preoperative lesions were not reported. In addition, a recent one-year clinical outcome study reported no evidence of diminished clinical success or significant complications related to implant treatment in patients with diabetes (Turkyilmaz, 2010). Consequently, implants in patients with diabetes can be successful; however, it should be considered that the duration of diabetes might be an important factor in implant failure (Olson et al., 2000). Avila et al. (2009) suggested that extracting a tooth and subsequently performing an implant placement could be done in the presence of a controlled systemic condition, but they suggested that one should proceed with caution. If a patient has a systemic condition that is not properly controlled, tooth conservation is advised because a surgical procedure may present an unnecessary risk for the patient. It is a well-known fact that some special medical conditions, such as bleeding disorders or conditions related to the sequelae of radiation therapy, require tooth preservation and the avoidance of extractions or other surgical procedures. In such instances, endodontic treatment is often preferable to an implant.

In the implant studies, smoking is frequently identified as a risk indicator associated with failure (Vehemente et al., 2002; Strietzel et al., 2007; Huynh-Ba et al., 2008; Abt, 2009; Alissa & Oliver, 2010); however, less information is available regarding the relation between the outcome of endodontic treatment and smoking. In one study, Marending et al. (2005) noted that smoking had no impact on the endodontic treatment outcome. Other authors suggested a possible negative influence of smoking on the prognosis of root canal-treated teeth, but this was mainly attributed to delayed bone healing and to an increased prevalence of periodontal disease and root caries in smokers (Duncan & Pitt Ford, 2006). A recent study by Doyle et al. (2007) suggested that smokers had a lower success rate and more failures in both single-tooth implants and endodontic restorations.

In patients with high caries activity, especially activity that is possibly related to dry mouth as a common side effect of several medications (e.g., antihypertensives, diuretics, antidepressants, atropine, anticonvulsants, spasmolysants and appetite suppressants) or associated with certain syndromes (e.g., Sjögren), less effort will be made to maintain a compromised tooth, and implant treatment may be favored (Zitzmann et al., 2009). At the same time, the use of certain medications (such as biophosphonates) may limit the use of dental implants (Glickman, 2003; Starck & Epker, 1995). If a patient has received intravenous bisphosphonates, a conservative non-surgical treatment is strongly recommended, and tooth conservation is advised because the prolonged use of bisphosphonates can cause a

pathologic condition affecting the jaws called bisphosphonate-associated osteonecrosis (Avila et al., 2009).

Oral hygiene or compliance of patients also can affect the treatment options that are appropriate for a patient. Patients who are unlikely to maintain a high level of oral hygiene should not be considered for an implant (Koutsonikos, 1998; Bader, 2002). While excellent oral hygiene is always desirable, a less than optimum condition does not preclude endodontic treatment (Cohn, 2005). Peri-implant tissues are subject to mechanisms of infection similar to periodontal disease (Bullon et al., 2004); however, implant sites have been shown to be more difficult to keep clean and healthy than natural tooth sites (Chang et al., 1999). These findings suggest that implants are perhaps at greater risk for eventual loss than natural teeth, especially in patients who are already prone to periodontal disease (Tang & Naylor, 2005).

Parafunctional habits of patients (such as bruxism) should also be addressed when choosing the appropriate treatment for patients (Cohn, 2005; Christensen, 2006). Because implants lack a periodontal ligament, they are at risk of damage from extreme mechanical forces developed as a result of parafunctional habits (Meffert, 1997; Misch, 2002; Blicher et al., 2008; Salvi & Bragger, 2009).

2.3 Duration of treatment

Patients frequently inquire about the length of time required to complete treatment because the duration of the treatment plan and the amount of chair-time may also affect the decision for both the patient and the clinician (O'Neal & Butler, 2002; Cohn, 2005; Moiseiwitsch, 2002). When the time for completion of treatment was evaluated as the time from the beginning of the treatment until time to function, implant treatment had a longer time-to-function than endodontic therapy (Doyle et al., 2006).

2.4 Esthetic concerns

Esthetic demand by the patients is of paramount importance for the clinicians. Therefore, when choosing the appropriate treatment, esthetic demands specific to the area of concern must be carefully considered (Davarpanah et al., 2000; Tang & Naylor, 2005; Torabinejad & Goodacre, 2006; White et al., 2006; Cohn, 2005; Christensen, 2006). When the potential for esthetic acceptability appears to be questionable with the planned implants and restorative therapy or especially in instances where the esthetic outcome is extremely important for the patient, retention of the affected tooth may be a better choice (Christensen, 2006). In such cases, failure to retain natural teeth and their subsequent replacement with implants can sometimes lead to unesthetic results. It has been stated that esthetic failures in implant dentistry are known to outnumber mechanical failures, especially in the anterior dentition (Goodacre et al., 2003). Many implant studies do not account for poor esthetics, implant malposition, soft tissue recession, bone maintenance, and unfavorable soft tissue configuration (Salinas & Eckert, 2007). If the practitioner disregards esthetic risk factors, such as high patient expectations, a high smile line, poor gingival quality, poor papillary morphology, and low bone height, the patient may not be satisfied with implant treatment (Renouard & Rangert, 1999). If these factors are not properly managed then predictable results are impossible to achieve (Tang & Naylor, 2005).

A natural tooth often achieves better results for coronal shade matching; however, if the treatment plan involves crowning the natural tooth, an implant crown may allow for a

better color match due to its thicker layer of porcelain (Torabinejad & Goodacre, 2006). Also, if the natural tooth is misaligned with the natural dentition, an implant may produce a more esthetic result (White et al., 2006).

Soft tissue management is an important aspect of esthetic management in implant dentistry. The soft tissue biotype of the location influences the esthetic results (Torabinejad & Goodacre, 2006; Cohn, 2005). When the periodontal biotype is thin but healthy around a natural tooth, then the preservation of the tooth through endodontic therapy might provide more appropriate soft tissue esthetics than a dental implant because a thin biotype is prone to recession (Torabinejad & Goodacre, 2006; Greenstein et al., 2008). The placement of a foreign body in the bone may have a negative effect on the marginal bone height and has a direct effect on soft tissue contours (Choquet et al., 2001; Gastaldo et al., 2004). Therefore, the relationship between the final restoration and surrounding bone height should be envisaged while making a treatment plan to achieve successful esthetic soft tissue contours around the final restoration.

Papillary symmetry between the contralateral sides of the dentition is important for esthetics. However, a predictable, esthetic result is sometimes difficult to achieve because of the short papillae between implants when two or more adjacent implants are placed in the anterior maxilla (Elian et al., 2003). Therefore, to attain the best esthetics, if two adjacent implants are to be placed, modification of the treatment plan may be necessary. If possible, consideration should be given to saving one tooth to avoid short papillae (Greenstein et al., 2008). In some clinical situations, judicious, strategic extractions of compromised teeth, even of some teeth that can be retained, may facilitate an optimal restorative result and permit the placement of implants in ideal positions (Davarpanah et al., 2000; Greenstein, 2005). At the same time, if esthetics is not important, the decision of whether to conserve or extract a tooth becomes less critical.

2.5 Financial status

The financial factor may influence the decision-making process for both clinicians and patients. Traditional restorative procedures or implant-supported restorations are usually more expensive than maintaining a tooth. By using the mean fees charged by general practitioners as reported by the American Dental Association 2005 Survey of Dental Fees, Christensen (2006) reported that an implant-supported crown costs about twice that of an endodontically treated tooth restored with a crown. The patients are not always aware of the additional cost, especially in the case of dental implants (Avila et al., 2009). Possible adjunctive procedures before the implant placement, such as a variety of radiographs, mounted study casts, surgical stents, sinus lifts, bone grafts and membranes that would increase the cost of an implant, may be required and are generally not presented during the planning process. Rustemeyer & Bremerich (2007) reported, after conducting a survey of 315 patients, that 61% had an unrealistic idea of the fees related to restorative therapy in which dental implants were used. Pennington et al. (2009) evaluated the cost-effectiveness of endodontic treatment for a maxillary incisor tooth in comparison with extraction and replacement with a bridge, denture or implant-supported restoration in a Markov model. After modeling the available clinical and cost data, they reported that the endodontic treatment and the orthograde re-treatment necessary when a root canal treatment fails are both cost-effective. If a surgical re-treatment is necessary, extending the life of the crown by replacment with a single implant is less cost effective (Pennington et al., 2009). In addition,

in terms of post-procedural treatment requirements, the study by Doyle et al. (2007) demonstrated that implants required nearly 5 times more post-treatment interventions as compared with restored endodontically treated teeth. Kim & Solomon (2011) evaluated the cost-effectiveness of four different treatment modalities (i.e., nonsurgical retreatment with restoration, endodontic microsurgery, extraction with fixed partial denture, and extraction with single implant-supported restoration) on a hypothetical clinical scenario of a failed endodontically treated first molar. According to these researchers, a single implant-supported restoration, despite its high survival rate, was the least cost-effective treatment option.
Consequently, from an economic standpoint, endodontic treatment might be a more favorable treatment option than implant-supported crowns.

2.6 Clinician's proficiency and preference

When dental implants were first introduced, it was mainly the oral surgeons who placed them. During the mid-1980s, periodontists began to place implants. More recently, a broader range of dental care providers, including general dentists, prosthodontists, and endodontists, are learning the skills of implant placement (Potter et al., 2009). Therefore, at present, there is yet no consensus on which expertise field should provide implant treatment and dental implant placement.
The decision to restore a diseased tooth with endodontic treatment or to extract the tooth and replace it with implant restoration might be influenced by the clinician's proficiency and clinical background. Bader & Shugars (1993) have previously reported on this aspect of treatment planning for restorative treatments. According to this report, among clinicians, there were differences in the recommended treatment for individual teeth with specific conditions, and the main reason for the differences was the variation in the dentists' practice profiles (Bader & Shugars, 1993).
If the patient feels that because of the expertise of the clinician, one or the other therapy has the greatest chance for success, then that therapy is the one that is chosen in that situation (Christensen, 2006). In addition, if the treatment options are presented in a biased manner to favor one option over the other, the patient is more likely to choose that treatment option (Foster & Harrison, 2008). If a clinician believes that he/she is unable to save a tooth, tooth extraction and future prosthetic replacement will most likely be recommended (Avila et al., 2009). Although it is recognized that clinicians vary in their experience, skills, and interests, these factors should not dictate the treatment plan because other members of the dental team are available to provide specialized care on a referral basis (Iqbal & Kim, 2008).

2.7 Risk factors and/or complexity of each treatment modality

Treatment of a compromised tooth requires the consideration of *prosthodontic factors* (such as the extent of caries, crown-root ratio, and dentinal wall thickness), *endodontic factors* (including root canal anatomy, periapical pathology, cause of primary failure in cases of retreatment, and the presence of root resorption or root fracture), and *periodontal factors* (such as mobility and furcation problems). If the longevity of a conserved tooth as related to these factors is questionable, the extraction of the tooth may sometimes be a better alternative than leaving the tooth in the mouth.
The type of restorations used for endodontically treated teeth and the quality of the coronal seal may have a greater impact on the long-term retention of treated teeth than the endodontic treatment itself (Saunders & Saunders, 1994). In other words, endodontic

therapy alone does not guarantee successful retention of the tooth or prevent its future loss. Extensively decayed or unrestorable tooth, tooth fracture, and periodontal disease, in conjunction with apical periodontitis, are more frequently indications for tooth extraction than the endodontic failure itself (Sorensen & Martinoff, 1985; Sjogren et al., 1990; Vire, 1991; Caplan & Weintraub, 1997; Chen et al., 2008).

A common issue with endodontically treated teeth is that when a failure does occur, the residual pathology can create potential problems for subsequent implant placement. Bone resorption and damage from infections of an endodontic origin can be extensive and require significant bone grafting and soft-tissue reconstruction (McGarry, 2008). However, it should be considered that endodontically treated teeth are associated with less complications and procedural interventions than implant-supported crowns and that complications associated with implant failure significantly impact a patient more negatively than when endodontically treated teeth fail (Morris et al., 2009).

While making a decision as to whether to retain and restore or to replace a tooth, the restorative prognosis of the tooth and the physical loading characteristics that it will be endured must also be kept in mind. For example, posts are often necessary to rebuild enough tooth structure to retain restorations when restoring compromised, root-filled teeth of the type that provide the subject for this discussion. However, the price for added retention may be an increased risk of damaged tooth structure (Caputo & Standle, 1976). The long-term ability of the implant to retain a crown is superior to that of a natural tooth, particularly one that is endodontically treated and supporting a post and core (Ruskin et al., 2005). Therefore, compromised teeth treated with posts should be carefully used in areas where they may be critical to the survival of other reconstructions, such as abutments for bridges or removable partial dentures (Dawson & Cardaci, 2006). However, implant treatment carries the risk of ongoing periodontal and occlusal complications, particularly esthetic problems. Some of the main advantages of an endodontic treatment compared to an implant-supported restoration are the proprioception and the adaptation under mechanical forces mediated by the periodontal ligament (Trulsson, 2006). In a recent study, endodontically treated teeth have been reported to have significantly higher maximum bite force, chewing efficiency, and total occlusal contact than single-tooth, implant-supported prostheses (Woodmansey et al., 2009).

The decision to extract or retain teeth affects the adjacent teeth, especially if they are to function as abutments for a fixed or removable partial denture. It has been reported that patients who used removable partial dentures over a 10-year period lost 44% of the abutment teeth (Aquilino et al., 2001). However, there are no studies indicating whether the loss of the bordering teeth occurs when implants are inserted. In contrast, a large edentulous area may require the span of a fixed partial denture to be extended to incorporate teeth that require endodontic or periodontal treatment, thereby possibly compromising the long-term stability of the prosthesis (Greenstein et al., 2008). In such cases, implant treatment might be advised. For each patient, the strategic value of the tooth in relation to the overall oral structure and function must be evaluated; in addition, clinicians must consider how any treatment they perform will affect future treatments (Bader, 2001, 2002; Ruskin et al., 2005; Pothukuchi, 2006). Sometimes, retaining a compromised and diseased tooth may lead to continued bone loss, which could complicate future implant placement (Perel, 1991; Heithersay, 2000; Curtis et al., 2002; Matosian, 2003).

One area of concern in recent years has been how implant placement would be affected by an adjacent tooth that had been treated endodontically. Some researchers suggest that implant failure may occur when the implant is positioned adjacent to teeth that are clinically symptomatic of periapical pathology or have radiographic periapical pathology (Shaffer et al., 1998; Tehemar, 1999; Brisman et al., 2001; Chou et al., 2010). According to these researchers, clinicians should be aware that if implant failure occurs in a tooth adjacent to one that has previously received endodontic therapy, further treatment or possible extraction of the previously treated tooth might be necessary before repeating the implant surgery. A recent study reported that the incidence of retrograde peri-implantitis might be reduced by increasing the distance between the implant and the adjacent tooth, and/or the duration from endodontic treatment to implant placement in the adjacent tooth (Zhou et al., 2009). However, some researchers suggested that the endodontic status of adjacent teeth has no effect on the prognosis of the implant (Shabahang et al., 2003; Doyle et al., 2007; Laird et al., 2008).

Local anatomy, such as proximity to the sinus or the type of bone, determines the potential need for additional procedures and/or whether the risk for complications will increase (Bader, 2001, 2002; Cohn, 2005; Torabinejad & Goodacre, 2006). Any area with questionable or abnormal bone density, or the presence of potentially problematic anatomical structures, should persuade clinicians to retain teeth and choose the endodontic alternative (Christensen, 2006). Quality of bone is considered the most important determinant in the loss of implants (Vigolo & Givani, 2000; Levin et al., 2006). However, in a recent study, Doyle et al. (2006) did not find the location of the restorative treatment a significant factor when comparing single-tooth implants and restored root-canal treated teeth.

The need for auxiliary procedures (for example, sinus lifts or grafts for implants and crown lengthening or orthodontic extrusion when restoring with endodontics) should be considered when determining the overall morbidity and potential for complications of each treatment option (Torabinejad & Goodacre, 2006; White et al., 2006). If orthodontics continues to be performed in the future, one must remember that dental implants cannot undergo orthodontic movement (Wittlinger, 2007).

For successful long-term service, restored implants require regular follow-up, and the patient must realize that this option will not eliminate the need for further dental care (Blicher et al., 2008).

3. Conclusion

When choosing the appropriate treatment for patients, it should be kept in mind that every patient and situation is unique. Specific patient and/or clinician factors weigh heavily in choosing whether to perform tooth preservation procedures or extraction procedures with the option of implant-supported restoration. Saving teeth when reasonable is still the goal, but long-term outcomes need to be better delineated in the dental literature. In reality, no guide that is designed to aid in the decision to extract or save a compromised tooth can be perfect. However, because there are usually contradictory indications for dental implants and endodontic treatments in such teeth, there is a need for the development of guidelines. It is the responsibility of the clinician to make the final decision by considering the specific aspects of each case. The aim of both implant and endodontic therapy is to facilitate the rehabilitation of patients' natural dentition. However, it should not be forgotten that

endodontic therapy is intended to retain teeth, whereas implant therapy is intended to replace missing teeth.

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19

Facial Prosthesis

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1. Introduction

The use of facial prostheses such as wax ears has been reported in ancient Egypt. The first historically documented evidence comes from sixteenth century, when the French surgeon Ambroise Paré describes the first nose prostheses from gold, silver and "papier mâché", which were held to the face by a string tied around the head. In late 19th century Claude Martin conceived an idea of an immediate prosthesis using tissue excised from the maxilla and mandible as a template for fabricating complex appliances. In 20th century, while the quality of lifelike craniofacial prostheses was considerably improved with introducing of silicone materials, the problem of their retention, which is important for aesthetics, function, and comfort, was not entirely solved. With increasing aesthetic requirements conventional fixation tools such as skin adhesives, skin pockets, skin loops, and glasses became unsuitable. It was Brånemark, who first placed a modified extraoral implant for a bone-anchored hearing aid in 1977 and for a bone-anchored auricular prosthesis in 1979. These events changed concepts of prosthetic maxillofacial reconstruction. Since then, osseointegrated extraoral implants are widely used for retention of orbital, ear, and nose prostheses. Their usage diminishes adhesive related problems like discoloration and deterioration of the prosthetic material. The skin and mucosal surfaces are less subject to mechanical and chemical irritation from intrinsic mechanical retention, adhesives, or adhesive solvents. Maintenance of fine feathered margins and simple positioning of an implant-retained craniofacial prosthesis greatly increased their aesthetic qualities. Lot of scientific and clinical studies confirm the success of their practical application and improvement of patient's quality of life.

Acquired facial defects, especially after radical surgical operations very often result in huge functional, cosmetic and psychological handicap in patients. A complex rehabilitation is necessary to be carried out by maxillofacial surgeons and prosthodontists. Plastic surgical reconstruction of these defects is frequently limited due to unfavorable conditions, such as vascular compromise of the surgical bed due to radiotherapy, insufficient residual soft and hard tissues. In such cases, rehabilitation of patients with large maxillofacial defects is done using craniofacial prostheses, which can offer an acceptable aesthetic solution.

Facial prostheses are constructed by maxillofacial surgeon, implantologists, prosthodonticts and technician, as an alternative treatment when facial defects cannot be surgically fulfilled. Facial prosthesis using dental implants and ball attachments, bars or magnetic abutments

are a method of choice in replacement of missing hard and soft facial tissues. Nose, eye and ear form, coloration, and texture must be as indiscernible from the surrounding natural tissues as possible. Rehabilitation efforts can be successful only when patients can appear in public without fear of attracting unwanted attention.

Osseointegrated implants have various advantages over either adhesive or spectacle-retained prostheses for the reconstruction of the facial defects. They provide better retention of the prosthesis, so that the prosthesis is properly positioned and the patient can wear it more confidently. There is no skin irritation from adhesive and the prosthesis does not need to have adhesive cleaned off each time it is used. The prosthesis can be made thinner, with feathered edges that blend with the skin, which offers the patient improved aesthetics. A pre-operative planning meeting with the patient and multidisciplinary team shows not only different prosthetic options but also e.g. cleaning of the abutments and prosthesis.

The implants have had a dramatic impact on patient acceptance of facial prostheses. Patients like the security, comfort, and convenience of implant-retained prostheses, benefits that are not attainable with earlier methods of retention. Surgeons have come to appreciate the reduced need for numerous complex surgical reconstructive procedures in many of these patients. For large defects, a multidisciplinary approach is recommended, combining flap reconstruction and implant-retained prosthetic rehabilitation to achieve optimal results. Earlier reports have shown that implants are not uniformly successful, and the failure rates in some patients/sites are quite high. The failures and complications appear to be site specific and radiation and time dependent.

Facial prosthesis with three dental implants is a method of choice in replacement of missing hard and soft orofacial tissues. Dental implants support arise confidence of the patient in public. Goal of the contribution is to analyze systematically the patients with the orbital surgical defects. Multidisciplinary therapy involves the following disciplines: ophthalmology, maxillofacial surgery, implantology and prosthodontics.

Midfacial defects can be divided into two major categories: midline midfacial defects, which include the nose and/or the upper lip lateral defects, which include the cheek and the orbital contents

The choice between surgical reconstruction and prosthetic restoration of large facial defects remains a difficult one and depends on the size and etiology of the defect, as well as on the wishes of the patient. Development and application of osseointegrated implants to facial defects has, in part, changed patient perceptions of facial prosthetics. Implants allow convenient and secure positioning of the prosthesis, leading to greater patient acceptance.

A retrospective review will be performed in patients, who had undergone reconstruction of facial prosthesis from 2005 to 2010. Case reports evaluate step by step material and methods including implants insertion.

The diagnoses that are indicated for surgical treatment are mainly three: oncological, traumatological diagnoses and genetic and/or obtained disorder. The aims of surgical and prosthodontic rehabilitation are replacement of missing soft and hard facial structures, rehabilitation of body handicap and social problem and quality of life.

2. Treatment protocol

The treatment of a patient with oral cancer or after mutilation trauma is a collaborative team effort among maxillofacial surgeons, radiation oncologists, and prosthodontists. Free tissue transfers are routinely used to reconstruct both the soft tissue and bone defect immediately

following the ablative surgery. A large percent of patients receive radiation 4 to 6 weeks postoperatively. The total radiation dose to the tumor bed depends on the presence or absence of microscopic disease at the surgical margin. The tumor dose is generally limited to 55 Gy for patients with clear margins, and up to 65 to 70 Gy in patients with close margins. Radiation positioners are used extensively, and radiation fields are configured to minimize exposure of the major salivary glands to high doses of irradiation; however, intensity-modulated radiation therapy was not employed. Radiation dose to bone can often be minimized in areas of proposed implant sites.
Approximately 6 weeks after the ablative surgery, it was anticipated that the subjects would receive radiation therapy for 5 to 7 weeks. New conventional prostheses were fabricated as soon as the healing from reconstructive surgery and radiotherapy would permit. It was planned that implants would be placed 4 to 6 months after reconstruction, depending on the need for postoperative radiation therapy. All implants were placed secondarily following healing of the osteotomy sites and resolution of acute radiation therapy effects. Three dental implants 10 mm or longer and 3.75 mm in diameter were placed. Implants were located in the available native bone and/or in the free vascularized bone of the reconstructed mandible. Surgical guides were fabricated for each subject to assist the surgeon in positioning implants for ideal prosthetic restoration. Segments of impeding reconstruction plates were removed at this surgery prior to the placement of implants.
The possibilities of prosthesis reconstruction are at first artificial anchorage of epithesis – classical rehabilitation and second dental implants and ball attachments, bars, magnets.
Patient prognosis is important, but even a year or two of good quality prosthetic rehabilitation may add considerably to the patient's quality of life. The benefits implant insertion and facial prosthesis is following. The optimal stability of the prosthesis guaranteed the patient recovery of his social life.

3. Nasal prosthesis

Clinical report

A 63 years old women with diagnosis recurrent basocellular cancer in the nose was treated. After ablation of the nose, external radiotherapy and chemotherapy were applied. Full oncological treatment was completed in 2007. The patient had had no other systemic problems, was in good health, she had no serious injuries, had just undergone the ordinary children´s diseases, and she did not suffer from any allergies. She did not drink alcohol, did not smoke and take drugs. The surgical and prosthodontic rehabilitation was started 1 year after termination of the treatment (Fig. 1, 2).
In the margin of the postoperative defect 3 intraosseal dental implants (Impladent, Lasak Ltd., Czech Republic) were inserted. The operation was done under general anesthesia with nasotracheal intubation. The primary implant site for nasal defects was the piriform ridge at the base of the nose (2 implants – left and right). Also the glabella was used as an implant site for our defect; the primary consideration was the degree of pneumatization of the frontal sinus and the quantity of overlying bone. The operation lasted 65 minutes and was without any complications. Healing of the wound was without an inflammatory process. Lincomycin (600 mg p.o.) provided an antibiotic covering. The fourth day after operation the patient was dismissed in good condition. Six months after implant placement and the healing period the prosthetic reconstruction began. The patient was screened with a control tomogram. Magnetic attachments were inserted and nasal epithesis was prepared following way.

The one-stage technique, the nasal prosthesis with freestanding abutments and magnet retention were used. The direction of emergence of the abutments was examined. It was desirable to have the retentive elements oriented to pull the prosthesis onto the shin surface. To achieve this and to have the retentive components in a position that is convenient to manipulate, hand-made cantilevered abutments were selected (Impladent, Lasak Ltd., Czech Republic). A try-on set of custom-made magnetic abutments were available to allow for selecting the appropriate cantilever angle.
The impression of the defect is recorded as a sectional alginate impression (Kromopan 100, Lascod). The impression was boxed and poured in the stone. Baseplate wax was used to form the borders of the designed acrylic-resin substructure. The wax pattern (wax up) was prepared and evaluated on the patient and finalized.
A stone overcast is constructed. The wax is boiled out and the surfaces of the cast and overcast are painted with separating medium and autopolymerizing acrylic resin (Duracryl, Dental). The acrylic resin is cured in a pressure pot. Prosthesis form, coloration and texture were finished with special silicone (Multisil Epithetic, Bredent). The completed nose was pumiced and polished. A magnet was attached to the face of the abutment. The interface between the abutment and the keeper was recorded with a one-phase silicone. The magnets were connected to the abutments.

4. Ocular prosthesis

The loss or absence of an eye may be caused by a congenital defect, irreparable trauma, tumor, a painful blind eye, sympathetic ophthalmia, or the need for histological confirmation of a suspected diagnosis. Orbital diseases are relatively rare but considering the anatomy of surrounding structures, they present a very serious disorder. Tumors in the orbit area represent between 0.2 – 0.5 % of the total. Eye and eye adnexa tumors are manifested by a number of symptoms: dystopia, bulbar motility dysfunction, exophthalmia, and diplopia. Depending on the severity of the situation, the surgical management may include one of 3 approaches: evisceration, enucleation, or exenteration.
Evisceration is a surgical procedure wherein the intraocular contents of the globe are removed, leaving the sclera, Tenon's capsule, conjunctiva, extraocular muscles, and optic nerve undisturbed; the cornea may be retained or excised.
Enucleation is the surgical removal of the globe and a portion of the optic nerve from the orbit.
Orbital exenteration is the en bloc removal of the entire orbit, usually involving partial or total removal of the eyelids, and is primarily performed in order to eradicate a malignant orbital tumor.
In particular, diagnostics is provided by an ocularist; otorhinolaryngologist and dentist examinations are also suitable. Auxiliary imaging methods are also indispensable part of the diagnostic procedure. These include X-ray images of the skull in dorsoventral, semiaxial and lateral projection. In addition, ultrasonography, computed tomography and often also nuclear magnetic resonance examination are also employed. According to the specific diagnosis it is possible to establish precisely the extent of the damage to the eye, surrounding structures in the orbital area and to determine a medical treatment. As for the treatment of solid tumors, radical surgical solution is usually the first step despites the risk of possible functional and aesthetic defects.

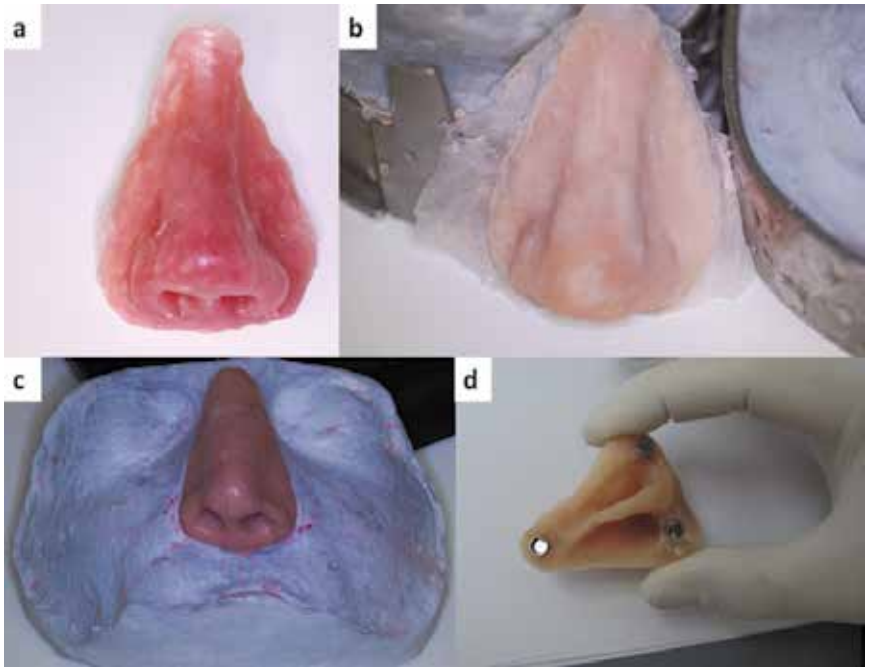

Fig. 1. Nasal prosthesis: a) wax up; b) polymerization, c) coloration; d) magnets insertion.

Fig. 2. Nasal prosthesis: a) CT after 3 implants insertion, b) magnet attachments in situ; c) patient after rehabilitation.

The disfigurement associated with the loss of an eye can cause significant physical and emotional problems. Replacement of the lost eye as soon as possible after healing is necessary to promote physical and psychological healing for the patient and to improve social acceptance.
Prosthetic rehabilitation that restores these facial disfigurements may improve the level of function and self-esteem for patients. However, difficulties with facial prostheses arise due to movable tissue beds, quality of prosthesis retention, and associated skin reactions to adhesives. The use of osseointegrated implants in the craniofacial region reduces prosthesis limitations associated with medical-grade adhesives and is a treatment option with high long-term success rate of facial prostheses.
Facial prosthesis with three dental implants is a method of choice in replacement of missing hard and soft orofacial tissues. Prosthesis form, coloration and texture must be as indiscernible from the surrounding natural tissues as possible. Rehabilitation efforts can only be successful when patients can appear in public without fear of attracting unwanted attention. Dental implants support gives the patient confidence in society. An important prerequisitte for successful treatment of such handicapped patients is high-quality osseous tissue of defect margins. The following case report demonstrates a step by step processing of the orbital epithesis.

Clinical report

21- years old man was referred to the Clinic of Dentistry and Maxillofacial surgery in Prague. In two years of age he was operated for retinoblastoma of the left eye. After enucleation, external radiotherapy and six cycles of chemotherapy were applied (Etoposid and cis-platina (cDDP). Full oncological treatment was completed in 1983.
Retinoblastoma occurs primarily during childhood (80 %), the incidence is 1:18 000 of the new-borns. The main age of presence is between 1 and 2 years of age. The etiology is unknown. Probably, there is a genetic load connected to Rb 1 mutation.
The patient had no other systemic problems, he was in good health, he had no serious injuries, had just undergone the ordinary children´s diseases, and he did not suffer from any allergies. He did not drink alcohol, did not smoke and take drugs. The patient did not use the bulbar prosthesis and he was very distressed about his facial disfigurement. The usual preoperative examinations, as well as the skull radiograph in semiaxial projection and magnetic resonance were obtained. According to the treatment plan were inserted 3 dental implants (Ankylos, Friadent). After their integration booting of the ball attachments and fabrication of orbital prosthesis with patrix/matrix system retention were used. The operation was done under general anesthesia with nasotracheal intubation. In March 2004, 2 implants were booted to the upper margin (diameter 3.5 mm, and length 8 mm) and 1 implant to the lower margin (diameter 3.5 mm, and length 9.5 mm) of the left orbit. Suturing material was Monofil. The operation lasted 65 minutes and was without any complications.
Healing of the wound was without an inflammatory process. Lincomycin (600 mg p.o.) provided an antibiotic covering. The fourth day after operation the patient was dismissed in good condition. Six months after implant placement and the healing period the prosthetic reconstruction began. Control semiaxial X-ray and magnetic resonance examination were made. Three ball attachments were booted to the implants. After that an impression of the anophthalmic socket with a stock acrylic resin tray designed for ophthalmic impressions was taken using the irreversible hydrocolloid (Kromopan 100, Lascod). Master cast was fabricated and composite resin plate (Duracryl, Dental) with 3 patrices was prepared. The

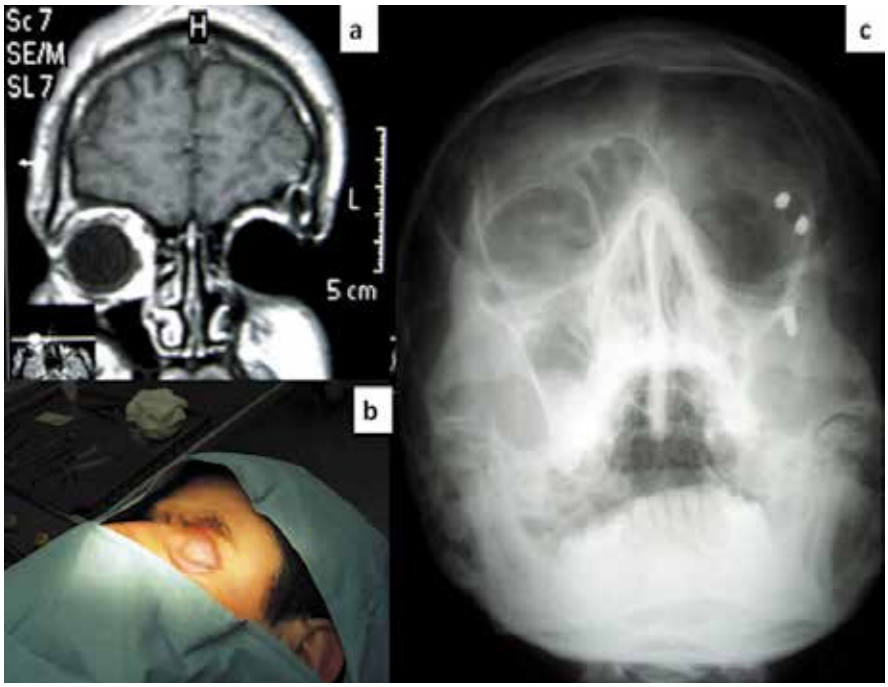

Fig. 3. Ocular prosthesis: a) CT before treatment; b) ocular area; c) implants insertion.

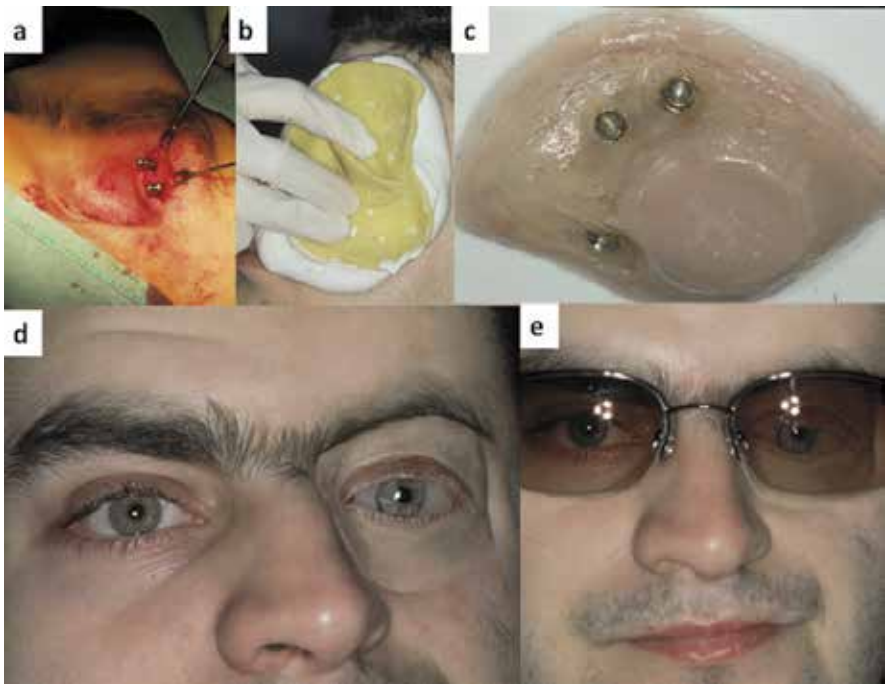

Fig. 4. Ocular prosthesis: a) implants insertion, b) impression; c) ball attachments and ocular prosthesis; d) prosthesis in situ; e) patient after reconstruction.

wax pattern was prepared and evaluated on the patient and finalized. The sculpting fitted the eye socket contours and lids configuration. After characterization was added, the process the ocular prosthesis with ocular bulbs, silicon and acrylic was finished (Multisil Epithetic, Bredent). Prosthesis form, coloration and texture must be as indiscernible from the surrounding natural tissues as possible. The completed eye was pumiced and polished and was inserted into the orbit. Glasses help to receive symmetry of the eye and face (Fig. 3, 4).

5. Auricular prosthesis

The indications for autogenously auricular reconstruction versus prosthetic reconstruction with osseointegrated implant-retained prostheses were outlined in Plastic and Reconstructive Surgery in 1994. The choice between the two remaining techniques, autogenously reconstruction and prosthetic reconstruction, depends more on the surgeon's training and tradition than on an analysis of which procedure is preferable in a given clinical situation. For example, most children with microtia in the United States are treated with autogenous techniques. In contrast, the same deformities in Sweden are more commonly treated with prosthetics. Patients with posttraumatic or postablative auricular defects are more often adults, and their defects differ from those of children with congenital deformities in several ways. First, the skin loss and scarring resulting from trauma or previous surgery may make standard autogenous reconstruction difficult. Second, the tragus is frequently preserved in the trauma/ablative patient, making the aesthetics of prosthetic reconstruction much more favorable. The presence of a tragus allows the anterior border of the prosthesis to be hidden, a major aesthetic benefit.

The auricular region was found to be the most dependable implant site; all potential auricular implant patients undergo a presurgical computed tomographic scan with radiographic stent markers in position. This allows for evaluation of the proposed bone sites in an attempt to maximize implant length. The mastoid air cells frequently pose logistical problems at the most inferior auricular implant sites, and occasionally implant position has to be recalculated. Exposure of the air cells at the time of implant placement does not appear to cause any detrimental effects. If there is adequate bone to provide stability, the implant may be left in position; otherwise, a new site will have to be found. The flange is a favorable feature in the auricular site, preventing accidental intrusion into the cranium and providing some initial stability for short implants. The use of three implants in the auricular region reduces the amount of cantilevering and provides a tripod effect for possible mechanical advantage. All implants are splinted together with a tissue bar, and retention is achieved with clips

Clinical report

A 45-year-old male patient missed his left ear during car accident, and was subsequently indicated for ear replacement with an auricular prosthesis (Fig. 5, 6).

The patient received the three implants in accordance with a two-stage surgical procedure. Screw-shaped titanium implants (Impladent, Lasak Ltd., Czech Republic) are inserted into the temporal bone using a delicate surgical technique and, after the implants have healed in, it is possible to penetrate the skin to establish a reaction-free percutaneous passage. During the first stage the implants were inserted into the bone surrounding the area with the craniofacial defect. After a previous computed tomography scan, coronal, axial and three-dimensional reconstruction images were used to measure the bone thickness in the mastoid

region (at least 6 mm). The patient went through the implant surgery under general anesthesia. A 4 mm longitudinal incision was made posterior to the external acoustic meatus and the temporal bone was exposed. The time taken for osseointegration was expected to be six months for implants inserted into the temporal bone.

The second stage consisted of thinning of the subcutaneous tissue, uncovering of the implants and attachment of abutments to the implants. This procedure included subcutaneous tissue reduction aimed at reducing the mobility between the implant and the skin. Healing caps were placed over the abutments and gauze soaked in ointment was wrapped around the healing caps to ensure good contact between the skin and the bone, and to prevent postoperative hematoma and swelling. The postoperative management plan included local hygiene instructions. The suture was removed after ten days and the patient did not complain of postoperative pain or complications during this period. The four weeks after the second stage, the prosthesis was constructed and attached to the implants.

Fabrication of the implant-retained prosthesis was started three weeks after abutment connection, which followed standard clinical and laboratory procedures. Retention was achieved by means of a bar-clip construction.

The fabrication of the implant-retained auricular prosthesis was based on shape and size of opposite ear. The right ear plaster model and image was prepared, the bar was cast and auricular prosthesis was made. The wax pattern was prepared and evaluated on the patient and finalized. The sculpting fitted the ear contours and configuration. After characterization was added, the silicon and acrylic ear was finished (Multisil Epithetic, Bredent). The completed ear was pumiced and polished and was inserted. The hairs help to receive symmetry of the eye and face.

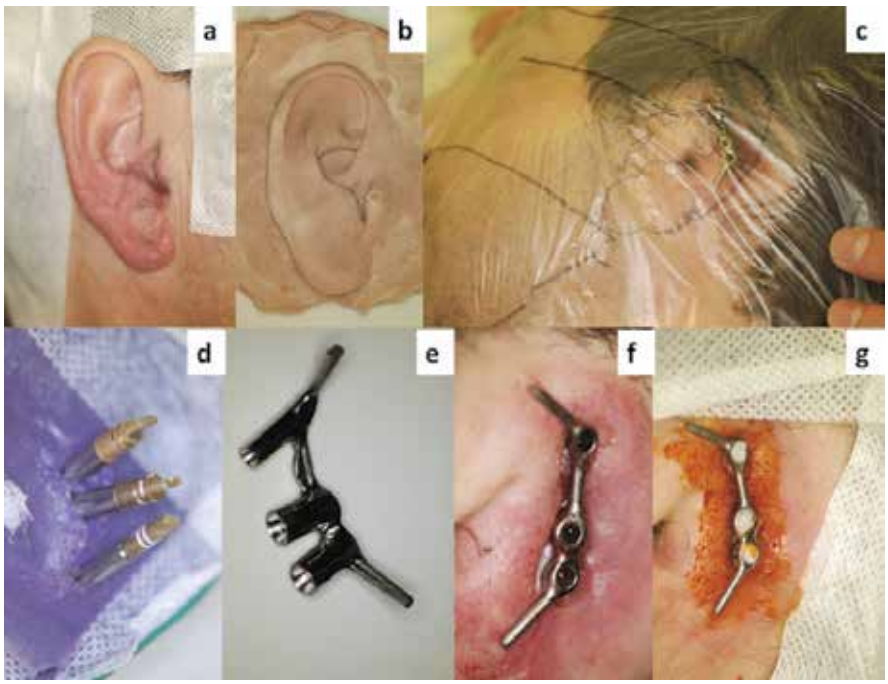

Fig. 5. Auricular prosthesis: a) healthy ear; b) plaster model; c) ear symmetry, d) polyether impression; e) bar with cantilevers, f) bar in situ, g) bar preparation

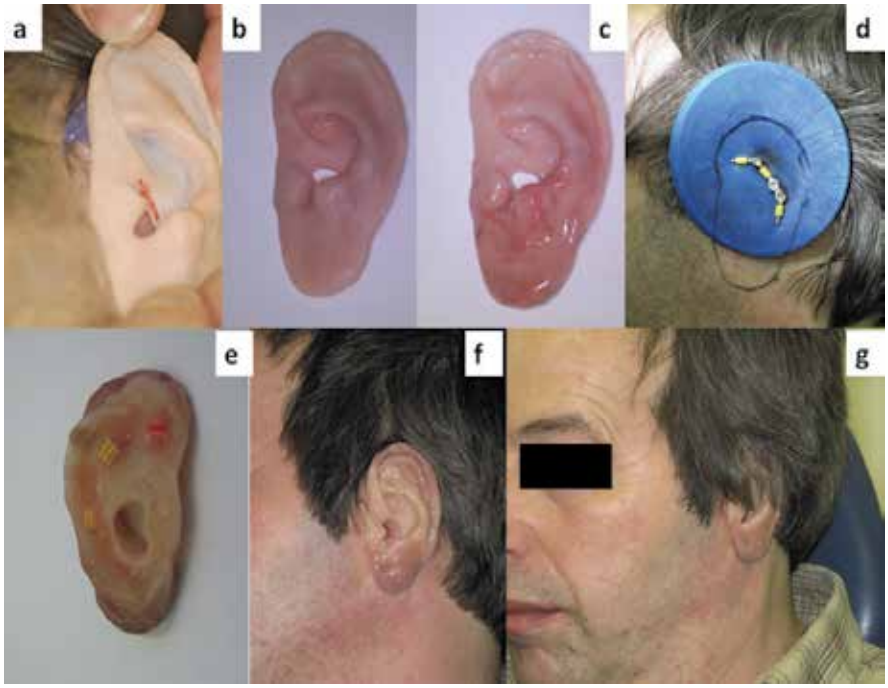

Fig. 6. Auricular prosthesis: a) position of future ear, b) ear preparation; c) coloration; d) bar in situ with clips; e) clips in situ; f) eye rehabilitation; g) patient after reconstruction.

6. Reconstruction of midfacial defects with implant insertion

The maxilla can be described as a geometrical structure with six walls (hexahedrium). Each wall is part of another anatomical structure in the face. The roof of the maxilla is the floor of the orbit and supports the ocular globe. The medial wall of the maxilla is the lateral wall of the nasal cavity and is part of the lacrimal system. Combining bone grafts with skin/soft tissue flaps simplifies reconstruction of the highly complicated three dimensional nature of the maxillary defect; the bone graft (vascularized or non-vascularized) is rigidly fixed in its appropriate position and the soft tissue flap (pedicled or free) with the skin islands is arranged separately in thein own respective locations. Considering this simple approach and having in mind the relationship between volume and surface area requirements, the following are the most important issues that must be addressed with regard to reconstruction of each of the different maxillectomy/midfacial defects.

Osseointegrated implants may be used in several different prosthesis designs. Implants may be used to complete support, retain, and stability the denture; in this situation the implants bear the entire load of mastication. This type of denture, defined as implant-borne, can be removed only by a prosthodontist or dentist, is rigidly fixed to the implants, and does not contact alveolar surfaces. Alternatively, implants may be used to assist in retention of the denture but not bear the entire load of mastication. This type of denture, defined as implant-retained, is secured to the implants with a clip-bar mechanism but is not rigidly fixed to the implants. The majority of an implant-retained denture is in contact with the denture-bearing surface, and it is easily removed and replaced by the patient. Conventional dentures which do not involve the use of implants are defined as tissue-borne.

Clinical report

A 58-year-old woman lost her right maxilla after car accident. She was scheduled for a definitive fixed denture anchored to three osseointegrated implants loco 13, 14, 16 (Fig. 7, 8, 9). Her general medical condition (nephropathies) allows surgical reconstruction. The patient's facial defect and surrounding anatomical structures were analyzed in 3-D CT images. Microvascular iliac muscles and bone tissue transfer has been prepared for reconstruction of the palate, midface, and maxilla. Microvascular free tissue reconstruction allows the transfer of adequate amounts of soft tissue and bone in a single-stage procedure, without the limitations of pedicle length or flap geometry. Two titanium plates (10 mm) with 4 screws supported the position of tissues. After 6 month 3 implants Impladent STIO-BIO (Lasak ltd., Czech Republic) 3.7 mm (loco 13) and 5.1/ 16 mm (loco 14, 16) were inserted. Healing of the wound was without an inflammatory process. Dalacin (300 mg p.o., PFIZER) provided an antibiotic covering.

After 6 month integration the prosthetic reconstruction was prepared. The X-ray examination (panoramic radiograph) checked the grade of osseointegration. Until this time the implants fixtures were still covered by mucosa. Based on the implant size a suitable healing cap was attached and after 2 weeks the attached gingiva was formed. The preparation of an individual impression tray was the first prosthetic step during reconstruction when performing Brånemark bridge (veneered resin bridge). The alginate impression (Kromopan 100, Lascod) of the upper jaw is performed and a open individual custom tray from denture base resin was prepared in the laboratory. The open tray was

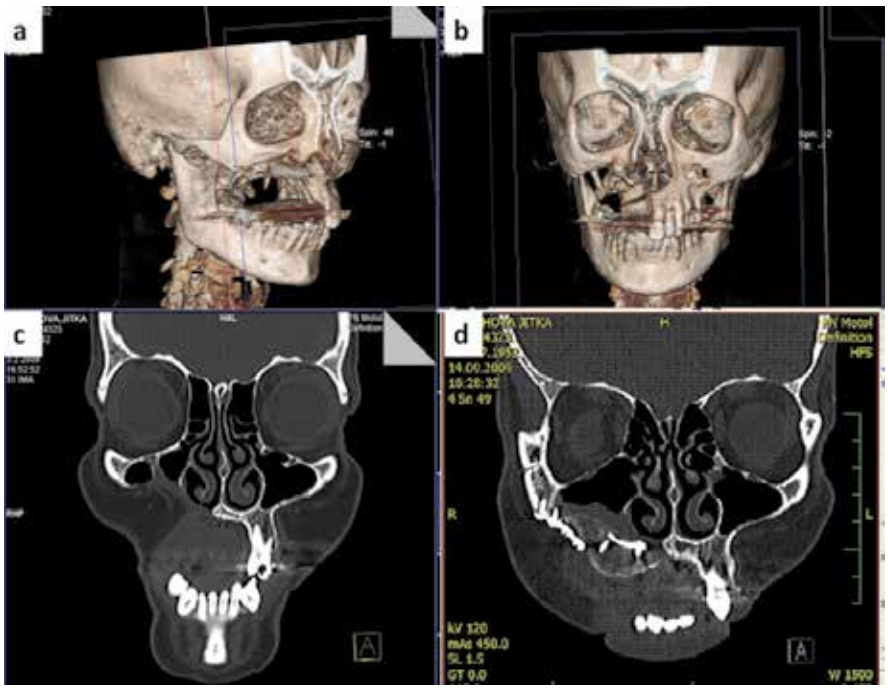

Fig. 7. Midfacial defect a) 3D CT reconstruction from lateral view; b) 3D CT reconstruction from frontal view; c) CT before reconstruction, d) CT after reconstruction.

perforated in the sites of the future abutments. The alginate impression in the opposite jaw bone was performed at the first visit and a plaster cast of the opposite dental arch was within prepared in the laboratory. Furthermore, a wax bite rim for determining of the intermaxillary relations is used.

The healing caps were unscrewed during the second visit and impression posts were screwed on using the special spines. The maxillary ridge was impressed using the polyether impression material (Impregum Penta Soft, 3 M ESPE), the posts were unscrewed and the impression was removed including the impression copings and spines. The laboratory analogs were attached. A dental technician filled the impression using the silicone gingival mask and created the master model using the plaster type IV (stone). He sealed the working models with the reconstructed maxillary position into the articulator. He attached the combustible impression copings on the laboratory analogues and finishes modeling the re-shape of the future construction. The titanium alloy (Grade 2, Orotig + Nd: YAG laser welding) and Cresco method were used to prepare the construction according to the instructions of the manufacturer.

Because the jaw bone was cicatrices and contained defects it was suitable to add not only hard but also soft tissues. As for the adjustment of the vertical maxillary relation, the construction was sectional with the addition of pink methylmetacrylate simulating marginal gingiva. After proving the metal framework, the bridge was completed to see whether it

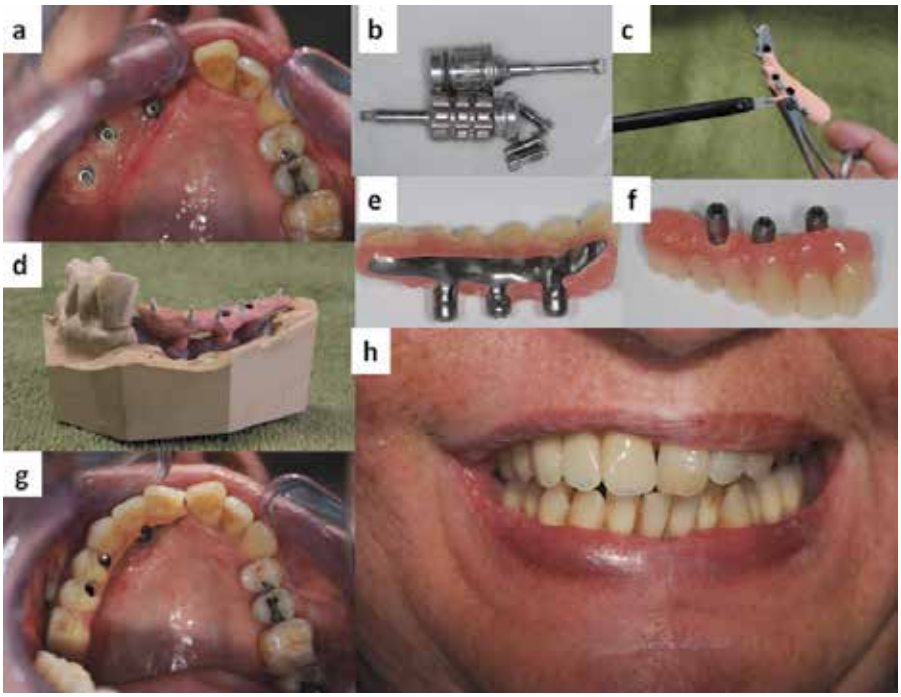

Fig. 8. Midfacial defect prosthesis: a) implant insertion; b) titanium screws and screw drivers; c) framework, d) framework before Branemark bridge preparation; e) implant supported denture – palatal view, f) denture – vestibular view, g) prosthesis in situ, h) smile line after therapy.

Fig. 9. Midfacial defect reconstruction: a) OPG before treatment; b) frontal view before therapy; c) OPG after reconstruction and implant insertion; d) 1-year recall

fulfilled the functional and aesthetic requirements. During the following few weeks (adaptation phase) the screw holes were closed using cotton pellets over the screw heads and glassionomer cement. The connection of the construction and implants should always be checked using an X-ray image.

7. Conclusion

Osseointegrated implants provide a viable option for treatment of patients needing a variety of orofacial prostheses. Implants can overcome many of the difficulties encountered in retaining large facial prostheses. Our findings indicate predictable high survival rates for implants in the auricular and piriform/nasal sites and a less favorable outcome in the orbital region, especially in irradiated sites.

The benefits magnetic implant insertion and facial prosthesis are following. The optimal stability of the prosthesis guaranteed the patient recovery of his social life. Three magnetic attachments are used in the framework positioned in the maxilla, glabella etc. The oral implants offered a wider surface for osseointegration. Magnet attachments ensure better surface stability than ball attachments while not obstructing or making epithesis handling more difficult for the patient. Dental bar is much more useful for auricular prosthesis due to surrounding muscles stress. Facial prosthesis using three dental implants is a method of choice in replacement of missing hard and soft orofacial tissues. Prosthesis form, coloration, and texture must be as indiscernible as possible from the surrounding natural tissues. Rehabilitation efforts can only be successful when patients can appear in public without fear

of attracting unwanted attention. Dental implants prosthesis support gives the patient confidence in society.

8. Acknowledgment

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Part 5

Risk Factors and Complications in Implant Dentistry

20

Clinical Complications of Dental Implants

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1. Introduction

Dental implant surgery has become routine treatment in dentistry and is generally considered to be a safe surgical procedure with a high success rate. However, complications should be taken into consideration because they can follow dental implant surgery as with any other surgical procedure. Many of the complications can be resolved without severe problems; however, in some cases, they can cause dental implant failure or even life-threatening circumstances. Avoiding complications begins with careful treatment planning based on accurate preoperative anatomic evaluations and an understanding of all potential problems. This chapter contains surgical complications associated with dental implant surgery and management.

2. Complications associated with implant surgery

2.1 Hemorrhage

The submental artery (2mm in average diameter) (Greenstein et al., 2008 as cited in Hofschneider et al., 1999) is a branch of the facial artery. The sublingual artery (2 mm in average diameter) arises from the lingual artery and is found coronal to the mylohyoid muscle (Greenstein et al., 2008 as cited in Martin et al., 1993). The arterial blood supply of the floor of the mouth is formed by an anastomosis of the sublingual and submental arteries. In the canine area, the vessels are located closer to the lingual plate and alveolar crest than they are in more posterior areas (Dubois et al., 2010). Intraosseous hemorrhage is not a serious event, and control of the hemorrhage can be ensured by compressing the area with a directional indicator, an abutment, or the implant (Annibali et al., 2009). However, severe bleeding and the formation of massive hematomas in the floor of the mouth are the result of an arterial trauma. A vascular wound may occur after detrimental surgical manipulations or tearing of the lingual periosteum, but in most cases, it is attributed to perforations of the lingual cortical plate. Mechanical pressure exerted by the expanding hematomas displaces the tongue and floor of the mouth both superiorly and posteriorly (Kalpidis & Setayesh, 2004). This occurrence may lead to extensive bleeding into the submandibular space, resulting in a life-threatening acute airway obstruction within the first few hours after surgery (Goodacre et al., 1999). The hemorrhage can easily spread in the loose tissues of the floor of the mouth (Fig. 1.), the sublingual area, and the space between the lingual muscles, which may require intubation or an emergency tracheostomy (Dubois et al., 2010). The surgeons also should consider other sources of potential hemorrhage and subsequent hematoma formation, including injuries to muscles or other soft tissues (Isaacson, 2004) (Fig.

2.). The escalating symptomatology of massive bleeding and progressive respiratory distress strongly resemble the clinical development of Ludwig's angina. Most important is the immediate bimanual compression at the suspected site of perforation and transport of the patient to the nearest hospital to secure the airway without delay (Dubois et al., 2010).

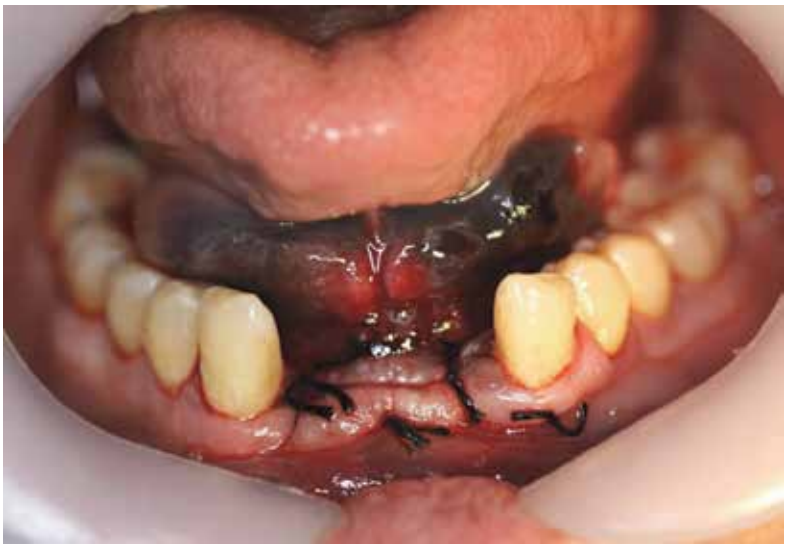

Fig. 1. A severe hematoma on the anterior floor of the mouth after implant placement in the anterior mandible.

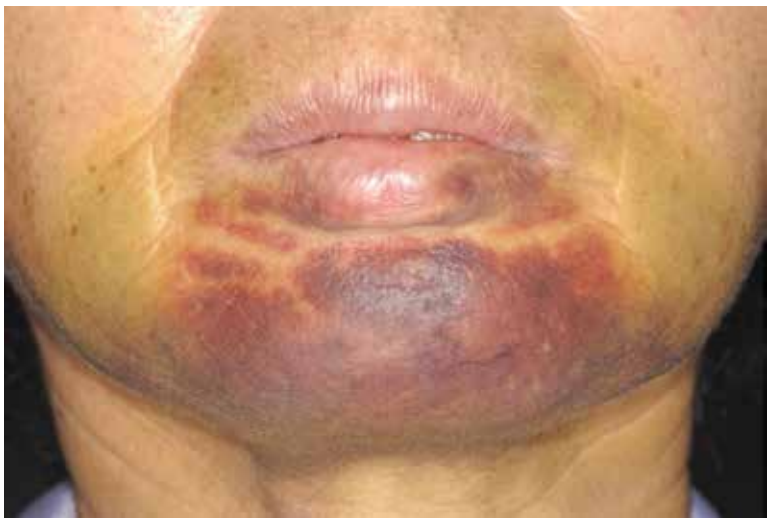

Fig. 2. Ecchymosis on the chin after implant placement in the anterior mandible.

Once the airway is controlled, efforts are undertaken for the definitive resolution of the hemorrhage (Kalpidis & Setayesh, 2004 as cited in Givol, 2000). Hemorrhages can be controlled by gauze tamponage, application of hemostatic agents, cauterization, or digital compression. If a hemorrhage cannot be controlled by these methods, ligation of the

bleeding vessel should be performed. An endovascular angiography is an alternative diagnostic tool that can overcome unsuccessful attempts to define and isolate the bleeding source (Fig. 3.) (Kalpidis & Setayesh, 2004). Incisions in the mucosa to relieve the hematoma should be avoided because they may promote further bleeding. The removal of an already inserted implant would also be ineffective (Fig. 4.) (Kalpidis & Setayesh, 2004) (Table 1).

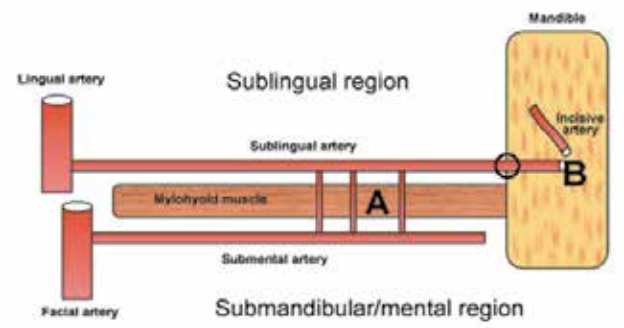

Fig. 3. A schematic representation of the arterial anatomy in the floor of the mouth (Kalpidis & Setayesh, 2004).

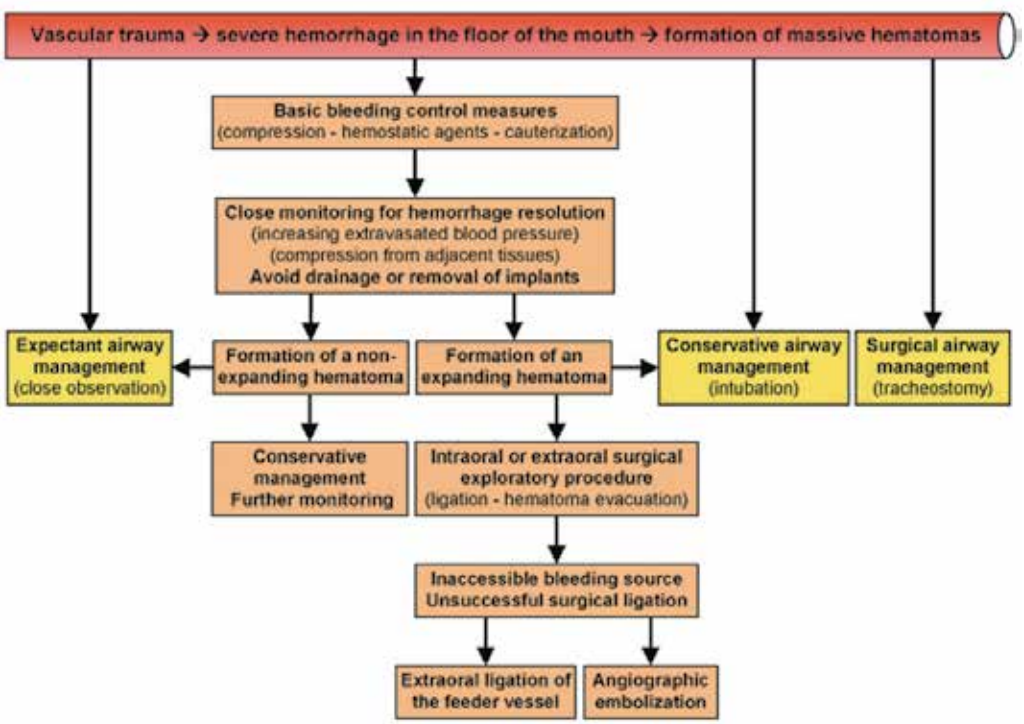

Fig. 4. A flow diagram of airway management and control of massive hemorrhage in the floor of mouth associated with implant placement in the anterior mandibular region (Kalpidis & Setayesh, 2004).

Bleeding site during implant osteotomy	Arteries	Treatments
Posterior mandible	Mylohyoid	Finger pressure at the site
Middle lingual of mandible	Submental	Surgical ligation of facial and lingual arteries
Anterior lingual of mandible	Terminal branch of sublingual or submental	Compression, vasoconstriction, cauterization, or ligation
Invading the mandibular canal	Inferior alveolar artery	Bone graft

Table 1. Treatment of a hemorrhage at an implant osteotomy site (Park & Wang, 2005)

To prevent unintentional hemorrhages in cases involving the immediate placement of implants or recent tooth extractions, the practitioner should be careful not to use the extraction socket as a guide for angulation because this may lead to the perforation of the lingual cortex (Isaacson, 2004 as cited in Givol, 2000). Soft-tissue management during the procedure is essential, and clinicians should make every attempt to avoid subperiosteal tears (Isaacson, 2004).

2.2 Neurosensory disturbances

The inferior alveolar nerve is midway between the buccal and lingual cortical plates in the first molar region (Tammisalo et al., 1992). In about 1% of patients, however, the mandibular canal bifurcates in the inferior superior or medial lateral planes. Thus, a bifurcated mandibular canal will manifest more than one mental foramen. This may or may not be seen on panoramic or periapical films. Accordingly, Dario suggested that clinicians should consider obtaining a preoperative tomogram to avoid nerve injuries prior to implant placement above the inferior alveolar canal (Greenstein & Tarnow, 2006 as cited in Dario, 2002).

A mean incidence of neurosensory disturbance incidence after implant surgery was 6.1% (Goodacre et al., 1999) to 7% (Goodacre et al., 2003), with a range between 0.6% and 39%. Nerve damage can have results ranging from mild paresthesia to complete anesthesia or even disabling dysesthesia (Table 2).

Neurapraxia	There is no loss of continuity of the nerve; it has been stretched or has undergone blunt trauma. The parasthesia will subside, and feeling will return in days to weeks.
Axonotmesis	Nerve is damaged but not severed; feeling returns within 2 to 6 months.
Neurotmesis	Severed nerve; poor prognosis for resolution of parasthesia.

Table 2. Classification of nerve injuries (Greenstein & Tarnow, 2006 as cited in Jalbout & Tabourian, 2004)

Possible causes of nerve injury include poor flap design, traumatic flap reflection, accidental intraneural injection, traction on the mental nerve in an elevated flap, penetration of the osteotomy preparation and compression of the implant body into the canal (Fig. 5.)(Misch & Wang, 2008). Nerve injuries may be caused indirectly by postsurgical intra-alveolar edema or hematomas that produce a temporary pressure increase, especially inside the mandibular canal. Direct traumas are the most frequent causes of nerve injury, and they may occur through five mechanisms: compression, stretch, cut, overheating, and accidental puncture

(Annibali et al., 2009). Finally, prolonged pressure from neuritis may lead to the permanent degeneration of the affected nerve (Park & Wang, 2005).

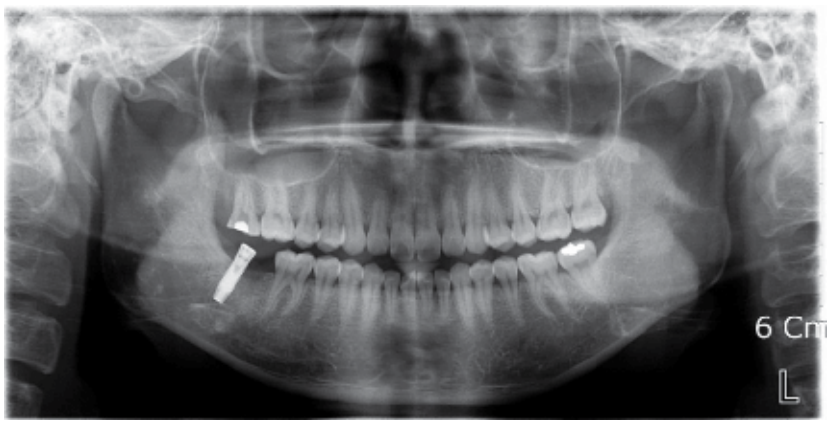

Fig. 5. An inferior alveolar nerve injury after implant placement of #47.

The mental nerve is at particular risk of iatrogenic injury because it arises from asymmetric foramina and forms a concave loop anteriorly. In edentulous patients, it may be very close to the bone surface or the top of the crest.

The nerve injury may cause one of the following conditions: parasthesia (numb feeling), hypoesthesia (reduced feeling), hyperesthesia (increased sensitivity), dysthesia (painful sensation), or anesthesia (complete loss of feeling) of the teeth, the lower lip, or the surrounding skin and mucosa (Greenstein & Tarnow, 2006 as cited in Sharawy & Misch, 1999).

Overpenetration occurs when the cortical portion of the alveolar crest places resistance on the drill. However, as it enters the marrow spaces, a drill may drop into the neurovascular bundle unless the surgeon has excellent control (Misch & Wang, 2008).

For implants placed in the atrophic posterior mandible, the routine use of intraoperative periapical radiographs during the drilling sequence can help avoid the risk of injury to the inferior alveolar nerve. Periapical radiographs used intraoperatively to obtain working length measurements are similar in concept to techniques used in root canal therapy. This method can reliably determine safe distances between the implant and the inferior alveolar canal, thus avoiding the risk of injury to the nerve altogether (Burstein et al., 2008).

The appropriate magnification correction factor should be used, and drill guards can be placed on burs to avoid the unintentional overpenetration of the drill. A safety margin of 2 mm between the entire implant body and any nerve canal should be maintained (Greenstein et al., 2008, as cited in Greenstein & Tarnow, 2006; Worthington, 2004). Additionally, surgical placements of implants should be at least 3 mm in front of the mental foramen (Greenstein & Tarnow, 2006). When placing implants in proximity to the mental foramen, the clinician must take into consideration the anterior loop of the nerve and the available bone above the mental foramen, because the inferior alveolar nerve often rises as it approaches the mental foramen (Kraut & Chahal, 2002). Finally, although the depths of the implant bur are variable, the drill bur may be longer than the implant according to the manufacturers (Table 3).

Be sure to include nerve injury as an item in the informed consent document. Measure the radiograph with care. Apply the correct magnification factor. Consider the bony crestal anatomy: If the ridge is thin buccolingually, is this useless bone or should an augmentation procedure be done? Is the buccolingual position of the crestal peak of bone influencing the measurement of available bone? Consider the buccolingual position of the nerve canal.	Use coronal true-size tomograms where needed. Allow a 1 to 2 mm safety zone. Use a drill guard. Take care with countersinking not to lose support of the crestal cortical bone. Use the aforementioned formula to calculate implant length. Keep the radiograph and the calculation in the patient's chart as powerful evidence of meticulous patient care.

Table 3. Recommendations to avoid nerve injuries during implant placement (Worthington, 2004)

The mental foramen may be located at or near the crest of an atrophic mandible. To avoid damage to the mental nerve in patients with atrophic mandibles, the clinician may need to make incisions in the area of the mental foramen that are lingual to the crest of the mandible (Kraut & Chahal, 2002).

If an implant is in danger of violating the canal, its depth should be decreased in the bone (i.e., by unscrewing it a few turns) and left short of the canal or removed. Because the altered sensation may be due to an inflammatory reaction, a course of steroid treatment or a high dose of nonsteroidal anti-inflammatory medication (e.g., ibuprofen [800 milligrams] three times per day) should be prescribed for three weeks (Kraut & Chahal, 2002). Adjunct drugs such as clonazepam, carbamazepine, or vitamin B-complex might alleviate neuritis via their known neuronal anti-inflammatory actions.

If improvement is noted at three weeks on the basis of a repeated neurosensory examination, the clinician can prescribe an additional three weeks of anti-inflammatory drug treatment. If the improvement is seen, however, the patient should be referred to a microneurosurgeon (Kraut & Chahal, 2002).

The patient should be referred for microsurgery if total anesthesia persists, or if after 16 weeks, dysesthesia is ongoing (Misch & Wang, 2008, as cited in Day, 1994; Nazarian et al., 2003).

Many studies have reported favorable patient responses to inferior alveolar nerve repairs. All have emphasized the need for repair before Wallerian degeneration of the distal portion of the inferior alveolar nerve has occurred; because this degeneration is a slow process, repair is possible four to six months after the injury has occurred (Kraut & Chahal, 2002).

2.3 Injury to adjacent teeth

Damage to teeth adjacent to the implant site may occur subsequent to the insertion of implants along an improper axis or after placement of excessively large implants (Figs. 6, 7.). This problem arises more frequently with single implants (Annibali et al., 2009). Adjacent teeth should be evaluated before implant placement. Pulpal and periradicular conditions such as small periapical radiolucencies, root resorption and large restorations in/near the vital pulp are often misdiagnosed. Dilacerated roots and excessive tilting in the mesiodistal direction that invades the implant space often prevent ideal placement (Misch & Wang, 2008). The tilt of adjacent teeth should be assessed before drilling. The damage of an

adjacent tooth by implant placement may cause the tooth to become non-vital, and the tooth may require subsequent endodontic treatment. This will not only result in damage to an adjacent tooth but also implant failure (Sussman, 1998). Use of a surgical guide, radiographic analysis and CT scan can help locate the implant placement, thereby avoiding damage to adjacent teeth. The angulation of adjacent teeth and dilacerations of roots must be radiographically assessed prior to implant placement. Ideally, 1.5 to 2 mm of bone should be present between an implant and the adjacent tooth. Furthermore, inspection of a radiograph with a guide pin at a depth of 5 mm will facilitate osteotomy angulation corrections (Greenstein et al., 2008). To prevent a latent infection of the implant from the potential endodontic lesion, endodontic treatment should be performed (Sussman, 1998). Discrepancies between the apical and crestal interdental spaces as a result of mesial or distal tipping of the roots can be corrected orthodontically (Annibali et al., 2009).

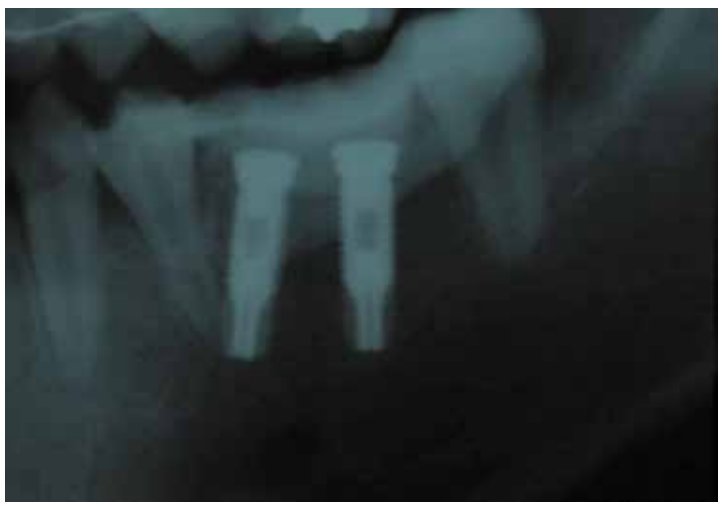

Fig. 6. Injury of an adjacent tooth by a malpositioned implant.

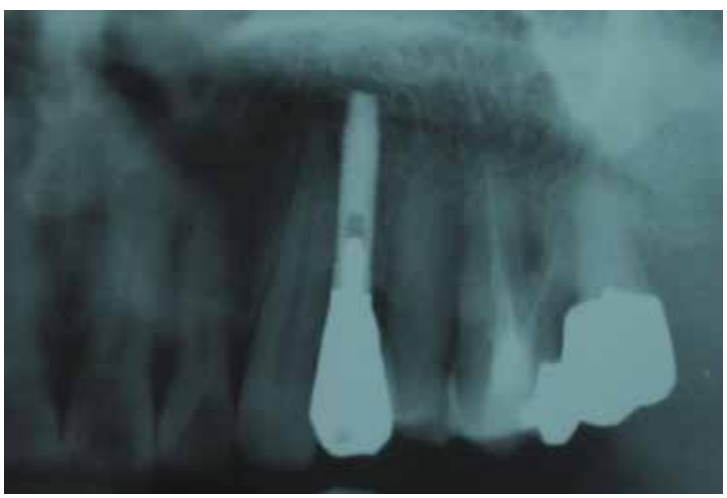

Fig. 7. A malpositioned implant hitting an adjacent tooth.

2.4 Flap dehiscence and exposure of graft material or barrier membrane

The most common postoperative complication is wound dehiscence, which sometimes occurs during the first 10 days (Greenstein et al., 2008). Contributing factors of dehiscence and exposure of the graft material or barrier membrane include flap tension, continuous mechanical trauma or irritation associated with the loosening of the cover screw, incorrect incisions and formation of sequestration of bone debris (Park & Wang, 2005). Premature exposure of barrier membranes may also cause contamination of the graft and its eventual loss (Figs. 8, 9.).

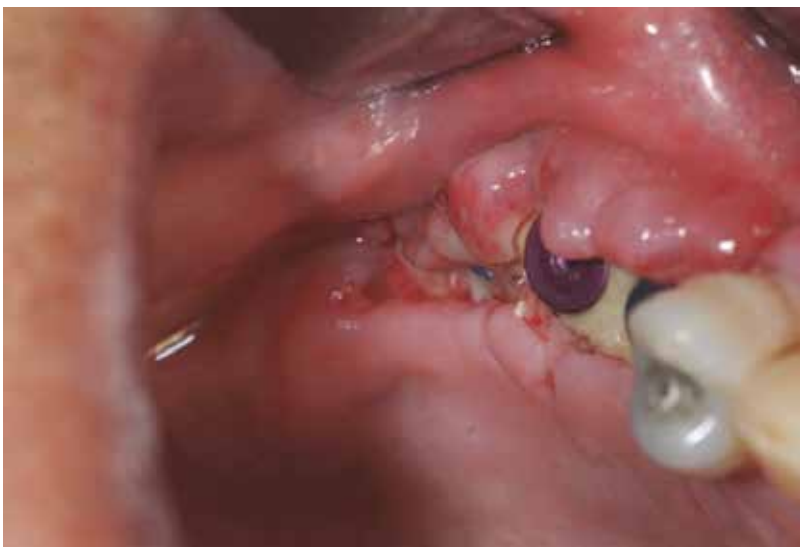

Fig. 8. A dehiscence after guided bone regeneration and implant placement using a non-resorbable membrane.

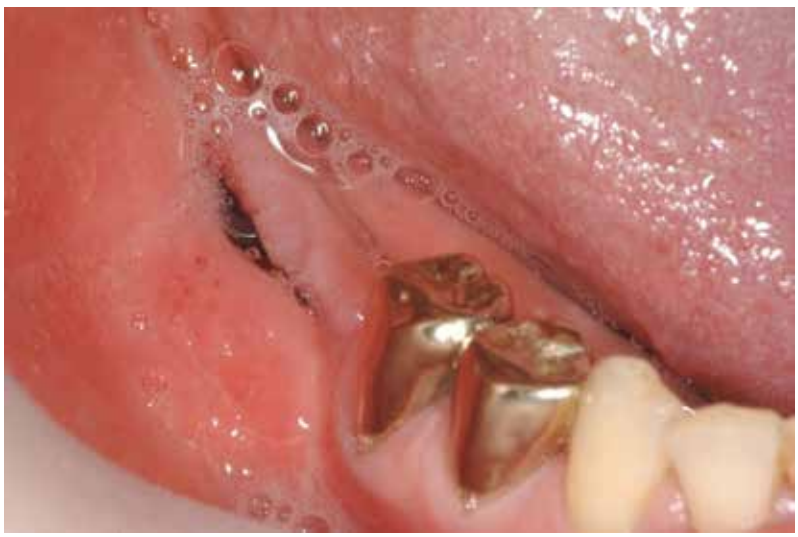

Fig. 9. A dehiscence after implant placement.

To avoid wound dehiscence, tension-free closure using a buccal releasing incision is most important. Dentures should be relieved with a tissue conditioner. Mattress sutures combined with interrupted sutures are also useful. When the dehiscence is small and occurs within 24 to 48 hours, the clinician can immediately resuture the dehiscence. Once the diameter of the wound is large (2 to 3 cm) or the time elapsed is > 2 days, it is suggested that the margins of the wound be excised and resutured (Fig. 10.) (Greenstein et al., 2008 as cited in Sadig & Almas, 2004). If the suture is not possible, chlorhexidine rinses twice a day and/or systemic antibiotics should be considered.

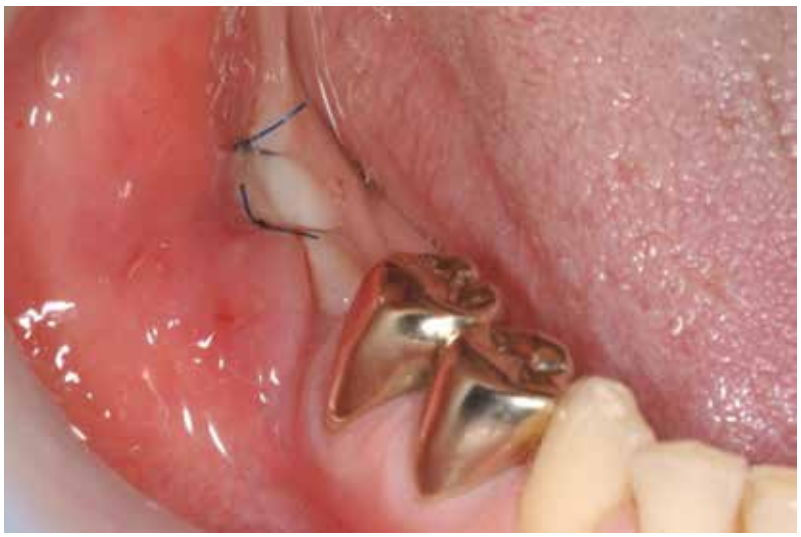

Fig. 10. Resuturing was performed to achieve closure of the dehiscence.

2.5 Bisphosphonate-related osteonecrosis

Bisphosphonates are drugs that inhibit bone resorption; they are widely used for the treatment of osteoporosis, multiple myeloma and skeletal complications of bone metastases (Table 4). The American Association of Oral and Maxillofacial Surgeons (AAOMS) states that patients are considered to have bisphosphonate-related osteonecrosis of the jaw (BRONJ) if they have the following three characteristics: current or previous treatment with a bisphosphonate, exposed or necrotic bone in the maxillofacial regin that has persisted for more than 8 weeks, and no history of localized radiotherapy to the jaws (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, 2007). The risk of BRONJ associated with oral bisphosphonates appears to increase when the duration of therapy more than 3 years. This time may be shortened in the presence of certain comorbidities. Type 2 diabetes mellitus (Abu-Id et al., 2008), prolonged steroid therapy (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, 2007), and health-threatening habits such as smoking (Wessel et al., 2008; Yarom et al., 2007) were suggested as predisposing conditions for the development of BRONJ.

If systemic conditions permit, discontinuation of oral bisphosphonates for a period of 3 months prior to and 3 months after elective invasive dental surgery may lower the risk of BRONJ. The risk reduction may vary depending on the duration of bisphosphonate exposure (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, 2007).

Active ingredient	Trade name	Administered
Alendronate	Fosamax®,Fosavance®	Orally
Etidronate	Osteum®, Difosfen®	Orally
Resedronate	Actonel®, Acrel®	Orally
Tiludronate	Skelid®	Orally
Zoledronate	Zometa®, Aclasta®	Intravenously
Pamidronate	Aredia®, Linoten®, Pamifos®, Xinsidona®	Intravenously
Ibandronate	Bondronat®	Orally, Intravenously
Clodronate	Bonefos®	Orally, Intravenously

Table 4. Different types of bisphosphonates in current usage (Montoya-Carralero et al., 2010)

Currently, there are no reliable or widely available tests for the risk of BRONJ. Marx et al. recommend a blood test, specifically involving a serum C-terminal telopeptide test (CTX) to assess a surrogate marker of bone turnover in patients taking oral bisphosphonates. Categorization of <100 pg/mL as high risk, 100 pg/mL to 150 pg/mL as moderate risk, and >150 pg/mL as minimal risk provides the clinician (Marx et al., 2007).

Many articles have confirmed that implant surgery in patients receiving oral bisphosphonate therapy does not result in BRONJ. (Bell &Bell, 2008; Fugazzotto et al., 2007; Grant et al.,2008; Jeffcoat, 2006) Nevertheless, patients taking bisphosphonates who either had implants that failed to integrate or had integrated implants that subsequently failed have been reported (Goss & Backhous, 2007; Stark & Epker, 1995; Wang et al., 2007).

The prognosis of dental implants that have been placed remains uncertain, and the use of osseointegrated dental implants is controversial.

AAOMS does not contraindicate dental implant placement in patients who have been taking bisphosphonates orally for less than three years prior to surgery, provided that they do not present other risk factors such as medications with corticosteroids or advanced age (e.g., older than seventy years). It has been reported that oral bisphosphonates had a lower risk because they took longer to develop bisphosphonate-induced osteonecrosis given their slower accumulation rates in bone (Ruggiero et al., 2004). Moreover, a drug holiday is recommended 3 to 6 months in duration before dental implant placement in patients with a history of oral bisphosphonate use for longer than 3 years (Ruggiero et al., 2009). Finally, current guidelines contraindicate the placement of dental implants in cancer patients treated with intravenous bisphosphonates (Ruggiero et al., 2009; Khan et al., 2008).

Although bisphosphonates tend to accumulate in sites of active bone remodeling like the jaws, surgical trauma to the alveolar bone during implant surgery could further stimulate the postoperative accumulation of the drug in the implanted site. The localized interference of bisphosphonates on areas of bone turnover may reduce the peri-implant bone resistance to oral bacteria in the long term, thus increasing the risk of peri-implantitis. The potential role of infection on implant failure and BRONJ occurrence is still debated. However, at least one study has reported a reduced incidence of BRONJ in patients who were given prophylactic antibiotics (Montefusco et al., 2008). In addition, the use of perioperative antibiotics and a chlorhexidene mouth wash have been suggested. Great attention should be paid to the oral hygiene and plaque control of implant-prosthetic restorations (Bedogni et al., 2010). Patients treated with bisphosphonates who receive implants should be followed for long periods of time. All patients treated with

oral bisphosphonates must be informed of the potential complications of implant failure and BRONJ development in both the short and long term before the placement of dental implants (Bedogni et al., 2010).
AAOMS has proposed the use of the following staging categories and treatment guidelines regarding BRONJ (Table 5).

BRONJ Staging	Treatment Strategies
At risk category: No apparent exposed/ necrotic bone in patients who have been treated with either oral or IV bisphosphonates	No treatment indicated Patient education
Stage 1: Exposed/necrotic bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse Clinical follow-up on a quarterly basis Patient education and review of indications for continued bisphosphonate therapy
Stage 2: Exposed/necrotic bone associated with infection as evidenced by pain and erythema in the region of the exposed bone with or without purulent drainage	Symptomatic treatment with broad-spectrum oral antibiotics, e.g., penicillin, cephalexin, clindamycin, or first generation fluoroquinolone Oral antibacterial mouth rinse Pain control Only superficial debridements to relieve soft tissue irritation
Stage 3: Exposed/necrotic bone in patients with pain, infection, and one or more of the following: pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border	Antibacterial mouth rinse Antibiotic therapy and pain control Surgical debridement/resection for longer term palliation of infection and pain

Table 5. Staging and treatment strategies (Advisory Task Force on Bisphosphonate-Related Ostenonecrosis of the Jaws, 2007)

3. Complications associated with maxillary sinus lift

3.1 Schneiderian membrane perforation

The Schneiderian membrane, which is characterized by periosteum overlaid with a thin layer of pseudociliated stratified respiratory epithelium, constitutes an important barrier for the protection and defense of the sinus cavity. The integrity of the sinus membrane is essential in maintaining the healthy and normal function of the maxillary sinus (Ardekian et al., 2006).
The mucociliary apparatus protects the sinus against infection while the membrane also acts as a biologic barrier. If a perforation occurs, the membrane perforation could represent a window for bacterial penetration and invasion into the grafted area (Zijderveld et al., 2008). Failure to atraumatically elevate the Schneiderian membrane may result in graft migration or loss, exposure of the graft or the implant to the sinus, and postoperative site infection. In addition to contaminating the recipient site, disruption of the mucosa may alter the normal

mucociliary flow patterns, causing retention of secretions and infections around the foreign body (Ward et al., 2008).

The most common intraoperative complication seems to be Schneiderian membrane perforation, which occurs in 10% to 60% of all procedures (Ardekian et al., 2006; Pikos, 1999; Proussaefs et al., 2004). The risk of membrane perforation increases when anatomical variations such as a maxillary sinus septum, spine, or sharp edge are present (Chanavaz, 1990; van den Bergh et al., 2000). Very thin or thick maxillary sinus walls create higher risks of perforating the Schneiderian membrane. The angulation between the medial and lateral walls of the maxillary sinus seemed to exert an especially large influence on the incidence of membrane perforation. For example, sharper angles observed at the inner walls of the sinus in the vicinity of the second upper bicuspid presents a higher risk of perforation (Zijderveld et al., 2008).

The occurrence of iatrogenic sinus membrane perforations during surgery does not seem to be related to sinusitis in healthy people (Ardekian et al., 2006). However, large tears can cause sinusitis, graft infection, or graft displacement into the sinus, which could compromise new bone formation and implant survival (Reiser et al., 2001).

To minimize Schneiderian membrane perforations, surgeons must evaluate the maxillary sinus anatomy while considering the lateral thickness of the lateral wall, slope of the sinus wall, location of septa, membrane thickness through the radiography and CT analysis before maxillary sinus augmentation. Piezoelectric surgery is usually more time-consuming than other techniques, though the frequency and number of Schneiderian membrane perforations or lacerations are generally lower. If the bony lateral wall is thick, a reduction of the thickness of the wall before formation of the lateral window is recommended. In cases involving a very thin maxillary sinus wall, careful reflection of the mucoperiosteum is recommended while the Schneiderian membrane already shines a dark grayish-bluish color through the sinus wall. It is advised that clinicians not begin the lateral door preparation with a round stainless-steel burr; they should use a round diamond bur directly, thereby reducing the risk of a membrane perforation (Zijderveld et al., 2008). To prevent a perforation, some additional small holes in the suction device are recommended to diminish the suction power and to avoid the direct contact of the suction device with the Schneiderian membrane (Zijderveld et al., 2008).

If a tear in the membrane occurs along the periphery of the osteotomy and it is difficult to reengage the membrane, this situation can be managed by extending the outline of the osteotomy several millimeters past the original window and reestablishing contact with the membrane (Greenstein et al., 2008). In general, small tears (<5 to 8 mm) are mitigated simply by folding the membrane up against itself as the membrane is elevated (Chanavaz, 1990). Larger tears do not lend themselves to closure by infolding, and they would need additional methods to contain the graft in its desired position. It has been reported that large sinus membrane perforations should be repaired with collagen or a fibrin adhesive. In severe perforations, some investigators have even suggested abandoning the procedure for 6 to 9 months while the membrane regenerates (Karabuda et al., 2006).

3.2 Hemorrhage

The blood supply of the maxillary sinus is derived from the infraorbital artery, the greater palatine artery and the posterior superior alveolar artery (Chanavaz, 1990; Uchida et al., 1998a). Bleeding during sinus augmentation is rare because the main arteries are not within

the surgical area. Although accidental laceration of the vessel is not life-threatening because of the small size of the artery, an impaired visualisation may compromise the elevation of the Schneiderian membrane and interfere with the placement of the graft material (Elian et al., 2005; Testori et al., 2010).

The blood supply to the buccal antral portions relevant to sinus floor elevation surgery occurs via two arteries: the posterior superior alveolar artery and the infraorbital artery, as well as their intraosseous branches and anastomoses (Solar et al., 1999). Anatomically, anastamosis between the posterior superior alveolar artery and infraorbital artery is always found at the lateral antral wall (Traxler et al, 1999); bleeding via damage to these arteries may occur during the formation of the lateral window. The average distance from the artery to the alveolar crest was 16.4 mm (Elian N et al., 2005) to 18.9 mm (± 2.82 mm) (Solar et al., 1999).

The height of the residual bony ridge appears to play a significant role in the location of the vessel. In classes A, B and C (Lekholm & Zarb classification (Lekholm & Zarb, 1985)), the vessel was found >15 mm from the alveolar crest, but in classes D and E, the value was >7 mm (mean 10.4 mm). It is recommended, therefore, to place the superior border of the osteotomy up to 15 mm from the alveolar crest in classes A, B and C, which is sufficient for sinus exposure and placement of long dental implants. In severely atrophic ridges, or classes D and E, where the surgeon has a tendency to place the osteotomy of the sinus wall too far cranially, there is a high probability of transecting the vessel (Mardinger et al., 2007b). Such bleeding can usually be controlled by pressure with a moist gauze pad (Fig. 11.)(Elian et al., 2005).

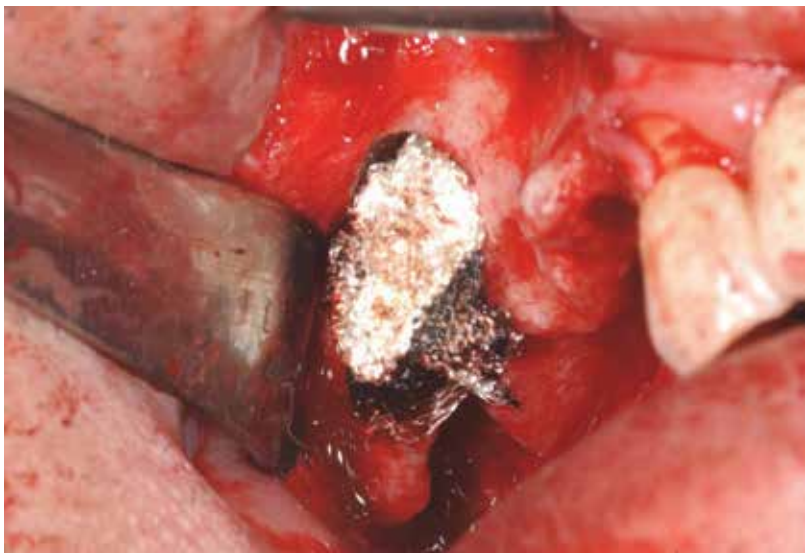

Fig. 11. Hemostasis was achieved using Surgicel during maxillary sinus augmentation.

A preoperative CT examination is essential to detect the location of the intraosseous anastomoses. In addition, piezoelectric surgical inserts may be beneficial in minimizing lacerations of vessels and membrane (Testori et al., 2010). A vestibular extraosseous anastomosis runs below the zygomatic process (Solar et al., 1999). This anastaomosis is located in the area of the periosteum overlying the lateral wall at a higher level than the intraosseous anastamosis. The vascular compromise would be the result of an inappropriate

anterior releasing incision or vertical incision (Elian et al., 2005). To avoid damage to the extraosseous anastomosis, vertical mucosal incisions should extend superiorly as little as possible, and the periosteum should be prepared carefully (Solar et al., 1999).

3.3 Loss of the implant or graft materials into the maxillary sinus

The displacement of implants or graft materials into the maxillary sinus can result in a foreign-body reaction and cause serious complications. Migration of a dental implant into the maxillary sinus may present a risk for the development of maxillary sinusitis. Immediate implant insertion should be performed only if the residual bone is stable and high enough to ascertain high primary stability (Becker et al., 2008).

An implant can easily migrate into the sinus without apparent force in the posterior maxilla, clearly showing a lack of osseointegration (Fig. 12.). Various mechanisms have been proposed to explain the migration of an implant into the maxillary sinus, which fall under three main categories: changes in intrasinal and nasal pressures; autoimmune reaction to the implant, causing peri-implant bone destruction and compromising osseointegration; and resorption produced by an incorrect distribution of occlusal forces (Galindo et al., 2005). The changes in intrasinal and nasal air pressures produce a suction effect because of the negative pressure exerted by these cavities. A portion of the bone grafting material can become dislodged in the maxillary sinus at either the initial ridge augmentation or during the implant placement surgery. The natural ciliary movement in the maxillary sinus will transport foreign material toward the ostium (Hunter et al., 2009). In cases with less than 5 mm of bone, mastication can cause the implants to move during the graft maturation timeframe (Peleg et al., 2006). The implants must be immediately retrieved surgically via an intraoral approach or endoscopically via the transnasal route to avoid inflammatory complications (Ueda & Kaneda, 1992). To avoid complications when bone volume is inadequate to support an implant with sufficient length, a bone reconstruction procedure of the maxilla should be performed.

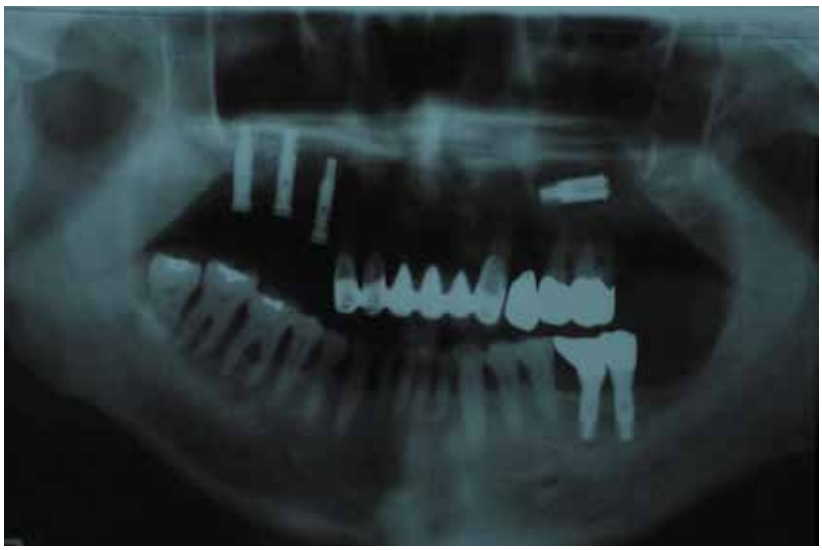

Fig. 12. Displacement of an implant into the maxillary sinus.

3.4 Postoperative maxillary sinusitis

The mean height of the maxillary sinus is 36 to 45 mm, the mean width mesiodistally is 25 to 35 mm, and the mean depth is 38 to 45 mm (laterally–medially). The average total maxillary sinus volume is 13.6±6.4 cc. The minimum maxillary sinus volume is 3.5 cc, while the maximum is 31.8 cc (Uchida, 1998b). The ostium is located on the superior aspect of the medial wall of the maxillary sinus above the first molar (van den Bergh et al., 2000). The normal drainage pattern of the maxillary sinus is into the middle nasal meatus by way of a naturally occurring ostium.

The ostium is usually 35 mm superior to the floor of the maxillary sinus (Zinner et al., 2008). This information can be used to prevent maxillary sinus complications such as sinusitis by the obstruction of the ostium. Radiographic imaging of the osteo-meatal complex is crucial in fully evaluating the physiologic health of the maxillary sinus and the likelihood of avoiding infections following maxillary bone grafting (Zinner et al., 2008).

Maxillary sinusitis can occur as a result of contamination of the maxillary sinus with oral or nasal pathogens or via ostial obstruction caused by postoperative swelling of the maxillary mucosa, hematoma and seroma. Mucosal swelling may lead to the reduction of the patency of the ostio-meatal unit (Figs. 13, 14.). This unit plays a key role in the development of sinusitis, through impairment of the mucociliar cleansing system (Bertrand & Eloy, 1992). Maxillary sinusitis can also occur because of non-vital bony fragments floating freely in the maxillary sinus. Another cause is the lack of asepsis during sinus augmentation (Timmenga et al., 2001). Maintenance of normal maxillary sinus physiology should be a major goal while ostium patency must be preserved. Therefore, the use of a systemic decongestant, such as pseudoephedrine, and a nasal spray containing a vasoconstrictor, such as phenylephrine, is recommended after implant surgery (Regev et al., 1995).

The development of sinusitis following sinus augmentation can be directly related to drainage disturbances, mainly as a result of septal deviation and allergies combined with oversized inferior and middle turbinates (Mardinger, 2007a). In the event of an inadvertent laceration or puncture of the Schneiderian membrane and inoculation of the maxillary sinus

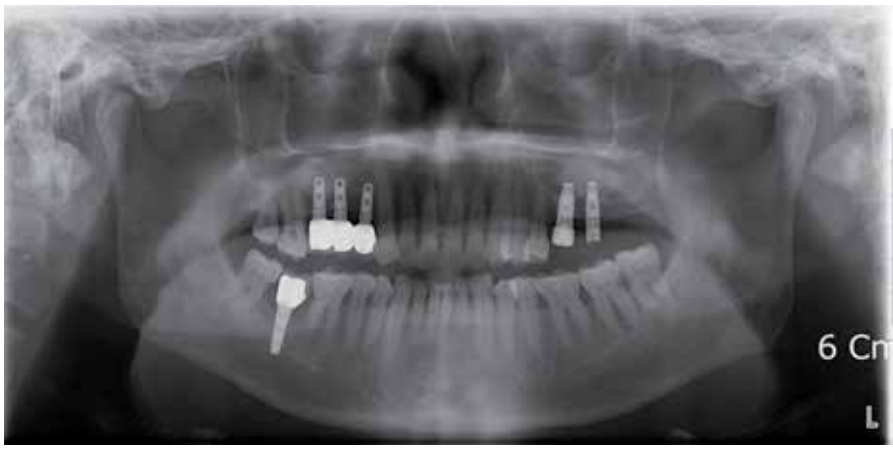

Fig. 13. Panoramic view showing an area of opacification on the left maxillary sinus.

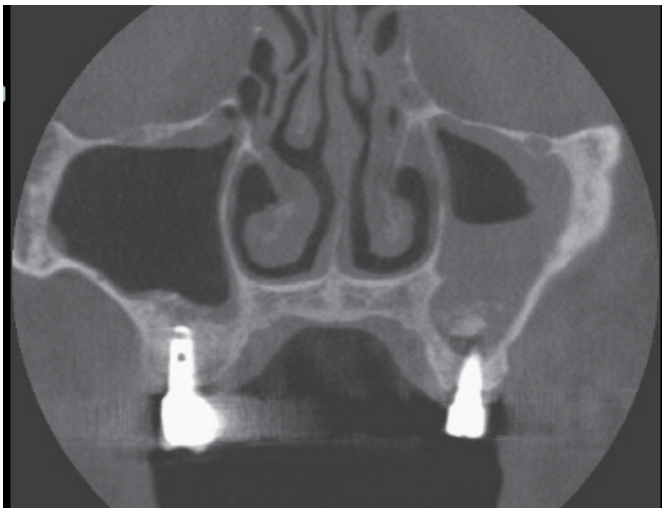

Fig. 14. Computed tomography scan clearly shows significant mucosal thickening along the entire lining of the sinus.

with oral bacteria, a healthy sinus with a patent osteo-meatal complex will usually remove the offending bacteria and remain healthy (Zinner et al., 2008). With no patent drainage pathway, the maxillary sinus quickly became obstructed, inflamed, and then infected (Hunter et al., 2009).

Timmenga et al. reported that the occurrence of postoperative sinusitis after bone grafting of the sinus floor is limited to patients with a predisposition for sinusitis (Timmenga et al., 1997). To minimize the occurrence of a postoperative infection, possible causes should be removed prior to sinus augmentation.

A history of excessive yellow or green nasal discharge, particularly with worsening nasal obstruction, is a relatively strong predictor of possible chronic bacterial sinusitis and may warrant further assessment for chronic sinusitis (Ward et al., 2008). A nasoendoscopic evaluation should be considered for patients with a history of frequent sinusitis to rule out the presence of an obstructive phenomenon as a risk factor before undergoing sinus augmentation (Manor et al., 2010).

Most implant failures occur 3 to 6 months after surgery, and they are usually not associated with an infection of the maxillary sinus (Becker et al., 2008). The clinical diagnosis of sinusitis is characterized by a triad of symptoms: nasal congestion, secretion or obstruction, and headache (Manor et al., 2010). If an infection develops (e.g., pain, redness, and tenderness) without fluctuance, antibiotics are administered. Once there is fluctuance, incision and drainage are performed in conjunction with systemic antibiotics (Barone et al., 2006; Regev et al., 1995).

Pathogens found have included *β-hemolytic* S*trepococcus*, *Enterococcus*, *Peptostreptococcus*, *Pneumococcus*, *Staphylococcus* (Doud Galli et al., 2001) and *Actinomycosis* (Roth & Montone, 1996). The antibiotics most effective in alleviating sinus infections are amoxicillin, trimethoprim sulfamethoxazole, and cefaclor. Amoxicillin with clavulanic acid and clindamycin also are commonly used (Regev et al., 1995). General guidelines for treatment of sinusitis was represented in Tables 6, 7.

Transient sinusitis	Chronic sinusitis
1. Use of decongestants and antibiotics 2. Follow-up after 2 weeks 3. If no recovery, transient sinusitis has possibly evolved into subacute sinusitis needing further treatment: a. Continuation of decongestants and antibiotics b. Maxillary drains for sinus irrigation c. CT scanning and consideration of functional endoscopic sinus surgery if no recovery within 3 weeks	1. Use of decongestants and antibiotics 2. CT scanning and functional endoscopic sinus surgery

Table 6. General guidelines for the treatment of transient and chronic maxillary sinusitis after maxillary sinus augmentation (Timmenga et al., 2001)

1. Preoperative evaluation of sinus clearance-related factors 2. Postsurgery: a nasal decongestant (xylomethazoline 0.05%) and topical corticosteroid (dexamethasone 0.01%) to prevent postsurgery obstruction of the ostium 3. Perioperative antibiotic prophylaxis (cephradine 1 g 3 times daily, starting 1 hour before surgery and continued for 48 hours after surgery)

Table 7. General guidelines for the prevention of transient and chronic maxillary sinusitis after maxillary sinus augmentation (Timmenga et al., 2001)

4. Conclusions

Although serious complications are uncommon, dental implant placement is not free of complications, as complications may occur at any stage (Table 8). Therefore, careful analysis via imaging, precise surgical techniques and an understanding of the anatomy of the surgical area are essential in preventing complications. One should be aware of the possible complications related to implant placement so that the patient can be properly informed. Prompt recognition of a developing problem and proper management are needed to minimize postoperative complications.

Problems	Possible causes	Solutions
Nerve injury	Mechanical injury by stretching, compression, and partial or total trans-section	Remove implant Wait for a period Rivotril®, Tegretol®, Vitamin B6
Hemorrhage during drilling	Injury of an artery	Extraoral pressure from the submental against the body of mandible Implant placement will stop bleeding

Fracture of mandible	Atrophic mandible	Immediate implant retrieval Bone graft Monocortical miniplates
Penetration of nasal/sinus floor	Type IV bone	Primary closure Antibiotic, decongestant, chlorhexidine
Lack of primary stability	Type IV bone, grafted bone, imprecise preparation, excessive countersinking	Remove implant, replace with larger diameter or longer implant
Maxillary sinus lift	Preexisting condition, surgical handling	Seal by folding the excess membrane, collagen membrane, bone graft, primary closure Antibiotics, decongestant, chlorhexidine
Significant bleeding	Subclinical bleeding diathesis, surgical handling	Atraumatic surgical technique, compression for >10min
Devitalization of adjacent teeth	Not enough space in between implant and adjacent tooth	Endodontic treatment

Table 8. Intraoperative surgical-related complications (Park & Wang, 2005)

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Bisphosphonate-Related Osteonecrosis of the Jaw Around Dental Implants

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1. Introduction

Bisphosphonate is the collective name for compounds in which the backbone of pyrophosphoric acid, a P-O-P structure, is converted to chemically stable P-C-P, and this structure shows the affinity of bisphosphonate for bone hydroxyapatite in the body (Fleisch et al. 2002). Administered bisphosphonate preparations (BPs) transfer to and deposit in bone, exhibiting a bone resorption-inhibitory effect. The chemical structure of the side chain bound to the carbon atom of P-C-P markedly influences bisphosphonate activity, and, particularly, side chains containing nitrogen molecules not only markedly increase the affinity for HA but also bone resorption-inhibitory activity (Migliorati et al. 2005). Because of this potent bone resorption-inhibitory effect, BPs are the first-choice treatment for osteoporosis worldwide (Russell et al. 2007), and their efficacy for malignant tumor-associated hypercalcemia (Body et al.1999), ostealgia complicating bone metastasis of solid tumors (Hortobagyi et al. 1998), and multiple myeloma accompanied by bone destruction (Berenson et al. 1996) has been shown. Adverse effects of BPs were previously considered to be relatively mild, such as digestive symptoms induced by oral preparations and fever induced by injections (Berenson et al. 1996), but the association of BPs with osteonecrosis of the jaw has been frequently described since Marx (2003) initially reported it (Ruggiero et al. 2004; Marx et al. 2005; Khosla et al. 2007)

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is clinically diagnosed when the following 3 conditions are met: 1) current or previous treatment with BPs, 2) persistent exposure of necrotized bone in the maxillofacial region for 8 weeks or longer, 3) no past medical history of radiotherapy for the jaw bone (AAOMS 2007; Ruggiero et al. 2009). BPs inducing BRONJ mostly contain nitrogen (NBPs). BRONJ frequently develops in patients under NBP treatment upon dental treatment, such as tooth extraction, implant placement, and surgical periodontal treatment accompanied by bone invasion, and inflammatory diseases, such as periodontal disease and abscess (Ruggieri et al. 2009; Vahtsevanos et al. 2009; Yoneda et al. 2010). BRONJ shows poor responses to the standard treatment for common osteomyelitis of the jaw, such as curettage/resection of necrotized tissue and antimicrobial drugs, and its intractability is the most serious problem.

Stack & Epker (1995) initially reported the influence of BPs on dental implant treatment. They introduced a case in which all 5 favorably functioning implants in the lower anterior tooth region were lost after the 5-month administration of a BP containing no nitrogen, etidronatedisodium (Didronel; Procter and Gamble, Cincinnati, OH), for osteoporosis. The details of the bone wound healing process after implant loss or whether BRONJ developed were not described, but the author concluded that Didronel administration is a risk factor for implant treatment. However, several recent studies reported that implant treatment in the presence of NBPs was possible when the NBPs were oral drugs. Fugazzotto et al (2007) evaluated that a retrospective analysis of case records of patients with a history of oral BPs therapy treated as part of routine periodontal and implant treatment. They reported that no osteonecrosis was noted immediately postoperatively or during follow-up period 61 patients, and all implants were functioning successfully 12 to 24 months post-insertion.Grant et al. (2008) evaluated the clinical results of 115 patients who received oral BPs during implant treatment. They showed that there was no significant difference in treatment results between patients with and without oral BPs during implant treatment. It was also reported that no patients developed ONJ after implant treatment. Bell & Bell (2008) reported that bone grafting for implant treatment in 42 patients who received oral BPs for osteoporosis treatment was conducted safely. Therefore, no conclusion has been reached regarding whether oral BPs are contraindicated for implant treatment. On the other hand, it has been clarified that the risk of developing BRONJ upon open dental treatment rises in patients treated with NBP intravenous injection showing a potent bone adsorption-inhibitory action, and implant treatment is considered contraindicated for such cases (Khan et al. 2008; Ruggiero et al. 2009). However, there have been fewer reports on the influence of intravenous BPs on implants which have already acquired osseointegration and are favorably functioning, and the actual state is unclear.

We experienced the case of a patient who developed ONJ around implants in the maxilla, considered to be caused by intravenous BP administration for osteometastasis treatment of breast cancer, and underwent partial maxillectomy to relieve inflammation (Shirota et al. 2009). This chapter introduces clinical findings, the treatment and its outcome, and peri-implant histopathological findings in the patient, and the developmental mechanism of peri-implant BRONJ is discussed with a literature review.

2. Patient and methods

2.1 Outline of the patient

The patient was a 54-year-old female who visited our hospital for chief complaints of peri-implant pain in the upper left molar region and bone exposure. The patient developed breast cancer about 6 years ago and underwent left mastectomy followed by irradiation and chemotherapy. However, multiple cancer metastases occurred about 2 years ago, and the patient underwent cancer chemotherapy and intravenous BPs injection.

The patient underwent implant treatment for the upper left molar region at a dental clinic immediately before the development of breast cancer, in which 2 implants were placed. These implants functioned without a problem for about 6 years, but peri-implant gingival recession, bone exposure, and pain appeared about one month ago, and the patient received antimicrobial drug administration, irrigation, and disinfection at a clinic, but the symptoms did not improve. Thus, the patient visited our department. On the first examination, brown-colored necrotized bone was exposed in the upper left first molar region on the buccal side.

The peri-implant gingiva was painful and swollen with slight flare, but no implant mobility was observed (Fig.1). On panoramic radiography, mild bone resorption was noted in alveolar bone in the implant neck. Computed tomography (CT) revealed sequestration with an irregular trabecular bone structure around the implant (Fig.2). Biopsy was performed in consideration of metastasis of breast cancer to the oral cavity, but only inflammatory cell infiltration was observed without tumor cells.

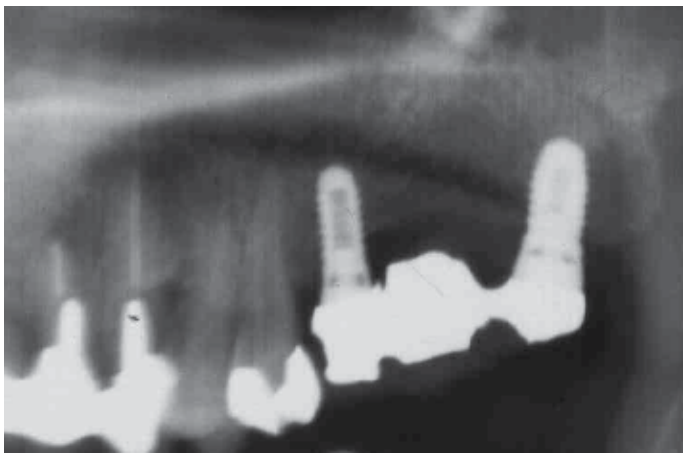


Fig. 1. Radiograph showing slight bone resorption around the implants.

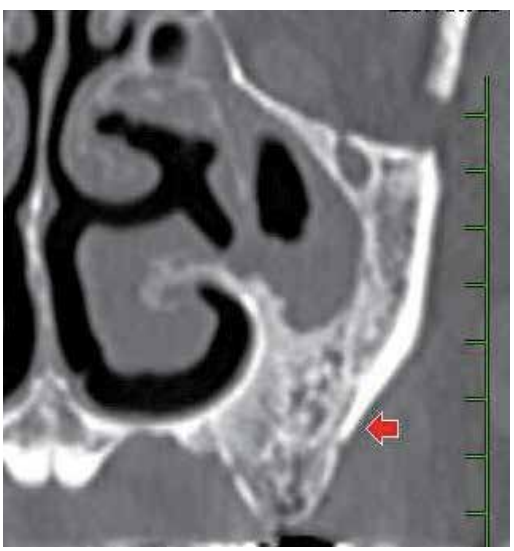


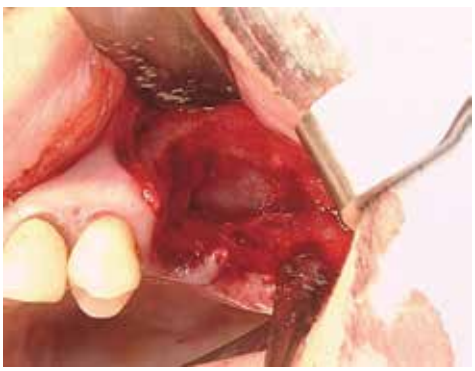
Fig. 2. Computed tomography (CT) image around the implants (arrow).

2.2 Diagnosis and treatment

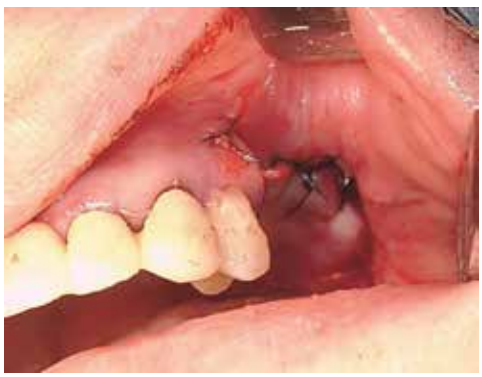
It is well-known that curative chemotherapy or long-term adrenocortical steroid administration for lymphoblastic leukemia and Hodgkin and non-Hodgkin lymphomas induces osteonecrosis of the femoral head (Kubo et al. 2001; Bojko et al 2003; Karimova et al.

2008). Many anticancer drugs were administered for breast cancer metastasis in this patient, but no osteonecrosis of the jaw caused by these drugs has been reported. In addition, the clinical symptoms of this patient met all diagnostic criteria of BRONJ proposed by AAOMS (AAOMS 2007; Ruggiero et al. 2009). Based on these findings, BP-induced osteonecrosis was diagnosed.

In the treatment, morbid bone tissue including implants was resected in consideration of the following 3 conditions: 1) early chemotherapy for metastatic cancer was necessary, for which removal of the infected lesion was necessary, 2) there was a possibility that continuation of the withdrawal of BPs would aggravate metastatic cancer-associated bone destruction and hypercalcemia, and 3) it was difficult to remit inflammation by employing conservative treatment proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS 2007; Ruggiero et al. 2009). After considering these points, sequestrectomy of the left maxilla was selected. The gingival margin was incised between the upper left first premolar and implant towards the maxillary tuberosity, and the lesion area was exposed by forming a buccal and palatal mucoperiosteal flap. The bone cortex of the lesion was brownish black, and necrotic bone was confirmed between the distal surface of the second premolar and mesial surface of the implant placed in the second molar area, but particularly around the implant placed in the first molar area (Fig.3a). The area for resection around the living bone in the lesion was determined after the extraction of the second premolar, and the pathological bone tissue including the implant was removed with a Lindeman bar and bone chisel, followed by the grinding of the bone surface of the resection stump until bleeding was confirmed. As a result, the instrument partially perforated the maxillary sinus floor, and the thickened maxillary sinus mucosa was exposed. This sinus mucosa was spared, and the surgical wound was completely closed by suturing the mucoperiosteal flaps (Fig.3b)



(a) Pathological bone including the implants was removed, and maxillary sinus mucosa was exposed.



(b) The surgical wound was completely closed by suturing the mucoperiosteal flap.

Fig. 3. Intraoperative view of the sequestomy of the left maxilla.

After surgery, antibiotic was intravenously administered for 3 days and oral antibiotic was administered for 3 days. In addition, hyperbaric oxygen therapy was performed. The efficacy of hyperbaric oxygen therapy for BRONJ is controversial (Ruggiero et al. 2004; Freiberger et al 2009), but, at least, it may be effective to promote mucoepithelial wound healing in the

sequestration-resected region. The wound was completely covered with healthy mucosa 2 weeks after surgery (Fig.4.). Since the remission of inflammation could be confirmed, anticancer drug and BP administration was initiated for metastatic cancer and bone metastasis-associated bone destruction. The patient died of multiorgan failure associated with multiple cancer metastasis 8 months after surgery, but BRONJ did not recur before death.

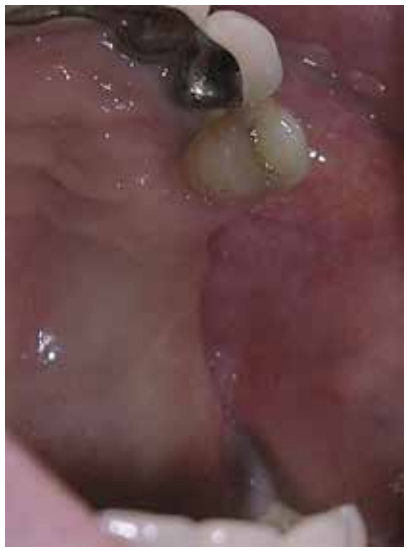


Fig. 4. Intraoral view at 4 weeks after surgery.

2.3 Macroscopic and μCT findings of the resected specimen

Implants were strongly fixed to the bone, and areas of brown sequestration were observed around them (Fig.5.). On μCT, no apparent abnormality, such as trabecular destruction, was observed, and the implant surface was in direct contact with the trabecula at various sites (Fig.6.).

Fig. 5. The resected specimen shows a portion of the left maxilla including two implants.

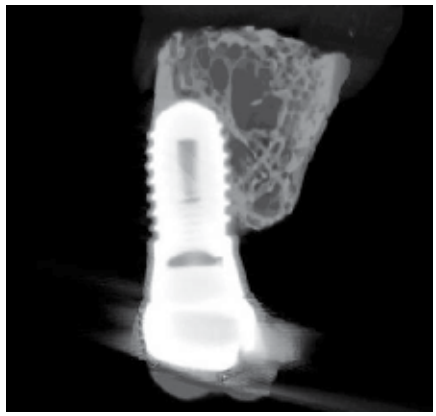


Fig. 6. μCT findings of the resected specimen.

2.4 Histopathological analysis

2.4.1 Histologic preparation

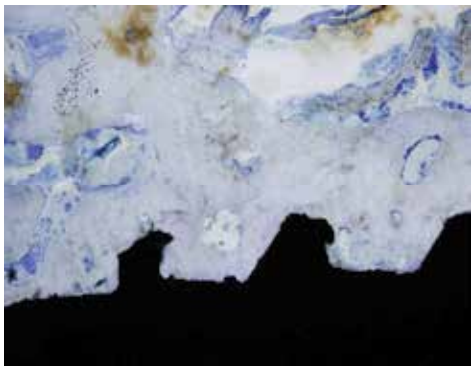
The resected specimen was divided into the lesion including the implants and peri-lesion, i.e., healthy tissue in the resected stump. The bone tissue around the implants was fixed, dehydrated, and embedded in polyester resin (Ligorac®, Wako Pure Chemical Industries, Ltd., Tokyo, Japan). Undecalcified ground sections 15 μm in thickness were cut along the long axis of the implant using the EXAKT Cutting-Grinding System (EXAKT, Norderstedt, Germany) and stained with 1% toluidine blue (pH 7.2), then the bone tissue around the implant was observed under light microscopy. Meanwhile, the bone tissue around the lesion was dehydrated and embedded in paraffin according to the conventional procedure. Some of the sections were stained with hematoxylin-eosin (HE) and AZAAN. Other sections were processed for immunohistochemical analysis by immunostaining with anti-human CD3, CD20, CD45 and CD68 (Daco, Carpinteria, CA).

2.4.2 Peri-implant histopathological findings in undecalcified ground sections

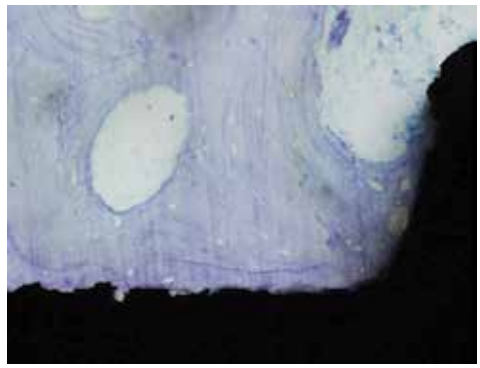
The implant surface was mostly in direct contact with bone tissue, suggesting that osseointegration was maintained until BRONJ development (Fig.7a). No osteocyte was present in the cavity of bone contacting implants or the surrounding trabeculae, nor were there cellular components on the bone surface, and bone tissue mostly showed sequestration (Fig.7b). The marrow cavity was filled with aggregates of actinomycete-like microorganisms, neutrophils, and other necrotized soft tissue (Fig.8a). In addition, adsorption cavities with a worm-eaten appearance were widely present. Normally, bone tissue necrotized in the body is absorbed by osteoclasts, shows sequestration, and is naturally excreted. However, no osteoclasts were present in the resorption cavity, suggesting that active resorption of the bone occurred in the BRONJ developmental process, rather than the resorption of necrotized bone by osteoclasts (Fig.8b).

2.4.3 Histopathological findings around lesions in decalcified sections

Osteocytes were present in the bone cavity (Fig.9a,b). The trabecular surface was smooth, and osteoid formation and osteoblast arrangement were observed. Reactive bone formation was also observed at various trabecular sites. Granulation tissue rich in capillary blood

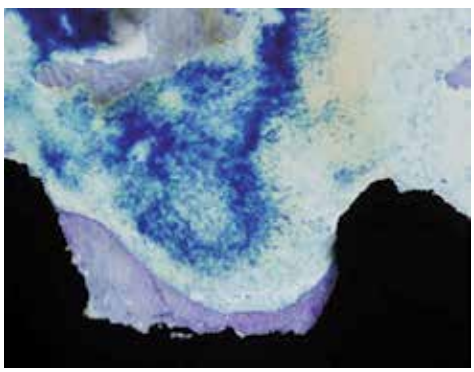


(a) Most of the implant surfaces are in direct contact with the bone (× 40).

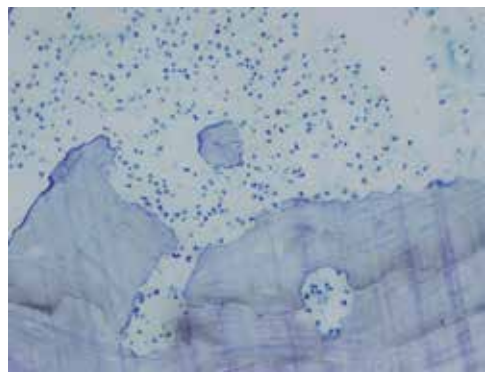


(b) The bone in contact with the implant sureface is necrotic (× 200).

Fig. 7. Histological findings of the tissue from the implants in an undecalcofied sections stained with toluidine blue.



(a) Growth of a bacterial colony into the marrow cavity is observed (× 200).



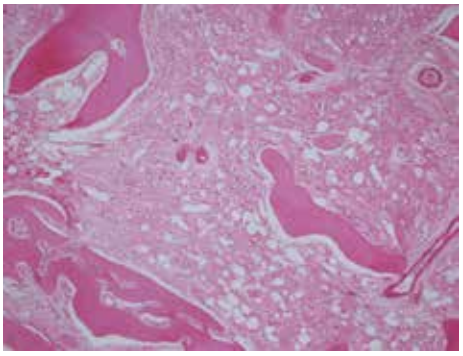
(b) Marked bone destruction with a moth eaten appearance is observed on the necrotic trabecular bone surface (× 200).

Fig. 8. Histological findings of the tissue from the implants in an undecalcofied sections stained with toluidine blue.

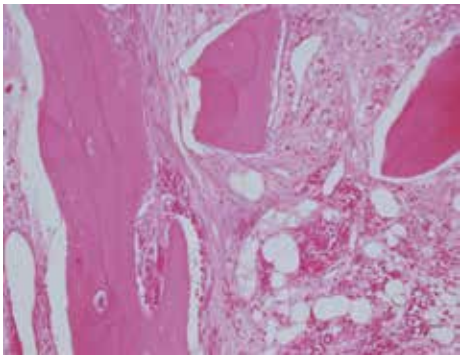
vessels invaded the bone marrow region (Fig.10a,b). On immunohistological staining, lymphocytes infiltrating the bone marrow were mostly CD3-positive, showing that the cells were derived from T cells. In contrast, only a few lymphoctyes were positive for CD20 and CD45 (Fig.11a,b), but they were considered not to be significant. Multinucleated giant cells strongly positive for CD68, assumed to be osteoclasts, were present at various sites on the trabecular surface (Fig.12a,b).

3. Discussion on the peri-implant BRONJ developmental mechanism

No viewpoint regarding the pathogenesis of BRONJ has been established. Based on clinical experience, mucosal injuries caused by poorly fitting dentures and oral surgical treatment, such as that for periodontal disease and tooth extraction, have been reported as local risk factors, but this patient received no surgical dental treatment during the BP administration

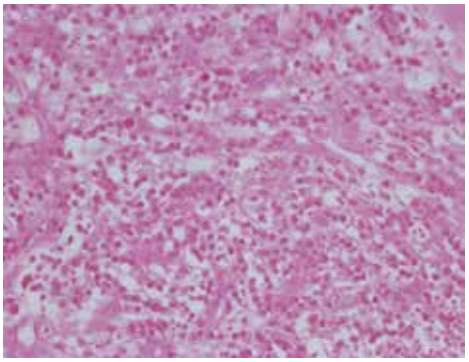


(a) The trabecular bone surface are smooth (HE stain; × 40)

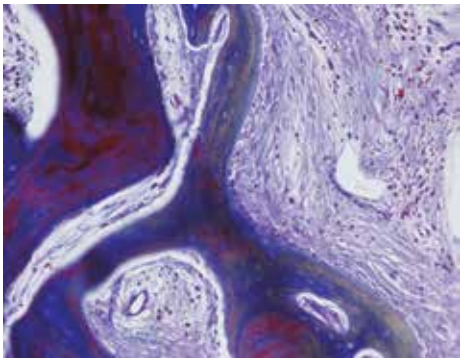


b) Growth of fibrous connective tissue and vascular formation are observed in the marrow(HE stain, × 100).

Fig. 9. Histological findings of the tissue around the lesion in a decalcified thin section.



(a) Numerous lymphoid cells are observed in the marrow (HE stain; × 200).



(b) Lining cells and osteoid formation are observed (AZAN; × 100).

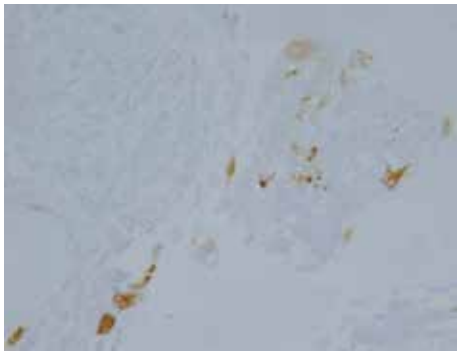
Fig. 10. Histological findings of the tissue around the lesion in a decalcified thin section.

(a) Many lymphoid cells are positive for anti-human CD3 (× 200).

(b) Only a few lymphoctyes are positive for CD20 (× 200).

Fig. 11. Immunohistological staining ot hte tissue around the lesion in a decalcified thin section.

(a) Only a few lymphoctyes are positive for CD45 (× 200).



(b) Multinuclear cells are strongly positive for anti-human CD68 antibody (× 200).

Fig. 12. Immunohistological staining ot hte tissue around the lesion in a decalcified thin section.

period, and no implant mobility was observed in the BRONJ site. Histologically, oseointegration was widely maintained on the implant surface, and no deep overgrowth of gingival epithelium was noted, suggesting that BRONJ in this patient suddenly occurred around favorably functioning implants, and was not induced by peri-implant inflammation.

Necrosis of the femoral head (Kerachian et al. 2006) and irradiation-induced osteonecrosis of the jaw (Marx 1983) are widely known as osteonecrotic lesions, and the cause is insufficiency of vascular formation in both diseases. Reportedly, zoledronate exhibits a potent vascularization-inhibitory effect (Giraudo et al. 2004), and the BP-induced obstruction of blood vessels in bone and necrosis of osteocytes around them have been reported (Hansen et al. 2007). Based on these findings, it is hypothesized that insufficiency of the blood supply is also involved in BRONJ, but, histologically, the absence of vascularization inhibition in BRONJ has been reported (Bedogni et al. 2008). Another important hypothesis suggests an influence of reduced bone remodeling due to the BP-induced inhibition of bone resorption by osteoclasts. It has been reported that osteocyte mortality increases when bone remodeling declines, i.e., BPs reduce bone remodeling, increasing osteocyte death, which is involved in BRONJ (Allen et al. 2009). However, many resorption cavities were present on the peri-implant-sequestered bone surface, and the growth of granulation tissue containing abundant capillary blood vessels and reactive bone formation in the resected stump were confirmed in this patient. Thus, it is difficult to explain the cause of BRONJ with insufficient blood supply and the bone remodeling-inhibitory effect of BPs alone.

Pamidronate and zoledronate administered intravenously to this patient are BPs that incorporate nitrogen. BPs containing nitrogen (NBPs) induce an inflammatory reaction by stimulating cells (Hewit et al. 2005; Endo et al. 1993; Nakamura et al. 1996). NBPs also exist on the surface of gram-negative cell walls, and increase inflammatory reactions to lipopolysaccharide (LPS), which has a strong inflammatory effect (Yamaguchi et al. 2000). Therefore, BRONJ may be caused by interactions among several factors differing among cases, not by a single cause. For example, in this patient, the following conditions may have influenced each other and caused BRONJ: 1) the excessive inhibition of bone turnover due to the NBP-related inhibition of bone resorption; 2) the occlusal force loaded on implants was directly transmitted to the bone, which activated local bone metabolism in the surrounding

region, releasing BP accumulated in the bone at a high level; 3) free NBP-induced inflammatory reactions, induction of osteoclast apoptosis (Roelofs et al. 2006), and inhibition of epithelial activity (Landesberg et al. 2009); 4) increased risk of bacterial infection due to suppression of the immune system; 5) enhanced inflammatory reactions due to interactions between gram-negative bacterial lipopolysaccharides and NBPs and 6) reduced local blood flow by vascularization inhibition and vascular obstruction (Fig.13).

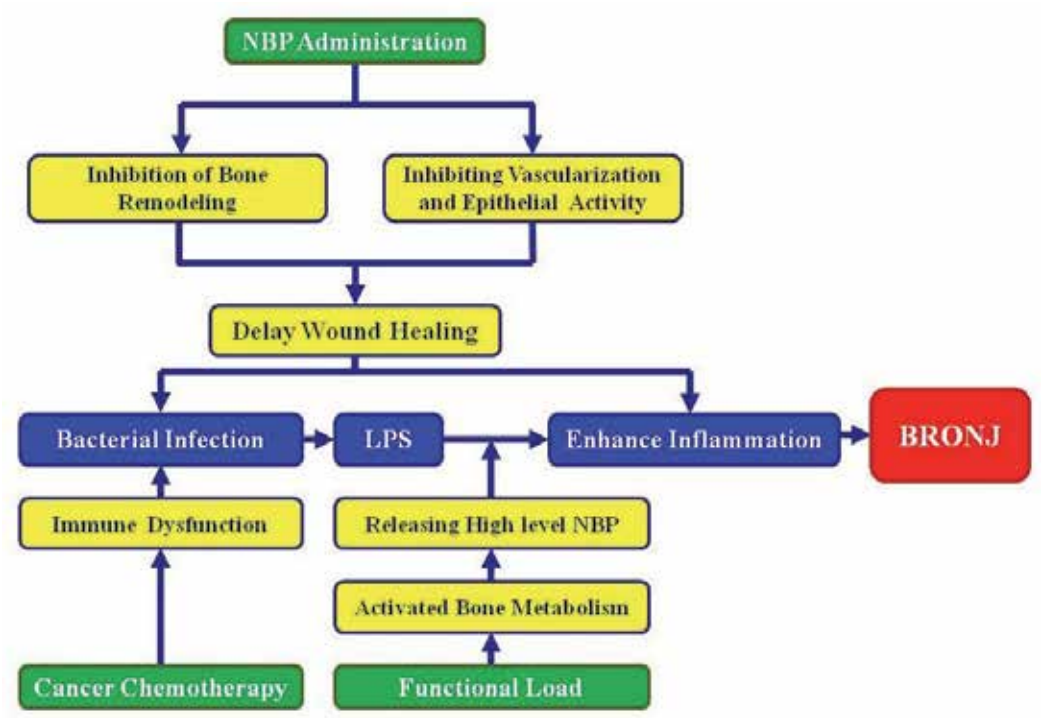


Fig. 13. Hypothetical mechanism of BRONJ aroud the implants.

4. Conclusion

BRONJ is intractable, and no treatment method has been established. Only guidelines mainly concerning prevention and conservative treatment have been proposed. When peri-implant BRONJ occurs, firstly, conservative treatment should be selected following the AAOMS treatment guidelines, placing great importance on the prevention of exacerbation of BRONJ, but when NBPs are administered to control bone metastasis, it should be a priority to re-start BP administration and prevent any delay in cancer chemotherapy. Accordingly, although the appropriateness and timing of sequestration site resection should be carefully investigated, active surgical treatment may be one choice for some patients. Implant treatment is no longer special treatment. It is widely introduced into routine dental practice as a method to recover the occlusal function of defective teeth. Therefore, NBP intravenous injections will be increasingly administered to patients with a past medical history of implant treatment, for which the establishment of a practical clinical policy for the prevention and treatment of BRONJ is strongly desired.

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22

Biological Reactions to Dental Implants

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1. Introduction

Generally, the cells' isolated systems are more sensitive than the tissues of the body at the contact with material outside the natural system. Although, the research by applying some viable methods *in vitro* is constantly growing, because the cellular mechanism of the toxicity assessment materials can be described through some simple and cheep experiments, that could represent viable alternatives for testing *in vivo* on animals bio bases and, finally, on people. Using these testing methods, the materials can be classified according to their degree of toxicity and chosen, if necessary, for further testing *in vivo*. To appreciate the materials' biocompatibility for implantation in human body and to provide their functionality *in vivo* in the maximum safety for the patient represent a rigorous complex process, with two important distinct steps (Black, 1992): conducting preliminary assessment tests such as cytotoxicity, awareness, the irritant potential, intracutaneous reactivity, systemic toxicity (acute), subchronic toxicity (subacute), genotoxicity, implantation, hemocompatibility, or conducting tests for complementary evaluation, that consist in testing the chronic toxicity, the carcinogenicity, the toxicity of reproduction and development (growth) and the biodegradation.

Through the process of testing *in vitro* the biomaterials can be assessed in a number of functions and characteristics of cells, as: integrity of membrane, cytoskeleton, viability, proliferation, proteins synthesis, oxidative response, mobility, secretion, response to growth factors, cell-cell interactions. To prepare the materials for testing the cytotoxicity has a great importance, because those physical and chemical properties strongly influence the cells response and the entire experimental system. Testing standards and how to prepare samples for testing *in vitro* are present at all professional bodies, including International Organization for Standardization (ISO), Ente Nazionale Italiano di Unificazione (UNI), British Standards Institute (BSI), Deutsches Institut fur Normung (DIN), Swiss Association for Standardization (SNN), Association Francaise de Normalisation (AFNOR), American Society for Testing and Materials (ASTM), American Dental Association (ADA). In such a standard are presented the requirements for physical and chemical form of materials, sterilization procedures, form and size of samples and any treatment required to obtain a sample suitable for cytotoxicity testing. The adoption of these specifications is recommended when pursued some comparisons between different laboratories or when

you need a report for a manufacturer; application of those standards among other things ensure that the material or its properties are not impaired by the procedure of preparation of samples for testing. In case of testing *in vitro*, solid materials are usually used when tested biomaterial surface affects the cell response clearly. In these cases, the combination of solid material - formed cell experimental system that reproduces the best situations arising *in vivo.* It is very important to know that only the mere change in form and the sample size studied can make the difference between obtaining as result a nontoxic effect or a very cytotoxic one (Brodbeck et al., 2001). Obtaining cell adhesion on biomaterials is considered a positive phenomenon in order to continue the test for studying the biomaterial behaviour after implantation. To assess cell adhesion to foreign surfaces is mainly used cell counting, and electron microscopy techniques and computer assisted measurements are used to assess the distribution and morphology.

2. Materials and methods for evaluation

The most popular standard of testing the biomaterials, ISO 10993, in the section dedicated to the *in vitro* tests (the 5ft part**),** does not specify the most important parameters for cytotoxicity testing, but only lists certain characteristics and properties that can be pursued during the course of the evaluation of biomaterials in vitro behaviour, to permit the research laboratories to determine their own steps to make on the cell type, duration of exposure, assessment method, etc. According to this standard, to be performed cytotoxicity tests must be met several conditions:

a. The tests must be performed on finished product or representative samples of the finished product or materials;

b. Choosing the testing methods must take account into:
   - nature, extent, duration, frequency and conditions of exposure or contact with the human body surface in normal use devices provided;
   - physical and chemical nature of the finished product;
   - toxic potential of chemical components of the finished product formula;
   - relationship between body size and device surface to which it is applied
   - existing information based on literature, experience and clinical trials**;**
   - protect humans and animals to perform experiments;

For the use in cytotoxicity testing of biomaterials are offered several types of cells and cell lines. At this point, it is still debated question of use *in vitro* testing fresh cells selected from explants, primary cells, or selected cellular lines. Likewise, it is not indicated the duration of cell exposure to materials / devices, as, generally, it is dictated by the test method applied, but it can be taken into account the average duration of implantation of the tested biomaterial. (Kilburn et al., 2003)

Currently, testing the cytotoxicity needs 24 hours, but, in many cases, this exposure can be diminished or extended. The duration of contact with the materials may be restricted to 1-2 hours, as it is recommended for the testing of some types of dental materials that will be applied to the oral mucosa only for a few minutes. This reduction in testing time in cell culture is because, having gone through a period of 24 hours of investigation can be obtained for a highly toxic material / device tested, which could lead to rejection due to raise awareness. If this material has unique properties and optimal performance *in vivo* short exposures, the benefit obtained by its use may be higher than the risk of patient.

The ISO 10993 standard indicates that for testing the cytotoxicity "the assessment type is at free choice". The Standard are presented in four categories of assessment types, including which we find a cell morphology one and some measurements of cell parameters. The same standard is specified also that, for original cataloging of materials, methods adopted by the laboratory must be technically simple, reproducible, and applicable to a broad spectrum. The initial cataloging of biomaterials, cell viability, or the number of dead cells and to determine cell growth inhibition are common parameters. Using the assessment of these factors can be measured the tests' toxicity, as the biomaterials are classified according to their cytotoxic effect. Although their cell viability and growth are clearly defined, the distinction becomes less clear when it used the same test method to measure both parameters.

If cell growth, although time consuming, cell counting hemocytometer or Coulter counter is still widely used. The cell counting methods have a high risk of inaccuracy, mainly because of the steps needed to obtain cells in suspension, including repeated washing and cell transfer. Since there is no need for a transfer cell after contact with the biomaterial, the staining procedure of microplates cultures of cells is used to quantify their DNA's**.** Currently, dye fixing cell cultures are used substances such as amido black, crystal violet and methylene blue, later on being obtained the solubilisation of the cell adsorbed color, as the absorption of blue color can be measured with a specific wavelength of color used (Puleo & Nanci, 1999).

The best demonstration of the ability of cells to grow *in vitro* in case of biomaterials testing consists of trying to form colony cells. The main limitation of this technique consists of the experiment duration: the results of an experiment can be obtained after two three weeks, since the materials that temporarily blocks cell division can be classified as cytotoxic if cells are prematurely processed. (Yan et al., 1997) To achieve ranking as cytotoxicity of biomaterials, it is necessary to apply quantitative methods. They are necessary also if biomaterials' cataloguing is required, but if it is imperative to have an answer for validation or invalidation of a product, while the morphological and qualitative methods provide important information, and can not dictate such a decision; qualitative methods can be used only to characterize the biomaterials. In the study of biomaterials' cytotoxicity should be measured the damages caused by them in cellular cultures, in order to define a limit of nontoxicity. The cytotoxic effect is expressed in terms of the proportion of surviving cells after the contact with the biomaterial; using the values expressed in percentages may be compared to the results of various test methods. (Dekker, 1994). In none of the documents mentioned above, any limit is established for estimating the maximum acceptable value of toxicity. Some authors classify materials as cytotoxic when the cell survival is less than 50% or 75%, while others resort to statistics to detect a significant difference between the materials and tests. A material can be used clinically, even if it has a relatively high toxicity, due to a lack of valid alternatives. From this point of view, especially for clinical applications may be chosen the least toxic materials available.

By analyzing the cellular inhibition' growth induced by biomaterial and the cellular cycle of used culture, the toxicity' grade was expressed as percentage depending the cellular proliferation inhibition (CPI%), by the formula: CPI% = 1 when the number of sample cells/the number of control cells equalizes 100. Using CPI%, 4 different levels of toxicity have been identified, namely: "high toxicity" (CPI%=50), "medium toxicity" (CPI%<50% & >25%), "low toxicity" (CPI%<25%) and nontoxicity (CPI%=0). (Hazan, 1993).

Currently, the apoptosis is detected by flow cytometry in most cases and only rarely by conventional electronic microscopy techniques or DNA electrophoresis site, which can be complementary techniques. The flow cytometry with complementary techniques such as optical microscopy, confocal fluorescence, scanning or transmission fully covers all the biochemical and morphological aspects that need to be taken into account in the biocompatibility of materials.

The release of high concentrations of implants and prosthetic components in the body, due to the occurrence of corrosion phenomenon, may favour the appearance of the necrotic phenomena and the inflammatory reactions of the surrounding tissue. However the release of these elements in the body may be followed by toxic effects, characterized by apoptotic phenomena: this situation is less serious, because the tissue adaptation to the implant is not seriously affected. In conclusion, although theoretically simple, the applicable to cellular culture tests to assess the biocompatibility requires a number of factor limits that are determined after a thorough analysis. As mentioned, the main items to consider include the preparation and handling of material, test methods and quantitative assessments. It is also very important the conclusion that the mechanism of occurrence of cell death induced by the material is uncertain, the final conclusions regarding the interactions between the biomaterials and implants or prosthesis can be explained by studying the reactions of tissues observed after *in vivo* implantation.

The compatibility with blood or the hemocompatibility materials and medical devices is determined by using uncurled blood (a major limitations of these test) and the evaluation of blood clots on the surface of test samples, and also the activation of the coagulation cascade, the adhesion of platelets, the complement system activation and the erythrocytes. Depending on the ultimate goal of biomaterial use, the hemocompatibility tests must be conducted in static or dynamic conditions. (Anselme et al., 2000).

The *in vitro* cellular culture models can be used to determine the effects of chemical compounds (the concentration of ions released during the corrosion of metals or molecules released during the degradation of polymers) on the body. The materials that do not meet the toxicity should not be further considered. Even if the materials pass the test of cellular culture, must be taken into account also the effects caused by the products resulting of degradation on cellular morphology, proliferation and other cell functions.

2.1 Biomaterials *in vitro* testing methods

As it has been previously described, the *in vitro* cellular culture models can be used in the preliminary assessment of biocompatibility of materials. As with other models, measures must be taken in interpreting the data correctly and avoid risks that may result from an incorrect extrapolation. Without doubt, these models are very useful in studying the cell functions, but still, this approach has its limitations. These results must be combined with those from *in vivo* tests to reveal all the aspects of biocompatibility.

Determining the safety of a biomaterial and its efficacy as a implanted device is finally made after its implantation on animals. Such studies, realized on an animal material correctly chosen, have been shown to be directly applicable in human subjects**.** The most biological processes, in particular wound healing, are also compatible. The specialized literature is replete with descriptions of animal models that were used to evaluate various materials and devices. Unfortunately, there are deficiencies in terms of the pathological data from the observations made on materials and implanted devices in human subjects. This deficiency is

linked to issues of recovery and histological evaluation of an implanted device when a patient's death was not caused by its presence. The choice of an animal species relies more on its cost and / or availability than on the relevance for the human situation. As provided in the ISO rules, the first phase of testing a new material is best performed in a tissue culture. The second phase of testing for any application is the subcutaneous or intramuscular implantation in rodents, with a histopathological evaluation of the tissue that develops around the test material. If you want to use it for orthopedic purposes, the material should be implanted into the rabbit femoral intramedullary cavity. The animal model chosen for the third phase of the complete testing the device depends on its final application. (Ilin & Skvortsova, 2002)

The ideal animal model should have many reproducible features to simulate an analogue or counterpart condition in which the material would find use in humans. The scientific criterion for selection of the animal model depends on the intention of applying the biomaterial. More specifically, should be taken into account the anatomical, biochemical, physiological, pathological and/or psychological characteristics. Over the years, it has been found through trial and failure that human systems resemble with different animal species. In addition to anatomic, pathologic and physiologic similarities with humans, that should be taken into account when choosing an animal model, the researcher conducting the experiment may be limited in choice, because practical considerations. The size and conformation of the animal may be one of the limits. The small animals cost less and are easier to handle. However, surgical procedures on large animals are easier to perform.

The bone healing and its reactions with biomaterials in goats, showed a similarity to those of humans on the type of cell, collagen structure, the structure of the soft and hard tissue, but also on the time of occurrence of the specific biological phenomena. In addition to management considerations, goats and sheep, as well as rats tend to develop ectopic ossifications in these structures, highlighting them as unviable models for researching the characteristics of artificial tendon healing. The rabbit represents an often test system used in Orthopedics. Even if an important part of special publications support the inadequacies of animal model in predicting similar behaviour of biomaterials implants in humans, it is still widely used. The reasons are probably more historical and economic. (Wennerberg et al., 2003)

The dental implants have been studied in dogs, monkeys, baboons and pigs. Although the specific anatomy of these species is quite different from that of human, the tissue responses to periodontal disease and gingival withdrawals are quite similar. This research area resembles Orthopedics.

The wound healing studies performed to observe the effectiveness of different treatments wounds are best performed on young domestic pig. The animals' use into laboratory for *in vivo* testing should be responsibly done and only after have been met the other conditions of preliminary biocompatibility, eventually after using computer simulation models and *in vitro* experiments. The main concern in using animals for *in vivo* testing is not to produce to the animal an unnecessary suffering or harm. Therefore, the researchers should carefully select the animals that will test and make a detailed planning investigation. All these things should be realized taking into account the national and international laws.

2.1.1 Classification of *in vivo* tests

The animal tests used to assess biocompatibility are classified into three main categories (Black, 1992):

- *The nonfunctional tests* can be applied in various forms, the implants being usually inserting into the soft tissue (subcutaneous, intramuscular or intraperitonal) with minor incisions, or into the hard tissue, through the practice of geodes or resection of the femoral head and the insertion of intramedullary implants. These studies are of short duration (days to months) and provide valuable information about local interactions between the implant and surrounding tissue, data being obtained in the absence of mechanical loads.
- *The ex vivo tests*, as arterio - venous and vein - venous suture type, are used to divert a portion of the blood of an animal to a material, and back into the circulatory system. In this case, vital information for determining the blood compatibility to the used materials is the accumulation of proteins, cell adhesion and clots' formation on the material' surface.
- *The functional tests* involve implantation into the animal organism of some reduced scale prostheses, for example hip or heart prostheses implantation in similar conditions to those in the human body. These tests are lengthy; require special conditions regarding the design, production, testing of various types of prostheses, while being complex and expensive.

The use of materials for implants and medical devices applied on animals provide valuable information on the complex interactions that occur between the implant and the body, the chronic and acute inflammatory responses and all the problems throughout the process. It also can cause pyrogenic, immunological and toxicological animals' responses to implants. Detailing the methods and procedures is available in the specialized literature and publications of standards institutions. Compared to scientific standards, the medical evaluations should be carried out lawfully. Furthermore, *in vivo* and *ex vivo* tests must meet

Location	**Influence factor**
Material	Chemical volume and chemical surface properties Surface roughness Superficial Porosity Superficial energy Surface charge Chemical and physical stability Chemical properties of degradation products The physical characteristics of breakdown
Implant	Size and Shape The elasticity mode /stiffness
Host Organism	Species (in animal experiments) Tissue type and location Age Genre General health Medications
Implantation method	Surgical techniques Fixing the tissue implant Infection

Table 1. Factors that may influence implant-tissue interaction (Black, 1992).

the requirements of empowered institutions. After received the acceptance of these institutions, the medical devices can be implanted in a small number of patients that will be closely monitored.

In all cases of testing the biomaterials, the ethical considerations are very important. The identity of those who take part in these tests must be kept confidential. The animal tests can provide very important information about materials and medical devices**,** the tissues in which they have been implanted, but also the implant acceptance by human or animal body. To conduct practical experiments necessary to evaluate the interactions occurring at the tissue implant interface, we chose the rabbit as animal model study, because it is an often used animal for clinical studies, has enough dimensions and does not involve special surgical conditions, and the postoperative monitoring and maintenance costs are relatively low. (Moiseev, 2004)

By performing the implantation tests, it seeks global response, the result of the interaction between implant and host tissue, the role of the phenomena on the tissue implant interface. Their progress may depend on the properties and characteristics of volume and shape of the implant, and its surface roughness. Generally, by evaluating tissue reactions at the implant interface may be a distinction between bioinert, biotolarated and bioactive materials and also can get information on biofunctionality, biocompatibility, biodegradation, and bioactivity. The overall response of the body, considered as a measure of biocompatibility is determined by reference to the factors presented in Table 1.

3. Experimental study on tissue biomaterial interaction

3.1 Determination of chemical composition of biomaterials

The first step in evaluating any biomaterial, metal or not, is up to the identification and characterization in terms of its chemical composition. Currently, it is available for conducting such investigations a variety of compositional characterization methods. To make the characterization in terms of chemical composition, the research presented in this paper, we used the following energy spectrometry (EDS), method that allows the materials assessment with sufficient precision for characterization and classification of selected biomaterials into specific ASTM standards groups. For the study of the interactions that occur at the interface implant tissue to cover as wide a range, we selected the most representative class of biomaterials and used metal groups, as follow: commercially pure titanium, titanium alloy Ti6Al4V type, CoCrMo alloy, and austenitic stainless steel to a medical purpose. The quantitative chemical determinations made by EDS spectrometry have allowed cataloging tested materials, see Figure 1, and their classification in terms of the compositional type in ASTM marks of the biomaterials. To avoid the phenomenon of contamination of samples, they were cleaned by ultrasonic in methanol at 50° C for 15 minutes and then doubly distilled pure water at 90° C, 30 minutes and dried in hot air.

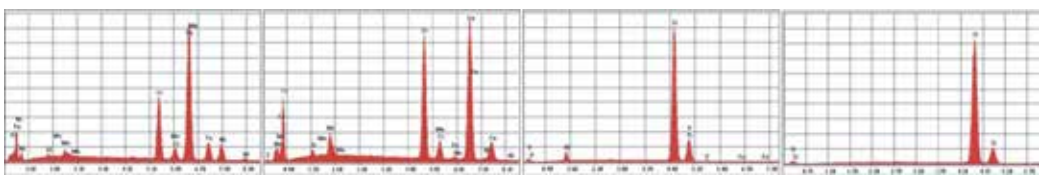

Fig. 1. EDS spectra characteristic chemical compositional analysis of the main classes of metallic biomaterials.

The experimentally determined values are within the limits imposed by ASTM standards, in the following classes: commercially pure titanium covered in ASTM F67; Ti6Al4V alloy type fall in ASTM F136; CoCrMo alloy type fall in ASTM F75; Type 316 austenitic stainless steel covered in ASTM F138.

3.2 Micro structural characterization of metallic biomaterials

The characterization of biomaterials in terms of micro is a particularly important factor in the interaction of the implant tissue interface due to at least three respects:

- corrosion resistance of biomaterial is correlated with its microstructure;
- microscopic surface inhomogenity, such as crystal grain boundaries or secondary phase precipitates, could be important in protein adsorption on metal surfaces uneven;
- formation of mineralized bone tissue is dependent on bone cells' activity, activity influenced by the superficial topography of the substrate.

The existence of conflicting results in terms of material influence on short-term interactions between bone cells and the various surface layers, may have as a possible explanation the fact that the correlations between various factors that manifest themselves such as umectability and topography of the substrate surface, respectively, the chemical processes at the interface implant biological environment. At a microscopic scale, the surfaces of biomaterials can act differently. On the surface of the biomaterials, can be portions or areas of different functionality, and they may interact differently with biomolecules. For example, many metallic biomaterials contain at least two different phases. Not only that reacts differently with molecules of different phases, and grain boundaries behave differently from the middle of grains. (Smith et al., 1992)

The selected samples were directly analyzed by light microscopy for evaluation according to ASTM standards for each biomaterial in part, in terms of the incluzionary status. After evaluation and compliance with standards in this regard, the samples were subjected to the metallographic attack by chemical reagents specific for each material. Whenever necessary, the metallographic attack was carried out electrochemically. Due to limited space, this paper presents a few representative images (see figure 2).

The sample type 316L austenitic stainless steel was obtained by implementing the solution hardening (1050°C/water) and plastic deformation at cold, with a degree of deformation of 30%. The chemical composition of type 316L steel falls within ASTM F138 limit, the determined percentage of molybdenum (2.19%) is to the lower limit, thus ensuring a low tendency of formation of δ ferrite. In the chemical composition of this steel, copper has not been detected (detection limit of copper by EDS method being 0.1% by weight), which is recommended by ASTM standard F138. The percentage of nickel located at the lower level (12.33%), in conjunction with a sufficiently low percentage of manganese (1.79%) led to the avoidance of appearance of the δ ferrite traces according ASTM F138. Metallographic speaking, the standard recommends the lack of the δ ferrite phase in its structure and also the average of the grain size not exceeding 5, which is a dimension of the grain size with a high degree of uniformity, less or equal than to 100μm. In accordance with the quantitative analysis obtained by the Underwood method (interception method), it has result a grain size according to ASTM E112, of 11.0, which shows a much smaller grain and more uniform than the maximum permissible value in the standard. The structure consists of austenite grains, relatively deformed in longitudinal section and stronger macle than the cross sectional. Following electrolytic attack, both in longitudinal section and cross-sectional, deformation

lines can be observed, where the attack occurred more stressed, which is obvious what is noticed in the images obtained through interferential phase contrast. The lack of compounds (carbides of Cr and Mo) in the structure leads to the assertion that the heat treatment of hardening of formal solution (1050°C/water) was well chosen and leaded. The hardness determinations have been registered a medium value of 341HB, which complies with the requirements of ASTM F138.

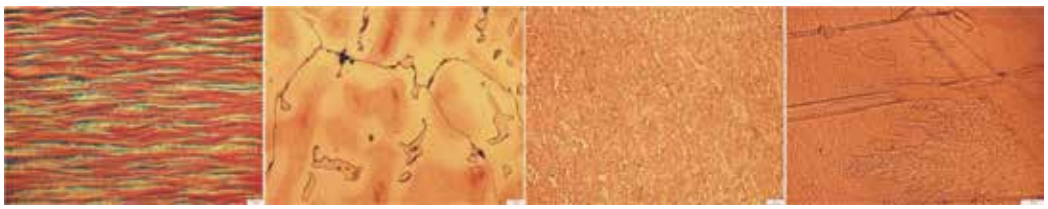

Fig. 2. Bright field optical microscopy images on the analyzed samples surface (from left to right - 316L austenitic stainless steel type, CoCrMo alloy type, Ti6Al4V and CP Titanium).

The examined CoCrMo alloy fits the ASTM F75 standard, both in terms of chemical composition and structural point of view. The able cast microstructure consists of a matrix rich in cobalt, alpha-phase strongly segregated, with interdendritic and limit grain separately compounds. These compounds are mainly formed with one of the carbons: Co, Cr or Mo (which is according date of the specialized literature). (Stanford et al., 2003) Carbide content may decrease the same time with a homogenization of alpha phase, by thermal annealing treatment later realized. According ASTM F75, strength criterion in selecting material for use in making medical implants is not recommended to be important for its rejection. The area occupied by a grain is about 4mm^2, the dendrites' orientation in the grain is predominantly by the grain growth direction. The samples were taken from a 30mm diameter ingot, which is why, because the relatively low speed of solidification, the grain size has large and irregular values. For the characterization of dendritic structure, it has been made measurements of the distances between their axes, resulting in values of maximum 86mm and minimum 4µm.

The Ti6Al4V alloy samples type "ELI" (Extra Low Interstitial) were plastically deformed by hot rolling at 900°C heat treated at 720°C for one hour / air cooling. The resulting structure consists of elongated grains of alpha phase, light, in a matrix of transformed beta phase. Alpha ASTM F136 is finely dispersed, as is the beta one. The Alpha phase is slightly distorted plastic, and the resulting structure after heat treatment is a typical one, which has been taken into account the temperature "beta transus". The quantitative microscopy studies have led to the identification of a score of the grain size of about 12, which shows a degree of advanced finishing the grain size, using the same analytical method as previously investigated biomaterial; this score has a direct effect on increasing resistance to fatigue of the material. The inclusionary state was characterized by measuring the length of the inclusions, resulting in minimum values of 1.44/1.07µm and maximum 37.87/14.25µm. In terms of distribution, it is noted that over 70% of the inclusions have a size smaller than 4.7µm. The average area occupied by inclusions is about 1%, which is an inclusionary state falling standard. The commercial purity titanium has been used to perform experiments covered in ASTM F67 standard and in terms of chemical composition of interstitial content elements that affect decisively technological and operating characteristics is corresponding to the three grade/level. The used biomaterial is in plastic deformed state, with a strain of

about 30%, the grains having diameters between 10 and 100μm, which is consistent with moderate plastic deformation undergone material; the grain size was determined by computerized quantitative analysis, ASTM E112 - Underwood interception method, resulting in a score equal to 11. Also, in the grains that have suffered a stronger deformation, it is noted the presence of slip lines parallel and straight, specific to the compact hexagonal crystallization system, characteristically of this metal; otherwise, it has also been the order of surface corrosion prepared by the attack of the Kroll reagent, used to highlight the structure: parallel slip lines, grain boundaries and ultimately subgrain limit.

3.3 Corrosion resistance of biomaterials evaluation

Based on current knowledge, it is impossible to provide the behaviour of metallic biomaterials in the biological environment, unlike to providing corrosion behaviour of metals in an inorganic fluid. Also, it is very difficult to track the details of the in vivo experiments or in real time. Most times the obtained results represent a collection of snapshots realized under very different conditions. The appreciation potential of the electrode and the variation in time can be determined by the corrosion resistance of a biomaterial. Based on the records can draw variation diagrams of stationary potential in time. A comparative study of curves obtained for the four metallic biomaterials (see figure 3), previously characterized micro structural, reveals that, in terms of stationary potential value, the most electropositive (so the best in terms of general corrosion) is titanium, followed in descending order of Ti6Al4V alloy type, alloy type 316L austenitic stainless steel, and CoCrMo alloy. Studying the potential variation over time, it notes that the first two alloys are stabilized by a relatively small active area, the potential remaining stationary and not representing sudden changes that indicate some form of localized corrosion.

Larger active zones present 316 and the CoCrMo alloys, but steady change in the potential of the two alloys is different in time. Thus, stainless steel has a stable and more electropositive steady potential in time, while in case of CoCrMo alloy (cast) occur sudden changes of the potential. These variations have as the main cause the presence of casting

Fig. 3. Tabulated results of benchmark tests for stationary potential variation over time.

defects. A comparative study of the corrosion cycles indicates that all the alloys present a field of passivation, but the value curve of passivation and the potential area in which appears this field is different.
The lowest intensity of corrosion and passivation current is presented by the titanium. In the case of CoCrMo alloy, which despite having a potential range of passivation current lower, both current corrosion intensity and current passivation intensity are below that of Ti6Al4V alloy and steel 316L, the latter showing values of these parameters higher than those of other materials. In the case of titanium and titanium alloy, the surface is unaffected by corrosion. In the case of type 316L stainless steel immersed surface is frosted, and with points of corrosion. The analysis of the distribution of chemical elements in a direction, the wren area, shows a decrease in iron concentration, in that area is identified chromium oxicarbure, which confirms the results of tests of the same type presented in the specialized literature. The CoCrMo alloy, after corrosion test, also shows a frosted surface on which it can be observed the presence of corrosion products with different shapes and morphologies. At the core configurations, molybdenum corrosion is found, surrounded by chromium carbide. The emergences of these formations that allow the release of large amounts of alloy elements contained in the test environment are due to obtain the worst results in terms of corrosion resistance.
Through the assessment of the corrosion tests, very important results have been achieved for the study of biomaterial - biological environment interaction, which fully comply with the data presented in the specialized literature and provide us a first qualitative ordering of classes of the studied metallic biomaterials (Miculescu et al., 2007). Thus, in descending order in terms of corrosion resistance, we can arrange biomaterials as fallows: commercially pure titanium, titanium alloy Ti6Al4V type, austenitic stainless steel, CoCrMo alloy respectively, results correlate with those obtained from microstructural measurements, which can be seen, in contested areas, the presence of the generating compounds of specific forms of corrosion. The bridging the electrochemical tests by scanning electron microscopy imaging and EDS microanalysis is an important factor in further developments of research because it provides certainty of correctness and validity testing.

3.4 *In vitro* evaluation of metallic biomaterials cytotoxicity

By using cell culture techniques, it can cause lysis (death) of cells, cell growth inhibition, and some specific effects on cells caused by the devices, materials and / or their extracts. By *in vitro* testing of biomaterials we can appreciate a number of functions and characteristics of cells, such as membrane integrity, cytoskeleton, viability, proliferation, protein synthesis, oxidative response, mobility, secretion, response to growth factors, cell-cell interactions.
For cytotoxicity testing of the shown biomaterials, we have prepared polished samples as disks with 5mm diameter and 2mm height. The purpose of processing in this manner is to ensure the unity of biomaterials surface reaction, without surface roughness becomes a factor influencing the behaviour of cell culture. After preparation, biomaterials have been cleaned with organic solvents and washed with distilled and doubly distilled water to eliminate any possibility of foreign elements or metal ions that come into reactive contact with the analyzed materials. Afterwards, the materials were subjected to dried sterilization at 1800º C for one hour, being manipulated in sterile conditions. The elaborated and used experimental models have persuaded the possibility to realize some multifactorial and monofactorial analysis which allow the correlation into a unified system of the needed results to evaluate the implantable biomaterials quality and the effect on the biological

environment. Determining the influence of various metal samples above the fibroblast culture has been done by direct observation using the optical microscopy.
In the short term cytotoxicity tests, it was used a VERO cell line containing fibroblast-like cells. Cells were seeded in sterile polymer plates with a density of 600,000 cells / well. The cells were grown like in some evolving cultures of the monolayer Eagle environment, Dulbeco modified (DMEM), supplemented with 10% fetal bovine serum (FBS) and with added antibiotics (PSN). The atmosphere in the cell culture chamber was 5% CO2 in humidified air. The extraction test (MEM) maintained the report between the outer surface of the material and fluid volume (average) and was constant in all series of materials placed in the experiment. After harvesting the environment (MEM), 2 - 3 washes were done with FBS, pH 7.2 and then were fixed in methanol for 2 3 minutes at 4° C. 10% Giemsa stain was used for staining. The evaluation of cell cultures was performed at 24, 48, 96 hours respectively. After completing 96 hours of the cell culture' development, the metal samples were taken from the culture plates, then they were washed with FBS and fixed in 0.1 M phosphate buffer, to analyze them by light microscopy and scanning electron microscopy, so we can evaluate the follow parameters: monolayer confluence, cells floating degree, morphological changes. The percentage growth inhibition was determined by counting the cells, and the measurements were corrected for control with a negative filter. As a reference experiment, we took a fibroblast culture in which no metallic sample was immersed, the culture being kept under the same conditions of the experiments in which were immersed metallic samples.
The optical microscopy images (see figure 4), during light phases' contrast, have aimed the cellular culture at the limit between cellular culture and immersed sample. At all the studied experiments, a cellular monolayer was obtained, without being registered any free spaces, in which fully lack the cellular culture. In the case of the cellular culture without metallic sample (blank), the fibroblast cells of the culture highlight morph-structural fairly uniform characteristics. Covering the well with cellular formation is about 90%, being obviously the cells' compaction and the appearance of the phenomenon of forming a multilayer culture.

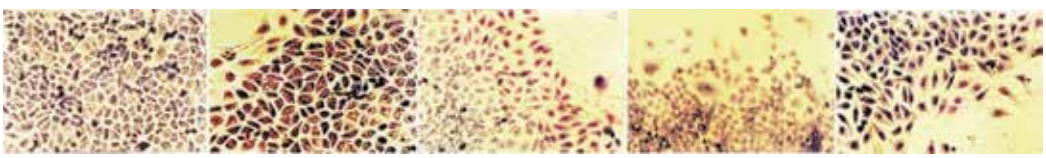

Fig. 4. Cell culture optical microscopy image of the analyzed samples (from left to right – blank, CP Titanium, Ti6Al4V, CoCrMo alloy type and 316L austenitic stainless steel type).

Maintaining the titanium in the presence of the fibroblasts has as result a normal behavior of cells development and a positive chemotactism/chemo attraction related to the material, expressed through the migration and adherence of cells to its surface. The cellular culture joins and forms monolayer, considered as a clear indicator of a favorable biomaterial cell interaction. It can be observed flattening of cell shape and appearance of the cytoplasm emissions which prove the adherence and movement on the biomaterial surface. Significant is the tendency to establish intercellular contacts through extensions, gradually becoming close contacts and cells forming a single compact layer. In all cases, the cells have normal appearance with kernel and obvious nucleoli, the cytoplasm is dense and rich in cellular organelles, and the peripheral cytoplasmic area leads to monolayer formation. This

area, with recognized vesicles in the cytoplasm, shows an intense functional activity, related to the synthesis and secretion of active substances that are necessary for the cells to migrate and establish the implant and other cells interrelations. Covering the studied area with cells is about 85%.

The fibroblast cultures maintained in the presence of Ti6Al4V alloy sample has coverage of 75% of the well area in which the study has been made. The fibroblasts morphology is still normal, the cell-cell and cell-biomaterial attachment being high. The cells' orientation towards the immersed sample in the fibroblasts culture confirms the results presented in the specialize literature on the increased biocompatibility of this alloy. (Futami et. al, 2000)

The cellular culture aspect studied in the presence of the sample made of CoCrMo alloy type is uniform and lighter, covering the well with cells being about 65%, similar to the results presented by many authors. (Puleo & Nanci, 1999). The cellular culture compactibility is hight till an appreciate distance from the biomaterial, in its closures being observed a small number of cells uniformly dispersed throughout the perimeter samples. Sample type 316L austenitic stainless steel has a high degree of toxicity, comparatively with other cells, the fact being highlighted by a reduce cells viability, confirmed by the specialized literature (Kocijan et al., 2004). Even though cell layer density represents approximately 55% from the analyzed surface, the fibroblasts' morphology is normal and uniform. The cells' attachment is manifesting also on the cell-cell interface, but on the biomaterial-cell interface. Finally, depending on the studied biomaterial type, we obtained the monolayer formation which had varied from 90 to 55% of the surface, in some cases, being noticed the pluristratification trend.

Watching the cellular culture *in vitro* tests during 96 hours of investigation, in witness and parallel groups in the presence of the metallic samples, demonstrated the evolution of evolution of cell populations in percentage of proliferating, mobility and adhesion which, even though they had presented some variations, were within general acceptable biocompatibility terms. Obtaining these results can be correlated with the release of ions and particles in the structure and composition of the material in the environment, which would be consistent with the results of corrosion tests. It was also noted that the fibroblasts reached the level of metallic biomaterials surfaces generally tend to migrate onto those surface, and the function of intercellular adhesion is slower (inhibited). The results experimentally obtained are similar to data of the specialized literature where it is presented the same order of the metallic biomaterials' cytotoxicity. (Brodbeck et al., 2001).

3.5 *In vivo* nonfunctional studies on animals

The implant surface structure has a significant influence, both for joining tissue and the strength of adhesion to tissue. As this force is defined as a fraction of the pressing force of the area on which it is exerted, loading in real conditions may be even greater as the surface area is bigger. From this simple consideration, it is clear that a soft surface of the implant, with small area of contact with tissue, presents a lower adhesive strength than a structured surface. The biomaterials' surface properties are commonly grouped into three categories: geometric, chemical and electrical. Geometrically speaking, the substrates with more pronounced topographical features will exhibit a bigger surface for the interaction with proteins.

If it should be used an implant which geometry included angles and edges, the interaction between it and the biological tissue would be influenced, because undesired tensions would

be introduced into the system. To avoid such problem we got implants with rounded edges. Since the rabbit is a relatively small animal, the implants were proportional, but with sufficient large areas that provide qualitative information and allow the production of normal phenomena and processes for such experiments. Given that the chemical, topographical, mechanical and electrical properties can affect the interaction between proteins and cells with the material, it requires a careful characterization of the surface.

The interaction of the intraosseous and intramuscular metal implants is influenced by their chemical composition and surface roughness. The design shape and size of implants was carried out primarily at obtaining nonfunctional specimens with surfaces that offer the possibility to investigate after conducting biological sampling, with many different preparation degrees in terms of roughness and smallest dimensions as possible, so the in vivo test could be done on small animals, cheep, easily maintained and monitored after surgery.

In vivo research undertaken on animals has focused on two areas:

- *The processes evolution of osseointegration of titanium implants*, goal in which have been made three samples of 99.99% pure titanium, metal considered by the specialized studies, as first on the biocompatibility scale, the samples having the parallelepiped shape with equal sides 2,5/2,5/5mm (L/l/h) transcortical implanted in the femoral head of three adult rabbits, according to the ISO 10993indications;
- *Osseointegration of metal implants by the degree of surface preparation*; of human functional prostheses were made rectangular samples with dimensions above mentioned. Each axial face of the sample was prepared by grinding on emery paper of different roughness: P1000 (metallographic polishing), P800, P600 P320 respectively. The samples thus prepared were transcortical implanted in the tibia same subject, an adult rabbit.

Before the implant, the samples prepared by the above methodology were sterilized with γ ray to be biological measured, also being ensured their protection until the implant surgery. To achieve the surgery, it had opted for the rabbit's tranquilization with 1% Vetranquil, followed by general intramuscular anesthesia by administration of 5mg / kg body of Ketamine. This administration was performed before preparing the operative field and about 15 minutes before surgery.

After the antiseptization and isolation of the operative field, it was performed a longitudinal incision along the antero-medial face of the calf for about 4,5cm. With the Pean forceps The Pean forceps the tegument was taken off till the muscular plane level obtaining two flaps "envelope" on both sides of the incision line.

After exposure and longitudinal incision of the tibial cranial muscle fascia, the site had been penetrated, with a Pean forceps, perpendicular to the muscle plan till the bone plane, among the fibers of this muscle. Selling the forceps' arms and its removal permitted the access towards the anterior medial tibia. After the dezinsertion of the muscular fibers the periosteum was taken off, exposing the diaphy bone plate up to the cranial epiphysis. At this level, with the help of rotary instruments at a speed of 5000rpm and under continuously irrigation with saline, are created the geodes, with shapes and sizes about equal to those of the transverse surfaces of implants. The implants are perpendicular inserted in geodes, by percussion. After hemostasis, the wounds are sutured with catgut wire in deep planes and with synthetic yarns in tegument plane.

The antibiotic prophylaxis was realized according standard norms, in unique doze, with cefazolin (cephalosporin generation I) – Lyzolin, which had been intramuscular

administrated 50mg/kg body 30 minutes before the surgery and 6 hours after surgery. 10 days after surgery, the sutures wires were removed.

3.5.1 Biological material sampling

The sampling was realized by sacrificing the subjects, at 2, 4 and 6 months after implantation (titanium implants), 2 months respectively after implantation (the type Ti6Al4V alloy and austenitic stainless steel type 316L) (see figure 5). To be investigated, the samples had been kept 6 hours in saline, had been fixed with 30% glutaraldehyde solution, after that being rewashed with normal saline and ultra pure deionized water, in order to remove organic particles resulting from the soft and hard tissue sectioning.

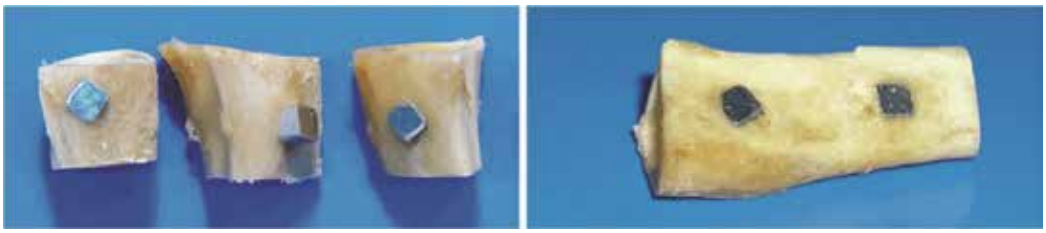

Fig. 5. The biological materials aspect after sampling: left-Ti 99,99% at 2, 4 and 6 months after implantation; right Ti6Al4V and 316L respectively, two months after implantation.

3.5.2 The osseointegration process evolution of the titanium implants

It was analyzed the morphology and topography of the periimplantary bone surface under which it could be systematized the gradual evolution of biological osseointegration processes of the titanium implants. There has been initially formed a periimplantar blood clot from the blood derived through the interruption of the continuity of the haversiene vessels from the edge of the bony defect created by drilling. This blood clot consisted of the figurative elements of blood (erythrocytes and platelets) situated in eyes of network or mesh of fibrin. The elements observed and described through the ESEM images demonstrate the existence of a complex process of periimplantar healing. In the neighbouring tissues of the implant, there are initially produced modifications of the inflammatory type represented by hyperaemia, plasmexodia and formation of a leukocyte and macrophagocyte infiltrate.

Alike bone fracture healing, in the peri-implant healing the blood vessels are damaged, and this results in haemorrhage and the formation of a blood clot, or hematoma. In the bone fracture healing the amount of blood loss from the circulation depends on the location of the fracture. In the femoral shaft, up to one litre of blood can be lost due to extravasation (Cormack, 1987) whereas the amount lost in dental implant placement is significantly less, with the healing site volume measured in millilitres (Davies, 2005). A few days after the implantation, a proliferation of two types of cells become visible: the fibroblasts that will form a periimplantar fibrous callus and endothelial cells that will generate a capillary network of new-formation observed by ESEM as a periimplantar vascular plexus (see figure 6).

This periimplantar well developed vascular network appears to be the result of the angioformation activity of the bone red marrow from the spongious bone. According other studies, angiogenesis is initiated predominantly from post-capillary venules, where endothelial cells degrade the subendothelial basement membrane and migrate and

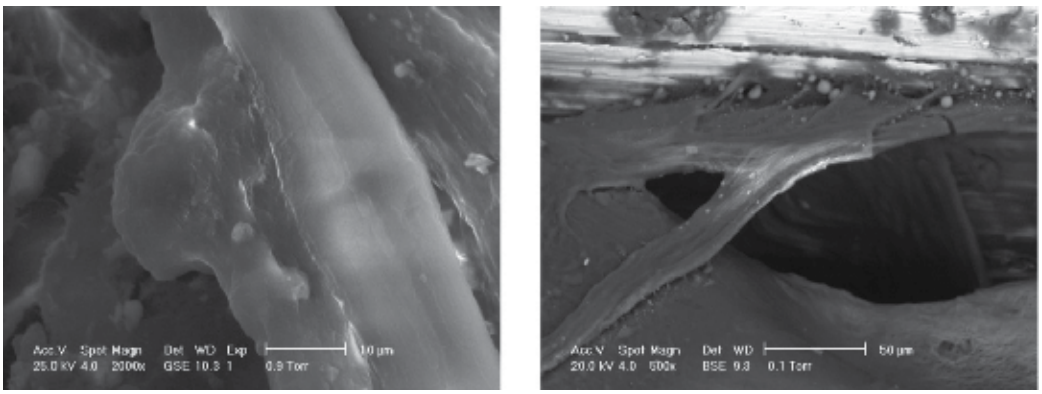

Fig. 6. Left - Extravasation of a blood cell at the level of the periimplantar bony tissue; right - ESEM microscopy image of the peri-implantar vascular plexus.

proliferate to form hollow capillary buds or sprouts. We now know a great deal concerning the molecular mechanisms of angiogenesis, (Lakey at al, 2000) but, at present, we still do not know how the patterns of angiogenesis may be affected by the presence, or surface design, of an endosseous implant, although some attempts have been made to image the vasculature that develops around endosseous implants. (Murakami, 1995;)
Interestingly, (Matsuo et al., 1999) showed some differences in the neovasculature in cortical bone around machined and plasma-sprayed implants that exhibited distance osteogenesis. Other works (Davies, 2005) has also demonstrated that implant surfaces, which are known to promote contact osteogenesis, also exhibit a richer immediate periimplant vascular supply within the healing compartment. The apparition of the neoformation vessels appearance is an important moment of the healing due to the fact that the bloodstream within periimplantar rennet being accomplished, it becomes possible both a number of cellular changes and the acceleration of the metabolism. Our observations showed that through the processes of proliferation of fibroblasts and vascular endothelium, the periimplantar clot is replaced by granulation tissue during 14 days from the surgical

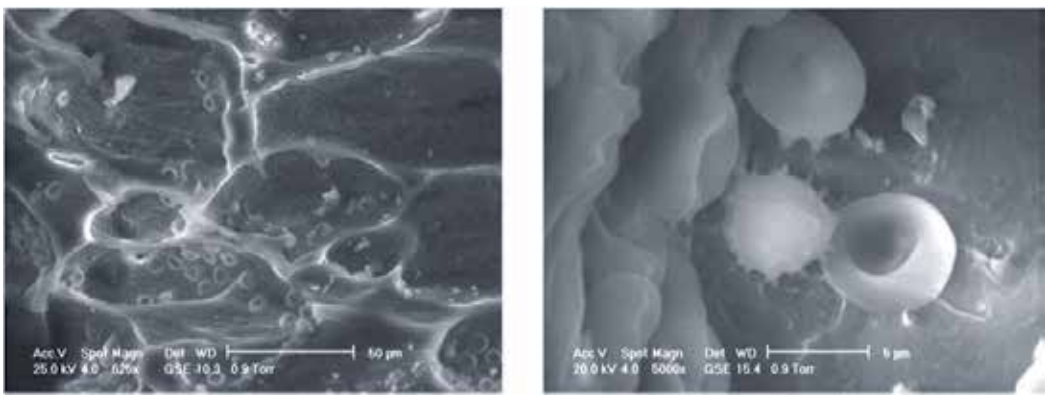

Fig. 7. ESEM image of the mature spongious bone tissue at the edge of bone defect created by drilling: osteoide trabeculae which delimit areoles filled with marrow blood tissue (left); platelets and hematite cells (right).

procedure. At the same time, a process of osteoclasis resorption at the edges of bone defect begins. ESEM technique, the unconditioning of the preliminary preparation of the biological specimen, and implicitly their deterioration, permitted the identification of a very intense cellular activity at the level of the implant-tissue interface. Immediately after implantation, the immune response triggered a proliferation of local macrophages.

While erythrocytes are clearly important in oxygen transport (see figure 7), they can reasonably be assumed to be of little importance in the mechanisms of early peri-implant healing. Platelets, however, are of considerable importance since their activation leads to a rearrangement in cell shape and to centralization of storage granules followed by the release of their contents into the extracellular environment (degranulation); and platelet degranulation releases a number of growth factors, such as platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF-b), together with vasoactive factors such as serotonin and histamine. (Davies, 2005). Conventional wisdom holds that these factors play an important role in the regulation of the wound-healing cascade, (Park et al., 2001) based on in vitro and in vivo evidence of their stimulatory effects on the proliferation and migration of various cell types. (Gruber et al., 2002) For example, both PDGF and TGF-b have been shown to be not only mitogenic for fibroblasts but also chemotactic factors for fibroblasts, neutrophils, and smooth muscle cells, (Lucas et al., 1988) as well as osteogenic cells. (Lind, 1998) Indeed, not only has PDGF been shown to stimulate the proliferation of human osteoblasts, (Tsukamoto et al., 1991) but also is able to stimulate the recruitment, migration, and profileration of bone marrow-derived cells. (Oprea et al., 2003) Following platelet degranulation, arachidonic acid metabolites are secreted that cause vasoconstriction. Within the surrounding tissue, factors VII and III (tissue factor) in the extravasated blood cause the activation of factor X that, together with factor V, causes the conversion of prothrombin to thrombin, which cleaves the fibrinopeptides from fibrinogen to produce the fibrin of the clot (Colman et al., 1987).

Since fibrin, which is the reaction product of thrombin and fibrinogen released into the healing site, can be expected to adhere to almost all surfaces, osteogenic cell migration may be expected towards any implanted material. However, as is well known in dermal wound healing models, connective tissue cell migration is concomitant with wound contraction, which usually begins around the fifth day postwounding. (Peacock, 1984) Indeed, the migration of fibroblasts has been recognized as responsible for wound contraction, with individual cell adhesive contacts transducing a contractile force. (Galbraith et al., 1997) This ability of cells to contract the matrix through which they migrate can be modeled in vitro (Oprea et al., 2003;) and, in the bony peri-implant site could possibly cause retraction of the transitory fibrin scaffold away from the implant surface. The fact that primary osteogenic cells can cause fibrin contraction can be demonstrated by treating primary osteogenic cell cultures with cytochlasin-D, which blocks actin-dependent cell processes, such as cell migration, by capping actin filaments. (Pederson et al., 2001) Thus, the ability of an implant surface to retain fibrin during this wound contraction phase of healing is critical in determining if the migrating cells will reach the former (see figure 8). The implant surface design will play an important role in this fibrin retention. (Dumitru et al., 2005) Indeed, if implants are recovered a few days after implantation, the adhesion of this transitory matrix to some surfaces can be easily visualized. (Ciocan et al., 2010) In our research, after a period of several weeks the replacement of the granulation tissue with immature conjunctive (fibrous) tissue begins.

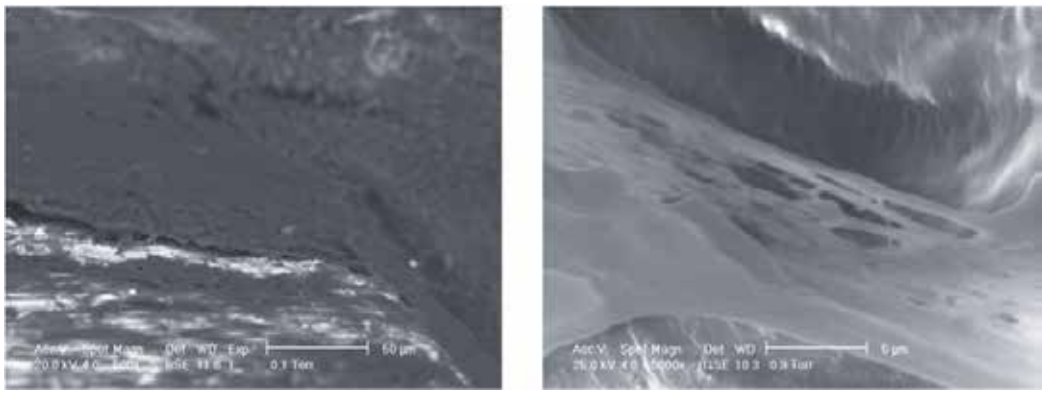

Fig. 8. ESEM images showing replacement of the granulation tissue with the periimplantar fibrous tissue (left) and continuous aspect of connective fibers and fibrocitary intense activity presence (right).

The conjunctive fibers (collagen) form a continuous texture on the implant surface in which there is identified a rich capillary vascularization while the cell population, dominantly of a fibrocitary nature, is much richer in younger elements. The most intense cellular activity was found in the area of biological tissue-implant interface. In the same period, the very first fine trabeculae of neoformation bone begins to appear.

Around endosseous implants, osteoblasts may lay down bone on the old bone surface or on the implant surface itself. This distinction was explored from the early 80'th as two phenomena, distance and contact osteogenesis, by which bone can become juxtapose to an implant surface. The periimplantar osteogenesis mechanism is still not completely elucidated. According to some authors, for about one month after the implantation, a partial bone marrow necrobiosis phenomenon occurs; similar biological phenomena are taking place for the heterotopy transplants. (Hutchinson, 2005) This mechanism seems to be responsible for the development of inductors, which determine the transformation of the mesenchymal cells from the receptor bed into osteoblasts. This phenomenon was confirmed by the image observations from this study. First, bone matrix is synthesized by only one cell: the osteoblast. While some would argue that osteoblasts from different anatomical sites represent different end members of this osteogenic differentiation pathway, the outcome remains the same: it is the osteoblast that makes bone matrix. Indeed, like most secretory cells, osteoblasts are polarized cells, and the direction of their secretory activity is away from the nuclear end of the cell (this is also true for the so-called reverse polarization of ameloblasts). Since the matrix secreted by osteoblasts becomes mineralized as bone tissue, the cell processes of osteoblasts become surrounded by mineralized matrix (and, with their canaliculi, form the only means of vital communication between surface osteoblasts and those that have become completed surrounded by matrix as osteocytes). Thus the osteoblast is irrevocably attached to the bone-forming surface.

The experimental results obtained have validated also the biomineralization three-phased experimental model described by Urist, 1965. According to this theory, the calcium ion is bounded to a protein in the first phase, it is associated in the second phase with phosphate forming Ca-PO_4 protein complex and finally in the third phase, there takes place the formation of the geometric configuration of a nucleation center. The degree of mineralization of conjunctive matrix around implant was counted by EDAX analisys (see

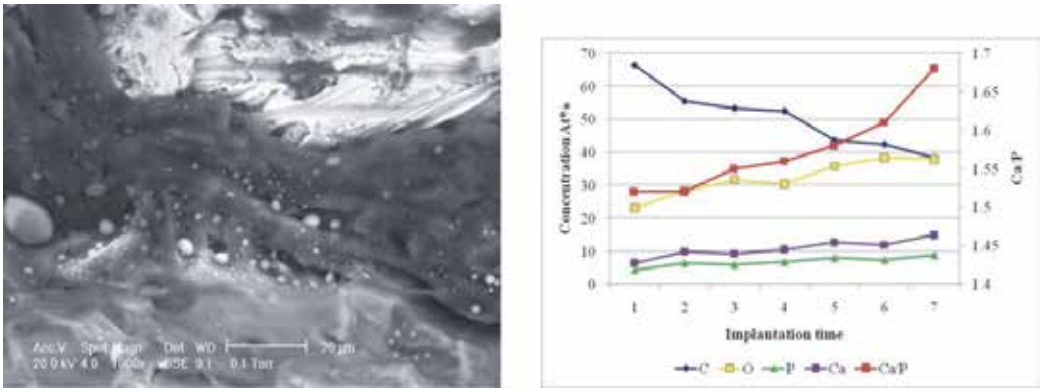

Fig. 9. Periimplantar phosphocalcic precipitations at the level of the vascular walls (left); Basic elements concentration (At%) variation with time after Ti implant insertion (right).

figure 9). The results of this analysis show the continuous mineralisation of the implant surrounding tissue during 6 month after implantation. This graphics presents the variation of the basic elements from the chemical composition of the bone in the "de novo" tissue that surrounds the titanium implants.

Although the concentration of the mineral elements (Ca, P) brought at the peri-implant healing site remain similar during time, the hydroxiapatite precipitations are continuous growing in the same time with reduction of organic fibrous tissue (see table 2). The inflection point of the curve appear at the second half of the 3rd month after insertion when the mineral content of the tissue around implant exceeds the organic matrix one. After about two months from the implantation, the periimplantar tissue consists of a conjunctive fibrous tissue rich in cell population, which suffers intense bony neotransformation processes.

Time	C%	O%	P%	Ca%	Ca/P
7 days	66,34	23,1	4,23	6,34	1,52
14 days	55,48	28,33	6,4	9,79	1,52
1 month	53,32	31,61	5,91	9,16	1,55
2 month	52,5	30,33	6,71	10,46	1,56
3 month	43,66	35,76	7,98	12,6	1,58
4 month	42,45	38,33	7,36	11,85	1,61
6 month	38,36	37,9	8,86	14,88	1,68

Table 2. Concentration (At%) of the chemical elements at the implant-bone interface

At four months from the intervention, the periimplantar fibrous tissue is almost disappeared while the newbone has already started the functional remodelling (see figure 10), while after 6 months from the implantation, the newly formed bone is matured and functional remodeled so that the boundaries of the original bony defect can be hardly seen by the help of the electronic microscope (see figure 11).

Intimate biological mechanisms adherence of bone tissue on the surface of the pure titanium implant is cohesively demonstrated by bone substrate. Contact osteogenesis relies upon

osteoconduction, (Osborn et al., 1980) or the recruitment and migration of differentiating osteogenic cells to the implant surface, together with "de novo" bone formation by those cells on the implant surface. Osteoconduction also occurs during normal tunneling remodeling in bone. In such remodeling, differentiating osteogenic cells are derived from undifferentiated peri-vascular connective tissue cells (pericytes), just as soft tissue fibroblasts have long been recognized as being derived from the mesenchymal cell populations of blood vessel adventia. (Ross et al., 1970) However, a more complex environment characterizes the peri-implant healing site.

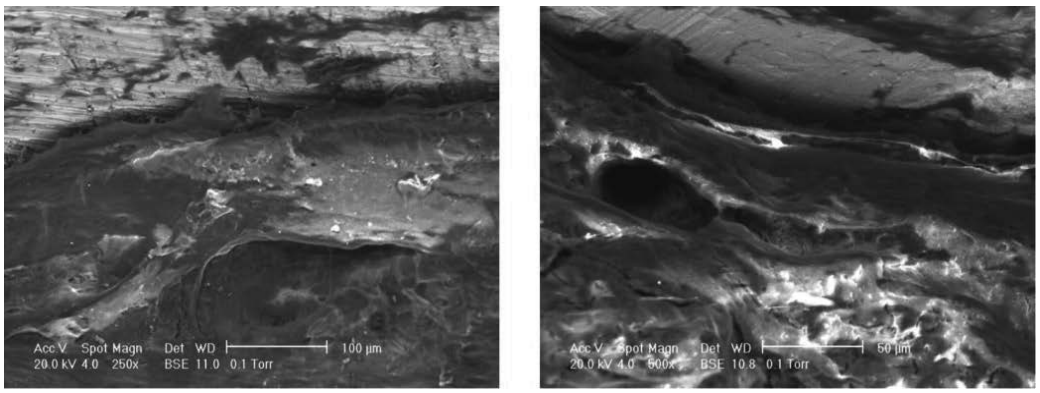

Fig. 10. Periimplantar fibrous tissue transformed into neoformation bony tissue after 3 month (left); after 4 month (right).

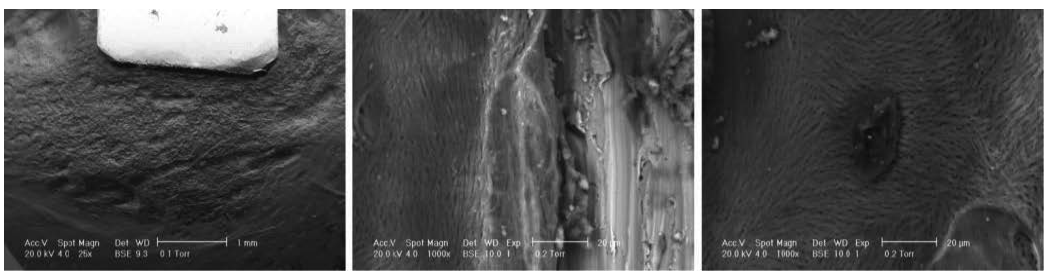

Fig. 11. ESEM macrography at 6 month- periimplantar new bone tissue in the full process of functional remodelling: left - bone wound healed around implant; center - mature bone connected to implant; right - osteon formatted in the periimplant new bone.

3.5.3 Osseointegration according to the roughness of the implant surface

Every samples was analyzed by electron microscopy (ESEM), using secondary electron detector in water vapor environment (GSE), retro scattered electron detector (BSE), respectively by qualitative and quantitative compositional analysis EDAX type. During the analysis by electron microscopy ESEM, it was identified the roughness of the surface, periimplantary hiatus sizes and periimplantary vascular plexus. It was also observed the thickness of the periimplantary fibrous callus under calcification and the morphology of the bone tissue neoformation (see figure 12). During an analysis of the sample of Ti6Al4V alloy under axial incidence, it was macroscopic (X20) noticed both filling the periimplantary

defect with neoformation bone tissue and covering the implant with this one, on some areas. Afterwards, the bone implant interface was examined on each side of the sample.

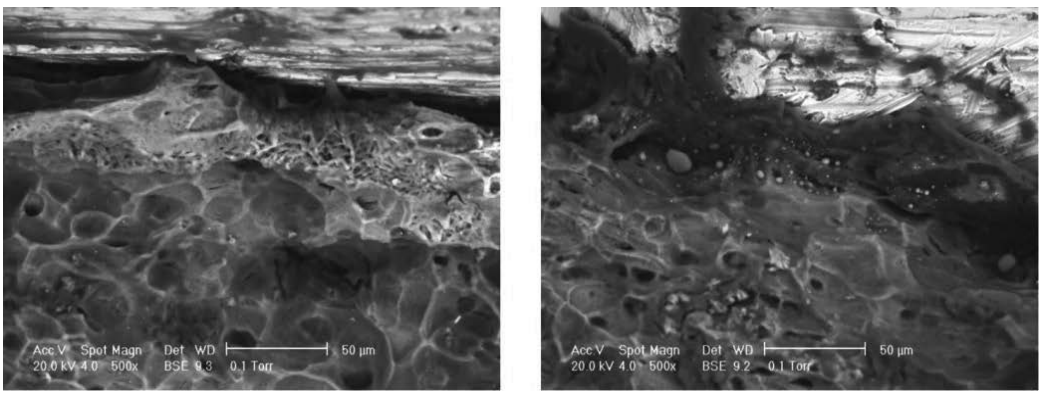

Fig. 12. Interface morphology of newly formed bone and the face 1 of the implant (left), and face 2, respectively (right).

The ESEM imaging identifies roughness surfaces. If training with roughness P600, the periimplantary hiatus has small dimensions, 5µm on average, the vascular plexus being absent. It is also noticed the lack of the fibrous tissue. The new formation of bone tissue presents a remodeling aspect. The surface roughness at this level (P320) (side 2) was the determining factor of the maximum neo-bony adhesion for this implant. However, the mineralization processes of the protean organic matrix are delayed from those presented in the side 1.

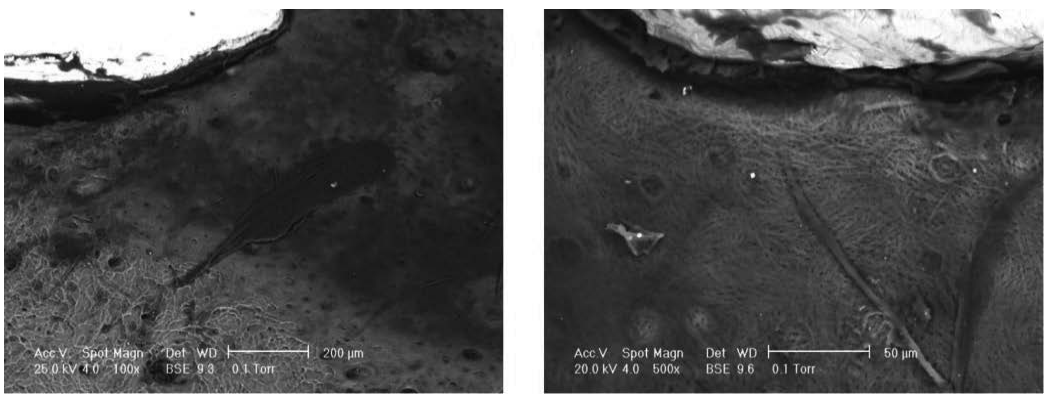

Fig. 13. Interface morphology of newly formed bone and the face 3 of the implant (left), and face 4, respectively (right).

At a roughness obtained with P1000 paper (face 3), on the periimplatary hiatus of 15µm large dimension, it is noticed the presence of a rich vascular plexus (see figure 13). The neoformation bone tissue presents Havers large and remote channels. At a roughness obtained with P800 paper (face 4), the hiatus is 10µm, periimplementary, being observed the presence of uncalcifying fibrous tissue, with thickness of 20 to 25µm. The image captures vascular axis of some Havers collateral channels.

4. Conclusion

In the context of the complexity of implant surfaces, due to the different structures and theirs roughness, also to different chemical compositions, the purpose of this study was to examine the processes of tissue implant interface. To achieve this desideratum, I performed, in this order, determinations regarding the biomaterials' microstructure, their resistance to the corrosion, their behavior and influence above the cellular cultures and, finally, *in vivo* tests on animals. I approached the interaction of implants made of metal biomaterials, with different structures and the surface roughness, with biological tissues, which included discussions on the mechanism of implants' incorporation and on the development and changes of living tissues during remodeling after insertion.

The surfaces of different implants were measured and compared to the bone surface, as it is known that these surfaces are covered, in many cases, with new bone deposits and therefore they serve as fixing points for newly formed bone. The structures' surfaces of the implants were characterized, measured and correlated to the morphometrical evaluations of the tissue - biomaterial contact.

By using cell culture techniques, it can cause lyses (death) of cells, cell growth inhibition, and some specific effects on cells caused by the devices, materials and / or their extracts. The percentage of the growth inhibition was determined by counting cells, and the measurements were corrected for control with a negative filter. As a reference experiment, we took a fibroblast culture in which no metallic sample was immersed, the culture being kept under the same conditions of the experiments in which were immersed metallic samples. It may be noted that a cellular monolayer was obtained, at all the studied experiments, without being registered any free spaces, in which fully lack the cellular culture. After analyzing the obtained images, it may be presented some important characteristics of the studied cellular cultures. In the case of the cellular culture without metallic sample (blank), the fibroblast cells of the culture highlight morph-structural fairly uniform characteristics. Covering the well with cellular formation is about 90%. It is obviously the cells' compaction and the appearance of the phenomenon of forming a multilayer culture. Finally, depending on the studied biomaterial type, we obtained the monolayer formation ranged from 90 to 55% of the surface, in some cases being noticed the pluristratification trend. The main indicators taken into account under the regulations existing standards were: cells' number, proliferation, cell adhesion to the substrate, cells' viability. The cellular culture system appears to be sensitive to the *in vitro* evaluation of metallic biomaterials with cells interactions and cellular response features. The experimental models, developed for investigations on cellular cultures, have been based on the overall assessment and namely that the cellular culture system is a useful means for testing the biomaterials' cytotoxicity and helps to reduce the experiments' number on animals.

The *in vivo* experimental study on animals regarding the interactions of the biomaterial-tissue interface showed that, whatever the samples' type was, it was macroscopically and microscopically found the bio-integrity of all implants. The speed of transforming the periimplantary fibrous tissue into a neo-differentiated bone tissue, respectively the "calcification" of the periimplantary fibrous tissue was significantly higher in terms of quality and quantity for the samples on which hydroxyapatite has been filed.

The observed and described imagistic elements allowed the real appreciation of the influence of metal surface preparation method on the bio-integrity complex process. For none of the samples were observed periimplantary osteolysis processes, which proves the

existence of a favorable interaction between the implanted biomaterial and the biological structure (bone tissue). Whatever the implant type, it was noticed a direct proportionality between the preparation degree of implant surface (mechanical preparation, blasting, chemical attack) and the degree and speed of transforming the periimplantary tissues into mature bone tissue (tissue neoformation inflammatory vascular plexus, fibrous tissue, bone tissue neoformation). The development and periimplantary organic matrix mineralization degree was closely correlated with biochemical changes at the interface. The neoformation bone tissue was intensely mineralized in the case of pure titanium implant, less mineralized in the case of the TiAl64V implant, poorly mineralized for the implantation of Co-Cr-Mo and scarcely mineralized for stainless alloy implant.

By the help of the scan electronic microscopy, using an ESEM XL 30 electronic microscope, it was possible the observation and standardization of the biointegration processes from the interface of the titanium implants. The images presented, show the intimate evolution of the healing processes from this level and represent the fundamental base for the theory for the metallic implant osseointegration**.**

This study made possible the understanding of the intimate cellular and tissue bony integration mechanisms of the titanium metal implants. A few days after the implantation, a proliferation of two types of cells become visible: the fibroblasts that will form a periimplantar fibrous callus and endothelial cells that will generate a capillary network of neoformation observed by ESEM as a periimplantar vascular plexus. Through the processes of proliferation of fibroblasts and vascular endothelium, the periimplantar clot is replaced by granulation tissue during 7 days from the surgical procedure. At the same time, a process of osseoclastic resorption at the edges of bone defect begins. In two weeks, around implant it will be developed an immature conjunctive fibrous tissue. After about two months from the implantation, the periimplantar tissue consists of a conjunctive fibrous tissue rich in cell population, which suffers intense bony neotransformation processes. At four months, the periimplantar fibrous tissue is almost disappeared while the newbone has already started the functional remodelling. In 6 months from the implantation moment, the newly formed bone is matured and functional remodelled so that the boundaries of the original bony defect can be hardly seen by the help of the electronic microscope.

Based on image observations for the surrounding tissues unaffected by the experiment, the validation of the results obtained was possible. The degree of mineralization of conjunctive matrix around implant was counted by EDAX analysis. Our results showed that the concentration of the mineral elements (Ca, P) brought at the peri-implant healing site remain similar during time, while hydroxiapatite precipitations are continuous growing and organic fibrous tissue is reducing. The inflection point of the curve appear at the second half of the 3rd month after insertion when the mineral content of the tissue around implant exceeds the organic matrix one.

There are still many aspects of peri-implant healing that need to be elucidated. According to the authors, there should be rigorously investigated further the chemical-enzymatic mechanisms underlying the osseointegration biological processes.

5. Acknowledgment

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23

Titanium: A New Allergen

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1. Introduction

Buccal allergies represent a growing problem and often go undiagnosed by health professionals. There is an increase in the prevalence of oral allergies to dental materials, and especially to metals used in dental materials.
Titanium, used in orthopaedic devices and oral implants, although considered an inert material, can actually induce toxicity or allergic type I or IV reactions.
Cases of an allergy to titanium described in the literature reflect the difficulty in the diagnosis of this allergy. In case of a suspected contact allergy, epicutaneous patch tests can be done, which consist of applying the allergens which are to be tested to the patient's back. These tests are known to have a diagnostic efficiency of 75% for metal allergy, and can therefore underdiagnose a titanium sensitization or allergy. Blood tests which can be used for the diagnosis of allergies are based on lymphoblastic transformation. They are more sensitive than patch tests, but sometimes lack specificity.
The occurrence of an allergy to titanium could be responsible for successive unexplained cases of failure of dental implants in some patients (known as "cluster patients"). It has been reported that the risk of an allergy to titanium is increased in patients who are allergic to other metals.
In these patients, an allergy evaluation is recommended, in order to exclude any problem with titanium dental implants.

1.1 Types of allergies

The term "allergy" is used to define a specific immune reaction to one or more exogenic substances (allergens).
Four types of allergies have been described. For a review see Gell and Coombs, 1963.
Type I allergy, known as immediate sensitivity, is characterized by interactions between an allergen and IgE present on the surface of mastocytes inducing histamine and other vasopeptide leakage. This is sometimes associated with atopy. This type of allergy may manifest clinically by acute reaction of anaphylaxis, which can represent a life-threatening condition. Type I allergy also causes urticarial reactions on the skin, in the form of erythematous plaques or papules, accompanied by pruritus or tingling sensations.
Type II allergy, known as cytotoxic, or antibody-dependent hypersensitivity, consists of an autoimmune cytotoxic reaction involving IgG and IgM and is encountered, for example, in acute transplant rejection or autoimmune haemolytic anaemia.

Type III allergy, or immune complex disease, is due to precipitation of immune complex formed by antigen-IgG in the blood vessel walls and can induce vasculitic lesions, manifesting in the form of the Arthus reaction, glomerulonephritis associated with streptococcal throat infection or systemic lupus erythematosus.
Type IV allergy, known as delayed-type hypersensitivity, or cell-mediated immune memory response, antibody-independent or contact allergy, is by far the most frequent type of allergy. It is defined as a cell-mediated delayed sensitization reaction (mediated by Langerhans cells and T-lymphocytes), and occurs after exposure to allergens for between ten days and several years. Type IV sensitization is induced by repeated contact of an allergen with skin or mucosa, and follows several steps (Figure 1). In the first step, a hapten penetrates through the skin or through the epithelium of the mucosa, and combines with endogenous proteins to form an antigenic molecule: the allergen. This allergen is captured by the Langerhans cells, which present it to the T-lymphocytes, which become sensitized and thereafter carry on their surface a specific receptor to the allergen. These lymphocytes are known as "memory lymphocytes", and are able to recognize the allergen. Following another contact, the allergen binds to the specific receptor of the memory lymphocytes, which multiply and produce a set of cytokines. An allergic cellular inflammatory reaction takes place within 48 to 72 hours, and is responsible for the clinical manifestations of type IV allergy (Axell, 2001, Grevers and Röcken, 2002, Gawrodger, 2005). Type IV allergy is more frequently encountered in the skin than in the oral mucosa. This has been explained by the fact that Langerhans cells are about ten times more numerous in the layers underlying the skin than in those underlying the oral mucosa. Another reason is the rich network of capillary vessels which characterizes oral mucosa vascularization and which, in turn, eliminates the allergens more quickly from the area (Forte et al, 2008). Clinically, it may manifest as chronic transplant rejection, or more often as chronic dermatitis (eczema).
Allergy types I, III and IV may manifest in the orofacial region (Axell, 2001, Grevers, 2002, Gawkrodger, 2005).
A hapten penetrates skin or mucosa and combines with endogenous proteins to form an allergen. Langerhans cells capture the allergen, and present it to the T-lymphocytes, which become sensitized and thereafter carry on their surface a specific receptor to the allergen. These lymphocytes are known as "memory lymphocytes".

1.2 Clinical manifestations of an allergy in the orofacial region

Patients with an oral allergy complain of various symptoms such as burning or tingling sensations, with or without swelling, oral dryness or loss of taste (Garhammer et al, 2001, Lygre et al, 2003, Gawrodger 2005), or sometimes more general symptoms such as headache, dyspepsia, asthenia, arthralgia, myalgia (Lygre et al, 2003, Vamnes et al, 2004).
The signs of an oral allergy include erythema of the oral mucosa, labial oedema or purpuric patches on the palate, mouth ulcers, hyperplastic gingivitis, areas of depapillation on the tongue, angular cheilitis, perioral eczematous eruption, or lichenoid reactions localized on the oral mucosa (Alanko et al, 1996, Leigh et al, 2001, Vamnes et al, 2004).
Type I allergy may manifest clinically in the orofacial region, in the acute form by Quincke's oedema, characterized by swelling, which, if it involves the upper respiratory tract, can become life-threatening for the patient. In serious forms, it gives rise to urticarial reactions and/or tingling sensations or pruritus, localized in the oral or pharyngeal cavity (Axell, 2001, Grevers and Röcken, 2002, Gawrodger, 2005).

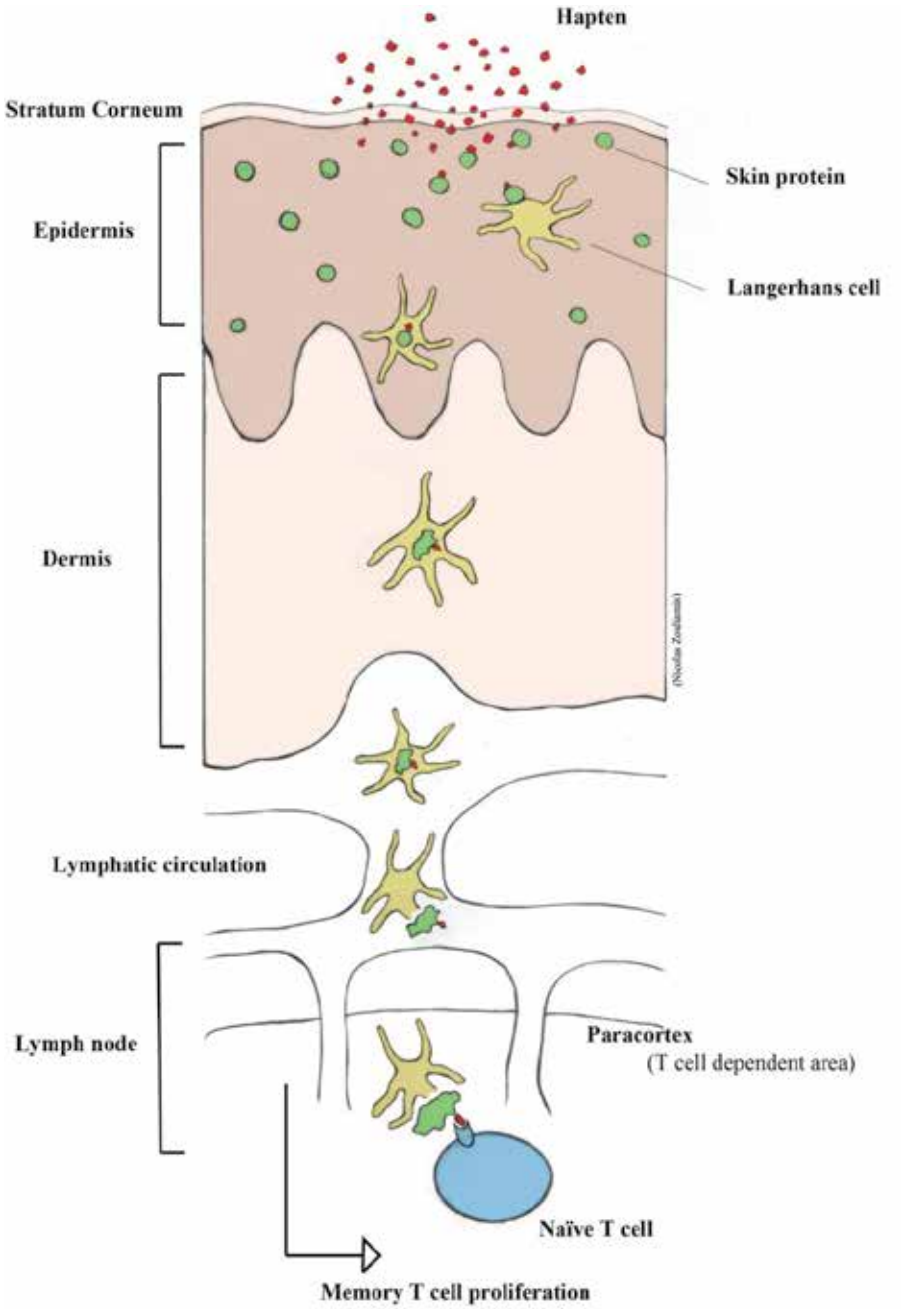

Fig. 1. Development of type IV sensitivity.

Type III allergy in the buccal area can take the form of aphthous ulcerations of the oral mucosa or, in more serious cases, the form of erythema multiforme, with large ulcerations of

the oral mucosa found in association with typical skin lesions "en cocarde" (Axell, 2001, Grevers and Röcken, 2002, Gawrodger, 2005).

Type IV allergy is by far the most frequent allergy encountered in the orofacial region (Gawkrodger, 2005). This type IV allergy may manifest clinically by eczema, angular cheilitis, cheilitis (Figure 2), erythema of the oral mucosa, hyperplastic gingivitis (Figure 3), lichenoid reactions of the oral mucosa (Figure 4), perioral dermatitis or a loss of lingual papillae that can mimic "geographical tongue" (Waroquier et al, 2009) (Figure 5) (Vamnes et al., 2004, Leigh et al., 2001, Alanko et al., 1996). Clinical lesions are generally localized next to structures containing the allergen, as illustrated by lichenoid reactions just in front of amalgam fillings containing mercury (Figure 6), or the mucosa of the palate next to a prosthesis containing methacrylate resin (Figure 7) (Evrard and Parent, 2010).

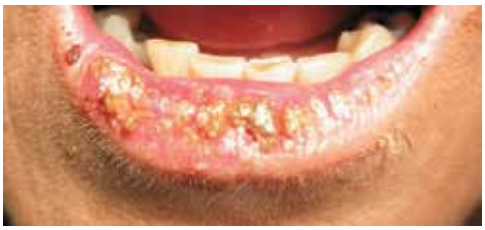

Fig. 2. Contact cheilitis in a patient who has developed an allergy to a component of her lipstick.

Fig. 3. Hyperplastic gingivitis associated with a contact allergy to gold. There is a prosthetic gold bar in the upper jaw.

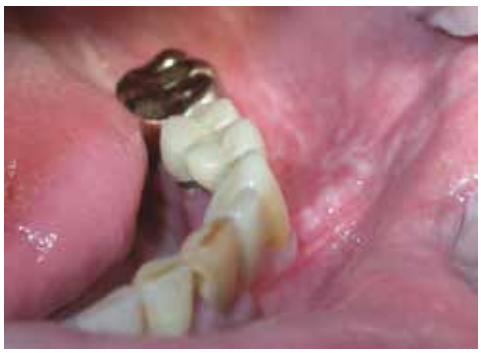

Fig. 4. Lichenoid reaction of the oral mucosa, associated with a contact allergy to gold. The patient has a gold crown on tooth 36.

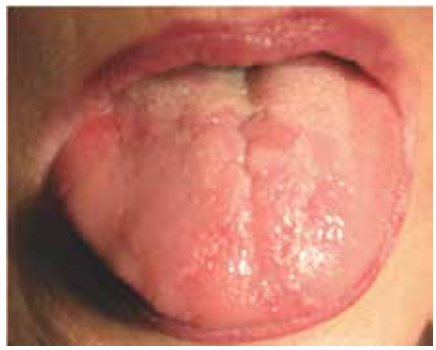

Fig. 5. Depapillation of the tongue, mimicking a geographical tongue, associated with a contact allergy to mercury and gold.

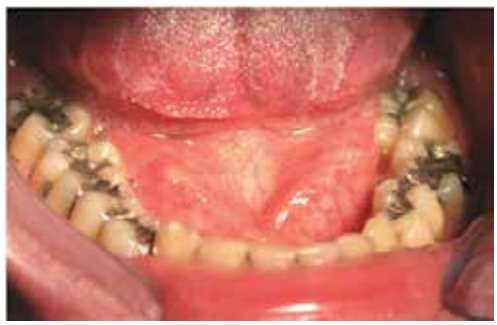

Fig. 6. Lichenoid reactions on the mucosa of the tongue, associated with a contact allergy to mercury. The patient has amalgam filling in his teeth.

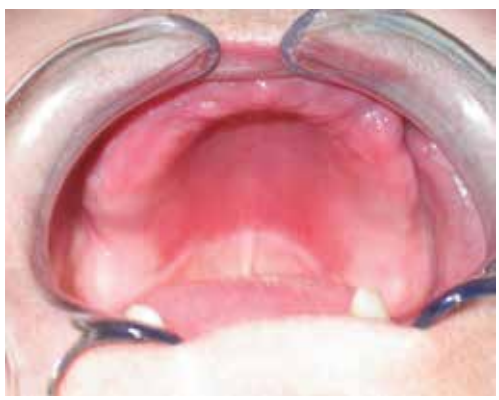

Fig. 7. Erythema of the palate in the area in contact with a resin prosthesis, in association with a contact allergy to methyl methacrylate.

In type IV allergy, patients complain of burning or tingling sensations of the oral mucosa, sometimes of dryness of the mouth, or a metallic taste (Lygre et al., 2003, Gawkrodger, 2005). Burning sensations ("burning mouth") can reach a frequency of 72% in patients with a contact allergy to dental materials (Garhammer et al, 2001, Waroquier et al, 2007). Other

causes can give rise to the same signs and symptoms as those found in allergy; in such cases it is necessary, when faced with burning sensations and/or erythematous patches on the oral mucosa, to exclude metabolic causes such as iron, B12 or folate deficiency by doing a blood test, and to rule out the possibility of a fungal infection, taking a swab of the lesion and culturing it, before going on to allergy testing.

1.3 Diagnostic tests for allergy

The diagnosis of a contact/type IV allergy is typically based on the patient's medical record, clinical findings and the results of epicutaneous tests.

Epicutaneous tests are known as "patch tests". The principle is to apply different allergens which are to be tested on the patient's back. The results are read after 48 and 72 hours for most allergens, and also after 10 days for gold testing (because gold can give rise to late reactions). If the test is positive for an allergen, the area of skin corresponding to the tested allergen will show an eczematous reaction: erythema and/or vesicles and pruritus (Alanko et al, 1996, Grevers and Röcken, 2002, Gawrodger, 2005). There is a limit to the utility of patch tests, given their poor sensitivity, which has been shown to be about 75% for type IV metal allergy (Forte et al, 2008). Some authors report a lack of standardization in the patch tests, especially for allergens such as titanium (Fischer, 2008, Forte et al, 2008). According to these authors, patch tests have been validated only for dermal sensitization to allergens, and their relevance for systemic sensitization to allergens such as titanium (mucosal and internal) is limited.

Thus, patch test may underestimate the real prevalence of a metal allergy.

Skin tests (prick tests) help in the diagnosis of a type I allergy. They consist of intradermal inoculation of the antigen (Yamauci et al, 2000). The results are read within 15 to 30 minutes. If the test is positive, there will be a red, papular and/or vesicular reaction of the skin. Prick tests are not routinely done for the diagnosis of an oral allergy to a dental material, because most of the reactions to dental material are Type IV. Nevertheless, prick tests are used in the diagnosis of a food allergy, which may manifest by aphthous lesions of the oral mucosa (Scully, 2004).

A blood test can help in the diagnosis of a type IV allergy. *In vitro* testing with the lymphocyte transformation test (LTT) can detect both dermally and non-dermally (mucosal) sensitizing allergens. It has been used to detect hypersensitivity leading to both local and systemic effects resulting from dental allergies, in particular in the optimized version of LTT known as MELISA (Stjekstal et al, 1994, Muller and Valentine-Thon, 2006). The patient's lymphocytes are exposed to the allergen to be tested. If they have previously been sensitized to the allergen, they will undergo proliferation, which is measured using incorporation of radioactive nucleotides (tritiated thymidine). Some authors have reported that non-relevant proliferation of lymphocytes could happen in non-sensitized patients (Fisher's, 2008), leading to some false-positive results.

It would be valuable in the future to have a test that would respond with good sensitivity and good specificity, thus providing a better diagnostic tool.

2. Allergy to dental materials

There are various dental materials that have been shown to be capable of triggering an allergic reaction in the oral cavity, and contain metals (nickel, cobalt, chromium, gold, palladium, mercury), fragrances (balsam of Peru, fragrance mix, eugenol, cinnamic

aldehyde, essential oils), topical medicines (including some synthetic steroids), preservatives, resins, colourings and other products contained in toothpastes (Lesueur and Lannias, 2003, Evrard and Parent 2010).
It has been shown that dental materials can give rise to type I, type III or type IV hypersensitivity. In type IV allergy, which is by far the most frequent type encountered in the oral cavity, signs and symptoms can appear between a few days and several years after the beginning of contact with the allergen (Gawrodger 2005, Vamnes et al, 2004, Garhammer et al, 2001, Lesueur and Yiannias, 2003, Evrard and Parent, 2010).

2.1 Dental metals involved in oral allergy

In the field of dentistry, dental metals are used in precious and non-precious alloys, for producing removable or fixed prostheses, or dental fillings. Titanium is used for its excellent biocompatibility in implantology and maxillo-facial surgery and will be the subject of Chapter 3.
Metals contained in dental alloys may corrode in an electrolytic solution such as saliva. Corrosion will be greater in the case of multiple metals, given the electric potential difference induced following contact between different metals (Messer and Wahata, 2002) (Figure 6).
It has been described that the mercury contained in amalgam dental fillings and gold used in alloys for fixed prostheses can give rise to allergic reactions, in the form of lichenoid reactions of the oral mucosa (Koch and Bahmer, 1999, Yiannias et al, 2000, Laine et al, 1997, Evrard and Parent 2010). In a study on 19 patients with lichenoid reactions of the oral mucosa in the vicinity of amalgam fillings (Koch and Bahmer, 1999), it has been shown that 78.9% of patients proved to be sensitized to mercury and that the removal of dental amalgams allowed healing of the mucosal lesions in 86% of cases. In another study on 46 patients with an oral lichen planus (Yiannias et al, 2000), 14 patients had an epicutaneous test positive to gold. In this study, after removal of gold from the mouth, the oral lichen planus disappeared in 10 patients out of 14. Another study on 118 patients with lichenoid lesions in the mouth (Laine et al, 1997), shows that 80 of them had a contact allergy (type IV allergy) to one or more metals: 78 to mercury, 11 to gold, 17 to nickel, 4 to cobalt, 3 to tin, 2 to palladium and 1 to chromium.
All the authors point out that healing of the lesions takes place in a large number of cases after removal of amalgam dental fillings or prostheses containing gold, in the case of a diagnosed contact allergy to mercury or gold (Lygre et al, 2003, Koch and Bahmer, 1999, Yiannias et al, 2000, Laine et al, 1997, Evrard and Parent 2010).
Cobalt is a metal used in alloys in removable or fixed prostheses, and represents a known allergen giving rise to oral manifestations in the case of an allergy (Forte et al, 2008). In a recent study (Waroquier et al, 2009), it has been shown that the burning sensations and intense pruritus on a geographical tongue were due to the cobalt contained in the hook of a removable resin prosthesis replacing a tooth 51 lost through trauma in a 7–year-old child. In this case, type IV allergy had been diagnosed by a positive patch test to cobalt. After removal of the hook containing cobalt, all the patient's signs and symptoms had disappeared.
Burning sensations represent a frequent complaint in patients allergic to one or more dental metals (Alanko et al, 1996). Our team conducted a pilot study to try and establish the prevalence of oral allergies to dental materials in patients complaining of burning sensations of the oral mucosa (Warroquier et al, 2007). In this study, other causes of burning sensations were excluded by a blood test (in order to rule out a metabolic disturbance such as iron, B12 or

folate deficiency), and by swabbing and culture, in order to rule out a fungal infection. Allergy testing revealed that, among that population of 26 "burning mouth" patients, 34.6% were allergic to nickel, 19% to chromium, 11.5% to gold, 11.5% to cobalt and 7.7% to mercury. Only 11.5% of the patients did not display a positive result for an allergy to any of the metals tested. These results are about three times higher than the known percentages of allergies to metals in the general European population, which have been reported to be 20% for nickel, 5.4% for chromium, 6% for gold, 6.5% for cobalt and 2.9% for mercury (Forte et al, 2008).
In a study on 294 patients complaining of both general and local signs (including burning sensations of the oral mucosa), epicutaneous tests have shown an allergy to nickel in 28% of the patients, to gold in 23%, to cobalt in 14%, to palladium in 9% and to mercury in 6% of cases.
All these studies show that the prevalence of allergies to metals in patients presenting signs or symptoms of an oral allergy is higher than the prevalence of allergies in a general European population.

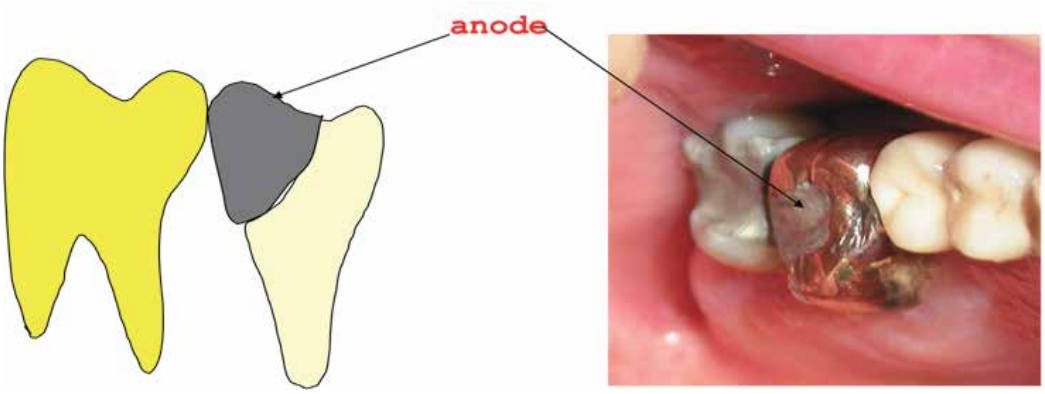

Fig. 6. Multiple metals in contact with each other.

Gold alloy in contact with silver amalgam restoration. The silver amalgam represents the anode pole, and gold alloy the cathode pole. There is an electric potential difference, and electrolytic corrosion within the electrolytic saliva solution may occur.

3. Titanium: a metal allergen of growing significance

Titanium is a metal used in medical and dental fields, because of its properties of strength, corrosion resistance behaviour and excellent biocompatibility due to the formation of an oxide layer on its surface (Steinemann, 2000). In oral and maxillofacial surgery, titanium alloys are used for ostheosynthesis plates used in traumatology or maxillofacial surgery, and for dental implants. In implantology, titanium is used most often in the form of "commercially pure" titanium (cpTi: grade I to IV alloys). CpTi contains trace elements (N, C, H, Fe, O, Al, V), that can represent 1% of its volume, and can enhance its mechanical properties and resistance to fracture (Steinemann, 2000, Messer and Wahata, 2002, Geetha et al, 2009). In implantology, titanium is used also in the form of an alloy (grade V titanium): Ti-6Al-4V, Nitinol (Ti-Ni), Ti-Co (Geetha et al, 2009) or titanium-zirconium, especially in cases where narrow implants are recommended (Evrard and Atash, 2009).

The insertion of titanium dental implants can cause internal exposure, and it has been proved that concentrations of 100-300 ppm titanium can be observed in tissues surrounding implants, as well as in regional lymph nodes and pulmonary tissue (Wennerberg et al, 2004). Under unfavourable conditions: acidic pH occurring in a peri-implantitis for example, or excessive mechanical forces on the implant, or close contact of the implant with another metal (amalgam, gold alloy), titanium may corrode and release titanium ions or microparticles of titanium in the area of bone surrounding the implant, which can induce inflammation in affected tissues (Messer and Wataha, 2002). It has been suggested that this mechanism may play a role in loosening orthopaedic endoprostheses (Nakashima et al, 1999), but it has not yet been demonstrated as a factor in the failure of dental implants. Titanium has also been reported to activate macrophages, which may secrete cytokines involved in various disease processes (Muller and Valentine-Thon, 2006). Titanium has a high affinity for proteins, and titanium ions (haptens) released by corrosion may combine with endogenous proteins to form antigenic molecules, captured by Langerhans cells, presented to T-lymphocytes, which in turn can cause the patient to be sensitized to titanium.
People are exposed to titanium through environmental sources. Numerous devices such as watches, jewellery and spectacle frames are made of titanium alloy. Most environmental exposure to titanium results from exposure to TiO2 (E171), which is used in cosmetics such as sunscreens, make-up and deodorants, and in food, medicines or toothpaste. It has been shown that our body can contain a concentration of 50 ppm of titanium (Forte et al, 2008). From then on, sensitization to titanium is possible, through environmental sources, and not necessarily from previous contact with dental implants.

3.1 Allergy to titanium

The first cases in which delayed sensitivity to titanium was suspected, with a local granulomatous reaction, have been described in patients wearing a cardiac pacemaker (Peeters et al, 1984, Yamauchi, 2000). In these cases, the diagnosis of a titanium allergy was made with, respectively, a positive patch test with a little square of the pacemaker placed in artificial perspiration (Peeters et al, 1984), and a positive intra-dermal reaction to an eluate of the surface of the pacemaker (Yamauchi et al, 2000).
More recently, a well documented case of type IV allergy to titanium contained in an osteosynthesis plate inserted for a fracture of the hand was described. The patient had developed eczema on the hand within a few weeks of the insertion of the plate, and an absence of bone healing. A lymphoblastic transformation blood test (LTT) proved positive, although the patch test for TiO2 was negative. Following the removal of the plate, the LTT gave negative results and the eczema disappeared (Thomas et al, 2006).
Admittedly, it may be difficult to extrapolate results in cases of dental and orthopaedic implants. The skin and the oral mucosa behave differently regarding their potential to develop an allergic reaction (the number of Langerhans cells is greater in skin, the vascular network is more highly developed in the oral mucosa, and the latter is less permeable to antigens). Moreover, implant prosthetic abutments are coated in the mouth with glycoproteins which act as a protective barrier hampering contact between the metal and the mucosa, and the intraosseous contact surface is smaller in dental implants than in orthopaedic ones (Fischer, 2008). In orthopaedic allergy cases, biopsies generally reveal a granulomatous reaction, with numerous macrophages in the vicinity of the prosthesis. This is not the case with dental implants, and different immunological mechanisms may be

involved in the two cases (Messer and Wataha, 2002, Nakashima et al, 1999, Muller and Valentine-Thon, 2006).

The case of a patient with facial eczema suggestive of type IV allergy to titanium following the placement of a mandibular dental implant has been reported (Egusa et al, 2008). In this case, an allergy to titanium was diagnosed by the combination of clinical signs (appearance of eczema within a few weeks of implant placement), and a positive blood test (LTT). The diagnosis of allergy to titanium was confirmed by the disappearance of eczema following removal of the implants.

More recently, it has been demonstrated that clinically-relevant hypersensitivity to titanium can occur following exposure to titanium (Muller and Valentine-Thon, 2006). In that study, 56 patients had developed severe health problems (muscle and joint pain, chronic fatigue syndrome, neurological problems, depression, or acne-like facial inflammation) after receiving Ti-based dental implants, orthodontic braces or endoprostheses. The authors used the MELISA test, which had proved effective in the diagnosis of hypersensitivity to metals (Stejskal et al, 1994), as well as patch tests. Of the 56 patients tested with MELISA, 37.5% were positive, 28.5% ambiguous and 33.9% negative to titanium. Among the 33.9% negative to titanium, 57.9% showed lymphocyte reactivity to nickel or other metals. All 54 patch-tested patients were negative to titanium. Following removal of the implants, a remarkable clinical improvement was noticed and among the 15 retested patients this clinical improvement correlated with normalisation of MELISA reactivity.

In a prospective study over a three-year period (Sicilia et al, 2008), 1500 patients with dental implants were monitored. In that study, an allergy to titanium was diagnosed on the basis of clinical signs of an allergy appearing following implant placement, or on the basis of an unexplained failure of the implant, and a patch test positive for titanium, tested in the form TiO2, or for a titanium metal powder in aqueous solution. The results of this study show that 0.6% (1/800) of patients with dental implants have a patch-test positive for titanium, but 0% (0/35) of the patients without implants have this result. The epicutaneous tests are positive in 50% (8/16) and 62.8% (5/8) of the patients who show signs, respectively, of an allergy following implant placement, and unexplained early failure of one or more implants. In patients having allergies to one or more metals (nickel, chromium, cobalt, gold or mercury), 5.3% (1/19) have a patch test positive for titanium. It should be noted that the authors do not report the characteristics of the titanium in their patients (titanium alloy or commercially pure titanium?). The rate of corrosion is higher with titanium-aluminium-vanadium implants, which may have an influence on the prevalence of allergic reactions.

All these reports reflect the difficulty in evaluating suspected titanium hypersensitivity. It is known that the epicutaneous tests used in the diagnosis of an allergy to titanium are still not very sensitive, and there is no standardized valid patch-test preparation for this. Moreover, the lack of concordance between the results of patch-tests and blood tests (MELISA) is illustrated in the above study (Muller and Valentine-Thon, 2006). Given the difficulties of diagnosing a titanium allergy, studies probably underestimate the true prevalence of titanium allergies in patients having dental implants.

3.2 Diagnosis of a titanium allergy

The above studies demonstrate that titanium can induce clinically relevant hypersensitivity and other immune dysfunctions in certain patients chronically exposed to this metal. Titanium should no longer, therefore, be considered biologically inert. In implantology, it is reasonable to say that allergy testing for titanium is indicated in some cases.

3.2.1 Before implant placement

It has been shown that many patients suffer from multiple allergies (Forte et al, 2008), and that people with a history of allergy to metals or jewellery have a greater risk of developing a hypersensitivity reaction to a metal implant (Hallab et al, 2001).
Furthermore, although titanium allergy has a low prevalence rate, for patients with a previous history of allergies, it may be advisable to carry out a metal allergy assessment and allergy testing before placing permanent implants, in order to avoid a failure of the implant due to an allergic reaction to titanium.

3.2.2 After implant placement

The failure of implants has been widely studied, and the main causes of dental implant failure are infection and overload (Esposito et al, 1999a, 1999b, 1999c). However, some failures are difficult to explain, such as spontaneous rapid exfoliation of the implant, or the successive failure of implants in the same patients, known as "cluster phenomenon", without any infection or overload risk factor identified. Authors agree that in these cases, there must be a systemic determinant of failure that has not been identified or understood (Wood and Vermilyea, 2004, Chuang, 2005).
An allergic reaction can be reasonably suspected after dental implant placement, on the basis of signs or symptoms associated with allergy, such as rash, urticaria, pruritus, swelling in the orofacial region, oral or facial erythema, eczematous lesions of the cheeks, or hyperplastic lesions of soft tissue (the peri-implant mucosa) (Mitchel et al, 1990). In these cases, allergy testing should be performed.

3.2.3 Tests available for the diagnosis of an allergy to titanium

As described in chapter 3.2, there is no consensus on how a sensitization and/or allergic reaction to titanium should be explored. It is also difficult to compare the results from different studies related to titanium allergies, because some refer to the use of patch tests, while others use prick tests and/or blood tests (LTT, MELISA) (Sicilia et al, 2008, Valentine-Thon et al, 2006).
To date, no standard patch test for titanium has so far been developed, and positive reactions to titanium have only rarely been demonstrated with skin testing (Forte et al, 2008).
The sensitivity of patch tests has been shown to be about 75% for type IV metal allergy. Some authors have suggested that 0.1% and 0.2% titanium sulphate solution and 0.1% and 0.2% titanium chloride are successful reagents for the skin-patch tests and could be a valuable alternative to the titanium oxide normally used for patch testing (Okamura et al, 1999), but so far no study related to dental implants allergies has used the method.
The MELISA test has been validated to detect sensitization to titanium and other metals (Sjekstal et al, 1999, Muller and Valentine-Thon 2006), but there can be some lack of specificity in lymphocyte proliferation.
It would be valuable to have a sensitive and specific test that could help in the diagnosis of titanium sensitization or allergy.

3.2.4 Future prospects in the diagnosis of sensitization or allergy to titanium

Interleukin-17 and Interleukin-22 are produced by a subset of a recently defined T–cell line, known as Th-17. IL-17 has been associated with many inflammatory diseases in humans, including rheumatoid arthritis, organ rejection and asthma. It has been showed that the

number of Th-17 cells and the expression of IL-17 was significantly increased in positive patch test biopsies, regardless of the nature of the antigen (Oboki et al, 2008, Zhao et al, 2009, Larsen et al, 2009).

IL-22 is a critical mediator in mucosal host defence, which has complex pro-inflammatory and anti-inflammatory and autoimmune effects. It has been shown that patients with contact dermatitis to nickel had a significantly higher IL-22 blood level, compared with control (Ricciardi et al, 2009), indicating a possible involvement of IL-22 in the pathogenesis of human allergic contact dermatitis.

It would be interesting to develop a blood test, based on the measurement of the production of IL-17 and/or IL-22 by lymphocytes, in order to be able to diagnose with certainty a sensitization to titanium.

Our team is currently trying to develop a technique, using flow cytometry, for the purpose of detecting the activation of lymphocytes stimulated by a metal, and measuring different mediators (cytokines, inflammatory mediators) released in response to the metal.

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