

CURRENT TRENDS IN SURFACE MODIFICATION FOR DENTAL IMPLANTS

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Abstract

Titanium and its alloys are amongst the most effective and commonly used biomaterials for the production of dental implants. But, in order to ensure long term success of these implants, surface modification techniques that improve osseointegration and prevent bacterial colonization are highly required. Until now, a variety of surface modification methods were proposed, the most basic ones involving mechanical or chemical processing to increase the roughness coefficient thus favoring osseointegration. However, this is not enough to prevent the common implant-related complications such as peri-implantitis. Therefore, an increased research interest was directed towards the development of functional coatings that can be tailored to both enhance osseointegration and prevent bacterial infections. This review aims to present the currently available titanium-based implants modification methods along with their main benefits and drawbacks. For a better understanding of the subject, the chemical structure and surface characteristics of titanium-based dental implants, and the main causes of implant failure were presented. Moreover, current trends such as nano-scale surface roughening and 3D printing of dental implants were also mentioned.

Keywords: titanium, implant failure, surface modification, osseointegration.

Introduction

Missing teeth are the result of genetic conditions (e.g. anodontia, ectodermal dysplasia, etc.), dental trauma, gum diseases or poor oral hygiene that leads to severe tooth decay. Left untreated, this affection can lead to the misalignment or shifting of the remaining teeth, speech and chew issues and jawbone loss together with facial collapse. Throughout time, various methods were proposed for teeth replacement (e.g. dental implants, implant or tooth supported bridges, removable dentures, flippers, etc.) but, amongst them, dental implants were found to be the most effective solution [1]. A dental implant is a medical device that is placed either beneath the oral mucosa and periosteum or within the bone, to ensure the retention and support of a prosthetic component such as a crown. The dental implant is made up of three components: a small cylindrical screw called post or fixture that is implanted into the tissue, an abutment which connects the post and the prosthetic and the prosthetic crown, bridge or denture, selected depending on the number of missing teeth and their position (Fig. 1) [2].

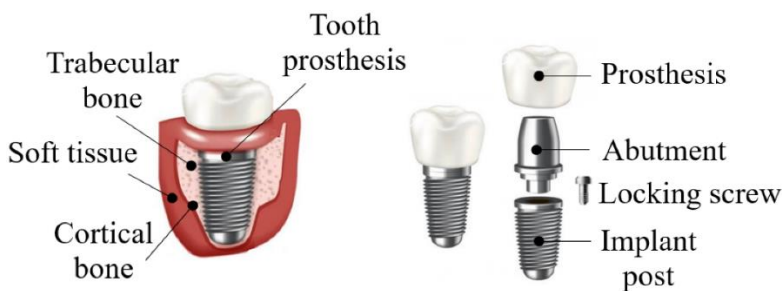


Fig. 1. The components of a dental implant [2]

The benefits of dental implants include a high success rate (approximately 90% after 10 to 15 years of implantation), mastication and aesthetic similarity to natural teeth, a lower risk of caries, endodontic issues or sensitivity of neighboring teeth, and preservation of the integrity of the jawbone and soft tissues at the implant site [3]. As per the American Association of Oral and Maxillofacial Surgeons, 26% of individuals lose their entire dentition by the age of 74, while 69% of adults between the ages of 35 and 44 lose at least one permanent tooth. Consequently, the number of dental implants implanted annually is predicted to be around 300,000, and the dental implant market is expected to rise from 4.73 billion USD in 2024 to 8.06 billion USD by 2032. Thus, it is imperative to create effective implants with enhanced osseointegration and antimicrobial properties. [4].

Selecting the ideal dental implant material is essential to achieving the greatest possible clinical result and prognosis for the patient. Biocompatibility, mechanical toughness, corrosion resistance, wear and fracture resistance, as well as the proper surface properties (microstructure, surface composition, etc.) that guarantee osseointegration are some of the qualities that these materials must have. [5]. Metals, ceramics, and polymers are the three primary material types employed in the fabrication of dental implants because of their unique physico-chemical characteristics.

The first modern dental implants were made of metals, such as titanium and its alloys, stainless steel, gold, tantalum, cobalt-chromium alloys, etc. A major contribution in dentistry was made by the Swedish physician Per-Ingvar Branemark. After thorough animal and human studies, he introduced the term of implant osseointegration in 1969 and, in 1978, he designed a titanium root-shaped implant secured with titanium screws named fixtures. The device was well integrated in the surrounding tissues within a six months' time period and had an average duration of 40 years following implantation [6]. After this discovery, the implantology field was in a continuous expansion and other types of implants with improved properties were developed (e.g. ITI-sprayed, Stryker, IMZ, Core Vent, etc.) [7].

Despite being the gold standard for dental implants, titanium and its alloys continue to raise concerns over its toxicity, immunostimulatory potential (due to the release of titanium ions into the surrounding tissues), and aesthetics [8]. As a result, research efforts were concentrated on creating new materials that have the potential to replace titanium in dental implants. Ceramics (such as silicon nitride, bioglass, zirconia, calcium phosphates, alumina oxide, etc.) and polymers (such as polymethyl methacrylate, polytetrafluoroethylene, polyethylene, polysulfone, polyether ether ketone, etc.) offer a viable substitute [9, 12, 13]. Ceramics work well in terms of osseointegration and tissue regeneration because of their inert nature, but their main flaw is that they don't have sufficient mechanical qualities, such as brittleness, low fracture toughness, and ductility [14]. Polymeric implants possess a series of advantages (e.g. high elastic modulus, excellent melt processability, possibility of secondary restorations in case of implant failure, etc.). Moreover, studies showed that polyether ether ketone reinforced with carbon fibers presents an elasticity modulus similar to the one of cortical bone (17.4 GPa) and has superior aesthetic

properties, therefore, it could represent a promising option for patients that are intolerant to titanium [15]. The main drawbacks associated with polymeric implants are high production costs and possibility of generating foreign body reactions [16, 17].

Considering these facts, the general conclusion is that the best option for producing highly performant and cost-effective dental implants is maintaining titanium as the main material and applying various surface modification techniques to overcome the disadvantages mentioned above [18]. It was found that the implant failure rate for titanium implants varies between 5 and 11%, depending on the implant composition, and the main causes for this phenomenon are of mechanical (e.g. implant overload or fracture) or biological nature (e.g. infection, excessive surgical trauma, impaired osseointegration, peri-implantitis, etc.) [19]. In response to these issues, throughout time, several types of surface modifications were proposed and according to their level of complexity, they were divided into five generations: 1st gen – mechanical, 2nd gen – morphological, 3rd gen – physicochemical, 4th gen – biochemical and 5th gen – biological modifications [3].

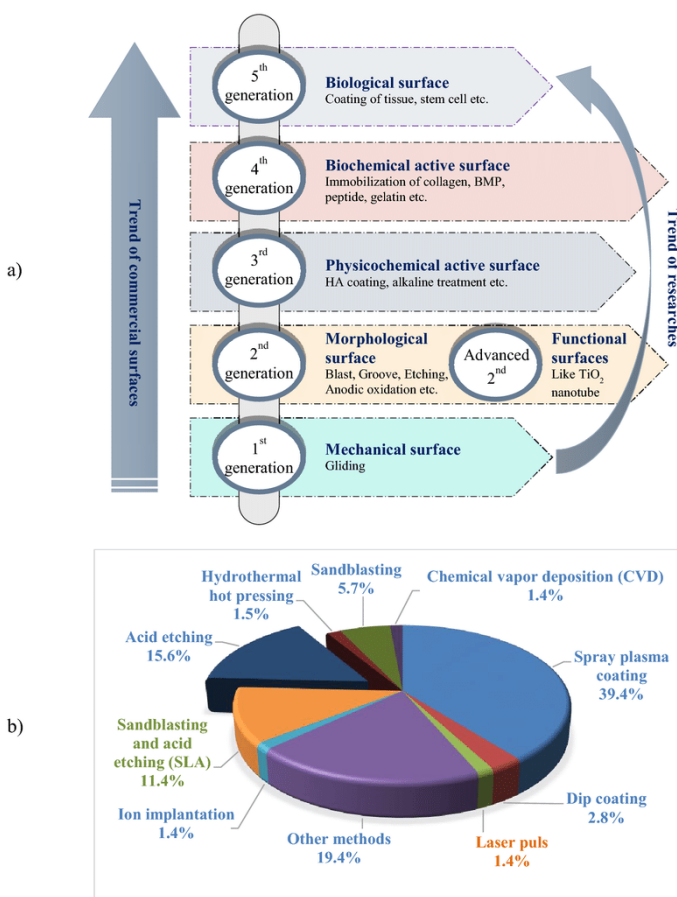


Fig. 2. a) Various generations of surface modifications for dental implants and b) frequently employed techniques for surface modification of dental implants made of titanium [20]

Surface modifications can be carried out by applying surface coatings designed to effectively promote osseointegration and reduce bacterial colonization, thereby minimizing the risk of peri-implantitis, or by directly altering the metal surface via machine grinding, sandblasting, chemical etching, laser abrasion, etc. (Fig. 2) [21, 23].

The primary causes of implant failure as well as the chemical makeup and surface features of dental implants made of titanium will be covered in this review. Also, an up-to-date summary of the different implant surface modification strategies, along with their benefits and drawbacks revealed by research studies and, in some cases, clinical application results are provided.

Chemical structure and surface characteristics of titanium-based dental implants

Six titanium-based biomaterial types were designated by the American Society for Testing and Materials to be used in dental implant manufacturing. These comprise two titanium alloys, Ti-6Al-4V and Ti-6Al-4V extremely low interstitial (ELI), and four commercially available pure titanium types with varying purity levels (marked I to IV) [24]. The oxygen, carbon, and iron contents of commercially pure titanium are used to determine its purity level. These elements also have a significant impact on the material's mechanical qualities. For example, grade I titanium has the highest corrosion resistance and ductility but the lowest yield strength (~170 MPa), while grade IV titanium possesses moderate ductility and highest strength (~483 MPa). In the case of titanium alloys, the elasticity modulus is relatively similar to pure titanium (~113 GPa vs 104 GPa for grade IV commercial pure titanium), but the mechanical strength is notably increased, particularly in the case of Ti-6Al-4V ELI alloys (~860 MPa) [25]. A high yield strength and lower elasticity modulus are preferred in the case of dental implants, as they provide resistance to occlusal forces, thus decreasing the risk of fractures, and ensuring a better force transmission to the bone. Moreover, the mechanical properties of cortical bone must also be taken into consideration when choosing a material for dental implants to avoid potential tissue trauma.

Considering these facts, along with the experimental and clinical results obtained so far, nowadays the majority of dental implants are produced from grade IV commercial pure titanium, and research is directed towards the decrease of the material's Young modulus for a higher similarity with the one of cortical bone [26]. Good results in this direction were obtained by applying repetitive micro-milling protocols before powder metallurgy sintering, to generate macro-pores in the material's structure [27]. Surface characteristics such as energy, hydrophilicity, and roughness degree are also important factors influencing the performance of dental implants. It was established that the surface charge determines the material's wettability, a positive charge yielding a hydrophilic surface and vice versa [28]. Furthermore, research revealed that while hydrophilicity is important for the selective absorption of proteins and macromolecules from blood plasma, hydrophilic surfaces outperform hydrophobic ones in terms of implant osseointegration [29]. From the topographical point of view, micro-roughness resulting from acid-etching, sandblasting, or other modification techniques has a positive influence on the osseointegration process because it increases bone-implant contact and boosts the osteoblast response during the tissue healing phase [30].

Potential causes for the failure of titanium-based dental implants

The concept of osseointegration was first proposed during the 1950's by Branemark, following several *in vivo* studies on bone marrow and joint tissue that investigated the tissue response to injuries. He observed that bone tissue was able to grow into thin spaces of titanium chambers, thus permanently incorporating them into the bone, the only way of separating those being by fracture [31]. Therefore, osseointegration was defined as "the direct structural and functional connection between bone and the surface of a load carrying implant". This process is essential for implant stability and is considered a vital aspect influencing loading and long term clinical success of dental implants [32]. Over time, it has been determined that six factors—implant material, implant design, surface quality, bone health, surgical technique, and implant loading conditions—are necessary to achieve dependable osseointegration [33].

Osseointegration is the targeted outcome following implantation, but, despite the well-documented biocompatibility of titanium-based materials, two other tissular responses were observed during clinical applications. The first is an inflammatory response brought on by implant surface wear and chemical corrosion, which releases tiny titanium particles into the oral tissues around the implant [34]. The second is called a foreign body reaction, and it occurs when a fibrous capsule forms between the host tissue and the implant. This fibrous tissue layer is a common cause of implant failure because it prevents the implant from being biomechanically fixed adequately [35].

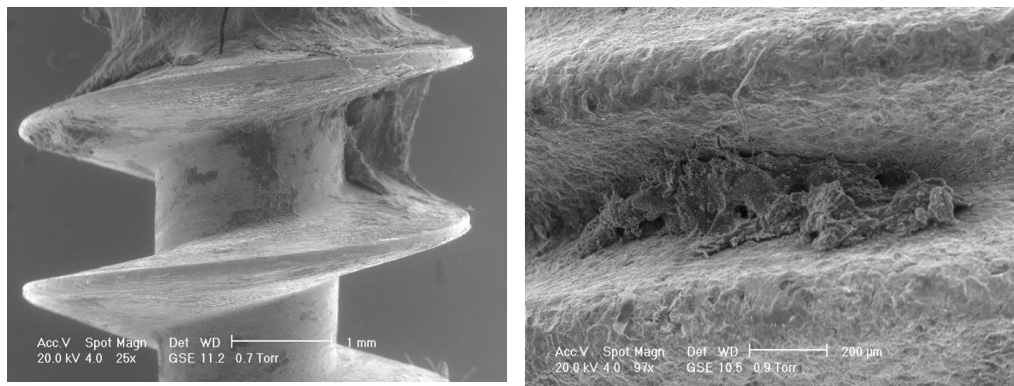


Fig. 3. SEM images shown the fibrous tissue at the surface of titanium-based dental implant with poor stability

Dental implant failure can be classified as early failure (implant rejection), which means that the implant becomes mobile before placing the prosthetic element, or late failure that occurs 1 to 3 years after implantation due to mechanical, immunological or genetic causes (e.g. excessive loading, retained subgingival dental cement, traumatic occlusion, incorrect crown placement, peri-implantitis, bruxism, etc.). Inflammation and foreign body response are early implant failure examples; other causes could be inadequate bone quality/quantity, systemic diseases (e.g. AIDS, diabetes, etc.), the use of certain drugs like bisphosphonates or corticosteroids, smoking, surgical trauma, etc. [36]. Due to the fact that titanium lacks antibacterial properties, micro-organism (most commonly spirochetes and mobile forms of Gram-negative anaerobes) have the tendency to adhere to implant collars, thus leading to biofilm formation and consequently peri-implant infections or peri-implantitis. Because peri-implantitis promotes inflammation in soft tissues and bone tissue loss around osseointegrated implants, it is thought to be the primary immunological cause of late implant failure [37]. The treatment for this affection focuses on infection modulation and implant surface decontamination via antibiotics and mechanical debridement coupled with the regeneration of the jawbone with grafting materials [38].

Early osseointegration ability and long-term antibacterial activity have been determined to be critical factors for successful implantation as implant failure causes have been researched and comprehended [39]. Surface morphology and chemical composition of titanium-based dental implants are highly dependent on implant geometry and the rate and quality of osseointegration [40]. Consequently, some surface treatments were developed to optimize these aspects, with the most important ones covered in the next chapter.

Surface modification techniques for improving the performances of titanium-based dental implants

To summarize, the osteogenic implant surface must have the ideal combination of biocompatibility, hydrophilicity, antibacterial qualities, and surface roughness in order to

promote tissue healing and rapid, high-quality osseointegration [41]. Surface hydrophilicity and roughness are two of the most targeted characteristics when it comes to dental implants surface modifications. The most accessible modification methods belong to the 1st (machine grinding) and 2nd generation (plasma spraying, grit-blasting, acid etching, anodization) modifications (Fig. 2) that involve mechanical and morphological alterations of the implants surface [42]. Machining was used since early dentistry and it basically represent the processing of the bulk material into the desired shape using a specific equipment. Following machining, the implant surface displays recurrent grooves and a minimally rough surface with a roughness average (R_a) of 0.4 to 0.8 μm , depending on the type of equipment and cutting angles. Still, studies showed that R_a values ranging between 1 and 2 μm improve the bone-implant biomechanical interactions with positive effects on osseointegration and osseoconductivity [43].

To achieve greater surface roughness profiles, second generation surface modification techniques were used. For instance, grit blasting creates a rather rough surface in the 1-2 μm range by saturating the implant surface with hard ceramic particles (such as alumina, titanium oxide, calcium phosphate, etc.). Acid etching is performed by immersing the implant for a predetermined time period in a concentrated solution of hydrofluoric, hydrochloric, nitric or sulfuric acid or a mixture of these acids. This roughening treatment generates micro pits with diameters ranging between 0.5 and 2 μm , this type of surface promoting rapid osseointegration and ensuring implant stability for at least 3 years. Strong acids, high current densities (200 A/m^2), and potentials (100 V) are also used in the anodization process to create micro- or nanoporous implant surfaces by galvanostatic or potentiostatic mechanisms. Finally, plasma spraying is a method commonly used to obtain R_a higher than 2 μm and is recommended for modifying implants that are placed in areas with low bone density. It involves putting hot titanium particles protruding onto the implant surface. The high treatment temperature causes the particles to condense and fuse together, creating a film that is between 30 and 50 μm thick and has a R_a of around 7 μm . This greatly enhances the implant's surface area and tensile strength [44]. These days, surface roughening techniques like Ice (machining), IMZ TPS (plasma spraying with titanium particles), OsseotiteFull (double acid etching using a mixture of nitric acid and hydrochloric acid), SLA (sandblasting followed by acid etching), and Replace Select (anodization) are commonly used for commercial implants [45]. The implant surface's microscopical characteristics following various roughening methods are depicted in Figure 3.

In order to improve osseointegration and provide antibacterial qualities, the third generation of modification techniques focused on coating the implant surface with diverse materials. Metal implants can now be coated using a variety of techniques, including electrophoretic deposition, sputter deposition, sol-gel coating, plasma spraying, and biomimetic precipitation. In clinical practice, however, titanium dental implants were only treated using the plasma-spraying technique [46]. As an illustration, applying hydroxyapatite (HA), a calcium phosphate, to the implant creates a bioactive surface that increases bone-implant interaction. Furthermore, it was noted that upon implantation, a biological apatite layer precipitated on the implant surface as a result of an increase in body fluid saturation brought on by the release of calcium phosphates in the peri-implant area. This coating of apatite facilitates the adhesion and proliferation of osteogenic cells and speeds up the process of bone mending surrounding the implant [47]. Additionally, polymeric coatings designed to trap calcium ions from the surrounding environment in order to promote the deposition of biological apatite have shown promising results [48]. Doped hydroxyapatite has been investigated lately as a potential new covering material.

By integrating various nanoparticles in HA structure (e.g. SiO_2 , Gd_2O_3 , CeO_2 , Ag, Mg, Cu, Zn, Cd, etc.), the mechanical stability of the coating is enhanced and it provides not only osteogenic but also angiogenic and antibacterial properties [49, 50]. A downside of using metal nanoparticles as constituents of dental implant coatings is related to the disposal of the materials after use, because accumulation of metal ions in water is an actual environmental

concern. Therefore, strict legislations must be instituted and followed when working with such materials [51, 52].

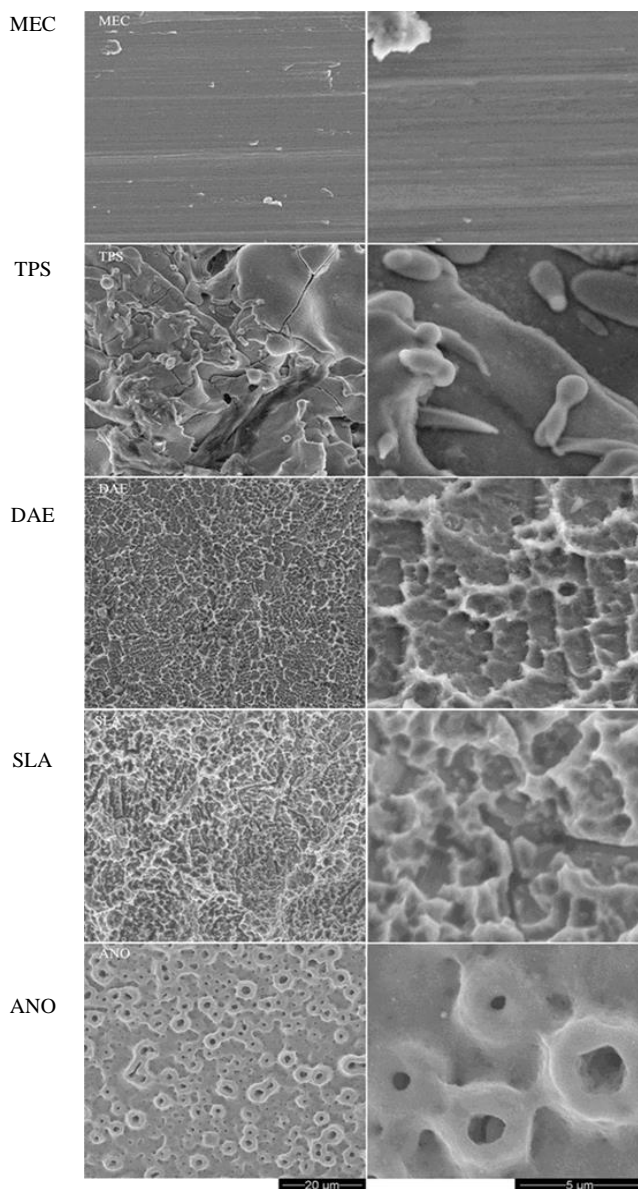


Fig. 4. SEM pictures of titanium dental implant root surfaces after they were subjected to several surface roughening processes, including anodization (ANO), double acid etching (DAE), sandblasting and acid etching (SLA), plasma spraying (TPS), and machine grinding (MAC) [45]

Fluoride is another compound applied for the coating of dental implants in virtue of its ability to promote osteoblast and alkaline phosphatase activity at the micro molecular level. Besides enhancing osseointegration, fluoride possesses antibacterial properties and can prevent the debut of peri-implantitis [53]. The performance of titanium implants covered with TiO_2 /calcium phosphate doped with varying concentrations of fluorine was studied. Fluoride was also utilized

as a doping agent for calcium phosphates. Compared to pristine implants, coated implants were found to have higher rates of osseointegration; however, the antibacterial qualities were only evident when at least 6wt% fluoride was included. Therefore, to attain the intended outcomes, fluoride content adjustment is crucial [54].

Good results in terms of antibacterial activity were obtained by infusing the implants surface with chlorhexidine [55], totarol [56] or various antibiotics [57], but it was concluded that encapsulation in either calcium phosphates or polymers is mandatory for a gradual release of the antimicrobial agent and prevention of potential toxicity towards osteoblasts [58]. Future trends for enhancing the antibacterial activity consist in designing artificial antimicrobial peptides normally found in the oral cavity (e.g. defensins, cathelicidins, statherin, histatins, etc.), and integrating them in the coatings currently used for dental implants [59]. Besides osteogenic and antibacterial compounds, molecules involved in bone remodeling processes such as bisphosphonates were also considered promising for the coating of dental implants. *In vitro* studies revealed that bisphosphonates inhibit osteoclast activity and increase alkaline phosphatase production, thus amplifying the osteogenic behavior of osteoblasts, while the *in vivo* assays showed increased bone density in the peri-implant area of bisphosphonate-coated implants vs neat titanium ones [60].

The progresses in molecular biology and genetical engineering gave rise to the 4th and 5th generations of surface modification techniques which consist in enhancing the implant surface with specific molecules recognized by osteoblasts such as amino acid sequences (e.g. arginine-glycin-aspartic acid - RGD), osteogenic proteins (e.g. vitronectin, OP-1, BMP-2, BMP-7, etc.), growth factors (e.g. TGF-1, PDGF, IGF-1 and 2, etc.), stem cells or even fully developed tissues [61]. In a study involving rat, canine, and non-human primate models, Wikesjo et al. implanted porous titanium dental implants coated with recombinant human BMP-2 (rhBMP-2) and rhBMP-7. They discovered that the altered surfaces, in every instance, promoted bone growth surrounding the implants' necks and produced a vertical enlargement of the alveolar ridge that was clinically significant [62]. The advantages of these types of modifications are low dosage of biological molecules required to observe a positive effect, and their natural association cascade of cellular differentiation and functionality. Still, the optimal methods of binding, retention and controlled release of these molecules at the implant surface are not yet defined and the costs associated with them are quite high [63]. A solution could be the functionalization of well-established coating agent (e.g. hydroxyapatite, carbonaceous compounds, cellulose acetate, etc.) with the desired biological molecule to ensure its physical retention and chemical stability [48]. Nemcakova et al., for instance, highlighted that Ti6Al4V implants functionalized with BMP-7 and coated with nanocrystalline diamond enhance extracellular matrix mineralization *in vitro* and accelerate osseointegration *in vivo* on rabbit models [64].

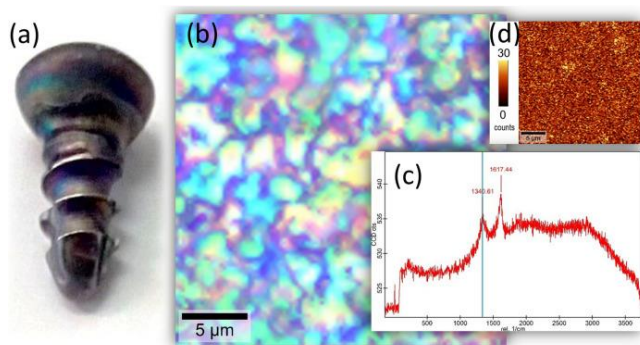


Fig. 5. Material composition and morphological attributes of the cortical screws coated with nanocrystalline diamond: (a) coated screw photo; (b) bright-field optical microscope image; and (c) Raman spectrum displaying distinctive properties of nanocrystalline diamond [64]

Conclusions

In virtue of their inert chemical character and superior mechanical properties, titanium and its alloys have a proved efficiency in the implantology field. But, despite these native advantages, without adequate surface treatment, they poorly integrate within the bone and soft tissues, and they are predisposed to bacterial colonization and biofilm formation, this eventually leading to dental implant failure. Throughout time, the surface modification techniques evolved from basic mechanical processing (e.g. machining, grit-blasting, etc.) to physico-chemical and biological modifications (e.g. acid etching, anodization, coating with bioactive agents or biological molecules, etc.) that not only increase the average roughness but also provide an osteoconductive and antibacterial character to the metallic surface thus favoring osseointegration and preventing the development of microorganisms.

Current trends in dental implantology involve the research and clinical application of implants with nanoscaled topography and. Nano roughening of implant surfaces involves the generation of fine irregularities (under 100 nm) via modified versions of the well-established mechanical and morphological techniques (1st and 2nd gen). The incentive is that, compared to conventional micro-rough surfaces, nano-rough ones are a more favorable substrate for the proliferation of osteoblasts and for the absorption of essential molecules involved in osseointegration (e.g. fibronectin, vitronectin, etc.). More than that, they have the ability to withstand bacterial adhesion and biofilm formation, thus preventing peri-implantitis. The advantages are also present from the mechanical point of view; nano-scaled surfaces greatly increasing the bone-to-implant area and consequently providing a higher mechanical stability that contributes to the firm anchorage of the implant in the bone tissue and ensure its long-term success. Since this is a relatively novel approach, only a few commercial implants with nanoscale surface topography modifications are present on the market. Some examples would be Osseo-Speed, produced by grit blasting followed by acid etching; Nanotite, a minimally rough titanium alloy implant modified with calcium phosphates nanoparticles by sol-gel or ion beam-assisted deposition, and HAnano Surface that is coated with nano-hydroxyapatite produced by a wet-chemical process [65]. Additive manufacturing or 3D printing technology is another trend with increasing popularity in the dental implantology and tissue engineering fields. This method generates customized implants with high precision and reproducibility based on a precise 3D model of the patient's teeth and gums. Bioactive agents such as proteins, cells or growth factors can be incorporated in the printing ink, the final result being an implant tailored accordingly for the patient's needs. Nevertheless, there is a long way until 3D printed bioactive dental implants could make a clinical transition, as their biocompatibility, mechanical strength and long-term effects on the surrounding environment are still in the research phase [66].

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