



Customisation of PVD coatings for biomedical devices[☆]

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ABSTRACT

In recent years, physical vapor deposition (PVD) has emerged as a powerful technique for surface modification, offering a wide range of possibilities to improve the properties of medical devices. This review explores the fundamentals and versatility of PVD coatings in biomedical applications, highlighting their potential to revolutionise the field. Biocompatibility is crucial in successfully integrating medical devices with the human body. The precise modification of thin films to improve biocompatibility, reduce adverse reactions, and promote better tissue integration is discussed. Osseointegration, another critical factor for the success of orthopaedic and dental implants, is also explored in the context of magnetron sputtering coatings. The ability of these coatings to provide a bioactive surface that promotes bone cell adhesion and growth is analyzed, shedding light on the potential of tailor-made coatings in improving implant success rates. Infections associated with medical devices pose a significant challenge in healthcare settings. Strategies, such as the incorporation of antimicrobial agents and surface modifications, are discussed, highlighting the potential of this waste-zero technique in effectively addressing this critical issue. Overall, the versatility, coupled with the ability to enhance corrosion resistance, mechanical properties, tribological performance, biocompatibility, osseointegration, and antimicrobial activity, makes PVD coatings highly promising for improving the performance and functionality of medical devices. Continued research and development in this field will undoubtedly lead to further advancements in PVD coatings, revolutionising the biomedical industry.

1. Introduction

In recent years, medical devices (MDs) have become increasingly critical in addressing the complex challenges faced by modern healthcare systems. With an aging global population seeking to maintain active lifestyles, the demand for advanced medical technologies, such as joint replacements, stents, and catheters, continues to rise [1–3]. These devices play a vital role in enhancing patient outcomes; however, their development and utilization present a host of challenges. Among these are the growing prevalence of bacterial resistance, which reduces the effectiveness of conventional antibiotics, and the need for materials with enhanced biocompatibility, extended bioactivity lifetimes, and robust resistance to infections [4–6].

Implantable devices used in orthopaedic, dental, and cardiovascular

applications are predominantly made from metals, polymers, and ceramics, with metals such as titanium (Ti) alloys, stainless steel (SS), cobalt-chrome (Co—Cr) alloys, zirconium-niobium (Zr—Nb) alloys, and magnesium (Mg) alloys being the most common [3,7]. These materials are valued for their durability, biocompatibility, and mechanical properties, including high strength, low modulus of elasticity, and excellent wear resistance [3,8,9]. However, despite their widespread use, these materials face limitations related to corrosion, wear, and biofilm formation [10,11]. For example, corrosion by-products can leach into surrounding tissues, causing inflammation and systemic toxicity [7,12], while tribological wear and debris can lead to adverse complications, including implant loosening, chronic inflammation, and even device failure [13–15]. Cardiovascular devices face additional challenges, such as hemolysis, thrombus formation, and excessive friction, all of which

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compromise device functionality and longevity [16,17].

Following the implantation of medical devices, a foreign body response (FBR) is triggered as part of the body's defense mechanism. While this response is natural, it often leads to chronic inflammation, posing a serious risk to long-term device success. Chronic inflammation interferes with the integration of the device into surrounding tissues, particularly in orthopaedic implants where osseointegration—mechanical and biological stability achieved through bone adhesion—is critical for functionality. The nature of the biomaterials used plays a key role in influencing FBR. Materials that exhibit cytotoxicity, often due to the release of toxic ions or degradation products, exacerbate the immune response, leading to tissue damage and prolonged inflammation [18,19]. Conversely biologically inert materials may also hinder osseointegration, as they fail to promote cellular adhesion, proliferation, and differentiation—essential steps for effective integration with bone tissue. This lack of bioactivity leads to the formation of fibrous tissue at the interface, reducing mechanical stability and increasing the likelihood of device loosening and failure [20,21]. Similarly, healthcare-associated infections represent a significant challenge for invasive devices such as catheters, where biofilm formation on material surfaces is a common cause of infection [4]. Conventional solutions, such as the incorporation of antibiotics, are becoming less effective due to the emergence of resistant bacterial strains, necessitating the development of alternative strategies [4–6]. Furthermore, single-use MDs, while effective in reducing cross-contamination and infection risks, pose another dilemma: their environmental impact [22,23]. Classified as infectious waste, these devices often require incineration, contributing to greenhouse gas emissions and pollution [22]. This tension between public health benefits and environmental sustainability underscores the urgency of developing eco-friendly alternatives.

To address these multifaceted challenges, advancements in materials science and surface engineering have emerged as key solutions. Material modifications, such as metal injection molding [24] and additive manufacturing [25,26], combined with innovative biomaterials like collagen [27] and hyaluronic acid [28], are transforming the landscape of MDs. Additionally, surface engineering techniques, including plasma

spraying, electroplating, physical vapor deposition (PVD) [8], and laser treatments, offer significant improvements in corrosion resistance, biocompatibility, bioactivity, and antimicrobial properties [8,29–32]. Among these, PVD—particularly magnetron sputtering—has demonstrated exceptional potential in tailoring material surfaces to better mimic biological systems, extend device lifespan, and enhance clinical outcomes (Fig. 1) [32,33].

This review focuses on coatings produced by magnetron sputtering, emphasizing advancements achieved over the past five years in the field of biomedical devices. To the best of our knowledge, this is the first time a detailed analysis has been conducted on how this technique can be tailored to optimize crucial film characteristics—such as composition, thickness, adhesion, morphology, and crystalline structure enabling the fine-tuning of physical, chemical, mechanical, and biological properties of thin films to meet specific medical application requirements. The discussion explores how PVD enhances key surface properties of medical devices. It addresses improvements in corrosion resistance to prevent material degradation in physiological environments, upgrades to mechanical properties and tribological performance for enhanced durability, and modifications to biocompatibility for improved tissue integration. Additionally, it evaluates PVD's role in fostering osseointegration for orthopaedic applications and boosting antimicrobial activity to combat biofilm formation and healthcare-associated infections. The main limitations of commonly used substrate materials are addressed, alongside an analysis of the most effective coatings designed to overcome these challenges. This comprehensive approach provides a detailed understanding of how magnetron sputtering not only addresses the limitations of traditional materials but also enhances the performance, reliability, and durability of medical devices, paving the way for next-generation biomedical applications.

2. Why PVD as surface engineering method for biomedical applications?

Surface engineering strategies offer promising solutions to enhance the functionalities of biomedical devices. These strategies involve various deposition techniques, which can be broadly classified into

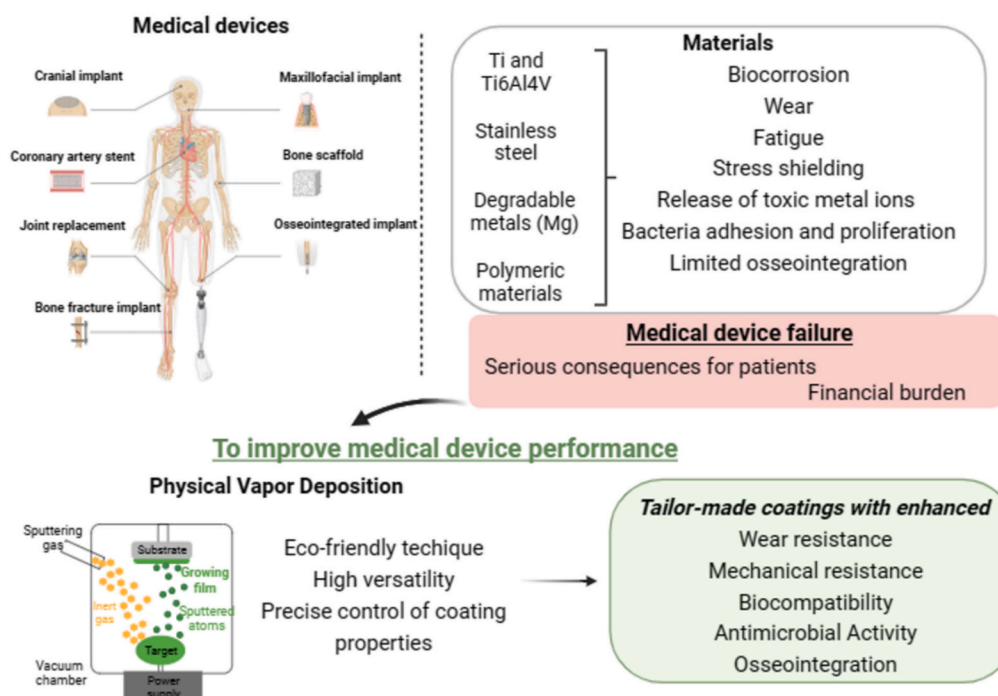


Fig. 1. Overview of medical devices and materials challenges, emphasizing the need for enhanced performance through tailored coatings. PVD highlighted as a precise and eco-friendly method to improve mechanical and biological properties of medical devices. Created in <https://BioRender.com>.

those involving chemical reactions, such as electrochemical deposition, sol-gel techniques, and chemical vapor deposition, and those involving physics concepts such as casting, spraying, and PVD [8]. Among these techniques, PVD stands out with its unique advantages, particularly in the field of biomedical devices. This technique involves physical processes, reducing chemical waste, and minimizing environmental impact. It offers exceptional versatility, enabling the deposition of almost any material onto biomedical devices. One of the key strengths of PVD lies on its ability to achieve precise control over surface properties at the atomic level, encompassing factors such as film thickness and chemical composition. Therefore, coatings with thicknesses that can vary from a few nanometers to several thousand nanometers, with the most diverse chemical composition, can be deposited [34]. Additionally, PVD ensures excellent adhesion, promoting long-term stability and performance of biomedical devices. The technique also enables the deposition of homogeneous layers with high purity, designed structures, graded properties, and controlled morphology. This level of control over film properties is highly advantageous for biomedical applications, where specific functionalities and performance characteristics are desired [35]. However, it is important to acknowledge certain limitations of PVD [36]. Coating larger or complex-shaped objects can pose challenges due to limitations in the size of the vacuum chamber or the uniformity of the coating across the entire surface. The line-of-sight nature of PVD deposition can lead to uneven or incomplete coverage on intricate surfaces. Additionally, PVD systems can be costly to acquire and maintain. To mitigate these limitations, researchers have implemented multiple strategies. For example, fine-tuning deposition parameters helps improve coating uniformity, while substrate manipulation techniques like rotation, tilting, or introducing a biased substrate holder can enhance coating uniformity on complex surfaces. The developing of new technologies also has contributed to overcome this situation. High-power impulse power sources have been employed in magnetron sputtering to achieve a uniform coating in complex surfaces [37]. In addition, advanced chamber designs have been developed to overcome the line-of-sight deposition limitation, allowing for more uniform coverage. Finally, combining PVD with other deposition techniques provides additional control and flexibility in the deposition process [38,39]. By considering these limitations and employing appropriate strategies, researchers can optimize PVD for biomedical applications and unlock its full potential in enhancing the performance and functionality of medical devices.

PVD is based on the deposition of thin films via either evaporation or sputtering of target materials in a high-vacuum environment, ensuring film purity and precise control over composition [40]. While evaporation requires high temperatures and is thus limited in coating heat-sensitive substrates, sputtering—particularly magnetron sputtering (MS)—can be performed at lower temperatures, making it suitable for applications such as medical devices. Common sputtering techniques include DC, RF, reactive sputtering, and HiPIMS, each offering specific advantages in tailoring film properties such as density, composition, and mechanical strength to meet diverse performance requirements [41].

2.1. Magnetron sputtering: a PVD process for fine-tuning thin film properties

In the context of medical devices, achieving precise control over the coating characteristics deposited by magnetron sputtering is crucial. This enables the customization of coatings to meet specific requirements, such as corrosion and wear resistance, low friction, biocompatibility, and antimicrobial activity, thereby enhancing their performance in medical applications. There are several effective approaches to fine-tuning the chemical composition of coatings deposited by MS. The primary determinant of the coating's chemical composition is the choice of target material. By selecting target materials with varying elemental compositions or combining different elemental target materials, coatings with complex chemical compositions can be

achieved [42]. Moreover, the addition of alloying elements or dopants can further add new properties to the film. For instance, by incorporating silver (Ag) [2,43–46], copper oxide (CuO, Cu₂O) [47], or zinc oxide (ZnO) [48–50] into a base-coating matrix, antimicrobial properties can be acquired. Similarly, the incorporation of tantalum (Ta) can enhance the osseointegration of dental implants [51–54] and improve the substrate's resistance to wear and corrosion [55,56]. Another approach is to use multiple targets simultaneously or sequentially [57]. This technique allows for the creation of multi-layered coatings or the incorporation of specific elements or compounds into the film structure, thereby enhancing their effectiveness in various applications [58–60]. For instance, titanium-copper (TiCu) coatings were obtained employing a co-sputtering system, depositing at the same time the mentioned elements. The obtained coatings have been proven to significantly enhance the corrosion resistance of stainless steel substrates with the Ti incorporation [61]. In another example, the sequential deposition of silicon/diamond-like carbon (Si/DLC) nanolayers has demonstrated its ability to improve the biocompatibility of the coating [62]. Furthermore, the use of silver/montmorillonite biocomposite multilayers showed promise in providing effective antifungal activity [63]. In addition to combining target materials, the introduction of reactive gases during sputtering is another effective method for altering the chemical composition of deposited films. For instance, by sputtering a titanium target with silver pins in an Ar/O₂/N₂ atmosphere, TiO₂:Ag,N coatings were produced, offering unique properties and functionalities [64]. In another example, Zr—C coatings were deposited on 304 L steel using a zirconium (Zr) target in an Ar—C₂H₂ atmosphere [65] to enhance the hardness and wear resistance of the steel substrate. Furthermore, a titanium-copper oxide (TiCuO) coating was deposited on Ti6Al4V discs, resulting in an enhanced antimicrobial activity [66]. By adjusting the flow rates of reactive gases in PVD, the extent of chemical reaction with the sputtered atoms can be controlled, enabling the customization of the composition of the deposited film [65,66]. For example, the manipulation of the on-off flow sequence of sputtering gas allows for control over the oxygen content and morphology of ZnO thin films [67]. The use of reactive gas-timing during deposition leads to the formation of grainy nanoporous structures in the thin films. On the other hand, the deposition process contributed to the increase of Zn—O bonding presence in the coatings, which is critical to develop the reactive oxygen species (ROS) antibacterial mechanism. A mixed action of morphology and ROS induced a higher antifungal activity in the ZnO coatings than uncoated Ti. Moreover, the fine-tuning of the chemical composition can be achieved by adjusting various process parameters, namely sputtering power, gas pressure and deposition. For instance, when a nano-layer of gallium oxide (Ga₂O₃) was deposited onto titanium dioxide nanotube arrays using a 50 W power, it exhibited lower levels of Ga³⁺ ions release compared to the same coating produced at 100 W. This can be explained by the morphological change in the samples. As the power increased, the nanotube arrays were more covered by the coating, which makes more material available to react with the surrounding media and hence, release more Ga³⁺ ions [68]. This resulted in coatings that demonstrated antibacterial and osteogenic properties without inducing cytotoxicity, making them highly promising for dental implant applications. By meticulously considering and fine-tuning these factors, magnetron sputtering offers a highly versatile platform that allows for precise control over the chemical composition of coatings.

The morphology of thin films is another critical factor that significantly impacts their chemical, physical, mechanical, and biological properties. By adjusting magnetron sputtering conditions, it is possible to tailor the morphology of these films to meet specific requirements. Higher sputtering power, for example, can lead to increased kinetic energy upon deposition, causing surface diffusion and rearrangement of atoms, resulting in a smoother and denser film morphology. For instance, El-Hossary and co-workers employed DC pulsed magnetron sputtering to deposit a Ti-Al-N thin film on AISI 316, varying the pulsed plasma powers between 100 and 175 W [69]. Among the different

power settings, the Ti-Al-N thin film deposited at a pulsed power of 150 W exhibited the highest cell proliferation rate. This positive effect was attributed to a higher surface energy and reduced surface roughness of the film. The bias applied during MS deposition can also have significant effects on the morphology of the deposited thin films. In a study conducted by Bait et al., the impact of ion bombardment, by applying a range of negative bias voltages from 0 to 100 V to the substrate, on the growth of TiO₂ films was investigated [70]. The bombardment resulted in enhanced nucleation, leading to smaller grain size and higher packing density of the TiO₂ films. Moreover, the increase in bias voltage also had positive effects on several mechanical and chemical properties, including hardness and wear and corrosion resistances [62,70]. The morphology of thin films has a profound impact on cell adhesion, proliferation, and differentiation [71]. Surface roughness and topographical features are particularly influential promoting cell attachment and reducing bacteria adhesion. In a study conducted by Wang et al. investigated the effects of oxygen content on the structure, composition, surface roughness, and wettability of TiO₂-CuO composite sputtered coatings [72]. As the oxygen content increased, the coating composition shifted from TiO₂-Cu to TiO₂-Cu₂O and TiO₂-CuO₂. Among the three coatings, the one containing Cu₂O exhibited the best multifunctional performance, displaying the highest antibacterial rate, cytocompatibility, and corrosion resistance. This outstanding performance can be attributed to the higher surface roughness and good surface wettability. These characteristics (i) facilitate the improved contact with cell growth medium, (ii) promote the release of Cu ions, and consequently (iii) enhance the coatings' antibacterial properties and biocompatibility. Similarly, Javid et al. conducted a study where they varied the working pressure and power density of a Cu target [73]. This manipulation allowed control over the morphology of the thin films as well as the amount of Cu ions released, permitting to optimize the antibacterial activity.

The crystalline structure of thin films also plays a significant role on their properties. The presence of some crystal phases can influence over the film's hardness, Young's modulus, and strength [74–76]. Moreover, the crystalline structure affects the surface roughness and topographical features of thin films and can impact biocompatibility and interactions with biological systems, influencing cell adhesion, proliferation, and differentiation. Ruan et al. deposited five different titania films (including one rutile, two anatase, and two amorphous titania), with varying levels of roughness, on polished titanium using RFMS [76]. The results demonstrated that the presence of the anatase phase with an increased roughness effectively enhanced the biocompatibility of the coatings. By manipulating the magnetron sputtering parameters, researchers can optimize the microstructures and crystalline arrangements in thin films. For instance, to investigate the potential differences in photocatalytic and antibacterial activities associated with different crystalline phases of TiO₂, Pataronto et al. deposited anatase, rutile, and mixture phases films onto commercially pure titanium (cpTi) [74,75]. The rutile-TiO₂ film had no antibacterial effect, whereas both anatase and mixture-TiO₂ films demonstrated statistically significant reductions in biofilm formation.

Overall, by carefully considering and optimizing all the factors mentioned, MS provides a versatile platform that allows for precise control over coating properties. This level of control enables the creation of tailored coatings with specific characteristics, greatly enhancing crucial aspects such as corrosion resistance, biocompatibility, osseointegration, or antimicrobial activity for medical devices.

3. How can PVD enhance the surface properties of medical devices?

The human body is a very complex and dynamic environment for inorganic materials exposed to it. Over the years, many trials have been documented to create a solid database of biocompatible materials tailored to specific body parts and their respective functions. Currently,

a wide range of medical devices, such as teeth, hips, and supporting screws, are readily available for use by medical professionals, and the research teams are trying to expand the options. Alloys such as Ti-6Al-4 V, AZ-series Mg or SS316L are considered biocompatible with the human body [77,78]. However, the used alloys can release toxic ions during their interaction with the biological environments, presenting crucial functional problems such as osseointegration inhibition [79–81] or poor corrosion resistance [82–84].

Coatings have been suitable for enlarging substrate functionalities in several fields, and biomedical devices are no exception. Overpassing the mentioned drawbacks and additional benefits can be addressed when the surface treatment is tailored to bring the best treatment to the human body while avoiding possible complications. Coatings applied by PVD have been abroad since supplying a stable and reliable performance in any substrate. Corrosion resistance, mechanical properties, tribological performance, and biocompatibility are some properties that can be improved in biomedical devices through PVD coatings. Examples of coatings developed by our research group are shown in Fig. 2. In the following sections, we attempt to summarise how PVD coatings have been applied to increase the base performance of different biocompatible substrates and enlarge their working benefits.

3.1. Improving corrosion resistance in MDs

One of the significant issues of applying metallic implants into the human body is the grade of degradation presented with the exposure time, creating additional health problems for the patients, as mentioned. Corrosion is a quite studied phenomenon that is transversal to all industries. Specific materials are commonly employed according to the working regime or specific solutions/environments they must deal with. For instance, stainless steel is a versatile material used to fight against this issue. Some metals can react with their surroundings, forming an additional layer over themselves, like a self-protective mechanism, which stops the external agent's action. This conformed layer is commonly known as the passive layer. However, the mentioned layer can also be affected by external agents (aggressive solutions) and actions (wear, erosion), which cause a corrosion event to happen.

In MDs, exist two common corrosion mechanisms reported in PVD coatings: (1) Pitting, which is the formation of pits provoked by specific breakdowns in a passive surface; (2) galvanic, which happens due to the dissimilarity of the metals in contact under the presence of an electrolyte, and corroding the more active material. Experimental tests such as potentiodynamic polarisation are suitable for provoking corrosion events in an accelerated way, and micrographic tests help to establish the type of corrosion presented. Fig. 3a exhibits the typical potentiodynamic polarisation plot, commonly named the Tafel plot. It contains several regions describing phenomena produced by the potential input in the sample. From negative to positive potentials, the plot is divided into various areas: cathodic reaction, anodic reaction, and passive region. Additional phenomena in this kind of plot are described elsewhere. The breakdown of the passive layer is a clear sign of corrosion action. The sudden current density increases and quickly decreases (see the region named “Breakdown of passive layer” in Fig. 2, is the standard signal when pitting happens during the polarisation test. Micrography assesses and shows the corrosion action on the specimens (example shown in Fig. 3b). In the following sections, we explore how common MD substrates were coated by other materials via PVD technologies, such as alloys (based in Ti or Mg), stainless steel or other biocompatible materials (polymers), and their impact on improving corrosion protection over biological environments, mainly focused on the human body conditions.

3.1.1. Stainless steels

Despite stainless steel being one of the most used alloys for MDs [90,91], releasing of toxic ions into the bloodstream, such as Ni²⁺ and Cr³⁺, is a big issue to overcome. Besides corrosion, which provokes the

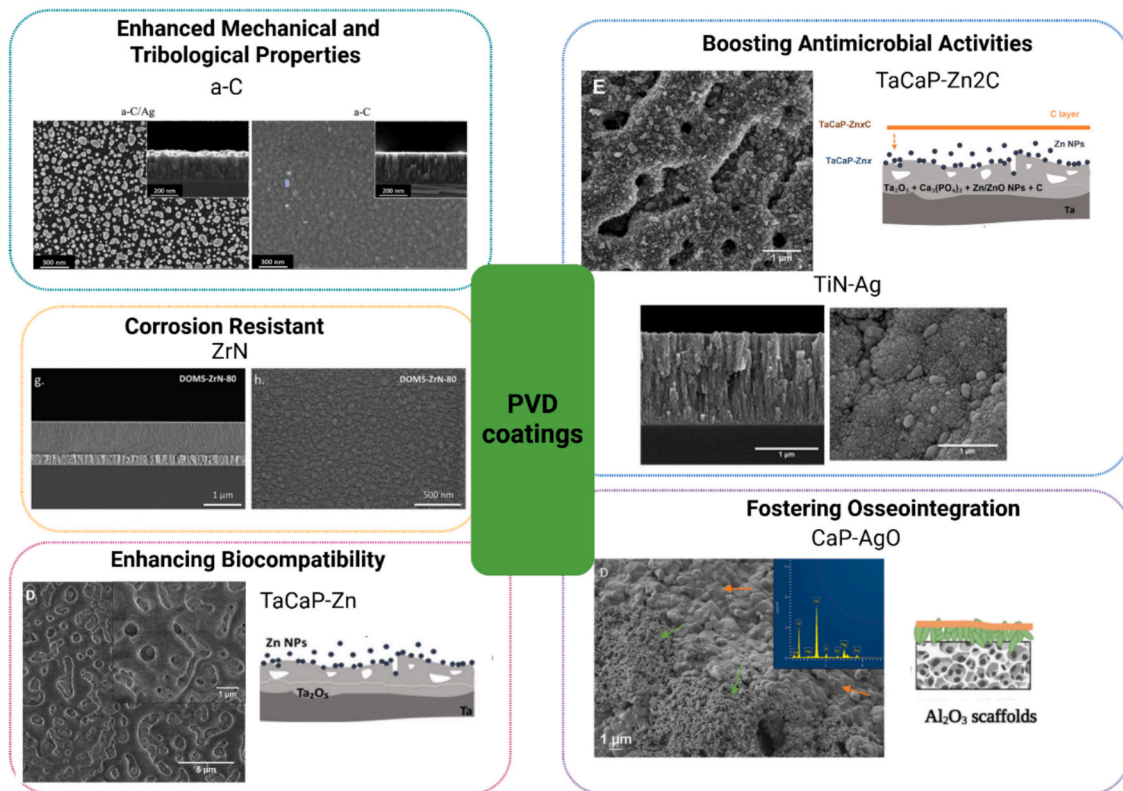


Fig. 2. Schematic overview of the main functional applications of PVD coatings for medical devices, illustrated by SEM micrographs and schematic diagrams. Corrosion-resistant ZrN coatings feature dense, defect-free structures that enhance protection in physiological environments [85]. a-C and a-C/Ag coatings improve mechanical performance through nanostructured, columnar growth [86]. TaCaP-Zn coatings promote biocompatibility by offering a favorable surface for cell adhesion [39]. CaP-AgO coatings support osseointegration through nano-rough, porous surfaces that encourage bone attachment [87]. TiN-Ag and TaCaP-Zn2C coatings enhance antimicrobial activity via silver and zinc nanoparticle incorporation [49,88].

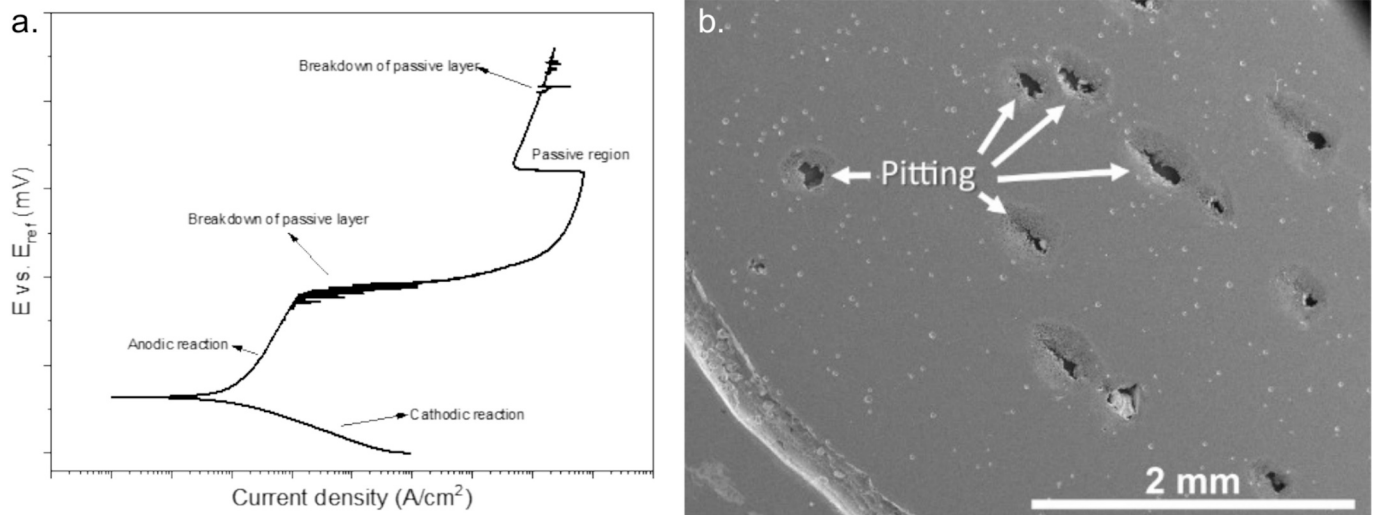


Fig. 3. Schema of a potentiodynamic polarisation plot (a) and SEM micrograph of SS316L coupon after polarisation test (b), which evidences the pitting corrosion. Image (b) was adapted from [89].

reduction of MD lifespan and functionality jeopardizes, there is the potential to cause problems such as bone erosion or aseptic loosening of the implant, which can have significant consequences on the patient's well-being and the success of the implant [91]. This situation compels the research teams to achieve surfaces with higher corrosion resistance in harsh biological environments. Different types of mix between metallic and ceramics have been used to coat this material and have

been tested, as shown in the following table.

Stainless steel is well-known as a material with self-healing properties when exposed to oxidising agents as human body fluids (Fig. 4). It is capable to form a passive layer composed by Cr_2O_3 to cover itself and stop corrosion. However, the passive layer is mechanically poor, hence it could be removed by external action easily, and consequently, creates some unprotected zones. Here, coatings are critical to reinforce the

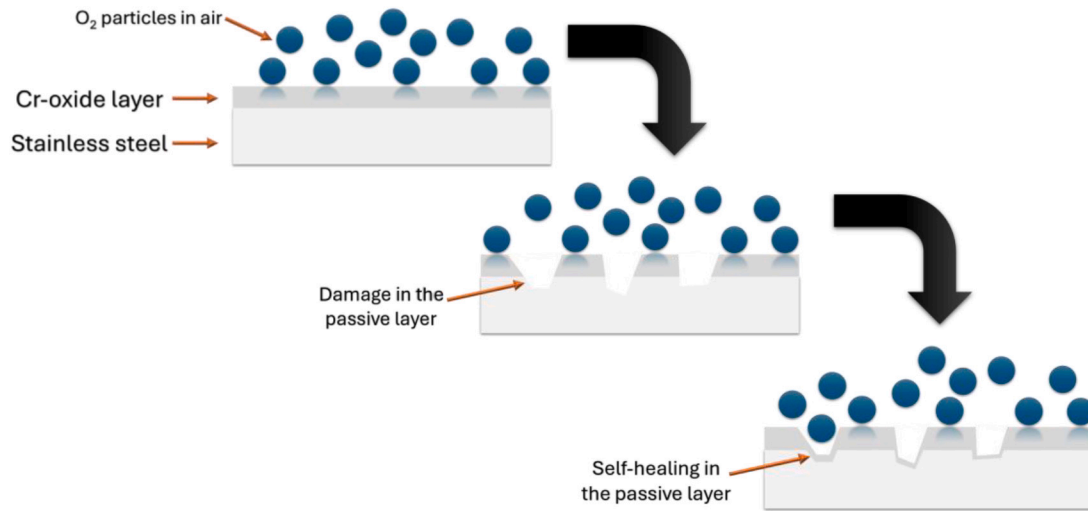


Fig. 4. Schema of a passive layer of stainless steel exposed to the air.

anticorrosion action in harsh environments such as human body. Table 1 exposes the main strategy in PVD coatings for MDs, which is employing passive materials such as C or ZrO_2 , commonly used to inhibit corrosion for other purposes due to their high chemical stability in severe working conditions. According to the summarised references in Table 1, passivation was the most common protection mechanism against corrosion under simulated biological conditions. It starts with ionising the surface metal atoms, which interact with the solution, initialising the electrochemical reactions with the release of electrons. Later, the metal ions react with the solution (commonly O and OH ions) to conform oxides and hydroxides that configure an outermost layer, which can act as a protective barrier.

On the other hand, other coatings in Table 1 shown pitting, which is explained for other possible reasons causing this behavior (for instance, superficial defects or heterogeneous chemical species) and not the interaction of the applied coating with the bio-liquid itself. Kao et al. [92] described that the defects (pinholes) found in TiN film acted as a starting point of corrosion, and Cubillos et al. [91] he imperfections in the 'as-deposited' condition film morphology. Besides, Qin et al. [61]

justify the reduction of pits after annealing the dense TiCu coatings by the uneven elemental distribution along the film surface. This could be another critical characteristic to explain the pitting process in compact surfaces. Free-defect surfaces with a uniform passive coating could prevent corrosion in coated stainless steel MDs.

In spite of the capacity of stainless steel to self-heal is outstanding, stopping the action of the external agents can comprise its integrity and protection performance. Especially, solutions that simulate body fluids, such as SBF and PBS, contain other ions, such as Na^+ , K^+ , Ca^{2+} , Mg^{2+} or Cl^- , being highly aggressive for stainless steel MDs. PVD coatings have demonstrated to be effective to enhance the protection of this material in biological environments, hence their application can be a suitable option to overcome corrosion in MDs.

3.1.2. Ti-based alloys

Titanium is probably the most used biocompatible material in human body implants because of its high toughness, easy machinability, and high corrosion resistance [77]. Similarly to stainless steel, Ti-based alloys often present a mechanically poor TiO_2 layer due to its self-healing/

Table 1

Corrosion/protection mechanisms of coatings used to functionalise stainless steels for biomedical devices.

Substrate/film	Applied technologies	Corrosion tests	Electrolyte	Protection/corrosion mechanism	Potential application	Ref.
SS316L/TiN	DCMS	PP	0.9 wt% NaCl solution	Pitting	Orthopaedic, cardiovascular and dental devices	[92]
SS304/calcium phosphate and calcium titanate	RFMS	PP	Hank's solution (@ 37 °C)	Passive layer	Femoral stem implants	[93]
SS420/TiAlN(Ag,Cu)	DCMS	EIS ^b & PP	1 wt% NaCl solution	Passive layer	Surgical and dental instrumentation	[90]
SS316L/(Ag, Ag-Au)a:C	DCMS	EIS & PP	Artificial urine (@ 37 °C)	Passive layer	Ureteral stents	[94]
SS316L/TiCu	DCMS & HiPIMS + annealing (up to 500 °C)	PP	PBS	Pitting	Not informed	[61]
SS304L/ZrC	Pulsed-DCMS	PP	Artificial saliva	Passive layer	Orthodontic wires	[65]
SS316L and SS304/ZrO _x N _y	DCMS	EIS & PP	3.5 wt% NaCl solution	Pitting	Implants	[91]
SS316L/HfC	RFMS	EIS & PP	PBS (@ 37 °C)	Not informed	Cardiovascular implants	[95]
SS316L/Cr ₂ O ₃	RFMS	PP	0.9 wt% NaCl solution	Passive layer	Orthopaedic implants	[96]
SS316L/Nb ₂ O ₅ -TiO ₂	RFMS	EIS & PP	Ringer's solution	Passive layer	Orthopaedic implants (joints)	[97]
SS316L/ZrO ₂	DCMS	EIS & PP	Hank's solution (@ 37 °C)	Passive layer	Orthopaedic implants (joints)	[98]
SS316L/a:C	DCMS	Immersion	Artificial saliva (@ 37 °C)	Passive layer	Orthodontic implants	[99]

^aPotentiodynamic polarisation.

^b Electrochemical impedance spectroscopy.

protection mechanism when is exposed to oxidising agents [80,81]. In recent years, commercial pure Ti (cp-Ti) or industrial-grade pure Ti (TA2) have gained attention due to their lower price than other Ti alloys (for instance, Ti-6Al-4 V) and other biomaterials.

According to Table 2, the coatings employed to avoid corrosion in Ti-based alloys have also been employed to enlarge the functionality of the MDs further to prevent the release of heavy metallic ions into the body. A large variety of materials have been employed to coat Ti-based alloys used in MDs: Pd/PdO [77], Zr [100,101], Zn [101], C (i.e., diamond-like carbon or DLC) [157], Ag [102], hydroxyapatite (HAp) [103], Ta [55], and Cu [104]. Here, magnetron sputtering versatility is evident to coat MDs according to the aimed property to enhance. Nevertheless, some coatings shown in Table 2 have been treated after deposition to activate some desired characteristics. For instance, Rafieerad et al. deposited Pd over Ti-6Al-4 V substrates through DCMS in an inert atmosphere to achieve approximately 2.3 μm thickness films and afterwards, the samples were thermally treated employing different temperatures (450, 550 and 650 °C) for 1 h under normal atmospheric conditions [77]. This processing was determined to provoke the diffusion from the film to the substrate, which contributes to reinforcing the substrate/coating adhesion and enhancing the coated alloy's corrosion resistance and mechanical properties. Wang et al. [101] used RF magnetron sputtering with micro-arc oxidation to obtain Zn-doped films of ZrO_2 over commercially Ti-6Al-4 V disks, obtaining an antibacterial effect through this coating treatment, which is critical in avoiding implantitis or related diseases. Chen et al. [105] deposited an Ir layer over cp-Ti, and after that, this layer was activated in an electrochemical way to create IrO_x species, increasing its corrosion resistance without provokes cytotoxicity. He et al. [106] obtained TiCu coating over TA2 substrates, and later, the samples were annealed at 600 °C for 2 h to get a TiO_2/CuO

configuration, showing an enhanced biocompatibility, high corrosion resistance and antibacterial activity. Thangavel et al. [102] deposited NiTi with Ag to achieve good corrosion resistance and cytocompatibility surfaces over cp-Ti substrates. Milan et al. [107] coated Ti-6Al-4 V coupons using magnetron sputtering in a reactive atmosphere of argon and methane, obtaining Cu/a-C:H (amorphous carbon) films with enlarged functionalities in terms of antibacterial properties, angiogenesis, and osteogenesis. These enhancements are fundamental for the long-term stability and success of the implant. These studies showcase the potential of PVD coatings to create surfaces with multifunctionality and enhanced properties directed to expanding the range of options for MDs.

The coatings employed to improve the corrosion resistance in Ti-based alloys shown passivation as the most common protection mechanism against simulated body fluids according to Table 2, which is expected when passive materials are used. As mentioned in the last section, this phenomenon also works as a self-protective layer against hazardous agents. Besides pitting corrosion, galvanic corrosion also appear and seem acts over two specific coatings: Si:N-DLC [157] and Cu-a-C:H [107]. As explained, galvanic corrosion appears when dissimilar materials are in contact into an electrolyte. Those two coatings contain carbon as constituent. Specifically, graphite, a very common phase in DLC and a-C:H coatings, is one of the most noble material according to the galvanic series [108]. Hence, most of the metals in contact with this material is prone to be corroded. According to Zhang [108], when the galvanic corrosion occurs, the anodic (or more active) member is released in order to protect the cathodic (or more noble) one. This particular dissolution could generate integrity problems in MDs as exhibits Fig. 5, reducing drastically in functionality and lifespan. To avoid this corrosion type, are commonly recommended since avoid dissimilar conductive materials contacts, isolation of the coupled materials from

Table 2
Corrosion/protection mechanisms of coatings used to functionalise Ti-based materials for biomedical devices.

Substrate/film	Applied technologies	Corrosion tests	Electrolyte	Protection/corrosion mechanism	Potential application	Ref.
TA2/ TiO_2 -CuO	Pulsed-DCMS + annealing (up to 600 °C)	EIS ^a & PP ^b (@ 36.5 °C)	SBF ^c	Passive layer	Implants	[106]
TA2/Si:N-DLC	Hybrid ion beam system	PP	SBF	Galvanic	Orthopaedic implants	[157]
Cp-Ti/Ag:NiTi	RFMS	EIS & PP	SBF	Passive layer	Orthopaedic implants	[102]
Cp-Ti/ IrO_x	DCMS + electrochemical activation	EIS & CV ^d	PBS ^e	Passive layer	Neural electrodes	[105]
Cp-Ti/ TiO_2 -CuO _x	DCMS + annealing (500 °C)	EIS & PP	SBF	Passive layer – Film densification	Orthopaedic and orthodontic implants	[72]
Ti-6Al-7Nb/Pd-PdO	DCMS + annealing (up to 650 °C)	PP	PBS	Passive layer	Orthopaedic implants (joints)	[77]
Ti-6Al-4V/Zn:ZrO ₂ -TiO ₂	DCMS + micro-arc oxidation	PP	SBF	Passive layer	Orthopaedic and orthodontic implants	[101]
Ti-6Al-4V/Zr-ZrO ₂	DCMS + micro-arc oxidation	PP	PBS	Passive layer	Orthopaedic implants	[100]
Ti-6Al-4V/ZrCuFeAlAg	DCMS	PP, PS ^f & EIS	Artificial saliva	Passive layer	Orthodontic implants	[109]
Ti-6Al-4V/TiSiN	Pulsed-DCMS + DCMS	PP & EIS	SBF (@36.5 °C)	Passive layer	Orthopaedic implants	[110]
Ti-6Al-4V/Ti _x N _y	DCMS	EIS	SBF	Passive layer - Film densification and large grain sizes	Orthopaedic implants and neural electrodes	[111]
Ti-6Al-4V/TiO ₂ -HAp-Al ₂ O ₃	RFMS + annealing (up to 600 °C)	EIS	SBF	Passive layer	Orthopaedic and orthodontic implants	[103]
Ti-6Al-4V/Cu-Ta ₂ O ₅	DCMS + RFMS	PP	SBF	Passive layer – Film densification	Implants	[104]
Ti-6Al-4V/Cu-a-C:H	DCMS	EIS	SBF	Galvanic	Orthopaedic implants	[107]
Ti-6Al-4V/TiZrNb	DCMS	PP & EIS	SBF	Passive layer	Implants	[80]
Ti-6Al-4V/Ta-Ti-Zr	DCMS	PP	SBF	Passive layer	Implants	[81]
Ti-6Al-4V/a-C:H:SiO _x	PACVD	Static immersion	0.9 wt% NaCl solution (@ 37 °C)	Passive layer	Cardiovascular devices (stents and valves)	[79]
Ti-6Al-4V/Ta _m O _n	DCMS	PP	PBS	Pitting	Orthopaedic implants	[55]
Ti-6Al-4V/Ti-Zr-Ta-Nb-W + Ag	DCMS	PP & EIS	PBS (@ 37 °C)	Passive layer	Orthopaedic implants	[112]
Ti-6Al-4V/Ta	DCMS	PP & EIS	SBF	Passive layer	Orthopaedic implants	[113]

^a Electrochemical impedance spectroscopy.

^b Potentiodynamic polarisation.

^c Simulated body fluid.

^d Cyclic voltammetry.

^e Phosphate buffer solution.

^f Potentiostatic polarisation.

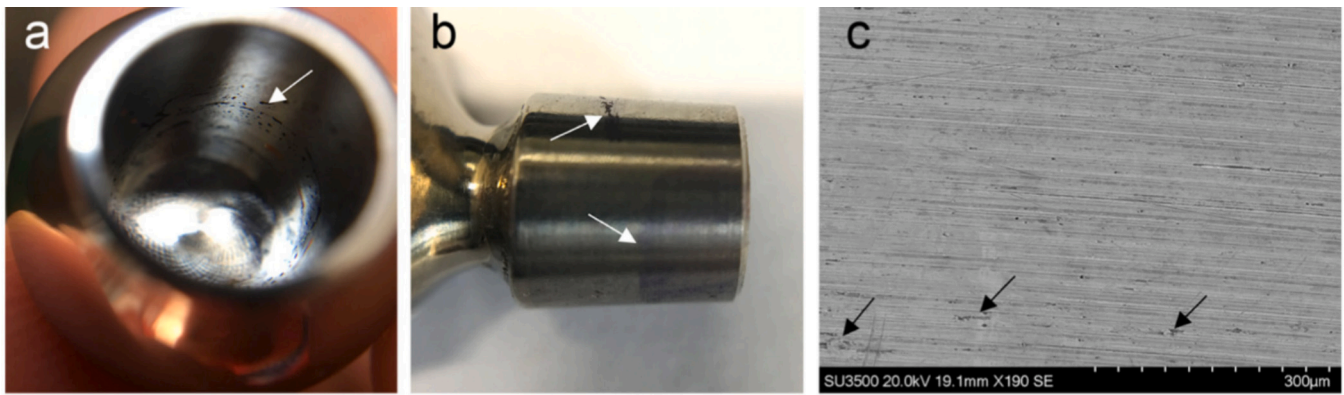


Fig. 5. Photos (a and b) and SEM micrograph (c) of CoCr femoral head-taper under galvanic corrosion. The arrows mark the selective dissolution, common in galvanic corrosion.

Adapted from [114].

the environment, among others [108].

3.1.3. Mg-based alloys

Magnesium (Mg) and its alloys are promising biodegradable materials for short-term medical devices such as cardiovascular stents [115], orthopaedic implants [116,117], and temporary scaffolds [84], among others [82]. Low density, high specific strength, and biodegradability are desirable characteristics in a clinical setting [83]. On the other hand, the principal drawback of Mg used in body MDs is its low corrosion resistance, associated with the H_2 evolution reaction, causing severe medical problems in vivo [82–84]. Reducing the corrosion rate and keeping the Mg characteristics would be crucial to achieving biocompatible implants that the human body can assimilate, reducing the surgical proceedings and, hence, the risks and medical costs for the patients. Several research teams have opted for coatings that could increase the functionality of Mg and Mg alloys, improving their essential characteristics and reducing corrosion. Table 3 summarises recent works aiming to enhance Mg performance.

According to Table 3, most of the coatings employed in Mg alloys showed pitting as the main corrosion mechanism. According to the Association for Materials Protection and Performance - AMPP (formerly NACE), this type of corrosion is initialised by damage (chemical or mechanical), deficient formation, or non-uniformities in the surface [118]. The last scenario seemed more plausible according to the reported literature. Rough surfaces harm the deposited films' anticorrosion performance, creating defects that serve as starting points for pitting. Corrosion studies of Mg point to $Mg(OH)_2$ as the primary corrosion product when interacting with different simulated body fluids [78,115,117]. This insoluble corrosion product does not fix on the

surface as quickly as other oxidised species produced during corrosion in other metals. On the contrary, it helps to create micro-galvanic pairs, which accelerate the corrosion process unevenly along the surface [82,84]. In this line, a correct surface preparation (i.e., polishing, etching, chemical cleansing, et cetera) can help to reduce the influence of the superficial defects over the coating heterogeneities. Other possible strategy to apply in MDs based on Mg-alloys could be the implementation of dense coatings applying HiPIMS technology to inhibit corrosion, as we have reported in other types of applications [85,119].

3.1.4. Other biocompatible materials

Not only alloys based in Fe, Ti or Mg have been used as substrates to be functionalised and used posteriorly in MDs. Coatings applied to polymers such as UHMWPE (Ultra-high molecular weight polyethylene) [120] or polyamide [121] have been explored in medical applications. Furthermore, metallic alloys such as FeMoTaTiZr [122] or CoCrMo [123] have been demonstrated to be biocompatible, which open the possibility to use them in implants. Here, coatings can play an important role in enlarging their functionalisation, similar to the exposed in coated Ti-base alloys. Another reported material in biocompatible applications is Zn, considered a next-gen biodegradable biomaterial [124]. Problems such as weak tribological performance [120] or poor corrosion resistance [125] must be overcome to consider these materials safe for medical devices. Table 4 recapitulates the different materials explored out of Fe-, Ti- or Mg-based alloys, and with the potential to become viable MDs.

As exposed, the coatings applied by different magnetron sputtering techniques shown surface passivation as the main protection mechanism under simulated body fluid conditions. This characteristic is more

Table 3

Corrosion/protection mechanisms of coatings used to functionalise Mg-based materials for biomedical devices.

Substrate/film	Applied technologies	Corrosion tests	Electrolyte	Protection/corrosion mechanism	Potential application	Ref.
ZK60 alloy/ Ta_2O_5	DCMS	EIS & PP	SBF	Passive layer	Orthopaedic implants	[82]
AZ91D alloy/Hf-PLLA	DCMS + czochralski method	EIS & PP	Hank's solution (@ 37 °C)	Pitting	Implants	[83]
MgCa ₄ Zn ₁ Gd ₁ alloy/ TiO_2	DCMS + spin coating + annealing (@ 300 °C)	PP	Ringer's solution	Pitting	Orthopaedic implants	[84]
MgZn alloy/ TiO_2	RFMS	PP	SBF (@ 37 °C)	Pitting	Cardiovascular stents	[115]
MgCa ₂ Zn ₁ and MgCa ₂ Zn ₁ Gd ₃ alloys/ TiO_2	DCMS	PP	Ringer's solution (@ 37 °C)	Pitting	Orthopaedic implants	[117]
ZEWX and WJK Mg-based alloys (>97 wt %)/CaP and SrCaP	RFMS	Immersion	SBF (@ 37 °C)	Pitting	Orthopaedic implants	[116]
AZ31 alloy/ Nb_2O_5	RFMS	EIS & PP	SBF (@ 37 °C)	Pitting	Implants (temporary)	[78]

Table 4

Corrosion/protection mechanisms of coatings used to functionalise different materials for biomedical devices.

Substrate/film	Applied technologies	Corrosion tests	Electrolyte	Protection/corrosion mechanism	Potential application	Ref.
UHMWPE/Ti, Zr & Ta	DCMS	EIS & PP	SBF (@ 36.5 ± 0.5 °C)	Passive layer	Orthopaedic implants (joints)	[120]
Al ₂ O ₃ , Ti foil, SS foil, Ni-based alloy foil, Pt-10%Ir alloy and glossy carbon/IrO ₂	Pulsed-DCMS	CV	PBS	No informed	Neural electrodes	[126]
Glass/Ti-Ag	RFMS	PP	Ringer's solution	Passive layer	Orthopaedic implants (joints)	[127]
Zn/Ti	DCMS	PP	PBS	Passive layer	Implants (temporary)	[125]
Zn/DLC	DCMS	PP & immersion	PBS	Galvanic	Orthopaedic and cardiovascular implants	[124]
FeMoTaTiZr/HAp-Zn	RFMS	EIS & PP	Fetal bovine serum	Pitting	Bone implants	[122]
CoCrMo/CrN-NbN	HiPIMS + plasma glow discharge	PP	Hank's solution	No informed	Orthopaedic implants	[123]
Polyamide/Al:ZnO	DCMS	EIS & CV	Deionised water solution with DNA primer	Diffusion	Biosensors	[121]
Si/(Zr-Ti)(Cu-Ag, Co-Ni)	DCMS & RFMS	PP & PS	PBS	Passive layer	Implants	[128]
Si/(TiTaNb, Ti-10Ta-6Nb)	DCMS & RFMS	PP & EIS	SBF (@ 37 °C)	Passive layer	Orthopaedic implants	[129]
Si/NbTaTiVZr(O)	RFMS	PP	0.1 M HCl solution	Passive layer	Orthopaedic implants and surgical instruments	[130]
NiTi/Ta _x O _y	DCMS	PP & EIS	SBF (@ 37 °C)	Passive layer	Stents	[131]

related to the composition of the coatings than the processing itself. However, magnetron sputtering demonstrates its capacity to achieve reliable and different high corrosion resistant coatings to diverse substrates explored in MDs. Despite the advantages of this technology, some mentioned examples pointed to the uneven elemental distribution in the coating, which increases the risk of galvanic couples and consequently, comprises the integrity of the MDs [61,79,115]. Another important factors such as superficial defects, cleaning process or surface roughness, can contribute to the coating effectiveness in corrosion protection [84,104,112]. The next-gen sputtered coatings to avoid corrosion in MDs should be ultra-dense, elementally uniform, and chemically stable, to be assimilated for the host without any undesired effect, prioritising biocompatibility above all. As mentioned, other problems associated with the substrate preparing and the process itself must also be overcome to help gain the desired characteristics. Of course, achieving all these characteristics is hard and finding the correct equilibrium among these would be the main challenge.

3.1.5. Strategies against corrosion in MDs

As exposed in the previous section, a large variety of materials have been proved prevent corrosion in MDs. Fig. 6 exhibits the potential

applications of the explored options. The implants are the most common research line where the coatings have been investigated. In fact, orthopaedic implants represent ~53 % of the studies in coatings for corrosion inhibition in MDs and 1/3 of these coating present passivation as the protection mechanism against simulated body fluids. Looking for the coating materials, most of them are transition metals oxides and here, it is possible to infer applying chemical inert materials is the main strategy in coating for corrosion inhibition in MDs. This is expectable when the component to be coated is exposed constantly to fluids inside the human body which are harsh to metals. However, this is not the only employed tactic to inhibit corrosion in MDs. Film densification [72,111], porosity reduction [97], superficial roughness decrease [92,98], surface defects diminution [98], or coating/substrate adherence improvement [102] have been employed as strategies to control the some of the problems with corroded MDs. According to the reported in the literature, the control of some deposition parameters such as bias voltage, deposition temperature/pressure or the implementation of technologies which allow more input energy in the targets (i.e., HiPIMS [123]), can help to improve the mentioned characteristics and brings a new margin of improvements in coatings for MDs. However, these uncharted approaches must be studied deeply before a scale-up from low

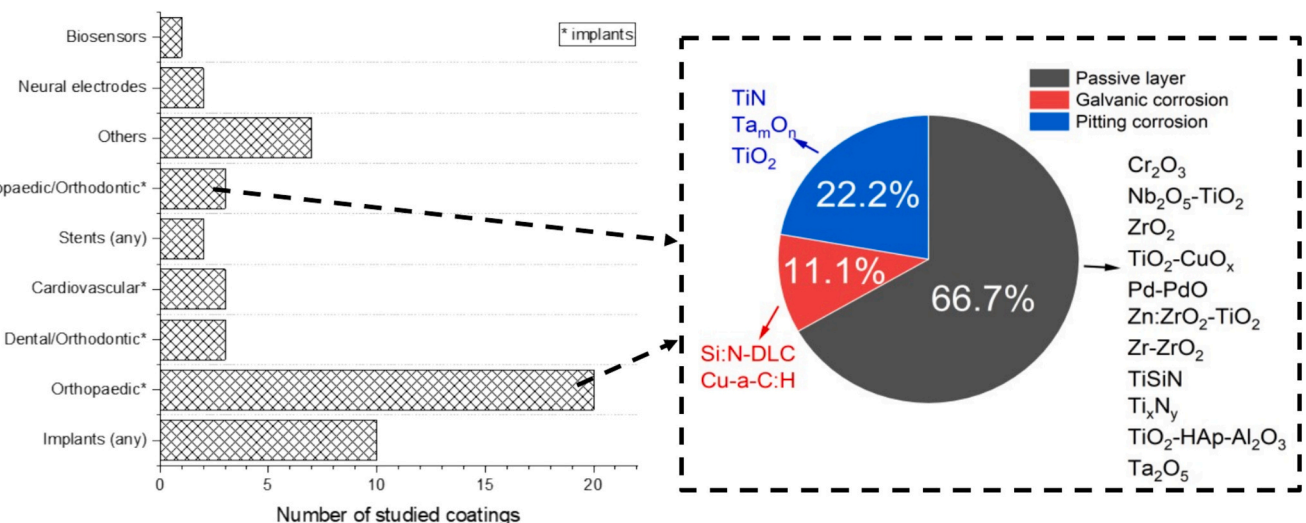


Fig. 6. Application of sputtered coatings to avoid corrosion in MDs (left) and the informed corrosion mechanism of these in the orthopaedic implants (right).

TRL (commonly found in laboratory tests reported in the consulted studies) to commercial production is viable. Chemically inert materials are a good starting point. Still, the emerging technologies in MS, such as deep oscillation magnetron sputtering (DOMS) or the integration with other fields like machine learning or artificial intelligence, could open the path to achieving viable sputtered coatings with an effective corrosion inhibition and tailored multifunctionality, which is the main objective of most of the consulted references.

Summarizing, the sputtered coatings demonstrated high effectiveness to protect the different materials used as substrates in MDs. Transition metal oxides are the most employed sputtered coating in MDs for corrosion inhibition. The selection of this kind of compound is likely justified due to their chemical inertness. Factors such as substrate surface state and elemental chemical distribution can contribute to the corrosion resistance response. New technologies such as HiPIMS, machine learning or artificial intelligence can provide the improvement of coatings for corrosion resistance in MDs.

As mentioned, any tested coating on the materials which commonly are employed for MDs, was applied exclusively for corrosion protection. Enlarge the functionality gathering other desired characteristics such as improving the tribological performance or the biocompatibility, is probably the most common objective of these studies. All of these pointed out to extend the MDs lifespan, reduce the risk associated with the implant rejection and to use materials economically viable to larger populations. This association of several properties is very important in applications as orthopaedic or orthodontic implants, which are the most common reported objective in coatings for MDs. Hence, in the next section will be exposed some developed coatings by MS, gathering mechanical properties and tribological performance, which are critical in these devices.

3.2. Upgrading mechanical properties and tribological performance in MDs

Other important features that must be considered when using coatings in MDs are their mechanical properties and tribological performance. Implants, stents, scaffolds, or medical instruments are just some appliances that must be wear resistant and have outstanding mechanical properties. Keeping the integrity of the coatings and the coated substrate is a determinant for the success of an implant and, hence the improvement of the patient's quality of life. As mentioned, the main drawbacks of different alloys used for implants or other MDs are ionic toxic release, weak corrosion resistance in body fluids and poor mechanical/tribological properties. Focusing on the latter, several authors have studied different coating/substrate interfaces to overcome this issue, which is summarised in Table 5.

Most of the informed coatings are focused in implant improving, especially in orthopaedic, orthodontic or cardiovascular applications, similarly to the reported in coatings for corrosion inhibition in the last section. Fig. 7 reveals the percentage of the reported coatings, categorized by application and the employed materials. In the case of coatings for diffusion barrier to avoid the releasing of the heavy ions to the bloodstream, two materials were employed in two different substrates: Ti-6Al-4 V coated by tantalum oxides and CoCrMo coated by CrN-NbN. Here, both coating implementing multilayered coatings to improve the interfacial effects and the bonding strength between the substrate and the coating and consequently, the improvement of the mechanical and tribological features. In fact, those are not the only coatings that employ this strategy to improve these properties. Ding et al. explored in AZ31 Mg alloy, commonly used in implants, the multilayered coating architecture mixing Mg and Nb₂O₅ and obtaining significant improvements in hardness (~3.6-fold increase) and consequently, the reduction of wear rate (from 2.5×10^{-3} in naked substrate to 4.4×10^{-5} mm³ N/m in M-Nb₂O₅).

In a wider point of view, the materials employed to overcome mechanical and tribological issues in MDs are similar to the reported in

corrosion inhibition. Most of them are based on transition metals, which are modified during deposition to be chemically inert through the reaction with a reactive gas (i.e., nitrogen, oxygen, carbon or a mix of these elements). This election is particular convenient because these materials are commonly used in other applications with severe working conditions such as cutting tools or automotive components; Hence, these must provide a certain stability in mechanical and tribological properties under extreme contact conditions [132]. On the other hand, the improvement in the mechanical properties (i.e., hardness and Young modulus) represents a substantial tribological performance improvement as revealed by the consulted studies. Generally, this connection is given by the H/E and H³/E² ratios which represent the elastic-strain-to-break parameter and the resistance to plastic deformation of the coating. Both mentioned ratios are often used as indicators of coating fracture resistance. Several studies report H/E is related directly with wear/erosion resistance, while H³/E² represent the resistance to crack initiation [133]. However, these are not only the parameters which can be crucial to determine the mechanical properties and the tribological performance in a coating. Microstructure and mechanical properties are intimately related; hence, the literature exhibits examples of other important details such as crystallographic structures identified like hard phases [119] or the elastic modulus mismatch between substrate and coating [133] or the increasing in coating compactness [134] can impact over the mechanical properties and the tribological performance. These three particular mentioned features are the basis in the implementation of mechanisms in enhancing the mechanical properties/tribological performance in coated MDs, as summarised in Table 6. Here, we have rementioned such as: (1) adhesion improvement between film and substrate, (2) raising the film compactness, and (3) occurrence of well-defined textures in the hard phases.

Concerning the adhesion improvement mechanism, a compatibility between coating and substrate is crucial. The transitions among despair material layers or substrate/coating for sputtered films could result in film delamination if they are dissimilar. A common strategy is employed buffer layers, which serve as transition between the substrate and the final coating, trying to decrease the risk of coating delamination. Ding et al. [55] explain that the mismatch properties between layer and substrate can increase the residual stress and compromise the bonding strength. Based on that, several layers between Ti-6Al-4 V substrates and Ta_mO_n coating were tried, passing through Ti, TiO₂ and Ta_mO_n-TiO₂ transition layers. Another approach used to improve the adhesion of a film to the substrate involves treating the surface of the substrate before applying the coating, as performed by Kao et al. [92], which employed nitriding of SS316L before depositing a TiN coating. This pre-treatment led to a substantial enhancement in adhesion, resulting in improved mechanical properties, such as higher hardness, and enhanced tribological performance, including a lower wear rate.

According to Table 6, other strategy to improve the mechanical properties and tribological performance in coatings is increasing the film compactness, which could play an important role in reducing the wear rate. Khojier and Moradi [98] established that with a lower amount of carrying gas (i.e., argon) during ZrO₂ deposition, smaller grains and a more compact structure are produced, which influence the mechanical and tribological properties positively. Furthermore, Alamdari et al. [112] discussed the role of compactness in refractory high-entropy alloys (RHEA) coatings over Ti-6Al-4 V substrates and concluded that, if it increases, the shear band motion is impeded, which originates improvement on the mechanical and tribological properties. The coating procedure could also determine the densification as, for example, the significant improvement in this coatings' characteristic achieved with HiPIMS technology or other enhanced plasma deposition methods. For instance, Hovsepian et al. [123] increased the compactness, as shown by SEM cross-section micrographs, of CrN/NbN multilayer film deposited by HiPIMS after nitriding of the substrate.

Other possible path to increasing the coating integrity against wearing or scratches is the occurrence of well-defined textures in the

Table 5
Mechanical and tribological properties of different coating/substrate systems obtained by PVD.

Substrate/film	Mechanical properties	Tribology performance	Test conditions	Overall results	Main application	Ref.
Ti-6Al-4V/ Ta _m O _n	H ^a = 7.9 GPa (@ 10 mN) E ^b = 156.3 GPa H/E = 0.051 H ³ /E ² = 0.020 GPa	Average COF ^c = 0.13 Wear rate = 3.99×10^{-3} mm ³ /Nm	Type: Reciprocating Counterbody: GCr15 Load: 6 N Sliding speed: 6 mm/s Track length: 6 mm Time: 5 min Distance: 2000 m	The positive interfacial effects and bonding strength in multilayered configuration showed the best performance.	Diffusion barrier (for toxic ions), implants.	[55]
CoCrMo/CrN-NbN	H = 23 GPa E = 294.9 GPa H/E = 0.078 H ³ /E ² = 0.135 GPa	COF = 0.6 Wear rate = 1.18×10^{-6} mm ³ /Nm	Type: Reciprocating Lubricant: 0.9 wt% NaCl solution Counter bodies: SS316L, Si ₃ N ₄ and Ti-6Al-4 V Load: 10 N Reciprocating frequency: 50 Hz Track length: 1 mm Time: 24 min	The processing (HiPIMS + Plasma nitriding) influences the film properties. An effective control over ionic releasing was registered.	Diffusion barrier, improved mechanical properties for implants.	[123]
SS316L/TiN	H = 21.9 ± 0.95 GPa (@ 35 mN)	COF = 0.59 (vs. SS316L); 0.78 (vs. Si ₃ N ₄); 0.68 (vs. Ti-6Al-4 V) Wear rate = 0.048 (vs. SS316L), 0.114 (vs. Si ₃ N ₄) and 1.682 (vs. Ti-6Al-4V) × 10 ⁻⁴ mm ³ /Nm	Type: Reciprocating Lubricant: 0.9 wt% NaCl solution Counter bodies: SS316L, Si ₃ N ₄ and Ti-6Al-4 V Load: 10 N Reciprocating frequency: 50 Hz Track length: 1 mm Time: 24 min	The hardness increasing in the nitrided substrate with the improved coating adhesion enhanced the functionalised surface.	Improve wear resistance, implants.	132
AZ31 alloy/ Nb ₂ O ₅	H = 3.2 GPa (@ 2 mN) E = 83.2 GPa H/E = 0.038 H ³ /E ² = 0.005 GPa	Mean COF = 0.22 Wear rate = 0.04×10^{-3} mm ³ /Nm	Type: Reciprocating Counterbody: GCr15 Load: 1 N Sliding speed: 6 mm/s Track length: 6 mm Time: 5 min	Multilayered structure significantly improves the damage resistance due to their higher adhesion and lesser defects.	Reduce Mg degradation in implants.	[78]
TA2/SiN-DLC	–	COF = 0.087	Type: Ball-on-disk Lubricant: SBF Counterbody: Al ₂ O ₃ Load: 2 N Speed: 2.5 mm/s Track length: 1 mm Time: 20 min	Graphitization of the film helps to reduce the friction and hence, the wear.	Dental and orthopaedic fixation parts.	[157]
SS316L/Cr ₂ O ₃	H = 29.76 GPa (@ 3 mN) E = 304.9 GPa H/E = 0.098 H ³ /E ² = 0.284 GPa	Average COF = 0.14 Wear rate ≈ 8.60×10^{-6} mm ³ /Nm	Type: Ball-on-disk (reciprocating) Lubricant: 0.9 wt% NaCl Counterbody: 440-C Load: 10 N Track length: 2.5 mm Cycles: 10000	The improvement in wear resistance was due to the chromium oxide coatings' high hardness and low friction coefficient and their firm adherence to 316 L substrates.	Orthopaedic implants.	[96]
Ti-6Al-4V/ ZrCuFeAlAg	H = 7.0 ± 0.3 GPa E = 116.1 ± 1.8 GPa H/E = 0.060 H ³ /E ² = 0.025 GPa	Average COF = ~ 0.52 (dry)/~0.75 (wet) Wear rate ≈ 4.48 (dry)/7.12 (wet) × 10 ⁻⁴ mm ³ /Nm	Type: Ball-on-disk (reciprocating) Lubricant: Artificial saliva Counterbody: Si ₃ N ₄ Load: 0.12 N Reciprocating frequency: 1 Hz Stroke: 0.5 mm Time: 33.3 min	Regardless the wear condition, the film formed an oxidated tribolayer which increases the wear resistance.	Dental implants.	[109]
SS316L/ZrO ₂	H = ~15 GPa E = ~179.5 GPa H/E = ~0.084 H ³ /E ² = ~0.108 GPa	Average COF = ~0.39	Type: Nanoscratch Indenter: Berkovich Load: 0.60 N Length: 0.004 mm Time: 0.58 min (35 s)	Increase of hardness and wear resistance were ruled by the compactness of the film.	Medical devices (wires, dental abutments, heart valve parts) and implants	[98]
Ti-6Al-4V/Cu-a-C:H	H = ~8.6 GPa E = ~48.8 GPa H/E = ~0.214 H ³ /E ² = ~0.532 GPa	–	–	Sample with the highest hardness showed the lowest elastic modulus. Nanocomposite structure formation rule this behavior.	Orthopaedic implants.	[107]
SS316L/ Nb ₂ O ₅ -TiO ₂	–	Average COF = ~0.095	Type: Sphere-plate (reciprocating) Lubricant: Ringer's solution Counterbody: Bone	Tribocorrosion results pointed that the Nb ₂ O ₅ -TiO ₂ presented an intermediate performance in corrosion and wear resistance, compared with the TiO ₂ and Nb ₂ O ₅ pure layers.	Orthopaedic implants (femoral head).	[97]

(continued on next page)

Table 5 (continued)

Substrate/film	Mechanical properties	Tribology performance	Test conditions	Overall results	Main application	Ref.
			pin Load: 5 N Reciprocating frequency: 1 Hz Stroke: 10 mm Time: 60 min Temperature: 37 ± 0.2 °C			
Ti-6Al-7Nb/ Pd-PdO	H = ~2.1 GPa (@ 3.5 mN) E = ~45.8 GPa H/E = ~0.044 H ³ /E ² = ~0.005 GPa	–	–	Nanoindentation tests revealed that the film with the highest temperature annealing (650 °C) exhibits the maximum hardness and elastic modulus.	Implants (hard tissue replacements and in cardiac applications)	[77]
Ti-6Al-4V/Ti-Zr-Ta-Nb-W + Ag	H = ~16 GPa (@ 3 mN) E = ~200 GPa H/E = ~0.080 H ³ /E ² = ~0.103 GPa	–	–	The mechanical properties were influenced by the film densification and the incorporation of Ag (softening effect).	Orthopaedic Implants (hip joints)	[112]
UHMWPE/Ti, Zr & Ta	H = 0.085 (Ti), 0.071 (Zr) and 0.072 (Ta) GPa (@ 3 mN) E = 1.39, 0.99 and 1.21 GPa H/E = 0.061, 0.072 and 0.060 H ³ /E ² = 0.0003, 0.0004 and 0.0003 GPa	COF: 0.92 (Ti), 1.64 (Zr) and 1.45 (Ta)	Type: Nanoscratch Indenter: Diamond Load: 0.05 N Length: 0.65 mm Time: 8.3 min	Results are mixed but Ti-PE showed the highest hardness and the lowest COF.	Implant mobile joints	[120]
SS316L/a:C	H = ~18.2 GPa (@ 5 mN)	–	–	Hardness increased with lower hydrogen content (empirically calculated) and higher fraction of sp ³ C—C bond (40–60 %).	Fixed orthodontic appliances (wires, bands, tubes).	[99]
Ti-6Al-4V/ Ti _x N _y	H = 30 GPa E = 450 GPa H/E = 0.067 H ³ /E ² = 0.133 GPa	–	–	The film texture (from XRD), the existence of Ti ₂ N phase and the internal stresses could be determinant for the disclosed mechanical properties.	Orthopaedic implants.	[111]
Cp-Ti/Ag:NiTi	H = 7.67 ± 0.6 GPa (@ 0.3 mN) E = 220.16 ± 13 GPa H/E = 0.009 H ³ /E ² = 0.035 GPa	Average COF = 0.12 Wear rate = 0.69 × 10 ^{−7} mm ³ /Nm	Type: Ball-on-disk (reciprocating) Counterbody: Al ₂ O ₃ Load: 0.01 N Speed: 2 mm/s Stroke: 2 mm Time: 30 min	Ag incorporation was determinant to influence the hardness (reduction as Ag increases). Besides, 3 at.% Ag showed the lowest COF and consequently, the lowest wear rate.	Dental and orthopaedic implants.	[102]
SS304L/ZrC	H = 22 GPa (@ 50 mN) E = 275 GPa H/E = 0.080 H ³ /E ² = 0.141 GPa	–	–	The participation of zirconium carbide phase influences the hardness and Young's modulus. Stoichiometric Zr—C film showed the best mechanical properties.	Implants	[65]
SS316L/HfC	H = 21.56 ± 0.3 GPa E = 265.24 ± 1.4 GPa H/E = 0.080 H ³ /E ² = 0.143 GPa	COF = 0.14	Type: Ball-on-disk (reciprocating) Counterbody: WC + 6 % Co Load: 1 N Speed: 8.3 mm/s Time: 30 min	The increase in bias voltage (higher than -150 V) influences the film texture and reduces the grain size, significantly improving the mechanical properties and tribology performance.	Different medical devices (implants, stents, or heart valve replacements)	[95]

^a Hardness.^b Young modulus.^c Coefficient of friction.

hard phases. It has been reported as a hardening or softening process in several coatings systems. Nemati et al. [111] explained how the texture change of the Ti₂N phase in Ti—N coating can influence the improvement of the mechanical properties. Other commonly reported hardening effects that our group has investigated include solid solution or Hall-Petch effects [135]. However, none of the reviewed articles regarding MDs reported these effects. On the other hand, some studies have reported other effects that led to wear reduction or improvement in frictional properties, for example, the formation of a tribolayer at the interface between the counterbody and the film [134]. However, these effects were observed in specific materials and under specific conditions.

In summary, mechanical properties and tribological performance enhancement supplied by sputtered coatings can increase MDs' lasting. Transition metal compounds (i.e., carbides, oxides and nitrides), high-entropy alloys and C-based coatings have been demonstrated to be useful to increase hardness and reduce wear rates, both critical in MDs, especially orthopaedic and orthodontic implants. As mentioned, some limitations must be overcome, and Table 6 shows the current strategies to achieve this objective.

Until now, the corrosion resistance, the mechanical reliability and the tribological performance have been boarded as desirable characteristics which must provide the coatings employed for MDs, especially

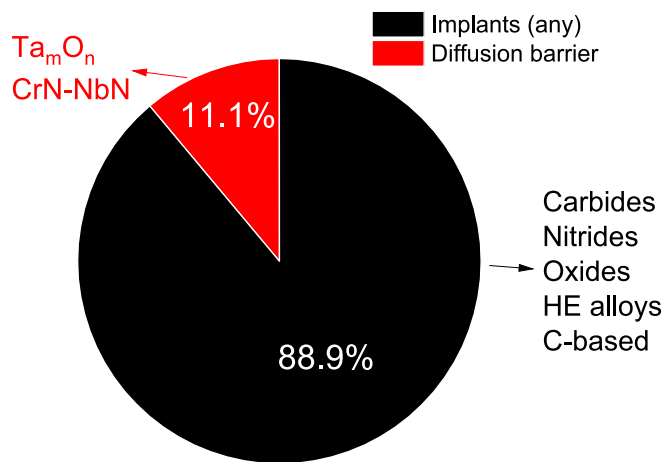


Fig. 7. Application of the enhanced sputtered coatings in mechanical properties and tribological performance. HE – high entropy.

Table 6
Strategies for mechanical and tribological improvement in PVD coatings.

	Adhesion improvement	Film compactness	Well-defined phases
Employed strategies	• Transition layers with intermediate properties between the hard phases and the substrate. • Pre-treatment before coating deposition	• Grain size refinement. • Application of high energetic plasma coating processing (i.e., HIPMS).	• Preferential plane growth. • Solid solution implementation. • Hall-Petch effect.

implants of any kind. However, the coatings also precise to be compatible with the human body and hence, these must possess this capability to be feasible. The next section will provide some insights into the sputtered coatings in enhancing the biocompatibility of MDs and their performance under simulated human body conditions.

3.3. Enhancing the biocompatibility

Biocompatibility refers to the ability of a material to perform its intended function without eliciting any undesirable or harmful local or systemic effects in the body [136]. A biocompatible device must be non-toxic, avoid provoking an adverse immune response, and integrate effectively with surrounding tissue, ensuring both long-term safety and functionality.

After the implantation of a biomaterial, the interaction between the material and host tissue triggers a cascade of events collectively referred to as the foreign body response (FBR) (Fig. 8). This process includes interactions with blood components, the deposition of a protein layer on the biomaterial, the formation of a provisional matrix, immune cell recruitment, acute and chronic inflammation, granulation tissue formation, a foreign body reaction, and ultimately, the development of fibrosis and a fibrous capsule [136,137]. The formation of a collagenous

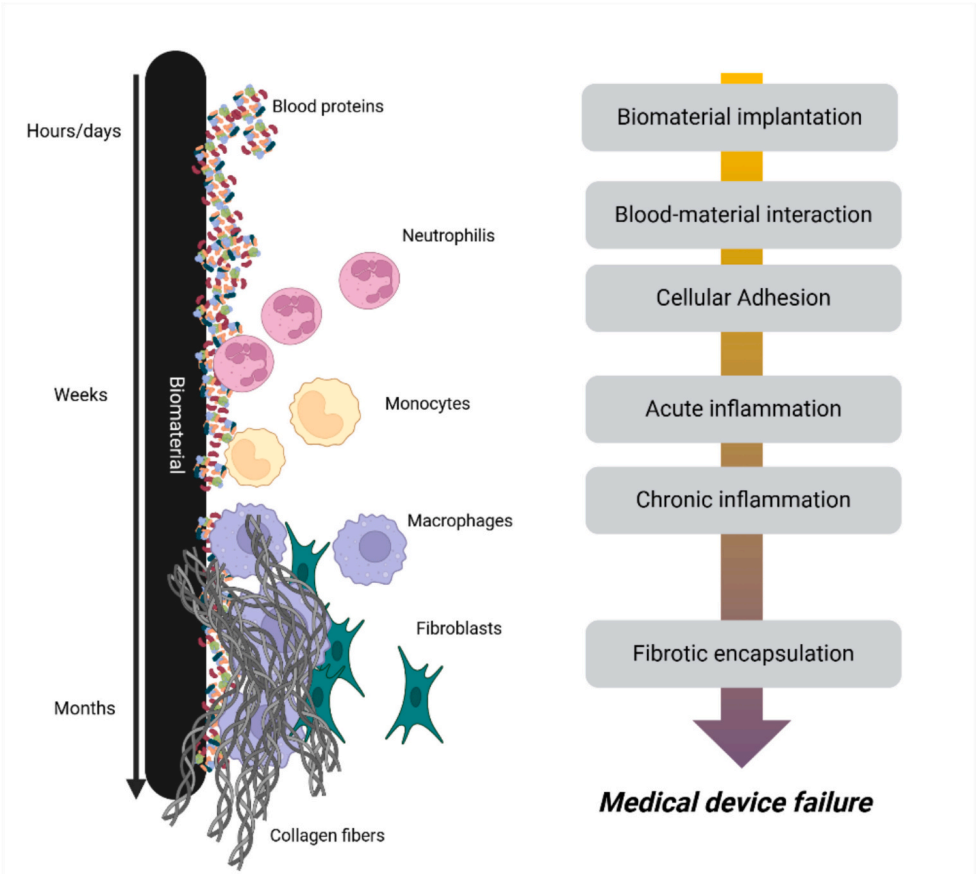


Fig. 8. The timeline and generalized responses that constitute the foreign body reaction. Created in <https://BioRender.com>.

fibrotic capsule can be problematic, as it may isolate the implanted device from the surrounding tissue, preventing proper integration. This lack of integration can lead to device malfunction or failure, as seen in cases where fibrotic capsules form around sensors and pacemakers, rendering them ineffective.

Blood, as the first biological fluid to interact with most implanted materials, plays a critical role in determining the biocompatibility of the biomaterial. Hemocompatibility, or blood compatibility, is a key aspect influencing the overall success of an implant [138]. Hemocompatibility refers to the material's capacity to regulate thrombotic and inflammatory responses upon blood contact. Blood-material interactions trigger a complex cascade of events, including protein adsorption, platelet adhesion and activation, coagulation, and thrombosis. A major challenge in the development of long-term blood-contacting devices is surface-induced thrombosis, driven by platelet-mediated reactions and plasma coagulation on the device surface. Although blood interaction with implants can promote tissue integration in some cases, certain biomaterials require minimized blood contact. For example, metallic stents, which are used to unblock constricted arteries, must be bio-inert to prevent the redeposition of arterial plaque, which can lead to thrombosis and hyperplasia. The release of nitric oxide (NO) by coatings on cardiovascular implants serves as a natural regulator of endothelial functions. NO inhibits platelet adhesion, possesses anti-inflammatory properties, and promotes vasodilation. These effects enhance biocompatibility, reduce complications, and improve the long-term performance of the implant [139,140].

Cell-biomaterial interactions are driven by biochemical and biophysical signals, such as molecular, topographic, and mechanical cues present on the material's surface. These interactions are vital in reducing the negative effects of the foreign body response. The properties of biomaterials can directly influence cell behaviors like adhesion, spreading, migration, proliferation, and differentiation by initiating specific molecular processes at the cell-biomaterial interface. When cell adhesion and proliferation are efficient, inflammation subsides faster, and fibrosis (excessive scar tissue formation) is reduced, preventing unwanted encapsulation of the implant. Modifying surface

characteristics—such as roughness, topography, chemical composition, and wettability—can affect cell adhesion, shape, proliferation, and differentiation (Table 7). Therefore, careful consideration and optimization of surface properties are necessary to achieve the desired cellular responses, improving biomaterial performance in biomedical applications. The surface chemistry has a significant impact on the biocompatibility and immunogenicity of materials. Cells can sense the topographical structure of the underlying surface and adjust their alignment and orientation accordingly. Surface wettability, determined by the adhesive force between a liquid and the solid material surface, influences the spreading of the liquid on the surface. It is widely known that hydrophobic surfaces tend to attract proteins, while hydrophilic surfaces are more conducive to cell attachment and proliferation. Surface energy is a critical factor that determines the wettability of biomaterial surfaces. Materials with low surface free energy exhibit less adhesion compared to those with high surface free energy. For example, to enhance the adhesion between the polymeric poly(methyl methacrylate) (PMMA) of the Boston Keratoprosthesis (BK), a commonly implanted artificial cornea, and the recipient corneal tissue, researchers have explored the use of a Ti coating [141]. The results showed that human corneal fibroblasts (HCFs) cultured on Ti-(p)PMMA exhibited similar cell proliferation compared to cells grown on casted Ti and tissue culture polystyrene (TCP) controls, with TCP being the gold standard for cell compatibility. The observed effect can be attributed to the enhanced hydrophilicity of the PMMA and the increased surface roughness of the Ti-(p)PMMA composite. The incorporation of silicon in carbon nitride (CNx) films also showed an increase in cell adhesion, being the bonding structure and surface energy crucial factors in improving biocompatibility [142]. Moreover, Bhaskar and co-workers demonstrated that SiC_xNyO_z coating not only enhanced the cell–material interaction by re-endothelialization but also could help to reduce bacterial adhesion and activation of blood cells [143]. This coating improves the adherence and growth of SVEC4-10 cells in comparison to a pure metallic Ti substrate. This enhancement can potentially be attributed to the reduced surface wettability and increased roughness of the coatings, both of which play a crucial role in facilitating cell-material interactions. Moreover, SiC_xNyO_z

Table 7
Enhancing biocompatibility of biomaterials: the impact of coatings on surface characteristics and biological response.

Substrate	Coatings	Applied technologies	Effect on surface characteristics	Biological effect	Potential application	Reference
Ti	TiO ₂ TiO ₂ -N TiON TiN	Pulsed-DCMS	Decrease SFE	Improve hemocompatibility by enhancing endothelialization	Vascular stent Vascular scaffolds	[66] [145] [146] [147] [148]
Ti	SiC _x NyO _z	RFMS	N incorporation increases polar component of SFE SiC1.3 N0.76O0.8 roughness of 17 nm and a SFE of 54.0 ± 0.7mN/m demonstrate the best combination of hardness, elastic modulus, and scratch resistance	Hemolysis < 4 % Extend the blood coagulation time Improve adhesion and proliferation of endothelial cells Effective inhibition of bacterial proliferation	Implantable devices (knee and hip joints, heart valves, coronary stents, and intraocular lenses)	[143]
SS	HfC	RFMS	Decrease roughness Improve corrosion resistance Decrease coefficient of friction	Improve hemocompatibility	Cardiovascular implants	[95]
Ti	DLC Si-DLC DLC/ DLC-Ti	DCMS–RFMS	Increase polar component of SFE Increase wettability	Protection against biocorrosion Improve cell proliferation	Hip-implant	[149,157] [150] [62]
Ti	Ti Ti-Zr-Ta	DCMS	Increase hydrophilicity Increase roughness Increase SFE	Enhance cellular adhesion and proliferation	Dental implants	[81] [109]
Ti6Al4V	Si-CN	DCMS	Decrease hardness and elastic modulus Increase surface roughness	Increase cell adhesion Down regulated the production of cytokines and chemokines by monocytes	Joint implants	[142]
SS	Ti-Al-N	DCMS	Decrease coefficient of friction	Enhance cell proliferation	Implants	[151]
SS	TaC	DCMS	Decrease roughness and wettability	Improve cell adhesion and proliferation	Implants	[152]

coatings were evaluated for their compatibility with erythrocytes and platelets *in vitro*. The hemolysis test showed that SiCNO coatings had a lower mean percentage of hemolysis compared to pure Ti substrate and DLC coatings. The improved blood compatibility and anticoagulant performance of SiCNO coatings can be attributed to their lower water contact angles and higher polar component of surface free energy. These surface properties likely facilitated the preferential adsorption of albumin proteins and reduced the adsorption of fibrin, resulting in less platelet adhesion.

Another important cellular response is cell proliferation. Surface modification can be designed to enhance cell proliferation by providing a favorable microenvironment for cell growth. This can be achieved through the incorporation of bioactive molecules or signaling proteins onto the surface of the biomaterial, which can stimulate cell division and proliferation. Furthermore, surface-modified biomaterials can affect cellular responses at the molecular level. For example, certain surface modifications can modulate the expression of specific genes or proteins within cells, leading to changes in cell behavior and function. This molecular-level control allows for precise manipulation of cellular responses in biomaterials.

Adverse immune reactions to implanted materials can have immediate negative outcomes, including intense pain, inflammation, rejection, or delayed effects such as chronic inflammation. Among the various immune cells involved, macrophages play a crucial role in mediating the immune response towards implanted materials, coordinating both the inflammation and tissue remodeling stages. Stankevich et al. investigated the influence of plasma treatment duration on poly (ϵ -caprolactone) (PCL) scaffolds during DC reactive magnetron sputtering of Ti–N films [144]. Through XPS analysis and DFT calculations, it was shown that the plasma treatment resulted in the cleavage of C–C and C–O bonds in PCL, leading to the formation of radicals. These radicals interact with nitrogen radicals from the plasma or water absorbed on the fiber surfaces and within the pores, leading to the formation of amine and amide groups. Concurrently, a TiO₂ layer forms on the scaffold surface. Longer treatment times led to deeper nitrogen-enriched TiO₂ penetration, confirmed by EDAX and XPS analyses, and enhanced hydrophilicity. These surfaces, known for promoting anti-inflammatory and pro-healing macrophage activity, reduced reactive oxygen species (ROS) production by monocytes while maintaining macrophage scavenging function. Recently, our research group developed a novel surface modification strategy involving the deposition of Zn–ZnO nanoparticles onto porous calcium phosphate (CaP)-enriched Ta₂O₅ surfaces via DC magnetron sputtering [49]. This plasma-assisted approach demonstrated that fine-tuning surface chemistry and topography—particularly through Zn incorporation and the presence of a carbon layer—plays a key role in guiding macrophage behavior. Our results showed a marked promotion of anti-inflammatory macrophage polarisation, a reduction in oxidative stress, and enhanced regenerative outcomes. This understanding of immune modulation is critical for designing biomaterials with improved biocompatibility, osseointegration, and regenerative potential. Therefore, the primary objective of biomaterial design is to create materials that can harness the body's natural defense and healing mechanisms. Thus, to promote tissue healing and integration while mitigating the adverse effects of FBR and fibrotic capsule formation, coatings have been developed that enhance endothelialization and promote cell adhesion and proliferation.

The following sections detail coatings for the most commonly used substrates, including Ti-based substrates, stainless steels, and biodegradable metal substrates.

3.3.1. Ti-based substrates

Titanium (Ti) stands out as a distinctive member of the biomedical alloys, widely used in applications such as dental implants, pacemaker housings, craniofacial implants, and spinal surgery staples and screws. Commercially pure Titanium (CP Ti) bioimplants exhibit excellent biocompatibility due to the formation of a titanium oxide layer (TiO₂) on

the surface. As discussed above, this layer is stable and strong, preventing oxygen diffusion and providing high resistance to corrosion. However, there are significant issues concerning the safety and long-term durability of Ti and its alloys as implants in the human body, often leading to secondary surgeries. A major concern is the potential release of ions from Ti and its alloys into the body, which can result in toxicity, inflammation, and thrombus formation. Moreover, the mismatch in Young's modulus between human bone (~30 GPa) and Ti implants (110–120 GPa) causes stress-shielding effects [138]. This phenomenon occurs when the stiffer implant bears most of the mechanical load, reducing the stimulation of the surrounding bone tissue. This can lead to bone resorption, tissue loss, and eventually implant failure. Titanium and its alloys are also widely used in cardiovascular devices, such as stents and heart valves, which is why one of the major challenges is preventing excessive endothelialization on the surfaces of these devices. Uncontrolled endothelialization can lead to serious complications, including thrombosis, prompting investigations into coatings that facilitate the release of nitric oxide (NO) as a preventive measure. For instance, Sun et al. conducted a study to investigate the impact of nitrogen doping on glass-supported TiO₂ thin films. [66] In the presence of a nitrogen (N₂) containing atmosphere, TiO₂-based thin films underwent nitrogen doping, enabling them to function as donors of nitric oxide (NO). Nitrogen-doped thin films exhibited comparable characteristics to pristine titanium dioxide thin films, including crystallite size, phase composition, roughness, and mechanical properties. However, the presence of nitrogen in thin films suppresses the proliferation and differentiation of human adipose tissue derived mesenchymal stem cells to osteoblasts. This cell growth suppressing effect of the deposited TiON thin films can be explained by the combined effect of oxidative stress created by reactive oxygen species (ROS) generated from the thin film surfaces [145], as well as to a lower polar surface energy component of the thin film surface. Moreover, coatings based on titanium nitride (TiN) [153,154], titanium oxide (TiO) [155], titanium oxynitride (TiON) [146], titanium aluminum nitride (TiAlN), and titanium carbonitride (TiCN) [156] have shown promising potential for enhancing the performance of cardiovascular implants [147] (Fig. 9). For example, Liu et al. showed that TiO film-modified stent exhibited rapid tissue coverage by the 2nd week, surpassing the bare stent in terms of speed of coverage [148]. This coating did not only demonstrate good biocompatibility but also did accelerate the process of endothelialization. Ti and Ti alloys can be also coated with DLC films, providing a protective layer against wear and corrosion [149,157].

Numerous studies conducted by various scientific groups have demonstrated that DLC films possess exceptional properties, including high wear resistance, favorable physiochemical properties, superior corrosion resistance, and excellent biocompatibility and hemocompatibility [158]. To further enhance the properties of DLC films, different elements can be incorporated into the carbon matrix. Silicon (Si) is one of the most extensively researched dopants for DLC coatings, known to improve hemocompatibility, cell proliferation, and antibacterial resistance according to the literature [149,159]. Moreover, the addition of Si to the DLC matrix enhances its chemical, mechanical, and tribological characteristics, leading to increased hardness, reduced friction coefficient, and residual stress [160]. In a study conducted by Bociaga et al., Si-doped DLC coatings were evaluated on Ti6Al7Nb substrates using co-sputtering of silicon and graphite targets [149]. The investigation highlighted that elevating Si concentrations, specifically at 22 % atomic, led to an augmented surface wettability. This enhancement on wettability, along with the increase in the polar component of the surface free energy (SFE) observed in coatings with higher Si content, was attributed to the heightened presence of Si–O bonds. While it is well-established that improved surface wettability fosters cell proliferation, this research introduces a nuanced perspective. The positive correlation between wettability and cell proliferation was evident only up to the threshold of 22 at. % Si. Beyond this point, despite further increases in wettability, cell proliferation diminished, indicating that biological

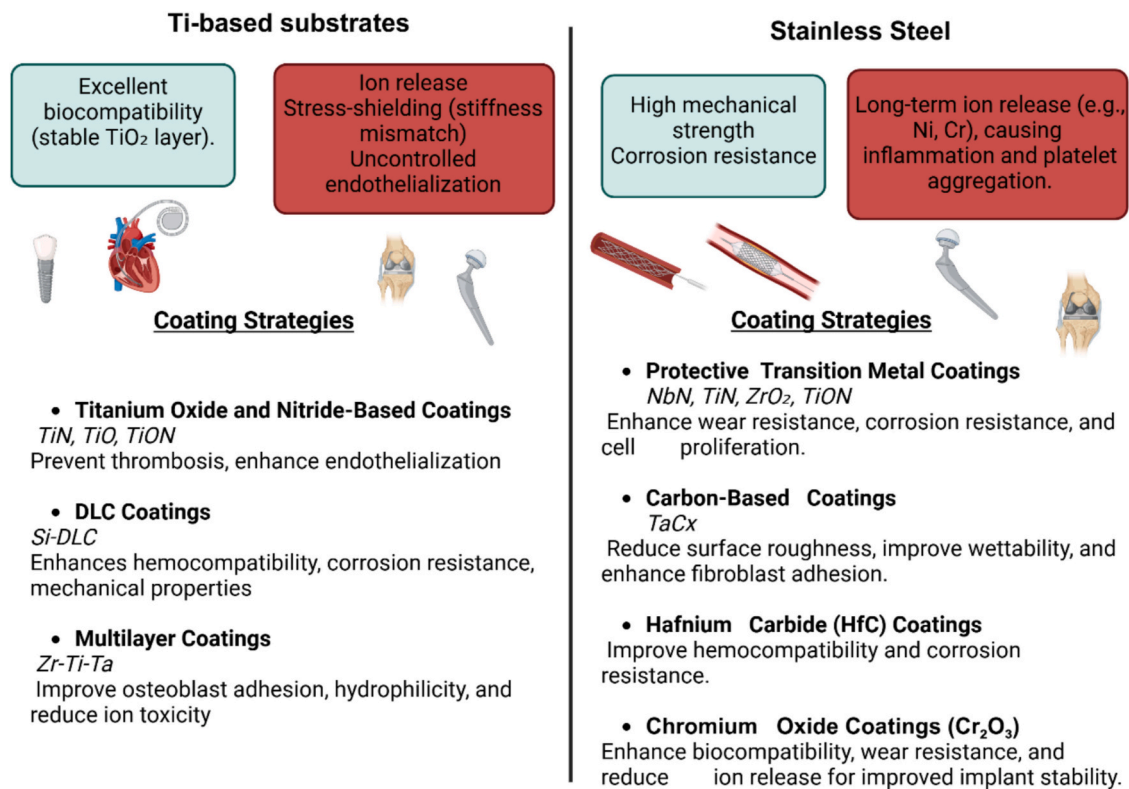


Fig. 9. Optimized coating strategies for Ti-based substrates and stainless steel implants: Tailored solutions to enhance biocompatibility, improve mechanical performance, and mitigate adverse effects such as ion release, stress shielding, and thrombosis risk. Created in <https://BioRender.com>.

responses are not solely dependent on wettability. Achieving a delicate equilibrium between the polar and dispersive components of the SFE becomes imperative to ensure the attachment of extracellular matrix proteins to the surface. Failure to strike this balance may result in the preferential attachment of water to the surface, thereby restricting the adhesion of cells. To further enhance Si-DLC coatings, adopting multi-layer periodic structures with alternating DLC layers and thin Si layers presents a promising avenue. In comparison to coatings composed of a single layer, or a nanocomposite with randomly embedded additives, a structured coating with multiple layers of distinct materials may offer additional advantages through synergistic effects [150]. Penkov et al. demonstrated the efficacy of this approach, revealing that a periodic structure comprising alternating nanolayers of Si and DLC enabled precise control of mechanical properties and enhanced biocompatibility of the coatings [62]. Notably, the study found that the bias mode and voltage had negligible effects on cell adhesion, emphasizing the significance of individual layer thicknesses. The thickness of DLC layers played a pivotal role, influencing hardness and cell adhesion inversely. A greater DLC thickness resulted in higher hardness but lower cell adhesion. Conversely, higher Si thickness improved the cell adhesion but compromised the hardness, leading to a reduced wear resistance. Striking a balance between these factors, the authors determined that thicknesses of 0.5 nm for Si and 1 nm for DLC layers were optimal for achieving the desired combination of mechanical properties and biocompatibility.

In vitro studies have revealed the biotoxicity of Al and V ions released by the Ti-6Al-4 V alloy, which hampers osseointegration [161]. To enhance the biological performance of the Ti-6Al-4 V alloy, mono-layer Ta coatings, as well as multi-layer Ti-Zr-Ta and Zr-Ti-Ta coatings, were prepared using magnetron sputtering on the alloy [81]. Remarkably, the droplet contact angle on all sample surfaces remained below 90° , indicating the hydrophilic nature of the coatings. The hydrophilic surfaces, when in contact with blood and biological fluids, foster protein adsorption that exposes adhesion motifs, thereby

promoting enhanced cell adhesion, proliferation, and differentiation. This was substantiated by live/dead cell staining images of osteoblast precursor cells (MC3T3-E1) cultured on the samples for 24, 96, and 168 h, revealing robust cell proliferation over time with no observed cell death [81]. Furthermore, DLC/DLC:Ti nanomultilayer films demonstrated a significant reduction in the release of harmful metals and the inflammatory response associated with medical Ti6Al4V prostheses [114,162].

Zr-based thin film metallic glasses (TFMGs) have garnered significant attention in dental applications in recent years. This is attributed to their notable capacity to enhance adhesion, resist fretting, mitigate biocorrosion, and improve overall biocompatibility of materials. A $\text{Zr}_{60.14}\text{Cu}_{22.31}\text{Fe}_{4.85}\text{Al}_{9.7}\text{Ag}_3$ bulk metallic glass (BG) system, free from toxic elements such as Ni and Be, was deposited onto a Ti6Al4V substrate using a single-target magnetic sputtering method [109]. In comparison to the Ti6Al4V alloy, the cell density on the TFMG remains similar. However, noteworthy differences in cell adhesion morphology are evident, with the TFMG displaying a more flattened cell shape and overlapping of adjacent cells. This observation suggests superior adhesion and healthy cell growth on the biocompatible TFMG surface as opposed to the Ti6Al4V alloy.

3.3.2. Stainless steels

Stainless steel (SS) is extensively employed in the fabrication of cardiovascular stents/valves, orthopaedic prostheses, and various other biomedical devices and implants due to its remarkable malleability and resistance to corrosion and fatigue. Despite these advantages, implants constructed from this material face a challenge of limited longevity under human physiological conditions, resulting in the leaching of metal ions.

In the quest for optimizing surface characteristics, improving resistance against wear and corrosion, and heightening biocompatibility, researchers have explored the application of transition metal films protective coatings (Fig. 9). Examples include NbN [163,164], TiN

[164], TiO₂ [70], ZrO₂ [101], and TiON [165]. These thin films have garnered significant attention due to their desirable properties, including high hardness, good wear resistance, excellent corrosion resistance, and high chemical stability [91]. The biocompatibility, and ability to enhance cell proliferation while reducing friction make titanium aluminum nitride (Ti-Al-N) one of the most favorable coatings for various biomedical applications [151]. Additionally, niobium oxynitride coatings have demonstrated the capacity to enhance the viability of human fibroblast cells [166], whereas metal-doped tantalum coatings contribute to a more robust antimicrobial and biocompatible profile [167–169]. Poladi et al. conducted a study to investigate the effect of various CH₄ concentrations (ranging from 0 to 30 %) on the wettability and biocompatibility of TaCx films deposited on SS316L [152]. The results showed that an increase in carbon content, resulting from higher CH₄ concentrations, caused phase changes in the coatings. Initially, the metallic phase transformed into a ceramic phase, and eventually into amorphous carbon. Additionally, the incorporation of carbon in the films led to a continuous decrease in roughness and wettability. The biocompatibility test and cell morphology results indicated that surface modification significantly improved cell functionality in terms of cell adhesion and spreading. Furthermore, the chromium oxide (Cr₂O₃) coating significantly improved the corrosion and wear resistance, reduced friction coefficient, and enhanced biocompatibility of the SS. This improvement was evident as significantly fewer chromium ions were released after immersion in a saline solution [96].

As mentioned above, numerous studies have provided substantial evidence that long-term implantation of SS316L cardiovascular devices, such as stents, results in the generation of toxic metal ions such as Ni, Cr, and Mo within the body. These ions have the potential to degrade cellular structures, trigger platelet activation, and induce the release of platelet granules. This cascade of events can promote coagulation, alter platelet morphology, and lead to increased stickiness, ultimately contributing to the aggregation of platelets and the occlusion of small vascular openings. One promising approach to address this issue is the development of coatings with enhanced blood compatibility. As an example, Pei et al. deposited hafnium carbide (HfC) coatings on 316 L steel and substantiated that meticulous control of the bias voltage offers a viable pathway to improve the mechanical properties, corrosion resistance, and hemocompatibility of the HfC coatings [95]. The hemocompatibility test results unveiled a noteworthy finding: HfC coatings prepared at both -150 V and -200 V showcased superior hemocompatibility in comparison to 316 L steel and the other two coatings produced at bias voltages of 0 V and -100 V. This remarkable enhancement can be linked to the progressive decrease in surface roughness and surface energy as the bias voltage exceeded -150 V. Consequently, these coatings were rendered more suitable for interaction with blood components. Furthermore, the HfC coating generated at a bias voltage of -200 V exhibited outstanding corrosion resistance, attributed to its smoother surface, improved adhesion, denser structure, and the lowest coefficient of friction against phosphate buffer solution (0.14).

3.3.3. Biodegradable metal substrates

Biodegradable metals, such as magnesium, zinc, and iron, are highly regarded as next-generation biomaterials for various biomedical applications [170]. These metals possess desirable properties that make them suitable candidates for use in medical implants and devices. They exhibit excellent biocompatibility, mechanical strength, and the ability to degrade over time within the physiological environment. This biodegradation process eliminates the need for implant removal surgeries, reducing patient discomfort and potential complications. Additionally, these metals have been shown to promote tissue regeneration and have potential therapeutic effects, making them promising materials for future biomedical advancements [171]. Nevertheless, it is important to acknowledge certain limitations associated with these materials. Specifically, their strength and ductility might fall short for meeting the

demands of load-bearing implants, particularly in applications such as cardiovascular and orthopaedic settings. In addition, cells exhibit a relatively low tolerance against Zn ions and a Zn concentration of 6.5 ppm can do severe damage to endothelial cells. To address this limitation and enhance the biomechanical performance of zinc implants, surface modifications such as titanium coatings [125], oxide layers [172], and titanium oxynitride coatings [117] have been strategically deposited. For instance, a smooth-surfaced titanium oxide coating, measuring 400 nm in thickness and composed of dense amorphous TiO₂ nanoparticles, was meticulously deposited onto the MgZn substrate. The application of this coating notably enhanced the corrosion resistance of the MgZn alloy. After a 14-day immersion in simulated body fluid (SBF), the TiO₂-coated sample exhibited less corrosion compared to the uncoated substrate. In terms of blood compatibility, the uncoated Mg alloys induced serious hemolysis and platelet aggregation, while the TiO₂-coated sample demonstrated a hemolysis ratio of <1 % and exhibited superior anti-platelet adhesion. Furthermore, the TiO₂-coated MgZn alloy demonstrated lower cytotoxicity, with endothelial cells attaching well to the surface, indicating excellent cytocompatibility [115].

3.3.4. Other biocompatible materials

In addition to the conventional materials commonly employed in biomedical devices, highlighted earlier, surface engineering modifications have also been extended to polymeric substrates, high-entropy alloys, and bulk metallic glasses [128] to enhance their biocompatibility.

High-entropy alloys (HEA) have arisen as a key class of advanced materials for biomaterials applications. Cemin et al. use a near-equimolar combination of Nb, Ta, Ti, V, and Zr transition metals to design a high-entropy amorphous coating, demonstrating superior in vitro biocompatibility with bone cells [130]. The remarkable in vitro biocompatibility of this coating, compared to its polycrystalline HEA prototype and the Ti (control) coating, can be attributed to factors such as material surface uniformity, smoothness, a stable chemical state, reduced concentration of vanadium, and enhanced corrosion resistance.

In contrast to their conventional crystalline metallic counterparts, bulk metallic glasses (BMGs) have unique amorphous structures, resulting in heightened strength, a lower Young's modulus, improved wear resistance, robust fatigue endurance, and excellent corrosion resistance. These distinctive attributes have generated considerable interest in the biomedical field, establishing BMGs as highly promising materials with versatile applications [173]. To determine excellent features of Zr-based metallic glasses for bioimplants, novel quaternary systems, namely Zr₄₀Ti₃₇Co₁₂Ni₁₁ and Zr₅₀Ti₃₂Cu₁₃Ag₅, were fabricated using the magnetron co-sputtering technique [128]. Electrochemical evaluations revealed superior corrosion resistance in Zr₅₀Ti₃₂Cu₁₃Ag₅ and Zr₄₀Ti₃₇Co₁₂Ni₁₁ metallic glasses, suggesting their efficacy in preventing adverse biological reactions. Furthermore, the quaternary metallic glasses exhibited substantial surface free energy, signifying enhanced cell interaction with the implant surface. Cytocompatibility assessments via MTS assay revealed minimal toxicity towards MC3T3-E1 preosteoblast cells.

In conclusion, PVD coatings play a pivotal role in enhancing the biocompatibility of medical devices by supporting cell adhesion, proliferation, and differentiation, while mitigating immune responses and limiting ion release. Applied to both conventional substrates like titanium and stainless steel, as well as emerging materials such as biodegradable metals, high-entropy alloys, and metallic glasses, these coatings offer versatile functionalization. Tailored coatings such as TiN, TiO₂, and DLC significantly improve hemocompatibility and suppress immune activation, whereas multilayer systems like Zr-Ti-Ta promote osteoblast adhesion and minimize cytotoxic effects.

3.3.5. Advancing biocompatibility testing: bridging the gap between in vitro and in vivo models

To evaluate the biocompatibility of biomaterials, it is essential to

perform a series of tests following the guidelines set by regulatory organizations. Over the years, there have been adaptations to the requirements and tests that determine the biocompatibility of materials, such as the ISO 10993-Part 22: Edition 1 standard, which aligns with FDA guidelines [174]. The limitations of several *in vitro* methods used to test biomaterials are evident as they fail to accurately replicate the dynamic and complex physiological conditions found in the human body. The *in vivo* environment is characterized by constantly changing fluids and cellular interactions, which cannot be fully captured in static *in vitro* tests. As a result, it is crucial to acknowledge these limitations and explore alternative approaches that can better simulate the *in vivo* conditions when evaluating the biocompatibility of biomaterials. 3D *in vitro* models are emerging as a more realistic representation of tissue, or organs compared to 2D models. These 3D models provide a more accurate prediction of various processes, such as cell proliferation or fibrosis, in the presence of implants. Furthermore, the development of bioinformatic models that allows the comparison between cytotoxicity data obtained from different research groups its crucial [175].

3.4. Fostering osseointegration

Biomaterials used in orthopaedic applications must meet various structural, mechanical, and biological criteria because of their essential role in the bone regeneration process [176]. Regarding their biological characteristics, it is crucial to consider the biocompatibility, osteoconductivity, and osteoinductivity. Biocompatibility, as mentioned above, refers to the material's ability to elicit an appropriate host response without any adverse effects such as cytotoxicity, mutagenesis, carcinogenesis, immunogenicity, or genotoxicity. Osteoconductivity

represents the biomaterial's capacity to promote cell adhesion, proliferation, and the formation of the bone extracellular matrix (ECM) by osteoblasts, thereby supporting bone growth. Osteoinductive biomaterials are highly desirable as they can induce the differentiation of mesenchymal stem cells into osteoblasts, which are responsible for bone formation. Altogether, these properties indicate the material's bioactivity and are critical to successful osseointegration of the implant with the host tissue [177]. Effective osseointegration indicates the implant's capacity to form bone-like apatite crystals on their surfaces and establish a direct connection with the surrounding host bone tissue without the formation of undesirable fibrous tissue.

Biomaterials used in bone tissue engineering are commonly categorized into polymeric, ceramic, metallic, and composite materials. Among these, metallic biomaterials such as titanium and its alloys, stainless steel, cobalt, magnesium and its alloys, nickel–titanium alloy (nitinol), and tantalum are widely used in bone implants. Despite the several advantages of metallic biomaterials, these materials can be cytotoxic due to corrosion when exposed to complex physiological conditions within the body and are biologically inert. This inherent characteristic presents challenges for its successful integration with bone tissue following implantation, resulting in prolonged postoperative healing time and potential complications, including implant loosening and failure. These issues can significantly impact the overall success and longevity of the implant, emphasizing the need for improved strategies to enhance the bioactivity and osseointegration of implants to improve patient outcomes (Fig. 10).

3.4.1. Ti-based or alloyed substrates

Calcium phosphate (CaP) biomaterials share similarities with bone

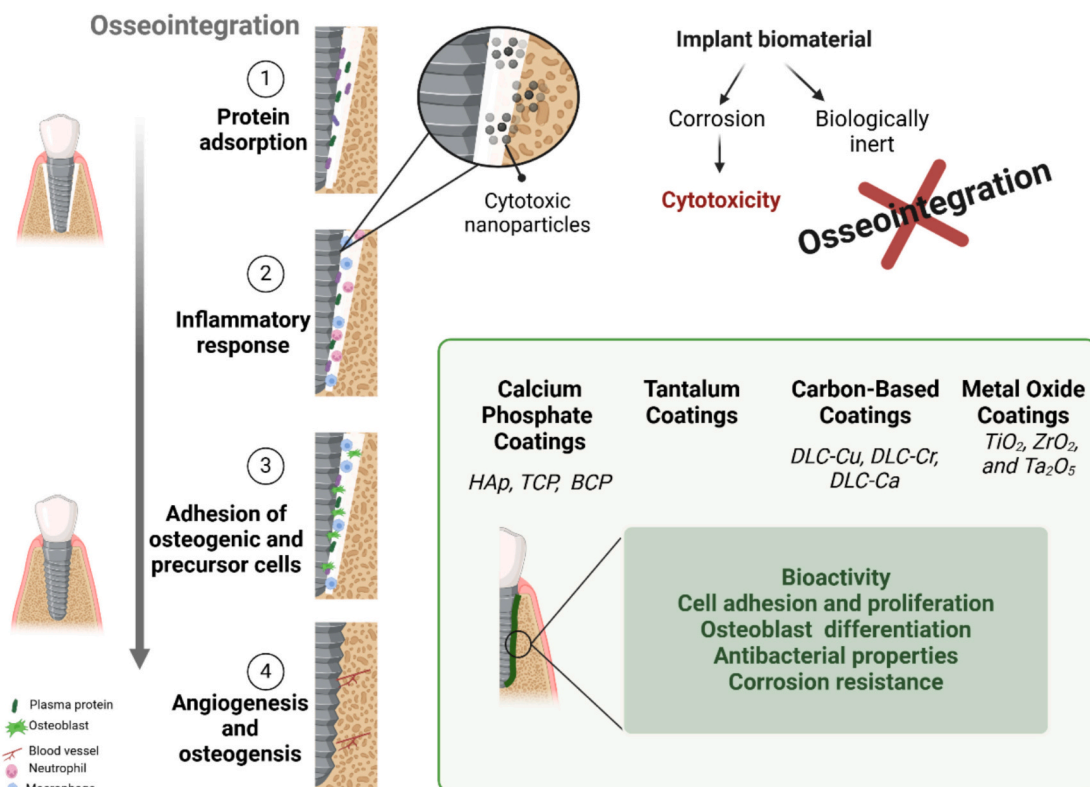


Fig. 10. The osseointegration process and its challenges. The diagram illustrates the key stages of osseointegration, starting with protein adsorption (1), followed by the inflammatory response (2), osteogenic cell adhesion (3), and concluding with angiogenesis and osteogenesis. Common metallic biomaterials such as titanium, stainless steel, and magnesium alloys face significant challenges, including corrosion and biological inertness. These limitations result in prolonged healing, implant loosening, and potential implant failure, underscoring the need for enhanced bioactivity. Advanced coating technologies, such as calcium phosphate, tantalum, carbon-based, and metal oxide coatings, are highlighted as effective solutions. These coatings improve bioactivity, enhance cell adhesion and osteoblast differentiation, provide antibacterial properties, and increase corrosion resistance, ultimately supporting successful osseointegration and improving implant performance. Created in <https://BioRender.com>.

minerals in terms of biodegradability, bioactivity, and osteoconductivity. In addition, the application of CaP-based coatings on metallic implants provides enhanced corrosion resistance, minimizing the release of metal ions into the implantation site [178]. This further contributes to the overall success of the implant by reducing potential adverse effects and promoting a more favorable healing environment. Therefore, biomaterials, particularly metallic implants, are usually coated with a layer of CaP such as hydroxyapatite (HAp), $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$, tricalcium phosphate (TCP), or CaP glass-ceramics to enhance the osseointegration. Biphasic calcium phosphate (BCP), which consists of hydroxyapatite (HA) and beta-tricalcium phosphate (β -TCP), is mainly used in artificial tooth and bone implants due to higher protein adsorption and osteoinductivity compared to HA alone. To obtain a better understanding and applications of BCP films, RF magnetron sputtering was used to deposit BCP films on Ti-6Al-4 V. [179]. The in vitro bioactivity results showed small globular and elliptical like structures on the surface of all BCP films after 14 days of SBF immersion, which indicates the coating films possess bioactivity.

Tantalum has garnered significant interest as both a porous bulk material and a coating for implants, particularly in the field of orthopedics [180]. This metal possesses several properties that make it highly appealing for such applications, including exceptional corrosion resistance in body fluids, improved osteoconductivity, and superior resistance to bacterial adherence compared to titanium. Bartkowiak et al. investigated the contribution of a protective tantalum interlayer deposited on titanium substrates on the growth of HAp crystals with hydrothermal synthesis method [181]. The diameter of HAp crystallites may be controlled and driven by nature of the interlayer (tantalum, tantalum oxide or titanium oxide) previously formed on the titanium substrate. Coatings with smaller diameters of HAp crystals (between 0.3 μm and 0.6 μm) synthesized on tantalum-based films were found to be more favorable for cell viability and attachment. Similarly, Cheon et al. revealed that the introduction of a Ta implanted layer, approximately 10 nm in thickness, onto the uppermost surface of poly(ether imide), resulted in sustained surface hydrophilicity and created an advantageous environment conducive to the adhesion, proliferation, and differentiation of MC3T3-E1 pre-osteoblasts [182].

Over the last few years, a wide array of carbon-based composites has been extensively explored and research has consistently shown that the inclusion of additional elements can markedly enhance their overall mechanical and biological characteristics [183]. Milan et al. showed the potential of Cu/a-C:H thin coatings, particularly those with an optimal combination of 36.8 wt% copper content and a sp^2/sp^3 ratio of 4, as promising candidates to improve the mechanical and tribological properties and enhance osseointegration of Ti-6Al-4 V-based implants [107]. The effect of DLC layers with different content of Cr on the adhesion and osteogenic differentiation of human osteoblast-like Saos-2 cells was also assessed in vitro [184]. The authors conclude that higher concentrations of chromium supported cell adhesion; however, DLC and DLC doped with a lower concentration of chromium supported osteogenic cell differentiation. Similarly, the incorporation of Ca nanoparticles not only enhanced the mechanical attributes of the a-C film but also notably fortified its adhesion to osteoblasts [185]. In an alternative approach, gradient multilayers composed of Ti and C were deposited onto a titanium alloy substrate using MS [57]. The resulting coating demonstrated improved wettability of the Ti alloy surface, leading to enhanced proliferation and adherence of osteoblast cells.

Silicon-containing materials have also garnered attention for their ability to stimulate the proliferation and differentiation of human osteoblast-like cells. One notable example is the use of silicate-based bioactive glasses, which release ionic dissolution products that have been shown to significantly enhance cell proliferation and osteogenic differentiation [186]. Titanium silicon nitride (TiSiN) thin films have demonstrated their potential in promoting the differentiation of human bone cells, surpassing the performance of the bare control Ti alloy [110]. This was evidenced by the increased production of alkaline phosphatase

and calcium. Moreover, TiSiN thin films offer improved corrosion resistance, effectively protecting the underlying metal from the harmful effects of the corrosive environment.

Metal oxide coatings, including TiO_2 , ZrO_2 , Nb_2O_5 , VO_2 and Ta_2O_5 , offer great potential as coatings for orthopaedic and dental implants [187]. These coatings possess numerous beneficial properties, such as their remarkable osseointegration ability, ability to enhance cell adhesion and proliferation, reduce inflammatory response, and exhibit antibacterial properties [189]. Additionally, they demonstrate excellent corrosion and wear resistance [190]. Horandghadim et al. established a noteworthy correlation between the concentration of Ta_2O_5 in HAp- Ta_2O_5 coatings and two vital factors in bone tissue engineering: osteoblast-like cell attachment and the growth of bone-like apatite [191]. This investigation underscores that as the Ta_2O_5 content increases, so does the propensity for cellular adhesion and the formation of apatite resembling natural bone. Building upon these findings, Wang et al. extended the exploration to titanium nanotubes coated with Ta_2O_5 , revealing substantial improvements in cell adhesion, viability, enhanced calcium deposition, and the expression of key osteogenic genes when compared to uncoated nanotubes [192]. Consistently, our group [193] and Huang et al. [194] corroborated these observations by reporting heightened viability of MC3T3 cells, human skin fibroblasts, and human osteosarcoma MG-63 cells when cultured on Ta_2O_5 -coated surfaces in comparison to bare titanium substrates. According to Lizárraga et al., ZrO_2 represented a potential alternative to TiO_2 , since ZrO_2 films promoted higher adhesion of MG63 cells, and had higher corrosion resistance due to their higher electrochemical stability and surface integrity compared to TiO_2 [195].

The application of a strontium titanate (SrTiO_3) nanoparticles coating on titanium surfaces has shown remarkable potential in enhancing adhesion, proliferation, and osteogenic differentiation of MC3T3-E1 cells [196]. To enhance the osteogenesis and antibacterial efficiency simultaneously, a new double-layer strategy (the precedent Ag nanoparticle layer and the overlaying SrTiO_3 layer) through two-step magnetron sputtering was developed [197]. Christensen et al. demonstrated in a rabbit model that the release of strontium (Sr) from a Ti-Sr-O-coated implant diffuses over several hundred microns into the surrounding bone tissue [198]. This diffusion was evident through the noticeable elevation in the Sr/Ca ratio, and these findings suggest the potential of SrTiO_3 to enhance osseointegration. Similarly, Li et al. showed that a substantial proportion of filopodia and actin fibers displayed optimal osteogenic properties among MC3T3-E1 cells cultured on ZrO_2/Sr substrates [199]. Furthermore, the ZrO_2/Sr coating exerted a significant upregulation in the expression of multiple osteogenic-related genes, including Runx2, COL-1, ALP, OPG, OPN, and OCN. These findings collectively establish highly favorable conditions for the proliferation and growth of osteoblast cells.

3.4.2. Mg-based substrates

Magnesium (Mg) and its alloys have attracted considerable research interest as promising materials for regeneration and support of functional bone tissue due to their lightweight nature, in vivo degradation, and mechanical properties that mimic natural bone [200]. Furthermore, Mg is an essential element for metabolic processes in the human body and is predominantly found in bone tissue. It stimulates the proliferation of bone cells and promotes bone regeneration. Despite being a new class of biodegradable metallic materials with potential orthopaedic applications, their limited osteoinductive properties have hindered their widespread use. Therefore, the surface modification of Mg-based materials plays a crucial role in improving cellular response while preserving desirable mechanical properties and enhancing osteogenic properties. In a study conducted by Cao et al., a composite coating of fluorinated hydroxyapatite (FHA) and Ta was developed on the surface of a Mg alloy using thermal synthesis and magnetron sputtering technologies [201]. The results of the study showed that the nano-needle structure of the FHA coating significantly increased the surface

roughness of the Mg alloy, while the Ta coating decreased the surface roughness and improved hydrophilicity. In vitro biological analysis confirmed that the FHA coating enhanced cell viability and promoted osteogenic properties on the Mg alloy surface. The FHA coating facilitated favorable interactions with cells, supporting their growth and differentiation. Furthermore, the release of Ta ions from the coating demonstrated antibacterial effects by reducing bacterial adhesion.

3.4.3. Other substrates

Codescu et al. devised a novel FeMoTaTiZr high-entropy alloy (HEA) through a vacuum arc remelting process. They subsequently applied a zinc-doped HAP coating to its surface using MS. This innovative approach aimed to synergize osteogenic and antimicrobial properties within the material [122]. Jang et al. coated polyether ether ketone (PEEK) filaments reinforced with internal TiO₂ nanoparticles with HAP using RFMS [202]. The hardness, tensile, compression strengths, and scratch test results demonstrated a considerable enhancement in the mechanical strength of the hierarchical PEEK/TiO₂/HAP hybrid composite structure compared to that of the conventional 3D-printed PEEK. In addition, this hybrid composite structure improved the proliferation and differentiation of MC3T3-E1 bone cells, whereas the external HA coating led to a more prevalent osteoblast absorption. Similarly, Xin et al. showed a more favorable cell adhesion and osteogenic differentiation for PEEK surfaces which were encapsulated with amorphous HAP. [203] Furthermore, as a proof of concept, the PEEK/TiO₂/HAP hybrid composite was successfully inserted into the femur of rabbits in vivo, and new bone regeneration without inflammation or infection in the contact area was registered even after 1 month.

NiTi alloy stands out as a preferred choice over conventional implant materials such as stainless steel, cobalt-based alloys, and titanium alloys across a broad spectrum of medical applications [204]. This preference arises from the alloy's exceptional superelastic and shape memory properties. For instance, it is widely used in dental archwires and cardiovascular stents, where its capacity to withstand deformation and promptly revert to its original shape is invaluable. Furthermore, its unique shape memory properties find extensive use as bone staples for rapid fixation of fractured bones, thereby accelerating the healing process [205]. Moreover, NiTi alloy has recently gained recognition as a promising material for orthopaedic implants and bone substitutes [206]. This is primarily due to its comparatively lower elastic modulus and stiffness when compared to traditional metallic biomaterials. These attributes play a pivotal role in minimizing stress shielding effects, reducing bone resorption, and lowering the risk of brittle bone and implant failure. Nonetheless, the utilization of NiTi alloy as a long-term implant remains a subject of debate, primarily attributed to its elevated nickel (Ni) content and the associated risk of allergic and adverse reactions stemming from the release of nickel into the surrounding environment. To tackle this concern, A. Motallebzadeh deposited a refractory high-entropy alloy (RHEA) film comprised of TiZrTaNbHf, with thicknesses measuring 750 and 1500 nm, onto a NiTi alloy substrate [207]. Subsequently, an extensive comparison was conducted between this RHEA film and a thermally grown TiO₂ film, focusing on their mechanical properties and in vitro biocompatibility. The results from the HAP formation tests, conducted in simulated body fluid over varying soaking time periods, demonstrated a significantly faster rate of HAP formation on the RHEA films in comparison to both the thermally grown TiO₂ and the uncoated NiTi substrate. This enhanced bioactivity and the formation of bone-like HAP on the RHEA film's surface can be attributed to the presence of oxides of constituent elements, especially TiO₂, Ta₂O₅, and ZrO₂ [208]. Furthermore, the RHEA film-coated specimens exhibited a toxic Ni ion release that was approximately half an order of magnitude lower than that of the thermally grown TiO₂-coated specimens, which can be partially explained by their scratch resistance and high adhesion strength.

3.4.4. Relationship between osseointegration and surface properties of coatings

Osteogenic cell differentiation can be influenced not only by the chemical composition of the material surface, but also by the surface micro/nano-roughness, wettability, stiffness, and electric conductivity [209,210] (Fig. 11).

Cells are highly responsive to micro-topography and can orient and migrate based on the underlying microstructural features. The roughness of a surface can impact cell attachment, proliferation, and differentiation. A surface rendered with 25- μ m particles creates a roughness that is comparable to the size of the cells themselves. Conversely, when coarser particles are assembled, the resulting roughness is large enough that osteoblast cells do not perceive it as rough anymore. Instead, these macro-rough surfaces appear locally smooth to the cells. On such smooth surfaces, cells can attach and proliferate, but they tend to exhibit relatively low levels of differentiation. In a study conducted by Sui et al., it was shown that the 5-day cell adhesion density on a nano-structured Ta layer was 1.26 times higher than uncoated Ti6Al4V and 1.32 times higher than pure tantalum. The nano-structured Ta layer, with its increased surface roughness compared to the uncoated substrate, played a significant role in improving the initial adhesion of MC3T3-E1 cells [113]. Likewise, the crystalline beta-Ta_xO₅ coating, which exhibited the highest roughness and surface energy values, positively influenced cell spreading and morphology. These findings highlight the potential of using such surface treatments for enhancing the performance of titanium-based implants [54]. On the other hand, surfaces with micro-structural roughness, typically with an average roughness of 4-7 μ m, are more favorable for cell differentiation [212].

The influence of surface topography on cell adhesion and migration has garnered significant interest at the intersection of microbiology, surface science, and material science. Ta₂O₅ surfaces have been developed with good biocompatibility, and their nano-topography plays a crucial role in regulating osteoblast adhesion. The surfaces with convex nano-curvature are created by applying reactive magnetron sputtering of tantalum over sub-monolayers of hydrocarbon plasma polymer particles [213]. Subsequent ultrasonication removes the particles from the coatings, resulting in surfaces with concave nano-curvature. Primary human osteoblasts have been found to maintain viability and mineralization ability on all types of these surfaces. However, Ta₂O₅ surfaces with concave topography exhibit restrained adhesion of the cells. The limited cell adhesion can be attributed to the closed nature of the concave cavities, which pose additional potential barriers for protein-mediated cell-surface interactions. Zapata et al. showed that the mouse mesenchymal stem cells adhesion of Ti6Al4V was favored both by the incorporation of the HAP-Si multilayer coating and by the increase in the roughness of the substrate (27 ± 5 nm to 52 ± 6 nm) [214]. Similarly, HAP-coated TiO₂ nanotubes showed significantly increased surface roughness and decreased water contact angle, which provided an enhanced cell attachment and growth when compared to as-anodized TiO₂ nanotubular and pure CP-Ti surfaces [211]. Nanotopography surface modifications have been employed in dental implants to enhance osseointegration immediately after implantation. In a study comparing two different nanotopography surface implants, the effects of osseointegration following tooth extraction were evaluated [215]. One implant featured TiO₂ nanotubes (NT-TiO₂) created through anodization, while the other had a nanotopography surface with strontium (NT-Sr) deposited using magnetron sputtering technology. Results demonstrated that the NT-TiO₂ surface exhibited nanotubes with diameters ranging from 15 to 80 nm, whereas the NT-Sr group displayed nanoparticles measuring 20 to 40 nm deposited on the surface. The NT-Sr surface exhibited superior interfacial bonding strength compared to the NT-TiO₂ group. Furthermore, the NT-Sr group displayed greater bone formation, higher bone-to-implant contact, and maximum pull-out force. These findings suggest that while the NT-TiO₂ surface exhibited favorable in vitro bioactivity, the NT-Sr surface, with its higher interfacial bonding strength, demonstrated superior in vitro osteogenesis.

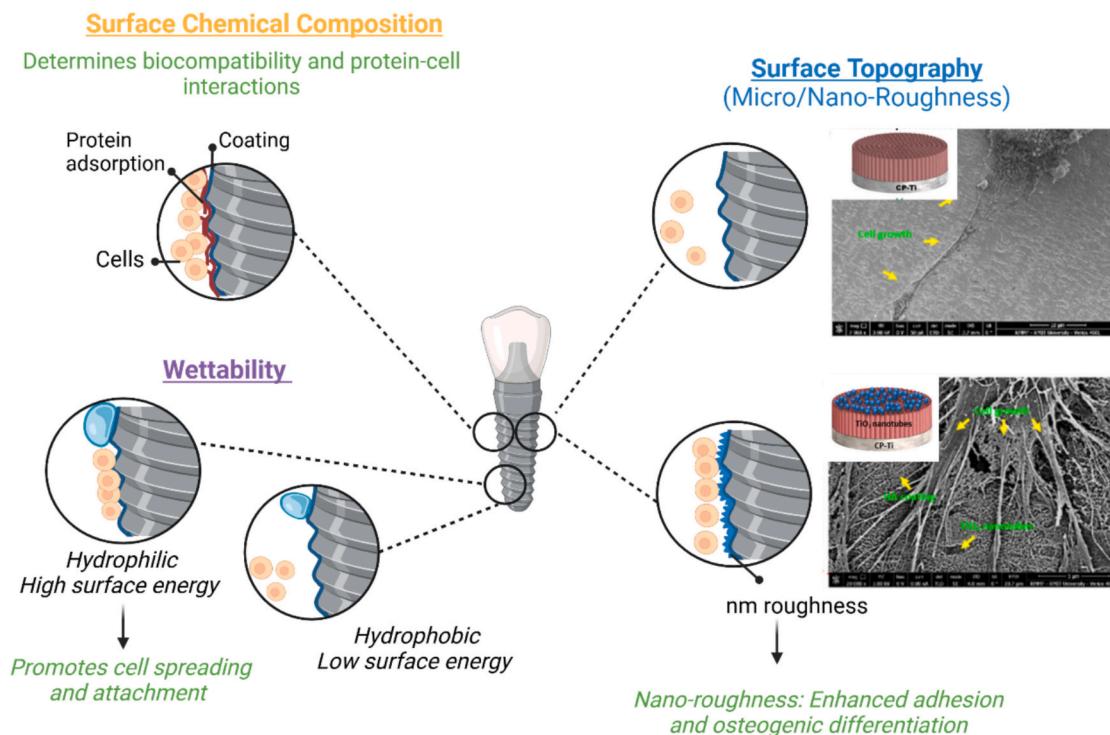


Fig. 11. Schematic representation of the relationship between osseointegration and surface properties of coatings. Key surface properties include Surface Chemical Composition, Surface Topography and Wettability. As example, images on the right illustrate nano-roughness effects, further enhancing adhesion and osteogenic differentiation [211]. Saos-2 cells on the bare CP-Ti exhibited a quasi-round shape with small filopodia, indicating poor cell spreading and adhesion. In contrast, Saos-2 cells on HA-coated surfaces were strongly attached, displaying a polygonal morphology with abundant elongated filopodia, highlighting the enhanced biocompatibility of the HA-coated surfaces compared to the bare CP-Ti. Created in <https://BioRender.com>.

To enhance the effectiveness of coatings in promoting cell growth and osseointegration, additional strategies can be explored. One such approach is the incorporation of growth factors, such as bone morphogenetic proteins, within the coating. This can significantly enhance cell growth and differentiation, leading to improved outcomes in tissue integration [216], [217].

Concluding this section, PVD coatings enriched with bioactive materials and nano-structured surfaces significantly enhance osseointegration, especially in orthopaedic and dental implants. While conventional metals like titanium and stainless steel are mechanically robust, their bioinert nature can hinder bone healing. Coatings such as calcium phosphate, tantalum, and TiO_2 improve osteoconductivity and corrosion resistance. Additives like strontium, fluorine, or growth factors further boost bone regeneration, ensuring long-term implant stability.

3.5. Boosting antimicrobial activity

Nosocomial infections caused by multidrug-resistant pathogens are a significant concern in public health settings. The rise of multidrug-resistant bacteria in community-acquired infections is also alarming. Biofilm formation on biomaterials contributes to chronic infections that are difficult to eradicate and have led to increased mortality rates [60]. Immuno-compromised hospitalized and elderly patients are particularly vulnerable, with implant-associated infections (IAIs) accounting for nearly 60 % of hospital-acquired infections [218]. The increasing variety and use of medical devices, including urinary and vascular catheters, as well as orthopaedic devices, have further increased the risk of device-associated infections due to the physical and chemical structure of foreign bodies that can facilitate microbial adherence [219].

Biofilms are dynamic ecosystems composed of a polymeric matrix that houses a diverse range of species engaged in social interactions. Compared to planktonic bacteria, bacteria within biofilms are incredibly

resilient, being 1000 time more resistant to antibacterial drugs [220]. This not only makes antibiotics less effective in treating infections caused by biofilms but also contributes to the growing problem of bacterial resistance. Among the pathogenic bacteria that cause IAIs, the Gram-positive *Staphylococcus aureus* is the most widely studied [221]. Other pathogenic bacteria that can cause IAIs include Gram-negative *Pseudomonas aeruginosa*, *Porphyromonas gingivalis*, and *Escherichia coli* and Gram-positive *Staphylococcus epidermidis* and *Streptococcus sanguinis*. As a result, there has been a recent emphasis on surface modification and the development of novel coatings to combat biofilm formation, reducing the need for antibiotics.

The biofilm formation process begins with the attachment of microorganisms to the surface of the biomaterial, followed by the accumulation of layers and the subsequent growth and spreading of microbial cells. It is important to note that only the initial attachment of bacteria is reversible during this process. Therefore, the prevention of initial bacterial attachment to the implant surface is crucial for inhibiting biofilm formation. To address this challenge, the application of antimicrobial coatings on material surfaces has emerged as a significant strategy [222] (Fig. 12). The properties of a surface, including chemical composition, roughness, and wettability, play a pivotal role in bacterial adhesion and aggregation. By carefully manipulating these surface characteristics, it becomes possible to influence the attachment behavior of bacteria and the subsequent formation of biofilms [223]. These advancements hold great potential for enhancing the performance and longevity of implants, thereby improving patient outcomes in various medical applications.

Hydrophobic coatings have been found to be effective in preventing bacterial adhesion initially, but over time, they can promote bacterial adhesion. For example, Zr—C coatings were deposited on 304 L steel using reactive magnetron sputtering in an $\text{Ar-C}_2\text{H}_2$ atmosphere with varying acetylene flow rates [65]. Different atomic carbon concentrations in the coatings were achieved, ranging from 21 to 79 at. %.

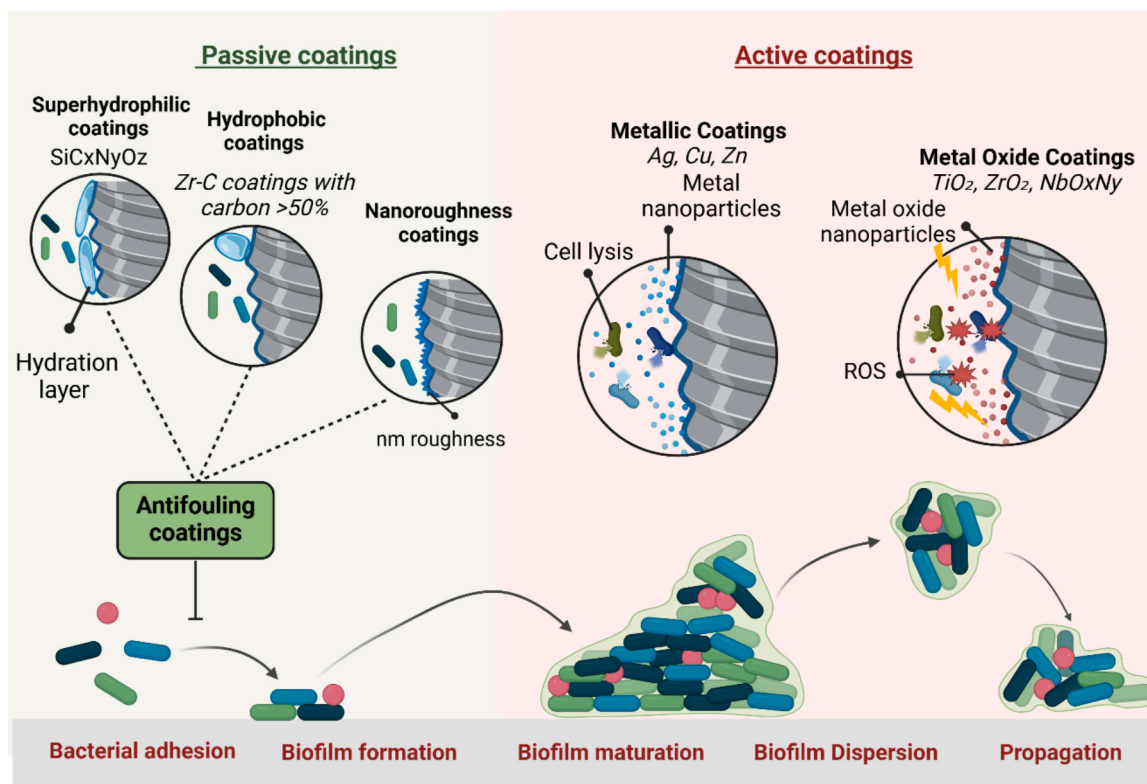


Fig. 12. Schematic illustration of passive and active antimicrobial coatings on biomaterials. Passive mechanisms inhibit bacterial adhesion through anti-adhesion effects facilitated by properties such as enhanced hydrophobicity, hydrophilicity, and nanoroughness. Active action eradicates bacteria through mechanisms such as the controlled release of antimicrobial agents. Created in <https://BioRender.com>.

Notably, the coatings with carbon concentrations above 50 at. % displayed a hydrophobic nature, as evidenced by the high contact angles, and demonstrated improved antibacterial properties compared to both uncoated 304 L steel surfaces and those coated solely with Zr. Bismuth oxide coatings also offer the advantage of hydrophobic surfaces that remain unchanged even under sub-band gap irradiation [224]. These coatings reduce the ability of microorganisms to adhere to the surface, making them more effective than conventional titanium dioxide-based photocatalytic coatings. In contrast, superhydrophilic coatings form a dense hydration layer with surrounding water molecules, creating a weak adhesion between bacteria and the surface [225,72]. This effectively prevents bacteria from approaching the implant surface and inhibits bacterial adhesion. For instance, the effective inhibition of bacterial proliferation by amorphous SiC_xNyO_z coatings on titanium surfaces was attributed to the presence of hydrophilic functional groups [143]. These functional groups create an electrostatic repulsion force between the surface and bacterial cells, effectively preventing their attachment and growth. Additionally, surfaces with higher roughness, such as SiC_xNyO_z coatings, exhibit stronger antimicrobial activities compared to smoother surfaces like titanium substrates [143]. The topography, high hydrophilicity, and low surface nanoroughness (< 20 nm) of TiN coating, commonly utilized in hip joint prostheses, contribute to its effectiveness in reducing bacterial adhesion [226]. In terms of microroughness, the antimicrobial properties of Ag coatings applied on microgroove surfaces are enhanced by the increased surface area, which promotes the release of Ag^+ ions and inhibits bacterial growth. However, a study conducted by Vladkova et al. revealed that the antimicrobial activity of $\text{TiO}_2/\text{SiO}_2/\text{Ag}$ coatings is not significantly influenced by surface wettability, surface energy, and topography [227]. Despite the hydrophilic nature of these coatings, the inhibition of *E. coli* growth is primarily determined by the presence of the antimicrobial agent Ag and its concentration (ranging from 9.66 to 19.75 at. %). In addition to the factors mentioned earlier, the microstructure of the

coating also plays a significant role in preventing bacterial adhesion. A study conducted on niobium-oxynitride-coated surfaces demonstrated that bacterial adhesion was lower compared to uncoated stainless steel, likely due to differences in surface energy and nano-structural surface topography [166]. The results further indicated that crystalline NbOxNy-coated surfaces exhibited reduced bacterial diffusion compared to amorphous and mixed amorphous-crystalline NbOxNy-coated surfaces. The polymorphic form of titanium dioxide, the structure and size of columnar crystals and crystallites forming the coating are also highly significant. $\text{TiO}_2:\text{Ag,N}$ coatings were produced by sputtering a titanium target with silver pins in an $\text{Ar}/\text{O}_2/\text{N}_2$ atmosphere, with the flow ratio of the reactive gases being varied [64]. Increasing the flow ratio of nitrogen and oxygen resulted in the formation of an amorphous matrix. However, through annealing at 500 °C for 1 h, the amorphous matrix transformed into refined crystalline phases, namely $\text{Ti}_{2.85}\text{O}_4\text{N}$, anatase, rutile, and silver. This combination of phases contributes to enhanced antibacterial properties that can be activated by visible light.

In addition to passive defensive surfaces, there have been numerous efforts to develop active-attack antibacterial surfaces through the application of a wide range of coatings (Fig. 12). Like antibiotics, antimicrobial nanomaterials act through one or more mechanisms to inhibit microbial growth or kill the invading organisms. Antibiotic therapy typically resolves the symptoms caused by planktonic bacteria released from the biofilm but fails to eradicate the biofilm itself. Metal nanomaterials are strategically advantageous as active antibacterial agents because their surface areas are exceedingly large relative to their size and can easily penetrate the biofilm [137]. For bacteria cell membranes, metallic materials can destroy the normal structure of proteins (enzymes) on the membrane. For example, Ag nanoparticles smaller than 6 nm can penetrate the entire depth of a biofilm [228].

Several studies have consistently demonstrated that the main bactericidal effect of silver is achieved through the release of Ag^+ ions via an oxidative reaction in aqueous solutions or biological mediums

[229]. Ag^+ is known to interact with cell thiol groups, binding to the primary functional groups found in certain components such as enzymes. This interaction prevents bacterial division, leads to damage of the cell envelope and disrupt the cell membrane, resulting in bactericidal effects. The induction of oxidative stress, caused by the production of ROS, including peroxides, superoxides, and hydroxyl radicals induces mitochondrial damage [230,231].

Wojcieszak et al. showed that the Ti—Ag and Ti—Au coatings displayed a biocidal effect, which can be attributed to the direct contact between their surfaces and microorganisms [232]. On the other hand, the antimicrobial activity of the Ti—Cu film had both direct and indirect characteristics, owing to the efficient ion migration process from the film surface to the surrounding environment. Some coatings are also capable of killing bacteria by production of reactive oxygen species (ROS). ROS produced by metallic nanomaterials can directly damage the constituents within the bacteria cytoplasm. Titanium dioxide, a well-known nontoxic photocatalytic material that can be incorporated into antibacterial paints or coatings for hospital touch-surfaces, when exposed to UV light undergoes photocatalytic processes on its surface, acting as an antimicrobial agent [233]. When excited by ultraviolet light, TiO_2 nanoparticles generate ROS that can destroy many organic molecules and can effectively kill various classes of microorganisms. For instance, in the case of pathogenic *P. aeruginosa*, photocatalysis triggered by TiO_2 nanoparticles can cause the downregulation of bacterial genes and proteins associated with regulatory, signaling, and growth functions. Similarly, N-doped TiO_2 coated orthodontic brackets have shown strong antimicrobial properties against *S. mutans* over a period of 90 days, preventing enamel decalcification during orthodontic therapy [234]. Additionally, Au and Ag nanoparticles were successfully formed on amorphous and crystalline TiO_2 thin films by depositing a thin film of silver and gold and annealing it. The TiO_2 surface with Ag nanoparticles exhibited higher antibacterial efficiency and stronger antibacterial activity against *Veillonella parvula* and *Neisseria sicca* species compared to Au nanostructured titanium oxide surfaces [235]. To further enhance photocatalysis under visible light and provide antimicrobial function even in dark environments, Fukumura et al. prepared a Cu/ SnO_2 nanobilayer coating using a magnetron sputtering method. The nano-copper layer had a thickness of approximately 7 nm, completely covering the SnO_2 layer and resulting in transparent bilayer films [236]. Post-annealing was conducted at 400 °C in air for 1 h to achieve a crystalline SnO_2 phase and simultaneously oxidize the copper layer to CuO. In dark conditions, CuO/ SnO_2 exhibited the same effect as the Cu-annealed film (CuO). However, under light conditions, CuO/ SnO_2 demonstrated at two orders of magnitude higher activity due to the advantageous photocatalytic properties obtained from the CuO/ SnO_2 nanocomposite bilayer coatings. When the CuO/ SnO_2 nanocomposite bilayer was exposed to light, electrons from SnO_2 were excited and transferred to the conduction band of CuO through interfacial charge transfer between both layers. As a result, the antimicrobial function was enhanced by the photocatalytic activity under indoor light exposure compared to the function of CuO alone. In the same trend, the antimicrobial activity of $[\text{Ca}_{24}\text{Al}_{28}\text{O}_{64}]^{4+}(4\text{e}^-)$ (C12A7:e⁻) nanoparticles was found to be higher than that of C12A7 nanoparticles, possibly due to the generation of ROS, such as O^{2-} and OH [237]. This finding is consistent with the effect of free electrons and free oxygen ions in a C12A7 cement structure on antimicrobial activity [238]. Furthermore, the enhancement of the host's innate immune responses also leads to a favorable antibacterial effect [239]. For instance, tantalum (Ta) can enhance the phagocytosis of bacteria by polymorphonuclear neutrophils (PMNs or neutrophils), while simultaneously reducing neutrophil lysis. Additionally, Ta nano-films promote the release of proinflammatory cytokines by macrophages, further contributing to the enhancement of local host defenses.

In recent years, significant efforts have been dedicated to the development of novel antimicrobial coatings, with a particular focus on metal and metal oxide-based coatings such as silver, copper, zinc, and other metalloid compounds [137]. These coatings have shown

promising antimicrobial properties and will be further discussed.

3.5.1. Silver-based coatings

Silver has garnered significant attention due to its potent antibacterial activity against a broad spectrum of microorganisms. Additionally, silver demonstrates a low susceptibility to bacterial resistance and possesses the ability to inhibit polymicrobial colonization. Silver and silver oxide nanoparticles have diverse antibacterial applications in dentistry, as scaffolds for tissue engineering and as wound healing materials [240]. They have also been used as antimicrobial materials in other industries including drinking water disinfection [241] and textile manufacturing [242]. As an example, Ag nanoparticles doped $\text{Ti}_{1.5}\text{Zr-Ta}_{0.5}\text{Nb}_{0.5}\text{W}_{0.5}$ refractory high-entropy alloy (with a 9 atomic % Ag content) deposited on a Ti6Al4V substrate reduced the colony forming unit of *P. aeruginosa* and *S. aureus* bacteria by 98.5 % and 90.9 %, respectively [243]. To enhance the antibacterial properties and promote bone formation on the surface of titanium implants, Ag and Ta co-doped amorphous calcium phosphate coating films were fabricated by RF magnetron sputtering [244]. The incorporation of both Ag and Ta elements ensures a sustained release of Ag^+ ions, providing long-lasting antibacterial effects. However, the continuous release of silver ions results in a gradual increase of the element's concentration within the adjacent media in contact with the film. This progression ultimately triggers toxic effects against mammalian cells. To address this challenge, dots of Ag/Zn galvanic couple were strategically deposited using template-assisted magnetron sputtering on cotton nonwovens and a poly (ϵ -caprolactone)/gelatin scaffold [225]. These Ag/Zn galvanic couples exhibited potent antibacterial activity against *S. aureus* and *E. coli*, relying on the synergistic interplay of microscale electric fields, metal ions, and reactive oxygen species. Moreover, the Ag/Zn composite demonstrated good cytocompatibility, credited to its minimal metal coating area percentage (17.5 %). Ag and silver-gold clusters were successfully incorporated into an amorphous carbon matrix and deposited onto polyurethane substrates commonly used in ureteral stents [245,86]. The primary goal of this study was to achieve antibacterial activity, as microbial colonization is a major cause of failure in these biodevices. The antibacterial activity of the coatings was found to be directly influenced by the silver ionization mechanisms. ICP-OES analysis revealed that the release of silver ions is primarily dependent on the amount of silver incorporated into the a:C matrix. Interestingly, the formation of a bimetallic alloy resulted in a reduced release of silver ions. To enhance the antibacterial properties of medical devices, Ag and AgO_x thin films were deposited using pulsed DC magnetron sputtering [246]. Our group successfully deposited Ag and AgO thin films on leather substrates through dc reactive magnetron sputtering [247]. The AgO_x -modified leathers not only exhibited enhanced frictional characteristics, but also demonstrated remarkable antimicrobial activity against *S. aureus* and *C. parapsilosis*. These findings suggest the potential application of AgO_x -modified leathers in the development of specialized footwear for individuals with diabetes. Moreover, by combining biomimetic deposition with DC magnetron sputtering, we created multifunctionalized alumina scaffolds coated with calcium phosphate (CaP) and silver-based thin films to enhance bioactivity and antimicrobial properties [87]. The study highlights that CaP-AgO coatings exhibited greater surface roughness and a more hydrophobic character compared to CaP-Ag coatings. Importantly, both types of coatings showed antimicrobial activity against *S. aureus*, with the CaP-AgO coating demonstrating superior efficacy due to higher silver ion release during the initial three days of immersion. This elevated release contributed to enhanced antimicrobial properties while maintaining bioactive performance. Furthermore, in a study conducted by Tsendzughul et al., an optically transparent mixed-phase silver oxide thin film biomaterial was successfully prepared by adjusting two deposition parameters: the oxygen flow rate and forward power, during reactive magnetron sputter deposition [248]. This research highlights the exceptional light transmission capabilities of silver oxide films, suggesting their potential

applications beyond antimicrobial surfaces in hospitals. These films hold promise for various fields, such as contact lenses and other areas where both optical transparency and antimicrobial activity are crucial.

3.5.2. Copper and copper oxide

Among the various inorganic bactericides of medicinal interest, there is a growing focus on copper and its oxide due to its low cost and effective antimicrobial properties [249,250]. The antibacterial activity of copper metallic surfaces is believed to occur through two complementary mechanisms: the surface-to-surface interaction between copper and bacteria (contact killing) and/or the surface oxidation of copper, leading to the release of antibacterial cupric ions [251,73]. Kim et al. utilized the magnetron sputtering method to directly deposit nanostructured copper (Cu) coatings on Si-TiO₂ and glass-TiO₂ substrates, allowing for control over the material properties [236]. By adjusting the target power density during deposition, the film properties were optimized, resulting in high crystallinity degree, low surface roughness, minimum surface energy, and low electrical resistivity. The antibacterial activity of *S. aureus* on the Cu films was analyzed and revealed that physical contact between the bacteria and the Cu film induced acute membrane damage, facilitated by effective electron transfer from the bacteria membrane to the highly conductive Cu film. Additionally, it was observed that films with lower resistivity demonstrated the most effective antibacterial activity. TaN/Cu nanocomposite coatings were prepared on a titanium modified SS alloy substrate (D-9) using pulsed magnetron sputtering [252]. The Cu content in the coating was varied in the range of 1 to 35 at. %. Among all, TaN/Cu with 10.5 at. % exhibited the lowest friction coefficient. The TaN/Cu coatings exhibited significantly higher antibacterial activity than Cu-free TaN against *Pseudomonas aeruginosa*. Wojciesz et al. conducted a study to investigate the influence of material composition on the structure surface properties of bioactive coatings based on Cu and Ti [253]. The bioactivity of the coatings was found to be associated with the ion migration process and the oxidation state of copper ions, specifically the amount of Cu⁺ ions present. A nanocrystalline coating with a lower copper content (25 at. %) exhibited nearly nine times more Cu⁰ and Cu⁺ ions compared to Cu²⁺, which are less bioactive. Importantly, the amount of copper was found to have an impact on the viability of the L929 cell line. In a similar study, Badaraev et al. demonstrated that surface-modified poly(lactide-co-glycolide) scaffolds with a medium and high amount of copper exhibited strong antibacterial properties, but also showed toxicity towards human gingival fibroblasts [254].

3.5.3. Zinc oxide

Zinc oxide nanostructures are known for their broad-spectrum antimicrobial properties [255,67]. In a study conducted by Widyastuti et al., zinc oxide thin films were created using the thermal oxidation method on zinc thin films initially grown through HiPIMS [256]. The research findings highlight the crucial role of sputtering power in achieving high levels of photocatalytic performance and antimicrobial activity. Specifically, a sputtering power of 500 W, combined with thermal oxidation, resulted in the formation of a well-structured ZnO crystal phase thin film with excellent compactness and enhanced antimicrobial activity. The antimicrobial effect of ZnO thin films against various pathogenic microbes can be attributed to multiple factors. Firstly, the intrinsic antimicrobial properties of Zn²⁺ ions released by ZnO contribute significantly to its antimicrobial activity. Additionally, the electrostatic interaction between ZnO and the microbe cell wall leads to the destabilization of microbial membranes. Finally, the formation of ROS through UV light radiation further enhances the antimicrobial effect of the ZnO thin films. To enhance the antimicrobial properties of ZnO thin films, carbon and copper were incorporated [257]. The addition of carbon in ZnO thin films increases their hydrophobic character, mainly due to the presence of C—C sp³ hybridized bonds. This integration of carbon allowed for the creation of metal-free surfaces with comparable results to those achieved with copper-doped thin films. In

the presence of these modified thin films, *Pseudomonas aeruginosa* experienced a loss of its characteristic shape, and leakage of intracellular media occurred. This can be attributed to the production and release of ROS, which promote the oxidation of cellular structures, thereby altering the permeability of the bacteria and ultimately leading to their disintegration. To enhance the osteoblastic cytocompatibility and antibacterial activity of tantalum-based surfaces, our group developed a surface modification strategy in which Zn/ZnO nanoparticles were deposited onto TaCaP samples prepared by micro-arc oxidation (MAO) using DC magnetron sputtering [39]. Additionally, a carbon layer was deposited over the nanoparticles, resulting in TaCaP-Zn-C. This carbon coating improved cell adhesion and proliferation by providing a smoother and more cell-friendly morphology. Furthermore, the carbon layer helped modulate the interfacial cellular interactions with the Zn/ZnO nanoparticles layer, reducing the toxicity caused by direct contact with Zn²⁺.

3.5.4. Other metal or metalloid-based coatings

In order to address concerns regarding environmental impact and toxicity associated with conventional metal-based coatings, significant efforts have been dedicated to the development of novel coatings. An example of these coatings is the incorporation of lanthanide element samarium (Sm) into the structure of hydroxyapatite using RFMS technique [258]. This approach has been found to significantly enhance the antimicrobial activity of the coating against bacteria such as *E. coli* and *S. aureus*, as well as against fungi like *C. albicans*. Cerium, a rare earth element, has been found to have the ability to stimulate the metabolic activity of organisms and possess antibacterial properties. Cerium-doped hydroxyapatite coatings were successfully generated on titanium substrates using plasma-assisted RFMS [259]. These coatings exhibited a biocidal effect against *E. coli* and *C. albicans* microbial strains after 72 h of incubation. In a study conducted by Andronic et al., transparent CeO₂ thin films were deposited on glass substrates using reactive MS [260]. These CeO₂ films were found to efficiently inhibit *Staphylococcus aureus* biofilms and planktonic growth, resulting in a significant reduction in bacterial cell counts by 2 to 8 logs. Germanium, a metalloid with chemical similarities to Si, has shown potential for applications in optics, sensors, catalysis, and even as an antimicrobial agent. In a recent study, the combination of tungsten and Ge in a W—Ge alloy was investigated as a composition material. The results demonstrated a significant reduction in the adherence of *Staphylococcus aureus* and *Pseudomonas aeruginosa* compared to control groups [261]. Boron exhibits high biological activity and plays a significant role in various physiological processes, namely in the formation and functioning of bone tissue and in the regulation of the immune response [262]. Moreover, studies have provided evidence that B ions can inhibit the formation of highly adhesive biofilms. It has been observed that boron suppresses the self-organization of bacteria, preventing the biofilm from establishing itself and adhering strongly to surfaces. For example, Ponomarev et al. prepared B-doped TiCaPCON films with varying B concentrations (8, 11, and 15 at. %) by MS technique using two composite targets (TiC-CaO-Ti₃PO_x and TiB₂) in a gaseous mixture of Ar + 15 % N₂ [60]. To assess the antibacterial characteristics of the B-doped TiCaPCON samples, they compared them with two-layer BO_x/TiCaPCON-B and TiO_x/TiCaPCON-B films obtained through three different methods: (i) deposition of a B₂O₃ top layer, (ii) annealing, and (iii) electrochemical oxidation of the as-deposited B-doped films. The results demonstrated that only the sample with a B₂O₃ top layer was able to completely inactivate *E. coli* cells and prevent biofilm formation. Notably, the surface of the two-layer B₂O₃/TiCaPCON-11 % B film exhibited simultaneous bactericidal properties against *E. coli* strains while remaining non-toxic to osteoblastic cells. Moreover, the biofilm inhibitory property of coatings containing boron can also be attributed to the impact of surface roughness on surface topography and its effect on biofilm formation. The nanometric range of the surface topographic features of boron carbon nitride (BCN) is much smaller than the size of microbial cells,

resulting in a substantial decrease in the contact area between the bacterial cells and the nanocoated surface [263]. This reduced contact area may influence the activation of bacterial adhesion genes and genes involved in the secretion of extracellular matrix, consequently affecting cell attachment and subsequent biofilm formation on BCN. These findings highlight the potential of boron in combating bacterial infections. Further research in this area may provide valuable insights into the mechanisms underlying boron's antimicrobial properties and its potential applications in biomedical field.

Moreover, in recent years, there has been growing interest in multi-element thin films as a promising category of nano-engineered surfaces. Among these, Zr-based films (such as Zr—Cu, Zr—Cu—Ag, ZrCN, Zr/ZrCN multilayer) [59], as well as Ti-based films (including TiN, TiCu, Ti—Zr—Si), have demonstrated remarkable properties, namely a superior combination of high mechanical strength, biocompatibility, and antibacterial activity [264]. Additionally, the desired combination of mechanical strength, biocompatibility, and antimicrobial activity can be achieved through the construction of multi-layers [63,64]. Notably, studies have revealed the potential antibacterial behavior achieved by incorporating Au, Cu, Zn, and Ag into Ti-based films. In a study conducted by Mina-Aponza et al., Ti/Ag films were fabricated using various configurations (monolayer and multilayer) via magnetron sputtering. The antimicrobial activity of these films was assessed against *Pseudomonas aeruginosa* and *Bacillus subtilis* bacteria, as well as *Candida krusei* and *Candida albicans* yeasts [265]. The findings indicated that the multilayer coating exhibited enhanced TiO₂ layer formation, resulting in excellent corrosion protection. Furthermore, it demonstrated stronger inhibition of colony-forming units (CFUs) when tested against *C. krusei* and *C. albicans* fungi. However, it is important to note that SEM micrographs of the film revealed the detachment of layers on the surface. This detachment presents a potential risk to the longevity of biomedical devices when implanted within a host organism. As previously discussed, numerous coatings have been developed to prevent bacterial infections in implants by releasing antibacterial ions. However, precise control over ion release to effectively eliminate bacteria without harming cells remains a challenge. To address this, Tan et al. propose an innovative approach: augmenting surface local alkalinity with a MgO film to disrupt bacterial respiration [266]. Biodegradable MgO films of varying thicknesses were meticulously fabricated on titanium using RFMS. As the film thickness increased, exceptional antibacterial efficacy against both *E. coli* and *S. aureus* was observed. The local alkaline microenvironment on the MgO film surface interferes with bacterial respiration by attenuating the transmembrane proton concentration gradient, thereby obstructing energy metabolism and inducing oxidative stress in bacteria. Furthermore, the MgO film exhibited a remarkable ability to selectively combat bacterial growth even in the simultaneous presence of bacteria and osteoblast cells. This dual functionality positions the MgO film as a promising candidate for enhancing implant safety and efficacy.

In summary, PVD coatings offer an effective strategy to prevent bacterial adhesion and biofilm formation on medical devices through both passive and active mechanisms. Passive approaches alter surface roughness, chemistry, or wettability to deter microbial attachment, while active coatings incorporate antimicrobial agents such as silver, copper, zinc, and magnesium to eliminate bacteria. Multilayer and doped films (e.g., Ti—Ag, Zr—Cu—Ag, MgO, ZnO) produced via magnetron sputtering have shown strong antibacterial effects and selective cytocompatibility. Emerging innovations include smart surfaces with controlled ion release, localized alkalinity, or light responsiveness, further enhancing antimicrobial efficacy and ensuring long-term device safety.

4. Challenges of PVD coating for biomedical implants

Recent literature highlights the significant potential of PVD—particularly magnetron sputtering—as a surface engineering technique for biomedical devices. Its proven ability to deposit thin, adherent, and

functional coatings has led to an increasing adoption in commercial applications. For example, Ionbond offers orthopaedic implants—such as spinal discs, pedicle screws, and guide rods—coated with TiN or CrN, which significantly enhance wear resistance and reduce ion release, thereby improving mechanical stability and biocompatibility [267]. Advanced coatings like AlTiN and TiAlN, provided by companies such as Star Arc and Ionbond, are applied to surgical instruments to reduce light reflection during minimally invasive procedures, endure aggressive sterilization cycles, and preserve cutting performance. Additionally, composite coatings such as tantalum (Ta) and titanium-strontium-oxide (Ti—Sr—O), deposited via magnetron sputtering, have demonstrated excellent osseointegration and bone anchorage in dental and orthopaedic implants [268,269]. Clinical outcomes from these applications report extended implant longevity, reinforcing the clinical relevance of sputtered coatings and supporting their continued translation from laboratory research to practical healthcare solutions [268,269]. Despite these advantages, magnetron sputtering presents notable challenges in biomedical applications. A key limitation is its line-of-sight deposition, which hinders uniform coating on complex or recessed geometries, potentially resulting in inconsistent thickness, suboptimal adhesion, and compromised functionality [270]. Additionally, the high-vacuum environment required for deposition entails significant equipment and maintenance costs, which can hinder scalability. Residual stresses induced during sputtering may also affect coating adhesion and mechanical integrity, issues particularly relevant for load-bearing implants. Other concerns include elemental inhomogeneity and pinhole defects, which can undermine the coating's barrier properties and lead to localized corrosion or early device failure. To address these limitations, advancements in both equipment and processing techniques are being explored. Approaches such as substrate rotation, tilting, biasing, and advanced methods like HiPIMS or hollow cathode sputtering have been developed to enhance coating uniformity and plasma ionization [271,272]. Moreover, innovations in chamber design and hybrid deposition systems—combining PVD with non-line-of-sight techniques—are under investigation to ensure uniform coating coverage on intricate geometries. Continued research in process optimization, materials development, and surface engineering is essential to fully realize the potential of PVD technologies in the next generation of biomedical implants.

5. Future directions

While the short-term benefits of PVD coatings—such as enhanced biocompatibility, corrosion resistance, and mechanical performance—are well documented, their long-term clinical reliability remains an important challenge. In vivo, biomedical implants are subjected to dynamic physiological conditions, including fluctuating pH, enzymatic activity, mechanical fatigue, and complex host responses. These factors can compromise the long-term integrity and functionality of coatings, emphasizing the need for comprehensive durability assessments. Although magnetron-sputtered coatings are recognized for their dense, adherent, and stable characteristics, longitudinal clinical data remain limited. Future research should therefore prioritize accelerated aging protocols and in vitro/in vivo evaluations that closely mimic realistic biological environments. Monitoring ion release, adhesion under cyclical mechanical stress, and evolution of surface morphology and bioactivity will be key to ensuring both safety and sustained performance in clinical use. In parallel, the incorporation of machine learning and AI-driven process optimization can accelerate material design, enabling the development of customized, adaptive coatings. Future innovations should also explore the integration of bioactive agents (e.g., growth factors or antimicrobial peptides), the creation of stimuli-responsive smart surfaces, and the fabrication of gradient or multifunctional coatings that simultaneously promote biocompatibility, osseointegration, and antimicrobial protection. Finally, the transition from laboratory research to clinical application will require

standardized preclinical validation, robust regulatory frameworks, and interdisciplinary collaboration among materials scientists, biomedical engineers, and clinicians. Such efforts are essential to fully harness the transformative potential of PVD coatings in next-generation medical devices—making them safer, more effective, and responsive to the complex demands of modern healthcare.

6. Conclusion

In conclusion, PVD has emerged as a valuable and versatile technique for surface modification in biomedical applications. Its ability to deposit thin films with controlled properties enables the functional enhancement of a wide range of medical devices. By adjusting deposition parameters, it is possible to tailor coatings to improve corrosion and wear resistance, biocompatibility, osseointegration, and antimicrobial performance. As research in this field progresses, PVD is expected to contribute significantly to the development of safer, more durable, and more effective medical technologies. Overall, the continued exploration and optimization of PVD processes hold great potential to support innovation and improve clinical outcomes across various biomedical fields.

CRediT authorship contribution statement

Daniela Santo: Writing – review & editing, Writing – original draft. **José D. Castro:** Writing – original draft. **Sandra Cruz:** Writing – original draft. **Isabel Carvalho:** Writing – original draft. **Albano Cavaleiro:** Validation, Supervision, Funding acquisition. **Sandra Carvalho:** Validation, Supervision, Funding acquisition.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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