Review

The Effects of Titanium Implant Surface Topography on Osseointegration: Literature Review

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Abstract

Background: A variety of claims are made regarding the effects of surface topography on implant osseointegration. The development of implant surfaces topography has been empirical, requiring numerous in vitro and in vivo tests. Most of these tests were not standardized, using different surfaces, cell populations, or animal models. The exact role of surface chemistry and topography on the early events of the osseointegration of dental implants remains poorly understood.

Objective: The aim of this study was to consider the major claims made concerning the effects of titanium implant surface topography on osseointegration. The osseointegration rate of titanium dental implants is related to their composition and surface roughness. The different methods used for increasing surface roughness or applying osteoconductive coatings to titanium dental implants were reviewed. Important findings of consensus were highlighted, and existing controversies were revealed.

Methods: This paper considered many of the research publications listed in Medical Literature Analysis and Retrieval System Online and presented in biomedical research publications and textbooks. Surface treatments, such as titanium plasma spraying, grit blasting, acid etching, alkaline etching, anodization, polymer demixing, sol-gel conversion, and their corresponding surface morphologies and properties were described.

Results: Many in vitro evaluations are not predictive of or correlated with in vivo outcomes. In some culture models, increased surface topography positively affects proosteogenic cellular activities. Many studies reveal increase in bone-to-implant contact (BIC), with increased surface topography modifications on implant surfaces.

Conclusions: Increased implant surface topography improves the BIC and the mechanical properties of the enhanced interface.

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KEYWORDS

implant interface; TPS; acid etching; alkaline etching; anodisation; polymer demixing; sol gel

Introduction

The elusive dream of replacing missing teeth with an artificial analogue, which is as close to its natural predecessor, has been a part of dentistry for thousands of years. The coincidental discovery of the tenacious affinity between living bone and tissues, termed as osseointegration, propelled dentistry to a new age of reconstructive dentistry. Branemark et al [1] started the era of implantology. Since then, this method still remains popular and reliable, with only shape and surface of the titanium implants having changed [2-4]. Interactions between implant biomaterials and biological environments occur at interfaces, and they are affected by the nature of the biomaterial, such as its surface chemistry and energy, roughness, and topography. These parameters play a role during implant integration in bone tissue, and they consequently play a role for osseointegration [5-7]. 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. There is a clinical impression that the amount of bone-to-implant contact (BIC) is an important determinant in the 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. The first generation of successfully used clinical titanium implants, which were machined with a smooth surface texture, now approach 50 years in clinical use. The second generation of clinically used implants underwent chemical and topographical modifications, usually resulting in a moderately increased surface topography [8]. The implant surface plays an important role in biological interactions for 2 reasons. First, the surface of a material generally differs in terms of composition and morphology, from the body of the material. These differences are because of molecular rearrangements and surface reactions and contamination. Second, materials may or may not release toxic or biologically active substances. Thus, the properties of a surface guide the biological response [9-11]. The significant challenge in implantology is the design of biomaterials that actively promotes a faster and more improved osseointegration process while avoiding undesirable tissue responses. This requires selective control of interactions at the tissue-implant interface, the site of a series of complex events that depend on synergistic parameters, including surface chemistry. This review focuses on the different surfaces and methods that aim to accelerate the osseointegration of dental implants. The physical and chemical properties of implant surfaces are discussed in relation to their biological and clinical behavior. This literature review also aims to elucidate implant surface topography and obtain a perspective regarding the topography of the implant surface, which could be beneficial to implant surgery when implemented in practice

Methods

Overview

Surface properties of oral titanium implants play decisive roles for molecular interactions, cellular response and, bone regeneration. It is increasingly recognized that interactions between biomaterials and host tissues are controlled by nanoscale features. Cells grow on nanostructured extracellular matrices, and biological events, such as signaling and cell-substrate interactions, occur at the nanometric level. Nanometer-scale surface features can increase the surface energy, thereby increasing the wettability of blood and the spreading and binding of fibrin and matrix proteins. This in turn favors cell attachment and tissue healing, particularly directly after implantation. It also directly influences cellular proliferation, differentiation, alignment, and, finally, osseointegration [10,12-18]. Currently, several techniques are commonly used to modify the smooth surface topography of dental implants to create nanosurface topography. Some techniques comprise adding matter to the implant surface, creating a dented surface (convex profile), and they are called additive techniques to increase the surface area and provide a more complex surface macrotopography, for example, titanium plasma spraying (TPS). Conversely, other techniques comprising eliminating matter from the titanium surface, creating pits (concave profile), are known as subtractive or ablative techniques, altering the microtopography or texture [19]. One or several of these methods are used to produce either an isotropic surface (ie, with surface asperities that are randomly distributed so the surface is identical in all directions) or an anisotropic surface (ie, surface with a directional pattern). The surface treatments are suggested to improve the capacity of anchorage into bone [20]. The additive methods employed the treatment in which other materials are added to the surface, either superficial or integrated, and they are categorized into coating—TPS, plasma-sprayed hydroxyapatite (HA) coating, alumina coating, and biomimetic calcium phosphate (CaP) coating—and impregnation. The common subtractive techniques are large-grit sands or ceramic particle blasts, acid etch, and anodization. Textbox 1 shows the ways through which surface roughness of dental implants can be obtained.

Textbox 1. Methods to obtain surface roughness.

- Mechanical modifications
  - Roughening of implants by titanium plasma-spraying
  - Roughening of implants by grit blasting
- Chemical modifications
  - Roughening of implants by acid etching
  - Roughening of implants by alkaline etch
  - Roughening of implants by anodization
  - Roughening of implants by sol gel
  - Roughening by polymer demixing
- Antibiotic coatings
- Stem-cell therapies and surface modification
- Shot peening/laser peening
- Photofunctionalization
- Biomolecular coatings
- Self-assembled monolayer in nanotextured titanium
- Fluoride-modified implant surfaces

Mechanical Modifications

Roughening of Implants by Titanium Plasma Spraying

This method comprises injecting titanium powders into a plasma torch at high temperature [21]. The titanium particles are projected onto the surface of the implants, where they condense and fuse together, forming a film about 30 µm thick. The thickness must reach 40-50 µm to be uniform [7]. Borsaria et al [22] compared the biological response of osteoblast-like cells with titanium surfaces with different roughness levels, and they concluded that the new ultrahigh roughness and dense coating provided a good biological response. In a preclinical study using pigs, the bone/implant interface formed faster with a TPS surface than with smooth-surface implants [7].

It has been shown that this 3-dimensional topography increased the tensile strength at the bone/implant interface. An extensive and close contact between the implant and the host bone surfaces is the condition that maintains primary stability and avoids excessive interfacial micromotion during bone healing, which may be detrimental to the osseointegration process. Ong et al [23] studied the bone interfacial strength and bone contact length at the plasma-sprayed HA and TPS implants in vivo, where noncoated titanium implants were used as controls. The interfacial strength between bone and TPS-coated implants was suggested to be governed by the bone ingrowth into the roughened titanium surfaces, thereby providing a mechanical bone-implant interlock, whereas the interfacial strength between bone and HA-coated implants was suggested to be attributed to bone apposition on HA surfaces.

Several techniques were proposed to adhere HA to titanium implants, but only the plasma spraying coating technique has been successfully used on commercial implants [24].

Roughening of Implants by Grit Blasting

Blasting is a technique that leads to the creation of a porous layer on the implant surface achieved through the collision with microscopic particles, such as ceramic, alumina, titanium oxide, and CaP particles [7]. The ceramic particles are projected through a nozzle at high velocity by means of compressed air. Depending on the size of the ceramic particles, different surface roughness can be produced on titanium implants. The thickness of the porous layer can be modulated by the granulometry of the particles [25]. Wennerberg et al [26-30] demonstrated in a rabbit model that grit blasting with different sizes of titania (TiO_2) or Al_2O_3 particles altered the commercially pure titanium topography and resulted in a similar enhancement of bone formation at the implant. These studies also demonstrated that specific surface modifications increased the biomechanical interlock of the implant with bone when measured with a torque device. TiO_2, when used as a blasting material, showed interesting results in experimental studies, being associated to a significant enhancement of bone-to-implant contact when compared with machined surfaces [31]. CaPs, such as HA, beta-tricalcium phosphate, and mixtures, have also been considered for blasting materials. These materials are biocompatible and osseoconductive. They are resorbable, leading to a clean-textured, pure titanium surface. Manoa et al [32], to achieve better osteoconductivity, used the blast coating method of spraying apatite powder on the surface of titanium implants. Apatite powder–coated implants generally showed a more rapid bone response and good osteoconductivity than noncoated implants. The rough surface created by blasting has been demonstrated to stimulate osteoblastic gene expression, as well as to enhance bone formation and bone-implant fixation, in a word, osseointegration [33,34]. Although an associated inflammatory response was reported [35], the overall success rate was satisfactory, with the majority of implants yielding good osseointegration and stability at 1 year after surgery [25]. Among the range of available materials, alumina is one of the most commonly used for blasting.

Chemical Modification

Roughening of Implants by Acid Etching

The combination of strong acids is effective in creating a thin grid of nanopits on a titanium surface [25], ranging from 0.5 to 2 µm in diameter. Etching with strong acids, such as HCl, H_2SO_4, HNO_3, and particularly HF, is needed to attack titanium for creating rough surfaces [7]. Etching is then stopped by adding water. The recovered disks are washed further with ethanol in an ultrasonic bath for 20 min and dried [36]. Variola et al [36] demonstrate that by varying etching parameters, such as solution composition, temperature, and exposure time, it is possible to modify the topography, oxide thickness, and wettability of commercially pure titanium. Thus, chemical oxidation with H2SO4 (conc)/H2O2 (aq) solutions is an efficient tool to achieve various physical and chemical configurations on this implant surface. Yi et al [37] have shown that controlled chemical oxidation of titanium using a mixture of H2SO4/H2O2 yields a nanotextured surface. The resulting nanotopography significantly influences the very early stages of in vitro osteogenesis. Such an early effect is needed to control the healing cascade from the very start. They also showed that the treated titanium substrate becomes highly porous and has a surface comprising nanosized pits, which have average diameters and fractal dimensions ranging between 20-22 nm and 1.11-1.17 nm, respectively. Atomic force microscopy revealed a 3-fold increase in surface roughness. The thickness of the oxide layer on the treated titanium surface is estimated to be ~32-40 nm [21].

HF is known to show a high ability to dissolve the passivation layer, mainly comprising TiO_2, on titanium-based materials. Therefore, a mixture of HF and HNO3 has been also used to create surface structures at the microlevel [33,38]. Moreover, it has been shown that fluoride incorporation into the created surface structures induces an enhanced osteoblastic differentiation, and it is favorable to the osseointegration of implants [39]. However, fluoride contaminations are known to have an ambivalent influence on the response of the host tissue [40]. Furthermore, dual acid etching with HCl and H2SO4 heated above 100°C has produced surface topography that is able to attach to fibrin scaffold and promote adhesion of osteogenic cells [21]. Various clinical studies have shown acid-etched (AE) implants to be successful in humans, with radiological evidence suggesting improved bone apposition rates compared with machined implants.

Roughening of Implants by Alkaline Etch (Sodium Hydroxide, Potassium Hydroxide, and $NaFl_2$)

Sodium hydroxide (NaOH) treatment catalyzes the production of titanium nanostructures outward from the titanium surface [41]. Treatment with an NaOH solution results in a sodium titanate hydrogel layer converted in an amorphous sodium titanate layer, with heat treatment at 600°C. Titanate gel layer allows HA deposition. This behavior has also been seen with other metals, such as zirconium and aluminum [42]. Titanium oxide nanotubes chemically treated with NaOH accelerated HA crystal growth in a simulated body fluid (SBF). Both chemical and topography changes are imparted [41,43].

Roughening of Implants by Anodization

Anodization is one of the most commonly used techniques to create nanostructures with diameters of less than 100 nm on titanium implants [44]. Voltage and direct current (galvanic current) are used to thicken the oxide layer among the implant surface. The titanium substrates serve as the anode in the process, whereas an inert platinum sheet provides the cathode. The anode and cathode are then connected by copper wires and linked to a positive and negative port of a 30 Volts/3 Amperes power supply, respectively. Diluted hydrogen fluoride (either at 0.5 wt% or 1.5 wt%) is used as electrolyte. Subsequently, a strong acid dissolves the oxide layer, creating a pattern that follows the convective lines of the galvanic current. Therefore, through the regulation of voltage and density, it is possible to control the diameters of nanotubes and the gap between them [25]. Kim et al [45] concluded that desired porosity and surface roughness can be achieved by adjusting the anodization conditions, such as voltage, solution concentration, and current density. By anodic oxidation, it is possible to get amorphous or crystalline oxide, depending on the applied voltage and electrolyte used [13,45]. Ercan et al [46] postulated that anodization can create novel nanotubular structures that can influence the concentration and conformation of adsorbed proteins to alter cellular interactions. Various studies have shown that in comparison with conventional titanium, the anodized nanotubular titanium showed increased osteoblast adhesion, osteocalcin production, alkaline phosphatase activity, and fibronectin adsorption [47,48]. It is also shown that osteoblasts are well spread, and they increase deposition of calcium-containing minerals on anodized nanotubular titanium [49]. Anodized surfaces result in a strong reinforcement of the bone response, with higher values for biomechanical and histomorphometric tests in comparison with machined surfaces [7]. A higher clinical success rate was observed for the anodized titanium implants in comparison with turned titanium surfaces of similar shapes [50]. A total of 2 mechanisms have been proposed to explain this osseointegration: mechanical interlocking through bone growth in pores and biochemical bonding [51,52]. Modifications to the chemical composition of the titanium oxide layer have been tested with the incorporation of magnesium, calcium, sulfur, or phosphorus. It has been found that incorporating magnesium into the titanium oxide layer leads to a higher removal torque value compared with other ions [7,52].

Roughening of Implants by Sol Gel (Titania, Calcium Orthophosphates, Hydroxyapatite, and Silica Coatings)

Sol gel is a technique widely used to deposit surface coatings on the dental implants, such as TiO_2, calcium orthophosphates ($CaPO_4$), HA, Silica, and TiO_2 [53-56]. The sol-gel technique involves the evolution of inorganic nanoscale networks in a continuous liquid phase through the formation of colloidal suspension, which is followed by gelation of the sol. In a typical sol-gel process, a colloidal suspension, or a sol, is formed from the hydrolysis and polymerization reactions of the precursors, which are usually inorganic metal salts or metal organic compounds, such as metal alkoxides. Complete polymerization and loss of solvent leads to the transition from the liquid sol into a solid gel phase. Thin films can be produced on a piece of substrate by spin coating or dip coating. A wet gel will form when the sol is cast into a mold, and the wet gel is converted into a dense ceramic, with further drying and heat treatment. A highly porous and extremely low-density material called an aerogel is obtained if the solvent in a wet gel is removed under a supercritical condition. Ceramic fibers can be drawn from the sol when the viscosity of a sol is adjusted into a proper viscosity range. Ultrafine and uniform ceramic powders are formed by precipitation, spray pyrolysis, or emulsion techniques. Under proper conditions, nanomaterials can be obtained [57-59].

Titania Coating

TiO_2 coatings on titanium have been used to improve the corrosion resistance of titanium. In practice, the very thin (at most, several tens of nanometers) oxide film on the titanium surface, which is formed in an aqueous environment, plays a decisive role in determining the biocompatibility and corrosion behavior of the titanium implant [60,61]. As the corrosion resistance is known to increase with the thickness of the oxide layer [61-63], many attempts have been made to form a thick TiO_2 layer on the titanium substrate, using various methods, such as anodization, thermal oxidation, and the sol-gel process.

Calcium Phosphate Coating

CaP coatings provided titanium implants with an osteoconductive surface. Following implantation, the dissolution of CaP coatings in the periimplant region increased ionic strength and saturation of blood, leading to the precipitation of biological apatite nanocrystals onto the surface of implants. This biological apatite layer incorporates proteins and promotes the adhesion of osteoprogenitor cells that would produce the extracellular matrix of bone tissue. Furthermore, it has been also shown that osteoclasts, the bone resorbing cells, are able to degrade the CaP coatings through enzymatic ways and create resorption pits on the coated surface. Finally, the presence of CaP coatings on metals promotes an early osseointegration of implants with a direct bone bonding as compared with noncoated surfaces. Finally, the presence of CaP coatings on metals promotes an early osseointegration of implants with a direct bone bonding as compared with noncoated surfaces. The challenge is to produce CaP coatings that would dissolve at a similar rate than bone apposition to get a direct bone contact on implant surfaces [61].

Roughening of Implants by Polymer Demixing

Polymer demixing is receiving particular attention, as it is a method that can develop topographies over a large area by a relatively cheap manufacturing method. By controlling the polymer concentration and the proportions of the polymers, different topographies can be produced. These can be pits, islands, or ribbons of varying height or depth. The ratio of the polymers used varies the topography shape, and the concentration of polymer in the casting solution changes the feature sizes [62]. A 2-polymer mixture is spin cast so that phase separation occurs, resulting in topographies distributed across the surface, with geometry determined by choice of polymers, solvent, substrate, and spin casting parameters, with cell response shown to vary with topography geometry. It can control not only the topography's pattern but also the scale of such topography within nanoscale (10-100 nm). Features created using this technique have a somewhat disordered spatial arrangement; yet, very precise control can be achieved in the vertical scale. However, nanometric features created by polymer demixing often tend to exhibit larger micrometric structures in 1 or more planes, and they can exhibit different chemistries in addition to topography. This technique has proved to increase adhesion, proliferation, cytoskeleton deviant, and gene expression on nanosurface created on titanium [59,63,64].

Chemical Vapor Deposition

Chemical vapor deposition is a process involving chemical reactions between chemicals in the gas phase and the sample surface, resulting in the deposition of a nonvolatile compound on the substrate [65]. The substrates are heated at high temperature to cause the gases to decompose, resulting in deposition. Vapor deposition processes usually take place within a vacuum chamber. If no chemical reaction occurs, this process is called physical vapor deposition; otherwise, it is called chemical vapor deposition. In chemical vapor deposition processes, thermal energy heats the gases in the coating chamber and drives the deposition reaction. Thick crystalline TiO_2 films with grain sizes below 30 nm, as well as TiO_2 nanoparticles with sizes below 10 nm, can be obtained with this method [66,67]. Surfaces created using this technique promote the adhesion of osteoblasts while minimizing the adhesion of fibroblasts [68]. Implant topography used to enhance the tissue-abutment interface remains largely unexplored. It should be noted that the currently available implants differ in their micron-level topography, their design, and their bulk material composition. It may be difficult to derive specific conclusions from the aggregate data regarding surface topography alone. However, for each example of current implant surfaces of available implants and cell culture, histological and clinical data suggest that surface modification offers incremental advantages to clinical problems where rapid bone accrual at the implant surface provides solutions.

Antibiotic Coatings

Antibacterial coatings on the surface have been studied as a possible way to prevent surgical-site infections. 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. It was seen that the bacterial adhesion by Streptococcus mitis and Actinomyces oris can be restricted by acidic pH and aerobic atmosphere [69].

Stem-Cell Therapies and Surface Modification

Surface treatment of titanium screw-shaped implants creates a nanopattern that has been demonstrated *in vivo* to be associated with an enhanced osteogenesis. Several studies confirmed the observation, stating the promotion of stem cells' growth, provided by oxidative nanopatterning. Furthermore, the most suitable nanoarrangement of TiO_2 nanotubes was with a diameter of 15 nm in a vertical alignment and was associated with a high spreading and differentiation of rat mesenchymal stem cells (MSCs) into the osteogenic lineage. Notably, 15 nm roughly correspond to the predicted lateral spacing of integrin receptors in the flourapatitecomplexes. In adults, the osteoblast is derived from a bone marrow stromal fibroblastic stem cell, termed the MSC, a nonhematopoietic multipotent stem-like cell vital for the osteogenic process capable of differentiating into both osteoblastic and nonosteoblastic lineages, thus enhancing the bone commitment and osseointegration [69-71].

Shot Peening/Laser Peening

Shot peening is similar to sand blasting, where the surface is bombarded with small spherical particles, each particle on coming in contact with the surface causes small indentations or dimples to form. Laser peening involves the rise of high-intensity (5-15 GW/cm^2) nanoscale pulses (10-30 ns) of a laser beam striking a protective layer of paint on the metallic surface. These implants demonstrate a regular honeycomb pattern with small pores [71].

Photofunctionalization

UV treatment of dental implant surfaces enhances bioactivity and osseointegration by altering the TiO_2 on the surface. By promoting interactions of cells and proteins to the implant on a molecular level, UV light is believed to enhance the osteoconductivity. UV treatment reduces the degree of surface hydrocarbon and increases surface energy and wettability by converting hydrophobic implants to superhydrophilic. UV light has been suggested to raise the level of protein absorption and cellular attachment to titanium surfaces, and it has been shown to restore bioactivity caused by age-related degradations. UV treatment is simple and cost effective for all types of titanium surfaces [72,73].

Biomolecular Coatings

The biomolecular coatings that can be used are the following: (1) bone morphogenic proteins (BMP), (2) non-BMP growth factors, (3) peptides, and (4) extracellular matrix. The surface-specific adsorbed biofilm determines cell adhesion, as proteins act as contact for the attachment of cells. This is accomplished by means of integrins, which are specific transmembrane receptors that bind to adhesive proteins on the biomaterials' surface and to components of the cytoskeleton through their extra and intracellular domains, respectively. In general, the biocompatibility of bone-replacing implant materials is closely related to osteoblast adhesion onto their surface. Osteoblast attachment, adhesion, and spreading will influence the capacity of these cells to proliferate and differentiate itself upon contact with the implant. These latter processes are quintessential for the establishment of a mechanically solid interface, with complete fusion between the implant surface and bone tissue without any intervening fibrous tissue.

Self-Assembled Monolayers on Nanotextured Titanium

The recent development of nanomaterial science raised a large interest in understanding the influence of nanoscale properties of materials on the behavior of biomolecules. In particular, it was shown that cellular adhesion can be governed by selective nanostructuring of biomaterials [74]. Self-assembly of molecular monolayers is another powerful approach to modify surface properties. Thiol-based self-assembled monolayers (SAMs) on metals, mostly on gold, have been extensively studied and used as model systems for a variety of applications. In general, these highly ordered SAMs can alter surface electronic levels, hydrophobicity, and adhesive properties, and they provide the surface with chemical functional groups. For oxide surfaces, a variety of molecules, including alkyltrichlorosilanes, phosphonates, and carboxylic acids, can be grafted on the surface, although the resulting films are generally not as well ordered as alkanethiols on gold. A recent interest has emerged for organic functionalization of the native oxide surfaces of tantalum, titanium, and related alloys in connection with their wide use as biocompatible materials, particularly in implants. For this purpose, phosphoric acid–terminated alkyl chains were shown as a good candidate for building SAMs on such materials because of their strong chemical bonding to surface oxides. However, similar functionalization of commercial titanium metal, which is more relevant to fabrication of bioimplants, leads to lower contact angles [66].

Flouride-Modified Implant Surfaces

The element fluoride was selected as a surface modification agent because of its specific qualities both in contact with calcified tissues and also in contact with titanium. Fluoride was known to have a particular affinity for calcified tissues, and it had proven an effect as a prophylactic agent against dental caries by binding to calcium forming calcium fluoride and fluorapatite, leading to an increased stability of the HA structure and resistance against acid attach [67].

The calcium-binding capacity of fluoride has also been successfully used in the treatment of systemic bone diseases, such as osteoporosis. Systemic treatment with fluoride was reported to give an increased trabecular density and further an induced calcification of bone, leading to a stronger bone, with improved load-bearing capacities and improved fracture resistance. There were indications in the literature that fluoride acted primarily on osteoprogenitor cells or undifferentiated osteoblasts, and fluoride thus had an effect at the cellular level, in addition to a physicochemical effect. It was reported in studies that fluoride treatment of bone triggered acute increases of intrinsic calcium levels, further indicating a cellular effect of fluoride [75]. A surface modification of titanium implants with fluoride incorporated into the superficial TiO_2 layer could thus lead to an implant with an improved bone response compared with nonmodified titanium implants. Studies were therefore initiated to establish a method for modifying titanium with the use of fluoride to create an implant intended to have improved biological properties. The nanoscale roughness created by the fluoride modification may add a further bone-promoting effect to the already seen by the microstructure because of the blasting. A unique nucleating effect is demonstrated by fluoride-modified titanium, in the case when the implant is immersed into a liquid saturated with respect to calcium and phosphate, it attracts these ions to the surface, and crystals of CaP start to grow [76].

Results

Coating the implant surfaces with rhBMP-2 and recombinant human vascular endothelial growth factor I65 (rhVEGFI65) affects osseointegration. On testing the effect of coating, there were 5 different groups of implants:

1. AE surface (control group);
2. CaP coated surface (CaP group);
3. CaP bearing incorporated rhBMP-2 (BMP group);
4. CaP bearing incorporated rhVEGFI65 (VEGF group); and
5. CaP bearing incorporated rhBMP-2+rhVEGFI65 (BMP+VEGF group).

On osseointegration, it was seen that the BMP and BMP+VEGF groups showed significant enhancement in bone volume density compared with the AE control group. All implants with CaP coating demonstrated significantly enhanced BIC rates compared with the AE controls at 2 weeks. However, the BMP+VEGF group did not significantly enhance BIC at 4 weeks. It was concluded that the biomimetic CaP-coated implant surfaces, with both BMP and VEGF, enhance bone volume density but not BIC [77].

Microstructured microrough surface topography implants provided by the grit-blasting/acid-etching process were further biofunctionalized using HA, bioactive peptide, or any bioactive substance. When (1) microstructured+HA+a low concentration of bioactive peptide (20 µg/mL), (2) micro-structured+HA, (3) microstructured, and (4) microstructured+HA+a high concentration of bioactive peptide (200 µg/mL) were compared, implants with 200 µg/mL peptide had the highest mean value of direct BIC. In addition, bone density analysis revealed that implant surfaces with 20 µg/mL peptide provided a higher adjacent bone density when compared with the other groups. Nevertheless, the differences among the groups were also not statistically significant. The authors concluded that biofunctionalization of the implant surface might interfere in the bone apposition around implants, especially regarding the aspect of bone density [78].

When a dual AE surface (minimally rough) had significantly higher rabbit-reverse torque (RTQ) values than when grit blasted (moderately rough) and plasma sprayed (rough) values were assessed to analyze the effect of coarse surface roughness, it was seen that coarse surface roughness had no benefit [79,80].

In recent years, studies on submicron, micron, and coarse roughness properties have been presented. It seems that all 3 layers play an important role in overall osseointegration, with each layer addressing bone formation at different time points. In vitro studies have evaluated the surface topography effects on bone formation through osteoconduction, including the steps of protein absorption, fibrin clot retention, and platelet interaction. For example, enhanced surface topographies, because of blasting or acid etching, displayed significantly greater fibrin retention forces than machined surfaces. Microtopographic surfaces, defined as those exhibiting features in the scale range of platelets (≤3 µm), displayed greater platelet activation than smoother surfaces. The new T3 implant (BIOMET 3i) has a surface addressing different aspects of osseointegration and periimplant health. The coronal aspect of the implant has a microtopography similar to the fully etched OSSEOTITE implant, comprising submicron features superimposed on 1-3 µm pitting, overlaid on a minimally rough surface topography (Sa<1.0 µm). From the base of the collar to the apical tip, the T3 implant has greater roughness. The resulting trilevel surface comprises submicron features of CaP nanoparticles superimposed on 1-3 µm pitting, overlaid on a moderately rough surface topography (Sa ~1.4 µm). The apical surface is designed to enhance osseointegration. As such, the included surface features have been researched to assess their potential impacts on de novo bone formation and the strength of the resulting bone-to-implant interface at different time points: nanoroughness to initiate osseointegration, double acid-etchedfor the next osseointegrative time point, and course micron features for long-term bone locking. Preliminary clinical results are promising in different bone qualities and locations. However, further follow- up is needed before definitive conclusions can be drawn about this implant surface.

Furthermore, it is seen that fluoride-modified titanium implants increase the expression of Runt-related transcription factor 1 (RUNX-2), osterix, type I collagen, and bone sialoprotein and increases *alkaline phosphatase* activity. In addition, fluoride modification augments the thrombogenic properties of titanium, promoting fibrinogen activation and rapid coagulation, resulting in a less dense fibrin clot that could promote osteoblast migration to the implant surface in vivo [81].

Discussion

Surface characteristics play a special role in the biological performance of implants. Mechanical properties, such as Young's modulus, and fatigue properties are mainly determined by the bulk of the material and chemical and biological interactions between the material and the host tissue. They are closely associated with the material surface properties. These interactions include early events, such as binding of water molecules, ions, and biomolecules, as well as mineralization at the implant surface. The original surface is thus a result of these early interactions with a conditioning layer, on which the cells will eventually interact. This is regarded as one of the factors that will determine the tissue regeneration around the implant [8]. It is a generally held and very widely supported principle that implants that have a roughened surface are much more likely to rapidly osseointegrate than implants with a smooth-machined surface, with the optimal roughness being in the range of 1-1 OpM. This may be because of implants with smooth surfaces being more susceptible to fibrous encapsulation than implants with roughened surfaces [82]. Fibrous encapsulation is the formation of a poorly vascularized collagenous capsule around the implant, which results in the failure of osseointegration. There are a number of factors that can cause fibrous encapsulation, including a sustained inflammatory response, lack of vascularization at the implant site, and low levels of osteoblast migration or attachment to the implant surface [83]. The ultimate result of fibrous encapsulation is that the tissue does not attach directly to the implant surface, leaving a space between the fibrous capsule and implant, which fills with fluid. This fluid-filled space provides an ideal environment for bacterial infiltration and a subsequent infection, which leads to bone resorption via a sustained inflammatory response.

Roughened surfaces also have a thicker titanium oxide layer, which is a reactive layer of surface particles thought to have a dynamic effect on surrounding tissues, encouraging attachment. There is a broad consensus that rough implant surfaces have superior osseointegrative potential than smooth implant surfaces. However, there is a broad range of methods to create roughened titanium surfaces, and there has been much discussion in the literature about which of these methods creates surfaces optimized for osseointegration. Surface roughness can be divided into 3 levels depending on the scale of the features: macro, micro, and nanosized topologies. The macrolevel is defined as one which has topographical features in the range of millimetres to tens of microns. This scale is directly related to implant geometry, with threaded screw and macroporous surface treatments giving surface roughness of more than 10 microns. The microtopographic profile of dental implants is defined as one where surface roughness is in the range of 1-10 um. This range of roughness maximizes the interlocking between mineralized bone and the surface of the implant [7,26,84]. At the nanoscale, a more textured surface topography increases the surface energy. Nanotopography might also directly influence cell proliferation and differentiation, as it has been suggested that nanopatterning can modulate cell behavior [25,61,85-88]. Repetitiveness and homogeneity are key parameters to define the nanostructure of an implant surface, but these are difficult to quantify and are considered as qualitative morphological parameters. If nanostructures are not clearly visible (no patterns, no particles, and insignificant texture) or not homogeneous and repetitive, the surface should be considered as nanosmooth. Grit blasting is one of the most common methods by which titanium dental implants are roughened. The increased osseointegration was confirmed by Rasmusson et al [89], who investigated the osteogenic properties of titanium grit-blasted surfaces. Wennerberg et al [7,26,30] also demonstrated with a rabbit model that grit blasting with TiO_2 or Al_2O_3 particles gave similar values of BIC, but it drastically increased the biomechanical fixation of the implants when compared with smooth titanium. These studies have shown that the torque force increased with the surface roughness of the implants while comparable values in bone apposition were observed. Nevertheless, Aparicio et al [34] highlighted some features related to alumina blasting for dental implants that could compromise osseointegration, such as particle detachment during the healing process and absorption by the surrounding tissues. The use of HA to roughen implant surfaces has been reported to result in similar rates of bone apposition around implants as other techniques, but HA has the advantage of being resorbable *in situ*. However, several in vitro and in vivo studies [7,26,30,89] suggested that grit-blasted titanium surfaces encourage osteoblast differentiation and, by extension, osseointegration. Cells from both osteoblast cell lines and primary mandibular bone from various species grown on grit-blasted titanium surfaces have been reported to increase expression of osteoblast specific messenger RNA and proteins, as well as increase mineralization compared with cell grown on smooth surfaces. Similarly, grit-blasted microimplants in humans have been shown to increase bone apposition compared with smooth-machined edges [90].

Another titanium implant surface treatment that has been reported to increase the chances of osseointegration is acid etching. Acid etching is often used in conjunction with grit blasting in implant manufacture. Cho et al [91] postulated that chemical acid etching alone of the titanium implant surface has the potential to greatly enhance osseointegration without adding particulate matter (eg, TPS or HA) or embedding surface contaminants (eg, grit particles). Several investigators [92] have reported that grit particles can remain impregnated in the implant material, and they are potentially a causative agent in observed tissue breakdown. Their study indicated that rough AE implants achieve greater resistance to reverse torque removal than machined-surface implants, which infers that chemically acid etching implant surfaces has higher strengths of osseointegration than machined-implant surfaces [91]. Lima et al [93] designed a study to measure implant osseointegration using 3 different surface treatments. fiber mesh, grit blasting, and acid etching, and they concluded that overall, AE surfaces demonstrated greater mean osseointegration than fiber mesh surfaces. A study conducted by Bana et al [94] indicates that etching with concentrated sulfuric acid is an effective way to modify the surface of titanium for biological applications. Guo et al [68] compared the osteoinductive and bone-specific gene expression in cells adherent to TiO_2-grit-blasted versus TiO_2 grit-blasted and HF-treated (TiO_2/HF) commercially pure titanium implant surfaces. They concluded that as a marker of osteoinduction, the increased levels of RUNX-2 in cells adherent to the TiO_2/HF surfaces suggest that the additional HF treatment of the TiO_2 grit-blasted surface results in surface properties that support adherent cell osteoinduction. Etching with strong acids has been shown to cause hydrogen embrittlement of titanium, which can cause microcracks on the surface, potentially undermining the structural integrity of the implant and ultimately leading to implant failure. Nevertheless, AE implants have a proven clinical track record, and they are still in use [95]. Plasma surface coating of HA or titanium is one of the most effective methods in developing these surface depositions, thus enhancing the surface roughness. A metastable CaP solution provides excellent bioactivity of the HA/YSZ/Ti- 6Al-4V composite coating, which has the ability to induce bone-like apatite nucleation and growth on implant surface. HA coatings promote better cell proliferation. According to Liu et al [96], the bonding strength of HA on titanium alloys decreased long hours of immersion time in the SBF. After an immersion in the SBF, the HA coatings became weak because of the intermellar or cohesive bonding degradation in the coating. However, Knabe et al [97] found that a plasma-sprayed titanium surface exhibits the highest surface roughness compared with a deep profile surface structure (the surface was acid etched and grit blasted), and in an *in vitro* test, the HA coating has less bone contact compared with other surface modifications. Some reports showed that the mechanical properties of HA can be significantly improved by the addition of yttria-stabilized zirconia. HA coatings reinforced with zirconia possessed better performance in bond strength and dissolution behavior of the titanium implants. Over the same period (4 weeks after SBF immersion), the HA/YSZ/Ti-6Al-4V composite coating showed a reduced tensile strength by ~27.7% compared with the pure HA coatings with ~78.8% [98]. It has been reported that more new bone is formed, and new bone grows more rapidly into pores of the surface of alkaline-modified plasma-sprayed implants, and this may be beneficial to reduce clinical healing times and consequently improve implant success rates. Kim et al [60] concluded that the HA layer was employed to enhance the bioactivity and osteoconductivity of the titanium substrate, and the TiO_2 buffer layer was inserted to improve the bonding strength between the HA layer and titanium substrate, as well as to prevent the corrosion of the titanium substrate. The sol-gel approach was favored because of the chemical homogeneity, high surface area in single step, fine grain size of the resultant coating, the low crystallization temperature, and mass producibility of the process itself [60]. Cordioli et al [79] reported no benefits by increasing coarse surface roughness at 5 weeks in an RTQ model, specifically demonstrating that a dual AE surface (minimally rough) had significantly higher RTQ values than grit-blasted (moderately rough) and plasma-sprayed (rough) surface. These findings are consistent with those of Klokkevold et al [80], who measured reverse torque (RTQ) for dual AE and moderately rough-surfaced implants 1 month after placement in rabbit tibias. The latter study included additional time points for testing reverse torque and showed that the rougher-surfaced implants had significantly higher RTQ results at 2 and 3 months after placement. The authors attributed the higher RTQ to the moderately rough surfaces' increased depth of topography and subsequent void volume, which permitted additional bone ingrowth for mechanical interlocking. In recent years, studies on submicron, micron, and coarse roughness properties have been presented. It seems that all 3 layers play an important role in overall osseointegration, with each layer addressing bone formation at different time points. In vitro studies have evaluated the surface topography effects on bone formation through osteoconduction, including the steps of protein absorption, fibrin clot retention, and platelet interaction. Becker et al [99] investigated bone formation onto sand-blasted and AE (control group), chromosulfuric acid surface–enhanced (CSA group), and recombinant human BMP-2 (rhBMP-2) biocoated CSA—BMP-A group: noncovalently immobilized rhBMP-2 (596 ng/cm2); BMP-B group: covalently immobilized rhBMP-2 (819 ng/cm2)—implants after placement in the mandibles and tibiae of dogs. After 4 weeks of healing, BIC values appeared to be highest for the BMP-B group, followed by BMP-A, CSA, and the control in both the mandible and the tibia. Wikesjo et al [100] studied whether adsorbing rhBMP2 onto a titanium porous oxide (TPO) implant surface might increase or accelerate local bone formation and support osseointegration in the posterior mandible (type II bone) in dogs. A similar study conducted by Wikesjo et al to evaluate local bone formation and osseointegration in the posterior maxillae (type IV bone) was analyzed in 8 adult monkeys. The authors concluded that rhBMP-2–coated TPO surfaces enhanced local bone formation in type IV bone in a dose-dependent fashion in nonhuman primates, resulting in significant osseointegration.

Nikolidakis et al [101] examined the effect of transforming growth factor beta 1 (TGF-beta 1) on the early bone healing around dental implants installed into the femoral condyle of goats. The authors concluded that a low dose of TGF-beta 1 has a negative influence on the integration of oral implants in trabecular bone during the early postimplantation healing phase. Schouten et al [102] investigated the effect of implant design, surface properties, and TGF-beta 1 on periimplant bone response, an extensive improvement of the bone response to titanium implants can be obtained by adding an electrosprayed CaP coating. The supplementation of a 1 µg TGF-beta 1 coating has only a marginal effect. The cellular response to fluoride-modified titanium implants has been assessed in different osteoblast cellular models using MSCs from different origin, primary cultures of osteoblasts, nontransformed clonal cell lines (MC3T3-E1), or osteosarcoma cell lines (MG63). The different cellular models, time-point of the analysis, or implant production might explain the differences in the reported results. Thus, although some studies have reported increased proliferation on fluoride-modified titanium implants, others failed [103,104]. In solution, fluoride has been proved to stimulate bone cell proliferation, but its effect varies according to the stage of differentiation of the cells; thus, the fluoride ion acts primarily on osteoprogenitor cells or undifferentiated osteoblasts rather than on more differentiated osteoblasts. In addition, some studies find higher cell adhesion in fluoride-modified titanium implants compared with control; other studies found no differences. In this regard, it is important to include the importance of the surface topography when discussing the number of cells attached on the surfaces, as the modification of titanium surface with HF is influenced by HF concentration, the exposure time, and the initial surface topography. In the same line, differences in the results of gene expression analysis might also be explained by differences in the roughness or chemical composition of the surfaces used in the different studies.

Thus, the future of dental implantology should aim to develop surfaces with controlled and standardized topography or chemistry. Different methods have been described to modify or embellish titanium substrates by mechanical and chemical methods. Modification of titanium endosseous implant surfaces enhances interfacial bone formation measured as BIC. The future of dental implantology should aim at developing surfaces with controlled and standardized topography or chemistry. This approach is the only way to understand protein, cell, and tissue interactions with implant surfaces. These therapeutic strategies should ultimately enhance the osseointegration process of dental implants for their long-term success.

Conflicts of Interest

None declared.

References

1. Brånemark PI, Adell R, Breine U, Hansson BO, Lindström J, Ohlsson A. Intra-osseous anchorage of dental prostheses. I. Experimental studies. Scand J Plast Reconstr Surg 1969;3(2):81-100. [Medline: 4924041]
2. Epifanov NS. [Pioneer of higher medical education in Siberia (on the 125th anniversary of the birth of E. G. Salishchev)]. Sov Zdravookhr 1976(7):76-79. [Medline: 798309]
3. Quirynen M, Bollen CM, Papaioannou W, van Eldere J, van Steenberghe D. The influence of titanium abutment surface roughness on plaque accumulation and gingivitis: short-term observations. Int J Oral Maxillofac Implants 1996;11(2):169-178. [Medline: 8666447]
4. Juodzbalys G, Sapragoniene M, Wennerberg A, Baltrukonis T. Titanium dental implant surface micromorphology optimization. J Oral Implantol 2007;33(4):177-185. [doi: 10.1563/1548-1336(2007)33[177:TDISMO]2.0.CO;2] [Medline: 17912958]
5. Albrektsson T, Brånemark PI, Hansson H, Lindström J. Osseointegrated titanium implants. Requirements for ensuring a long-lasting, direct bone-to-implant anchorage in man. Acta Orthop Scand 1981;52(2):155-170. [Medline: 7246093]
6. Carinci F, Pezzetti F, Volinia S, Francioso F, Arcelli D, Marchesini J. Analysis of osteoblast-like MG63 cells response to a rough implant surface by means of DNA microarray. J Oral Implantol 2003;29(5):215-220. [Medline: 15008929]
7. Le Guéhennec L, Soueidan A, Layrolle P, Amouriq Y. Surface treatments of titanium dental implants for rapid osseointegration. Dent Mater 2007 Jul;23(7):844-854. [doi: 10.1016/j.dental.2006.06.025] [Medline: 16904738]
8. Palmquist A, Omar M, Esposito M, Lausmaa J, Thomsen P. Titanium oral implants: surface characteristics, interface biology and clinical outcome. J R Soc Interface 2010 Oct 6;7(Suppl 5):S515-S527 [FREE Full text] [doi: 10.1098/rsif.2010.0118.focus] [Medline: 20591849]
9. Smith D, Pilliar R, Metson J, McIntyre N. Dental implant materials. II. Preparative procedures and surface spectroscopic studies. J Biomed Mater Res 1991 Sep;25(9):1069-1084. [doi: 10.1002/jbm.820250903] [Medline: 1663952]
10. Kieswetter K, Schwartz Z, Dean DD, Boyan BD. The role of implant surface characteristics in the healing of bone. Crit Rev Oral Biol Med 1996;7(4):329-345. [Medline: 8986395]
11. Ratner B, Johnston A, Lenk T. Biomaterial surfaces. J Biomed Mater Res (A1) 1987;21:59-90. [Medline: 3571303]
12. Lavenus S, Ricquier JC, Louarn G, Layrolle P. Cell interaction with nanopatterned surface of implants. Nanomedicine (Lond) 2010 Aug;5(6):937-947. [doi: 10.2217/nnm.10.54] [Medline: 20735227]
13. Lavenus S, Louarn G, Layrolle P. Nanotechnology and dental implants. Int J Biomater 2010 Jun 16;2010(12):915327 [FREE Full text] [doi: 10.1155/2010/915327] [Medline: 21253543]
14. Yim EK, Reano RM, Pang SW, Yee AF, Chen CS, Leong KW. Nanopattern-induced changes in morphology and motility of smooth muscle cells. Biomaterials 2005 Sep;26(26):5405-5413. [doi: 10.1016/j.biomaterials.2005.01.058] [Medline: 15814139]
15. Webster TJ, Ejiofor JU. Increased osteoblast adhesion on nanophase metals: Ti, Ti6Al4V, and CoCrMo. Biomaterials 2004 Aug;25(19):4731-4739. [doi: 10.1016/j.biomaterials.2003.12.002] [Medline: 15120519]
16. Variola F, Vetrone F, Richert L, Jedrzejowski P, Yi JH, Zalzal S, et al. Improving biocompatibility of implantable metals by nanoscale modification of surfaces: an overview of strategies, fabrication methods, and challenges. Small 2009 May;5(9):996-1006. [doi: 10.1002/smll.200801186] [Medline: 19360718]
17. Dorozhkin S. Nanodimensional and nanocrystalline apatites and other calcium orthophosphates in biomedical engineering, biology and medicine. Materials 2009 Nov 27;2(4):1975-2045. [doi: 10.3390/ma2041975]
18. Palin E, Liu H, Webster T. Mimicking the nanofeatures of bone increases bone-forming cell adhesion and proliferation. Nanotechnology 2005;16:1828-1835. [doi: 10.1088/0957-4484/16/9/069]
19. Wennerberg A, Albrektsson T. Effects of titanium surface topography on bone integration: a systematic review. Clin Oral Implants Res 2009 Sep;20(Suppl 4):172-184. [doi: 10.1111/j.1600-0501.2009.01775.x] [Medline: 19663964]
20. Jokstad A, Braegger U, Brunski JB, Carr AB, Naert I, Wennerberg A. Quality of dental implants. Int Dent J 2003;53(6 Suppl 2):409-443. [Medline: 14725421]
21. Shrestha S. Current concepts in biomaterials in dental implant. Sci Res 2014;2(1):7-12. [doi: 10.11648/j.sr.20140201.12]
22. Borsari V, Giavaresi G, Fini M, Torricelli P, Tschon M, Chiesa R, et al. Comparative in vitro study on a ultra-high roughness and dense titanium coating. Biomaterials 2005 Aug;26(24):4948-4955. [doi: 10.1016/j.biomaterials.2005.01.010] [Medline: 15769530]
23. Ong JL, Carnes DL, Bessho K. Evaluation of titanium plasma-sprayed and plasma-sprayed hydroxyapatite implants in vivo. Biomaterials 2004 Aug;25(19):4601-4606. [doi: 10.1016/j.biomaterials.2003.11.053] [Medline: 15120505]
24. Le Guéhennec L, Soueidan A, Layrolle P, Amouriq Y. Surface treatments of titanium dental implants for rapid osseointegration. Dent Mater 2007 Jul;23(7):844-854. [doi: 10.1016/j.dental.2006.06.025] [Medline: 16904738]
25. Bressan E, Sbricoli L, Guazzo R, Tocco I, Roman M, Vindigni V, et al. Nanostructured surfaces of dental implants. Int J Mol Sci 2013 Jan 17;14(1):1918-1931 [FREE Full text] [doi: 10.3390/ijms14011918] [Medline: 23344062]
26. Wennerberg A, Albrektsson T, Andersson B, Krol JJ. A histomorphometric and removal torque study of screw-shaped titanium implants with three different surface topographies. Clin Oral Implants Res 1995 Mar;6(1):24-30. [Medline: 7669864]

27. Wennerberg A, Albrektsson T, Andersson B. An animal study of cp titanium screws with different surface topographies. J Mater Sci Mater Med 1995 Feb;6(5):302-309. [doi: 10.1007/BF00120275]
28. Wennerberg A, Albrektsson T, Lausmaa J. Torque and histomorphometric evaluation of cp titanium screws blasted with 25- and 75-microns-sized particles of Al2O3. J Biomed Mater Res 1996 Feb;30(2):251-260. [doi: 10.1002/(SICI)1097-4636(199602)30:2<251::AID-JBM16>3.0.CO;2-P] [Medline: 9019491]
29. Wennerberg A, Ektessabi A, Albrektsson T, Johansson C, Andersson B. A 1-year follow-up of implants of differing surface roughness placed in rabbit bone. Int J Oral Maxillofac Implants 1997;12(4):486-494. [Medline: 9274077]
30. Abron A, Hopfensperger M, Thompson J, Cooper LF. Evaluation of a predictive model for implant surface topography effects on early osseointegration in the rat tibia model. J Prosthet Dent 2001 Jan;85(1):40-46. [doi: 10.1067/mpr.2001.112415] [Medline: 11174677]
31. Ivanoff CJ, Hallgren C, Widmark G, Sennerby L, Wennerberg A. Histologic evaluation of the bone integration of TiO(2) blasted and turned titanium microimplants in humans. Clin Oral Implants Res 2001 Apr;12(2):128-134. [Medline: 11251662]
32. Mano T, Ueyama Y, Ishikawa K, Matsumura T, Suzuki K. Initial tissue response to a titanium implant coated with apatite at room temperature using a blast coating method. Biomaterials 2002 May;23(9):1931-1936. [Medline: 11996033]
33. Ellingsen JE, Johansson CB, Wennerberg A, Holmén A. Improved retention and bone-tolmplant contact with fluoride-modified titanium implants. Int J Oral Maxillofac Implants 2004;19(5):659-666. [Medline: 15508981]
34. Berglundh T, Abrahamsson I, Albouy JP, Lindhe J. Bone healing at implants with a fluoride-modified surface: an experimental study in dogs. Clin Oral Implants Res 2007 Apr;18(2):147-152. [doi: 10.1111/j.1600-0501.2006.01309.x] [Medline: 17269959]
35. Stanford CM, Johnson GK, Fakhry A, Gratton D, Mellonig JT, Wanger W. Outcomes of a fluoride modified implant one year after loading in the posterior-maxilla when placed with the osteotome surgical technique. Appl Osseointegr Res 2006;5:50-55.
36. Nanci A, Wuest JD, Peru L, Brunet P, Sharma V, Zalzal S, et al. Chemical modification of titanium surfaces for covalent attachment of biological molecules. J Biomed Mater Res 1998 May;40(2):324-335. [Medline: 9549628]
37. Yi J, Bernard C, Variola F, Zalzal SF, Wuest JD, Rosei F, et al. Characterization of a bioactive nanotextured surface created by controlled chemical oxidation of titanium. Surf Sci 2006 Oct;600(19):4613-4621. [doi: 10.1016/j.susc.2006.07.053]
38. Ellingsen JE. Pre-treatment of titanium implants with fluoride improves their retention in bone. J Mater Sci Mater Med 1995 Dec;6(12):749-753. [doi: 10.1007/BF00134312] [Medline: 16112191]
39. Cooper LF, Zhou Y, Takebe J, Guo J, Abron A, Holmén A, et al. Fluoride modification effects on osteoblast behavior and bone formation at TiO2 grit-blasted cp titanium endosseous implants. Biomaterials 2006 Feb;27(6):926-936. [doi: 10.1016/j.biomaterials.2005.07.009] [Medline: 16112191]
40. Bauer S, Schmuki P, von der Mark K, Park J. Engineering biocompatible implant surfaces. Prog Mater Sci 2013 Apr;58(3):261-326. [doi: 10.1016/j.pmatsci.2012.09.001] [Medline: 312456520]
41. Mendonça G, Mendonça DB, Aragão FJ, Cooper LF. Advancing dental implant surface technology--from micron- to nanotopography. Biomaterials 2008 Oct;29(28):3822-3835. [doi: 10.1016/j.biomaterials.2008.05.012] [Medline: 18617258]
42. Uchida M, Kim HM, Miyaji F, Kokubo T, Nakamura T. Apatite formation on zirconium metal treated with aqueous NaOH. Biomaterials 2002 Jan;23(1):313-317. [Medline: 11762851]
43. Lakstein D, Kopelovitch W, Barkay Z, Bahaa M, Hendel D, Eliaz N. Enhanced osseointegration of grit-blasted, NaOH-treated and electrochemically hydroxyapatite-coated Ti-6Al-4V implants in rabbits. Acta Biomater 2009 Jul;5(6):2258-2269. [doi: 10.1016/j.actbio.2009.01.033] [Medline: 19251497]
44. Yao C, Slamovich EB, Webster TJ. Enhanced osteoblast functions on anodized titanium with nanotube-like structures. J Biomed Mater Res A 2008 Apr;85(1):157-166. [doi: 10.1002/jbm.a.31551] [Medline: 17688267]
45. Kim KH, Ramaswamy N. Electrochemical surface modification of titanium in dentistry. Dent Mater J 2009 Jan;28(1):20-36 [FREE Full text] [Medline: 19280965]
46. Ercan B, Webster TJ. Greater osteoblast proliferation on anodized nanotubular titanium upon electrical stimulation. Int J Nanomedicine 2008;3(4):477-485 [FREE Full text] [Medline: 19337416]
47. Yao C, Perla V, McKenzie JL, Slamovich EB, Webster TJ. Anodized Ti and Ti6Al4V possessing nanometer surface features enhance osteoblast adhesion. J Biomed Nanotechnol 2005 Mar 1;1(1):68-73. [doi: 10.1166/jbn.2005.008]
48. Rodriguez R, Kim K, Ong JL. In vitro osteoblast response to anodized titanium and anodized titanium followed by hydrothermal treatment. J Biomed Mater Res A 2003 Jun 1;65(3):352-358. [doi: 10.1002/jbm.a.10490] [Medline: 12746882]
49. Yao C, Slamovich EB, Webster TJ. Enhanced osteoblast functions on anodized titanium with nanotube-like structures. J Biomed Mater Res A 2008 Apr;85(1):157-166. [doi: 10.1002/jbm.a.31551] [Medline: 17688267]
50. Jungner M, Lundqvist P, Lundgren S. Oxidized titanium implants (Nobel Biocare TiUnite) compared with turned titanium implants (Nobel Biocare mark III) with respect to implant failure in a group of consecutive patients treated with early functional loading and two-stage protocol. Clin Oral Implants Res 2005 Jun;16(3):308-312. [doi: 10.1111/j.1600-0501.2005.01101.x] [Medline: 15877751]
51. Schüpbach P, Glauser R, Rocci A, Martignoni M, Sennerby L, Lundgren A, et al. The human bone-oxidized titanium implant interface: a light microscopic, scanning electron microscopic, back-scatter scanning electron microscopic, and

energy-dispersive x-ray study of clinically retrieved dental implants. Clin Implant Dent Relat Res 2005;7(Suppl 1):S36-S43. [Medline: 16137086]
52. Sul Y, Johansson C, Wennerberg A, Cho L, Chang B, Albrektsson T. Optimum surface properties of oxidized implants for reinforcement of osseointegration: surface chemistry, oxide thickness, porosity, roughness, and crystal structure. Int J Oral Maxillofac Implants 2005;20(3):349-359. [Medline: 15973946]
53. Fröjd V, Linderbäck P, Wennerberg A, Chávez de Paz L, Svensäter G, Davies JR. Effect of nanoporous TiO2 coating and anodized Ca2+ modification of titanium surfaces on early microbial biofilm formation. BMC Oral Health 2011 Mar 8;11:8-9 [FREE Full text] [doi: 10.1186/1472-6831-11-8] [Medline: 21385428]
54. Nguyen H, Deporter D, Pilliar RM, Valiquette N, Yakubovich R. The effect of sol-gel-formed calcium phosphate coatings on bone ingrowth and osteoconductivity of porous-surfaced Ti alloy implants. Biomaterials 2004 Feb;25(5):865-876. [Medline: 14609675]
55. Advincula MC, Petersen D, Rahemtulla F, Advincula R, Lemons JE. Surface analysis and biocorrosion properties of nanostructured surface sol-gel coatings on Ti6Al4V titanium alloy implants. J Biomed Mater Res B Appl Biomater 2007 Jan;80(1):107-120. [doi: 10.1002/jbm.b.30575] [Medline: 16680691]
56. Afrooz L, Abdollah A, Aliasghar B. Sol-gel derived titania coating on titanium substrate. Iran J Pharm Res 2008;4(1):17-22 [FREE Full text] [doi: 10.4028/www.scientific.net/AMM.117-119.332]
57. Chen X, Mao SS. Titanium dioxide nanomaterials: synthesis, properties, modifications, and applications. Chem Rev 2007 Jul;107(7):2891-2959. [doi: 10.1021/cr0500535] [Medline: 17590053]
58. Mansor AH, Ismail AB. Preparation of titanium dioxide (TiO2) thin films by sol gel dip coating method. Malay J Chem 2003;5:89-91.
59. Kumar PS, Kumar S, Savadi RC, John J. Nanodentistry: a paradigm shift-from fiction to reality. J Indian Prosthodont Soc 2011 Mar;11(1):1-6 [FREE Full text] [doi: 10.1007/s13191-011-0062-0] [Medline: 22379298]
60. Kim HW, Koh YH, Li LH, Lee S, Kim HE. Hydroxyapatite coating on titanium substrate with titania buffer layer processed by sol-gel method. Biomaterials 2004 Jun;25(13):2533-2538. [Medline: 14751738]
61. Vetrone F, Variola F, de Oliveira PT, Zalzal SF, Yi JH, Sam J, et al. Nanoscale oxidative patterning of metallic surfaces to modulate cell activity and fate. Nano Lett 2009 Feb;9(2):659-665. [doi: 10.1021/nl803051f] [Medline: 19159323]
62. Cabrini M, Cigada A, Rondelli G, Vicentini B. Effect of different surface finishing and of hydroxyapatite coatings on passive and corrosion current of Ti6Al4V alloy in simulated physiological solution. Biomaterials 1997 Jun;18(11):783-787. [Medline: 9177856]
63. Brown R, Alias M, Fontana R. Effect of composition and thickness on corrosion behavior of TiN and ZrN thin films. Surf Coat Technol 1993;62:467-473. [doi: 10.1016/0257-8972(93)90285-V]
64. Vaquila I, Vergara L, PasseggiJr M, Vidal R, Ferron J. Chemical reactions at surfaces: titanium oxidation. Surf Coat Technol 1999;122:67-71. [doi: 10.1016/S0257-8972(99)00420-X]
65. Dalby MJ, Riehle MO, Johnstone H, Affrossman S, Curtis AS. In vitro reaction of endothelial cells to polymer demixed nanotopography. Biomaterials 2002 Jul;23(14):2945-2954. [Medline: 12069336]
66. Love JC, Estroff LA, Kriebel JK, Nuzzo RG, Whitesides GM. Self-assembled monolayers of thiolates on metals as a form of nanotechnology. Chem Rev 2005 Apr;105(4):1103-1169. [doi: 10.1021/cr0300789] [Medline: 15826011]
67. Rølla G, Ogaard B, Cruz R. Topical application of fluorides on teeth. New concepts of mechanisms of interaction. J Clin Periodontol 1993 Feb;20(2):105-108. [Medline: 8436628]
68. Guo J, Padilla RJ, Ambrose W, De Kok IJ, Cooper LF. The effect of hydrofluoric acid treatment of TiO2 grit blasted titanium implants on adherent osteoblast gene expression in vitro and in vivo. Biomaterials 2007 Dec;28(36):5418-5425. [doi: 10.1016/j.biomaterials.2007.08.032] [Medline: 17868850]
69. Tomsia AP, Lee JS, Wegst UG, Saiz E. Nanotechnology for dental implants. Int J Oral Maxillofac Implants 2013;28(6):e535-e546. [doi: 10.11607/jomi.te34] [Medline: 24278949]
70. Variola F, Brunski JB, Orsini G, de Oliveira PT, Wazen R, Nanci A. Nanoscale surface modifications of medically relevant metals: state-of-the art and perspectives. Nanoscale 2011 Feb;3(2):335-353 [FREE Full text] [doi: 10.1039/c0nr00485e] [Medline: 20976359]
71. Parekh RB, Shetty O, Tabassum R. Surface modifications for endosseous dental implants. Int J Oral Implantol Clin Res 2012;3(3):116-121 [FREE Full text] [doi: 10.5005/JP-Journals-10012-1078]
72. Smeets R, Stadlinger B, Schwarz F, Beck-Broichsitter B, Jung O, Precht C, et al. Impact of dental implant surface modifications on osseointegration. Biomed Res Int 2016;2016 [FREE Full text] [doi: 10.1155/2016/6285620] [Medline: 27478833]
73. Ogawa T. Ultraviolet photofunctionalization of titanium implants. Int J Oral Maxillofac Implants 2014;29(1):e95-102. [doi: 10.11607/jomi.te47] [Medline: 24451893]
74. Balasundaram T, Webster TJ. A perspective on nanophase materials for orthopedic implant applications. J Mater Chem 2006;16:3737 [FREE Full text] [doi: 10.1039/B604966B]
75. Kassem M, Mosekilde L, Eriksen E. Effects of fluoride on human bone cells in vitro: differences in responsiveness between stromal osteoblast precursors and mature osteoblasts. Eur J Endocrinol 1994 Apr;130(4):381-386. [Medline: 8162169]

76. Ellingsen JE. On the properties of surface modified titanium. In: Davies JE, editor. Bone Engineering. Georgia, United States: Em Squared Inc; 2000:183-189.
77. Ramazanoglu M, Lutz R, Ergun C, von Wilmowsky C, Nkenke E, Schlegel K. The effect of combined delivery of recombinant human bone morphogenetic protein-2 and recombinant human vascular endothelial growth factor 165 from biomimetic calcium-phosphate-coated implants on osseointegration. Clin Oral Implants Res 2011 Dec;22(12):1433-1439. [doi: 10.1111/j.1600-0501.2010.02133.x] [Medline: 21418332]
78. Barros RR, Novaes AB, Papalexiou V, Souza SL, Taba M, Palioto DB, et al. Effect of biofunctionalized implant surface on osseointegration: a histomorphometric study in dogs. Braz Dent J 2009;20(2):91-98 [FREE Full text] [Medline: 19738939]
79. Cordioli G, Majzoub Z, Piattelli A, Scarano A. Removal torque and histomorphometric investigation of 4 different titanium surfaces: an experimental study in the rabbit tibia. Int J Oral Maxillofac Implants 2000;15(5):668-674. [Medline: 11055134]
80. Klokkevold P, Johnson P, Dadgostari S, Caputo A, Davies J, Nishimura R. Early endosseous integration enhanced by dual acid etching of titanium: a torque removal study in the rabbit. Clin Oral Implants Res 2001 Aug;12(4):350-357. [Medline: 11488864]
81. Thor A, Rasmusson L, Wennerberg A, Thomsen P, Hirsch J, Nilsson B, et al. The role of whole blood in thrombin generation in contact with various titanium surfaces. Biomaterials 2007 Feb;28(6):966-974. [doi: 10.1016/j.biomaterials.2006.10.020] [Medline: 17095084]
82. Abron A, Hopfensperger M, Thompson J, Cooper LF. Evaluation of a predictive model for implant surface topography effects on early osseointegration in the rat tibia model. J Prosthet Dent 2001 Jan;85(1):40-46. [doi: 10.1067/mpr.2001.112415] [Medline: 11174677]
83. Ellingsen JE, Thomsen P, Lyngstadaas SP. Advances in dental implant materials and tissue regeneration. Periodontol 2000 2006;41:136-156. [doi: 10.1111/j.1600-0757.2006.00175.x] [Medline: 16686931]
84. Wennerberg A, Hallgren C, Johansson C, Danelli S. A histomorphometric evaluation of screw-shaped implants each prepared with two surface roughnesses. Clin Oral Implants Res 1998 Feb;9(1):11-19. [Medline: 9590940]
85. Mendonça G, Mendonça DB, Simões LG, Araújo AL, Leite ER, Duarte WR, et al. The effects of implant surface nanoscale features on osteoblast-specific gene expression. Biomaterials 2009 Sep;30(25):4053-4062. [doi: 10.1016/j.biomaterials.2009.04.010] [Medline: 19464052]
86. Dalby M, McCloy D, Robertson M, Agheli H, Sutherland D, Affrossman S, et al. Osteoprogenitor response to semi-ordered and random nanotopographies. Biomaterials 2006 May;27(15):2980-2987. [doi: 10.1016/j.biomaterials.2006.01.010] [Medline: 16443268]
87. Dalby M, McCloy D, Robertson M, Wilkinson CD, Oreffo RO. Osteoprogenitor response to defined topographies with nanoscale depths. Biomaterials 2006 Mar;27(8):1306-1315. [doi: 10.1016/j.biomaterials.2005.08.028] [Medline: 16143393]
88. Ehrenfest DM, Coelho PG, Kang BS, Sul YT, Albrektsson T. Classification of osseointegrated implant surfaces: materials, chemistry and topography. Trends Biotechnol 2010 Apr;28(4):198-206. [doi: 10.1016/j.tibtech.2009.12.003] [Medline: 20116873]
89. Rasmusson L, Kahnberg KE, Tan A. Effects of implant design and surface on bone regeneration and implant stability: an experimental study in the dog mandible. Clin Implant Dent Relat Res 2001;3(1):2-8. [Medline: 11441539]
90. Ivanoff CJ, Hallgren C, Widmark G, Sennerby L, Wennerberg A. Histologic evaluation of the bone integration of TiO(2) blasted and turned titanium microimplants in humans. Clin Oral Implants Res 2001 Apr;12(2):128-134. [Medline: 11251662]
91. Cho SA, Park KT. The removal torque of titanium screw inserted in rabbit tibia treated by dual acid etching. Biomaterials 2003 Sep;24(20):3611-3617. [Medline: 12809791]
92. Darvell B, Samman N, Luk WK, Clark RK, Tideman H. Contamination of titanium castings by aluminium oxide blasting. J Dent 1995 Oct;23(5):319-322. [Medline: 7560379]
93. D'Lima DD, Lemperle SM, Chen PC, Holmes RE, Colwell CW. Bone response to implant surface morphology. J Arthroplasty 1998 Dec;13(8):928-934. [Medline: 9880187]
94. Ban S, Iwaya Y, Kono H, Sato H. Surface modification of titanium by etching in concentrated sulfuric acid. Dent Mater 2006 Dec;22(12):1115-1120. [doi: 10.1016/j.dental.2005.09.007] [Medline: 16375960]
95. Yokoyama K, Ichikawa T, Murakami H, Miyamoto Y, Asaoka K. Fracture mechanisms of retrieved titanium screw thread in dental implant. Biomaterials 2002 Jun;23(12):2459-2465. [Medline: 12033593]
96. Liu R, Poon WY, Kwok CH, Chu PK, Ding C. Plasma surface modification of titanium for hard tissue replacements. Surf Coat Technol 2004;186(1-2):227-233. [doi: 10.1016/j.surfcoat.2004.02.045]
97. Knabe C, Klar F, Fitzner R, Radlanski RJ, Gross U. In vitro investigation of titanium and hydroxyapatite dental implant surfaces using a rat bone marrow stromal cell culture system. Biomaterials 2002 Aug;23(15):3235-3245. [Medline: 12102195]
98. Gu YW, Khor KA, Pan D, Cheang P. Activity of plasma sprayed yttria stabilized zirconia reinforced hydroxyapatite/Ti-6Al-4V composite coatings in simulated body fluid. Biomaterials 2004 Jul;25(16):3177-3185. [doi: 10.1016/j.biomaterials.2003.09.101] [Medline: 14980413]
99. Becker J, Kirsch A, Schwarz F, Chatzinikolaidou M, Rothamel D, Lekovic V, et al. Bone apposition to titanium implants biocoated with recombinant human bone morphogenetic protein-2 (rhBMP-2). A pilot study in dogs. Clin Oral Investig 2006 Sep;10(3):217-224 [FREE Full text] [doi: 10.1007/s00784-006-0049-0] [Medline: 16683108]

100. Wikesjö UM, Xiropaidis A, Qahash M, Lim WH, Sorensen RG, Rohrer MD, et al. Bone formation at recombinant human bone morphogenetic protein-2-coated titanium implants in the posterior mandible (Type II bone) in dogs. J Clin Periodontol 2008 Nov;35(11):985-991. [doi: 10.1111/j.1600-051X.2008.01318.x] [Medline: 18976395]
101. Nikolidakis D, Meijer G, Oortgiesen D, Walboomers X, Jansen J. The effect of a low dose of transforming growth factor beta1 (TGF-beta1) on the early bone-healing around oral implants inserted in trabecular bone. Biomaterials 2009 Jan;30(1):94-99. [doi: 10.1016/j.biomaterials.2008.09.022] [Medline: 18838161]
102. Schouten C, Meijer G, van den Beucken JJ, Spauwen P, Jansen J. Effects of implant geometry, surface properties, and TGF-beta1 on peri-implant bone response: an experimental study in goats. Clin Oral Implants Res 2009 Apr;20(4):421-429. [doi: 10.1111/j.1600-0501.2008.01657.x] [Medline: 19298297]
103. Guida L, Annunziata M, Rocci A, Contaldo M, Rullo R, Oliva A. Biological response of human bone marrow mesenchymal stem cells to fluoride-modified titanium surfaces. Clin Oral Implants Res 2010 Nov;21(11):1234-1241. [doi: 10.1111/j.1600-0501.2010.01929.x] [Medline: 20497444]
104. Isa Z, Schneider G, Zaharias R, Seabold D, Stanford C. Effects of fluoride-modified titanium surfaces on osteoblast proliferation and gene expression. Int J Oral Maxillofac Implants 2006;21(2):203-211. [Medline: 16634490]

Abbreviations

AE: acid-etched
BIC: bone-to-implant contact
BMP: bone morphogenic protein
CaP: calcium phosphate
CSA: chromosulfuric acid
HA: hydroxyapatite
MSC: mesenchymal stem cell
NaOH: sodium hydroxide
RTQ: rabbit-reverse torque
RUNX-2: Runt-related transcription factor 1
SAM: self-assembled monolayer
SBF: simulated body fluid
TGF-beta 1: transforming growth factor beta 1
TiO_2: titania
TPO: titanium porous oxide
TPS: titanium plasma spraying
VEGF: vascular endothelial growth factor

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