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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.

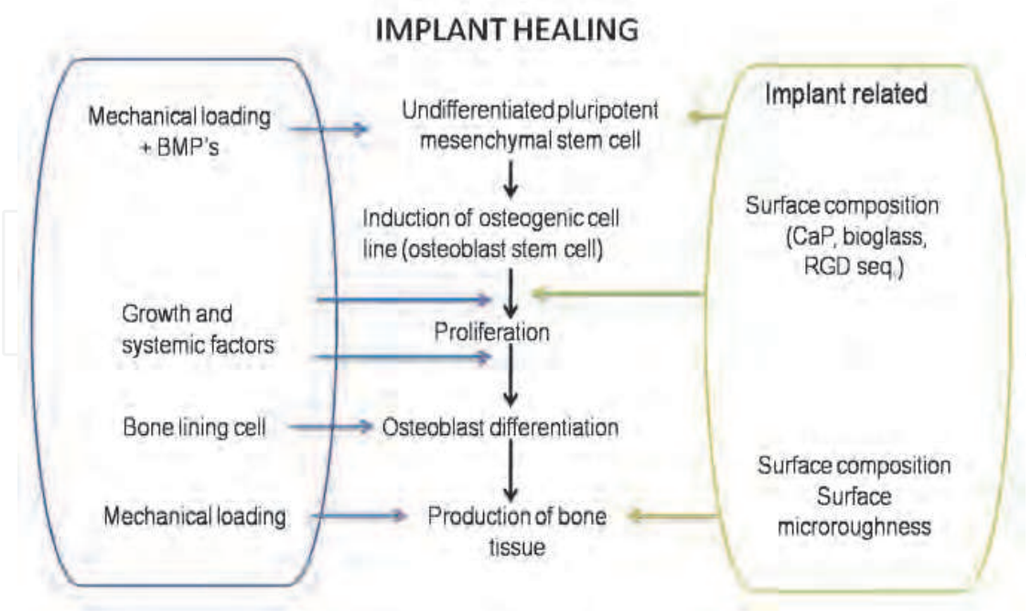

Fig. 1. The implant healing process - The surface composition, roughness and topography are interrelated surface characteristics that influence the biological response to an implant.

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.

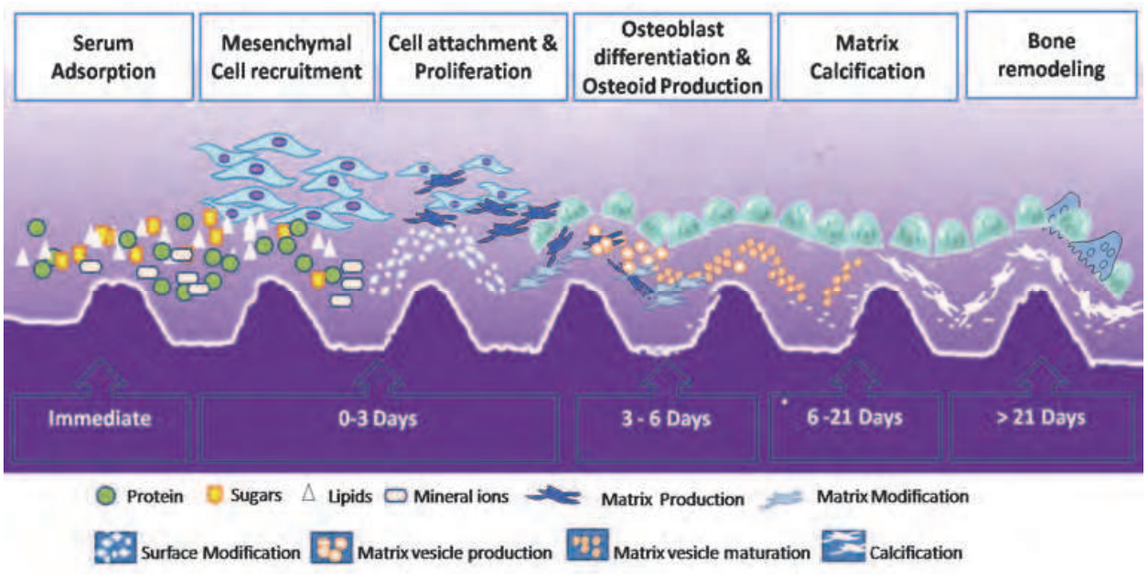

Fig. 2. Illustration showing the cellular phenomena at the implant bone interface during healing of implant

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.

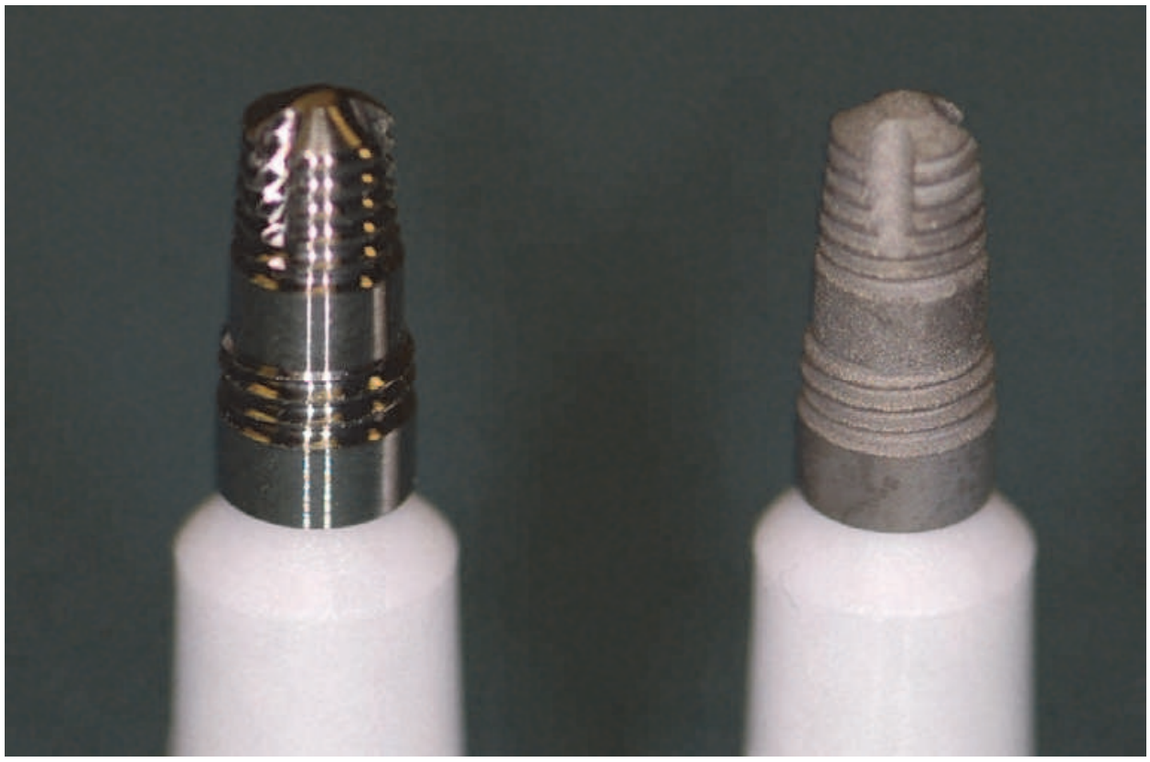

Fig. 3. The machined and nano etched implant surface

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.

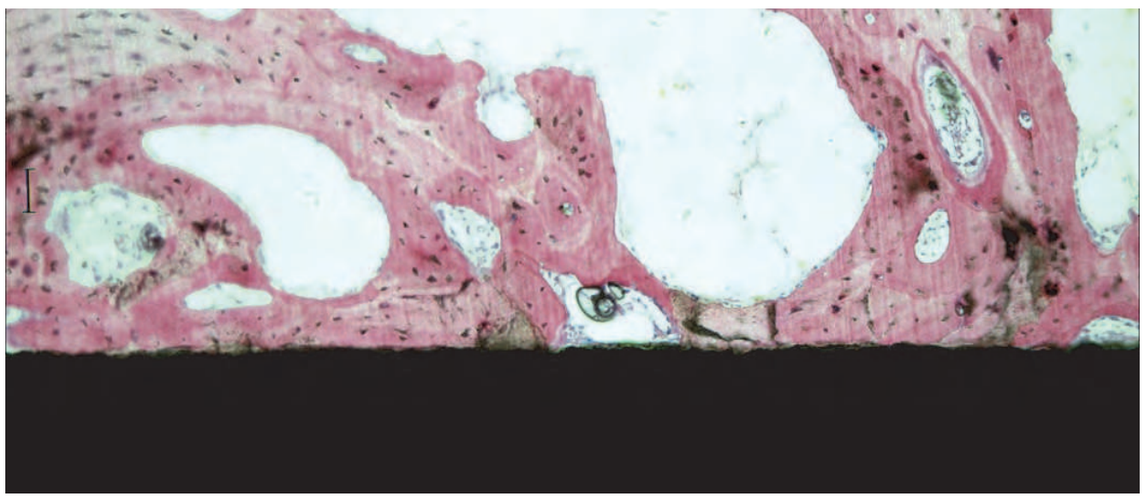

Fig. 4. Showing bone healing at the nanorough surface

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).

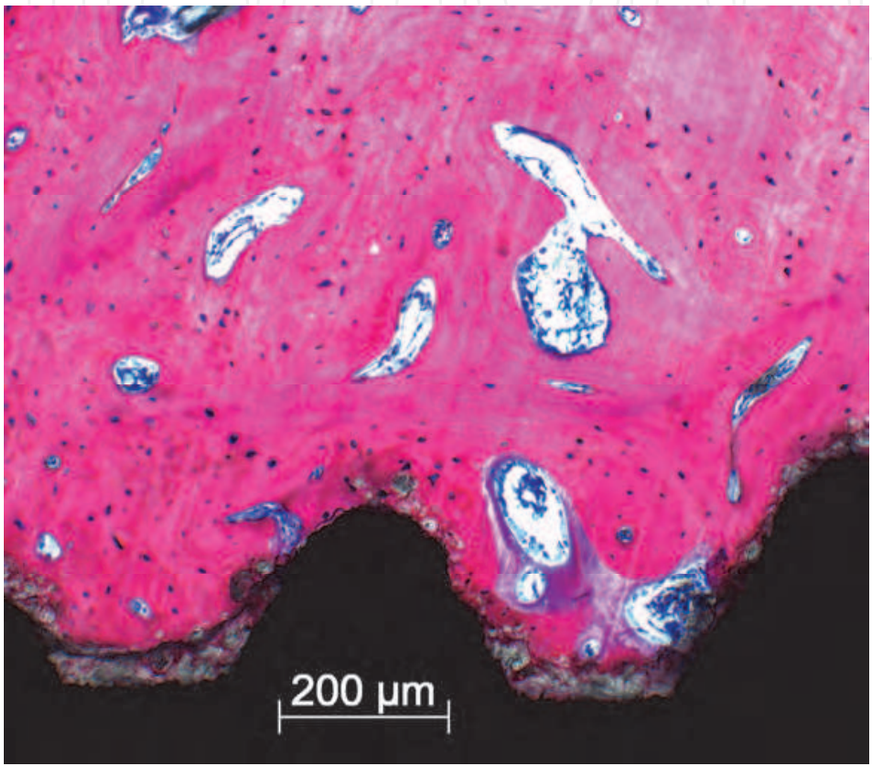

Fig. 5. Showing accelerated bone formation on the coated implant surface

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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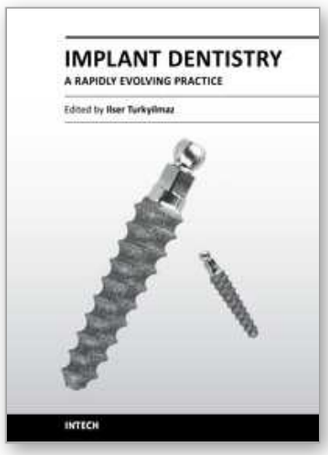

Implant Dentistry - A Rapidly Evolving Practice

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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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