



Improvements in Clinical Durability From Functional Biomimetic Metallic Dental Implants

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The current aim in dentistry is to return the patient to normal function in terms of esthetics and speech as well as health, regardless of injury, disease, or atrophy of the stomatognathic system. Dental implant, involving the emplacement of a fixed permanent artificial root to support prosthetic dental crowns, offers the obvious treatment choice for partial and complete edentulism. Even though the rates of survival are high, dental implant failures in long-term situations still occur. This will cause the removal of implants and additional health and financial burdens. These failures are attributable to mechanical instability, poor implant integration, necrosis, inflammation, and infections and are associated with lengthy patient care, loss of function, and pain. Therefore, the objective of the current publication is to detail the main types of implants along with the current and developing approaches and technologies for surface and bulk alteration that are used to increase biological and mechanical performance under function. Notable research is highlighted regarding the present development of dental implants with biologically active surfaces and their influence on osseointegration. In addition, dental implants based on the functionally graded concept inspired by human bone are reviewed.

Keywords: dental implant, surface modification, biomimetic process, osseointegration, bone regeneration, functionally graded materials

OPEN ACCESS

Edited by:

Francesco Baino,
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Specialty section:

This article was submitted to
Biomaterials,
a section of the journal
Frontiers in Materials

Received: 15 January 2020

Accepted: 06 April 2020

Published: 22 May 2020

Citation:

Al-Zubaidi SM, Madfa AA, Mufadhal AA, Aldawla MA, Hameed OS and Yue X-G (2020) Improvements in Clinical Durability From Functional Biomimetic Metallic Dental Implants. *Front. Mater.* 7:106. doi: 10.3389/fmats.2020.00106

INTRODUCTION

Patients experiencing tooth loss due to age, injury, or disease often suffer not only from functional constraints but also from the accompanying psychological and social consequences. The replacement of missing teeth is frequently accomplished by inserting single-tooth implants or implant-supported prostheses. Dental implant is considered the best treatment decision for the

Abbreviations: Ti, titanium; TiO₂, titanium oxide; BIC, bone-implant contact; HA, hydroxyapatite; ECM, extracellular matrix; BMP, bone morphogenetic protein; rhBMP, recombinant human bone morphogenetic protein; PRGF, plasma-rich growth factor; rhbFGF, recombinant human basic fibroblast growth factor; rhIGF-1, recombinant human insulin-like growth factor-1; FGFFN, fibroblast growth factor-fibronectin; CP, calcium phosphate; PLGA, poly lactide-co-glycolide; bFGF, basic fibroblast growth factor; rhbFGF, recombinant human basic fibroblast growth factor; rhVEGF, recombinant human vascular endothelial growth factor; rhVEGFI65, recombinant human vascular endothelial growth factor 165; FGMs, functionally graded materials; FG, functionally graded; SLA, sandblasted and acid-etched; SBF, simulated body fluids; SLM, selective laser melting; SLS, selective laser sintering; EBM, electron beam melting.

replacement of missing teeth for restoring patients' appearance, speech, and health (Esposito et al., 1999; Nag and Banerjee, 2012).

A dental implant is entirely installed into the jaw to support the dental prosthesis (Cheng et al., 2014). It is positioned in the jaw in such a way that it extends from the inside to the outside of the bone. Inside of the jaw, bone sympathy and stress relaxation are important, and, outside of the bone, in the oral cavity, adequate strength is necessary (Hedia H., 2005). However, the biomechanical performances of bone structures and dental implants are affected by many factors that interact with one another (Zarone et al., 2005, 2006). In the oral environment, many factors influence the long-standing success of prosthesis implantation. Some of these factors are reliant on the parameters such as load intensity and direction, occlusion, wear, quality of supporting tissues, temperature, and moisture, while others are not manageable, like fatigue, structural integrity, and time. Moreover, bone and materials that are used for fabricating implants are influenced by inherent physical characteristics that are accountable for their mechanical behaviors throughout their functioning over time (Van Noort, 2014). The chemical as well as the physical properties of implant materials, such as the surface composition of the implant, its microstructure, and its characteristics, are recognized factors that affect the clinical durability and outcome of dental implant (Smith, 1993).

The environmental circumstances in the oral cavity lead to an urgent need to develop newer and better implant materials and designs. Fundamentally, the implanted material should have much more reliable biocompatibility, no corrosion in body fluid, fracture and wear resistance, mechanical strength, low density, low elastic modulus, and high fatigue resistance (Smith, 1993; Okazaki et al., 1996; Sykaras et al., 2000).

Conventionally, dental implants are often fabricated from biomedical-graded materials, including titanium (Ti) and its alloys and/or ceramic (Osman and Swain, 2015). Among previously used materials, Ti and its alloys were selected for constructing most implants owing to their inertness, biocompatibility, and notable mechanical properties (Özcan and Hämmerle, 2012). As bone has a heterogeneous structure, insertion of homogeneous materials causes high mechanical divergence between the surrounding bone structure and implants (Özcan and Hämmerle, 2012), thereby increasing the vulnerability to loss of the dental implants during exposure to mechanical stresses (Schiefer et al., 2009; Merdji et al., 2012). In addition, the stiffness of Ti (110 GPa) is higher than that of human cortical cancellous bone (17–20 GPa and 4 GPa, respectively) (Hedia H., 2005; Krishna et al., 2007). Additionally, the variance in the thermo-physical properties of these materials might produce thermal stresses at the interface while drinking cold and hot fluids. The mechanical load applied during mastication subsequently superimposes these undesirable stresses that work at the interface between bone and implants. In addition, the fatigue type of failure and the jeopardizing of interface integrity can result from the cyclic nature of thermal loads (Hedia H., 2005; Yang and Xiang, 2007; Mehrali et al., 2013). Furthermore, and since bone is a self-motivated vital tissue that goes through continuous alterations by bone-forming as well as bone-eating cells in reaction to applied external signals,

this results in decreased mechanical loading of bone, which leads to resorption of the bone, relaxation of the implant, and, finally, failure of dental implants (Hedia H., 2005). Moreover, dental implant underoverloading generates large stresses in local sections of bone, which may encourage the resorption of the bone (Isidor, 2006). An additional concern is the shape of the implant, which has been shown to be a critical factor at the bone–implant interface and can stimulate osseointegration. Inside the bone, the implant material is required to have osseointegration so that the new bone can be formed quickly and attached directly to it (Raghavendra et al., 2005). Previously, several efforts have been made to develop the mechanical and biological properties of many materials to make them well-matched with the tissue of the bone. Most of these trails improve certain substantial interaction structures at the interface of bone tissue and implant surface. Current developments in bone tissue engineering scaffolds and dental implant designs have all contributed to creating novel porous Ti surfaces, and these arenas use and take advantage of each other's technologies. Therefore, this review paper presents a brief history of dental implants and new approaches to their production to improve their performance under function. Notable research is highlighted regarding (i) conventional surface modification techniques, (ii) biomimetic surface modification to enhance osseointegration, (iii) antibacterially coated implants, and (iv) dental implants based on the functionally graded concept.

CONVENTIONAL SURFACE MODIFICATION TECHNIQUES

Osseointegration is defined as “direct contact between living bone and implant. It is also histologically defined as the direct anchorage of an implant by the formation of bony tissue around the implant without the growth of fibrous tissue at the bone–implant interface”. Osseointegration is the chief requirement for the long-term clinical success of the implantation process, in which functional joining between the implant surface and the bone tissue should be achieved (Javed et al., 2013; Parithimarkalaignan and Padmanabhan, 2013; von Wilmsowky et al., 2014). The osseointegration rate, quality of the bone, and bone in contact with the implant all affect the long-term success of oral implant rehabilitation (Scarano et al., 2017b). Therefore, many attempts had made to improve osseointegration, such as improvement of surgical technique, a longer healing period, and alteration of the implant surface; among them, surface alteration has been evaluated by many researchers (Yin et al., 2012). On the whole, investigation trails on metallic biomaterials have been focused on the development of superficial modifications that improve their biological and mechanical properties (Del Fabbro et al., 2017).

Many studies found that the morphology, structure, and implant surface wettability are major factors in osseointegration (Gittens et al., 2014; Rupp et al., 2014; Li et al., 2015; Hotchkiss et al., 2016; Ozdemir et al., 2016; Sartoretto et al., 2017). Ti and its alloys are broadly applied biomaterials in the production of dental implants used in maxillofacial surgery

and in orthopedics, but Ti and its alloys do not directly create connections with the living bone (Oldani and Dominguez, 2012; Khan et al., 2014; Sidambe, 2014). Surface alterations, therefore, are the utmost essential approaches applied for the improvement of osseointegration (Goel et al., 2014; Chia and Wu, 2015; Mandracci et al., 2016). Surface modification of dental implants is considered an ideal strategy to obtain rapid secondary stability, improving the bone-to-implant interaction, and reducing the time required for the replacement of missing teeth (Smeets et al., 2016). The significance of the alteration of the implant surface is to maintain the important physical properties of the implant while altering only the outer surface layer to enhance the circumstances for rapid osseointegration, which is crucial to the long-term clinical success of an implant (Ellingsen et al., 2006; Puleo and Thomas, 2006; Le Guehennec et al., 2007). However, Salerno et al. (2015) evaluated implant topography before and after implantation in bovine bone using atomic force microscopy or 3D profilometry. They reported that no major changes happened in surface topography on implantation for most implants.

In recent years, various techniques and methodologies have been used for altering the topographical or chemical properties of traditional implant surfaces to enhance the bonding of the implant material with bone cells (Wirth et al., 2017). The alterations in the surfaces of a Ti implant permit it to stimulate the tissue of the bone, minimizing the period for osseointegration, and achieving superior transmission of occlusal mechanical loads from the implant to the bone (Al-Nawas and Wagner, 2017). Attempts to increase the osseointegration are normally approached by making surfaces rough, which in turn increases the surface area obtainable for binding the bone to the implant and enhances firmness as well as stability (Mello et al., 2016; Prasad et al., 2017). However, the biological reactions of the adjacent tissues to implant surfaces are mostly controlled by their chemical and/or morphological surface characteristics (Kasemo, 2002; Chaturvedi, 2009; Wennerberg and Albrektsson, 2010).

Physicochemical Methods

Many methods have been used to roughen Ti implant surfaces. These methods can be categorized by addition and subtraction into chemical, physical, and mechanical approaches. The methods include electrochemical deposition, laser ablation, acid or dual-acid etching, sandblasting with TiO₂, Al₂O₃, or hydroxyapatite (HA), combinations of such treatments, or coating with organic biomaterials. Many biomaterials have been applied for the modification of implant surfaces such as CaP, HA, or micro/nano-coating. All of these treatments of the implant surface modify the charge, energy, and composition of the current surface, which make possible for the implant surface improved growth and cell proliferation, enhanced wettability, and improved osseointegration (Mangano et al., 2017, 2018; Scarano et al., 2018; Sinjari et al., 2018). Baier and Meyer (1988) reported that surface energy plays an essential role in protein adsorption, cell attachment, and spreading. Likewise, Meyle (1999) stated that the surface charge affects both the cellular or molecular direction and cellular metabolic activity. Several reports have shown how the microstructure increases

removal torque and increases angiogenesis (Scarano et al., 2014). Moreover, surface nanoroughness is regarded as having an influence on the biological reaction to the implant (Mendonça et al., 2008; Ehrenfest et al., 2010; Durmus and Webster, 2012; Rani et al., 2012; Webster and Yao, 2016). Surface treatment techniques, with some current commercial examples, are shown in **Table 1**.

Modification of Implant Surface Roughness at the Macroscale Level

During the early stage of osseointegration as well as in long-term bone remodeling, the topography of the surface of implants is essential for hold and for differentiation of osteoblasts (Bruschi et al., 2015; Smeets et al., 2016). The first-generation implant surface design was a machined implant surface with a turned surface implant (Barfeie et al., 2015; Smeets et al., 2016). These earliest attempts introduced surface macro-irregularities such as grooves, pores, steps, threads, or other macroscopic irregularities. Coelho et al. (2015) stated that a suitable microgeometry, together with appropriate drill-hole preparation for implant, is the essential source of a successful clinical outcome for implantation. However, these authors found that the stability of the implant drops in the first weeks of bone healing as a result of density necrosis of adjacent bone and subsequent remodeling of bone. The high demand for initial stability and optimal interfacial bone remodeling led to a continuous search for further improvements in surface quality.

Modification of Implant Surface Roughness at the Microscale Level

In the beginning, dental implants had mainly machined surfaces (Buser et al., 2012), meaning that they were manufactured through milling, turning, or polishing (Esposito et al., 2014). Faults along these surfaces enable osteogenic cells to attach and to deposit bone, thereby creating a bone-to-implant contact (BIC). The time for healing of those implants is about 3–6 months, dependent on the quality of the bone as well as the anatomical location (Abraham, 2014). Therefore, 1–100 μm microscopic surface irregularities have been added to the Ti implant, introduced via various industrial methods including machining, sandblasting, grit-blasting, anodization, acid-etching, and different coating techniques (Dohan Ehrenfest et al., 2010). Microscopic imperfections in the surface appear to deliver an ideal degree of roughness to encourage osseointegration. Grooves, pits, and protrusions characterize the microtopography and set the stage for biological reactions at the interface between the bone and the implant surface (Albrektsson and Wennerberg, 2004). Many studies have revealed that increased micro-scale roughness of the surface clearly influences bone response to the implant due to the larger exposed surface area, which improves biomechanical joining between bone and implant compared to smooth a surface (Li et al., 2002; Ronold et al., 2003; Shalabi et al., 2006; Coelho et al., 2009; Wennerberg and Albrektsson, 2009, 2010; Ehrenfest et al., 2010). According to Shibata and Tanimoto (2015), alterations in the topography of the surface change the metabolism, growth, and migration in addition to the cytokine and growth factor creation of osteogenic cells. Modification

TABLE 1 | Surface treatment techniques with some current commercial examples.

Treatment level	Surface treatment technology	Example	Manufacturer
Microscale level	Sandblasting	Kontakt	Biotech Dental
	Chemical etching	Kontakt S	Biotech Dental
	Grit-blasting and acid etching	SLA surface (e.g., Roxolid implant)	Strumann Holding AG, Basel, Switzerland
		Camlog Promote surface	Camlog, Basel, Switzerland
		Semados (S, SC/SCX, RS/R SX, and RI lines)	BEGO
	Grit-blasting, acid-Etching, and neutralization	Integra-Ti FRIADENT plus surface (ANKYLOS, XIVE, and FRIALIT implant systems)	BICON DENTSPLY Implants, Mannheim, Germany
Nanoscale level	Sandblasting, etching and +CP coatings with ++DCD	Osseotite surface (NanoTite™/3i T3 implants)	BIOMET 3i, Palm Beach Gardens, FL, United States
	Laser ablation	Laser-Lok implant	BioHorizons, Birmingham, AL, United States
	Anodization	TiUnite	Nobel Biocare Holding AG, Zurich, Switzerland
	TiO ₂ blasting and acid-etching with fluoride-modified nanostructure coating	OsseoSpeed™	DENTSPLY Implants, Mannheim, Germany
Coating	Titanium plasma spraying	Kohno HRPS	Sweden & Martina, Due Carrare, Italy
	Blasting and etching with a final immersion in a NaCl physiological solution (hydrophilic implants)	SLActive	Strumann Holding AG, Basel, Switzerland
	Sandblasting, etching and +CP coatings with ±IBAD	Integra-CP	BICON

procedures for implant surfaces at the microscale level are recognized and have been clinical routine for many years.

Some implant producers have concentrated on the Ti implant surface, forming a film about 100 nm with increased micro-porosity (30–50 μm deep) through Ti plasma spraying. The resulting coating has a roughness about 7 μm, which increases the surface area of the dental implant. Some authors found that this micro-porosity through Ti plasma spraying improved the tensile strength at the bone–implant interface (Buser et al., 1991; Palmer et al., 2002). However, Urban et al. (2000) reported particles of Ti in the bone neighboring implants. The same authors also reported finding wear particles from implants in small aggregates of macrophages in the spleen and liver and in the lymph nodes (Urban et al., 2000). Metal ions could possibly be released from implants through dissolution, wear, and fretting and could be a source of concern because of their carcinogenic effects either locally or systemically (Browne and Gregson, 2000; Martini et al., 2003). Currently, there is evidence of clinical benefits of implanting reasonably rough-surfaced implants compared to utilizing rough plasma-sprayed implant surfaces (Xie et al., 2012).

An alternative method for abrading the surface of a Ti implant consists of blasting (also called sandblasting or grit-blasting) the implants with ceramic particles. Titanium oxide (TiO₂), alumina, and calcium phosphate (CP) particles are applied for this purpose (Kim et al., 2012; Shrestha, 2014). In grit blasting, high-velocity particles of various diameters (150–350 μm) are shot at the implant surface to achieve different degrees of roughness. The abrasive atoms are impacted against the material at high pressure. The resulting highly roughened implants have been shown to benefit mechanical

anchorage and primary joining to bone. Clinical studies reported higher survival rates due to higher levels of marginal bone for blasted implants than for machined implants (Gotfredsen and Karlsson, 2001). However, the effect of the remnant blasting particles on the implant surface after cleaning remains controversial, because alumina is insoluble in acid and is therefore difficult to eliminate from the Ti surface. A number of authors have shown accelerated bone formation, while others have reported hampered osseointegration, which may be explained by competition with calcium ions (Cochran et al., 1996). This is due to these particles sometimes being freed into the adjacent tissues and restricting the osseointegration process. Furthermore, this chemical heterogeneity of the implant surface may reduce the exceptional corrosion resistance of Ti in physiological environments (Aparicio et al., 2003; van Drunen et al., 2011). Therefore, for materials blasting, the particles should be biocompatible and chemically stable and not obstruct the osseointegration process of the Ti implants.

Some authors used TiO₂ for blasting Ti implants. Ivanoff et al. (2001) blasted micro-implants with TiO₂ on and found significant improvement in BIC compared to machined surface implants (Ivanoff et al., 2001). Additional reports established that Ti-blasting of surfaces enhanced BIC (Gotfredsen et al., 1995; Rasmusson et al., 2001). Likewise, some clinical studies achieved high success rates up to 10 years after implantation for Ti-blasted implants (Gotfredsen and Karlsson, 2001; Rasmusson et al., 2005). Other relative clinical studies also noted higher levels of marginal bone and higher survival rates for implants blasted with TiO₂ than for turned implants (Astrand et al., 1999; van Steenberghe et al., 2000). Abron et al. (2001) observed that increasing the surface roughness of the implants led to

a rise in torque force while maintaining equivalent values in bone apposition.

Calcium phosphates are used as other possible blasting materials for roughening Ti implants due to their osteoconductive, biocompatible, and resorbable properties. Calcium phosphates can be resorbed, resulting in a clean, textured, pure Ti implant surface. Some authors have established that this achieves a higher BIC than with machined surfaces (Novaes et al., 2002; Piattelli et al., 2002) and that the BIC was comparable to that noticed with other methods such as blasting surfaces when osseointegration is accomplished (Mueller et al., 2003).

Another manner of roughening Ti implants is etching the implant surfaces with strong acids, for instance, HCl, HNO₃, H₂SO₄, and HF. Acid etching creates micro-pits on Ti surfaces with sizes ranging from 0.5 to 2 μm in diameter (Massaro et al., 2002; Zinger et al., 2004). This method considerably accelerated osseointegration by enhancing the attachment of fibrin and osteoblasts (Wong et al., 1995). Cervino et al. (2019) found that the time necessary to obtain osseointegration and secondary stability on the part of implants is shortened through this surface treatment before implantation. Therefore, the treated surfaces guarantee enhanced cellular adhesion.

A form of macroroughness termed the Sandblasted, Large grit, Acid-etched (SLA) surface is fabricated by Straumann Holding AG, Basel, Switzerland (Figure 1). Such a surface is produced by large grit sandblasting with 0.25–0.5 mm corundum particles at 5 bar (Wennerberg et al., 2011). A chemically altered surface based on the sandblasted and acid-etched Straumann Institute surface has been revealed to exhibit increased surface free energy and hydrophilicity, mainly due to reduced hydrocarbon contamination (Rupp et al., 2006). Acid etching of the implant surface can be used after sandblasting to produce a clean and rough surface with subsequent better osseointegration (Orsini et al., 2000; Jemat et al., 2015). The microtopographic surface structure is attributable to a subsequent process of acid etching with HCl/H₂SO₄ at high temperatures (Fischer and Stenberg, 2012), creating a rough surface with an active surface area and improved cell adhesion (Abraham, 2014). A comparable

approach is used to produce a surface topography with 1.3 μm microroughness (Dohan Ehrenfest et al., 2011), such as the Camlog Promote surface (Camlog, Basel, Switzerland). Buser et al. (1991) found that surface modification of an implant with SLA had superior BIC than numerous other surface alterations such as electropolishing or titanium plasma-sprayed implants. Li et al. (2002) revealed that the values of removal torque were considerably enhanced in SLA implants compared to machined and acid-etched implants. Fischer and Stenberg (2012) evaluated the clinical outcomes of 139 SLA implants in 24 edentulous patients over a 10-year period. They noticed that the survival rate of an implant was 95.1% and that there was a 1.07 mm mean of bone loss. In 303 partially edentulous patients over a 10-year period, Buser et al. (2012) assessed the clinical outcomes of 511 SLA implants. They showed that the implant has a 98.8% survival rate. In 120 patients, Cochran et al. (2011) installed 385 SLA implants. They reported a success rate of 98.8% after 5-year follow-up. In a retrospective study performed by Lixin et al. (2010), 353 implants with the Camlog Promote surface were positioned in 40 edentulous patients, and the survival rate was 99.2% after 4-year follow-up.

The FRIADENT plus surface (DENTSPLY Implants, Mannheim, Germany) is an example of a grit-blasted, acid-etched, and neutralized implant surface that has been adjusted for use in DENTSPLY's ANKYLOS, XiVE, and FRIALIT implant systems (Figure 2). It is manufactured by large grit blasting (354–500 μm), followed by etching in HCl, H₂SO₄, HF, and H₂C₂O₄, and, finally, an exclusive neutralizing technique (Rupp et al., 2004). Junker et al. (2009) found that the macroroughness is interspersed with uneven micropores 2–5 μm in size.

Streckbein et al. (2014), in their beagle dog model, assessed the formation of bone adjacent to four implant types and found that the BIC was not significantly influenced. In a minipig model, Mendonça et al. (2008) displayed that FRIADENT plus-surfaced implants had successful osseointegration under the advanced clinical condition of immediate loading. After 4 months of healing, Neugebauer et al. (2006) found that immediately loaded implants demonstrated an even higher degree of bone formation and remodeling than unloaded implants. Novaes et al. (2004)

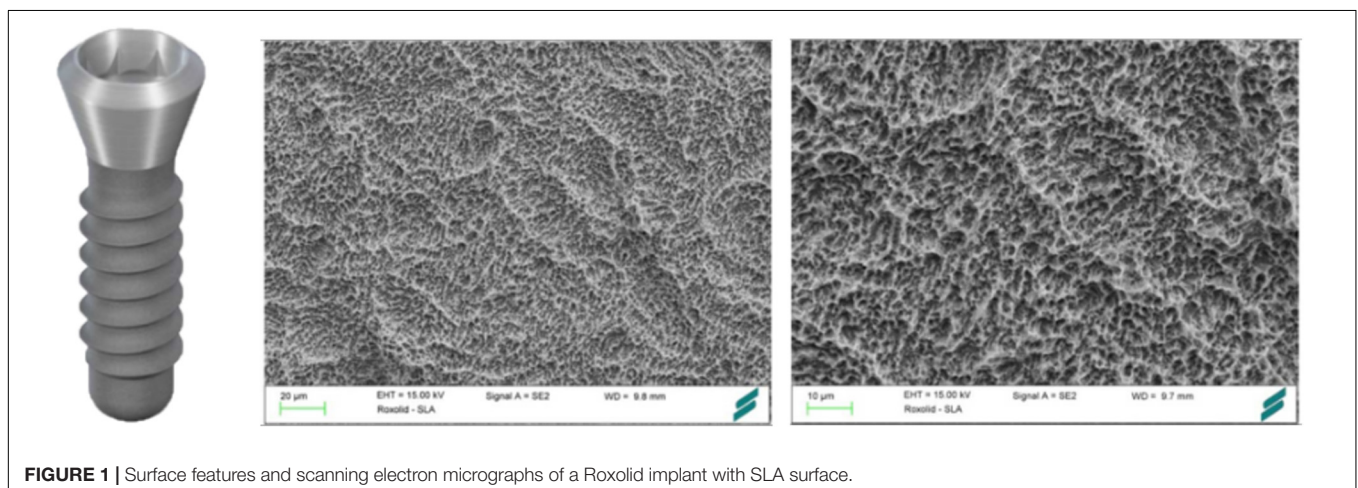


FIGURE 1 | Surface features and scanning electron micrographs of a Roxolid implant with SLA surface.

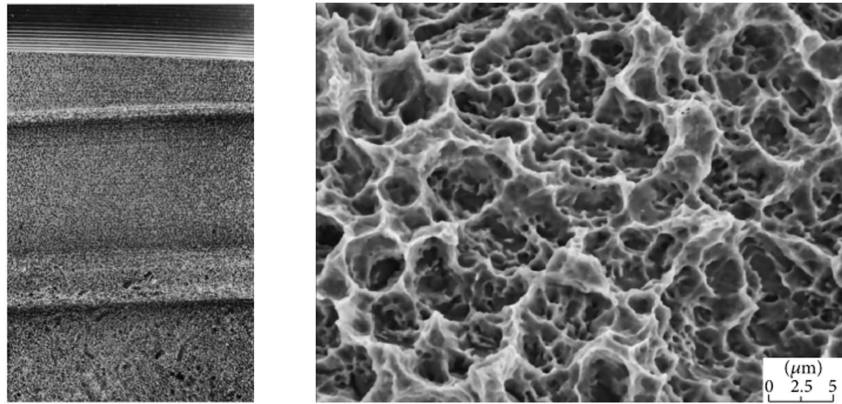


FIGURE 2 | Surface features and scanning electron micrographs of a FRIADENT plus surface.

revealed that FRIADENT plus-surfaced implants used in a dog model of periodontitis achieved an acceptable BIC. Degidi et al. (2006), in their clinical study, compared the FRIADENT plus implant with three different DENTSPLY implant types. Based on parameters of primary implant stability, 802 implants were assigned to an immediate or delayed loading protocol. They found that the overall success rate for the FRIADENT plus implant was 99.6% after 1 year of placement.

Some authors treated Ti implants with fluoride solutions as another possibility for enhancing bone integration because Ti is very sensitive to fluoride ions, creating soluble TiF_4 species. Modification of the surfaces of a Ti implant with fluoride produced a combination of surface roughness and fluoride that encouraged the osseointegration process of the implant (Ellingsen, 1995; Ellingsen et al., 2004). Other studies elsewhere also found improved biomechanical anchorage and enhanced bone integration (Ellingsen et al., 2004; De Bruyn et al., 2013; Han et al., 2016). Additionally, the immersion of the implant in a fluoride solution can lead to osteoblastic differentiation (Cooper et al., 2006). Conversely, Affairs (ADA Council on Scientific Affairs, 2003) reported that fluoride adversely affected the protective oxide layer on the surface of a Ti implant.

To improve the mechanical properties of an implant, ion implantation methods are used. Sioshansi (1987) implanted nitrogen into Ti and noticed a considerable reduction in wear. Buchanan et al. (1990) implanted iridium into a Ti-6Al-4V alloy to increase its corrosion resistance. Jabbari et al. (2012) found that implanted dental materials coated with titanium nitride and/or nitrogen ions potentially offer superior advantages to uncoated counterparts.

Modification of Implant Surface Roughness at the Nanoscale Level

Recent efforts in dental implantation have emphasized the significance of nanotechnology in modifying the surface morphology to achieve better similarity to the surface roughness characteristics of the natural bone and to favor positive integration with cells (Özcan et al., 2012; Rani et al., 2012; Huang et al., 2013; Dalby et al., 2014; Li et al., 2015; Shen et al., 2015;

Zhao et al., 2015). The alteration of implant surface roughness at the nanoscale level is believed to affect cell-implant integrations at the protein and cellular levels (Mendonça et al., 2008).

Previous studies found that materials based on TiO_2 are particularly significant for surface alteration due to their thermal stability, high corrosion resistance, and good osseointegration properties (Lee H. et al., 2010; Lee K. et al., 2014; Brammer et al., 2012; Kiran et al., 2012; Tan et al., 2012; Wang et al., 2012; Jemat et al., 2015; Das et al., 2018), as shown in **Figure 3**. TiO_2 materials of different nanoarchitectures, including nanofibers (TNFs), nanotubes (TNs), and nanowires (TNWs), have been intensively investigated for implant fabrication (Lee H. et al., 2010; Lee K. et al., 2014; Brammer et al., 2012; Kiran et al., 2012; Tan et al., 2012; Wang et al., 2012; Jemat et al., 2015; Das et al., 2018). TiO_2 TNT layers are specifically studied because of their facile synthesis, the ability to control their length, diameter, and microstructure, and their improved cellular responses. The improvement in encouraging cellular behavior has been confirmed with the utilization of various types of cells, for instance, chondrocytes, osteoblasts, fibroblasts, mesenchymal stem cells, and endothelial cells (Park et al., 2007; Das et al., 2009; Peng et al., 2009; Brammer et al., 2010; Smith et al., 2011; Azadmanjiri et al., 2016). The TiO_2 TNW and TNF coatings can be shaped on the implant surfaces due to their large surface to volume ratio, high porosity, and morphology, which is comparable to the usual extra-cellular matrix (Azad et al., 2010;

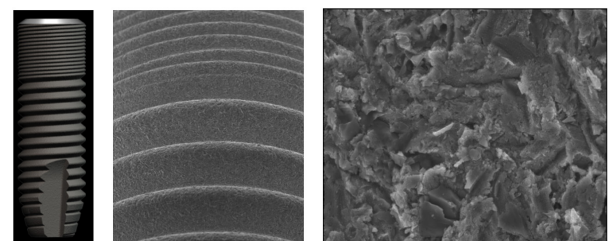


FIGURE 3 | Surface features and scanning electron micrographs of a OsseoSpeed dental implant surface.

Tavangar et al., 2011; Pramanik et al., 2012). TNWs and TNFs can be produced by using an electrospinning method, hydrothermal treatment, anodization, laser ablation, and gas-phase reactions (Tan et al., 2013).

Many studies stated that the alteration of surface roughness of a dental implant at the nanoscale level stimulates cell adhesion and protein adsorption (Anselme et al., 2002; Bigerelle et al., 2002; Zhu et al., 2004; Zhang et al., 2013a,b) and thereby potentially promotes osseointegration (Puckett et al., 2008; Park et al., 2009; McNamara et al., 2010). This modification alters the implant's surface interaction with proteins, ions (i.e., configuration, adsorption, bioactivity, etc.), and cells. Further advancements in the surface design of dental implants are critical to improve the outcomes of sophisticated clinical situations such as implantation immediately after tooth extraction and initial loading protocols and in patients with compromised bone or impaired wound healing abilities (Gomez-de Diego et al., 2014).

Nanosurface modification of dental implants induces chemical and biological interaction between the surface of a dental implant and cells, biomolecules, and ions. These cellular and tissue interactions enhance the mechanical stability and biological functionality of nanosurface implants compared to conventional implants (Ji and Gao, 2004; Wei and Ma, 2008). Compared with traditional implants, nanotechnological modification of dental implants reduces the time needed before loading. This advantage is due to the structural similarity between the implant surface and the surface topography of the ECM within natural tissue, which is typically between 10 and 100 nm in size (Tomisa et al., 2011). Moreover, the nanostructure implants enhance early osseointegration, tissue engineering, and mechanical stability compared with conventional implants (Gutwein and Webster, 2004). This structure-mimicking has been demonstrated to induce cell interactions, such as adhesion, proliferation, and differentiation, that are essential to improve osseointegration. Moreover, a nanostructure implant may play a role in preventing bacterial infection associated with implants. The size and shape of nanoparticles prevent bacterial adhesion due to its antimicrobial activity (Pal et al., 2007). Studies have shown a

marked decrease in bacterial adhesion and biofilm formation on nanostructured TiO₂ compared with conventional TiO₂ implants, regardless of the fact that these nanosurface implants encourage osteoblast adhesion and differentiation. Implants with nanophase TiO₂ surfaces have antimicrobial activity against oral infections (*S. aureus* and *P. aeruginosa*). On the other hand, it increased osteoblast adhesion and proliferation (Bhardwaj and Webster, 2017). Tsimbouri et al. (2016) used hydrothermal oxidation to produce TiO₂ nanowires and reported a decrease in *P. aeruginosa* growth in the early stage of bacterial adhesion compared to Ti with a polished surface. Truong et al. (2010) found that prokaryotic and eukaryotic cell attachment on Ti surfaces can be organized by altering the topography of the surface into micro- or nano-structures. Furthermore, the addition of silver nanoparticles into TiO₂ nanotubes contributes long-term antimicrobial activity to implants. The antibacterial activity of silver is via the induction of reactive oxygen species (Shokuhfar et al., 2014).

Some implant producers have increased surface roughness through Discrete Crystalline Deposition (DCD). The NanoTite implant is fabricated by BIOMET 3i, Palm Beach Gardens, FL, United States (Figure 4). Calcium phosphate (CaP) particles 20–100 nm in size are placed on a double acid-etched surface by DCD. This technique makes the surface area about 50% rougher due to the deposition of CaP particles (Bonfante et al., 2013) and achieves a greater adhesive force to the surface of the implant than previous CaP deposition methods (Kitsugi et al., 1996; Franchi et al., 2004). Rodriguez y Baena et al. (2012) Evaluated bacterial adhesion on machined titanium, OsseoTite, and NanoTite discs and found that bacterial adhesion to the NanoTite surface was lower than to the predecessor Osseotite surface.

Mendes et al. (2007) found in the distal femur of rats that the disruption force at the bone–implant interface was significantly higher in bone-bonding to Ti surfaces fabricated by DCD of CaP nanocrystals compared to non-DCD samples. Mendes et al. (2009) also found improved osteoconduction of DCD-treated implants than the predecessor control. In a rabbit model, Calvo-Guirado et al. (2015) showed only a tendency of improved

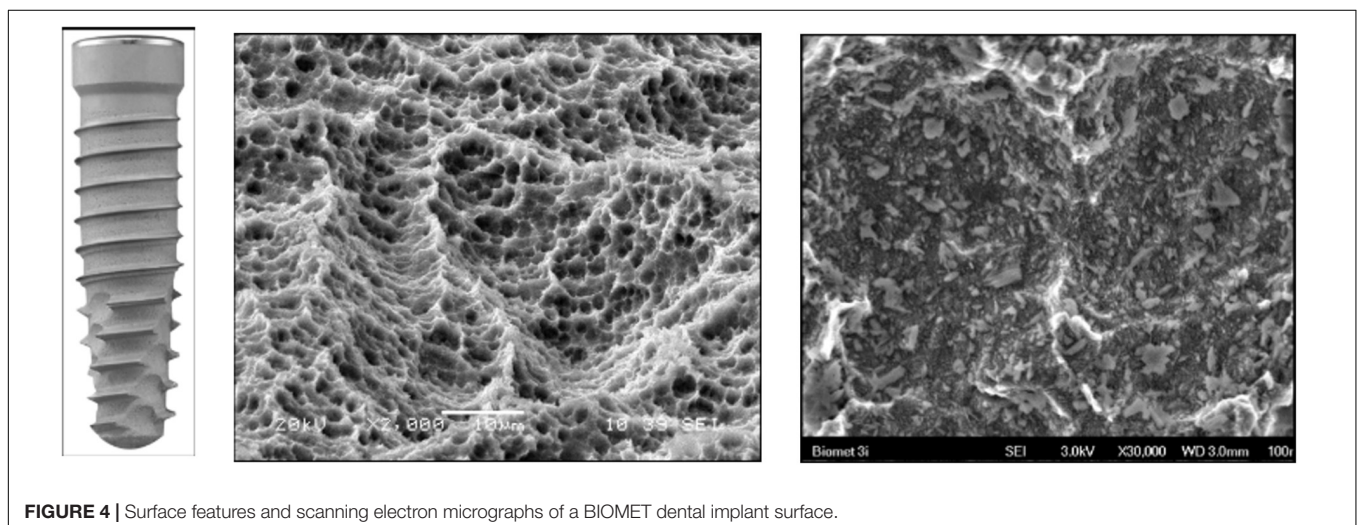


FIGURE 4 | Surface features and scanning electron micrographs of a BIOMET dental implant surface.

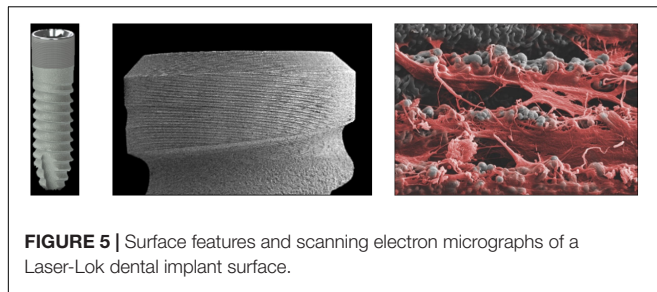


FIGURE 5 | Surface features and scanning electron micrographs of a Laser-Lok dental implant surface.

BIC for DCD implants. In a prospective 1-year clinical trial, Östman et al. (2013) placed 139 NanoTite tapered implants in 42 patients and found the survival rate to be 99.4%, with an average marginal bone resorption of 1.01 mm. The same authors (Östman et al., 2010) found a survival rate of 94.9% for 335 NanoTite implants placed in 185 patients after 1-year follow-up.

To improve the roughness of Ti implant surfaces, another approach is to apply various laser-based techniques (Bauerle, 2000). Lasers are used for the ablation of surfaces because of the perfect control of the light frequency achievable, the capability to focus and rasterize the light, the high energy density, the wide range of frequencies available, and the capability to pulse the source and control the reaction time. Lasers frequently applied for surface alteration are ruby, Nd:YAG, CO₂ argon, and excimer (Gaggl et al., 2000; György et al., 2002).

The Laser-Lok implant (BioHorizons, Birmingham, AL, United States) is an example of a laser ablation surface (Figure 5). This implant has been treated in a laser micromachining step to produce a pattern of micro- and nanoscale microchannels. Nevins et al. (2010) revealed that the creation of connective tissue adjacent to Laser-Lok abutments is structured in a perpendicular way. In 15 patients, Pecora et al. (2009) placed 20 Laser-Lok implants and found growth in connective tissue around the implants. Other authors also found that microtextured implant collars have a favorable effect on soft tissue attachment and crestal bone maintenance (Botos et al., 2011; Guarnieri et al., 2014).

After 2-year follow-up, Farronato et al. (2014) reported a rate of survival of 96.1% for Laser-Lok dental implants.

Other implant producers increase surface roughness through a chemical process called anodization. This involves the dielectric breakdown of a TiO₂ layer by applying an increased voltage to produce a micro-arc and creates a porous layer on the surface of the Ti implant with significantly increased oxidation (Li et al., 2004). This modification has been shown to increase BIC (Sul et al., 2002; Wennerberg et al., 2015; Smeets et al., 2016), biocompatibility, cell adhesion, and bone formation (Gupta et al., 2010). The following procedures should be followed: “decontaminating the implant surface from the organic and inorganic impurities that could affect the formation of the oxide layer,” (Mandracci et al., 2016) “avoiding ion release to the surrounding hard and soft tissues, increasing the corrosion resistance, improving the wear resistance, and increasing the biocompatibility and bone formation with the possibility of adding Mg, which is vital for the absorption of calcium minerals in bone cells” (Shayganpour et al., 2015).

The TiUnite implant (Nobel Biocare Holding AG, Zurich, Switzerland) is an example of anodization (Figure 6). The surface of this implant is electrochemically altered by anodic oxidation to increase the thickness of the TiO₂ layer to 600–1000 nm rather than the 17–200 nm in traditional titanium implants (Sul et al., 2002). The terms Ti porous oxide (Rocci et al., 2013) or anodized Ti surface implant (Zechner et al., 2003) have also been used to refer to this type of implant surface. TiUnite implants have been shown to possess nanoscale surface characteristics (Sul et al., 2008). Ti surfaces generated at the nanoscale level by anodic oxidation have been found to augment the proliferation, adhesion, and extracellular matrix deposition of human gingival fibroblasts (Guida et al., 2013).

Sul et al. (2002) have shown in a rabbit model that the BIC with anodized implant surfaces is somewhat superior to that with pure Ti implants that are available commercially. These findings were confirmed by Zechner et al. (2003). The BIC of TiUnite implants was significantly greater than that of machined implants 6 and 12 weeks after implant placement (Rocci et al.,

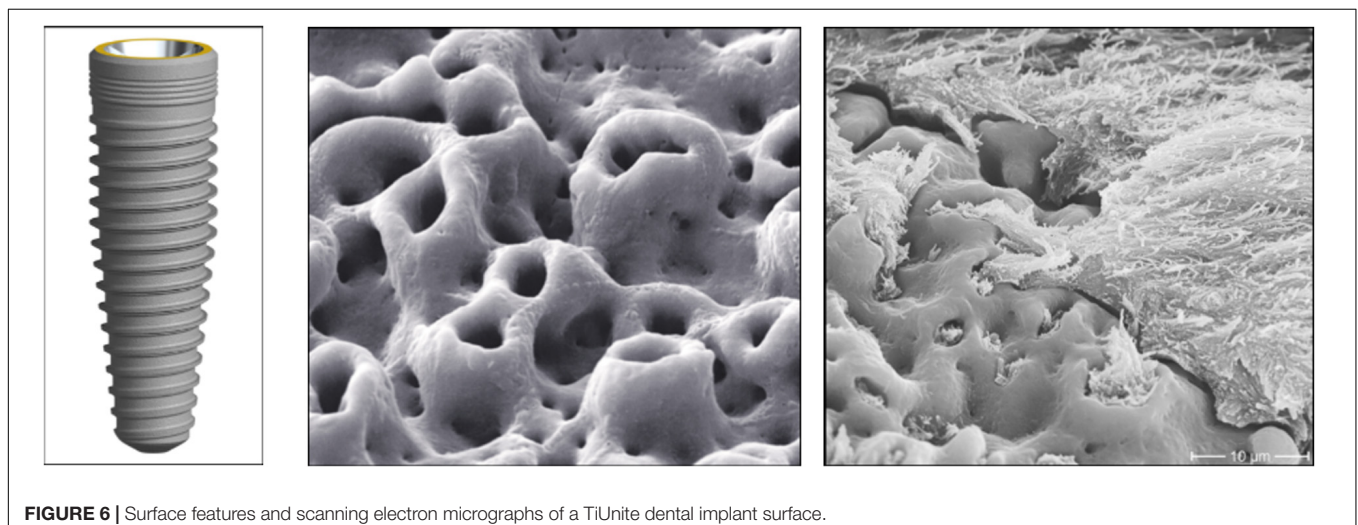


FIGURE 6 | Surface features and scanning electron micrographs of a TiUnite dental implant surface.

2013). Ivanoff et al. (2003) showed an increased BIC with TiUnite microimplants compared to machined titanium microimplants. They found a considerably greater BIC around anodized implants in the maxilla and the mandible. Jungner et al. (2005) found that the survival rate for TiUnite implants was 100% after 5-month follow-up. In spite of the increased roughness of the anodized surface, the surface with porous oxide does not assist improved biofilm formation (Quirynen and Van Assche, 2012).

Recently, Ozdemir et al. (2016) introduced Chemical Mechanical Polishing (CMP) as another method for bio-implant surface structuring. Schmutz et al. (2008) found in their study that CMP could encourage the synergistic influence of surface nanostructuring while changing the chemistry of the surface to reduce the corrosion of the surface and ion dissolution through the promotion of the creation of a self-protective surface oxide film.

Calcium Phosphate-Coated Implants

The combination of HA coating with Ti alloy implants has received attention because of its attractive characteristics, such as increased biocompatibility and good mechanical properties (Simmons et al., 1999; Poinern et al., 2009). Histological studies performed by some researchers in dogs showed that implants coated with HA provided more rapid bone formation after 1 and 4 months compared to uncoated implants (Block et al., 1987, 1989). After 6 months, in the healed sites of the molar region of rhesus monkeys, Lum et al. (1991) also observed that HA-coated implants were associated with direct contact with the bone.

Various procedures have been established to coat Ti implants, for instance, sol-gel coating, plasma spraying, electrophoretic deposition, sputter deposition, or biomimetic precipitation. Among these methods, only plasma-spraying has been used for Ti implants in clinical practice. This allows a thickness from a few micrometers to a few millimeters to be deposited on the implant surface (Knabe et al., 2002; Le Guehennec et al., 2007). Even though Ti implants coated with HA layers by plasma spraying have provided favorable results (De Groot et al., 1987; Freeman, 1992), this method has some shortcomings, such as coating delamination. In addition, the remarkably high temperatures (above 10,000°C) involved in creating the HA coatings make combination with biologically active molecules difficult. Furthermore, HA-coated implants are more prone to colonization by the bacteria compared to uncoated Ti implants owing to their surface roughness and hydrophilicity (Johnson, 1992). The inconsistency in dissolution between the different phases that create the coating has led to particle release and delamination, and therefore the implants may fail clinically (Wheeler, 1996; Tinsley et al., 2001). Moreover, a number of investigators have claimed that HA coatings are more prone to bacterial infection, are unstable, and might be prone to rapid bone failure (Jovanovic et al., 1993; Wolinsky et al., 1989).

Nevertheless, many clinical studies reported that implants coated with HA promote faster bone attachment, have a higher integration rate, and achieve more direct bone bonding than uncoated implants (Golec and Krauser, 1992; Duraccio et al., 2015). However, there are many controversies about the long-term prognosis of coated implants (Aoki, 1991; Buser et al., 1991; Matsui et al., 1994; Wheeler, 1996; Tsui et al., 1998a).

Wheeler (1996) showed that the survival rate was initially more for HA-coated implants but reduced considerably after 4 years. In addition, Matsui et al. (1994) reported signs of the covering material of HA-coated implants separating from the implant surface, which might encourage foreign body reactions (Buser et al., 1991; Matsui et al., 1994). Tsui et al. (1998a,b) reported finding some amorphous and metastable phases in the HA coating produced through the plasma-spraying procedure and inferred that may account for the poor mechanical strength and low crystallinity of HA coatings (Aoki, 1991). Despite the negative reputation of plasma-sprayed HA-coated implants in dental practice, Lee et al. (2000), in their meta-analytic review, revealed that their long-term survival rates were not lower than those of other types of implant.

Surface Wettability

Among the various surface alterations of Ti implants (Junker et al., 2009), many have been established to increase surface wettability or hydrophilicity. "Wettability is measured by contact angle measurement, usually of water, at the solid/liquid interface while surrounded by a gas phase or another liquid phase and provides gross surface characterization" (Gittens et al., 2014). Many studies have confirmed the role of wettability or hydrophilicity at the protein and cellular levels (Sawase et al., 2008; Aita et al., 2009; Olivares-Navarrete et al., 2012; Hirakawa et al., 2013; Gittens et al., 2014). These studies showed that hydrophilic surfaces could improve the early stages of cell adhesion, differentiation, and proliferation as well as bone mineralization (Eriksson et al., 2004; Bornstein et al., 2008). After 1 week and up to 2 weeks, Schwarz et al. (2007a) confirmed that hydrophilic surfaces produce superior performance compared to hydrophobic surfaces, with higher BIC. Tugulu et al. (2010) treated the implant surface with diluted alkaline solution and found that the hydrophilic surface reduced the adhesion of the fibrinogen and thereby reduced the inflammation around the implant. Olivares-Navarrete et al. (2012) studied the effects of surface characteristics such as surface roughness and wettability and found significantly higher BIC for surfaces with these characteristics compared to machined surfaces.

Straumann Holdings AG, Basel, Switzerland introduced the SLActive dental implant (**Figure 7**). Its surface is modified to a higher level of hydrophilicity from the standard large grit-blasted and acid-etched SLA implant (Wennerberg et al., 2011). Wennerberg et al. (2011) claimed that the hydrophilic SLActive surface stimulates the maturation of osteogenic cells and cell adhesion, encourages a bone-forming microenvironment, and fosters neoangiogenesis. In a dog model, Schwarz et al. (2007b) found that SLActive implants achieved higher affinity of the initial blood clot to the implant surface, improved neoangiogenesis, increased BIC, and better bone density compared to SLA implants within the first 2 weeks of bone healing. At 2 and 4 weeks after implant placement, Buser et al. (2004) showed that SLActive implants had a higher BIC compared to SLA implants. After 12 weeks of implant placement, Calvo-Guirado et al. (2010) found a better BIC and less crestal bone resorption for hydrophilic implants.

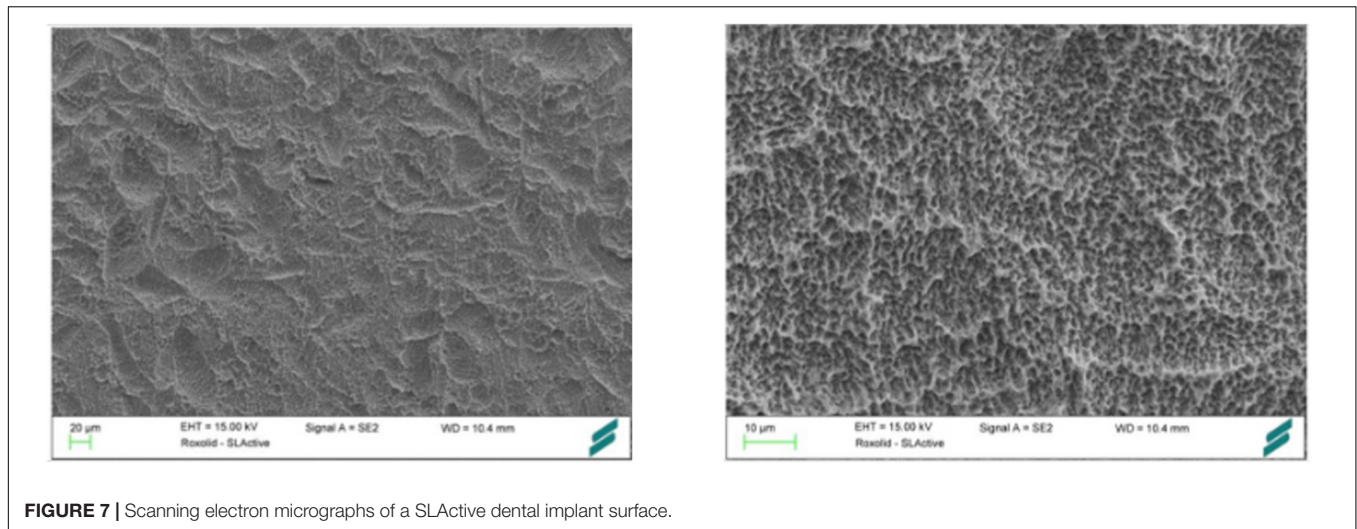


FIGURE 7 | Scanning electron micrographs of a SLActive dental implant surface.

BIOMIMETIC PROCESS

The common feature of the implants on the market is rough surfaces created through physical or chemical modification. The enhanced performance of these implants can mainly be assigned to increased stimulation of bone anchorage, since rough surface topographies have an influence on osteogenic cells and platelet activation (Park et al., 2001; Boyan et al., 2003). However, in situations where exactly these mechanisms are impaired, e.g., at implantation sites with low bone density, low vascularization, or insufficient bone quantity, there is still a potential to improve cell adhesion to the implant surfaces (Morra, 2007). Achieving appropriate cell adhesion to the surface is particularly important in order to cause the surface to be occupied by living cells, therefore making it less susceptible to bacterial colonization (Gristina, 1987).

The investigation of the remarkable properties of natural and novel artificial hard tissues has the potential to give insight into biomimetic material design and the development of novel functional materials (Nazarpour, 2013). Therefore, recent trends in the development of modern implants are to fabricate dental implants with biological and biomechanical behaviors that mimic those of natural tooth under function (Huang et al., 2007; Nazarpour, 2013).

Biomimetic Calcium Phosphate-Coated Implants

The success of implants depends critically on the surface alteration, which is correlated to osteoconductivity and osteoinductivity. Osteoconduction is defined as “the ability to grow bone on the surface of an implanted material or scaffold. This process is particularly important to the fields of dentistry and bone biology as it is necessary for implant replacement” (Wilson-Hench, 1987). Osteoinduction means “that primitive, undifferentiated, and pluripotent cells are somehow stimulated to develop into the bone-forming cell lineage. One proposed definition is the process by which osteogenesis is induced”

(Williams, 1987). Huge developments have been accomplished in the osteoconductivity of implants by coating their surfaces with a layer of CP (Wong et al., 1995). However, the approaches used to deposit a CP layer on the implant surfaces, for instance, plasma spraying, hot isostatic pressing, sol-gel deposition, ion-assisted deposition, high-velocity oxy-fuel spraying, electrochemical deposition, sputter coating, electrophoretic deposition, and pulsed laser deposition (Wolke et al., 1994, 1998a,b), are markedly non-physiological owing to the high temperatures involved. These high temperatures prevent the integration of a biological agent, for example, an osteogenic growth factor. Therefore, in most circumstances, biological agents can only be absorbed directly onto the implant surfaces (Kawai et al., 1993; Ripamonti et al., 1993; Hollinger et al., 1998; Noshi et al., 2001).

In recent times many methods have been trialed for the deposition CP layers on the surfaces of Ti implants under more physiological or “biomimetic” temperature and pH conditions (Barrere et al., 1999; Wen et al., 1999). Furthermore, the structure of the crystals made (carbonated apatite) is more akin to that of bone mineral than are those of HA and tri- or tetra-CP (Nagano et al., 1996), which are produced at exceedingly high temperatures.

In order to overcome the disadvantages of other coating methods, researchers established new coating methods based on a biomineralization process, using simulated body fluids (SBF) to precipitate calcium phosphate crystals onto the Ti surface to form a thin coating at room temperature (Le Guehennec et al., 2007).

Generally, biomimetic deposition is “a solution-based method conducted in an environment that mimics the human body condition. In most cases, such [a] body-like environment is provided by an SBF at 37°C. The temperature, pH, and other parameters of the conditions for biomimetic deposition are carefully controlled to simulate the body environment” (Sharifi et al., 2016). Biomimetic synthesis of calcium phosphate on Ti implants with the aim of increasing biocompatibility and promoting osseointegration (Bigi et al., 2005; Zhang et al., 2005; Forsgren et al., 2007). Many biomimetic methods have been applied and reported for the precipitation of CP apatite

crystals onto the Ti surface from SBF to form a coating at room temperature (Leeuwenburgh et al., 2001; Ágata de Sena et al., 2002; Habibovic et al., 2002; Wang et al., 2003, 2004; Barrere et al., 2004; Yang et al., 2004; Bose and Tarafder, 2012; Shadanbaz and Dias, 2012). In preclinical models, the osseointegration of Ti implants coated with biomimetic CP has been examined (Barrere et al., 2003; Habibovic et al., 2005).

Many studies found that the biomimetic coating procedure is cost-effective and easy to achieve and can be used even for heat-sensitive, non-conductive, and porous materials of large sizes and with complex surface geometries. This technique has the capability to integrate biologically active molecules, which can be co-precipitated with the inorganic components. However, the structure of the coating could be affected by the coating time, and the coating process takes days (Barrere et al., 2001; Liu et al., 2001; Waterman et al., 2011; Habraken et al., 2013).

Biomimetic Surface Modification

Several biologically functional molecules can be immobilized onto Ti surfaces to improve the regeneration of the bone at the implant device interface (Puleo and Nanci, 1999; Jenny et al., 2016). However, Meng et al. (2016) concluded that bioactive surface alterations on implant surfaces do not have a permanent favorable influence on osseointegration. On the other hand, some investigators reported that surface modifications of Ti implants with biologically functional molecules appear to stimulate peri-implant bone formation, causing improved osseointegration throughout the initial phases of healing. Therefore, clinical reports with long-term follow-up are desirable to confirm this result (Matarese et al., 2017; Ciccì et al., 2018).

Natural extracellular matrix (ECM) contains multiple types of biomolecules, for example, adhesive peptide, polysaccharide, and growth factors, which interact with cells to initiate a cascade of cell attachment, proliferation, spreading, and differentiation. Furthermore, ECM has nanoporous structures that permit attachment of cells and ingrowth and sufficient mass transport of nutrients and waste products during tissue neogenesis. Therefore, producing biomimetic ECM may be an effective technique for increasing the bioactivity of implant devices. A mixture of multiple biologically functional molecules and nanostructures is preferred for biomimetic ECM to generate the best microenvironment for cell affinity and for regulating cellular functions (Wang et al., 2016).

Many strategies for organic coating are used, such as the immobilization of ECM peptide or proteins (collagen, etc.) as modulators for bone cell adhesion, immobilization of DNA for structural reinforcement, deposition of cell signaling agents to activate new bone formation, and enzyme-modification of Ti surfaces for improved bone mineralization (de Jonge et al., 2008; Wennerberg et al., 2015). Sooner or later, bone implant surfaces will be enhanced with biologically functional molecules to promote the bone healing procedure (Coelho et al., 2009; Wennerberg and Albrektsson, 2009; Ehrenfest et al., 2010).

Modification of Implant Surfaces With ECM Proteins

ECM proteins are involved in diverse processes with respect to cell adhesion, multiplication, and differentiation

(Stevens and George, 2005; Morra, 2006; Frantz et al., 2010). In native tissues, ECM presents its adhesion proteins, for example laminin, fibronectin, collagen, and vitronectin, to effect cell attachment through the binding between integrin receptors on cell surfaces. Therefore much work is being done to enhance the biocompatibility of polymeric tissue-engineered scaffolds to create a biochemical-like environment on the biomaterial surface (Ma et al., 2005).

Type I collagen may be one of the major applicable biomaterials for realizing tissue-engineered grafts and is one of the proteins that play critical roles in the mineralization of bone (Scarano et al., 2017a), bone healing (Ao et al., 2016), osteoblastic adhesion and differentiation, enhancing blood compatibility, and extracellular-matrix secretion (Maghdouri-White et al., 2014). **Table 2** shows the influence of implant surfaces modified with ECM proteins.

Morra et al. (2006) examined the influence of collagen incorporation on anodized Ti surfaces in rabbit femur trabecular bone. They found that surface modification with collagen can enhance osseointegration. However, Alghamdi et al. (2013) concluded that implant surfaces alternating with collagen did not improve the formation of peri-implant bone in the mandibles of dogs. Schliephake et al. (2006) coated machined Ti implant with a composite of CP and collagen (I) and found enhancement in BIC and peri-implant bone formation. Lee S.W. et al. (2014) evaluated the effects of implant surfaces coated with HA and type I collagen on peri-implant bone formation and found considerably enhanced new bone formation and BIC. Stadlinger et al. (2007) examined the effect of ECM coatings on implant stability and osseointegration. They stated that bio-functional coating of the implant surface with bisphosphonate, CP, or collagen containing chondroitin sulfate appeared to have the ability to improve peri-implant bone healing. Stadlinger et al. (2008b) assessed the effect of immobilizing ECM components on implants in pigs. They implied that implant surfaces coated by collagen containing chondroitin sulfate might result in a higher degree of bone formation. In pigs, Stadlinger et al. (2008a) examined whether the addition of recombinant human bone morphogenetic protein (rhBMP-4) and chondroitin sulfate to a collagen-coated implant could further increase osseointegration. They proposed that the addition of chondroitin sulfate to a collagen-coated implant might encourage osseointegration. Stadlinger et al. (2009) tested a collagen and chondroitin sulfate-coated implant and found that it encouraged bone formation. Morra et al. (2010) tested the influence of collagen covalently linked to acid-etched implant surfaces and reported that peri-implant bone formation during early healing could be enhanced. Stadlinger et al. (2012) assessed whether ECM coating on implant surfaces increases bone formation in minipigs. They reported that the coating of ECM displayed no advantageous influence in the aspects of BV density and ISQ value. Bae et al. (2018) exhibited an improvement in bone healing and osseointegration with collagen type I cross-linked by gamma irradiation. Rotenberg et al. (2016) reported that type I collagen could offer superior resistance to pre-implantitis and can be used for treating the hard tissue loss related with peri-implantitis around SLA implants. Korn et al. (2014) showed that Ti implants coated with type I collagen

TABLE 2 | Dental implant surfaces alteration with extracellular matrix proteins.

References	Surface modification	Study model	Study length	Results
Morra et al. (2006)	Collagen incorporation on anodized Ti implant surfaces	Rabbits	4 weeks	Can enhance osseointegration
Alghamdi et al. (2013)	Implant surfaces alternating with collagen	Dogs	1 and 3 months	Did not improve the formation of peri-implant bone
Schliephake et al. (2006)	Coated machined Ti implant with a composite of CP and collagen	Dogs	1 and 3 months	Enhanced BIC and peri-implant bone formation
Lee S.W. et al. (2014)	Implant surfaces coated with HA and type I collagen	Rabbits	6 weeks	Enhanced new bone formation and BIC
Stadlinger et al. (2007)	ECM coatings on implant to improve stability and osseointegration	Pigs	22 weeks	Improved peri-implant bone healing
Stadlinger et al. (2008a)	Immobilizing ECM components on implants	Miniature pigs	6 weeks	Showed a higher degree of bone formation
Stadlinger et al. (2008b)	Adding of rhBMP-4 and chondroitin sulfate on a collagen-coated implant	Miniature pigs	6 weeks	Might encourage osseointegration
Stadlinger et al. (2009)	Collagen- and chondroitin sulfate-coated implant	Miniature pigs	1 month	Can encourage bone formation
Morra et al. (2010)	Collagen covalently linked to acid-etched implant surfaces	Rabbits	2 and 4 weeks	Peri-implant bone formation during early healing could be enhanced
Stadlinger et al. (2012)	ECM coating on implant surfaces	Miniature pigs	4 and 8 weeks	No advantageous influence in terms of BV density and ISQ value
Bae et al. (2018)	Collagen type I cross-linked by gamma irradiation	Rats	4 weeks	Improvements in the bone healing and osseointegration shown
Rotenberg et al. (2016)	Porcine collagen-coated bovine bone around SLA implants	Human	12 months	Can offer superior resistance to pre-implantitis
Korn et al. (2014)	Ti implants coated with type I collagen	Miniature pigs	4 and 8 weeks	Improved early osteogenesis, improved BIC, and increased bone density
Scarano et al. (2019)	Implant surface coated with type I collagen	Rabbits	15, 30, and 60 days	Increased the BIC, bioactivity, and bone around the dental surface

improved early osteogenesis. The authors also found improved BIC and increase bone density. Scarano et al. (2019) examined an implant surface coated with type I collagen in a rabbit model. They showed that surfaces coated with collagen increased the BIC, bioactivity, and bone around the dental surface compared to control implants.

Modification of Implant Surfaces With Peptides

Another approach is the functionalization of implant surfaces with Arginine-Glycine-Aspartate (RGD)-containing peptides, which represents a further method of influencing cell adhesion to the surfaces, thus improving implant-tissue interactions (Garcia and Reyes, 2005; Morra, 2006). RGD-containing peptides are an essential type of signal molecule that are normally immobilized on biomaterial surfaces to control cell performance. RGD is an amino acid sequence (Arginine-Glycine-Aspartate) that is recognized by cells through integrin receptors (Ruoslahti and Pierschbacher, 1987; Zhang et al., 2018). **Table 3** shows the influence of implant surfaces modified with peptides.

Germanier et al. (2006) examined the influence of an RGD-peptide-modified polymer on implant surfaces, and, in the very early stages of bone healing following implant placement, they found more bone apposition. In the mandibles of dogs, Barros et al. (2009) examined the influence of a bio-functionalized implant surface on osseointegration. They concluded that a bio-functionalized implant surface could affect the bone apposition around implants. In adult pigs, Yang et al. (2009) assessed the effect of RGD-coated implant surfaces on bone-bonding ability. They reported that RGD-coated implants have higher

BIC. Lutz et al. (2010) tested the effect of a biomimetic active peptide (P-15) coated implant on early implant osseointegration. They concluded that implant surfaces coated with biomimetic active peptide have higher percentages of BIC and superior peri-implant bone density. In rabbits, Yoo et al. (2015) investigated the effect of an implant surface coated with poly lactide-co-glycolide (PLGA) and BMP-2 on bone growth and found that it facilitated osseointegration during initial healing.

Modification of Implant Surfaces With Transforming Growth Factor- β

Another approach to influencing the processes occurring at the implant-tissue interface is to coat the implant surface with growth factors (for instance, BMP, insulin-like growth factor, or platelet-derived growth factor) (Le Guehennec et al., 2007; Chen et al., 2013). Such growth factor coatings may be effective in modulating cellular functions by, e.g., attracting circulating osteoprogenitors or promoting the differentiation of stem cells or osteoprogenitors into osteoblasts and could therefore improve bone repair around implants (Lieberman et al., 2002; Goodman et al., 2013).

After dental implantation, various studies reported that BMP enhanced and improved osteogenesis, chondroblast activity, osteoblast activity, and osseointegration. Many researchers found that BMP-2 and BMP-7 are the most effective derivatives for inducing bone morphogenesis (Jiang et al., 2013; Ramazanoglu et al., 2013; Dolanmaz et al., 2015; Bouyer et al., 2016). They reported that local application of BMP-2 and BMP-7 can achieve and promote cellular differentiation, which

increases the capacity for bone repair in a diversity of circumstances comprising bony defects, extraction sockets, non-union fractures, and osseointegration (Hunziker et al., 2012; Jiang et al., 2013). BMPs (including rhBMP-2) form a monolayer on the surface of implants, which leads to cell proliferation (Urist, 1965; Sakou, 1998). **Table 4** shows the

TABLE 3 | Dental implant surfaces alteration with peptides.

References	Surface modification	Study module	Study length	Results
Germanier et al. (2006)	RGD-peptide-modified polymer on implant surfaces	Miniature pigs	2 and 4 weeks	Enhanced bone apposition during the early stages of bone regeneration
Barros et al. (2009)	Bio-functionalized implant surface	Dogs	12 weeks	Could affect the bone apposition around implants
Yang et al. (2009)	RGD-coated implant surfaces	Rabbits	4, 8 and 12 weeks	Have higher BIC
Lutz et al. (2010)	Biomimetic active peptide (P-15) coated implant	Pig	14 and 30 days	Has higher BIC and superior peri-implant bone density
Yoo et al. (2015)	Implant surface coated with poly lactide-co-glycolide (PLGA) and BMP-2	Rabbit	3 and 7 weeks	Facilitates osseointegration during initial healing

TABLE 4 | Dental implant surfaces alteration with Transforming Growth Factor- β .

References	Surface modification	Study module	Study length	Results
Jiang et al. (2013)	BMP-2 coated surfaces on roughened or sandblasted implant	Rabbits	2, 4, and 8 weeks	Important in accelerating the osteoinductivity around implants
Kim et al. (2015)	SLA implants coating with BMP-2	Dogs	8 weeks	More active in improving osseointegration
Liu et al. (2007)	BMP-2 and its method of delivery on the osteoconductivity implants	Pigs	3 weeks	Osteoconductivity of implant surfaces can be adversely modulated by BMP-2 and its method of delivery
Hunziker et al. (2012)	Influence of BMP-2 coated implants by various delivery method on peri-implant bone formation	Pigs	1, 2, and 3 weeks	No benefit found for any delivery method
Huh et al. (2012)	BMP-2 coating on anodized implants	Dogs	8 weeks	Increased bone formation and improved implant stability
Becker et al. (2006)	BMP-2 immobilized by covalent and non-covalent approaches on chromosulfuric acid surface-enhanced implant surfaces	Dogs	4 weeks	Surfaces appeared to be stable and stimulated direct bone apposition in a concentration-dependent manner
Lan et al. (2006)	Effect of BMP-2 coated implants on bone-implant osseointegration	Rabbits	12 weeks	Increased the quality and quantity of implant-bone osseointegration
Wikesjö et al. (2008a)	BMP-2 adsorbed onto a Ti porous oxide implant surface	Dogs	8 weeks	Induced peri-implant bone remodeling
Wikesjö et al. (2008b)	BMP-2-coated Ti porous oxide implant surfaces	Monkeys	16 weeks	Improved local bone formation
Lan et al. (2007)	rhBMP-2 and rhIGF-1 or rhbFGF	Rabbits	4 and 8 weeks	rhBMP-2 capable of acting synergistically with rhIGF-1 and rhbFGF to enhance osseointegration
Xing et al. (2017)	Biofunctionalized polyelectrolyte multilayers (PEMs) with polyethylenimine as the excitation layer and gelatin/chitosan loaded with IGF1 on the surface of a titanium implant	Rats	8 weeks	New implants can promote osseointegration in osteoporotic conditions and provide a new strategy for implant repair in osteoporotic patients.
Anitua (2006)	PRGF on the surface of an implant	Goats	8 weeks	Enhanced osseointegration
Park et al. (2006)	Anodized implants coated with fibroblast growth factor-fibronectin (FGFFN) fusion protein	Rabbits	12 weeks	Will possibly improve osseointegration
Nikolidakis et al. (2009)	Influence of coated implants with TGF- β 1 on the early bone healing around dental implants	Goats	6 weeks	Has a negative effect on the incorporation of oral implants in trabecular bone
Schouten et al. (2009)	Titanium implants coated with osteoinductive growth factor (TGF- β 1)	Goat	12 weeks	Showed substantial improvement of the osteogenic response
Lee S.Y. et al. (2010)	PLGA in combination with basic fibroblast growth factor (bFGF) coating on an anodized implant surface	Rabbits	12 weeks	May possibly improve bone formation near the implant surface
Ramazanoglu et al. (2011)	rhBMP-2 and recombinant human vascular endothelial growth factor I65 (rhVEGF165) coating implant surfaces	Pigs	1, 2, and 4 weeks	Biomimetic CP-coated implant surfaces with both BMP and VEGF did not improve BIC but did increase BV density
Schliephake et al. (2015)	Effect of coated implant with Recombinant human vascular endothelial growth factor (rhVEGF) on peri-implant bone formation	Rats	1, 4, and 13 weeks	Can speed up BIC to a certain extent

influence of implant surfaces modified with Transforming Growth Factor- β .

Jiang et al. (2013) found much greater cell feasibility on the surfaces of a roughened or sandblasted implant coated with BMP-2 compared to uncoated control surfaces. The same authors concluded that BMP-2 genes are important in accelerating the osteoinductivity around implants. Kim et al. (2014) established that implants coated with BMP-2 could be effective in the stimulation of initial and late osteoblast differentiation. They reported that bone regeneration was considerably higher near the implants coated with BMP-2 compared to near uncoated implants. However, Lee S.W. et al. (2014) noticed that the formation of peri-implant bone formation was superior for the HA and CO group, whereas BMP did not increase peri-implant bone formation. Bouyer et al. (2016) evaluated the influence of BMP-2 concentrations with crosslinking levels of EDC10 (ethylene imine linear poly) and EDC30. They reported that EDC30 crosslinking levels have no considerable effect on the volume ratio of the bone. Sun et al. (2012) examined the creation of new bone in peri-implant bone defect by BMP2/7 heterodimer, comparing these BMP2 or BMP7 homodimer. The findings supported the utilization of heterodimers and, afterward, they displayed greater regeneration of the bone. Kim et al. (2015) examined the effects of BMP-2 dose on osseointegration in dogs. They reported that SLA implants coated with BMP-2 were more active in improving osseointegration. Liu et al. (2007) evaluated the influence of BMP-2 and its method of distribution on the osteoconductivity of implants. They noticed that the osteoconductivity of implant surfaces can be adversely modulated by BMP-2 and its method of delivery. Mantripragada and Jayasuriya (2016) applied BMP-7 by different delivery methods and examined bone repair. They reported no significant difference among various delivery methods. Hunziker et al. (2012) assessed the influence of mode of delivery of BMP-2 on peri-implant bone formation and found no benefit for any specific delivery method. Xiao et al. (2016) investigated osteogenic function for different surface topographies and found that Ti implants coated with BMP-2 genes enhanced bone creation around the implants. Yeo (2014) reported that an oxidized implant surface coated with BMP encouraged bone osseointegration. Huh et al. (2012) investigated the effect of BMP-2 coating on anodized implants in dogs. They observed that coating with BMP-2 increased bone formation and improved implant stability. Becker et al. (2006) found that BMP-2 immobilized by covalent and non-covalent approaches on chromosulfuric acid surface-enhanced implant surfaces appeared to be stable and stimulated direct bone apposition in a concentration-dependent manner. In the femurs of rabbits, Lan et al. (2007) studied the effect of BMP-2 on bone-implant osseointegration and reported that BMP-2 increases the quality and quantity of implant-bone osseointegration. Wikesjö et al. (2008a) observed that BMP-2 adsorbed onto a Ti porous oxide implant surface induced peri-implant bone remodeling. Wikesjö et al. (2008b) assessed local bone formation and osseointegration in monkeys. They found that BMP-2-coated Ti porous oxide implant surfaces improved local bone creation in type IV bone in a dose-dependent manner in non-human primates, leading to considerable osseointegration.

Lan et al. (2006) evaluated the influence of combining rhBMP-2 and recombinant human insulin-like growth factor-1 (rhIGF-1) or recombinant human basic fibroblast growth factor (rhbFGF) on osseointegration. They noted that rhBMP-2 was able to act synergistically with rhIGF-1 and rhbFGF to enhance osseointegration. According to Xing et al. (2017), the biofunctionalized polyelectrolyte multilayers loaded with IGF1 coated on titanium implant of implant encourages bone consolidation under osteoporotic situations and offers innovative strategies for implant repair in osteoporotic patients. Anitua (2006) found that applying PRGF on the surface of an implant before insertion into the alveolar bone enhanced osseointegration. Park et al. (2006) assessed the bone response around anodized implants coated with fibroblast growth factor-fibronectin (FGFFN) fusion protein in a rabbit tibia model and found that this coating will possibly improve osseointegration. Nikolidakis et al. (2009) studied the influence of transforming growth factor β 1 (TGF- β 1) on the initial bone healing around dental implants. They reported that a small dose of TGF- β 1 has an undesirable effect on the incorporation of oral implants in trabecular bone during the early post-implantation healing stage. Schouten et al. (2009) examined the effects of implant design, surface properties, and TGF- β 1 on peri-implant bone response. They found that adding an electrosprayed CP coating extensively improved bone response. Lee S.Y. et al. (2010) examined the effect of PLGA in combination with basic fibroblast growth factor (bFGF) coating on an anodized implant surface. They suggested that Ti implant coating with PLGA combined with bFGF by electrospraying may possibly improve bone formation near the implant surface. Ramazanoglu et al. (2011) examined whether rhBMP-2 and recombinant human vascular endothelial growth factor I65 (rhVEGFI65) implant surface coating can enhance osseointegration. They found that biomimetic CP coated implant surfaces with both BMP and VEGF did not show improved BIC but did increase BV density. Schliephake et al. (2015) analyzed whether recombinant human vascular endothelial growth factor (rhVEGF) stimulates peri-implant bone formation. They observed that rhVEGF can speed up BIC to a certain extent.

ANTIBACTERIALLY COATED IMPLANT

Various studies found that the implant surface is prone to infection due to the creation of a surface biofilm and compromised immune capability at the interface of implant and tissue. The protein layer made under physiological conditions, which is responsible for the biocompatibility of the implant, is suitable for bacterial colonization and biofilm formation (Dunne, 2002; Harris and Richards, 2006; Hetrick and Schoenfisch, 2006). Inflammatory lesions affecting the tissue surrounding the implant caused by bacterial infection are known as peri-implant diseases (Zitzmann and Berglundh, 2008). Therefore, some authors attempt functionalization of the implant surface with the aim of preventing biomaterial-associated infections. Such antibacterial approaches are mainly designed to prevent bacterial colonization of the implant

surface before biofilm formation can occur (Zhao et al., 2009; Campoccia et al., 2013).

Several techniques have been used in order to attach antibiotics and anti-inflammatories to implant surfaces, such as CP coatings, sol-gel coatings, biodegradable polymer coatings, or loaded nanotubes (Zhao et al., 2009; Chen et al., 2013). According to Bose et al. (2011), potential materials should have the capacity to integrate a bioactive agent chemically or physically, hold it until arrival at the particular target, provide the active agent in an organized way over time, and be gradually degraded. Calcium phosphates and their composites meet all of these criteria. Several studies have incorporated various antibiotics into CP to make the implant antibacterial (Radin et al., 1997; Takechi et al., 1998; Gautier et al., 2001; Ratier et al., 2001; Baro et al., 2002; Zhang and Zhang, 2002; Peter et al., 2005; Oyane et al., 2006; Laurent et al., 2008; Zhang and Kataoka, 2009; Luginbuehl et al., 2010; Altomare et al., 2012; Rajesh et al., 2013; Govindan and Girija, 2014; Fu et al., 2015), for instance, gentamicin (Baro et al., 2002; Laurent et al., 2008; Altomare et al., 2012; Rajesh et al., 2013; Govindan and Girija, 2014), tobramycin (Brohede et al., 2009), cephalothin (Wang et al., 2003), amoxicillin (Brohede et al., 2009; Merdji et al., 2012), tetracycline (Ratier et al., 2001; Luginbuehl et al., 2010), vancomycin (Radin et al., 1997; Gautier et al., 2001), zoledronate (Peter et al., 2005), streptomycin (Fu et al., 2015), and flomoxef sodium (Takechi et al., 1998). However, using an antibacterial agent based on antibiotics raises the concern that antibiotics-resistant bacteria will develop.

Integrating antibacterial ions and NPs into the calcium phosphates is a potentially attractive alternative method. Due to the antibacterial properties of silver, a number of studies have incorporated it in calcium phosphates (Chimutengwende-Gordon et al., 2014; Massa et al., 2014; Yan et al., 2014; Xie et al., 2015; Yan et al., 2015). Silver shows low toxicity in the human body. Although the human body has no biological use for silver, the toxicity of silver is low, and when applied topically, swallowed, inhaled, or injected, it will collect irreversibly in the body, mainly in the skin. ZnO NPs are another type of antibacterial ion, and these NPs can be integrated into calcium phosphates as an alternative to silver (Grenho et al., 2015; Huang et al., 2015). However, ZnO NPs have apparent toxicological influences, as reported by Morejón-Alonso et al. (2007).

Several approaches have been used for the placing of antibiotics in the calcium phosphate, including *in situ* deposition (Altomare et al., 2012), mixing powders throughout the production of scaffolds and pressed coatings (Shadanbaz and Dias, 2012), absorption in microspheres during CP synthesis (Sivakumar and Rao, 2002), covalent protein immobilization in microspheres (Belcarz et al., 2009), co-precipitation (Tadic et al., 2004), dip-coating (Tadic et al., 2004), etc. The transporters comprise, among others, chitosan (Sivakumar and Rao, 2002) and gelatin (Baro et al., 2002; Sivakumar et al., 2002; Tadic et al., 2004; Belcarz et al., 2009; Altomare et al., 2012). Calcium phosphate coatings have mostly been applied by plasma spray technology. However, because of the extremely high processing temperatures involved, this procedure cannot incorporate antibiotics during the coating process (Goodman et al., 2013). Therefore, a post-treatment has been employed,

typically physical absorption, to incorporate antibiotics into such coatings (Goodman et al., 2013). Previous studies used an immersion technique to incorporate a diversity of antibiotics into biomimetically prepared carbonated HA coatings. They reported that some antibiotics were well integrated, depending on their chemical structure. Furthermore, they exhibited that the release rate varied between antibiotics, reaching only 1-day release for gentamicin (Stigter et al., 2002, 2004).

Antimicrobial peptides have recently been introduced to treat septic infection owing to their capability to stimulate innate immune responses and for the difficulty microorganisms have in developing resistance toward them. Controlling the surface of an implant by generating an interface composed of peptides may thus open up new potentials to cover the implant site and tailor it to an appropriate bioactivity (Yucesoy et al., 2015). Yazici et al. (2016) designed bifunctional peptides that were characterized both in solution and on the Ti surface to determine their concomitant solid-binding property and antimicrobial efficacy against three bacteria, *Streptococcus mutans*, *S. epidermidis*, and *E. coli*. The same authors exposed that surfaces modified with both of two chimeric peptides had a considerable reduction in bacterial adhesion against all three bacteria compared to bare titanium. Doxycycline, an antibiotic that belongs to the group of tetracyclines, is an attractive candidate. It is effective against both gram-negative and gram-positive aerobic and anaerobic pathogens (Cunha et al., 1982). Surfaces coated with doxycycline by means of cathodic polarization have been demonstrated to exhibit antibacterial properties and to promote bone formation (Walter et al., 2014; Xing et al., 2015). The topic of antibiotics-incorporated calcium phosphates has been studied in detail in other reports (van de Belt et al., 2001; Lin et al., 2015).

DENTAL IMPLANT BASED ON THE FUNCTIONALLY GRADED CONCEPT

Functionally graded materials (FGMs) display either a gradient in chemical composition or in structure within them. They involve a number of constituents that reveal a compositional gradient across the thickness of the material. Subsequently, FGMs permit properties to be obtained that cannot be accomplished by each constituent material. Teeth and bones are examples of natural materials of this type and are the basis for the development of the FGM idea, with its origin concerning their sophisticated properties (Pompe et al., 2003; He and Swain, 2009; Senan and Madfa, 2017). The investigation of the remarkable properties of natural and novel artificial hard tissues has the potential to give insight into biomimetic material design and the development of novel functional materials (Huang et al., 2007). Continuous alterations of tissue composition, as well as of structure, have been widely identified in biology. For instance, the density of bone changes from outside (stiff cortical bone) to inside (cancellous bone) and gives rise to the notion that functional gradation has been used by biological adaptation (Hedia H., 2005; Hedia H.S., 2005; Hung et al., 2013). In the body, this functional gradation has been used and has been accepted as a method for implant alteration in previous years. Thus, a

fabricated implant must reveal a similar gradation to that of the natural bone. This has been applied in the development of dental implants based on the functionally graded concept, with the proposition of adding porosity gradients, adding surface layer coatings, and forming composite materials made fundamentally of ceramics (e.g., HA) and metal that should promote the implant to act comparably with respect to biocompatibility and stress distribution (Hedia H.S., 2005; Lin et al., 2009; Hung et al., 2013).

For functionally graded dental implants, a cylindrical shape was designed, with the structure changing axially. The upper part necessarily has more strength so as to transmit stress down to the inferior parts, which are implanted inside the cancellous bone, where more biocompatible materials are required (Watari et al., 2004).

Some studies added CP coatings to Ti and/or zirconia that could be prepared to a functionally graded scheme to offer a gradient of bioactivity and good mechanical strength (Bishop et al., 1993; Takahashi, 1993; Matsuno et al., 1996, 2000; Hisbergues et al., 2009). Matsuno et al. (1998) showed the ability to produce a laminated HA/PSZ composite material through sintering. Later on, Guo et al. (2003) used spark plasma sintering to prepare functionally graded HA/yttria stabilized tetragonal zirconia (Y-TZP) composites. They reported a development in the mechanical properties of the functionally graded (FG) HA/Y-TZP composites when compared with pure HA ceramics. Chu et al. (2003) successfully fabricated asymmetrical HA/Ti FGM by a hot pressing method. They then analyzed the stress in the sintered HA/Ti FGM composites by x-ray testing, and the results were consonant with the calculated values. The gradual rise of the HA contents from the core region toward the coating causes relaxation of thermal stresses and enhances the mechanical properties of the coating layer. Comparable findings were obtained by Watari et al. (2004). Using the plasma spray method, three layered functionally graded HA/Ti-6Al-4V coatings were fabricated optimally by Khor et al. (2003). This composite coating showed improved microstructure, microhardness, porosity, density, and Young's modulus. Additionally, no sharp interface between the different layers was detected under the electron microscope. Furthermore, Yamada et al. (2001) fabricated HA/glass FG coatings on a Ti substrate using the Cullet method. The gradient increase in glass contents from the core region to the outer surface resulted in improved bonding of the coating to the Ti substrate. Hedia and Mahmoud (2004) found that the maximum stress in the bone for optimally designed HA/Ti FGM decreased by 22% in comparison to a monolithic Ti implant. Using 3D FEM, Yang and Xiang (2007) conducted a comprehensive parametric study of the biomechanical behavior of an FG dental implant, taking in consideration the interaction of the implant and the surrounding bone under static conditions as well as under normal occlusal forces. The maximum stress difference at the FG implant-bone interfaces was reduced significantly. Moreover, Wang et al. (2007) considered the thermal variation in daily oral activities in their investigation of the thermo-mechanical behavior of HA/Ti FGM dental implants using FEM. They found that the FGM with a gradually changing HA concentration behaved almost equally well, while Ti caused much higher von Mises stress. Roy et al. (2011) applied the laser

engineering net shaping process to place TCP on commercially pure Ti, and a compositionally graded nature was achieved. Marković et al. (2015) fabricated nanostructured FG via sintering. Farnoush et al. (2015) used electrophoretic deposition to create an FG HA-TiO₂ nanostructured composite coating on a Ti-6Al-4V substrate. Another study by Kumar and Wang (2002) calculated the hardness and modulus of elasticity of FG HA/Ti and HA/β-TCP/Ti coatings. Cattini et al. (2014) utilized the suspension plasma spraying technique to produce different bioactive glass/HA coatings.

Porosity gradient has been studied as another way to fabricate an FG implant structure (Hunziker et al., 2012). Becker and Bolton (1997) suggested using porous FGM Ti alloys for dental implants. By controlling the pore size and distribution, the mechanical properties of porous dental implants can be changed and optimized (Mehrali et al., 2013). A graded porosity from the core to the surface layer is offered for implant fabrication. This will lead to a reduction in the stiffness difference at the implant/bone interface (Traini et al., 2008), thereby reducing the stress shielding-induced bone resorption.

A variety of methods have been established in recent years to produce dental implants that mimic the behavior of natural tooth under function (Tolochko et al., 2002). Lifland et al. (1993) used electron-discharge compaction to create a porous surface on a commercially available dental implant. Kutty and Bhaduri (2004) utilized one-step microwave processing to make graded-porosity dental implants. A number of scientists have developed additive manufacturing methods such as selective laser melting (SLM), selective laser sintering (SLS), and electron beam melting (EBM) (Hrabe et al., 2011; Mangano et al., 2012). These methods are applied for the fabrication of porous structures with different unit cells (Ahmadi et al., 2014) and high resolution (i.e., small cell sizes) (Cheng et al., 2014), based on building up a three-dimensional structure from a computer-aided design model (Ryan et al., 2006).

Tolochko et al. (2002) used Ti powders to create dental implants with a compact core and irregular porous shell via SLM for the solid core and SLS for the porous surface. Traini et al. (2008) used a laser sintering procedure to fabricate implants, integrating graduated porosity from the inner core of the structure to the outer surface using Ti alloy (Ti-6Al-4V) powders. On the other hand, Mangano et al. (2009) recommended using a fully porous structure to make it possible to construct implants with irregular and narrow intercommunicating crevices and shallow depressions using Ti-6Al-4V powders. Murr et al. (2010) used EBM to create open cellular foams with solid and hollow cell wall structures. Li et al. (2010) developed Ti-6Al-4V implants with versatile porosity via EBM. They found that the compressive properties of implants are variable with pore architecture and can be equivalent to those of natural bone. Laoui et al. (2006) found that by utilizing laser gas nitriding using a CW Nd:YAG laser, the coating layer formed was capable of resisting more stress cycles without fracturing. However, at the junction area of the shell and core of the implant, stress concentrations could arise due to the rapidly changing mechanical properties, as reported by Hao et al. (2003). Therefore, Cook et al. (1988) recommended a post-sintering heat treatment to minimize the residual stresses. They reported that the fatigue strength of Ti alloy improved

by about 15%. Nevertheless, producing FG structures could be suitable for preventing the concentration of stress between the interface layers (Joshi et al., 2013).

The concept of constructing FG structures in porous materials by changing the structure of the lattice has also been investigated (van Grunsven et al., 2014). Witek et al. (2012) used laser sintering to make dental implants with a porous layer and compared them with a sandblasted-acid etched implant. They examined the BIC and removal torque and found that porous implants created by the sintering process showed better biomechanical properties and biocompatibility. Bandyopadhyay et al. (2010) proposed laser-engineered net shaping to make porous structures from Ti-6Al-4V alloy that can be tailored to mimic human cortical bone. To produce porous Ti/HA composites, Nomura et al. (2010) suggested an infiltration method in a vacuum with sintering.

Some authors designed FG scaffolds based on pore-graded CP to meet both biological and mechanical requirements (Vaz et al., 1999; Wang et al., 1999). Werner et al. (2002) established that bending strength was approximately 50% higher for a pore-graded CP scaffold than that of an HA scaffold.

FG coatings can also help in antibacterial activity. Manjubala et al. (2000) fabricated an FG coating in which Ag was added onto coralline HA. Manjubala and Kumar (2000) created an FG CP scaffold based on TiO₂, HA, TCP, and Ag₂O to increase the scaffold's mechanical stability and antibacterial activity. Bai et al. (2010) emplaced a series of FG coatings based on HA. The authors incorporated various percentages of silver, utilizing ion beam-assisted deposition.

FG CP can also be applied for simulating interfaces (Li et al., 2009; Samavedi et al., 2011; Sartoretto et al., 2017) or bone-cartilage (Erisken et al., 2008). Li et al. (2009) made a gradient in mineral content for the simulation of a tendon–bone interface in which stiffness changed, as did the activity of preosteoblast cells. To mimic the bone-cartilage interface, Erisken and collaborators (Erisken et al., 2008) utilized twin-screw extrusion to create a graded scaffold made of PCL/β-TCP. Using this hybrid method, they were able to tailor a graded scaffold with a β-TCP content of 0–15 wt.%. They noticed markers akin to the type of variations observed in a typical bone-cartilage interface after four weeks of seeding cells into the scaffold.

Many authors have studied the biological interaction of dental implants with porous surface geometry. Mangano et al. (2012) applied a laser sintering procedure to create implants with interconnected pores and irregular crevices. They reported that success was 95% 1 year post-operation. Teixeira et al. (2012) used different industrial methods and reported a good range of bone ingrowth in porous Ti implant. Hollander et al. (2006) demonstrated that osteoblast cells entirely roofed the porous structure. Bandyopadhyay et al. (2010) reported that the

concentration of calcium ions increased proportionately with the increasing porosity percentage after 16 weeks. Laoui et al. (2006) found clear bone growth into the porous structure within a porous surface layer. They also noticed no signs of inflammation at the interface. Tolochko et al. (2002) established that the porous implant they tested was firmly joined into the alveolar ridge with a maximum gap width of 200–300 μm between the bone and the implant.

CONCLUSION AND FUTURE PERSPECTIVES

This review has studied the dental implant, giving its possible disadvantages and making suggestions for its improvement. Several design parameters have been assessed, and many designs have also been examined.

Biomimetic surface modification and bioinspired functionally graded structures can address the challenges currently faced by existing implants. Surface functionalization of dental implants via a biomimetic process showed improvement in osseointegration and enhancement in bone regeneration. Furthermore, the bioinspired functionally graded structure can be used to fabricate dental implants. These dental implants with similar biological and mechanical properties to those of natural tooth and bone might potentially result in better long-term clinical performance under function.

More research on implant structure, design parameters, surface treatment technologies, and analysis techniques are still required to improve outcomes. Therefore, further studies are needed to assess the potential of progressive manufacturing approaches to optimize the surface functionalization of implants and enhance their graduation structure.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

AMa contributed to the research concept, supervision, literature collection, technical steps, writing the original draft, and reviewing and editing the final manuscript. SA-Z contributed by searching, literature collection, and writing the original draft. AMu, MA, and OH contributed to the research concept, literature collection, and writing the original draft. X-GY contributed to the research concept and writing the original draft.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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