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Review Article

Composition and Modifications of Dental Implant Surfaces

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Since Brånemark discovered the favorable effects of titanium in bone healing in 1965, titanium has emerged as the gold standard bulk material for present-time dental implantology. In the course of years researchers aimed for improvement of the implants performance in bone even at compromised implant sites and multiple factors were investigated influencing osseointegration. This review summarizes and clarifies the four factors that are currently recognized being relevant to influence the tissue-implant contact ratio: bulk materials and coatings, topography, surface energy, and biofunctionalization. The macrodesigns of bulk materials (e.g., titanium, zirconium, stainless steel, tantalum, and magnesium) provide the mechanical stability and their influence on bone cells can be additionally improved by surface treatment with various materials (calcium phosphates, strontium, bioglasses, diamond-like carbon, and diamond). Surface topography can be modified via different techniques to increase the bone-implant contact, for example, plasma-spraying, grit-blasting, acid-etching, and microarc oxidation. Surface energy (e.g., wettability and polarity) showed a strong effect on cell behavior and cell adhesion. Functionalization with bioactive molecules (via physisorption, covalent binding, or carrier systems) targets enhanced osseointegration. Despite the satisfying clinical results of presently used dental implant materials, further research on innovative implant surfaces is inevitable to pursuit perfection in soft and hard tissue performance.

1. Introduction

In the last 30 years the application of dental implants increased significantly for the functional and aesthetic rehabilitation of patients needing tooth replacement [1]. Several types of dental implants have been on the market over the years varying in material, shape, and surface characteristics, depending on how the device is inserted and anchored to the bone. In the beginning the clinical goal was to develop the optimal design (as shape and geometry) to avoid any implant failure due to intraoral forces and loading [2, 3]. Endosseous implants are currently the most successful type, directly inserted into the alveolar bone where osseointegration provides a strong structural support in the long term [1, 4]. Primary mechanical stability is enabled by the friction between the threads and the host bone [5]. Currently the success rate of endosteal implants is around 95% in the maxilla and 97% in the mandible after 10 and 15 years of follow-up period, respectively [6, 7]. However, despite the high success rate, there is still ongoing research to enhance the clinical performance in more challenging conditions, such as poor bone quality or quantity [8]. The increase of life expectancy in the population results in more compromised implant site conditions, due to age related changes of bone [9]. The current trend is to modify implant surfaces in order to improve cell-surface interaction, which leads to an increase in local bone density and acceleration of healing time even in elderly or pathologic bone [10]. "Osseointegration" is a pivotal point for the survival of implants and it has been demonstrated that the biological fixation is strictly related to the surface characteristics of the implant. Therefore, different materials, coatings, and surface treatments have been proposed to enhance biomechanical properties of the interface area [5, 11]. This paper reviews the possible surface modifications of dental implants and the factors that mainly influence events at the tissue-implant interface. Four factors are considered being relevant to affect the contact with bone and soft tissue besides the shape: materials and surface treatments, topography, surface energy, and biofunctionalization [12].

2. Bulk Materials

Materials for dental implants are requested to be biocompatible, hypoallergenic, chemically inert, corrosion resistant, and stable [13, 14]. Metals are the most common choice so far, due to their suitable mechanical properties. Many metals such as titanium, zirconium, hafnium, vanadium, niobium, tantalum, chromium, molybdenum, gold, platinum, silver, steel, and cobalt have been exploited in clinics or in experimental settings in the past. Nowadays, the majority of dental implants are constructed of titanium with increasing implementation of zirconium [15–17].

2.1. Titanium and Related Alloys. Titanium (Ti) is a transition metal within the group IV of Mendeleev's periodic table. Since transition elements have a partially filled *d* subshell, they are very reactive and in presence of oxygen, an oxide layer is immediately formed on their surfaces [13, 18]. Clinicians recognize two types of titanium implant materials: commercially pure (CP) titanium and titanium alloys. The American Society for Testing and Materials (ASTM) distinguished, furthermore, the composition of these two general groups: 1–4 CP and 5–31 Ti alloys [19]. The grade of CP titanium (1–4) depends on the degrees of purity given by oxygen, iron, and carbon content [20]. Contamination by other elements is the lowest on Grade 1 and the highest on Grade 4. Brånemark implants (Nobel Biocare, Zurich, Switzerland), for example, were composed of Grade 1 while ITI implants (Straumann, Basel, Switzerland) were composed of Grade 4 [21]. The success of titanium derived from the properties being light, strong, ductile, and highly biocompatible [22]. The oxidation process is the main cause for its biocompatibility. After implant insertion, recruited granulocytes trigger a severe oxidative stress at the implant site by overproducing oxygenated derivatives, such as H_2O_2. Lysis of H_2O_2 into reactive oxygen species and subsequent incorporation into the surface causes the thickening of the titanium dioxide (TiO_2) layer on the implant [20]. Calcium and phosphorus ions from the osseous matrix are also incorporated into this porous layer together with oxygenated derivatives leading to a highly dynamic interface between bone and implant. Biomolecule absorption is reflected by an increased cell adhesion and subsequent osseointegration [23]. This passive layer of titanium and its alloys is usually 15 nm thick and guarantees a high corrosion resistance to Ti and its alloys [24]. The oxide layer, preventing direct contact between metal and the environment, acts as a protective layer, thus minimizing ion release [25]. Noble metals, such as gold, platinum, or palladium, are missing the ability to form a stable oxide layer and thus are not applied for endosseous implants but for dental suprastructures [26].

Alloying elements for titanium can be subdivided into three categories in view of their microstructure at room temperature: α-stabilizers (Al, O, N, C), β-stabilizers (Mo, Nb, Ta, Fe, V), and neutrals (Zr). The basic properties of the α-group are high corrosion resistance but limited strength at ambient temperature compared to $\alpha+\beta$ alloys. The β-group is characterized by high strength and the combination of lower elastic modulus and superior corrosion resistance [13, 27]. Grade 5 titanium is also known as Ti-6AL-4V indicating that the alloy contains 6% aluminum and 4% vanadium, which lead to an improved mechanical strength and fracture resistance [28]. This alloy was applied in several medical devices before being introduced in dentistry, due to its superior physical and mechanical properties when compared to those of CP Ti [29]. New alloys have been exploited such as Niobium (Nb), Zirconium (Zr), Molybdenum (Mo), and Tantalum (Ta), and Hafnium (Hf) [30–32]. Several *in vitro* studies have been performed to prove the biocompatibility and absence of hemolytic activity on different alloys, as Ti-Nb, Ti-Al-Nb, Ti-Nb-Zr, and Ti-Nb-Hf [31–34]. Lee at al. [35] showed that the alloy Ti-15Mo-1Bi could improve surrounding bone *in vivo* up to 249% compared to Ti-6Al-4V and the alloy Ti-7.5Mo up to 100% when inserted in rabbit femur [35, 36]. Lavos-Valereto et al. investigated Ti-6Al-7Nb as dental implant in dogs affirming that osseointegration and stable implant anchoring were reached even in absence of further coatings or surface treatments [37]. In spite of ongoing research on titanium alloys for biomedical use, commercially pure titanium (grade 1–4) still remains the most common material of choice in implant dentistry.

2.2. Zirconium. Zirconium has been widely applied for medical use and found its way into implant dentistry due to an increased interest in aesthetic implants. Zirconium is highly reactive with water and oxygen and the crystalline dioxide form is called zirconia (ZrO_2). Zirconia exists in 3 temperature dependent crystallographic structures: monoclinic, tetragonal, and cubic [38]. The volumetric expansion generated during transformation from tetragonal to monoclinic can break the zirconia crystal; therefore, doping agents are utilized as stabilizers, such as calcium oxide (CaO), magnesium oxide (MgO), cerium oxide (Ce_2O_3) yttrium oxide (Y_2O_3), and aluminium oxide (Al_2O_3) [39, 40]. The dark colour of titanium could become visible in thin gingival tissue or due to gingival recession [41]. Therefore, zirconia became a suitable material for dental implants exhibiting a tooth-like ivory colour and mechanical and biological properties comparable to titanium [39]. Zirconia revealed biocompatibility in several *in vitro* studies, improving osteoblast adhesion and proliferation [42], and osseointegration has been observed in several animal studies [43, 44]. Quantitative histomorphometric results of Schultze-Mosgau et al. [45] indicated that significantly improved bone healing in minipig mandibles was observed on the ZrO_2 surface in comparison to titanium. A new titanium zirconium alloy (commercially called Roxolid), developed by the Straumann Institute AG (Basel, Switzerland) and containing 13–17% zirconium (TiZr), showed improved mechanical properties compared to pure Ti with respect to elongation and fatigue strength. Gottlow et al. [46] demonstrated that stability and bone response to this type of material were enhanced when inserted into minipig mandible. Kohal et al. [43] suggested that zirconium implants might withstand occlusal loads over a long time period. However, middle and long-term studies are still missing.

2.3. Tantalum. Tantalum is a type of refractory metal, belonging to group V in the table of elements. It shows a good corrosion resistance, due to its natural passivating oxide layer Ta_2O_5. It was exploited as bulk material or surface coatings for implants [47] and showed excellent physical and biological properties such as inertness, flexibility, mechanical stability, and biocompatibility [17, 48]. *In vitro* comparative studies using mesenchymal stem cells and osteoblastic cells reported no significant differences on cell morphology, proliferation, and differentiation between Ta and Ti [49–51]. Matsuno et al. [15] tested tantalum in both soft and hard tissues of rats and demonstrated the absence of any material corrosion after 4 weeks and no signs of inflammatory response caused by the material. Producing tantalum through a vapour deposition technique leads to a porous structure similar to trabecular bone also called Trabecular Metal. It possesses an elastic modulus (3 GPa) not comparable to titanium (110 GPa) but closer to cancellous bone (1.2 GPa) enabling its application as hip, knee, or limb replacement implant [52–54].

2.4. Magnesium. Magnesium (Mg) is an alkaline earth metal and, since the end of 1800, it has been investigated as a resorbable implant [55, 56]. Mg is a natural component of the body and, being able to degrade under physiological conditions, became of interest to avoid second surgery for implant removal. It does not interfere with bone growth and regeneration during fracture healing especially in paediatric cases [57, 58]. Magnesium is more suitable for load-bearing applications compared with ceramics, due to strength and wear resistance. Moreover, it shows density and an elastic modulus (45 GPa) closer to natural bone [59]. The main limitation is the fast degradation process which is not in equilibrium with the healing time leading to a fast loss of mechanical stability [55] and production of gas cavities in the surrounding tissue [60]. The corrosion rate strongly affected cell spreading and adhesion even *in vitro* [61]; therefore, recent studies focused on finding the appropriate alloy composition, surface treatments, or coatings to slow down the degradation process and gas formation. Zreiqat et al. [62] showed an increased cell expression of the integrin receptor $\alpha 5\beta 1$ and collagen I when cells were grown on magnesium alloys. Castellani et al. [57] demonstrated *in vivo* that bone mass was greater and bone structure was more mature around several magnesium-based alloys compared with titanium, confirming previous results obtained by Witte et al. [63]. Magnesium has been also applied by Zhao et al. [64] as titanium coating material to dope hydroxyapatite (HA) and, although it promoted cell viability and alkaline phosphatase activity *in vitro*, there was no statistical difference compared with standard HA coatings *in vivo*. Nevertheless many studies are under development to enhance magnesium implant properties being a biodegradable metal and possessing a great potential for the application in bone regeneration [56].

2.5. Stainless Steel. Due to the low cost and easy manufacturing, stainless steel has been also used as implant material. However, it leads to a strong release of metallic ions into the body during a long-term application [65]. Therefore, it was mainly applied only for temporary implants [66]. *In vitro* tests showed toxicity in osteoblastic cells with respect to proliferation and differentiation via DNA damage [67]. To improve the passivation behaviour it was stabilized by chromium (12-13%) as a layer of chromium dioxide and molybdenum (2-3%) [68, 69]. In the past also Nickel (Ni) was applied to further improve corrosion resistance. But Nickel ions were released reducing the implant biocompatibility. Hence Ni was substituted by nickel-free alloys [69]. Numerous surface modifications, especially film coatings, have been also performed to reduce corrosion and ion release in presence of body fluids and to improve the bioactivity of the material [70].

3. Coating Materials

As mechanical properties (Young's modulus, fatigue, etc.) are dependent on the bulk material, the biological effects are strictly associated with the implant surface and its properties [71]. Pure titanium appears to be well integrated; however, surface modifications are widely investigated to enhance the bond of host tissue to the implant via either precipitation of bone mineral or protein deposition or direct cell stimulation [22].

3.1. Calcium Phosphate/Hydroxyapatite. Calcium phosphate (CaP) $[Ca_3(PO_4)_2]$ mainly constitutes the inorganic component of mineral phase in bones. Hydroxyapatite (HA) $[Ca_{10}(PO_4)_6(OH)_2]$ is the most stable form of calcium phosphate [72, 73]. Due to brittleness of HA as bulk material, it cannot be applied to substitute loaded bony structures such as joints, and consequently it is commonly used as coating material on metallic implants [74]. HA coating tends to accelerate the initial rate of osseointegration due to the release of Ca and PO_4 ions in the surrounding tissues and it is able to form a chemically bonded interface with bone without the intervention of a connective tissue layer [75]. CaP can be resorbed by osteoclasts, which in turns activate osteoblasts to form new bone [76]. The rate of ion release is influenced by chemical composition, structure, and porosity of the coating layer. For coating the metal substrate of dental implants with a calcium phosphate layer, several techniques have been investigated to overcome the problem of detachment. The plasma spray coating process (TPS) produced coatings that typically contain 60–70% HA [26]. This coating technique was observed to accelerate peri-implant healing together with bone formation [5]. Other approaches were investigated such as the pulsed laser deposition (PLD), ion-beam and radio frequency (RF) sputtering although their present costs do limit their clinical application. Other more cost effective methods include the immersion onto simulated body fluids (SBF) after a pretreatment with hydroxyl or oxide groups or by dipping the implant in a gel containing calcium and phosphorus (Sol-gel) [24, 77]. The micro-arc-oxidation (MAO) has been reported by Li et al. [78] to promote cell differentiation and osseointegration.

3.2. Bioactive Glasses. Bioactive glass (BG) is a glass-ceramic derived by the Bioglass 45S5 developed by Hench in 1971 and constituted by 45% SiO_2, 24.5% NaO_2, 24.5% CaO, and 6% P_2O_5 [79]. It has been defined as bioactive since it is able to form a layer of carbonate-substituted hydroxyapatite-like (HCA) structure on the surface, when in contact with body fluids [80]. This positive effect confers a high biocompatibility to BG and enables a tight bone-implant contact without intervention of fibrous tissue [81]. However, bioactive glasses are slowly degraded to HCA and possess a low mechanical strength. Therefore, subsequent chemical modifications have been introduced to improve the performance such as the partial or total substitution of SiO_2 with B_2O_3, to generate borosilicate of borate bioactive glasses [82], or with P_2O_5 producing phosphate glasses [83]. Since they are slowly absorbed by the body, BG have been also utilized as a substrate for binding or incorporating elements, such as drugs or ions (Zn, Cu, F, Mg, Sr, B, P) [84] to promote bone generation [85], or treating infections [86]. Several studies have been carried out *in vitro* and in animal models to compare the efficacy of BG coating in comparison to HA [32, 87, 88]. In 2011 Mistry et al. [89] demonstrated that silicate bioactive glass coated dental implants possess the ability to achieve osseointegration comparable to HA coating after insertion in human jaw bone.

3.3. Strontium. Strontium (Sr), within the group IIA of the periodic table of elements, follows directly calcium as alkaline earth metal. Due to their chemical and physical similarities, strontium can be accumulated in the skeleton and influence bone formation by inhibiting osteoclasts resorption [90]. Nowadays, the application of strontium on metallic implants is more and more investigated. Several studies are focused on substituting calcium in apatite lattice or on Sr-HA complex to increase the strength under weight loading conditions [91, 92]. *In vitro* experiments showed cell proliferation and attachment to its surface and *in vivo* stimulation of bone formation was comparable to HA coatings [91]. Park et al. [93, 94] investigated the incorporation of strontium in the titanium dioxide layer and they demonstrated an improvement in implant osteoconductivity and in implant bone healing by increasing bone deposition on the surface and higher bone-implant contact. The possible mechanism behind strontium activity is correlated to the activation via strontium divalent cations (Sr^{2+}) of the calcium-sensing receptor (CaR), which is expressed by bone cells. The activation of CaR triggers cell proliferation and differentiation in osteoblasts (via ERK kinase phosphorylation) [95] and, at the same time, apoptosis in osteoclasts (via phospholipase C stimulation) [96], thereby promoting bone formation and reducing bone resorption.

3.4. Diamond and Diamond-Like Carbon. Diamond and diamond-like carbon (DLC) coating received attention as a potential material for biomedical applications due to its high hardness, low frictional coefficient, high wear and corrosion resistance, chemical inertness, high electrical resistivity, infrared-transparency, high refractive index, and smoothness [97]. Carbon in nature can exist in three different hybridizations, sp^3, sp^2, and sp^1 forming different crystalline and disordered structures. Pure diamond is characterized by the tetrahedral sp^3 configuration. Graphite consists of sp^2 flat layer of coordinated carbons. A diamond coating is characterized by pure sp^3 hybridization, whereas DLC is a metastable form of amorphous carbon containing a mixture of sp^2 and sp^3 carbon bonds [98]. Physical properties of DLC lie between those of graphite and diamond, which led to the term "diamond-like carbon" [99]. The sp^3 bonding of DLC is responsible for some beneficial properties, such as its mechanical hardness, chemical and electrochemical inertness, and elastic modulus, but has significantly lower production costs. High plasma density enhanced chemical vapor deposition (PECVD) reactors can increase the content of sp^3 bonding; however, the specific properties of an individual DLC coating depend on the different deposition methods that are well reviewed by Robertson [98]. Modern DLC coatings are reported to adhere strongly to several metallic and polymeric biomaterials. Such an inert, chemically resistant protective layer is suggested to improve the tribological properties of articulating surfaces. Therefore, Allen and coworkers [99] investigated the effects of DLC coatings on the musculoskeletal system. Both *in vitro* and *in vivo* examinations revealed excellent biocompatibility of DLC-coated substrates. Mohanty et al. [100] investigated the long tissue response on DLC modified titanium implanted in the skeletal muscle of rabbits. The influence of DLC films on stainless steel have been reported by Huang et al. [101] to protect against corrosion and improve friction and wear performances of the steel substrate. Interpretation of the different *in vitro* and *in vivo* results is difficult since there is a lack of an exact characterization of the DLC coating and determination of its surface properties. Further problem is the spontaneous delamination of the coating due to high residual compressive stress if the DLC adhesion to the biomaterial is insufficient [97]. Despite the strong potential of DLC for biomedical applications due to its biocompatibility, Grill [102] summarized that long-term investigations are still lacking. Coating with diamond crystals can offer a wide range of size, starting from microcrystalline diamond (MCD), nanocrystalline (NCD) with a diameter of 20–100 nm, and diamond particles (DP) (5–20 nm) [103, 104]. Nanosized crystallites still keep the properties of diamond and at the same time increase the surface area available for binding bioactive molecules. These features led to several applications in medicine such as surgical tools and medical implants [105, 106]. Oxygen treatments such as plasma treatment, wet chemistry, or thermal oxidation [104] produce hydrophilic NCD surfaces showing higher binding energies towards biomolecules like BMP-2, than hydrophobic NCD surfaces [107]. Since oxygen containing groups are bound to nanocrystalline diamond, the surface positively influences proliferation and differentiation of osteogenic cells [108], promoting desirable conditions for cell adhesion, spreading, and viability [109].

4. Topography

Surface topography is mainly constituted by pits, protrusions, and grooves and can be described by surface roughness

parameters. A roughness value can either be calculated on a profile (line) or on surface (area). The profile roughness parameters (e.g., R_a, R_z) are more common. R_z represents the difference between the highest and lowest point of the surface, whereas R_a is the height mean value and can be quantified and measured at the microscale (R_a 1–100 μm) or nanoscale (R_a 1–100 nm) level. However, the 3D area roughness parameters (S_a, S_q) give more significant values. Due to micro- and nanotopography the implant contact area with the tissue is increased enabling further cell-implant interaction [22].

4.1. Microroughness. Most of currently available dental implant surfaces have a moderate surface roughness with a complex microtopography (S_a 1-2 μm) [110] since several studies indicated that implants with rough surfaces have a higher healing potential than implants with a smooth surfaces. Wilkinson et al. [111] observed *in vitro* with human primary osteoblasts that adhesion, mineralization, and production of osteospecific proteins such as osteopontin, RUNX2, can positively vary depending on roughness degree of the surface. These findings are in accordance with previous studies performed by Lincks et al. [112], which showed enhanced local osteogenic factors production on rough surfaces, indicating an improved cell differentiation. The observation of an increase in platelet adhesion towards surfaces of greater roughness could be explained by an increased surface area, resulting in increased adsorption of fibrinogen [75]. After platelets activation, upregulation of neutrophils and macrophages is greater, followed by a rapid recruitment of osteogenic cells, which are now available for the *de novo* bone synthesis [113, 114]. The effect of different values of surface roughness in the titanium alloy Ti-6Al-4V was investigated for human bone marrow cells and protein adsorption. The roughness of Ti alloys influenced cell response since cell attachment and proliferation increased. The rough substrate bound a higher amount of serum protein especially fibronectin explaining the increased cellular attachment on roughened Ti alloys. It was further observed that human bone marrow cells were able to detect changes in roughness in the range of 0.60 μm [114]. Several studies demonstrated clinical success of roughened implant surfaces in comparison with polished surfaces, even in situations with poor bone quantity or insufficient bone quantity [115]. Sullivan et al. [116] reported a success rate of 93.7% in poor bone quality sites with specific chemically etched pure titanium dental implants. The success of microtopography, such as improvement of early fixation and long-term mechanical stability [117], led to numerous methods of implant surface roughening:

(i) anodization: it implies the application of strong acids to thicken the oxide layer in titanium up to 1 μm via the formation of an electrical circuit where the implant is the anode [118];

(ii) acid-etching: implant is dipped into a heated solution of strong acids, forming pits on the surface with a diameter of 0.5–2 μm [119];

(iii) sandblasted acid-etching: sandblasting the implant prior to etching leads to a macroroughness of 10–20 μm on top of the microroughness conferring an increased bone anchorage up to 110% more after 12 weeks compared with solely etched surfaces [120];

(iv) plasma sprayed (TPS): due to plasma high temperature, the coating material is sprayed at high speed against the surface until reaching a thickness of 40–50 μm; TPS implants are associated with the detachment of Ti granules from the implant; therefore, it is no longer considered to be a suitable surface for clinical applications [121];

(v) grit-blasting: ceramic particles are shouted through a nozzle at high speed against the surface and depending on grain size; different grade of roughness can be reached [119]; titanium implants grid-blasted with titanium dioxide particles are already well-established with proven success in diverse *in vitro* [122, 123] and *in vivo* [124] investigations, as well as in clinical prospective studies [125, 126];

(vi) micro-arc oxidation (MAO): another technique leading to a TiO_2 layer on the surface of a titanium implant. the oxide layer morphology is influenced by the treatment conditions: by raising the applied voltage, the roughness and thickness of the oxide layer increase as well as the amount of calcium and phosphate ions are incorporated; it was observed that these changes resulted in increased cell differentiation in early stages whereas cell proliferation rate decreased; thus, on the basis of biological response, the micro-arc-oxidation appears to be a promising way of modifying implant surfaces [78];

(vii) modification with carbon-oxygen (CO): this treatment is based on the acceleration of charged atoms or ions towards the surface, embedding the ions into the material; when compared with commercially treated implants, such as double acid-etched, sandblasted, and acid-etched or oxidized, implants treated with CO ion implementation showed significant higher BIC values at 3 and 6 months and demonstrated higher osseointegration at early stages [127].

4.2. Nanoscale Level. Surface roughness can also be achieved at the nanoscale level (R_a = 1–100 nm). Whilst surface microtopography is thought to have influence on cell-surface interaction, nanotextured surfaces act on protein-surface interaction, leading to cell behavioral changes and favoring adhesion [128]. Research on implants is focused in designing biomaterials that enhance cell and tissue growth by mimicking nanostructured environment; however, the extra cellular matrix (ECM) has a complex structure that spans several orders of magnitude (nm to cm scale) and up to now most of the macro- and microfabrication techniques have been unable to recreate the subtleties of the ECM [129]. In native tissues, nanoscale protein interactions are crucial in controlling cell functions such as proliferation, migration, and ECM production [130]. Currently several methods

for creating nanostructures on CP Ti implants are being investigated such as self-assembly of monolayers (SAMs), deposition of nanoparticles, lithography, and diverse physical and chemical approaches [128]. The first method utilizes molecules with high affinity for the substrate in order to form self-assembled monolayers onto the surface, which expose specific functional end groups. One molecule of interest, applied in this technique, is the cell adhesive peptide domain RGD (arginine-glycine-aspartic acid) linked to polyethylene glycol (PEG) [131]. The second method includes the sol-gel technique: dipping or spinning into colloidal solution in order to deposit nanoparticles on the surface. It is commonly used for HA coating; however, poor adhesion to the substrate limits its application [24]. Another method for nanostructure pattering is electron beam lithography: the implant surface is coated with a film layer called "resist" before being irradiated with an electron beam, subsequently either irradiated or unirradiated regions of the film can be removed. After covering with a light-sensitive material, the remaining film pattern is transferred to the implant surface via etching or lift-off [132]. Several materials have been applied as resist, such as polymethylmethacrylate (PMMA), colloidal particles (metal oxide particles), and polymers [129]. Since the topography of the surface affects the phenomenon of cell movement guidance, this may prevent epithelial downgrowth on dental implants and may favor stable osseointegration [76]. It was also suggested that even minute changes in nanogeometry, such as nanopit dimension and conformation (i.e., highly ordered or controlled disordered), influence the mechanics of cell adhesion and subsequent cell function [133]. Gentile et al. [134] showed that cell adhesion and proliferation are maximized with a roughness of $R_a \sim 10–45$ nm. Moreover, nanostructures, introduced by immobilized gold nanoparticles with an average size of 58 nm, can reduce the immune complement activation up to 50% [135] and inflammatory cytokines production (IL-6, IL-8) [136]. Although the influence of nanotopography was demonstrated *in vitro* [137–139], there are just few indications that bone response is improved in presence of nanostructures and little is known about the influence on tissue behavior *in vivo* [140].

5. Surface Energy

In addition to topography, the surface energy significantly influences cell behavior and adhesion [141]. Surface energy describes the perturbation of intermolecular bonds occurring when surfaces are generated. Bulk atoms surround each other in a regular manner and they experience no net forces. However, those at the surface see this only on one side of the interface. Therefore, they possess higher energy compared to the molecules in the bulk of the material. This difference is measured as surface energy [142]. Surface energy influences consequently polarity and wettability, which is defined as the ability to let a liquid spread and adhere over the surface [143]. Higher surface energy has been hypothesized to be desirable for enhancing interaction between the implant surface and the biologic environment because of the increased wettability [110, 144]. Surface hydrophilicity is another factor that determines biocompatibility of biomaterials and is mainly dependent on surface energy [110].

5.1. Hydrophilic Surfaces. The importance of hydrophilic groups (e.g., hydroxyl, carboxyl, carbonyl, and amino groups) for the stabilization of the blood clot and subsequent osseointegration led to chemically modified ultrahydrophilic titanium implants [145]. Conventional titanium dental implants lose their hydroxylated oxide surface (chemically active) due to a drying process. Comparison of water contact angles between conventional and hydrophilic surfaces showed a reduction from 139.9° to 0° [146, 147]. The water contact angle measurement characterizes surface wettability and can be used to determine the surface energy. Hydrophilic surfaces have very low contact angle values whereas hydrophobic ones reveal a contact angle of >90° [147]. Surface energy and wettability play an important role on the interaction with the proteins on the implant surface and influence strongly cell adhesion [116]. This is an important step towards osseointegration, since the type of tissue that will be developed at the interface between bone and implant surface is determined by the specific composition of adsorbed proteins [145]. Titanium implants with hydrophilic surface resulted in an improved cell growth and osteoblasts differentiation, characterized by increased synthesis of alkaline phosphatase and osteocalcin as well as TGF-β1 and BMP-2 [148]. The influence of surface wettability has been demonstrated in both *in vitro* and *in vivo* situations. Buser et al. in 2004 showed in the mandible of minipigs a significant higher percentage of direct bone/implant contact ration (BIC) and enhanced bone apposition at two and four weeks after insertion of hydrophilic implants in comparison to conventional [143]. Schwarz et al. [145] investigated in dogs the initial and early stages of osseointegration around the two different surfaces via histology and immunohistochemistry: after 4 days, granulation tissue and provisional connective tissue were adjacent to the conventional titanium surface, whereas a dense connective tissue surrounding hydrophilic surfaces showed first signs of osteocalcin synthesis. Furthermore, the immunohistochemical analysis of transglutaminase II, expressed on vessel walls, clearly indicated a direct correlation between neovascularization and new bone formation after seven days. After two weeks, wound healing was differentiated by the formation of new bone on hydrophilic titanium surfaces [121].

5.2. Nanocrystalline Diamond. The properties of diamond as coating material have been previously described [105]. It is important to mention that nanocrystalline diamond (NCD) film (surface roughness of 15 nm and thickness of 800 nm) leaves the overall texture of the substrate unchanged [149]. However, not only nanoscale feature is playing a role for osteablastic cell adhesion but also surface wettability of NCD surfaces, as demonstrated by an analysis of Kalbacova et al. [109]. Cell attachment was observed to be preferential on hydrophilic O-terminated NCD surfaces, compared with the hydrophobic H-terminated. Lechleitner et al. [104] investigated the suitability of differently terminated NCD

coated surfaces to support cell growth. Cell attachment and proliferation were inhibited at the H-terminated or highly hydrophobic NCD in contrast to O-NCD showing an increase. These observations indicate the importance of functional groups and subsequent wettability with respect to nanostructures. Therefore, not only micro- and nanotopography but also polarity or surface charge distribution determines the performance of cell attachment, growth, and differentiation. These results are in accordance with an investigation of Amaral et al. [105], who described human fibroblast adhesion and spreading on NCD surfaces. No cytotoxic effects were detectable and NCD coating improved human osteoblast growth and differentiation in comparison to standard polystyrene tissue culture plates, in a biocompatibility assay. Furthermore, NCD is considered as ideal for coating since they prevent metallic ions release by serving as protective barrier between implant and the host environment [105].

5.3. Plasma Treatment. Recently, it was demonstrated that plasma treatment leads to positive charged surfaces, which beneficially influence osteoblast adhesion [150]. The basic principle of plasma polymerization is the transformation of low-molecular-weight molecules (monomers) into high-molecular-weight molecules (polymers) via the assistance of energetic species such as electrons, ions, and radicals. The polymer is anchored to the surface during the formation and can be used to covalently bind extracellular matrix proteins such as fibronectin, laminin, or amino acid sequences. This method can play an important role in the biofunctionalization of surfaces of inorganic materials [151]. Puleo and colleagues [76] immobilized BMP-4 on a titanium alloy by using plasma polymerization of allylamine. There are several plasma treatments of biomaterial surfaces, which have been summarized in an extensive review by Chu et al. [151].

6. Biofunctionalization

Since bone integration is mediated by biochemical interactions between cells and the implant surface, coating with components of extracellular bone matrix (ECM) have been investigated to enhance implant integration and bone healing. Cytokines, growth factors, and integrins are able to interact with bone cells and influence migration, growth, adhesion, and differentiation [152]. As soon as the implant is inserted into the organism, it is immediately covered by a biofilm constituted of different biomolecules, blood platelets, ions, and proteins. The protein layer is produced through a sequence of several steps followed by cell adhesion. Therefore, the type of tissue that will develop at the tissue-implant interface is greatly influenced by the specific composition of the adsorbed proteins [145]. Biochemical modifications of implant surfaces, such as the immobilization of proteins, enzymes, or peptides, are suggested to control the implant-tissue interface with molecules anchored directly to the interface and, in contrast to calcium phosphate coatings, organic components are applied [14]. Three different methods have been investigated in order to control concentration, retention, and/or release of molecules from implant surfaces: physisorption, covalent binding, and carrier system [76].

6.1. Physisorption. The physical adsorption (or physisorption) characteristics depend on the surface features of the implanted biomaterial (i.e., roughness, charge, chemistry, and wettability) [153] and are described as a phenomenon of spontaneous adsorption on the surface caused by electrostatic and van der Waals forces [154]. A general problem with the adsorption method is the lack of control over the delivery of molecules. As a consequence, the initially retained proteins can desorb from the implant surface in an uncontrolled manner. The dipping method in presence of HA coating can lead to a burst release of the physisorbed molecules, up to 80–90% in 1 hour [155, 156]. Liu et al. [156] showed that superficially adsorbed BMP-2 was released rapidly, generating high local concentration at a very early stage of healing, which severely impaired the implants osteoconductivity. Thus, Puleo et al. [76] affirmed that this method is not practical for clinical applications. The physisorption of proteins to biomaterials is greatly influenced by the higher surface area to volume ratio, which in due course influences surface energy [157]. However, little is known about the combination of nanostructures and immobilized ECM proteins or growth factors. Steinmüller-Nethl et al. [107] demonstrated that proteins such as BMP-2 can stably bind to nanocrystalline diamond via physisorption comparable to covalent binding. Moreover, BMP-2 retains its bioactivity when in combination with hydrophilic NCD (O-NCD) and can improve alkaline phosphatase production *in vitro*. Diamond coating combines two characteristics: nanotopography and wettability. NCD possess a grain size of 10–50 nm whereas diamond nanoparticles (nDP) with 5 nm size are available. The dangling bonds after film deposition are hydrogen-terminated and hydrophilicity is only reached after a subsequent oxidation process [106]. Kloss et al. [149] evaluated the activity of BMP-2 *in vivo*. In comparison to conventional titanium, H-NCD, H-NCD/BMP-2, and O-NCD coated implants, the implant-bone interface of O-NCD/BMP-2 showed remarkably high levels of BMP-2 and higher concentration of osteoblasts in the immunohistochemical analysis at one week after operation, suggesting that BMP-2 remained physisorbed to O-NCD over a prolonged period *in vivo*. Furthermore, after four weeks the area surrounding O-NCD/BMP-2 was covered with mineralized bone in contrast to fibrous tissue partially detected at the surface of conventional titanium, H-NCD, and H-NCD/BMP-2. The biological effects of NCD coating in combination with firmly physisorbed ECM proteins have to be further investigated. However, NCD is able to achieve stable binding of the biomolecules without losing their biological activity and without burst release avoiding unwanted systemic effects [107, 158].

6.2. Covalent Binding. Another possibility to make the surface more attractive for cellular adhesion and prevent systemic effects is to anchor ECM-proteins via covalent binding. Cell adhesive proteins are applied such as collagen I, osteopontin, fibronectin, or vitronectin [159, 160], which

are known to contain the Arg-Gly-Asp (RGD) adhesive sequence. In order to avoid the expense of isolation and possibility of immunogenicity of native ECM, mimetic peptide fragments possessing functional domains, such as RGD, can be applied for implant biofunctionalization [161]. The RGD sequence is recognized by integrins and since Dee et al. [162] showed that it can synergistically promote mineralization *in vitro*, such surface implant modifications have gained importance. The Arg-Gly-Asp sequence, however, lacks selectivity among integrins and, therefore, initiates nonspecific cell attachment [163]. Proteins can be bound directly to the surface or through a spacer or linker and, usually, hydroxyl (–OH) or amine (–NH) groups are needed for the immobilization of molecules [164]. It is essential that the biological activity and structure of molecules are not compromised by solvents or by the binding method chosen [165, 166].

6.3. Carrier System. A further biofunctionalization method implies the direct integration of molecules into the coating material, which acts as a carrier system. Carriers currently in use are polylactide, polyglycolic acid [167], hydrogels [168], polypyrrole [169], and calcium phosphate/HA coating [155, 156]. In the last case, in order to avoid that temperature-sensitive protein can be damaged during the coating procedure due to high temperatures, a new technique has been established under physiological conditions [170]. Proteins or growth factors are diluted in a calcium phosphate or HA solution and they are entrapped into crystals formed during precipitation on the substrate [171]. When growth factors or antibiotics are incorporated into a HA coating by this method, they can be delivered in a physiologic-like manner, as giant cells and osteoclast mediate the degradation of the crystals. This slow-release system is in contrast to a burst-release of the drug, such as HA physisorbed BMP-2 [156]. The protein amount loaded into the carrier can be 10 times higher compared with adsorption [170]. Furthermore, carrier systems cannot prevent systemic effects as the protein is released during the degradation process of the coating layer [172]. Jennissen [173] criticized carrier/delivery systems to show different results in a large range. Liu et al. [174] showed strong induction of bone formation in ectopic *in vivo* sites with usage of low pharmacological levels of BMP-2.

7. Conclusion

The classification system proposed in this review follows a scheme reported in other studies [12, 22]. The aim was to give an overview of different implant surface modifications and the factors that mainly influence events at the tissue-implant interface besides shape and design. Since implants are required to be biocompatible, functional, of high success rates, and of best aesthetic results [14, 39], several investigations focused on different materials, coatings, topographies, wettabilities, and biofunctionalizations in order to achieve these purposes. Originally, endosteal dental implants were developed for functional rehabilitation; it was, therefore, necessary to investigate materials that could be inserted into bone without being rejected by the host immune system. Materials such as Ti alloys, zirconium, tantalum, niobium, and hafnium have proven to be biocompatible in *in vitro* and *in vivo* studies; however, biocompatibility of these materials was limited to an acceptance by the host bone rather than a guided tissue response. Subsequently, research focused on implant surface modifications to avoid or reduce several drawbacks such as bone and soft tissue recession, peri-implantitis, and implant loss [14]. Implant surfaces have been modified in order to guide bone regeneration via osteoconductive and osteoinductive properties [22]. Coating with calcium phosphate (such as hydroxyapatite), bioglasses, and strontium improved osteoconduction and accelerated the rate of osseointegration during the early stage of bone healing, which is considered the most critical phase after implantation [75, 89, 175]. Besides the implant materials, surface roughness and wettability appeared to promote cell attachment and subsequently osseointegration [176]. Roughness has been further improved reaching the nanoscale level to control the protein-surface interaction [128], and hydrophilic surfaces are able to positively influence protein adsorption leading to enhanced bone apposition [145]. Implant site conditions become more challenging in poor bone quality and several studies focused on biofunctionalization of dental implants in order to improve the success rate [108]. The aim of biofunctionalization is to immobilize proteins while retaining their bioactivity [152]. In order to reduce problems associated with high delivery dosage, different methods to bind bioactive substances to the surface, such as physisorption, covalent binding, and carrier systems, have been targeted. Since nanotopography has been shown to promote initial protein adhesion and cell alignment, the combination of nanostructures and immobilized growth factors may lead to the most desirable results [107].

This review summarizes numerous reports of different surface modifications with promising results. However, it is difficult to evaluate not only the potential of the investigated surface itself but also its significance in comparison with the established ones. Further comparative studies will be necessary to highlight significant differences among the different surface characteristics and to assess their potential for clinical application. Reviews of implant surface modifications are thereby useful in updating and evaluating current implant surface designs.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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