Dental Implants

Enhancing Biological Response Through Surface Modifications

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KEYWORDS

• Dental implants • Bone-implant interface • Osseointegration • Micro-topography • Nano-topography • Wettability • Chemical modification • Biofunctionalization

KEY POINTS

- Topographic, physical, or chemical modification of a dental implant surface enhances biological response, particularly bone-healing response to the modified surface.
- The micro-topographical modification of an implant surface enhances bone response, which occurs by mimicking the resorption pits by osteoclasts on natural bone surfaces. Two representative modified surfaces of grade 4 commercially pure titanium, sand-blasted, large-grit, acid-etched, and electrochemically oxidized surfaces have been evidenced in the clinical long-term implant survival.
- Nano-modifications of implant surfaces include alterations of the topographic, chemical, and physical properties. These nano-alterations are usually combined with micromodifications and warrant further clinical investigation.
- The application of biofunctional molecules to implant surfaces seems promising because of their potential to alter the bone-healing capacity of the local environment surrounding the implant, which would be beneficial to patients with compromised bone metabolism who are contraindicated for an implant treatment.

INTRODUCTION

The characteristics of implant surfaces are key factors for long-term clinical success.[1] Since the 1970s, dental implant surfaces have changed in clinical application from the machine-turned surface of grade 1 commercially pure titanium (cp-Ti) to the micro-roughened surface of grade 4 cp-Ti or grade 5 Ti alloy.[2,3] Nanostructural modifications (arithmetical mean roughness over the surface, or Sa, between 1 and 100 nm), chemical modifications, or wettability control technology are applied to dental implant surfaces based on roughening methods at the microlevel (Sa between 1 and 10 μm).[2–5] Recently, the aforementioned techniques have modified the surfaces of new

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biomedical materials, including zirconia and tantalum, for their use as an oral implant, despite cp-Ti or Ti alloy being the materials of choice.[6–11]

Although a screw-shaped dental implant is prepared by milling with a computer numerical control machine, its original surface is a basic surface without modifications.[3] It is called a turned surface, and the turned cp-Ti surfaces had been actively used in clinical implant dentistry until the 1990s.[12–15] The introduction of surface modifications to an endosseous screw-shaped dental implant began with changes in surface topography and roughness, along with the application of both physical and chemical modifications by hydroxyapatite to cylinder-shaped implants.[16,17] The sandblasted, large-grit, acid-etched (SLA) Ti surface and the anodically oxidized Ti surface are two major surface modifications that are topographically different at the microlevel and widely used clinically. Since the 1990s, nano-approaches to the modification of dental implant surfaces have been investigated.[5,18–22] Initially, the effect of nano-modification was questionable because complete bone ingrowth does not occur in spaces considerably smaller than 100 μm.[23] Considering the dimensions of an osteon and the response of bone ground substances to surface micro-irregularities, it is difficult to show evidence for nano-modifications in enhancing the bone response.[24,25] However, surface nano-topography and chemistry have been reported to affect protein adsorption, osteogenic cell behavior, and bone–implant interaction.[2,26–31]

Proposing modifications of dental implant surfaces require an understanding of the nature of osseointegration. Osseointegration was originally a phenomenological term, defined as the direct contact between a bone and the implant surface, visualized through light microscopy.[1] Considering this definition, the biocompatibility of a material in contact with the bone was a major issue while investigating the formation of bone surrounding implants.[3,22] Surface modification at the level of micro-topography and micro-roughness focused on quantitating bone apposition. However, the modifications also altered cellular behavior in vitro and bone physiology in vivo.[4,32,33] Osseointegration is considered a type of bone healing with an inflammatory response,[22,34] and a dental implant surface has been modified in its nano-topography, surface chemistry, and surface energy to enhance the healing.[2,27,29,35–37]

A dental implant system inserted into a patient's mouth comprises five interfaces associated with a biological response. The suprastructure interface to the oral cavity and the suprastructure–abutment interface in the salivary environment are both considered to be present outside the body, which involves numerous factors. The soft tissue–abutment interface is in the transgingival region, a special area connecting the outside and inside of the body. The biological response to this interface necessitates understanding another interface, an implant–abutment interface.[15,38] The last is the bone–implant interface in the body. This review briefly explores surface modifications of dental implants designed to enhance hard tissue response at the bone–implant interface. This article deals with healing physiology around implants and interactions between the bone and the characteristics of modified implant surfaces.

HEALING PROCESS SURROUNDING DENTAL IMPLANTS

Drilling a hole for implant insertion in dental surgery leads to bleeding and hemostasis in the bone from surgical trauma, which lasts for minutes to hours. The procedure of implant drilling generates bone debris which releases various cytokines and bone matrix proteins activated by the trauma.[39] Bleeding and damaged endothelium from injured blood vessels form platelet plugs, simultaneously provoking the coagulation cascade toward hemostasis.[40,41] The surface of an implant initially contacts blood during the implant insertion into the hole. Surface wettability, charge, and topography

play an important role in initial bone healing.[5,29,32,42] Protein adsorption occurs on the surface; initially, this is by high mobility proteins at higher concentration in the plasma, which are then replaced by other proteins having a higher affinity for the implant surface (Vroman effect) (**Fig. 1**A).[40,43] This process gets delayed on a hydrophobic surface, thus highlighting the importance of a hydrophilic surface in preserving the tertiary structures and activities of proteins adsorbed on the surface.[40,43] Mesenchymal stem cells subsequently bind to the adsorbed extracellular matrix proteins (ECMs), which include fibronectin and vitronectin.[4,40,42]

Vitronectin on the implant surface binds platelets and activates them, thus forming a platelet plug.[40] This plug binds thrombocytes, resulting in their degranulation. Such platelet degranulation releases growth factors and causes cytokine degranulation, thus leading to the inflammatory phase that begins after approximately 10 minutes and lasts for some days following the implant installation surgery.[40] Neutrophils indicate acute inflammation, and the presence of mononuclear cells implies that wound healing around the dental implant is in the chronic inflammatory stage (**Fig. 1**B).[44] These inflammatory responses usually subside at a biocompatible interface within 2 weeks.[44] Subsequently, macrophages arrive at the implant site and adhere to the dental implant surface, with some fusing to form foreign-body giant cells. The aforementioned adhesion and fusion are supported by vitronectin via integrins, the transmembrane proteins of cells, which implies that granulation tissue is forming at the bone–implant interface.[44–47]

Granulation tissue is identified by new extracellular matrix, fibroblast infiltration, and neovascularization.[40,44] Macrophages are activated by certain physical and chemical properties of implant surfaces.[48] These macrophages stimulate fibrogenesis by fibroblasts, an essential component in wound healing (**Fig. 1**C).[41,44,49] Various cytokines released from the macrophages contribute to wound healing, as does the primary

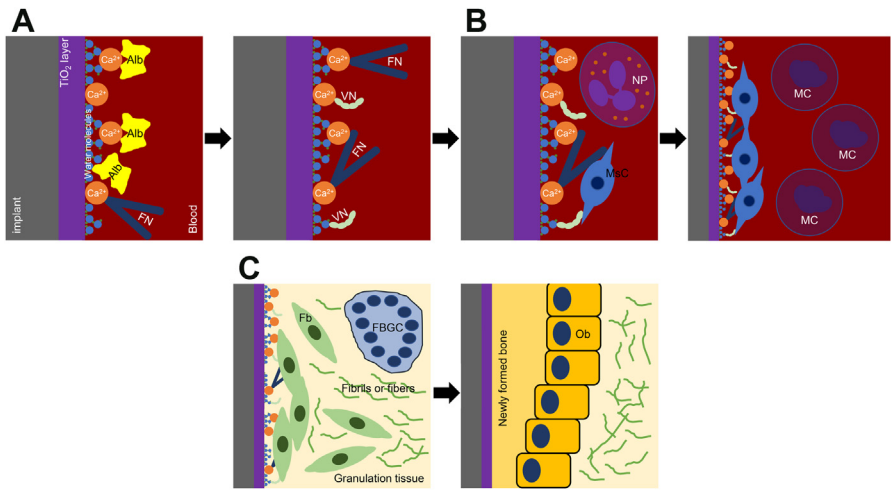


Fig. 1. Bone healing on an implant surface. (*A*) Initial adhesion on the surface is by plasma proteins in higher concentration, such as albumin. Later, higher affinitive proteins (fibronectin, vitronectin, and so forth) replace them. (*B*) Inflammatory phase. Neutrophils and mononuclear cells are found in this stage. (*C*) Stimulation by foreign-body giant cells, fibrogenesis, and various cytokines differentiate mesenchymal stem cells into osteoblasts that form new bone around the implant surface. Alb, albumin; Fb, fibroblast; FBGC, foreign-body giant cell; FN, fibronectin; MC, mononuclear cell; MsC, mesenchymal stem cell; NP, neutrophil; Ob, osteoblast; VN, vitronectin.

stability of the implants.[40,44] The loss of primary stability, or micromovement, of the implant produces shear stress that disrupts normal bone healing.[40] Simultaneous angiogenesis occurs at the wound site, which is stimulated by macrophage-secreted molecules.[40,44] Bone morphogenetic proteins (BMPs) are stored in and released from the old bone matrix and drive new bone formation.[40,50] They are activated by bone trauma, such as implant drilling, and stimulate the differentiation of mesenchymal stem cells into osteoblasts.[40] Newly formed bone, also known as woven bone, then establishes contact with the implant surface, typically 1-week post-implant placement when the surface has been modified (see **Fig. 1**C).[32,51]

Bone remodeling matures the woven bone into lamellar or compact bone. This process can continue for years depending on the load distribution around the implant and the strain induced within the bone.[40,52] This load distribution and bone strain are more affected by the implant geometry and the implant–abutment connection structure than by the implant surface quality.[15,38] Osteoclasts play an important role in bone remodeling by providing space for the lamellar bone. Bone resorption by osteoclasts is balanced with bone formation by osteoblasts.[40,41] The osteogenic cells lining the cement line dissolve the osteoid with collagenases, thereby exposing RGD (tripeptide arginine, glycine, and aspartate) endings from the surface and causing cell detachment.[40,53] Migrating osteoclast precursors are attracted by the recently exposed bone surface and become attached. These precursors differentiate into osteoclasts, which are phenotypically different multinucleated giant cells, and form a resorption apparatus, also termed ruffled borders. This in turn seals the margin and the Howship's lacuna where the mineralized bone matrix gets disintegrated.[40,44,54] Osteogenic cells are able to recognize the texture of the bone surface in the lacuna.[55,56] These cells obtain information about the bone quantity necessary to fill the lacuna.[56] The aforementioned characteristic may be involved in the enhanced osteogenic activity of the cells by sensing the irregularities of micro-topographically modified surfaces.[55,57] The osteon, the fundamental functional unit of the new lamellar bone, is formed to effectively withstand the load transferred via the endosseous screw-shaped implant.

IMPLANT SURFACE TREATMENTS TO ENHANCE BONE RESPONSE

Modifications for Micro-topographical Surface Change

Methods to micro-roughen the implant surface mimic the resorption pits created by osteoclasts, thus stimulating the bone formation process.[55] The combination of acid-etching and sandblasting the surface is one of the best known methods for implant surface modification. The resulting surface, also termed the SLA surface, has been clinically used in implant dentistry for approximately 30 years.[58–60] Generally, an SLA surface on grade 4 cp- Ti is obtained by etching with hydrochloric, sulfuric, nitric acid or combinations of these acids after sandblasting the surface with alumina particles measuring 75 to 500 μm.[3,55,61,62] The blasting procedure on a zirconia surface is similar to that on Ti.[55,63] However, etching on the zirconia surface is usually performed with bases and not acids, because the polycrystalline zirconia is unaffected by acids, such as hydrogen fluoride (HF), which are typically used for dental ceramics containing a glassy matrix, such as porcelain.[55,63,64] The roughness (Sa) of commercial SLA surfaces is approximately 1.5 μm, which is considered optimal for bone healing.[25,29,47,65]

Anodic oxidation is another well-known method for the modification of a dental implant surface.[62] Because the anode is defined as the site of oxidation in an electrochemical cell, the term electrochemical oxidation is a more suitable description than

anodic oxidation. When a Ti dental implant is configured as the anode in an electrochemical cell, an applied electrical potential accelerates the oxidation of the implant surface such that the Ti oxide (TiO_2) layer on the surface thickens and becomes micro-roughened compared with the TiO_2 film spontaneously formed in the atmosphere.[3] This oxidized Ti surface has a microporous structure with multiple volcano-like irregularities.[41,66]

Micro-topographical features influence bone responses to implant surfaces because osteogenic cells recognize the topographic characteristics on the implant surface similar to the way they recognize sites of resorbed bone.[55,67] However, the efficacy in bone healing of honeycomb- or crater-like microstructures resulting from SLA as compared with the volcano-like microporous irregularities resulting from oxidation is unknown (**Fig. 2**). Several studies involving in vivo comparisons of micro-topographically varied surfaces have not demonstrated significant histomorphometric differences, despite better efficacy of osteogenesis shown with implant surfaces that are morphologically similar to osteoclast resorption pits.[68–71] Furthermore, it is difficult to directly compare the surfaces clinically due to different implant design factors, including implant–abutment connection structures and implant thread shapes.[15,65]

Both types of micro-roughened Ti implant surfaces have displayed high long-term survival rates in clinical studies. Previous 10-year clinical studies reported that the survival rates of SLA dental implants were greater than 95%.[72–74] For the oxidized surface, clinical investigations analyzed data obtained from clinical use for $\geq$10 years and also reported high survival rates.[13,75,76] Various other factors, including clinicians' skills and placement arch (maxilla or mandible), exert effects on the clinical success or survival of dental implants.[12,14] However, these two types of micro-roughened surfaces have been shown to have greater reliability for long-term clinical use than the unmodified surface, when the modified surfaces are on grade 4 cp- Ti and roughness is within the optimum range (1–2 μm in S_a).[3,5,13,72,73,76,77]

Modifications for Nano-Topographical Surface Change

The effect of nano-modification of the implant surface is often questioned, because complete bone ingrowth does not occur in spaces considerably smaller than 100 μm.[23] Therefore, it is difficult to attribute accelerated osteogenesis to nano-modification, considering the dimensions of an osteon and the response of bone ground substance to surface micro-irregularities, which are 10 to 500 μm and 200

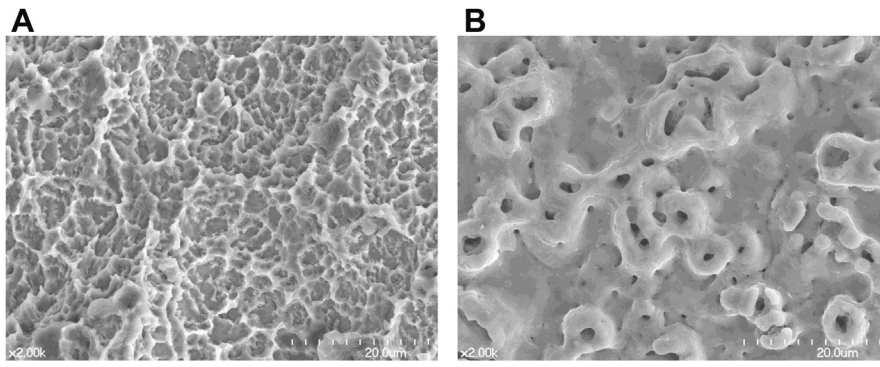


Fig. 2. Representative scanning electron microscopy (SEM) images of SLA (*A*) and oxidized (*B*) surfaces. The honeycomb-like appearance of the SLA and the volcano-like appearance of the oxidized surface are very different.

to 1000 μm for cortical and cancellous bones, respectively.[2,24,25] Nano-topography does not exert a notable effect on the responses of osteogenic cells or on the bone at the interfacial area.[78,79] However, surface nano-topography has recently demonstrated its usefulness in protein adsorption, osteogenic cell behavior, bone–implant interaction, drug delivery capability, and antibacterial action.[2,26–31,80,81] The nano-topographical characteristics of Ti implant surfaces affect the initial bone responses, including the activities of both osteoblasts and osteoclasts.[82,83]

By controlling the electric current, temperature, electrolyte concentration, oxidation voltage, and oxidation time in a fluoride-based solution, electrochemical oxidation can be used to nano-topographically produce a TiO_2 nanotube layer on the implant surface.[82,84] The TiO_2 nanotube-arrayed implant surface is highly biocompatible, despite the optimal nanotube diameter remaining under investigation.[82,85–88] Therefore, the modified surface has great potential in biologic and clinical applications. However, the TiO_2 nanotube-based surface has yet to be applied in the clinical situation. The interfacial bond strength between the TiO_2 nanotube layer and the underlying Ti surface is weak when exposed to frictional forces, such that the nanotube layer becomes easily delaminated on insertion of a nanotube-layered dental implant into the bone.[84]

Hydrophilicity

Water molecules establish the first contact with the implant surface during implant placement. Therefore, a hydrophilic surface is considered desirable for promoting the initial stages of bone healing.[3,5] The water-friendly surface of some successful dental implants comprises a hydrophilic SLA surface, termed modified SLA, or SLActive (Institute Straumann AG, Basel, Switzerland).[3] The SLActive surface maintains biological availability by retaining surface hydrophilicity, which is achieved by the prevention of hydrocarbon contamination during implant production and packaging.[5] This type of surface having a combination of wettability and micro-roughness has shown excellent long-term clinical success.[89]

Another approach to producing a hydrophilic implant surface is the decontamination of the surface by removal of the hydrocarbons that cause reduced biocompatibility.[90] Ultraviolet (UV) irradiation of implant surfaces to eliminate hydrocarbon contamination and increase surface hydrophilicity is particularly close to routine clinical use.[91] The wavelength of UV-C ranges from 200 to 280 nm and is most effective in the removal of carbon and contributing to excellent interfacial bone-healing results.[3,29] Without a notable nano-topographical change of an implant surface (**Fig. 3**), UV treatment increases the surface charge, improves the adsorption of plasma proteins, and enhances the activities of osteogenic cells on the surface to promote excellent bone-to-implant contact during in vivo experiments.[3,29,92] Despite few prospective clinical studies with observation periods $\geq$10 years, some prospective and retrospective clinical investigations have reported greater than 95% success rates of the UV-treated dental implant surfaces.[91,93] UV-treated turned Ti surfaces have demonstrated excellent bone-to-implant contact ratios, similar to those of micro-roughened SLA Ti surfaces, which are globally accepted in dental clinics. This type of photofunctionalized surface might be clinically more advantageous for the removal of biofilms on implant surfaces and in the treatment of peri-implantitis, compared with micro-roughened SLA and oxidized implant surfaces.[15,29,92]

Elemental Modifications on Surface

The application of chemicals with known osteogenic activity to an implant surface is another approach to nano-modification through surface chemistry. The coating of the implant surface by a calcium–phosphorus compound and the treatment of the

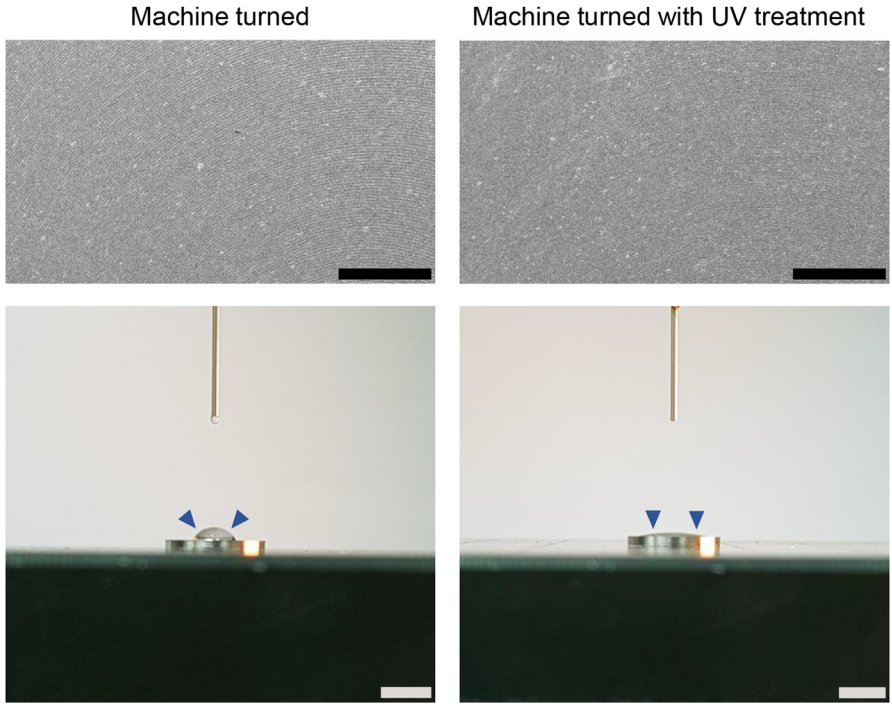


Fig. 3. In the SEM images of Ti discs (*top row*), little topographic difference is found after UV treatment. However, the contact angles (*bottom row*) indicating surface hydrophilicity are notably different (*blue arrowheads*). Scale bars = 500 μm.

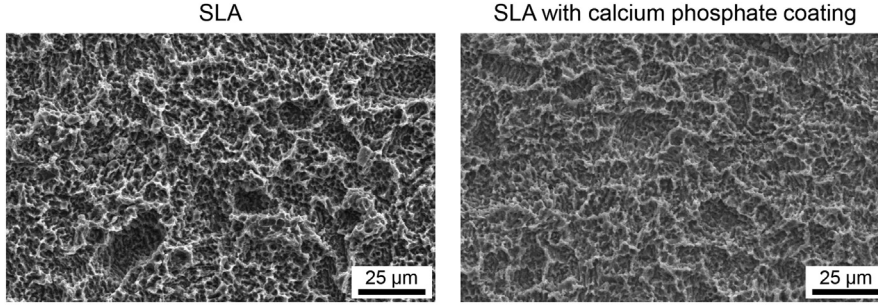
surface with fluoride ion traces have been clinically applied to dental implants. In contrast, biologic molecules, such as proteins and functional peptides, have not yet been applied to implant surfaces and tested clinically.[3,27,28,47]

It is difficult to detect fluorides using energy dispersive spectroscopy. Small amounts of fluoride exist on a Ti implant surface reduced at the cathode in a low concentration of hydrofluoric acid solution in an electrochemical cell.[3] The fluoride ions are useful in bone mineralization and accelerate bone healing principally by stimulating undifferentiated osteogenic cells.[94] Micro-roughened Ti implant surfaces modified with a trace amount of fluoride have an average mean height or S_a within the optimal range of approximately 1.5 μm.[65] This fluoride-modified implant demonstrates high survival rates for long-term clinical service.[95] However, only one implant design has thus far been clinically used with this fluoride modification, and it is not yet known if the implant design itself or the surface characteristics are the key to clinical success.[15,96]

Calcium–phosphorus compounds, particularly hydroxyapatite, which is the principal component of human bone, are the major coating materials that have been tried for dental implants. Hydroxyapatite and other calcium–phosphorus materials are considered bioactive and osteoconductive to the surrounding bone.[3] However, the biodegradation of calcium–phosphorus particles caused by wear of the coating and the weak binding between the coating layer and underlying surface are major issues in the application of these coatings.[97] Researchers are developing various methods, including conventional plasma spraying, magnetron sputtering, and laser patterning to prepare more stable and biocompatible coating layers by controlling their physical topography, crystallinity, and calcium–phosphorus ratios (**Fig. 4**).[97–99] Previous animal

studies have suggested that the hydroxyapatite coating accelerates osteogenesis at the interfacial area during the initial stage of bone healing.[100] The survival rates of hydroxyapatite-coated dental implants have been shown to be greater than 90% for 5 years or more, despite reports on rates less than 90%.[101,102] There are no clinical studies estimating the application of other calcium–phosphorus compounds to dental implant surfaces for long-term use. Despite the biocompatibility of calcium–phosphorus compounds, their application to the implant surface is considered unreliable by dental clinicians and they are still under investigation for biocompatibility, biodegradation, and immunologic response to the wear particles.

Biofunctional proteins and peptides are candidates for the biological linking between the tissue and surface of inserted medical devices. These molecules have the potential to alter a local environment to biologically favorable circumstances, which can be important to patients with systemic metabolic diseases. There are supposedly two categories of the aforementioned molecules involved in the healing of bone surrounding the implants, namely adhesion molecules and cytokines.[27,47,103] Fibronectin and vitronectin are ECMs for osteogenic cell adhesion, which is the first step for osteogenesis, or bone healing. ECMs are substituted for plasma proteins, which play an important role in blood clotting. Initially, the plasma proteins cover the implant surface, followed by the ECM. However, treatment of the implant surface with these adhesion proteins or functional peptide derivatives accelerates osseointegration at the bone–implant interface.[27,40,44,45,47] Functional peptides have lower antigenicity and easier applicability than the original proteins.[27] Several cytokines contribute to bone healing around an implant. Particularly, BMPs, a subset of growth factor cytokines, are direct enhancers of bone formation.[40,103,104] Recombinant human BMP-2 (rhBMP-2) has been clinically used for bone regeneration; however, no dental implant using this recombinant protein has yet been applied to patients. Some in vivo studies reported on faster osseointegration at the interface between the bone and rhBMP-2-treated implant surfaces.[105,106] However, biological responses to such cytokines are diverse and sensitive to concentration.[3,107] Certain complications, including osteolysis, are disastrous to both patients and dental clinicians, thus necessitating a functional peptide derivative from the original growth factor to reduce undesirable side effects and increase the clinical applicability.



EPMA results (atomic %)

Ti	O	Ca	P
26.4	73.6	0	0

Ti	O	Ca	P
31.9	56.4	9.1	2.5

Fig. 4. Calcium phosphate is nano-coated on SLA surface by ion-bombing. As shown in the results of electron probe microanalysis (EPMA), the surface compositions are different without a large change in microtopography.

The above-mentioned biofunctional molecules are useful for implant surface modification to enhance bone healing. Particularly, adhesion proteins, cytokines, and their derivatives are considered valuable for patients with bone metabolic diseases, because these factors can help to restore compromised bone-healing capacity in the local environment by stimulating osteogenic cell adhesion, osteoblast differentiation, or bone formation activity. At least two problems need to be solved before the clinical use of dental implant surfaces modified with these molecules. The first is the weak binding between the molecules and implant surfaces. Several molecules used for surface functionalization are only physically adsorbed on the surfaces.[108] Physical adsorption can be inadequate for molecule delivery in environments, such as implant surgery that is characterized by high friction between the bone and the functionalized surface.[108] The second is the undesirable side effects of these molecules. Proteins usually exert various effects on a living system. For example, vitronectin is not only beneficial for cell adhesion but also triggers growth factor release by binding to platelets.[40] It is helpful to derive a core amino acid sequence from the original protein for lowering the probability of side effects.[27] However, this core sequence occasionally exerts an unexpected effect than the original protein, thus warranting extensive investigation before considering clinical use.[109]

SUMMARY

The nature of osseointegration is still under investigation. It remains unknown if an implant surface is actively involved in the formation of new bone or if the bone response to this surface is merely a healing process with inflammation. However, topographic, physical, or chemical modifications of the implant surface can change the behavior of cells related to bone healing. Micro-topographical modification is most widely applied to dental implants used in clinics. The resultant surface micro-topography mimics the resorption pits formed by osteoclasts, thus stimulating osteogenic cells to produce bone material. Previously, implant surface treatment at the nano-level was considered ineffective for osteogenesis due to the dimensional aspects of an osteon and incomplete bone ingrowth. Recent evidence suggests that nano-topographical, physical, or molecular changes on the implant surface influence the initial bone response. An implant surface with modified nano-topography has yet to be clinically tested; however, the clinical use of a dental implant has evidence for increased surface hydrophilicity that accelerates the initial bone response. Modified surfaces have been clinically examined in dental implantology with the treatment of some osteogenic elements, such as fluoride anion and calcium–phosphorus compounds. Clinicians have not yet used biofunctional molecules originating from biological adhesion proteins or growth factors. However, these molecules might be bioactive following the treatment of functionalized implant surfaces or useful for improved osseointegration effects in patients with bone metabolic diseases that are currently contraindicated for dental implants. Conjugation problems between biofunctional molecules and implant surfaces and the control of unexpected side effects are under investigation.

CLINICS CARE POINTS

- The sandblasted, large-grit, acid-etched (SLA) surface has shown evidence of success in long-term clinical investigations using implants made of grade 4 commercially pure titanium (cp-Ti). However, the results of SLA surfaces should be evaluated for implants comprising zirconia or materials other than cp-Ti.

- The electrochemically oxidized grade 4 cp-Ti has been shown to be successful in long-term clinical investigations. However, other key factors, including implant design, should be considered as additional factors determining success.
- The use of dental implants modified at the nano-level needs further clinical investigation, despite the use of some physically (hydrophilic surface) or chemically modified surfaces (fluoride-treated and hydroxyapatite-coated surfaces) in dental clinics.

DISCLOSURE

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