Review

Innovative Coatings of Metallic Alloys Used as Bioactive Surfaces in Implantology: A Review

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Abstract: Metallic implants are widely used in the field of implantology, but there are still problems leading to implant failures due to weak osseointegration, low mechanical strength for the implant, inadequate antibacterial properties, and low patient satisfaction. Implant failure can be caused by bacterial infections and poor osteointegration. To improve the implant functionalization, many researchers focus on surface modifications to prepare the proper physical and chemical conditions able to increase biocompatibility and osteointegration between implant and bone. Improving the antibacterial performance is also a key factor to avoid the inflammation in the human body. This paper is a brief review for the types of coatings used to increase osseointegration and biocompatibility for the successful use of metal alloys in the field of implantology.

Keywords: metallic implants; orthopedic implants; modified surfaces; osseointegration; bone fixation; antibacterial properties; active surfaces; coating performance

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1. Introduction

Inserting implants into living organisms must be carried out in accordance with the natural conditions of living systems; considering that the functionality of the human body is achieved through the normal activity of each physiological system, any organ dysfunction thus is transmitted to the whole living system [1]. Implants can partially or totally replace a damaged element of the body under the conditions of their acceptance by the host environment [2,3]. Among the metallic materials approved for use in medical practice (orthopedics and dentistry), the most frequently used are: stainless steels with small amounts of carbon (316L), Co-Cr alloys, such as Co-Cr-Ni-Mo, precious metal alloys, Ti and its alloys (TiAlV, TiAlVMoFe, and TiAlZr), and biodegradable alloys [4]. Improvement in the long-term utilization of implantable materials is achieved by modifying its surface exposed to physiological and biological environments [5]. In numerous studies, it has been observed that metallic biomaterials undergo a series of corrosion reactions in human body fluids. These reactions result in release of metallic ions, which are toxic at high concentrations. Metal implants have different compositions and various structures than human bone, thus, the healing process takes longer as the bone/implant interface forms more slowly [6]. Along with heat treatments, laser treatments are also employed for covering the surfaces of metal implants with thin layers; these are sometimes structured at micro- and nanolevel obtained by more sophisticated or simpler chemical and electrochemical techniques that are overall more efficient than the bare metal surface. The criteria for the inclusion of biocompatible materials in international standards for the selection of implantable materials for prostheses are based on their biocompatibility [7] and are as follows:

- Chemical and electrochemical criteria: the implant material in human tissue must be inert and must not suffer corrosion (local or general) in relation to mechanical, chemical, and bacteriological stresses.
- The biological criterion is that the implant or particles on the implant surface should not release ions, atoms, or chemical compounds that have allergic, toxic, or carcinogenic effect.
- The mechanical criterion imposes the limits of the performance of resistance to fatigue to mechanical demands such as those to which the human body is subjected during life.

Respecting these criteria, the fields of use of metal implants are wide ranging, i.e., from pumps, implant and artificial valves, to artificial joints.

In 1958, a Swiss company introduced a set of instruments and implants using Cr-Ni-Mo stainless steel as an implant material, and later, Branemark performed the osseointegration of Ti [8]. The advantages of the qualities offered by Ti and its alloys allowed the extension of their use [9], but the main disadvantage related to price still limits this extension. In this situation, the investigation of Co-Cr-Mo alloys, with improved compositions and/or surfaces covered with layers with superior performance for applications in orthopedics, dentistry, and stent materials, remains an important option in research with not only scientific but also social and economic motivations for applications in orthopedics and dentistry as well as for stent materials [10,11].

The properties and operating behavior of alloys in the Co-Cr-Mo system for implantology are influenced by a few factors, including the composition and type of technology used to obtain finished parts, processing, finishing, polishing, and possibly coating with additional ceramic or polymeric layers [12].

Regarding the influence of the composition, Co increases the modulus of elasticity, mechanical strength, and hardness of the alloy and ensures the fluidity of the molten metal. Cr improves corrosion resistance by passivating the surface due to the formation of stable oxides (Cr_2O_3) and promotes the formation of carbides. Mo influences the physical properties, increases the hardness [13], and decreases the ductility of the alloys. It also plays a role in finishing the microstructure by reducing the size of crystalline grains [14].

Mn has a positive effect on mechanical properties and increases the ability of Cr to absorb nitrogen.

The biocompatibility of these alloys is a consequence of the presence of the oxide surface layer. In physiological and biological environments, the physical and chemical properties and interface processes of metal implants are determined by this layer of oxides and not by the metal on which it is formed [15]. The first interaction on implant exposure in tissues is of great importance in the clinical success of implant integration. Research on the microscopic structure of tissues (histological information) demonstrates that tissue-implant interactions take place between oxides on the surface of the metal implant and tissue, and not between the metal surface and tissue [16].

To increase and improve the mechanical, chemical, and biological (biocompatibility, antimicrobial, and drug release) performances of metallic implants, a multitude of coatings have been proposed and investigated [17]. Functional coatings such as calcium phosphate coatings [2], titanium oxides [18], composite coatings [19], multilayer coatings [20,21], polymeric coatings [22], or antibacterial coatings [23] were used by surface modification techniques. In this review, the purpose of developing these types of coatings and the recent progress made on this subject is of interest, because the creation of bioactive surfaces is the mandatory condition for osseointegration of implants in tissue [24].

In this review, we recapitulate the main types of coatings on metal implants existing in the literature that are used to increase the implant biocompatibility, to obtain osseointegration, and to obtain a good antibacterial activity. The main categories of coatings mentioned in this review as well as some advantages and disadvantages are summarized in Table 1.

Table 1. Coating Types and Their Properties.

Coatings	Properties (Advantages and Disadvantages)
Hydroxyapatite and calcium phosphate	<ul style="list-style-type: none"> - Very good osteointegration; - Good bioactivity and biodegradability; - Weak mechanical properties; - Used as bone graft materials; - Chemical and mechanical properties such as the major inorganic Component of bone; - High solubility and bioresorbability; - Promotes cell growth and bone growth on the implant surface;
TiO ₂ and valve metal oxides	<ul style="list-style-type: none"> - Promote osteointegration; - Resistant to corrosion; - Does not show osteoconductivity; - If it is thick and dense, then it shows biocompatibility; - Can absorb Ca²⁺ ions and phosphate groups forming at the bone–implant interface—the nucleation sites for bone-like apatite (carbonated hydroxyapatite); - Favors the adsorption of proteins; - Hardness for coating is 5.5–6.6 GPa, modulus of elasticity of 259 GPa; - Increase bioactivation;
Composite (metal oxide formed on the surface natively with ceramics: ZrO ₂ , TiN, TiO ₂ , SiO ₂ , and SiC; various thin multicomponent coatings)	<ul style="list-style-type: none"> - High strength; - Excellent fatigue and tensile strength; - Superior corrosion and wear resistance; - Good biocompatibility and bioactivity; - Hardness between 30 and 39 GPa; - Elastic modulus of 220 GPa; - Coefficient of friction between 0.11 and 0.19; - Excellent biocompatibility; - High adhesion to the substrate; - Strength and mechanical strength; - Elastic modulus and reduced wear and friction;
Multilayer	<ul style="list-style-type: none"> - High adhesion resistance; - Adhesive strength higher than 100 N; - Promote the growth of a new bone and the adjacent coating; - Increase in binding strength from 14.2 ± 3.1 to 23.1 ± 3.4 MPa; - Good biocompatibility; - Superior biocompatibility;
Antibacterial (loaded with antibiotics, loaded with non-antibiotic organic bactericides, surface doped with inorganic bactericides, and adhesion resistance surfaces)	<ul style="list-style-type: none"> - Protect the host's defense system; - Achieve long-term implant fixation; - Minimize implant-associated infection;
Polymeric	<ul style="list-style-type: none"> - Biocompatible; - Facilitate the biological fixation of the implant in the human body; - Promote osteointegration; - Promote cell proliferation; - Facilitate cell proliferation, tissue repair and growth, and the delivery of biomolecules; - Biodegradable.

2. Surface Modification: Coatings to Increase Bioactivity and Biocompatibility

2.1. Coatings with Hydroxyapatite and Calcium Phosphate

Osteointegration represents a continuous, structural, functional, and coexistent symbiotic relationship between differential and appropriately remodeled biological tissues and components obtained synthetically from materials (implants) with specific clinical functions accepted by the body without initiating any rejection mechanism. In practice, osseointegration represents the process or mechanism of anchoring a non-vital component (implant) in a bone from a living organism that remains for a long time unchanged even under mechanical stress. An implant is considered osseointegrated when there is no relative progressive displacement between the implant and the bone with which is in direct contact.

Bioactivity is the characteristic of a biomaterial (used in making an implant) to form a connection with living adjacent tissues [25]. A layer of bioactive material must meet two conditions: to develop a positive biological interaction and induce the growth of bone tissue in the periphery, in order to achieve a bone–implant connection. The biological activity of the bioactive material [26] should be moderate, since too rapid growth of bone tissue causes a chaotic development of bone components, with the formation of cavities and structures that are not properly interconnected. In the long run, appearance of infection and resistance to the development of bone in some areas is possible.

The integration of an implant with a bioactive surface in the bone [27] is realized through multiple interfaces due to several cationic species.

The mechanism of osseointegration is presented schematically in Figure 1 for a bioinert and a bioactive implant. Immediately after surgery, the implant surface is surrounded by blood. Healing occurs for several weeks after the intervention. During this time, new bone is formed from the remaining hematoma via the formation of callus. These processes happen in the presence of both implant types. However, in the case of the bioactive implant, the additional ions present on the surface accelerate and favor the formation of more and denser bone tissue. Additionally, the phosphate coating produces a rougher implant surface that increases the surface contact with the bone.

Figure 1. Schematic representation of implant osseointegration for bioinert and bioactive implants.

Interfaces rich in calcium phosphates, over time and under certain chemical and temperature conditions in the environment, can turn into hydroxyapatite, responsible for attracting cells together thus performing bone reconstruction [28]. Calcium phosphate-based materials have become interesting for practice as potential candidates for the manufacture of implants in the human body. Otherwise, they are already used in dentistry for dental crowns, on account of special aesthetic appearance, high compressive strength, and no chemical reactions in contact with human body biofluids.

Calcium phosphates have long been used to make artificial bones, and recently, with the development of new manufacturing techniques, are used for the fabrication of whole implants or only as solid or porous coatings of metallic implants [29].

Calcium phosphates consist of three main chemical components: the cations calcium (Ca^{2+}), phosphorus (P^{5+}), and oxygen (O^{2-}), as part of phosphate anions. Due to the

great diversity of combinations of oxides, calcium and phosphate (both in the presence or absence of water), calcium phosphate compounds are distinguished in terms of phosphate anion groups: ortho- (PO_4^{3-}), meta- (PO_3^-), pyro- ($\text{P}_2\text{O}_7^{4-}$), and poly- ($(\text{PO}_3)_n^{n-}$) [29]. Dorozhkin et al. in 2007 [30] discusses about calcium orthophosphates, as they represent the major component of all calcified tissues in humans.

Referring to the atomic lattice, the calcium orthophosphate crystal contains PO_4 groups that restore the stability of the structure. According to LeGeros in 1991 [31] and Wopenka and Pasteris in 2005 [32], calcium orthophosphate crystals are easily soluble in water and easily dissolve in acids but are insoluble in alkaline solutions. Calcium orthophosphates are a major inorganic constituent of the human skeleton, and they are also found in deer antlers and in some species of shells as well as in pathological forms (urinary stones, atherosclerotic lesions, or calcifications). In the biological system, they are present in the weakly crystallized state with hydroxyapatite substituted with Na^+ , Mg^{2+} , and non-stoichiometric carbonate-substituted ions, known as biological apatite. Calcium orthophosphate-based bioceramics have long been used clinically. Because to their weak mechanical properties, they are limited to the non-bearing component of the skeleton.

Eleven calcium orthophosphates are known to have different Ca/P molar ratios, from 0.5 to 2.0. The main parameters that influence the properties of calcium orthophosphates are the molar ratio Ca/P, alkalinity or acidity, and their solubility in different solvents. The ratio between Ca and P also depends on the pH of the solution. Acidity and solubility in water increase inversely with the Ca/P molar ratio [33].

Because of their similarity with biological apatite from chemical composition point of view, calcium orthophosphates such as hydroxyapatite (HA), amorphous calcium phosphate (ACP), tricalcium phosphate (TCP), and octocalcium phosphate (OCP) have been used as bone graft materials [34,35].

Synthetically sintered hydroxyapatite has chemical and mechanical properties similar to the major inorganic component of bone and can bind strongly to bone [36,37].

The higher solubility of calcium orthophosphates facilitates the stimulation of bone regeneration with several Ca and P ions.

β -TCP and α -TCP are the most popular materials for making bone scaffolds that are designed to support bone regeneration [38], because they have higher bioresorbability than HA due to their higher solubility in physiological fluid. OCP has a structure similar to HA and is a precursor of HA [38].

Unlike HA, OCP possesses osteoinductivity and the ability to generate bone tissue [39,40].

Suzuki et al. compared in vivo performance for OCP and HA by implanting these materials in a bone defect belonging to a rat, a study that was performed for 6 weeks [40].

After 6 weeks of implantation, it was found that the OCP was completely biodegraded, much more than HA or TCP. Implants made of OCP showed a maximum amount of bone tissue regeneration, which is extremely positive in its use not only as a source of calcium and phosphorus but also as a model for bone formation. Research into the clinical application of OCP is not fully known or studied, and therefore, many potential problems, such as from synthesis of OCP to bulk materials technology from OCP, need to be investigated. Despite the good bioactivity qualities of these families of calcium orthophosphates, the mechanical properties of those materials are not suitable for the supporting components of skeletons.

HA is mainly used as a coating material for implants, due to its lower solubility and higher crystallinity than other calcium orthophosphates.

HA can remain on the implant for a longer time and form a relatively firm bond with the substrate. After covering a metal implant with HA, it took only 20 days for a patient to recover from immobilization, to be able to move [41] and it took 100 days of recovery from immobilization for the empty metal implant [42].

Furlong and Osborn were the first research group to report the use of HA-coated implants for clinical trials [43].

According to a 10-year study, Yang et al. showed that HA coatings improved the clinical effect, and the implantation failure rate was less than 2% [44].

In the last 30 years, the application of HA on the surface of metal implants by PLD (plasma deposition) technique has determined their successful use in the field of dentistry and orthopedics.

During bone remodeling, the degradation of the HA sheath was observed due to the presence of osteoclastic activity [45,46].

During the bone remodeling process, the HA coating was replaced with bone and the result was the loss of this HA coating.

However, there is still much controversy regarding the coverage of dental and orthopedic implants with HA.

Research on HA and Ca and P-based coatings has focused on both the coating itself and the optimization of this process in order to obtain a maximum tissue response [47,48].

Regarding HA coatings on implants, the Food and Drug Administration (FDA) and the International Organization for Standardization (ISO) have established guidelines for minimum requirements for HA coatings [44,47].

HA and Ca phosphates, obtained by different methods, have thicknesses that can vary from submicron to several hundred microns; thickness being an important parameter in terms of the stability over time of the implant, the mechanical properties of the coatings must be considered. Ca phosphates have poor mechanical strength when the layer is too thick and mechanical fractures can occur. If the coating is too thin, the Ca phosphate layer has a risk of dissolving and then the bioactivity of the implant is affected. Although HA has the second lowest solubility among Ca orthophosphates, it has been reported that it could be resorbed by approximately 15–30 μm annually [49]. Several aspects related to mechanical strength, bioactivity, chemical stability, and long-term fixation were considered to obtain the optimal properties of HA and Ca phosphate coatings for implants (Table 2).

Table 2. HA Coating Requirements [44].

Property	Specification
Thickness	5–70 μm
Crystallinity	62% minimum
Phase purity	95% minimum
Ca/P ratio	1.67–1.76
Density	2.98 g/cm^3
Heavy metals	<50 ppm
Tensile strength	>50.8 MPa
Shear strength	>22 MPa
Abrasion	Mass loss < 65 mg at 100 cycles

Another important parameter to consider is the adhesion of coatings with HA and Ca phosphates. In order to have a good reliability of the coating process, the adhesion that must be satisfactory to the adjacent substrate must be taken into account. Hence, to evaluate the adhesive performance, tensile adhesion test (TAT), according to ASTM C633, was performed. It has been reported in the literature that the adhesion strength of HA coatings obtained by plasma spraying is in the range of 20–30 MPa [50–52], although, according to TAT, in industry, a typical resistance to adhesion is in the range of 10–15 MPa. A few literature studies have addressed this topic. The disadvantage of the TAT method is that the mechanical damage of the coating occurs inside the thick coatings and not at the interface between the coating and the substrate. The defects appear unevenly distributed on the surface and a local defect appears in the layer.

For very thin or very porous coatings, the adhesive used to anchor the stretching devices can penetrate the layer and adhere directly to the substrate. For this reason, the measured adherence is not a real one [53]. Other methods for determining adhesion strength at the interface between implant and HA coating, such as determining fracture resistance [52] and using laser for shock adhesion tests (LASAT), have been proposed [53].

Another important factor when talking about HA coatings is related to their crystallinity, which influences both stability and bioactivity [54]. It is recommended, to maintain the adhesion resistance between the implant and the coating, that structures without resorption or with a reduced one that usually have high crystallinity be used for clinical trials. This statement contradicts the fact that the ideal interface between the coating and the surrounding tissue must match the replaced tissue. It is considered that the crystallinity of the HA coating is the most important factor for the bioactivity of the HA coating. The coating should have low crystallinity but may weaken the bond strength between layer and substrate in vivo. The initial processes that take place on the surface covered with HA after implantation involve the dissolution of the coating. It is recommended that these coatings should be less crystalline and thus more resorbable to promote the bone growth [55].

Tsui et al. concluded that the ideal HA coating should have a dense structure, with strong cohesion strength, low porosity, substrate adhesion, high degree of crystallinity, high chemical purity, and phase stability [52]. However, so far, there are no techniques to determine the perfect coatings, without pores, without cracks, or without secondary phases. All these “defects” can cause problems related to the durability of the implant and the dissolution of the coating in the physiological fluid. However, in 11-year clinical trials, satisfactory results have been reported for elderly patients (approximately, 53 years) who have undergone primary arthroplasty using HA-coated implants [45].

2.2. Coatings with TiO₂

Ti oxides are used to promote osteointegration [56] and are classified into rutile, anatase, and brookite if their crystalline structure is considered. At low temperatures, the brookite turns into rutile. For this reason, only anatase and rutile are of interest. Ti and its alloys oxidize easily in air and form a layer of TiO₂ on the surface of the metal. This layer is called native, has thicknesses between 3 and 7 nm, and contains the amorphous phase. Native oxide provides very good chemical stability manifested by increased corrosion resistance [57]. The concentration ratio between Ti and O gradually varies from 1 to 2 [58]. Ti and its alloys are stable and resistant to corrosion; however, the literature has considered the amount of Ti ions that can be released in the tissues adjacent to the metal implant used [59]. The release of Ti ions into tissues indicates that its corrosion has occurred in vivo. Native TiO₂ is bioinert and cannot promote a direct link with living bone, which implies that TiO₂ does not show osteoconductivity and osseointegration. To increase biocompatibility, the TiO₂ layer needs to be thick and dense.

TiO₂ has a molecule composed of a positive Ti⁺ ion and two O^{2−} negative ions. When Ti is in contact with electrolyte solutions (body fluids, saliva, and plasma), OH[−] can easily bind to the Ti cation in the TiO₂ and Ti-OH groups. Acidic or basic Ti-OH groups can form on the surface of Ti [60].

The pH of the electrolyte influences the charge on the Ti surface. When the pH is less than 4, the Ti-OH groups will become [Ti-OH₂]⁺ and will determine the positive charge of the surface.

For pH values above 9, Ti-OH yields a proton and forms the [Ti-OH][−] anion, and thus, the Ti surface is negatively charged. When the pH is between 4 and 9, Ti-OH is observed simultaneously in oxide, acid hydroxides, as well as basic hydroxides forms.

The isoelectric point (IEP) of TiO_2 is in the narrow range of pH 5–6. It indicates the pH value of a solution where the net charge on the surface of Ti is zero.

Negatively charged surfaces can attract cations such as Ca^{2+} , Na^+ , and Mg^{2+} , whereas H_2PO_4^- or HPO_4^{2-} anions are attracted to the positively charged surface.

TiO_2 can absorb Ca^{2+} ions and phosphate groups forming at the bone–implant interface, the nucleation sites for bone-like apatite (carbonated hydroxyapatite). This layer of apatite can trigger cell growth and bone growth on the implant surface, resulting in a good bone fixation (Figure 2). For these reasons, the modification of the TiO_2 layer becomes a priority in the sense of increasing the biocompatibility and osseointegration of the Ti or Ti alloys implant materials.

Figure 2. Possible mechanism for the initial adsorption of macromolecules on Ti implants. TiO_2 has an overall negative charge at the interface with the physiological fluids. Ca attracts on the surface, and further, it binds to the macromolecules on the surface of the implant.

The TiO_2 layer favors the adsorption of proteins or other electrically charged macromolecules. Protein attachment occurs immediately after implantation and is important for subsequent cell growth on the implant surface. Sunny and Sharma showed that the TiO_2 layer obtained by anodic oxidation from a few nanometers to 200 nm showed a 7-fold increase in the albumin/fibrinogen protein absorption ratio [61]. Huang et al. reported that there is a 1.5-fold increase in coagulation time when the thickness of the TiO_2 layer increases from 10 to 250 nm through a process of thermal oxidation [62]. Using a TiO_2 -coated Ti implant, inserted in a dog, Yang et al. showed that no thrombi formed on the surface and coagulation took place on pyrolytic isotropic carbon (LTI-carbon) [63].

TiO_2 is also used to change mechanical properties, wear resistance, and corrosion resistance [64]. In terms of mechanical properties, the suggested hardness for coating is 5.5–6.6 GPa [65]. Various mechanical nano-indentation tests were performed to cover Ti with oxide at 600 °C obtaining a modulus of elasticity of 259 GPa and a hardness of 14 GPa. Mandl et al. showed an increase in the average lifetime for an alloy based on Ti and Ni in case of its oxidation at 250 °C [66]. Chiu et al. approached a coating of a NiTi alloy by sol-gel technique, which determined the increase in corrosion resistance in Hank's solution compared to the substrate. [67].

Rohanizadeh et al. analyzed the production of TiO_2 for in vivo deposition of hydroxyapatite [68].

There are four methods for making the TiO_2 layer on Ti [69]:

1. heat treatment at 750 °C for 90 min.
2. oxidation in 30% H_2O_2 combined with subsequent heat treatment.
3. the method of coating by soaking/centrifuging with a rutile/gelatin.
4. anatase/gelatin suspensions.

The bioactivity of the substrates obtained after using the 4 types of treatment was followed by immersing the samples in calcium phosphate solution for 2 weeks.

It was observed that the percentage of the area covered with hydroxyapatite in ascending order is: (4) submerged in anatase suspension > (3) submerged in rutile suspension > (2) treated with H_2O_2 > (1) heat treated > untreated [69].

The structure of the anatase and the rearrangement of Ti-OH can increase the attraction of calcium and phosphate ions by Ti-OH groups.

Uchida et al. reported that the network plane (001) of apatite fits crystallographically with the plane (110) of anatase, rather than with (101) the plane of the rutile [70]. The best crystallographic phase of anatase and apatite results from the hydrogen bond that is formed between the hydroxyl group of apatite and the oxygen of anatase. A smaller number of -OH groups were obtained on the heat-treated Ti surface. The adhesion resistance of apatite on the substrate of the treated samples is in ascending order as follows: (2) H_2O_2 treated > (3) soaked in rutile suspension > (1) heat treated > (4) soaked anatase suspension > untreated [69].

The excellent adhesion of the H_2O_2 -treated samples is probably due to the presence of cracks. Such cracks provide the places of mechanical blockage between the apatite crystals and the Ti substrate, resulting in the adhesion of the apatite to the substrate.

Nanostructured TiO_2 is the favorite subject lately for many researcher groups [71,72] due to the advantage of obtaining large specific area, to increase bioactivation [73–76].

2.3. Composite Coatings

To be used as implants, the materials must have high strength, excellent fatigue and tensile strength, superior corrosion and wear resistance, good biocompatibility, and bioactivity. Even if the metallic materials used in implantology can meet some of the mechanical requirements, their interfacial connection with the host tissue when they are introduced into the human body is weak, which can compromise the long-term fixation of the implant. As a result, the researchers' interests focused on obtaining biocompatible and bioactive multifunctional composites. Over the years, a wide variety of composite coatings have been obtained to increase the performance of stainless steel [77,78] or metal alloys used in implantology [19,79,80].

As a result, it was considered to mix the metal oxide formed on the surface natively with ceramics, namely ZrO_2 , TiN, TiO_2 , SiO_2 , and SiC. The best known and used ceramic is zirconia (ZrO_2), which began to be investigated in the late 1960s. Due to its excellent wear resistance, ZrO_2 was used as a material for ball heads in artificial hip joints [81]. Composites with matte wear resistance, corrosion resistance, and good biocompatibility were obtained, which were used as applications in dental prosthesis, as components of the heart valve or for replacing the hip joint [82]. Obtaining composite coatings based on TiN and TiO_2 has been shown to have excellent hemocompatibility [57].

Composite coatings formed of TiO_2 and SiO_2 can favor the formation of apatite in simulated body fluid (SBF) due to a negative charge on the surface owing to pH of body fluid [83].

Bolz and Schaldach have shown that, using amorphous SiC coatings, the biocompatibility of artificial heart valves has increased considerably [84]. The aim is to obtain composite coatings that offer the possibility of using them for a wide variety of biomedical applications.

Shtansky et al. followed various thin multicomponent coatings based on Ti-Ca-C-O-(N), Ti-Zr-C-O-(N), and Ti-Nb-C-(N) [85]. Composites composed of $TiC_{0.5} + CaO$, $TiC_{0.5} + ZrO_2$, and $TiC_{0.5} + Nb_2C$ were obtained.

The composite coatings Ti-Ca-C-O-(N), Ti-Zr-C-O-(N), and Ti-Nb-C-(N) showed a hardness between 30 and 39 GPa, the elastic modulus of 220 GPa. The friction coefficients were evaluated by the friction tests. The best coverage was the one with the composition Ti-Ca-C-O-(N), which had reduced coefficient of friction from 0.29 to 0.23 and showed no wear on the total sliding distance of 1000 m after 29,000 cycles. The Ti-Ca-C-O-(N) coatings did not show any wear generated until the completion of the tests at 10,000 cycles, and

the coefficient of friction was measured from 0.16 to 0.22. The coefficient of friction of the Ti-Nb-C-(N) coatings was from 0.11 to 0.19.

These composite coatings showed improved mechanical properties and wear resistance. Both in vitro and in vivo biocompatibility were evaluated, and after 16 weeks of subcutaneous implantation, the evaluation of the seeded cell population on the Teflon plates coated with Ti-Ca-C-O-(N) and Ti-Zr-C-O-(N) layers revealed that these coatings were very biocompatible and without any inflammatory reactions in mice.

Composites containing Ti-Nb-C-(N) layers with epithelial cells and fibroblasts cultured on them showed disturbed actin cytoskeleton. As a result, Ti-Ca-C-O-(N) and Ti-Zr-C-O-(N) are the two promising candidates of tribological coatings in which they can be applied to artificial joints and teeth.

In general, multicomponent Ti-based coatings with adjustable composition and structure are of great importance because they offer excellent biocompatibility, high adhesion to the substrate, mechanical strength, and elastic modulus and reduced wear and friction [86].

An extremely important factor related to the long-term durability of implants is the resistance to the interfacial connection between the coating and the substrate. The metal phase can be introduced in the process of depositing the composite coating. This metal phase is an intermediate coating or a second phase (continuous or dispersed) in the HA matrix, to strengthen the interfacial bond. Zheng et al. demonstrated that the inclusion of Ti in HA could result in increased adhesion resistance of plasma coatings [87].

Our research group elaborated a complex ceramic coating on Ti plates, containing TiO₂ nanotubes, carboxylate multiwalled carbon nanotubes (MWCNTs-COOH), and hydroxyapatite, by electrodeposition. The research led to a new hybrid material, which can be used in biomedical applications, with improved characteristics. MWCNTs induced an increase in microhardness and the hemolytic index, indicating a better biological adhesion, and further, the osteoblasts response confirmed these observations [88–90].

The researchers' interest was extended to obtain nanocomposite materials, with new and high-performance properties, composed of polymers doped with various nanoparticles required in dentistry, e.g., PMMA doped with TiO₂ nanoparticles [91].

2.4. Multilayer Coatings

To be successful in the long run, the coatings of metal implants must have not only a good biocompatibility but also a high adhesion resistance. Dual [88] or multilayer coatings are used that had promising results in terms of biocompatibility. The double layer of HA/ZrO₂ showed a bond strength of 39.8 ± 6.2 MPa ($p < 0.05$), while for HA, a single layer was 28.1 ± 4.3 MPa [92]. Narayan introduced between the HA-metal coating a layer of DLC interface obtained by the pulsed laser method at room temperature, thus obtaining HA adhesion to metal alloys [93]. Sun determined that the adhesive strength of the TiN/ZrO₂ multilayer coating was rated to be greater than 100 N.

To increase the bonding resistance of the coating to the metal substrate, the grading of the composition of the material at the interface is used. It is known that the existence of defects, cracks, and discontinuities at the interface between the coating substrate comes from the difference in thermal expansion coefficients (CTE) for these materials. A graduated intermixed layer with CTE between the CTEs of the substrate and the CTE of the coating will be introduced to reduce the stresses induced due to the mismatch of the CTEs. Gradual coatings are obtained that do not give rise to so many fractures. The result is a stronger adhesion, the outer layer of the coating being created to promote the growth of a new bone and the adjacent coating favoring a high resistance to binding.

A buffer layer is formed between these two layers (from the surface and adjacent), which possess intermediate properties. Chen et al. obtained multilayer coatings of hydroxyapatite/titanium composed of an underlying Ti-bonded layer, an intermix layer and an outer HA layer on Ti alloys, using plasma spraying [94]. By varying the different deposition parameters, a strict control was obtained from the composition point of view

for the multilayer coating. They have a remarkable increase in binding strength from 14.2 ± 3.1 to 23.1 ± 3.4 MPa.

After 1 million cycles of cyclic fatigue of the multilayer coating, the adhesive strength of the graded coatings after fatigue testing (≈ 22 MPa) was not abruptly deteriorated compared to the graded coatings before fatigue testing. However, monolayer coatings with HA decreased to 10.9 MPa.

Inagaki et al. obtained HA/Ti composite coatings with different compositions, synthesized by plasma deposition, by changing the RF power during laser deposition determining that the breaking strength can be increased by increasing the plasma strength due to the increase in the coating density [95].

In vitro studies have shown improved biocompatibility of multilayer coatings. Braic et al. performed cell response studies on multilayer Ti/TiAlN coating. Research has revealed good biocompatibility through cell density, cell morphology, and cell viability [96]. It has been shown that a larger number of cells attach to the Ti/ZrO₂ surface than to the bare surface [92] and they also successfully attach and spread on the surface of the HA/multilayer coating, confirming the previous result that HA/ZrO₂ possesses superior biocompatibility.

2.5. Antibacterial Coatings

Implant infection due to bacteria is a serious problem that can lead to several side effects and even death. However, no matter how well controlled the surgical procedures are, the bacteria can also be seen in traumatic surgery. The presence of bacteria on the surface of the implant can cause the formation of biofilms that protect the underlying bacteria from the host's defense system and antibacterial substances.

The metal implants used to replace the hard tissues were fixed with PMMA cement loaded with antibiotics. However, cemented fixations cause undesired effects and osteoconductive apatite layers have been successfully applied to the implant to achieve long-term implant fixation.

The incidence of infection in orthopedic surgeries is about 10% for fracture fixators and 85% for external fixators.

Although it has been reported that only 1–2% is the rate of infection observed in total hip arthroplasties, the actual figures are high and have increased with an aging population.

Antibacterial coatings have been widely researched to minimize implant-associated infection. The simplest method to prevent infection is to avoid the adhesion of bacteria and their subsequent colonization.

To evaluate the antibacterial properties for implantable alloys, the use of Gram-negative pathogenic bacteria such as *Pseudomonas aeruginosa* and Gram-positive *Staphylococcus aureus* was required. The methods used were aimed at determining the degree of inhibition, determining the colony forming units, CFU, and the halo method [71,88,97,98]. HA coatings or TiO₂ coatings on Ti alloys put in evidence that the inhibition rate is higher for coatings compared with uncovered metallic alloys.

Various research in the field of antibacterial coatings have been carried out on a large scale [99]. An advantage of these coatings is the provision of local therapeutic agent. Bacterial killing agents, such as antibiotics [100], phenols [101], and heavy metals [102–104], were incorporated in the antibacterial coatings by spraying or soaking and capturing the hydrogel [105,106]. Chemical changes in coatings have been investigated to give the medical device the ability to kill bacteria on contact [107].

Osteoconductive materials, such as apatite, are preferable carrier materials because they can improve the bioactivity of implants. Usually, antibacterial coatings are grouped into 4 classes: coatings loaded with antibiotics, coatings loaded with non-antibiotic organic bactericides, surface doped with inorganic bactericides, and coatings with adhesion resistance. Depending on the nature of the bacterial habitat, coatings can be defined as either passive or active.

Some of the coatings require a material containing antibacterial agents that degrade in a controllable manner to deliver antibiotics in a reasonable dose. Antibacterial coatings are grouped into 4 categories: antibiotic-laden coatings, non-antibiotic organic bactericide-laden coatings, surface doped with inorganic bactericides, and adhesion-resistant coatings. Coatings can be defined as either passive or active. A selection of antibacterial coatings is presented in Figure 3. Antibiotic coatings are considered killing coatings. Antibiotics interfere with the metabolism of bacteria. Non-antibiotic organic bactericides are usually enzymes that can bind with the membrane of the bacteria, thus destroying it further. Biofilms are also destroyed with this method. Inorganic bactericide particles include a variety of usually metallic nanoparticles (e.g., Ag and Cu) that produce reactive oxygen species (ROS). Surface architecture can kill bacteria by physically piercing their membranes. Nonkilling antibacterial surfaces include coatings of electrostatic repellants that interfere with the charge of the surface of the bacteria and low surface energy coatings that inhibit bacterial adhesion.

Figure 3. Schematic representation of some antibacterial coatings.

The incorporation of silver into the surface of the metal implant has been investigated for many years [108–110]. Instead of releasing bactericidal agents into tissues, some coatings can inhibit bacterial adhesion. The presence of a silver-based coating destroys the ability of bacteria to multiply. Silver nanoparticles bind to the bacterial cell wall and cell membrane [98,111–113].

It has failed to find widespread use due to the danger and unwanted toxicity problems induced by silver, so the amount of silver introduced into the body must be minimized using nanoparticles to maximize the active surface but control the amount of Ag introduced into the body [114]. One of the advantages of antibacterial silver coatings is that it is unlikely to induce resistance to bacteria. Bacterial resistance to silver but also to antibiotics has been reported in a clinical case in which bacteria coexisted with silver particles [115].

The development of resistant bacterial strains due to improper and excessive use of antibiotics is the main driving force for research into the development of new antibacterial substances.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a bacterium that causes infections that are difficult to cure.

The efficacy of a peptide on MRSA killing in a rabbit species has been shown [116].

After carrying out some studies to increase the wettability of the Ti-6Al-4V surface, Ti-6Al-4V was obtained by UV irradiation treatment. A study determined the amount of reduced initial bacterial adhesion and the number of bacteria retained on the surface after passing through the two air–liquid interfaces [117]. Other antibacterial coatings

release previously incorporated antibacterial substances, such as antibiotics, antiseptics, silver particles, and NO. Although these types of coatings showed antibacterial effects, the release took place only in a limited period, which is sufficient only to prevent early post-surgical infection. The main objective in the manufacture of these types of coatings is how to maintain the concentrations of the released substances at an efficient level, above the minimum inhibitory concentration (MIC) throughout the life of the implant. MIC indicates the minimum concentration of antibiotics dedicated to killing a certain type of bacterial strain.

Novelties have emerged regarding the development of intelligent coatings that provide bactericidal agents only when bacteria are attached to the coating [118,119].

Such passive coatings are highly preferred because they can be introduced inside the body for a relatively long time without local and side effects, while their antibacterial capacity can be maintained [120].

2.6. Polymeric Coatings

The polymer-based coatings are biocompatible and facilitate the biological fixation of the implant in the human body. With the help of these polymer-based coatings, the osseointegration process is facilitated, the possible infections related to the fixation of the metal implant being minimized. Using polymers, the interaction with the cellular material increases, forming a structural support for the formation of new tissue. Using polymeric materials, an increase in the corrosion resistance of biodegradable implants (such as Mg and its alloys) is also obtained [121].

The porous structure created using these types of coatings determines the optimal condition for cell proliferation.

Polymer coatings can be deposited on the surface of implantable materials not only by immersing them in various polymer solutions (dip-coating), by chemical vapor deposition (CVD), by spin-coating, by self-assembled monolayers, and layer-by-layer films but also by chemical grafting obtaining polymer brushes [122], by electrochemical polymerization, and electrophoretic deposition [123].

Some polymers are more commonly used in medicine due to their mechanical properties and their degradation rates (Table 3).

Table 3. Commonly used Polymers and Their Properties.

Polymer	Chemical Formula	Properties	Degradation Rate
PGA—polyglycolide [124]	$C_3H_7O_7P$	Aliphatic polyester, Crystalline, semipermeable	6–12 months
PLLA—polylactic acid [125]	$(C_3H_4O_2)_n$	aliphatic polyester, crystalline, porous; rough looking due to the open-pore structure	>24 months
PLGA—poly(lactic acid-co-glycolic acid) [126]	$C_5H_8O_5$	Semipermeable	6–12 months
PCL—polycaprolactone [127]	$(C_6H_{10}O_2)_n$	Semipermeable, amorphous	<12 months
Collagen [128]	$C_{65}H_{102}N_{18}O_{21}$	Semipermeable	1–9 months

2.6.1. Antifouling Coatings

To attach bacteria to the surface of an implantable material, we must take into account the types of interactions that may be specific or nonspecific. Specific interactions take place through a protein.

The antifouling properties refer to coating of material with polymeric films capable of reducing protein adsorption. The antifouling properties satisfy the following functions: hydrophilicity, ability to form water bonds, and conformational flexibility [129].

The reduction in protein adsorption by antifouling polymers is due to a steric stabilizing force that has two major contributions, a volume component and a blending component. The volume component is highlighted by an elastic response due to decreased entropy when proteins are near the surface, in this case, the loss of freedom of movement of the

polymer chain due to protein adsorption leads to protein repulsion. The blending/mixing component is caused by the reduced validity of the conformation of some segments of the molecule that lead to either compression or non-penetration of the protein chain [130,131].

The polymers used for their weak fooling properties can be hydrophilic or zwitterionic polymers.

PEG as an antifouling polymer or PMMA forms hydrogen bonds with water [132,133].

Zwitterionic polymers are molecules charged with positive and negative electrical charges, neutral from an electrical point of view, which form strong hydrogen bonds with water, giving the antifouling character [134,135].

2.6.2. Polymeric Cations

Various types of cationic polymers destroy bacteria by damaging the cell membrane through a process called lysis, which causes the release of components inside the cell into the solution in which they are present. The adsorption of cationic polymers on the cell surface of the bacterium occurs due to the negative electrical charge of the bacterial membrane, the presence of teichoic acid protein in Gram-positive bacteria, or negatively charged phospholipids in Gram-negative bacteria. The polymer present on the surface of the metallic material used for implantation penetrates the cell membrane, thus, disturbing it [43]. Most cationic polymers contain quaternary ammonium, sulfonium, and phosphonium groups linked to the polymer chain [58,136–139]. In the case of Ti, poly(hexamethylenebiguanadine) [140], pyrrole electropolymerization [141], and poly(ethylene imine) [142,143] were used.

2.6.3. Biodegradable Polymer Coating

Polymer coatings with various inorganic ions can facilitate cell proliferation, tissue repair and growth, and the delivery of biomolecules.

A group of researchers present a layer of polymer that is degraded in the body along with its carrier [144]. Scientists from the Karlsruhe Institute of Technology, the University of Michigan (Ann Arbor, MI, USA), and Northwestern Polytechnic University (Xi'an, China) have synthesized, for the first time, a polymer with biodegradable properties by CVD technique. The team applied the copolymerization of two special types of monomers: paracyclophanes commonly used for this method were combined with cyclic acetal ketones.

The degradation rate can be adjusted for the desired application. Using cell cultures, researchers have already shown that neither the polymer nor its degradation products are toxic [144].

Polymeric hybrid materials can be prepared as “smart” materials, using which functionality can be achieved through physical, chemical, or biological stimuli [145]. Biodegradable polymer coatings can prevent corrosion postimplantation [146,147].

For surface coatings, a wide varieties of biopolymers, such as polyvinylidene fluoride (PVDF), polymethyl methacrylate (PMMA), polypropylene (PP), polydimethylsiloxane (PDMS), polyurethane (PU), polylactic acid (PLA), poly(lactide-co-glycolic) acid (PLGA), polycaprolactone (PCL), and polyethylene (PE), were used; some natural polymers such as collagen and chitosan were also used for various biomedical applications [146,148]. Polymers such as poly(L-lactide-co-trimethylene carbonate) P(L/TMC), poly(L-lactide-co-trimethylene carbonate-glycolide) P(L/TMC/G), and poly(D,L-lactide-glycolide) (PLGA) were used to obtain biodegradable coatings enriched with active substance (ciprofloxacin) formed on Ti6Al7Nb alloy [149], with biodegradation ability and drug-eluting properties as modified Ti implants.

A biodegradable polymer was used as a flexible covering for a breast implant; it contained one or more drugs for delivery at the surgical site, particularly for treating or preventing infection, pain, inflammation, capsular contracture, scarring or other complications associated with breast augmentation or breast reconstruction [150].

In addition, biodegradable polymers were used in dental tissue engineering and regeneration [151], which have replaced traditional non-degradable materials in maxillo-

facial surgery, with application in bone regeneration and periodontal care, due to their ability to break down and be absorbed by the body without producing harmful degradation products, along with their great potential for controlled drug delivery, wound management, dental restorations, and tissue engineering.

3. Conclusions

In the last four to five decades, extraordinary progress has been made regarding the modification of metal surfaces for using them in implantology, considering the acceleration of osseointegration. The use of coatings to increase biocompatibility is extremely varied while achieving additional antibacterial effects. Coating treatments could have beneficial effects in terms of not only avoiding inflammation of the tissues adjacent to the implant and reducing the risk of infection but also improving the mechanical performance of the metal implant. The transition to nanocoatings has led to a progression of coatings by increasing the specific surface area and limiting any cytotoxic effects caused by certain metal ions. The topic of nanostructured coatings is a growing field that will further discover many benefits in restorative works for many decades.

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