ARASHI
SCIENTIFIC PUBLISHERS

Arashi Journal of Metals & Material Sciences
2024, Vol. 1, No. 1, pp. 21–33
DOI: 10.54646/jmms.2024.0004
www.asp-jmms.com

EXTENDED REVIEW

Functional coatings on biometals: A strategy to combat implant-associated infections

Pirathiba Selvaraj[1], Preetha Mohan[2] and Antinate Shilpa S[3]*

[1]Department of Environmental Engineering, Park College of Technology, Coimbatore, Tamil Nadu, India
[2]Department of Biotechnology, KVM College of Arts and Science, Cherthala, Kerala, India
[3]Medical Bionanotechnology, Karpaga Vinayaga Institute of Medical Sciences & Research Center, Maduranthagam, Tamil Nadu, India

***Correspondence:**
Antinate Shilpa S,
shilpajoy17@gmail.com

Received: 02 December 2024; **Accepted:** 22 January 2025; **Published:** 05 February 2025

சுருக்கம்:
சமீப காலங்களில், உயிரியல் உலோகங்களில் செயல்பாட்டு பூச்சுகள் உலோகங்கள் மற்றும் உலோக கலவைகள் போன்ற இம்ப்ளாண்டுகளின் செயல்திறனை கணிசமாக மேம்படுத்தி, மருத்துவ இம்ப்ளாண்டுகளுக்கு புதிய பயன்பாடுகளை வழங்கி வருகின்றன. இயற்கை உடலியக்க அமைப்புகளுக்கு மாற்றாக, ஓர்தோபடிக்ஸ் துறையில் பொதுவாக பயன்படுத்தப்படும் இம்ப்ளாண்டுகள் (பயோமேட்டல்ஸ்) சில குறைகளை கொண்டுள்ளன. இவை எலும்புடன் ஒத்த அமைப்பை உருவாக்குவதில் பிரச்சினைகள், தொற்று ஏற்படும் ஆபத்து, மற்றும் போதிய இயந்திர பண்புகள் பற்றாக்குறை போன்ற சவால்களால் பாதிக்கப்படுகின்றன. பயோமேட்டல்ஸில் தொற்றுகளை குறைத்து, பைஓபிலிம் உருவாக்கத்தை தடுக்க கூடிய பாக்டீரியா எதிர்ப்பு திறன் கொண்ட பொருட்களை செயல்பாட்டு பூச்சடையாக பூசுவது ஒரு முக்கிய அம்சமாகும். ஆனால், பாக்டீரியாவின் ஜெனஸ் மற்றும் ஸ்பீஷீஸ் போன்ற வேறுபாடுகள், செயல்பாட்டு பூச்சாடையின் பாக்டீரியா எதிர்ப்பு திறனை குறிப்பிடத்தக்க வகையில் தீர்மானிக்கின்றன. அதனால், சமீபத்திய தரவுகளையும் மருத்துவ விமர்சனங்களையும் மதிப்பாய்வு செய்வதன் மூலம், இந்த ஆய்வு பயோமேட்டல்களுக்கு செயல்பாட்டு பூச்சாடைகளில் மேற்கொள்ளப்பட்ட முன்னேற்றங்களை ஆராய்கிறது. குறிப்பாக, பாக்டீரியா காலனித்துவம் மற்றும் பைஓபிலிம் உருவாக்கத்தை தடுக்கவும், பயோமெடிக்கல் இம்ப்ளாண்டுகளின் ஆயுட்காலத்தையும் செயல்திறனையும் மேம்படுத்தவும் இது கவனம் செலுத்துகிறது. இதன் மூலம், நோயாளிகளில் சிறந்த விளைவுகளை வழங்க முடியும். எதிர்காலத்தில், பன்முக செயல்பாட்டு பூச்சாடைகள் குறித்த ஆராய்ச்சிகள் மருத்துவ பயன்பாட்டுக்கான ஒழுங்குமுறை பிரச்சினைகளில் கவனம் செலுத்த வேண்டும்.

Abstract:
Recent trends in functional coatings at biometals have greatly improved the capabilities of implants like metals and metal alloys, thus offering new applications for biomedical implants. Despite being used most commonly as biomedical implants in orthopedics, the biometal has limitations like inconsistent properties to form a bone-like structure, infection susceptibility, and inadequate mechanical properties. Coating biometals with antibacterial agents that can reduce infection and stop biofilm formation is one aspect of functional coating. However, variations in bacterial genus and species, also determine the antibacterial efficacy of the functional coating. Thus, by reviewing the most up-to-date data and clinical review, this paper reviews the developments made in functional coatings for biometals in biomedical implants with respect to the enhancement of resistance to bacterial colonization and biofilm formation to improve biomedical implants life and performance, benefitting their outcome in patients. Future research on multi-functional coating should focus on regulatory issues for clinical usage.

Keywords: biometals, functional coatings, implants, antibacterial, implant-associated infections

Introduction

Orthopedic implants, such as fracture fixation devices, artificial joints and intervertebral disc prostheses, and bone defect fillers, play a vital role in maintaining, supporting, and restoring the structure and function of the musculoskeletal system. Common implant materials in orthopedics include alloys, ceramics, metals, and polymers, with alloys and metals

being the most prevalent (1–3). However, prolonged presence of these implants inside the body encourages infection. Implant-associated infections (IAIs), such as fracture-related infections and prosthetic joint infections, create serious orthopedics complications. Biofilms formed by the microorganisms over implants are very difficult to eradicate owing to the extracellular polymeric substances secreted by the microorganisms, which protects them from the host immune system and antibiotics (4). Combat strategies for IAIs prevention and treatment have been innovated, including antibacterial metal materials development through alloying techniques using materials like cobalt, tantalum, titanium, and biodegradable metals (5, 6). Substantial advancements have been made in creating biodegradable alloys based on iron (Fe), magnesium (Mg), and zinc (Zn) that exhibit antibacterial characteristics, making them suitable for use in orthopedic implants (7).

Bone defects are significant complications often resulting from infections, tumors, or trauma. Recently, tissue engineering has explored alternative scaffold materials, with metals being a key focus. To advance the development of *in-vivo* testing models that are relevant clinically for evaluating metallic biomaterials in bone defect repair, it becomes crucial to create models that assess their degradation, interactions, and biocompatibility with host tissues. Titanium (Ti) alloys demonstrate exceptional osteocompatibility, biocompatibility, and corrosion resistance, as evidenced from previous research, which makes them promising candidates to be utilized for engineering bone tissue (8). The conventional bone plates are manufactured using titanium alloy or stainless steel, and have shown effective results in treating bone fractures. However, traditional bone plates still face several limitations, such as getting loose and reduced stress shielding, instigated by the modulus difference between the metal implants and tissues of bone, which can hinder optimal healing of the fracture. Furthermore, due to changes in demographic conditions and abnormal loading conditions, the number of patients with complex fractures, like osteoporotic and comminuted fractures, is rising, presenting a significant challenge for the conventional bone plates designed for repairing standard fractures (9).

Currently, biodegradable materials sought significant attention in temporary devices for medical implants, eliminating the need for subsequent implant removal surgery (10). Significant advancements have been made in the research of biodegradable magnesium-based alloys, and coating them with active agents, leading to their increased use in the medical industry (11, 12). These alloys offer several advantages, including reducing reliance on conventional permanent implants made from metals and their biocompatible alloys, such as cobalt-based alloys, stainless steel, and Ti alloys, which typically require another surgery for their removal. These procedures can cause undesirable effects like the release of metal ions and stress shielding. These complications negatively impact patients' emotional and physical well-being while increasing costs for both patients and healthcare systems. In contrast, biodegradable implants dissolve naturally in the body, eliminating the need for removal after the bone has healed. Magnesium alloys are particularly favored as biodegradable implants in orthopedics because of their natural biodegradation, excellent biocompatibility, low modulus of elasticity (similar to natural bone), and lightweight nature, making them ideal temporary biomaterials (13). Functional gradient materials (FGMs) represent a contemporary class of materials that provide multiple functionalities and can closely replicate the hierarchical and gradient structures seen in natural systems. The human bone structure is anisotropic, meaning it biologically possesses functionally graded properties that vary in different directions. As a result, a variety of orthopedic implants, like knee and hip replacements, as well as bone plates, can perform better if they are FGM. In this regard, the use of additive manufacturing (AM) has greatly advanced the development of FGM for orthopedic applications, enabling the customization of the anisotropic properties (14). Since biomedical implants often replace bone tissue, and our bone itself is an organic, naturally occurring FGM, the application of the FGM concept in implants is quite logical. One of the main benefits of FGMs is their capability to offer customized morphological characteristics, resulting in graded physical as well as mechanical properties along specific directions. These gradual changes in composition, constituents, grain size, microstructure, texture, and porosity stretching towards one or more directions lead to variations in functional properties. This can help address challenges like stress shielding, promote better osseointegration, and enhance both electrochemical performance and wear resistance. Composites of metal and metal-ceramic are a few significant types of metallic FGMs, many of which are specially fabricated for biomedical applications (15). The average expectancy of implant life and the need for reconstruction of bone tissue, both are increasing, warranting the development of load-bearing implantable materials. These materials encourage significant osseointegration and prevent the postoperative infections. To address this challenge, strategies involving surface modification are needed for the metallic load-bearing scaffolds and implants (16). However, while incorporating surface features to improve osteocompatibility can enhance bone integration, it can also raise the risk of infection by promoting the formation of bacterial biofilm. Therefore, the engineering of multifunctional coatings that simultaneously meet these complex and competing demands is critical (17, 18). These coatings must also be versatile, cost-effective, and scalable to facilitate mass production and clinical application (19, 20). In this review we shall discuss about the various functional coatings on biometals and alloys that are developed for being utilized in orthopedic implants. PubMed, Google Scholar, MEDLINE, and the cross-references and references of authors' lists were searched

for mining the related articles published since 2020. The search terms were used primarily were "functional coatings" and "orthopedics." The search terms that are singly or in combination used included "functional coating" and "orthopedics," "metals," "biometals," "alloys," "biodegradable materials," "bioceramics." Further references were sourced from individual articles.

Process of bone fracture healing

In bone fracture healing, a number of cellular and biomechanical factors interact, including a series of events. Approximately 5–10% of bone fractures do not heal properly, leading to delayed healing or nonunion. The healing of bone fractures can be classified into 2 types: primary healing and secondary healing. The primary healing process involves restoring the bone cortex directly after a fracture, and can only occur if fracture fragments are aligned perfectly and are stabilized internally, with interfragmentary strain kept at minimal levels. The periosteum and surrounding soft tissues participate in secondary healing, resulting in the formation of calluses. Micromotion is beneficial in this type of healing, but stiff fixation can hinder it. A secondary healing process involves both endochondral and intramembranous ossification, and each of these procedures contributes to fracture repair in different ways (21–23).

Hematoma formation occurs in the gap of the fracture within the initial hours after a fracture because of acute inflammation happening in the surrounding soft tissue. Various inflammatory and immune cells populate this hematoma, which releases biological factors that trigger a cascade of cellular events. A small number of osteoblasts and osteoprogenitor cells differentiate into osteoblasts near the fracture site, followed by differentiation into chondrocytes. The hematoma tissue is then gradually replaced by a cartilaginous callus, while intramembranous ossification leads to hard callus formation in the subperiosteal area. As the process progresses, hypertrophicity is seen in the chondrocytes releasing calcium, undergoing apoptosis, and initiating endochondral ossification. The differentiation of monocytes leads the osteoclast-like cells to break down the calcified cartilage, while the mesenchymal stem cells continue towards osteoblastic differentiation, filling the resorption spaces with new bone. This results in the woven bone formation with a trabecular structure, as there is the replacement of the cartilaginous callus with a hard callus. The final stage, bone remodelling, involves coordinated activity between osteoblasts and osteoclasts over several months, during which the fracture callus is remodelled into lamellar bone (24–26). The remodelling of stem cells is known to be directed by the extracellular matrix (27, 28). The bone healing process is shown in **Figure 1** [adapted from (29)].

Repairing, reconstructing, and replacing congenital malformations, as well as addressing iatrogenic or exogenous tissue and defects in organs, necessitates the use of a wide variety of personalized biomaterials. Mimicking of natural bone healing is executed by the artificial implants, which not only give mechanical support but also accelerate the healing process. Selected metals are known to play a vital role as an implant material (9). In addition to traditional materials like stainless steel, additional options such as pure titanium, titanium alloys, cobalt-chromium alloys, and newer alloy materials, including tantalum-based alloys, are increasingly being utilized in clinical settings. Notably, porous tantalum trabecular metal has gained popularity in the field of orthopedics. Comparisons of surface passivation films across different metals in various environments reveal that tantalum exhibits excellent electrochemical corrosion resistance, with minimal metal ions release and reduced cellular damage. Furthermore, studies in protein adsorption, cytology, molecular biology, and hematology, along with consistent patients' follow-up observations using porous tantalum trabecular metal, confirm its outstanding biocompatibility. Given its superior biocompatibility and corrosion resistance, tantalum metal holds significant potential for clinical applications (30). Scientists have established that copper (Cu) possesses biological activities that are especially advantageous for the orthopedic biomaterial applications, including implant coatings and biodegradable bone substitutes. Cu has antibacterial properties, promotes angiogenesis, and enhances osteogenesis—key factors for successful biomaterial integration and healing. Copper-doped biomaterials exhibit antibacterial effects, becoming a promising alternative for prophylactic antibiotics and reducing the antibiotic resistance. Additionally, by stimulating the growth of blood vessels and promoting the formation of new bone, Cu significantly enhances the bio-integration of biomaterials, making it an excellent doping agent for orthopedic implants (31). As the field of implants has progressed, the surface functionalization or addition of effective coating has been added to them for improved and effective implants free from bacterial contamination *in-vivo*.

Interaction between bacteria and orthopedic implant

In IAI, there are 3 major contributors involving bacteria that make the implant unsuccessful.

Surface adhesion of bacteria

Bacteria tend to adhere to material surfaces more readily than to their surrounding aqueous environments. The initial stage is bacterial adhesion on implant surfaces involving chemical and physical interactions that are reversible and non-specific.

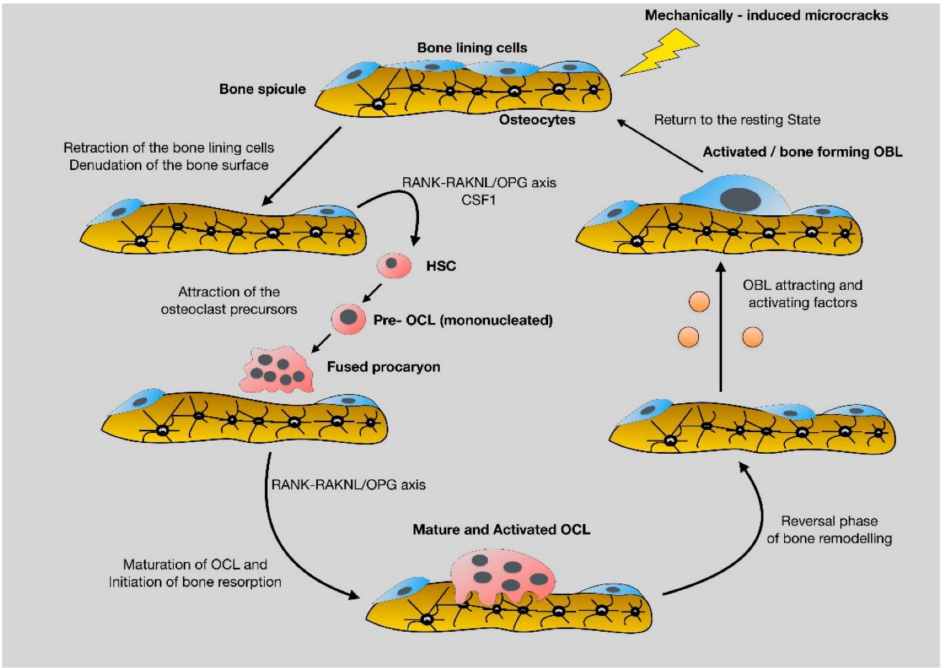

FIGURE 1 | Cycle of bone remodelling processes (29).

Subsequently, specific, and irreversible interactions at the molecular and cellular level occurs where physical forces, such as gravitational forces, Brownian motion, Lifshitz–van der Waals attraction, hydrophobic interactions, and surface electrostatic charges, attract the bacteria towards the surface of the material. Following this attraction, adsorption of the cells, and attachment takes place. During the second stage, certain structures of bacteria, like the capsules, flagella, and nanofibers, establish a close and irreversible bond with the implant surface. Furthermore, the bare surface of the material quickly becomes coated with the protein of the extracellular matrix (ECM) adhesins; e.g., microbial surface components that recognize the adhesive matrix molecules, are crucial in mediating the binding between bacteria and the ECM proteins on the surface of the coating, promoting bacterial aggregation. In summary, bacterial adhesion is influenced by the characteristics of the bacteria, the properties of the material surface, conditions of the microenvironment, and hydrodynamic factors (32).

Formation of biofilms

Biofilm formation is a dynamic procedure that consists of several stages: adhesion of bacterial, formation of microcolony, maturation of biofilm, and finally dissipation of biofilm. Initially, individual, sparingly distributed bacteria gets adhered to the surface and progressively cluster for small colony formation. These colonies secrete an ECM that encases them. The biofilm then matures through signalling processes, developing a tower-like assembly that establishes a tight attachment to the substrate. This biofilm offers a protective 3-dimensional structure fostering the bacteria. Key factors contributing to the biofilm's boosted antibiotic resistance and immunity to the host include biofilm network impermeability, horizontal transfer of genes, and the phenotypic variations between the different microbes within the substrate. ECM primarily consists of extracellular DNA (eDNA), proteins, extracellular polysaccharides, and teichoic acid. In the case of *S. epidermidis* and *S. aureus*, the polysaccharide intercellular adhesion expression and eDNA release are crucial mechanisms for the formation of biofilm. In unfavourable environments, a few bacterial cells may self-sacrifice to create a more appropriate living environment needed for other living bacteria. The autolyzed cells release the eDNA, which facilitates the maturation, and stabilizes the matrix of the biofilm (33–37). The mechanism of biofilm formation is shown in **Figure 2** [adopted from (38)].

Once the biofilm is formed, it becomes nearly impossible to treat the infection of the implant, leading to detrimental effects on the patient.

Interaction amid bacteria and the host cell

The pathogenic bacteria can access the prosthesis site in orthopedic IAI through both hematogenous (blood-borne) routes and contiguous spread. Cells of the innate immune system, such as macrophages and neutrophils, are employed at the site of infection via pattern recognition receptors, including Toll-like receptors, that can bind to the bacterial pathogen-associated molecular patterns. This binding activates the signalling of nuclear factor kappa B, leading to an inflammatory response (39). In this

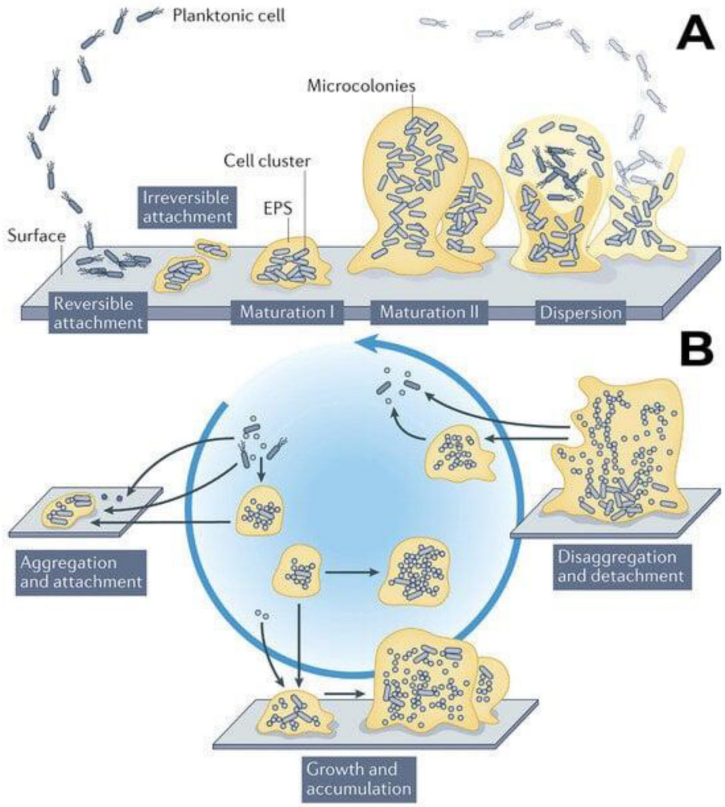

FIGURE 2 | Stages of biofilm development: classic **(A)** and **(B)** modern [adapted from (38)].

environment, immune cells secrete various cytokines and chemokines and employ mechanisms such as reactive oxygen species generation, phagocytosis, degranulation, antimicrobial peptides (AMPs), and neutrophil extracellular traps to engulf and eliminate the bacteria (40). Additionally, activation of the adaptive immune system can lead to antibody production, providing protection against recurrent infection for a long time. While effective clearance of planktonic bacteria is achieved by this type of immune response in the absence of implants, the presence of an implant triggers the innate immune response, as the implant itself gets recognized as a foreign body (41).

The above examples instigate the researchers to develop a functional coating on the implant material that can combat the evasion of bacteria, disrupt the formation of biofilms, and do not evoke an immune response against the host.

Functional coatings for orthopedic implants

There are many types of coating techniques. However, coatings applied under an electric field are used for the modification of the surface of the biomaterials. Recently, ceramic, metallic, polymer, and various composite electrodeposited coatings have been developed, each with distinct microstructures and properties (42–44).

Methods of synthesis

Methods such as direct cathodic electrodeposition, electrophoretic deposition, pulse cathodic deposition, plasma electrochemical oxidation in phosphate- and calcium-rich electrolytes, electro-discharge, and electro-spark techniques are employed to engineer these coatings. Of these, the most widely used are electrophoretic deposition and direct and pulse cathodic electrodeposition. Key factors like electrolyte composition, pH, potential and current, and temperature play a significant role in the coating process. Biocoatings, intended for biological applications, mostly employ metals, polymers, ceramics, bioglasses, or composites. They can be either co-deposited or surface-layered (hybrid or sandwich coatings) using various techniques, including the abovementioned methods and plasma vapor deposition, magnetron sputtering, chemical vapor deposition, and pulsed laser deposition. These coatings can be applied to solid or porous substrates (45). Various coatings and their synthesis methods are depicted in **Figure 3**.

Laser techniques-based surface treatments enhance the adhesion of coatings to substrates while improving the biological characteristics of functionalized medical devices without compromising their mechanical properties. Among these techniques, pulsed laser deposition, matrix-assisted laser deposition, and both simple and double laser writing stand out compared to additional well-known methods of

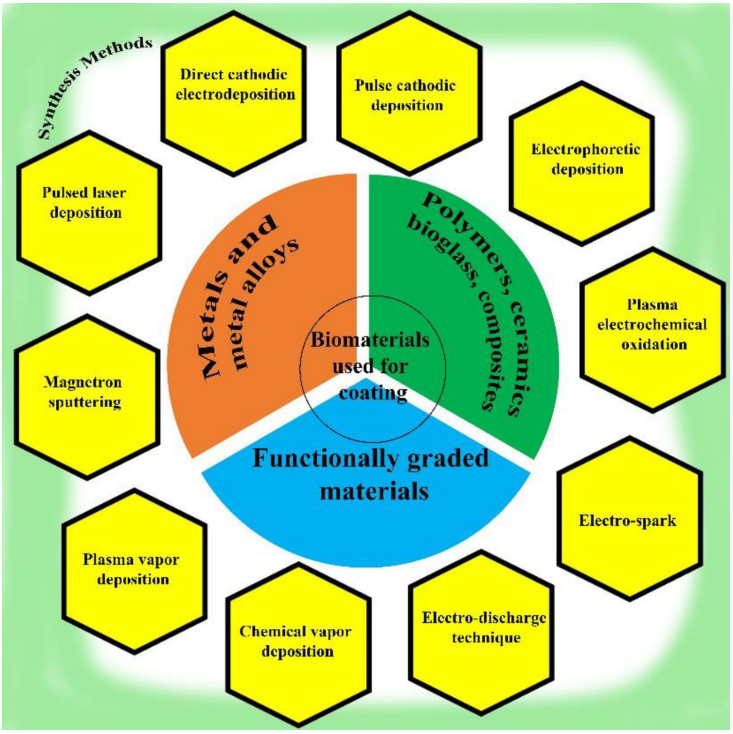

FIGURE 3 | Coating materials for orthopedic implants and their synthesis methods.

deposition, such as 3D bioprinting, magnetron sputtering, extrusion, inkjet printing, dip coating, fused deposition modelling, and plasma spray. Each of these methods can be adapted for surface functionalization to modify the local morphology, crystal structure, and their chemistry, which in turn influences the behaviour of biomaterials for specific applications. Laser-based functionalization techniques of the surfaces can be precisely controlled in a confined area for effective delivery of the concentrated energy (46, 47).

Functional coating research

Orthopedic implants are often made from Ti, stainless steel, and CoCrMo alloys, but these materials can fail due to factors such as infection, corrosion, inflammation, stress shielding, elastic modulus mismatch, and wear, and tear. To improve the performance of implants, advancements in design, materials, and surface modifications have been developed, with coating techniques being particularly successful (48, 49). Techniques like physical vapor deposition, electric arc oxidation, chemical vapor deposition, sol-gel, and plasma spraying are used to enhance the biocompatibility, corrosion resistance, and improved mechanical properties of the metal implants. Coatings such as hydroxyapatite (HA), bioactive glass, and titanium nitride have shown substantial performance improvements (50, 51). Magnesium-based alloys coated with silk fibroin, Zr, and coatings with nanosilver and vitamin E on biodegradable implants have also been explored with improved properties. Nonetheless, issues related to the adhesion, stability, and degradation of these coatings still pose challenges for widespread industrial use. Recent research indicates that adding materials such as tantalum, chitosan, graphene oxide, biodegradable metals, and titanium dioxide to HA or biphasic calcium phosphate (BCP) coatings can enhance their properties (52–56). Moreover, hybrid coatings with inner layers have been shown to improve both biocompatibility and mechanical performance. Coating layers with releasable metal ions enhances bioactivity, with multiple ions synergistically boosting antibacterial properties and cellular compatibility. For instance, calcium (Ca) and magnesium (Mg) ions support osteoblast growth, while copper (Cu) and silver (Ag) ions offer strong antibacterial effects. Scientists have done extensive research on the advancement of functional antibacterial coatings on orthopedic implants (48, 57). **Table 1** summarizes the recent developments in the field of functional antibacterial coatings. From the table, it is noticed that both organic and inorganic types of coatings were utilized for the developing antibacterial coatings over medical implants that could substantially avoid bacterial cell adhesion leading to IAIs. Other functional coatings are summarized in **Table 2**.

Potential clinical use of antimicrobial implants in orthopedics

Antimicrobial coatings of orthopedic implants are useful in reducing bacterial colonization and biofilm formation

TABLE 1 | Antibacterial coatings for orthopedic implants.

Sl. no.	Coated implant	Outcome of the study/overview	Ref.
1.	Quercitrin-Coated Porous Ti-6Al-4V Implants	Quercitrin-coated porous Ti-6Al-4V implants can be placed within the structure of an orthopedic medical device combining antibacterial properties with porosity-reactive aspects. These implants, at 500 μm pore size and 52% porosity, have an extremely uniform property distribution over their 3-D surface. Quercitrin coatings have been shown to increase biocompatibility and cell adhesion *in-vitro* with the control groups and increase the production of osteocalcin without changing the mechanical properties of the scaffold (Young's modulus), which is measurable. Furthermore, both normally and on exposure to bacterial lipopolysaccharide, alkaline phosphatase activity increased in quercitrin-coated implants. By far, when the entire picture is taken into account, the prospects offered by the quercitrin-modified porous titania are superior in terms of orthopedic application.	(60)
2.	Vitamin E	Vitamin E, with its antioxidant, anticancer, anti-inflammatory, and antibacterial properties, was coated onto a chemically treated Ti alloy to improve its performance in orthopedic applications. Characterization techniques, such as reflectance spectroscopy and contact angle measurements, confirmed that the coating was continuous, hydrophobic, and low in surface energy. The vitamin E coating showed anti-adhesion properties, preventing human mesenchymal stem cells from attaching while maintaining their viability. Also, it showed tremendous antifouling effects on the *S. aureus* and *E. coli*.	(61)
3.	Hyaluronic acid bisphosphonates coatings for PEO-modified titanium implants	In this study, researchers developed biocompatible coatings using bisphosphonic acid derivatives of hyaluronic acid on nanostructured and coarse-grained Ti Grade 4 with a plasma electrolytic oxidation (PEO) sublayer. Organic molecules were adsorbed onto the PEO-modified titanium, significantly reducing the adhesion of pathogens *P. aeruginosa*, *S. aureus*, and *E. faecium*. These hybrid PEO-organic coatings show promising results for enhancing antifouling properties on metal implants.	(62)
4.	Dual-functional antimicrobial coating based on quaternary ammonium salt from rosin acid	Researchers developed an effective dual-functional coating with synthetic terpolymers combining dopamine, maleopimaric acid quaternary ammonium cation, and zwitterionic 2-methacryloyloxyethyl phosphorylcholine. Characterized by SEM-EDS, XPS, and water contact angle measurements, the coating showed bactericidal efficacy with log reductions of 1.00 for *Staphylococcus aureus*, 1.09 for *Escherichia coli*, and 0.94 for *Pseudomonas aeruginosa*, effectively inhibiting biofilm formation. This coating holds therapeutic potential for addressing clinical challenges posed by pathogenic biofilms and related inflammation.	(63)
5.	Polyester coatings on Ti-6Al-4V Hard-Tissue Implants	This study examined poly(D,L-lactide) and poly[D,L-lactide-co-methyl ether poly(ethylene glycol)] polymers, varying PEG content (20–40% w/w) to test its antifouling effectiveness. Silver sulfadiazine (Ag SD) at ≤5% w/w was added as an antimicrobial agent to PEGylated polymers, creating coatings with both antifouling and antimicrobial properties. Spin coating was used to apply these polymers onto Ti-6Al-4V samples. Results showed that PEG above 20% w/w and Ag SD above 1% w/v effectively reduced bacterial adherence of biofilm-forming *Staphylococcus aureus* and *Pseudomonas aeruginosa*.	(64)
6.	Protein-engineered polymers and antimicrobial peptides coatings on implants	This study developed an extracellular matrix-mimicking coating using elastin-like recombinamers (ELRs) for covalent anchoring of AMPs, creating a hybrid antibiofilm surface. Tested in a drip-flow biofilm reactor for *in-vivo* condition stimulation, the AMP-infused coatings showed robust antibiofilm action against clinically relevant biofilms (microcosm biofilm models and monospecies) and high cytocompatibility with gingival fibroblasts. These findings highlight the potential of ELRs as versatile platforms for AMP delivery, enabling advanced coatings that combine antibiofilm efficacy with customizable biomechanical properties.	(65)
7.	Class II organic–inorganic films coatings on Ti-6Al-4V implants	Researchers have developed durable class II organic–inorganic antibacterial coatings for Ti-6Al-4V implants, utilizing chitosan (20–80 wt.%) bonded with GPTMS and TEOS, and incorporating antimicrobial silver nanoparticles (Ag NPs). Applied to acid-etched Ti-6Al-4V substrates, these coatings demonstrated strong adhesion (15–20 MPa) in cross-hatch and tensile tests. In studies with *Staphylococcus aureus* and *Escherichia coli*, the coatings effectively inhibited biofilm formation, with antibacterial properties further enhanced by the presence of Ag NPs and higher chitosan content. These results underscore the promise of these hybrid films as long-lasting, firmly adherent antibacterial coatings for Ti-based implants.	(66)
8.	Titanium coated with Ag NPs and lactoferrin (Lf)	Ti surfaces were functionalized with a multifunctional coating that consisted of lactoferrin (Lf) and silver nanoparticles (Ag NPs) for antibacterial activity and tissue regeneration. The functionalized surfaces were characterized using physicochemical methods and evaluated *in-vitro* for the adhesion, viability, and osteogenic differentiation of preosteoblasts. Antibacterial efficacy against *S. aureus*, the bacteria commonly associated with prosthetic infection, was assessed. The results showed that Lf was well adhered to both the untreated Ti and Ti surfaces with Ag NPs. The addition of Lf with Ag NPs showed a marked increase in the preosteoblast adhesion, proliferation, and differentiation, and the bacterial colony formation was reduced to 97.7%.	(58)
9.	Self-assembled antimicrobial amphiphiles, decorated with Ag NPs to coat etched Ti (eTi) surfaces	Researchers synthesized self-assembled antimicrobial amphiphiles from the AMP GL13K, decorating them with Ag NPs to coat eTi surfaces. Strong hydrogen bonds existing between the AMP amphiphiles and polar eTi resulted in a stable coating. The hybrid nanocoating demonstrated significantly greater antimicrobial potency against various implant-related bacteria than single Ag NPs or AMP coatings and was effective in an *in-vivo* model for subcutaneous infection induced in rats. This study supports the potential of Ag NPs/AMP nanocomposites as effective anti-infection coatings for implants.	(67)

Continued

TABLE 1 | Continued

Sl. no.	Coated implant	Outcome of the study/overview	Ref.
10.	Hybrid ZnO/chitosan	A biocomposite coating of chitosan and ZnO on porous TiO_2 has been developed to combat implant-related infections in orthopedic and dental applications. This coating consists of a nanoporous TiO_2 inner layer, topped by a chitosan matrix embedded with ZnO NPs. While chitosan alone had limited effectiveness in preventing bacterial adhesion, the addition of ZnO increased its antibacterial activity against *E. coli* by 1.2 times and effectively prevented biofilm formation. The ZnO/chitosan coating also demonstrated superior bioactivity, corrosion resistance, and compatibility with MG-63 cells compared to pure Ti. The enhanced antibacterial effects are attributed to the release of Zn^{2+} ions, and the coating has twice the scratch resistance of the chitosan-only variant.	(68)

TABLE 2 | Functional coatings for orthopedic implants.

Sl. no.	Coated implant	Outcome of the study/overview	Ref.
1.	Multilayer TaN coatings on CoCrMo biomedical alloy (anti-corrosive coating)	CoCrMo alloy is commonly used in artificial orthopedic joints as they possesses excellent mechanical properties. On the other hand, the release of high concentrations of metal ions from the surfaces of these alloys can lead to toxic and allergic reactions in patients during *in-vivo* use, limiting the implant's lifespan and potentially causing joint failure. To address this issue, multilayer coating of the alloy the surface was achieved using a closed-field unbalanced magnetron system, for enhancing the resistance to corrosion, and reduce the release of metal ions. The protective effectiveness was evaluated through potentiodynamic polarization tests, while static immersion tests were conducted over 45 days, 60 days, and 90 days using simulated body fluid to monitor the metal ion release. Using an inductively coupled plasma mass spectrometry device, the fluid's metal ion concentration was measured, showing a significant reduction in metal ion release. Electrochemical corrosion testing concluded 93% protection in terms of corrosion resistance of the multilayered coating. These properties enabled the coated material a superior choice for implants.	(69)
2.	PMMA coating on ISO5832-9 and Ti-6Al-4V biomaterials (compatibility)	Acetabular and femoral prosthetic components, made from specialized steel and Ti alloys, are typically fixed to bones using poly(methyl methacrylate) (PMMA)-based orthopedic cement. To enhance the compatibility of implant materials with the human body, the bioactive responses of ISO 5832-9 steel and Ti-6Al-4V alloy coated with electrospun PMMA nanofibers were evaluated. The metallic substrates underwent surface pretreatments, including sanding alone or combined with acid etching, before PMMA nanofibers were deposited via electrospinning. The coated surfaces were then characterized for morphology, chemical composition, and roughness. Nanometric PMMA fibers formed a homogeneous, and uniform layer on both the metal surfaces, without any adhesion differences. Fibroblasts were cultured on the samples for 7 days to assess biocompatibility, which showed excellent biocompatibility. To enhance cell-material interaction, hydroxyl radicals were incorporated inside the PMMA chain using electrospinning-induced surface activation, which was then redissolved and further electrospun to make nanofibers. Good adhesion of cells was observed for both PMMA and hydroxylated PMMA (PMMA-OH) nanofibers, although PMMA-OH induced a denser cell monolayer, suggesting improved cell-material interaction. Functionalization using hydroxyl (OH) promotes cell behaviour by acting as a linker that interacts with proteins, quickening cell growth, enhancing cell migration, and differentiation, extracellular matrix synthesis, and tissue morphogenesis. This simple 2-step method successfully produced bioactive, OH-functionalized PMMA nanofibers atop metallic implant samples, significantly enhancing the cellular response.	(70)
3.	Transcript-activated coatings on Ti (compatibility)	Various biomolecules have been employed in drug delivery systems to enhance the integration of implants into the bone tissue vicinity. Chemically modified mRNA (cmRNA) represents a novel bone healing stimulating agent, which in combination with biomaterials can create transcript-activated matrices that can locally produce proteins with osteoinductive properties. In this study, researchers developed bone morphogenetic protein 2 (BMP2) transcript-activated coatings over Ti implants. Three biocompatible materials—poly-D, L-lactic acid (PDLLA), fibrinogen, and fibrin—were used to coat Ti surfaces. *In-vitro*, cmRNA release, cell viability, transfection efficiency, as well as osteogenic activity, were evaluated for these cmRNA-coated Ti disks. The study revealed a significant delay in cmRNA release on Ti surfaces pre-coated with biomaterials, leading to a marked improvement in transfection efficiency. Among the coatings, transfection efficiency was improved for PDLLA in a concentration-dependent manner, with lower PDLLA concentrations resulting in better outcomes. On the other hand, coatings with fibrinogen and fibrin demonstrated even higher transfection efficiencies than PDLLA. For fibrin coatings, lower thrombin concentrations yielded better transfection results. Fibrinogen coatings provided the best overall transfection efficiency. All biomaterial-coated Ti surfaces enhanced cell viability and proliferation, with fibrinogen-coated disks showing the most noticeable improvements. Fibrinogen-coated surfaces also supported significant *in-vitro* BMP2 production by C2C12 cells. Osteogenesis was established on BMP2 cmRNA fibrinogen-coated Ti disks, with alkaline phosphatase (ALP) activity increasing in response to cmRNA concentrations of 250 ng or more. Additionally, mineralization levels rose with increasing concentrations of cmRNA. Overall, these findings support fibrinogen as the optimal material for delivering cmRNA on Ti-coated surfaces, facilitating improved transfection efficiency, cell proliferation, and osteogenic activity.	(71)

Continued

TABLE 2 | Continued

Sl. no.	Coated implant	Outcome of the study/overview	Ref.
4.	Bioactive ceramic composite coatings on Zn–Mn–Mg alloy (compatibility and anticorrosion)	In a recent study, researchers created calcium phosphate (CaP) coatings over micro-arc oxidized zinc (Zn) alloy utilizing hydrothermal treatment (HT), inspired by CaP-based minerals found in the natural bone tissue. Adjustments were made in the HT duration to optimize the morphology of the coating, resulting in a uniform micro-CaP coating structure. The cell viability was enhanced, and adhesion improvement of MC3T3-E1 preosteoblasts and L-929 cells was observed on these materials. Compared to the control group, samples treated with micro-arc oxidation and HT exhibited reduced cell toxicity, an increased number of cells, and well-preserved cell morphology. Cell adhesion studies indicated that longer HT times improved the distribution of cells. Moreover, there was a reduction in zinc ion release after CaP coating from the bulk material at the time of degradation. The micro-CaP coating structure, along with the controlled release of zinc ions, primarily contributed to the improved biomineralization and cytocompatibility of CaP-coated Zn biomaterials. In conclusion, applying a CaP coating to Zn-based biomaterials presents a promising strategy to enhance biocompatibility and regulate the degradation rate.	(72)
5.	Hexafluoroiso propanol-based silk fibroin coatings on AZ31 biometals (compatibility and anticorrosion)	Silk fibroin (SF) derived from aqueous solvents has shown as a promising coating for magnesium alloys; however, a process of pretreatment is essential due to their susceptibility to corrosion in water. In this study, an SF coating using the solvent (hexafluoroisopropanol (HFIP)) was developed without any pretreatment to enhance adhesion. The coating was stabilized using ethylene glycol diglycidyl ether through increased chemical crosslinking. Morphological analyses and nano-scratch tests demonstrated that the HFIP-based SF coating was more compact and had a high strength of adhesion compared to the aqueous-based SF. The corrosion resistance significantly improved, as revealed by electrochemical evaluations and *in-vitro* degradation studies in simulated body fluid. Tests on cytoskeleton structure, cell adhesion studies, and cell cytotoxicity using MC3T3-E1 cells confirmed the increased cell adhesion of the silk coating along with enhanced biological activity.	(59)
6.	Metal-organic Zn-zoledronic acid and 1-hydroxy ethylidene-1,1-diphosphonic acid nanostick-me diated zinc phosphate hybrid coating on biodegradable Zn (compatibility and anticorrosion)	The clinical use of metallic Zn and its alloys presents challenges for the healing of bone fractures due to their irregular degradation patterns, the burst release of Zn^{2+} ions, and inadequate osteo-promotion and osteo-resorption regulation. A metal-organic hybrid nanostick was fabricated using Zn^{2+} coordinated with zoledronic acid (ZA) and 1-hydroxyethylidene-1,1-diphosphonic acid. This nanostick was then added to a zinc phosphate (ZnP) solution to facilitate the deposition and crystal growth of ZnP, resulting in a uniformly integrated micro-patterned metal-organic/inorganic hybrid coating on the Zn substrate. There was a significant reduction in localized corrosion of the Zn substrate, and Zn^{2+} release. Additionally, the modified zinc demonstrated osteo-compatibility and osteo-promoting properties, showing promising osteogenic effects both *in-vitro* and *in-vivo* through a composed pro-osteoblast, and anti-osteoclast response. These beneficial traits can be attributed to the zinc ions and bio-functional ZA, as well as the unique micro- and nano-scale structure of the coating.	(73)
7.	Zirconium (Zr) coating on Mg alloys (compatibility and anticorrosion)	To address issues of rapid degradation and insufficient strength, the direct current magnetron sputtering technique was utilized to apply surface coatings on Mg-based alloys with varying concentrations of Zr. The method enhanced corrosion resistance, preserved biocompatibility, and improved strength without hindering osseointegration. The Mg–Zr coatings demonstrated "hydrophilic" properties, while the Young's modulus remained consistent at approximately 80 GPa throughout all samples. In contrast, the hardness showed significant improvement in all samples with lower corrosion rates, making them promising candidates for functional biodegradable materials in temporary bone implants.	(74)
8.	Chelated silk fibroin coating on Mg-based implants (compatibility and anticorrosion)	This study presents an innovative protein coating for Mg alloys that incorporates calcium and strontium ions with silk fibroin. By employing a binary solvent system to facilitate microcrystal nucleation, the β-sheet content in silk fibroin is increased significantly to 45.4%. This enhanced β-sheet structure reinforces the "labyrinth effect" at the nanoscale, leading to a marked enhancement in resistance to corrosion, shown by a reduction of 3 order of magnitude in corrosion current density compared to the uncoated alloys. Careful doping of Ca^{2+} and Sr^{2+} ions, ensured steady chelation with the silk fibroin amorphous segments. The controlled release of these ions activated the Wnt signalling pathway, enhancing osteogenic activity. This coating system of silk fibroin, simultaneously improves corrosion resistance as well as osteogenic potential in magnesium alloys used for biomedical applications.	(75)

on implant surfaces. Biofilms are difficult to eliminate, being structured communities of bacteria encased in a self-produced polymeric matrix, and account for the vast majority of chronic infections (34). By integrating antimicrobial agents into a coating, using, for instance, silver nanoparticles, quaternary ammonium compounds, or natural extracts that contain quercitrin, the adhesiveness of the bacteria can greatly be reduced, which in turn boosts the longevity as well as successful implementation of an orthopedic device (58). Silver coatings prevent the replication of bacteria, notably *Staphylococcus aureus* and *Escherichia coli* (50). Magnesium-based alloys will be able to provide temporary

TABLE 3 | Comparative analysis of functional coatings for orthopedic implants.

Sl. no.	Functional coating	Antibacterial activity	Biocompatibility	Key metrics	Ref.
1.	**Magnesium-based alloys**	Moderate	High	Effective against some bacteria, good bone tissue integration.	(59)
2.	**Chitosan-ZnO composites**	High	Moderate	Strong antibacterial properties.	(68)
3.	**Quercitrin-coated Ti-6Al-4V**	High	High	Superior osteogenic differentiation and cell adhesion, which effectively lower bacterial viability.	(60)
4.	**Vitamin E-coated titanium alloy**	Moderate	High	Offers anti-adhesion and oxidation resistance.	(61)
5.	**Dual-functional coatings**	Very High	Moderate	Combines several antibacterial activity pathways and exhibits potential in both *in-vivo* and *in-vivo* investigations.	(63)

structural support and reduce infection risk. Magnesium alloys, as they biodegrade, ensure that the patients will have no more surgeries to remove permanent implants, which increases the outcome of the patients and decreases health care costs (59). In addition, the magnesium ions help in increasing the osteogenic activity, thus assisting in healing bone tissue (12). Despite this great potential of the antimicrobial implant, several challenges still remain. The demerit of these coatings is that the release of antibacterial agents may gradually decline with time, leading to infection (6). Further, some antimicrobial agents are also cytotoxic in nature. The regulatory approval for new coatings is a time-consuming and highly complex processes that requires *in-vivo* testing for the safety and efficacy of the product (20).

Comparative analysis of functional coatings on orthopedic implants

Table 3 presents a comparison of key performance metrics to give a clear picture of the effectiveness of different functional coatings. The table lists the antibacterial activity, biocompatibility, and economic viability of the coating materials taken into consideration, including chitosan-ZnO composites, magnesium-based alloys, and others.

Discussion

Antibacterial activity

Quercitrin-coated Ti-6Al-4V and the dual-functional coatings derived from quaternary ammonium salts present superior antibacterial activity; thereby, these coatings diminish the adhesion of bacteria as well as the formation of biofilms considerably. For instance, quercitrin, apart from improving the biocompatibility, induces osteogenic differentiation, and is considered to be an excellent potential for orthopedic use (60). However, the long-term stability of such coatings in the physiological environment is a concern, since the release of antibacterial agents may decrease with time, and recurrence of infection might be possible.

Biocompatibility

Vitamin E-coated Ti alloys exhibit excellent biocompatibility with anti-adhesive properties. They are thus essential for the use of temporary implants (61). On one hand, though they prevent the adherence of bacteria, they could impair the essential process of osseointegration in permanent implants for long-term successful integration with bones. There should be proper clinical assessment regarding these potential compromises where infection would be prevented with simultaneous promotion for integration with bones.

Mechanical properties

In this regard, hydroxyapatite coatings exhibit extraordinary bioactivity and have the ability to speed up the process of osseointegration. However, there are instances in which these coatings are brittle and are unable to withstand certain mechanical pressures that are placed *in-vivo* (50). On the other hand, polymers, particularly those composed of silk fibroin, are both flexible and durable. However, their long-term durability and wear resistance in a dynamic biological environment should be investigated further (59).

Scalability and cost

Coating technologies are also costly and difficult to implement on a large scale due to their high-cost constraints in clinical applications. Certainly, the high-efficiency techniques, such as magnetron sputtering and pulsed laser deposition, are remarkable (47). However, they are expensive and challenging to scale for mass production. Electrophoretic deposition and other older methods are cheaper and easier to use on a large scale, but they are not as good at evenly covering and sticking things together.

Challenges with regulatory approval

These coatings face clinical translation challenges with regulatory approval. As they often requires *in-vivo* testing in

a multitude of animals and a complete checklist of approved protocols for safety and effectiveness to create new coatings possible for clinical usage, which can take its time (20).

Conclusion

The development of functional coatings on biometals is a viable technique for improving the performance and lifetime of orthopedic implants while also addressing the serious challenge faced by implant-related infections. This review focuses on the several strategic techniques that have been used to develop coatings that have antibacterial agents in them to avoid the formation of biofilms and the infections that could result from them, in addition to having mechanical attributes that are biocompatible. Advanced materials like biodegradable metals, ceramics, and polymers combined with cutting-edge coating processes have shown great promise in enhancing implantation and mitigating the negative side effects of commonly used metallic implants. Current studies on a variety of functional coatings, such as the recently developed bioactive ion release and biomedical natural chemicals, show that surface characteristics must be customized to satisfy the diverse requirements of orthopedic applications. As a result, hybrid coatings and their development of multipurpose materials pave the way for future advancements in implants that will benefit patients more, produce better results, and save healthcare costs. Addressing regulatory issues and ensuring the scalability of these coatings for clinical usage are crucial as the industry develops. Long-term *in-vivo* tests and the development of standardized procedures for evaluating the effectiveness and safety of these novel coatings should be the main objectives of future research.

References

1. Thanigaivel S, Priya AK, Balakrishnan D, Dutta K, Rajendran S, Soto-Moscoso M. Insight on recent development in metallic biomaterials: strategies involving synthesis, types and surface modification for advanced therapeutic and biomedical applications. *Biochem Eng J*. (2022) 187:108522.
2. Rokaya D, Bohara S, Srimaneepong V, Kongkiatkamon S, Khurshid Z, Heboyan A, et al. Metallic biomaterials for medical and dental prosthetic applications. In: Jana S editor. *Functional biomaterials: Drug delivery and biomedical applications*. Singapore: Springer (2022). p. 503–22.
3. Sathishkumar S, Paulraj J, Chakraborti P, Muthuraj M. Comprehensive review on biomaterials and their inherent behaviors for hip repair applications. *ACS Appl Bio Mater*. (2023) 6:4439–64.
4. Priyadarsini S, Mukherjee S, Mishra M. Nanoparticles used in dentistry: a review. *J Oral Biol Craniofacial Res*. (2018) 8:58–67.
5. Jiao J, Zhang S, Qu X, Yue B. Recent advances in research on antibacterial metals and alloys as implant materials. *Front Cell Infect Microbiol*. (2021) 11:693939.
6. Feng JB, Chen R, Li B, Jiang BH, Li B. The current trend of antibacterial prostheses and prosthetic surface coating technologies to prevent prosthetic joint infection for artificial joint replacement. *J Biomater Tissue Eng*. (2023) 13:1046–60.
7. Wang N, Ma Y, Shi H, Song Y, Guo S, Yang S. Mg-, Zn-, and Fe-based alloys with antibacterial properties as orthopedic implant materials. *Front Bioeng Biotechnol*. (2022) 10:888084.
8. Al-allaq AA, Kashan JS, Abdul-Kareem FM, Alani AM. Review of in vivo investigations on metal implants for bone tissue engineering. *Regen Eng Transl Med*. (2024):1–25. doi: 10.1007/s40883-024-00352-2
9. Li J, Qin L, Yang K, Ma Z, Wang Y, Cheng L, et al. Materials evolution of bone plates for internal fixation of bone fractures: a review. *J Mater Sci Technol*. (2020) 36:190–208.
10. Paiva JCC, Oliveira L, Vaz MF, Costa-de-Oliveira S. Biodegradable bone implants as a new hope to reduce device-associated infections—a systematic review. *Bioengineering*. (2022) 9:409.
11. Rahim SA, Joseph MA, Sampath Kumar TS. Recent progress in surface modification of Mg alloys for biodegradable orthopedic applications. *Front Mater*. (2022) 9:848980.
12. Mishra TN, Kumar A, Prasad SB. Magnesium based implants: alloying and coating strategies for improvement in its biomechanical and biocorrosion properties. *Proc Inst Mech Eng Part L J Mater Des Appl*. (2024):14644207241269608. doi: 10.1177/14644207241269696
13. Tsakiris V, Tardei C, Clicinschi FM. Biodegradable Mg alloys for orthopedic implants–a review. *J Magnes Alloy*. (2021) 9:1884–905.
14. Rouf S, Malik A, Raina A, Haq MIU, Naveed N, Zolfagharian A, et al. Functionally graded additive manufacturing for orthopedic applications. *J Orthop*. (2022) 33:70–80.
15. Shi H, Zhou P, Li J, Liu C, Wang L. Functional gradient metallic biomaterials: techniques, current scenery, and future prospects in the biomedical field. *Front Bioeng Biotechnol*. (2021) 8:616845.
16. Keerthiga G, Simi VS, Mohan L. Surface modifications of biometals. In: Kaya S, Yesudass S, Arthanari S, Bose S, Serdaroğlu G, editors. *Materials development and processing for biomedical applications*. Boca Raton, FL: CRC Press (2022). p. 197–210.
17. Lakhani A, Khatri K. Orthopedic applications of implant coatings. In: ul Islam S, Hussain CM, Shukla SK, editors. *Antiviral and antimicrobial coatings based on functionalized nanomaterials*. Amsterdam: Elsevier (2023). p. 589–604.
18. Yang X, Xiong S, Zhou J, Zhang Y, He H, Chen P, et al. Coating of manganese functional polyetheretherketone implants for osseous interface integration. *Front Bioeng Biotechnol*. (2023) 11:1182187.
19. Kim S, Chen JB, Clifford A. Tuning the biointerface: low-temperature surface modification strategies for orthopedic implants to enhance osteogenic and antimicrobial activity. *ACS Appl Bio Mater*. (2021) 4:6619–29.
20. Syeddan SA. Research methodology and mechanisms of action of current orthopaedic implant coatings. *J Long Term Eff Med Implants*. (2023) 33:51–66.
21. Phillips AM. Overview of the fracture healing cascade. *Injury*. (2005) 36:S5–7.
22. Einhorn TA. Enhancement of fracture-healing. *JBJS*. (1995) 77:940–56.
23. Claes L, Recknagel S, Ignatius A. Fracture healing under healthy and inflammatory conditions. *Nat Rev Rheumatol*. (2012) 8:133–43.
24. Einhorn TA, Gerstenfeld LC. Fracture healing: mechanisms and interventions. *Nat Rev Rheumatol*. (2015) 11:45–54.
25. Ono T, Takayanagi H. Osteoimmunology in bone fracture healing. *Curr Osteoporos Rep*. (2017) 15:367–75.
26. Kolar P, Gaber T, Perka C, Duda GN, Buttgereit F. Human early fracture hematoma is characterized by inflammation and hypoxia. *Clin Orthop Relat Res*. (2011) 469:3118–26.
27. Girigoswami K, Devender NS, Girigoswami A. Fate of stem cells grown on the extracellular matrix isolated from cancer cells and their possible applications in tissue engineering. *Curr Sci*. (2021) 120:1616.
28. Girigoswami K, Saini D, Girigoswami A. Extracellular matrix remodeling and development of cancer. *Stem Cell Rev Rep*. (2021) 17:739–47.

29. Papachristou DJ, Georgopoulos S, Giannoudis PV, Panagiotopoulos E. Insights into the cellular and molecular mechanisms that govern the fracture-healing process: a narrative review. *J Clin Med*. (2021) 10:3554.
30. Li H, Yao Z, Zhang J, Cai X, Li L, Liu G, et al. The progress on physicochemical properties and biocompatibility of tantalum-based metal bone implants. *SN Appl Sci*. (2020) 2:1–14.
31. Jacobs A, Renaudin G, Forestier C, Nedelec JM, Descamps S. Biological properties of copper-doped biomaterials for orthopedic applications: a review of antibacterial, angiogenic and osteogenic aspects. *Acta Biomater*. (2020) 117:21–39.
32. Filipović U, Dahmane RG, Ghannouchi S, Zore A, Bohinc K. Bacterial adhesion on orthopedic implants. *Adv Colloid Interface Sci*. (2020) 283:102228.
33. Zhang K, Li X, Yu C, Wang Y. Promising therapeutic strategies against microbial biofilm challenges. *Front Cell Infect Microbiol*. (2020) 10: 359.
34. Arciola CR, Campoccia D, Montanaro L. Implant infections: adhesion, biofilm formation and immune evasion. *Nat Rev Microbiol*. (2018) 16:397–409.
35. Makabenta JM, Nabawy A, Li CH, Schmidt-Malan S, Patel R, Rotello VM. Nanomaterial-based therapeutics for antibiotic-resistant bacterial infections. *Nat Rev Microbiol*. (2021) 19:23–36.
36. Flemming HC, Wingender J, Szewzyk U, Steinberg P, Rice SA, Kjelleberg S. Biofilms: an emergent form of bacterial life. *Nat Rev Microbiol*. (2016) 14:563–75.
37. Okshevsky M, Meyer RL. The role of extracellular DNA in the establishment, maintenance and perpetuation of bacterial biofilms. *Crit Rev Microbiol*. (2015) 41:341–52.
38. Perchikov R, Cheliukanov M, Plekhanova Y, Tarasov S, Kharkova A, Butusov D, et al. Microbial biofilms: features of formation and potential for use in bioelectrochemical devices. *Biosensors*. (2024) 14: 302.
39. Fournier B. The function of TLR2 during staphylococcal diseases. *Front Cell Infect Microbiol*. (2013) 2:167.
40. Amin Yavari S, Castenmiller SM, van Strijp JA, Croes M. Combating implant infections: shifting focus from bacteria to host. *Adv Mater*. (2020) 32:2002962.
41. Seebach E, Kubatzky KF. Chronic implant-related bone infections—can immune modulation be a therapeutic strategy? *Front Immunol*. (2019) 10:1724.
42. Chowdhury S, Arunachalam N. Surface functionalization of additively manufactured titanium alloy for orthopaedic implant applications. *J Manuf Process*. (2023) 102:387–405.
43. Al-Shalawi FD, Mohamed Ariff AH, Jung DW, Mohd Ariffin MKA, Seng Kim CL, Brabazon D, et al. Biomaterials as implants in the orthopedic field for regenerative medicine: metal versus synthetic polymers. *Polymers (Basel)*. (2023) 15:2601.
44. Grigoriev S, Sotova C, Vereschaka A, Uglov V, Cherenda N. Modifying coatings for medical implants made of titanium alloys. *Metals (Basel)*. (2023) 13:718.
45. Zielinski A, Bartmanski M. Electrodeposited biocoatings, their properties and fabrication technologies: a review. *Coatings*. (2020) 10:782.
46. Badiceanu M, Anghel S, Mihailescu N, Visan AI, Mihailescu CN, Mihailescu IN. Coatings functionalization via laser versus other deposition techniques for medical applications: a comparative review. *Coatings*. (2022) 12:71.
47. Meng M, Wang J, Huang H, Liu X, Zhang J, Li Z. 3D printing metal implants in orthopedic surgery: methods, applications and future prospects. *J Orthop Transl*. (2023) 42:94–112.
48. Hussain M, Askari Rizvi SH, Abbas N, Sajjad U, Shad MR, Badshah MA, et al. Recent developments in coatings for orthopedic metallic implants. *Coatings*. (2021) 11:791.
49. Solangi NH, Karri RR, Mubarak NM, Mazari SA. Mechanism of polymer composite-based nanomaterial for biomedical applications. *Adv Ind Eng Polym Res*. (2024) 7:1–19.
50. Nawaz MH, Aizaz A, Ropari AQ, Shafique H, Imran OB, Minhas BZ, et al. A study on the effect of bioactive glass and hydroxyapatite-loaded Xanthan dialdehyde-based composite coatings for potential orthopedic applications. *Sci Rep*. (2023) 13:17842.
51. Palierse E, Roquart M, Norvez S, Corté L. Coatings of hydroxyapatite–bioactive glass microparticles for adhesion to biological tissues. *RSC Adv*. (2022) 12:21079–91.
52. Tan J, Li L, Li B, Tian X, Song P, Wang X. Titanium surfaces modified with graphene oxide/gelatin composite coatings for enhanced antibacterial properties and biological activities. *ACS Omega*. (2022) 7:27359–68.
53. Silva AO, Cunha RS, Hotza D, Machado RAF. Chitosan as a matrix of nanocomposites: a review on nanostructures, processes, properties, and applications. *Carbohydr Polym*. (2021) 272:118472.
54. Bouammali H, Bourassi L, Bouammali B, Siaj M, Challioui A, Touzani R. Graphene and chitosan innovative materials for water treatment. *Mater Today Proc*. (2023) 72:3577–88.
55. Nie L, Hou M, Wang T, Sun M, Hou R. Nanostructured selenium-doped biphasic calcium phosphate with in situ incorporation of silver for antibacterial applications. *Sci Rep*. (2020) 10:13738.
56. Ebrahimi M, Botelho MG, Dorozhkin SV. Biphasic calcium phosphates bioceramics (HA/TCP): concept, physicochemical properties and the impact of standardization of study protocols in biomaterials research. *Mater Sci Eng C*. (2017) 71:1293–312.
57. Tripathi S, Raheem A, Dash M, Kumar P, Elsebahy A, Singh H, et al. Surface engineering of orthopedic implants for better clinical adoption. *J Mater Chem B*. (2024) 12:11302–35.
58. Ghilini F, Fagali N, Pissinis DE, Benítez G, Schilardi PL. Multifunctional titanium surfaces for orthopedic implants: antimicrobial activity and enhanced osseointegration. *ACS Appl Bio Mater*. (2021) 4:6451–61.
59. Li H, Si S, Yang K, Mao Z, Sun Y, Cao X, et al. Hexafluoroisopropanol based silk fibroin coatings on AZ31 biometals with enhanced adhesion, corrosion resistance and biocompatibility. *Prog Org Coatings*. (2023) 184:107881.
60. Llopis-Grimalt MA, Arbós A, Gil-Mir M, Mosur A, Kulkarni P, Salito A, et al. Multifunctional properties of quercitrin-coated porous Ti-6Al-4V implants for orthopaedic applications assessed in vitro. *J Clin Med*. (2020) 9:855.
61. Gamna F, Cochis A, Scalia AC, Vitale A, Ferraris S, Rimondini L, et al. The use of vitamin E as an anti-adhesive coating for cells and bacteria for temporary bone implants. *Surf Coatings Technol*. (2022) 444: 128694.
62. Parfenova LV, Galimshina ZR, Gil'fanova GU, Alibaeva EI, Danilko KV, Pashkova TM, et al. Hyaluronic acid bisphosphonates as antifouling antimicrobial coatings for PEO-modified titanium implants. *Surf Interfaces*. (2022) 28:101678.
63. Chen C, Li Z, Li X, Kuang C, Liu X, Song Z, et al. Dual-functional antimicrobial coating based on the combination of zwitterionic and quaternary ammonium cation from rosin acid. *Compos Part B Eng*. (2022) 232:109623.
64. Zermeño-Pérez D, Chouirfa H, Rodriguez BJ, Dürig T, Duffy P, Cróinín TÓ. Bioresorbable polyester coatings with antifouling and antimicrobial properties for prevention of biofilm formation in early stage infections on Ti6Al4V hard-tissue implants. *ACS Appl Bio Mater*. (2024) 7:5728–39.
65. Acosta S, Ibañez-Fonseca A, Aparicio C, Rodríguez-Cabello JC. Antibiofilm coatings based on protein-engineered polymers and antimicrobial peptides for preventing implant-associated infections. *Biomater Sci*. (2020) 8:2866–77.
66. Gouveia Z, Perinpanayagam H, Zhu J. Development of robust chitosan–silica class II hybrid coatings with antimicrobial properties for titanium implants. *Coatings*. (2020) 10:534.
67. Ye Z, Sang T, Li K, Fischer NG, Mutreja I, Echeverría C, et al. Aparicio, Hybrid nanocoatings of self-assembled organic-inorganic

amphiphiles for prevention of implant infections. *Acta Biomater*. (2022) 140:338–49.

68. Lin MH, Wang YH, Kuo CH, Ou SF, Huang PZ, Song TY, et al. Hybrid ZnO/chitosan antimicrobial coatings with enhanced mechanical and bioactive properties for titanium implants. *Carbohydr Polym*. (2021) 257:117639.
69. Aslan AK, Bahce E, Güler MS. Electrochemical corrosion and metal ion release protective efficiency of the multilayer TaN coatings on CoCrMo biomedical alloy. *Mater Sci*. (2021) 27:416–24.
70. Camargo ER, Serafim BM, da Cruz AF, Soares P, de Oliveira CC, Saul CK, et al. Bioactive response of PMMA coating obtained by electrospinning on ISO5832-9 and Ti6Al4V biomaterials. *Surf Coatings Technol*. (2021) 412:127033.
71. Fayed O, van Griensven M, Tahmasebi Birgani Z, Plank C, Balmayor ER. Transcript-activated coatings on titanium mediate cellular osteogenesis for enhanced osteointegration. *Mol Pharm*. (2021) 18: 1121–37.
72. Zhu X, Shi Y, Yang L, Chen Q, Luo X, Zhang Q, et al. Creation of bioactive ceramic composite coatings on Zn–Mn–Mg alloy via micro-arc oxidation and hydrothermal treatment for orthopedic implant applications. *ACS Appl Eng Mater*. (2023) 1:734–43.
73. Qian J, Qin H, Zeng P, Hou J, Mo X, Shen G, et al. Metal-organic Zn-zoledronic acid and 1-hydroxyethylidene-1, 1-diphosphonic acid nanostick-mediated zinc phosphate hybrid coating on biodegradable Zn for osteoporotic fracture healing implants. *Acta Biomater*. (2023) 166:685–704.
74. Benzarti Z, Itani S, Castro JD, Carvalho S, Ramos AS. Design multifunctional Mg–Zr coatings regulating Mg alloy bioabsorption. *J Magnes Alloy*. (2024) 12:1461–78.
75. Li H, Ma T, Zhang J, Mao Z, Liang H, Sun Y, et al. Boosting corrosion resistance and osteogenic activity of magnesium-based implants with metal ions chelated silk fibroin coating via binary solvent system. *Chem Eng J*. (2024) 485:149905.