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Review

Materials for Orthopedic Bioimplants: Modulating Degradation and Surface Modification Using Integrated Nanomaterials

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Abstract: Significant research and development in the field of biomedical implants has evoked the scope to treat a broad range of orthopedic ailments that include fracture fixation, total bone replacement, joint arthrodesis, dental screws, and others. Importantly, the success of a bioimplant depends not only upon its bulk properties, but also on its surface properties that influence its interaction with the host tissue. Various approaches of surface modification such as coating of nanomaterial have been employed to enhance antibacterial activities of a bioimplant. The modified surface facilitates directed modulation of the host cellular behavior and grafting of cell-binding peptides, extracellular matrix (ECM) proteins, and growth factors to further improve host acceptance of a bioimplant. These strategies showed promising results in orthopedics, e.g., improved bone repair and regeneration. However, the choice of materials, especially considering their degradation behavior and surface properties, plays a key role in long-term reliability and performance of bioimplants. Metallic biomaterials have evolved largely in terms of their bulk and surface properties including nano-structuring with nanomaterials to meet the requirements of new generation orthopedic bioimplants. In this review, we have discussed metals and metal alloys commonly used for manufacturing different orthopedic bioimplants and the biotic as well as abiotic factors affecting the failure and degradation of those bioimplants. The review also highlights the currently available nanomaterial-based surface modification technologies to augment the function and performance of these metallic bioimplants in a clinical setting.

Keywords: bioimplants; orthopedic; metallic biomaterials; degradation; surface modification; coatings; nanomaterials

1. Introduction

Orthopedic bioimplants play a significant role in improving the quality of human life [1]. In this regard, bone–implant interface greatly influences bone healing through an osseointegration process [2]. The appropriate surface properties of orthopedic bioimplants include modulation of the differentiation of mesenchymal stem cells to express osteogenic phenotype [3,4]. Besides, surface modification of these bioimplants can also facilitate the biodegradation process [5,6], improve the mechanical properties commensurate with the native bone and improve integration with host tissue nearby. Furthermore, surface modification can provide antibacterial properties to avoid any post-surgery infections [7]. The above requirements of surface modifications can be adapted by metallic materials that have inherent bulk properties to be used in orthopedic applications.

Metallic bioimplants are manufactured by innovative manufacturing technologies to meet the ever-increasing demand for orthopedic applications [1]. Among the various bioimplants that have been developed for orthopedic, bioimplants used to assist bone fracture are currently in demand [8,9]. Amid the reported metallic biomaterials, materials such as stainless steel (SS 316L), titanium alloy (Ti-6Al-4V) and cobalt-chromium (Co-Cr) alloy have been investigated a lot owing to their suitable bulk properties [10]. Other non-metallic materials that have been explored in bone fracture fixation that include alumina (Al_2O_3), nylon 6/6, polymethyl methacrylate (PMMA), etc. [8,9,11,12]. Efforts have also been directed towards the modification of bulk properties of metallic biomaterials to render them with mechanical properties commensurate with that of a native bone, which could reduce stress shielding at an interface of tissue and bioimplant [12,13]. The excellent biocompatibility, hemocompatibility and high fatigue strength have positioned the metallic biomaterials as most suitable materials for orthopedic applications [14]. However, these bioimplants are prone to problems of wear and corrosion in a blood/tissue milieu [15,16]. The leachates of corrosion and infection labile nature of metallic surface may trigger immunological reactions [17,18], leading to the need for heavy intake of immunosuppressant or other treatments causing deleterious effects on the patient's health [19]. The major limitations of metallic biomaterials are their non-integration with host tissue owing to the above-mentioned inappropriate surface properties, vulnerability to post-surgery microbial infections, and other related risks that may demand a revision surgery and removal of bioimplants [8,12,20].

Although efforts have been directed to overcome the challenges associated with bulk and surface properties of these metallic bioimplants, nanomaterials have of late emerged as an alternative to alter the surface properties for their better integration with host tissue, reducing the immunogenicity, providing an infection-free surface and enabling the drug loading [21–26].

Surfaces of the orthopedic bioimplants serve as the site of interaction for surrounding living tissue. Hence, it is imperative to enhance the biological performance of these bioimplants using bioactive nanomaterials [27–32]. Surface engineering using nanomaterials and other suitable coating technologies aims to design and develop the bioimplants with improved osseointegration for orthopedic applications [28,33,34]. The commercialized surface treatment strategies for several of the orthopedic metallic bioimplants have already been developed; those include grit-blasting followed by washing with non-etching acid and distilled water, spark anodization in the presence of calcium phosphate, sandblasted and acid-etched (SLA) treatment for the generation of macro/micro scale topography, laser-lok technology to generate structured grooves and channels, chemical treatment for the creation of nanoscale topography, molecular impregnation of calcium phosphate on a surface, plasma treatment, and acid etching [35–42]. Some of the common commercial generated surfaces include tiunite surface on titanium implants (Nobel Biocare Implant System) [43], SLA surfaces on Roxolid™—an alloy of titanium and zirconium (Straumann Implant System) [44], Microchannelled surfaces through laser-lok technology (Bio-horizons Implant System) [45], micro textured surface created by grit-blasting on titanium (Zimmer Implant System) [46], NanoTite™ surfaces on bone implants (3i Dental Implants) [47], and others. Surface modification processes such as grit blasting are achieved by bombardment of bioimplant surfaces by means of silica, hydroxyapatite, alumina, or TiO_2 nanomaterials, and thereafter the surface is treated with a non-etching acid and distilled water to clean the un-bonded

nanomaterials [37,39,42]. Acid-etching treatments are generally performed using strong acids such as hydrofluoric, nitric, or sulphuric acid to create micro/nanoscale roughness on the surface of the bioimplants [35,37,38]. Several other techniques such as deposition techniques including dip coating, laser technology that creates hydrophilic and chemically active surface that promote osseoconductivity, surface patterning by micro/nanochannels/groves for cellular infiltration, thermal spraying, biomimetic deposition of calcium phosphate and hydroxyapatite for better bone integration, and sol-gel deposition have also been developed to alter the surface of the metallic bioimplants [40,48]. These techniques have already been clinically accepted and have been used as a surface treatment solution for several orthopedic bioimplants.

The current review incorporates the description of the metals and metal-alloys that are commonly used in manufacturing of different orthopedic bioimplants. The review critically discusses the biotic as well as abiotic factors responsible for the degradation and failure of metallic/metallic-alloy bioimplants. It also highlights the currently available advanced nanomaterial-based surface modification technologies to enhance the function and performance of these metallic bioimplants. To further stimulate the exchange of ideas among the experts in the field, the opinion from some of our experts is also included to make this review more interesting and appealing for future readers, expecting more practical and mature orthopedic bioimplants to be explored to improve human health.

2. Materials for Orthopedic Bioimplants

Appropriate selection of materials to support fracture and healing is critical for the long-term success of orthopedic bioimplants. The choice of a bioimplant is primarily driven by the intended application, amenability to manufacturing, and the potential market size. Among the different types of biomaterials, metallic biomaterials including metals and metal alloys are widely used for manufacturing of orthopedic bioimplants because of their biocompatibility, low cost, rich in resources, and appropriate mechanical properties such as high tensile strength that provides strength to the fractured bones [1]. Some of the key metals and metal alloys used for orthopedic bioimplant manufacturing are discussed. Table 1 summarizes the different biomedical metals, their properties and the manufactured bioimplants from these metals and their applications.

Table 1. Biomedical metals, properties, manufactured bioimplants, and their applications.

Biomedical Metals	Properties	Applications	Ref.
Ti and its alloys	Biocompatible, high fatigue strength, flexible, low Young's modulus, expensive, low wear and corrosion resistance, good tensile strength, reduced Stress shielding, good osteointegration	total knee replacement (TKR), total hip replacement (THR), bone screws and plates for bone fracture fixation, screws/plates for maxillofacial application in the cranio-facial and mandibular areas.	[7,49–61]
SS 316L	Biocompatible, low fatigue strength, high Young's modulus, cheaper, high tensile strength, Stress shielding	Bone plates, medullary nails, screws, pins, sutures and steel threads used in fixation of fractures.	[10,12,13,49,62,63]
Co-Cr alloy	Biocompatible, high tensile strength, high Young's modulus, stress shielding	Orthopedic prostheses for the knee, shoulder, ankle and hip as well as fracture fixation devices	[10,13,49,64,65]
Magnesium (Mg) and its alloys	Biocompatible, good osteointegration, lower Young's modulus, high strength, biodegradable, no stress shielding	Used as a mesh cage for segmental defect in long bone, 3-D scaffold design (tissue engineering) for bone regeneration	[20,66–72]

2.1. Titanium (Ti) and Ti-Alloys

Titanium (Ti) and its alloys have the characteristics of low density, high mechanical strength and excellent biocompatibility [73]. Ti in combination with other metals forms biocompatible Ti-alloys, which are widely used in bioimplant manufacturing. One of the most commonly used Ti-alloy is Ti-6Al-4V. It occupies approximately 45% of the total industrial production of Ti-based bioimplants [74]. The Young's modulus of Ti alloys is in the range of 55–110 GPa, which is higher than that of a native bone [52]. Therefore, the stress shielding effect remains an issue that can only be reduced, but currently

impossible to avoid [74]. Ti and its alloys are non-toxic and inert at in vivo environment due to their corrosion resistant properties [73]. However, some studies have reported that aluminum and vanadium ions released from Ti-6Al-4V alloys can potentially damage vital organs [75]. Vanadium ions are cytotoxic and known to cause poor osteointegration, while aluminum ions are known to cause neurological disorders [76,77]. These concerns have led to the development of Al/V-free α + β type Ti alloys with improved mechanical, tribological, and biological properties. These Ti-alloys have almost similar characteristics as that of Ti-6Al-4V. However, elastic modulus is still much higher than that of cortical bones (30 GPa). Thus, the generated stress shielding effect may further loosen the implanted bioimplants [53]. Other new generation β-type Ti-alloy includes Ti35Nb2Ta3Zr, Ti-Nb-Ta-O, Ti-Nb-Ta-Zr, Ti-35Zr-5Fe-6Mn, and Ti-33Zr-7Fe-4Cr, which have shown their respective advantages for manufacturing of orthopedic bioimplants [51,54,57–61]. β type Ti-alloys are known to consist of β-stabilizing elements such as Nb, Mn, Sn, Ta, and Zr. These elements are considered as safe for human health and hence the alloys are considered as biocompatible in nature.

To overcome the challenges of infection and support better osseointegration, the surface of Ti-alloys were modified through nanotexturing by the surface mechanical attrition treatment (SMAT) process [50,56,78]. Other methods such as coating technologies using micro-arc oxidation (MAO) have also been used to enhance the surface characteristics, biocompatibility, and osseointegration of the bioimplants manufactured from Ti-alloys, especially of β type. For example, TiO_2 doped calcium-phosphate coating (Ca-P) and calcium-phosphate-strontium coating (Ca-P-Sr) were used to improve the surface properties of Ti35Nb2Ta3Zr to enhance the in vitro and in vivo performance of the bioimplant [79].

Titanium or their alloys are used to develop the tibial tray that accommodates tibial polyethylene component in prosthesis for total knee replacement (TKR), femoral stem of endoprosthesis for total hip replacement (THR), and bone screws and plates to fix fractures and plates/screws for maxillofacial applications in the cranio-facial and mandibular areas [55,80,81].

2.2. Stainless Steel (SS)

Stainless Steel (SS) is one of the most widely used metallic biomaterials in orthopedics because of their ease of manufacturing, low cost, and wide resource availability. SS contains a minimum of 10.5% chromium and varying amounts of other elements such as iron, carbon, etc. [82]. As a result of chromium addition, the surface of SS develops a thin and relatively passive metal oxide layer that protects the surface against corrosion. In addition, at least 0.03% carbon in stainless steel (SS 316L) increases its mechanical strength and maximizes the corrosion resistance properties and improves the overall tribological performance of the bioimplants [82]. The SS 316L is inexpensive, reliable, and widely used in orthopedic bioimplant manufacturing [12]. It has a lower carbon content than SS 316 (a stainless-steel grade having 0.08% carbon) and offers excellent toughness to the overall bioimplant. SS 316L exhibits relatively good biocompatibility compared to SS316 [49,82]. It has much higher elastic modulus (about 200 GPa) than that of a typical human femur cortical bone (10–30 GPa) [11]. This may result in high stress-shielding at bioimplant–tissue interface leading to the failure of the implanted bioimplant [13,82]. In addition, SS bioimplants also succumb to fatigue damage due to their low fatigue strength [62]. SS-based bioimplants either need revision surgery or to be used as a permanent bioimplant after bioactive coating or surface modification using bioactive nanomaterials. The modification of SS with bioactive hydroxyapatite (HA) improves the osseointegration and bio-integration properties of an orthopedic bioimplant [63,83,84]. Typical applications include bone plates, medullary nails, screws, pins, sutures, and steel threads used in fixation of fractures [14,85–90].

2.3. Cobalt (Co) Alloy

Co alloys are wear, corrosion, and heat-resistant metallic materials used in bioimplant manufacturing [64]. In vitro and in vivo tests confirmed that these alloys as biocompatible and appropriate materials for manufacturing of surgical bioimplants such as orthopedic prostheses for the

knee, shoulder, and hip as well as fracture fixation devices. Typical Co-based alloy (Co-Cr-Mo alloy) in conjunction with an ultra-high molecular weight polyethylene (UHMWPE) is used in prosthetic knees and ankles [91]. The major alloying elements include Co, Cr, Mo, and Ni. Although these are essential trace elements in a human body, they have been well proven to be toxic when leached out in a body due to corrosion of cobalt alloys. The excessive presence of these trace elements (Co, Cr, and Mo) has been reported to damage organs such as the kidney, liver, lungs, and also blood cells [92]. The elastic modulus and ultimate tensile strength of the Co-alloys are 200–230 GPa and 430–1028 MPa, respectively, which is approximately 10 times higher than that of a human bone [49]. Hence, the bioimplants manufactured from these materials may result in stress-shielding effect at a bioimplant–tissue interface [13]. The surface modification of Co-Cr-Mo alloy implants could be achieved by low temperature plasma treatment, where surface get alloyed with nitrogen and carbon through S-phase transformation [65]. This process improves the hardness, corrosion, and wear resistant properties of Co-Cr-Mo alloys.

2.4. Biodegradable Metals

Biodegradable metal-based orthopedic bioimplants eliminates the complications associated with the long-term presence of bioimplants in human body. Once these materials degrade, the degradation products can be metabolized to fulfill the elemental requirements of the metabolic pathways [20,66]. Among the different metals, magnesium (Mg) shows a great promise as a biocompatible and biodegradable material [66,69]. The attractive characteristics of Mg are its high strength, elastic modulus, and a close resemblance to the modulus of a human bone. The properties such as high mechanical strength can reduce the amount of bioimplant material needed for an applied load and hence to manufacture the bioimplant. The reduced elastic modulus of the bioimplant can prevent the modulus mismatch between a bone and Mg-based bioimplant, leading to the reduction in the stress shielding at bone–bioimplant interfaces [66]. The mechanical properties of the Mg alloys can be enhanced by alloying with aluminum and other alloying elements [68]. Current investigations are centered on identifying the new Mg-alloys with no or low cytotoxicity. Various biomedical Mg-alloys such as Mg-Y-Nd [93] and Mg-Ca [94] have been studied for the development of biodegradable Mg-alloy-based orthopedic bioimplants. Alloying metals have to be carefully selected to avoid metal-related toxicity and corrosion [20]. The major limitation of Mg and Mg-alloys is their low corrosion resistance. Low corrosion resistance results in rapid release of the degradation products due to fast in vivo degradation. These necessitate the surface modification of these materials too [71]. Mg-alloys are also being explored for tissue engineering (3-D scaffold design) for bone tissue regeneration [67,68,70,95].

3. Degradation of Orthopedic Bioimplants

Degradation is one of the major considerations in bioimplant design, processing, and application. Biodegradable implants are expected to degrade progressively over a period of time to assist in the healing process and compensate for the clinical need. Bioimplants are designed either to degrade or remain inside a body rather than their removal after their function is served. Degradation of the bioimplants is desirable in several cases such as absorbable sutures, drug delivery system, and tissue engineering [3,96,97].

3.1. Metallic Bioimplant Degradation: Role of Biological Factors

Metallic materials used for the manufacturing of orthopedic bioimplants are high strength and corrosion-resistant metals and metal alloys. The prospective applications of these materials are to provide long-term mechanical support to the biological structures, while remaining inert and interacting minimally with the neighboring biological tissues [98]. However, these metallic materials undergo degradation following a time-dependent kinetics after being in contact with biological moieties for a long period of time (Figure 1a). Biological components are also chemically active, generating various ionic species during their metabolism. These chemical moieties are known to interact with the surface

of metal/metal alloy-based bioimplants [99]. After initial phases of adsorption and surface oxidation, the proteins slowly interact with the implant surface in a size-dependent manner, with smaller proteins interacting being the initiator. Johnson et al. reported the degradation effects of fetal bovine serum (FBS) on a Mg-alloy bioimplant [100]. The investigation demonstrated an oxidized Mg-Yttrium (MgY) was much more resistant to degradation in FBS compared to a native Mg-Y. The response of host body chemistry to the implant such as inflammation-dependent release of reactive oxygen species (ROS) creating an oxidative environment determines the degradation pattern of metal and metal-alloy [101].

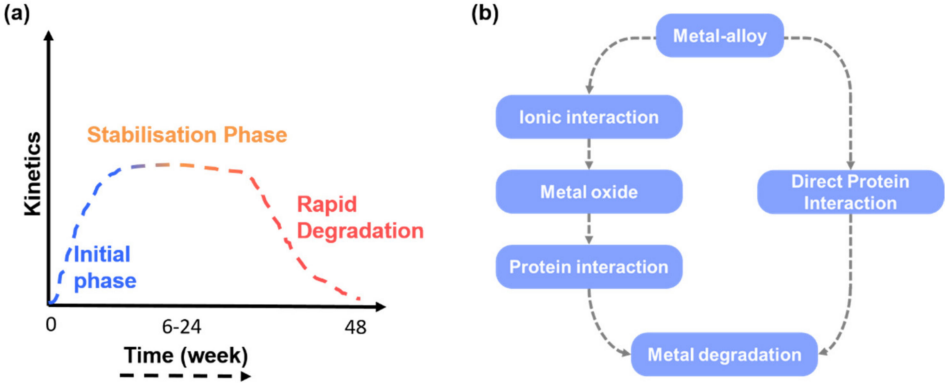

Figure 1. (**a**) Graphic illustration of the degradation kinetics of a typical metal bioimplant and (**b**) cyclic representation of metallic bioimplant degradation pathway [99]. Adapted with permission from [99]; 2018 Springer.

3.2. Time Dependent Degradation Effects

The degradation process starts immediately after the bioimplants are implanted inside the body. The overall degradation is a time dependent process, as illustrated in Figure 1a. The degradation pattern of a metallic bioimplant (for example, Mg-alloy-based bioimplant) undergoes an initial linear degradation that includes the oxide layer formation followed by a metal-protein-based degradation mechanism. The process is further followed by an encapsulation of a bioimplant by a fibrous tissue causing a complete isolation of a bioimplant from the surrounding tissue site. In the final step, the chronic inflammation starts clearing up the metallic implant materials via secretion of alkaline enzymes and ROS [102]. The transition from an early phase of metal-alloy chemistry to late stage of macrophages engulfing results in the erosion of metal particles, elevating the inflammation, and rapid degradation of the bulk material. Long-term studies on metallic degradation (6–24 weeks) have shown a time dependent decrease in the metal ion release in the tissue compared to the incremental degradation observed in nature. This type of degradation was also found to pass through a stabilization phase during a period of 6 to 24 weeks as shown in Figure 1a. Furthermore, it is also evident that some proteins can bypass the normal route of metal-alloy interaction and directly bind to the metal surface without the formation of an oxide layer as shown in Figure 1b. In addition, initiation of localized corrosion at the load-bearing site contributes towards the metal erosion to a greater extent than the other parts [99].

3.3. Degradation Mechanism

Metal and metal alloy-based bioimplants are prone to corrosion in a tissue and blood milieu. The corrosion process is a hallmark of a degradation process. It usually starts with the redox reactions and hydrolysis at the interface involving electron or proton exchanges (Figure 2a). These reactions yield hydroxides that precipitate over the metal surface. These precipitates are known to cause foreign body reactions, further resulting in a severe inflammation and long-term fibrous tissue development. Metals such as silver (Ag) and gold (Au) are more resistant to the corrosion as compared to iron (Fe) or aluminum (Al). These precious metals are sometimes used as a coating to modulate the corrosion

rate of the bulk metals used in manufacturing of the load bearing bioimplants for an orthopedic application. Iron or related materials usually precipitate as metal-protein complexes in the subsequent steps (Figure 2b). Steinemann et al. have reported that the produced metal–protein complexes are insoluble in a body fluid and determine the stability of the hydrolyzed products [103]. In addition, metal oxidation depends on the physical properties of a metal such as crystalline or amorphous nature of a metal [104]. It has been observed that the rate of degradation is lower for the amorphous metal oxides compared to the crystalline oxides [104]. The slow degradation of any amorphous oxides is due to the higher capacity of amorphous metal oxides to form organic complexes compared to crystalline metal oxides in an aqueous medium dominated by hydroxyl ions. The observed effect could also be due to weaker metal-oxide bonding with each other owing to larger inter-atomic distances in amorphous metal oxides. This weaker bonding could be easily leveraged by the macromolecules such as proteins, giving rise to the complexes (metal–proteins) that protects the underlying metal layer [105]. In this contest, metals such as Ti form the most stable oxide layer. The metal alloy-based orthopedic bioimplants manufactured from titanium–aluminum–vanadium (TiAlV) have further shown promising resistance to corrosion and metal ion release in the presence of proteins compared to the bioimplants made from metal-alloys such as SS 316L [73]. In addition, the physical imperfections and long-term wear and tear are also responsible for the corrosion of metal implants. Santos et al. have reported the initiation of degradation in metallic screws and plates at the site of wear/tear that have undergone specific corrosion at the load bearing areas [106]. In the implants such as screws and plates that bear regular load, there is a greater tendency to accumulate maximum precipitate at the grain boundaries of these metal/metal alloys implants (Figure 2c). Deposition of a larger precipitate at the grain boundary in combination with the regular abrasive motion on the surfaces deems them much susceptible to corrosion [106,107]. Furthermore, physical imperfections have also been known to contribute towards the localized corrosion, precipitation, and aggregation of a large quantity of metal–protein complexes at the specific site, thereby weakening the load-bearing structures. The physical imperfection also leads to fretting corrosion that is a combined form of local imperfections and micro motion, observed specifically in screw plate models of orthopedic bioimplants (Figure 2d).

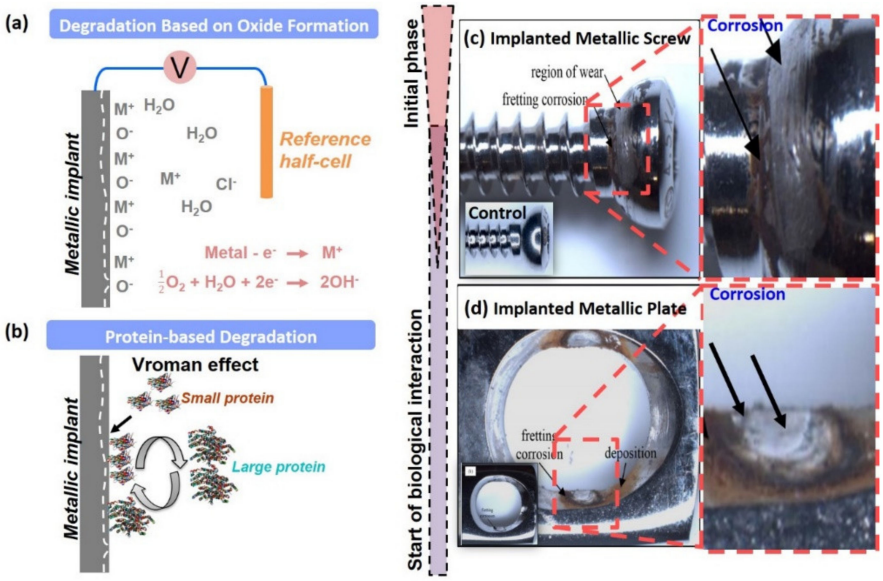

Figure 2. Mechanism of metallic bioimplant degradation (**a**,**b**) [15,16] and fretting corrosion tests on orthopedic plates and screws made of ASTM F138 stainless steel (**c**,**d**) [106]. Adapted with permission from [15]; 2008 John Wiley & Sons; Adapted with permission from [16]; 2003 Springer.

Following ionic interactions, proteins are known to get adsorbed relatively quickly within seconds to hours, even on a metal's surface with similar charges. The differences in the kinetics of adsorption

of the different proteins leading to an intense competition for binding to the oxide layer on the metallic surface. Moreover, this oxide layer formation is itself influenced by the surface properties like roughness, surface energy, and others [108]. The formation of these metal oxide–protein complexes accelerates the degradation process. Several other factors in an in vivo environment such as ionic strength of the local environment, pH, and physical stress on the oxide layer further govern the degradation kinetics [108]. For example, albumin with high concentration in synovial fluid strongly binds to the metal surfaces. The presence of any defect further enhances these phenomena generating metal–protein complexes, which in turn reduce the rate of erosion of a metal surface [109].

3.4. Metal Self-Induced Biological Responses

Metal–protein conjugates can act as signaling molecules for the secondary inflammation that is more intense than the primary inflammation [102]. The debris of the materials can sensitize the immune system depending upon the size of debris (nano or macro size), which induces increased cellular responses causing rapid degradation [110]. In in vivo environment, bioimplants subjected to mechanical stresses are more vulnerable to degradation. Hence, metal-alloy bioimplants that are mostly used in the high stress and load bearing conditions need to be evaluated for their long-term fatigue and friction-based degradation [111]. Oxidative stress in the tissue due to an increased ROS generation, Fenton chemistry-based corrosion in combination with fatigue-based degradation, significantly promotes the degradation rate [112].

4. Surface Modification Effects

Surface modification is usually carried out to minimize bacterial adhesion, inhibit biofilm formation, and provide effective bacterial extermination to protect the implanted biomaterials [7,28,113,114]. Furthermore, their role is to provide stealth properties to a bioimplant for any immunogenic reactions, better integration with the surrounding tissue, and enable appropriate cellular responses. For example, Ag nanoparticle coating over the Ti surface has been carried out to construct an improved bioactive and biocompatible surface (Figure 3a–c) [115]. Ti-based bioimplant and tissue integration could be promoted by surface decorated with Ag nanoparticles, through the promotion of H_2S production. The production of H_2S upregulates the expression of sulphur containing proteins such as albumin that is highly beneficial for the enhanced metal–protein interactions. Further the tissue could well interact with the Ti-Ag complex, resulting in an enhanced bone regeneration as shown in the Figure 3b. Controlled degradation behavior of Ti-Ag complex could cause the local release of Ag^+ ions, resulting in an enhanced tissue integration, anti-bacterial effect, osteoconductivity, and long-term low toxicity (Figure 3c). These effects could demonstrate multiple therapeutic effects of Ag-nanoparticle coating on a bioimplant surface. Similarly, different strategies are employed to prevent infection on a metallic bioimplant surface using antibiotics, antimicrobial peptides, inorganic antibacterial metal elements, and antibacterial polymers [116]. Certain surface modifications could also cause changes in the mechanical and biological properties of the bioimplant material. The physical/bulk modification is performed to obtain an optimum shape and size of a biomaterial with an appropriate mechanical behavior, while chemical modification is carried out to render bioactivity to the surface of a material. These alterations to materials empower them with improved cell adhesion, attachment, and eventually proliferation [115,117]. The tissue interacts predominantly with these materials at an interface where nanomaterials decorate the surface of a bioimplant. As shown in the Figure 3d, Ag-nanoparticle could act as a focal point of tissue adhesion and bone growth through interaction with calcium that regulates the biological responses. Nanomaterials are the advanced materials that could be effectively utilized to improve the surface and bulk properties of orthopedic bioimplants. A class of nanomaterials in response to electric/magnetic fields or polarization exhibit anti-bacterial properties without affecting the surface chemistry of bioimplants [118]. Nanotechnologies could improve the antibacterial response of the prosthetic bioimplants, which include compositional modification, surface chemistry alteration, as well as the application of properly tuned external stimuli [7,118]. Various desirable surface properties

such as protein adsorption, osteoblast attachment, osteoblast differentiation, antibacterial activity, biocompatibility with living tissues is achieved through nanomaterials. Further, corrosion resistance of the bone–bioimplant interface has been achieved by modifying the surface of the bioimplants through nano-structuring and functional nanocoating. A number of antibacterial agents, such as Ag, Au, zinc oxide (ZnO), zirconium nitrate ($Zr(NO_3)_4$), zirconium oxide (ZrO_2), titanium oxide (TiO_2), have been incorporated in a hydroxyapatite (HA) matrix to develop HA-based antibacterial coatings for orthopedic metallic bioimplants, which allows no bacterial growth on the bioimplant substrate and improves bio-integration properties [25,119–123].

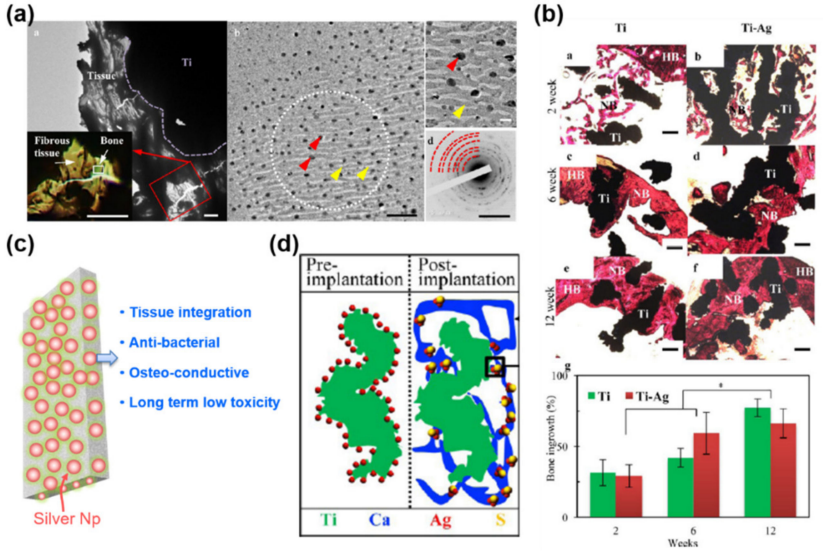

Figure 3. (**a**) Ti-based bioimplant–tissue integration promoted by Ag nanoparticles; (**b**) H&E staining at 2, 6, and 12 weeks of implantation showing enhanced bone growth around the bioimplant. (**c**) Controlled release of Ag-nanoparticle (Ag NPs) from Ti surface causing enhanced tissue integration, anti-bacterial effect, osteoconductivity, and long-term low toxicity; (**d**) Schematic showing AgNPs acting as focal point of tissue adhesion and bone growth through interaction with calcium that regulates the biological responses [115]. Adapted with permission from [115]; 2017 American Chemical Society.

5. Improving the Surface Properties of Bioimplants Using Integrated Nanomaterials

A proper design of a bioimplant material is aimed to provide durability, functional stability, and an appropriate biological response. Durability and functionality depend on the bulk properties of the material, whereas biological response depends on the surface chemistry, surface topography, and surface energy of a biomaterial. Surface modifications of bioimplants play a vital role in matching the complexities of the biological system and improving the performance of the bioimplant materials [25]. In this context, nanomaterials could be effectively utilized to improve the surface properties of several orthopedic bioimplants [26,124].

5.1. Surface Coating Using Ag-Based Nanocomposites

Silver (Ag) possesses an inherent antibacterial property and low toxicity to human cells, rendering it as an appropriate antibacterial agent for biomedical applications [125]. Ag can be used in the form of ions and compounds to destroy the bacterial cells [26,121,125]. Ciobanu et al. introduced a method for synthesizing Ag-doped nanocrystalline hydroxyapatite (HA) [126] in which Ag doped nanocrystals of HA was synthesized at 100 °C in deionized water. The Ag-doped nano-HA materials demonstrated an excellent cell adhesion and cell proliferation resulting in the synthesis of bone-related proteins and deposition of calcium. These hybrid nanomaterials could be used as a promising candidate for the coating and the surface modification of orthopedic bioimplants. There are two major mechanisms primarily responsible for the antibacterial response of Ag in several nanomaterials [127]. Primarily,

it forms Ag^+ ions during its oxidation, which is highly reactive with bacterial cells. These ions in the form of nanoparticles can bind to DNA, RNA, and proteins in bacterial cells to further inhibit the growth of bacteria [128]. Ag^+ ions are also responsible for bringing the structural changes in the bacteria and promote cell distortion. The antibacterial activity of Ag-based nanocomposite could also be attributed to the formation of ROS, which includes free radicals such as super oxides, hydroxyl radicals, etc. These super oxides and hydroxyl-free radicals are responsible for the antibacterial response from these surface modified orthopedic metallic bioimplants [121]. In order to induce antibacterial properties to Ti bioimplants, Yang et al. utilized friction stir processing (FSP) to embed silver nanoparticles (AgNPs) in a Ti-6Al-4V (TC4) substrate. Here, silver nanoparticles placed in the preformed grooves on the surface of TC4 when subjected to FSP, they get homogenously distributed in the surface of TC4 matrix. The distribution profile of AgNPs is dependent on the depth of the preformed grooves [129,130]. On examination, it was observed that silver-rich NPs with a size ranging from 10 to 20 nm were diffused into the substrate. Thus, both FSP and the addition of silver increase the corrosion resistance and reduce the infection rate. The antibacterial effect is independent of Ag^+ ion release and is likely due to the number of embedded silver NPs on the surface. TC4/Ag metal matrix nanocomposite is a potential nanocomposite that embeds AgNPs on a biomaterial surface for creating balance between the antibacterial effect and biocompatibility. The modified surface possesses an antibacterial properties [129,130].

5.2. Surface Coating Using Nano-TiO_2 and TiO_2-Based Metal Nanocomposites

Titanium oxide (TiO_2) nanomaterials have an excellent biocompatibility and chemical stability for which these nanomaterials have been used as coating over the metallic bioimplants [131]. In presence of light, TiO_2 oxidizes to produce free radicals (e.g., hydrogen peroxide, superoxide and hydroxyl free radicals). These free radicals have already demonstrated to elicit antibacterial responses [132]. TiO_2 coating on metallic bioimplants could be activated using direct organic coating like spray coating of polymers where doped antibacterial metal ions (Ag^+) are released as an "antibiotic" providing antibacterial property to a bioimplant surface. In this process, Ti-based bioimplant surface is doped with Ag^+ through hydrothermal treatment on polyethylene glycol (PEO), which significantly modulates the surface chemistry of the metallic bioimplant. The remodeled surface undergoes a patterned and slow degradation releasing Ag^+ ions in a controlled manner, leading to increase in the expression of ROS that is detrimental to the bacterial cell wall integrity (Figure 4a) [121]. The other method could be the unique redox photochemical induced mechanism that promotes enhanced bone–bioimplant integration [123]. The inorganic coating onto the bioimplant serves as a site for the redox photochemical reaction. The photochemical reaction results in the development of an electrolytic process by release of ions from the bulk material surface upon exposure to ultraviolet rays. The redox photochemical-based deposition of TiO_2 demonstrated highly active surface-induced antimicrobial activity by its capacity to generate cations (Figure 4b). The later mechanism also creates an excellent corrosion resistance TiO_2 layer over the bioimplant surface that protects an orthopedic bioimplant from bacterial attack as well as corrosion. TC4 surface modification is being explored by FSP to create a nanocomposite of TiO_2 and TC4. It is a method where an intense, localized plastic deformation is produced on the surface of a TC4. This results in the formation of nanocrystalline and amorphous TiO_2 on the surface of TC4. The presence of nanocrystalline and amorphous TiO_2 improved the surface properties like surface microhardness, biocompatibility, and resistance to corrosion [133]. The FSP also resulted in the uniform incorporation of TiO_2 particles to the surface of TC4 matrix. Due to the grain refinement and phase transformation, the surface microhardness and corrosion resistance properties of modified TC4 was improved. In vitro studies demonstrated an enhanced cell adhesion and proliferation capability of the TC4 substrate and modulated the biocompatibility of TC4 substrate [133,134].

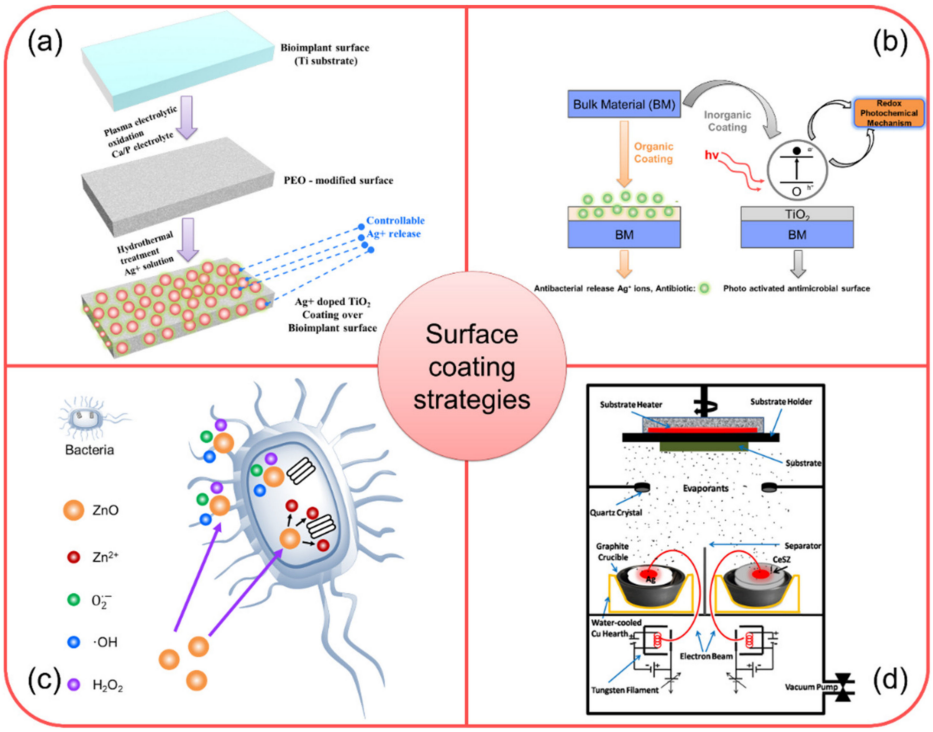

Figure 4. (**a**) Schematic demonstrating stepwise fabrication of antibacterial responsive coating of Ag^+ doped TiO_2 [121]; (**b**) Schematic showing the deposition and antibacterial action of TiO_2 coated bioimplant via redox photochemical method [123]; (**c**) Schematic illustration of antibacterial response of ZnO-based nanomaterial coating [118]; (**d**) Schematic showing ion beam assisted coating of antibacterial Ag-CeSZ-based nanomaterial coating [120]. Adapted with permission from [118]; 2018 ACS Publications; Adapted with permission from [120]; 2019 Elsevier; Adapted with permission from [123]; 2011 SAGE Publications.

5.3. Surface Coating Using ZnO-Based Nanocomposite

The surface modification using HA-ZnO nanocomposite can reduce ions leaching from a metal alloy and prevents the bacteria colonization over a bioimplant surface (Figure 4c) [118]. The experimental investigation suggested that the number of bacterial colonies could be reduced to 13% from 50.45% when ZnO content was increased from 1.5% to 30% (wt) in a HA-ZnO nanocomposite. The antimicrobial responses of ZnO-based composites are due to the formation of ROS and release of Zn^{2+} ions as shown in Figure 4c [119]. ROS are toxic to gram-negative bacteria, while Zn^{2+} ions are responsible for killing of gram-positive bacteria. ROS reacts with lipid layer of the cell wall (gram-negative bacteria) leading to the distortion of the bacterial cell wall. Such distortion destroys the cell wall and eventually leads to bacterial cell death. Zn^{2+} ions diffuse inside the cell (Gram-positive bacteria) and disrupt the amino acid metabolism and enzymes, resulting in a cell death [119].

5.4. Surface Coating Using Ag-CeSZ Nanocomposite

The surface modification using silver-ceria stabilized zirconia (Ag-CeSZ)-based nanomaterials have well proven to offer better mechanical properties and fracture toughness to the bioimplant compared to a conventional yttrium stabilized zirconia [120]. Three source electron beam physical vapor deposition (EBPVD) is used for the deposition of these coatings over several orthopedic bioimplants (Figure 4d). Silver block (99.99% purity) and CeSZ sintered pellets are taken in two separate graphite crucibles and kept separately in a water-cooled copper hearth. The electron beam is then generated and controlled with an accelerating voltage of 8 kV. The filament current is varied between 30 and 60 mA using a 30 kV TT controller. In a case of Ag-CeSZ nanocomposite coating, both Ag and CeSZ are evaporated separately using two E-beam guns. The substrates are kept at

the temperature of 673 K and the thickness of the coating can be controlled in a range of 2 µm. Ti bioimplants when coated with Ag-CeSZ nanocomposite coatings show improved mechanical and biological properties. The mechanical properties of Ag-CeSZ nanocomposite coatings are due to its crystalline nature. The coating also demonstrates excellent cell adhesion, antibacterial activity and resistance to sodium fluoride (2%), showing its promising multifunctional importance in orthopedic coating technologies [135].

5.5. Surface Coating Using Ti/SiC Metal Matrix Nanocomposite

The metal matrix composites offer increased stiffness, strength, and wear resistance over monolithic matrix materials. Nanocomposites based on silicon carbide (SiC) have exhibited enhanced mechanical properties. Recent reports on SiC have indicated that its biocompatibility is comparable to that of HA, with respect to the long-term osteogenic properties [136]. The crystalline SiC surface promotes adhesion, proliferation, and differentiation of the primary cultured osteoblast cells. Interestingly, SiC also improves the wear resistance and hardness of the bioimplant on which it is coated. During FSP, the metallic surface undergoes a plastic deformation, leading to an effective grain refinement. This ultrafine-grained metal substrate produced by the application of plastic deformation provides superior cell substrate attachment and biocompatibility. The surface nanocomposites produced by FSP exhibit excellent bonding with the underlying metallic substrate. Zhu et al. have fabricated a novel Ti/SiC metal matrix nanocomposite (MMNC) using FSP and investigated its microstructure and mechanical properties. Additionally, the proliferation and osteogenic differentiation properties of rat bone marrow stromal cells (BMSCs) on the sample surface were investigated and it was demonstrated that the modified surfaces supported the cell attachment and osseointegration [137].

6. Conclusions and Future Recommendation

Manufacturing of bioimplants often involves the integration of processes of material selection, design, and fabrication of bioimplants, and surface modifications through micro/nano texturing or nanomaterial coating. Engineering native metals by converting them into alloys amalgamate best properties of different metals in a single formulation. This provides the flexibility in tailoring the bulk properties of metals as per the orthopedic requirements. However, the surface properties of bioimplants based on alloys/metals require appropriate modification to elicit favorable biological responses. The surface modification of bioimplants through nanocomposites materials have the potential to enhance the host response in the long-run. These nanomaterials play a key role in minimizing the bacterial adhesion to further inhibit biofilm formation to protect the implanted biomaterials from microbial attack. They also play a vital role in eliciting appropriate cellular responses like cell migration through contact guidance on patterned deposition of nanomaterials, cellular differentiation, and gene expression through modulation of stiffness/hydrophobicity of the surfaces, initiation of degree of immunogenicity, delayed surface erosion, and degradation and composition of microenvironment at or in the vicinity of the bioimplant site. Advanced nanomaterials can also serve as a reservoir of drugs to be delivered at the bioimplant site. Thus, coated nanomaterials have the potential to alter the surfaces of various metallic materials for their adoption in orthopedic applications. However, care must be taken during the preparation and deposition of the nanomaterials on the surface of bioimplants like control over the size distribution of the nanomaterials, bonding of the nanomaterials with the bioimplant surface, thickness of the deposited nanomaterial, and eventually, the scalability of the process being used during nanomaterial deposition. In summary, it is imperative to say that the modulation of the degradation process and surface modification using emerging nanomaterials is going to generate a plethora of bioimplants for orthopedic applications in the near future. Therefore, the application of nanotechnology would be critical for the future success of orthopedic bioimplants.

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discussions. S.R. provided critical comments on which H.S.N., P.K., and Y.Z. have worked and revised further. All authors have read and agreed to the published version of the manuscript.

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