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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

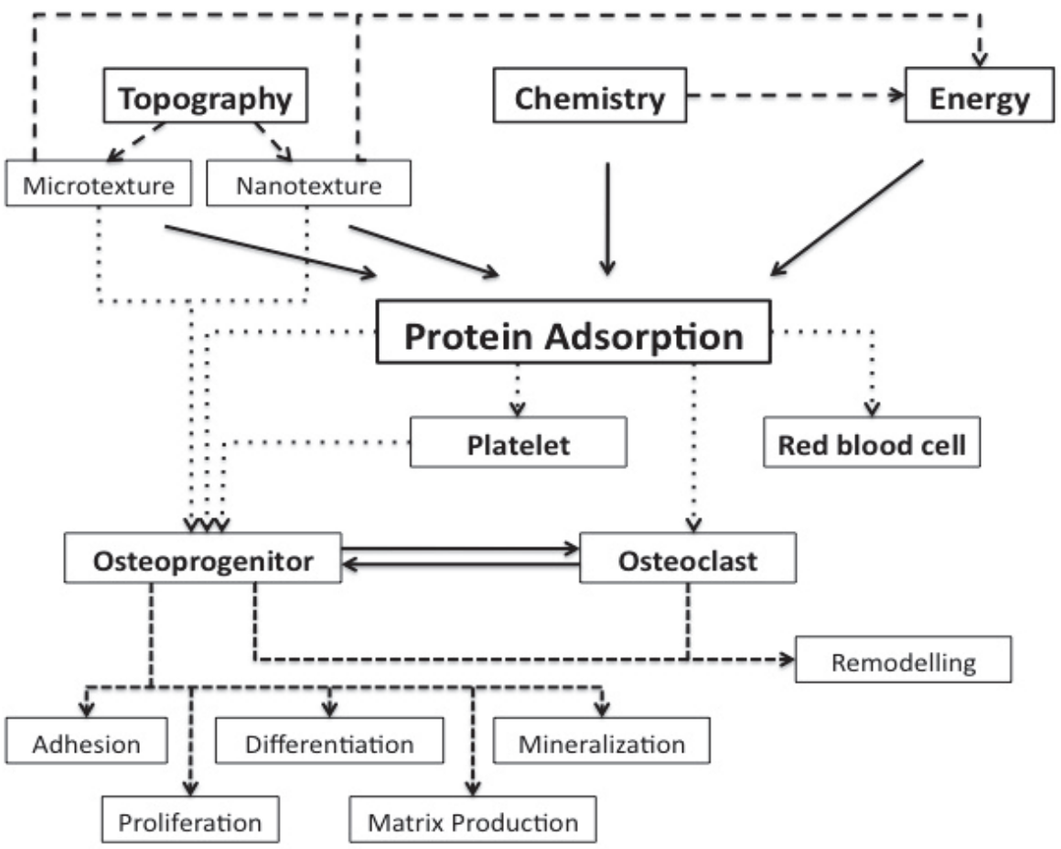

Fig. 1. Effect of submacron surface characteristics of the implant on the osteogenic response

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)

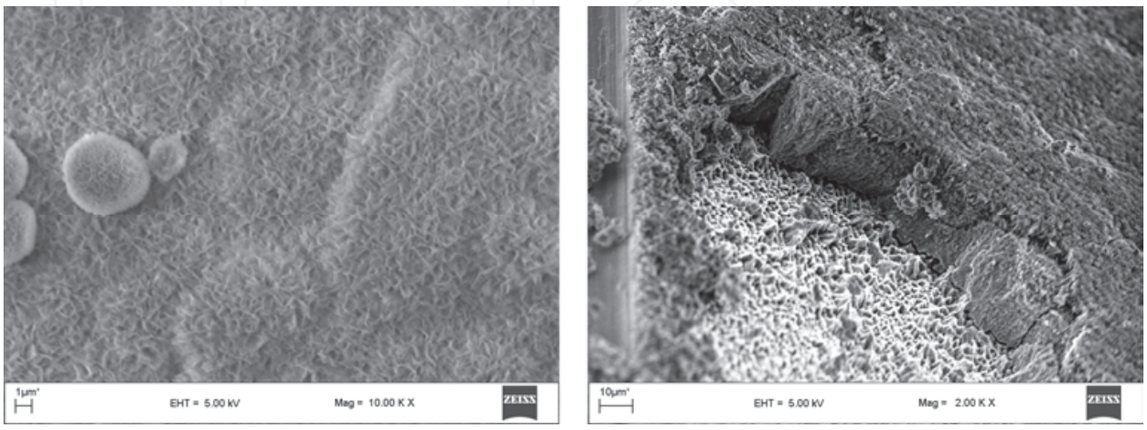

Fig. 2. Top and cross sectional SEM images of biomimetic Ca-P coatings

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).

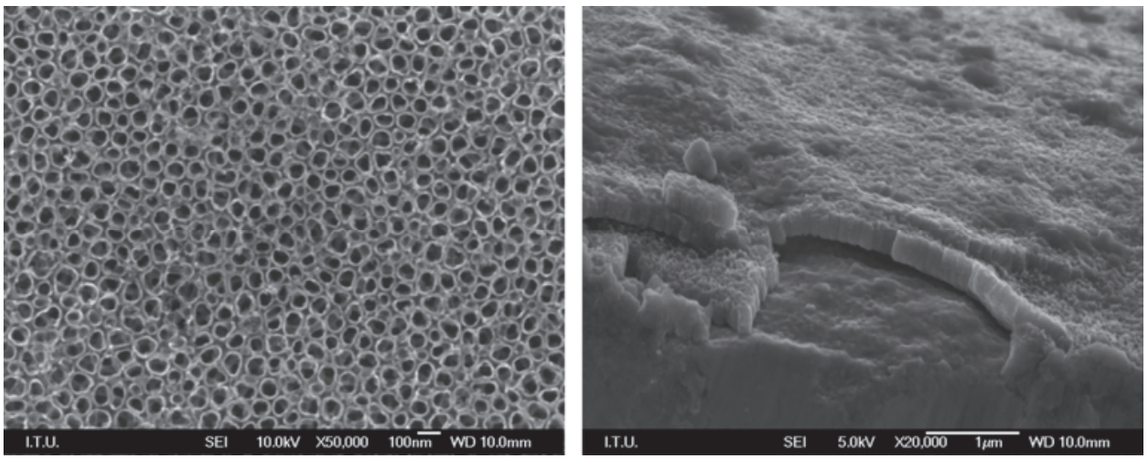

Fig. 3. Top and cross sectional SEM images of titania nanotubes

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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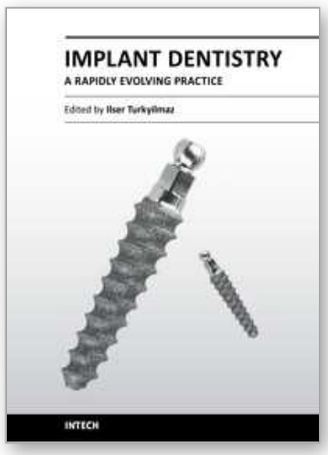

Implant Dentistry - A Rapidly Evolving Practice

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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. 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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