Received: 27 January 2021 | Accepted: 1 April 2021

DOI: 10.1002/cbin.11604

MINI-REVIEW

Cell Biology International WILEY

Biosensitive and antibacterial coatings on metallic material for medical applications

Wolfgang H. Goldmann

Department of Biophysics, Friedrich-Alexander-University of Erlangen-Nuremberg, Erlangen, Germany

Correspondence

Wolfgang H. Goldmann, Department of Biophysics, Friedrich-Alexander-University of Erlangen-Nuremberg, Henkstr. 91, Erlangen 91052, Germany.
Email: wgoldmann@biomed.uni-erlangen.de

Funding information

European Union Horizon 2020 program (Phys2BioMed), Grant/Award Number: 812772; German Science Foundation (DFG), Grant/Award Number: FA 336/13-1

Abstract

Metallic materials are commonly used for load-bearing implants and as internal fixation devices. It is customary to use austenitic stainless steel, especially surgical grade type 316L SS as temporary and Ti alloys as permanent implants. However, long-term, poor bonding with bone, corrosion, and release of metal ions, such as chromium and nickel occur. These ions are powerful allergens and carcinogens and their uncontrolled leaching may be avoided by surface coatings. Therefore, bioactive glasses (BGs) became a vital biomedical material, which can form a biologically active phase of hydroxycarbonate apatite on their surface when in contact with physiological fluids. To reduce the high coefficient of friction and the brittle nature of BGs, polymers are normally incorporated to avoid the high-temperature sintering/densification of ceramic-only coatings. For medical application, electrophoretic deposition (EPD) is now used for polymer (organic) and ceramic (inorganic) components at room temperature due to its simplicity, control of coating thickness and uniformity, low cost of equipment, ability to coat substrates of intricate shape and to supply thick films in composite form, high purity of deposits as well as no phase transformation during coating. Although extensive research has been conducted on polymer/inorganic composite coatings, only some studies have reported multifunctional properties, such as biological antibacterial activity, enhanced cell adhesion, controlled drug release ability, and mechanical properties. This review will focus on biodegradable coatings, including zien, chitosan, gelatin, cellulose loaded with antibacterial drugs/metallic ions/natural herbs on biostable substrates (PEEK/PMMA/PCL/PLLA layers), which have the potential of multifunctional coating for metallic implants.

KEYWORDS

bioceramics, biocomposites, biomaterials, biopolymers, bone and teeth implants

1 | INTRODUCTION

Stainless steel-based implants are frequently used in orthopedic and other applications. These implants have limitations due to their bioinert nature and the potential of uncontrolled release of metallic ions under physiological conditions, which restricts the use of stainless steel for clinical applications (Rehman, Bastan, et al., 2017; Rehman, Ferraris, et al., 2017; Torkaman et al., 2017). One of the inherent problems of prosthesis implantation is the fixation and maintenance of a stable interface between the device and the host tissue at the cellular and organ

level (Kitsugi et al., 1996). The method of prosthesis fixation is based on mechanical fixation (through screws, bolts, nuts, etc.), bone cement fixation (pure or composite cement), biological fixation (simple porous ingrowth or modified by electrical and pulsed electromagnetic field stimulation), and direct bonding fixation (chemical) (Duan & Wang, 2006). However, most frequent fixation problems are related to (i) infection, (ii) wear, (iii) migration and failure of implants, and (iv) implant loosening (Anthony et al., 1990; Geetha et al., 2009). These problems manifest into osteolysis in the bone bed, which is the major cause of long-term implant loosening (Maloney et al., 1990; Purdue et al., 2006). Therefore, there is a need for development of material for orthopedic implants that has a low wear rate.

Wear is the mechanical removal of material during the process of relative motion between two or more contacting surfaces, which can affect the performance of joint prosthesis. Abrasive, adhesive, fatigue, and corrosive mechanisms can be applied through the wear of metal components of joint prostheses. In addition, severe wear followed by mechanical damage may lead to the premature failure of prostheses (Kamachimudali et al., 2003), and corrosion of bioimplants in the physiological environment takes place via electrochemical reactions (Gurappa, 2002; Manivasagam et al., 2010). The electrochemical reactions that occur on the surface of the implanted alloy are identical to those observed during exposure to seawater, that is, aerated sodium chloride. Metals and alloys used as surgical implants induce passivity by the presence of surface protective films, which inhibit corrosion and limit, to some extent, the usage (Rondelli & Vicentini, 1999). Major types of corrosion faced by currently used implant material are pitting, crevice, galvanic, intergranular stress-corrosion cracking, corrosion fatigue, and fretting corrosion (Barbosa, 2016). It is, therefore, customary to use austenitic stainless steels, especially surgical grade type 316L SS as temporary implants (Kamachimudali et al., 2003). Surgical grade type 316L stainless steel orthopedic implants could corrode in the physiological environment and release toxic metal ions, such as iron, chromium, and nickel, which are powerful causes for allergies and carcinogens (Hanawa, 2004). Failure analyses of grade implants have shown that about 90% of them were triggered by pitting and crevice corrosion (Sivakumar & Rajeswari, 1992).

To date, many aspects have been addressed by modifying the surface of stainless steel and other metallic implants, such as titanium (Ti) alloys. The surface modification of metals can improve the interface between the implant and surrounding tissue at biological, chemical, and physical levels (Pishbin et al., 2013; Seuss et al., 2015; Torkaman et al., 2017). Surface coatings also address various other aspects, such as bioactivity, corrosion resistance, and cell adhesion by fabricating composite coatings, for instance, by thermal and plasma spraying of hydroxyapatite (HA) (Cordero-Arias & Boccaccini, 2017; Radda'a et al., 2017). The lack of bioactivity of metals has been addressed by using bioactive glass (BG) (Ciraldo et al., 2019; Wajda et al., 2018), first invented by Hench (2006), which supports the formation of bonds between the implant and bone (Kumar et al., 2017). The mechanism might be the slow release of calcium and silicon ions at critical concentrations, which stimulate cell proliferation and growth. The relatively high stiffness of BG can cause long-term stress shielding in high load-bearing applications (Hench & Jones, 2015). Metallic ions, including silver, strontium, and copper and many more are now incorporated in BG (Rehman, Bastan, et al., 2017; Rehman, Ferraris, et al., 2017; Tejido-Rastrilla et al., 2019; Yang et al., 2018), and exhibit features, such as antibacterial effects and angiogenesis (El-Rashidy, Waly, Gad, Röther, et al., 2018; Kaya et al., 2018; Goodman et al., 2013; Williams, 1987).

Composite coatings comprising biopolymers and BG reduce (i) the stress shielding effect, (ii) inhibit the uncontrolled release of toxic ions, and (iii) improve the attachment and proliferation of osteoblasts (Mehdipour & Afshar, 2012). These support the cellular interaction between the natural bone and implant. Thus, implanted medical devices should also provide resistance against the growth of bacterial biofilms (regardless of the implant material), which is one of the primary reasons for implant failure (Navarro et al., 2008). Consequently, there is a need to inhibit the growth of biofilms because they are resistant to the immune system and antibiotics (Boccaccini et al., 2010; Ferraris et al., 2010, 2012; Pishbin et al., 2013; Seuss et al., 2015). Systemic drug management is less useful because of improper blood circulation and low concentration of antibiotics at the injury site. However, the local delivery of drugs and metallic ions, including copper, silver, zinc, and biomolecules (i.e., antibacterial peptides) is a way to deal with infections because local delivery systems maintain a high concentration of bioactive agents at the desired site. Furthermore, local drug delivery systems allow the controlled release of drugs, thus decreasing possible cytotoxic effects associated with uncontrolled drug release (Baino et al., 2016; Chen et al., 2014; Ouyang et al., 2016; Pishbin et al., 2013, 2014). Nevertheless, extensive use of antibiotics has triggered the growth of antibacterial-resistant strains, which are regarded now as a "global threat." As a result, alternative procedures for dealing with bacterial infections need to be pursued (Ferraris et al., 2010, 2012; Pishbin et al., 2013).

2 | IMPLANTABLE BIOMATERIALS

Biomaterials are mostly of natural or synthetic nature, and normally a product of multiple components that interact with the biological system. They can be classified into the following groups: metal, bioceramics, biopolymers, and biocomposites (Ballarre et al., 2020; Gritsch et al., 2018a, 2018b; Thamaraiselvi & Rajeswari, 2004; Valiev et al., 2008). Another classification of biomaterial was proposed by Hench and Thompson (2010) for orthopedic implants on the basis of their bioactivity and resorbability, for example, "class A" biomaterials, which are osteo-productive (their surface is colonized by osteogenic stem cells in vivo); and "class B" biomaterials, which are osteoconductive and act as a scaffold for cells (Jones, 2013).

Normal metals are bioinert and easy to mold into any shape. They possess high mechanical strength, are fatigue-resistance but corrosive, and can cause toxicity due to active ion release. Passive metals, however, including gold, titanium, chromium, zirconium, have acceptable low corrosion rates, and their corrosion products, although in small amounts, can be found in surrounding tissues and can cause adverse effects (Williams, 1987). Therefore, in modern medical engineering, these metals are coated with

ceramics as these polymers have excellent elastic moduli and are useful as scaffolds for complicated structures. Bioceramics are of versatile nature (bioinert/active/degradable), of good biocompatibility, and able to regenerate bone. They have been used for the repair and reconstruction of damaged parts of the skeleton (Hench, 1991). Natural forms of biopolymers are derived from living organisms, including collagen, cellulose, chitosan, and synthetic polymers, such as polyurethane, polytetrafluoroethylene, polylactic acid, which can be fabricated with tailored properties and architecture from different monomers. Synthetic biopolymers have, however, better mechanical properties and controlled degradation rates compared with natural polymers; thus, their degradation product can cause some local effects, that is, lowering of pH that may lead to cell or tissue necrosis (Mohanty et al., 2005).

Orthopedic implants are important for treating bone traumas caused by disease or accident. Over the years, the demand for implantable biomaterial that can be used in orthopedics, cardiology, dental and vascular therapy, trauma, spine, and wound care has risen sharply (Łapa et al., 2019, 2020; Unalan, Endlein, et al., 2019; Unalan, Slavik, et al., 2019; Winkler et al., 2018). Now, they have become standard practice in modern medicine and range from small implants, such as bolts and nuts to stabilize fractured bones or dental implants to replace teeth, to total hip replacements. Metallic implants, including 316L stainless steel, titanium, and cobalt–chromium alloys are those most extensively used for fracture fixation and bone remodeling. Due to their longstanding stability under a highly aggressive physiochemical in vivo environment and outstanding mechanical properties, they have good wear, corrosion, and friction resistance. But in the physiological environment, these materials may be degraded and trigger the release of unwanted metal ions that damage local tissues, cause inflammatory reactions, and osteolysis of surrounding tissue. These reactions can damage the fixation, which can be seen as the possible origin of implant failure. Stainless steel implants are considered inferior to Ti alloy implants with regard to osseointegration, biocompatibility, and corrosion resistance. Hence, 316L stainless steel is to date only used for short-term bone fracture fixation in the form of fracture plates, nails, and screws (Sumita, 1997).

When the implant comes in contact with body tissue, a biofilm can form on its surface. In the initial phase, bacteria engage passively with the surface of the implant. During the later stage, a biofilm develops that can grow by forming extracellular polymeric substances and polysaccharide intercellular adhesins, which are especially dangerous if caused by multiresistant bacteria contracted during surgery; this can lead to infections and implant rejection (Arciola et al., 2012).

With the increased demand for metallic implants for body part replacements, it is, therefore, imperative to overcome the infection-related limitations of the materials by designing implants to be infection-resistant. Furthermore, the issue of low osseointegration of orthopedic implant material with the adjacent bone tissue needs to be addressed. As infections give rise to bacteria forming a biofilm on the implant, implant surfaces must be functionalized to inhibit or prevent biofilm growth. There are several methods, such as adding silver ions or antibacterial drugs to the surface and modifying the surface roughness (Campoccia et al., 2013).

3 | BONES, TEETH, AND HA

The main inorganic components of bone and tooth enamel are calcium phosphate (Ca:P) comprising calcium cations together with orthophosphate, pyrophosphate, and metaphosphate anions and sometimes with hydroxide or hydrogen ions (Eliaz & Metoki, 2017). Calcium phosphate (Ca:P) at a ratio of 1.67 has a similar composition to natural bone and is the most widely used form of HA (Lertcumfu et al., 2016). It can be extracted from natural sources or is prepared in the laboratory. HA forms crystals in a physiological medium and binds strongly to the bone; it is biocompatible, bioactive, and osteoconductive and is considered to be an excellent bone graft material (Sobczak-Kupiec et al., 2017). Nano-HA (1–100 nm), which possesses a high surface area, can easily be integrated into cells and promotes osteoblast adhesion, differentiation, proliferation, and osteointegration (Mondal et al., 2017). Due to its uniform microstructure and chemical homogeneity, it enhances the calcium deposition on its surface leading quickly to newly formed bone tissue and inhibiting abnormal growth of cancer cells in bone, liver, and throat. The physical properties (solubility, degradability, and mechanical behavior) depend on the particle size, and its degradation rate can stimulate bone growth in a physiological setting and exhibits excellent mechanical strength compared with bulk particles. A lot of research has been done on synthesizing nano-HA particles with physical, mechanical, chemical, and biological properties similar to natural bone. To improve the biological properties of the HA nanoparticles, a number of researchers have synthesized metal-doped or metal-substituted HA nanoparticles. Ion substitution in the HA structure, for example, replacing OH^- ions with ions of comparable charge and size, such as F^- and Cl^- is possible. The sites for PO_4^{3-} ions can also be substituted by silicate ions and calcium cations by Ag^+, Zn^{2+}, Ce^{3+}, Mg^{2+}, or Sr^{2+}. Some ions, such as Cu^{2+} occupy, however, an interstitial position in the HA lattice structure. In a partial exchange, fractions of anions or cations can be replaced by substitution (Cacciotti, 2016).

Nevertheless, differences in ionic radii and surface charge for the incoming versus departing ion can be critical. Doping ions of different charge, for example, phosphate with carbonate ions, is also conceivable. Under this condition, a positively charged vacancy is created, which is then counteracted by the synchronized loss of one calcium (Ca^{2+}) cation and one hydroxyl anion (OH^-). Metal doping or ion substitution can change the physical properties of HA. Ion doping has a wide range of applications in biomedical sciences, including biocompatible coatings, enhanced bone regeneration, drug delivery, and biomarkers for medical and antimicrobial purposes (Dorozhkin, 2013; Karthika et al., 2015; Ratnayake et al., 2017; Tite et al., 2018).

4 | RESPONSES TO IMPLANTS

Cell attachment is connected with the interaction of the biomaterial with collagen, adsorption of proteins, and cells on biomaterial surfaces followed by bone formation. In a physiological environment, the biomaterial can release ionic products, which increase local concentration, for example, Ca^{2+} and PO_4^{3-} ions, and the precipitation of apatite layer on its surface bonds to bone (Choi et al., 2014). Bone grafts and implants must be biocompatible and should not elicit local or systemic toxic effects. Four kinds of tissue responses to implants are known: (i) if toxic material is present, the surrounding tissue will die; (ii) if a graft/material is nontoxic but inert, fibrous tissue will surround the material; (iii) if the material is nontoxic and bioactive, then an interfacial bond will be formed between the material and tissue; (iv) if the material is nontoxic and dissolves, then the surrounding tissue will be replaced. Many studies have shown that all kinds of calcium phosphate are biocompatible both in vitro and in vivo (Eliaz & Metoki, 2017). The first body response on the implantation of a bone graft or biomaterial is inflammation, which is followed by the ingrowth of preosteoblasts and their differentiation into osteoblasts. This process can take a few days, depending on the implanted material and is followed by osteoinduction, osteoconduction, and mechanical support, which takes weeks to years and depends on the nature of the biomaterial.

5 | METAL IONS AS DOPANTS

Over the years, there has been a huge rise in antibiotic-resistant bacterial strains, which has limited the use of antibiotics in infection control. Microorganisms express resistance against antibiotics through a variety of mechanisms, that is, preventing the penetration through the cell membrane, expulsion via efflux pumps, modification of the target, and inactivating proteins. Another cause of the ineffectiveness of antibiotics is biofilm formation around orthopedic implants, as antibiotics cannot penetrate through biofilms (Li & Webster, 2018).

Consequently, metal ions have been used as dopants in bioceramics and biomaterials to induce resistance against fungi and bacteria. These include silver, zinc, copper, cerium, strontium, magnesium, nickel, titanium, europium, yttrium ions, and anions, such as selenium and fluoride (Alshemary et al., 2015; Ciraldo et al., 2018; El-Rashidy, Waly, Gad, Hashem, et al., 2018; El-Rashidy, Waly, Gad, Röther, et al., 2018; Gritsch et al., 2018a, 2018b; Łapa et al., 2019, 2020; Wajda et al., 2019). Thus, the antimicrobial properties of these metals depend on their physical state and surface properties, which rely on the method of synthesis. Radovanovic et al. (2014) synthesized silver-substituted HA by the coprecipitation method, which showed antibacterial action against *Staphylococcus aureus*, *Klebsiella pneumonia*, *Providencia stuartii*, and *Citrobacter freundii*. Unalan, Slavik, et al. (2019) demonstrated that Cu-HA coating deposited on titanium substrate by the electrophoretic deposition (EPD) method had a significant antibacterial effect on *Escherichia coli* strains. Co-substitution of Ag-(tri-calcium phosphate [TCP]) lattice with copper ions showed even higher antibacterial properties than Ag-TCP used against *E. coli* and *S. aureus*, and co-substitution of copper and magnesium in TCP lattice and copper–zinc–HA coating increased the antibacterial properties even more. Zinc incorporation as a secondary ion in HA also improved MC3T3-E1 cell proliferation, initial adhesion, and antibacterial efficiency, and Sr^{2+} ions in combination with copper in HA reduced the toxic effect in cells (Ciraldo et al., 2020; Huang et al., 2016).

The mechanism for the antibacterial action of metallic ions in bioceramics (HA, calcium phosphate) is not entirely clear. It is believed that potent ions enter the bacterial cell disturbing the intracellular ATP production that interrupts the DNA replication activity. They accumulate inside the bacteria changing the membrane permeability by affecting the steady release of lipopolysaccharides and proteins. The metallic ions produce reactive oxygen species with constituents of the bacterial membrane and wall that modify the bacterial structure leading to its death (Gutierrez et al., 2011). The response of surrounding cells toward synthesized biomaterial is also crucial for biomedical application (Supova, 2015). When a bone graft is implanted in the body, it undergoes immediate body inflammation, hemorrhaging, and the formation of new blood vessels. After the implantation, osteoinductive proteins trigger the migration of mesenchymal stem cells into the graft site, where they change into osteoblasts and osteoclasts. Bone grafts take about 1 month to become part of the body when new bone is formed around the old, necrotic bone. A recent study has shown that cells behave distinctly to different types of implant material as the osseointegration between biomaterial and cells depends on material surface properties, such as chemistry, topography, and surface energy. These characteristics determine the adsorption of biological molecules on the surface of the biomaterial and their orientation. Cell adhesion mostly involves van der Waal's or ionic forces, which are short-term and rapid and induce signal transduction, promote transcription, and regulate gene expression in the presence of biological fluid followed by proliferation and differentiation.

Deligianni et al. (2005) have shown that surface roughness and hydrophobicity determine the surface charge, which influences cell attachment and protein adsorption on positively/negatively charged surfaces. Furthermore, it was reported that the orientation and 3D structure of adsorbed proteins on biomaterial affect cell morphology, proliferation, and differentiation. Additionally, the size of the particles has a significant influence on cell attachment; human bone-derived cells MG-63 and U-2OS, for instance, were shown to respond more quickly to minor variations in chemistry and surface properties compared with other cells. Biological studies displayed that both human and animal osteoblasts (MC3T3-E1, MG-63, and SaOS-2) attached more readily to HA and TCP leading to increased cell proliferation (Czekanska et al., 2014). Xu et al. (2012) argued that different shapes, sizes, and surface areas of HAs affect the biological properties of osteoblast proliferation, cellular activity, apoptosis, and osteogenic gene expression.

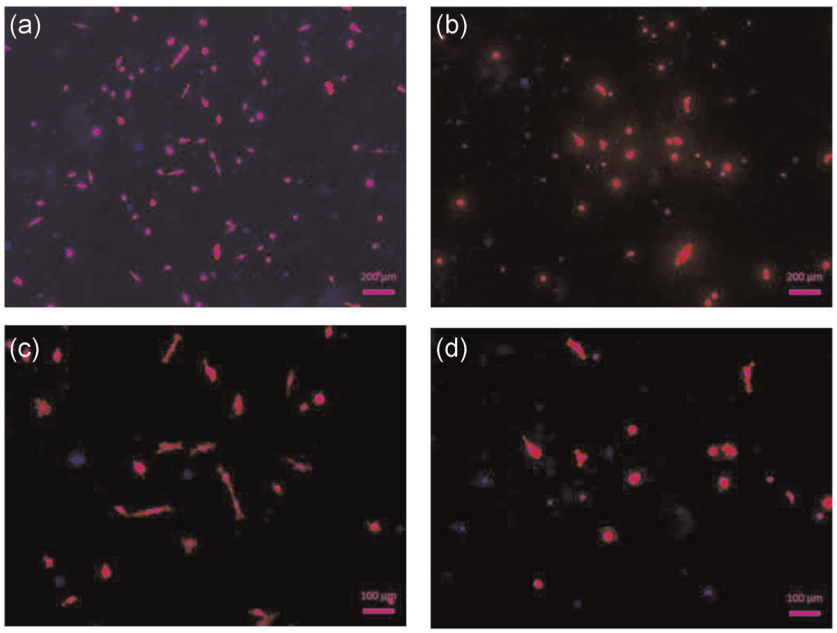

FIGURE 1 Fluorescence images of bone murine stromal cells ST-2 on stainless steel coated (a) with chitosan-gelatin electrophoretic deposition (EPD); (b) with chitosan-gelatin-SiGe NPs EPD; (c) chitosan-gelatin EPD coating; and (d) SS chitosan-gelatin-SiGe NPs EPD. Magnification (a, b) at ×100 and (c, d) at ×200. Nucleus staining in blue (4′,6-diamidino-2-phenylindole [DAPI]) and cell cytoplasm in red (phalloidin). Taken from Aydemir et al. (2020) with permission from Elsevier

6 | COMPOSITE COATINGS BY EPD

The incorporation of metallic nanoparticles and natural herbs in biomedical devices has gained much attention in the last few years (Ferraris et al., 2010, 2017; J. S. Kim et al., 2007; Maráková et al., 2017; Mokhena & Luyt, 2017; Pishbin et al., 2013). Although nanoparticles have been used in numerous applications, their possible cytotoxic effect has not been studied adequately (T. S. Kim et al., 2017; Wijnhoven et al., 2009). Moreover, natural herbs might reduce the cytotoxic effect but maintaining antibacterial properties requires a specific design for orthopedic implants. Therefore, a technological need to improve metallic implant surface properties is called for to develop multifunctional bioactive polymer/inorganic composite coatings. Extensive research has, therefore, been carried out on polymer/inorganic composite coatings by EPD. However, only a few reports of multistructured coatings, which address aspects of

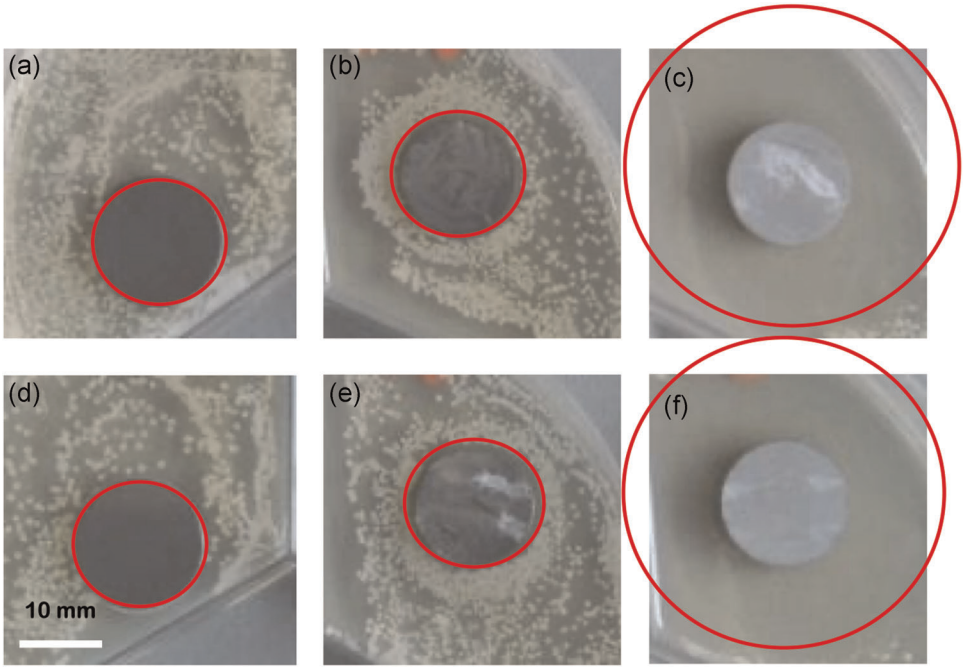

FIGURE 2 Bacterial inhibition test over 24 h. Incubation of *Staphylococcus aureus* (a–c) and *Escherichia coli* (d–f) with bare stainless steel (a, d); stainless steel coated with chitosan-gelatin electrophoretic deposition (EPD) (b, e); stainless steel coated with chitosan-gelatin-SiGe NPs EPD (c, f). Taken from Aydemir et al. (2020) with permission from Elsevier

bioactivity, antibacterial activity, enhanced cellular attachment, controlled drug release capability, and mechanical integrity have been prepared (Aydemir et al., 2020; Boccaccini et al., 2006; Sun et al., 2008; Zhitomirsky et al., 2009) (Figures 1 and 2).

Only recently, comprehensive research investigations focusing on EPD of biodegradable coatings (e.g., chitosan/gelatin/zein loaded with gentamicin/lawsone/curcumin and other substances) on biostable substrates (polyetheretherketone [PEEK], polymethyl methacrylate [PMMA], titanium, 316L SS, etc.) and biodegradable substrates have led to a new family of multifunctional coatings for metallic implants (Ciraldo et al., 2019; El-Rashidy, Waly, Gad, Hashem, et al., 2018; Gritsch et al., 2018a; Rehman et al., 2018; Unalan, Endlein, et al., 2019). Therefore, to address the increasing problem of bacterial infections, biodegradable coatings will in the future provide targeted drug delivery systems of incorporated natural herbs, metallic ions, and biological molecules to improve corrosion and wear resistance, bioactivity, biocompatibility, and antibacterial resistance of the metallic orthopedic implants (Virk et al., 2019).

7 | CONCLUSIONS

In general, metallic implants have excellent mechanical properties; however, they are bioinert. Applying bioactive coatings, especially metal ion-substituted HA to the surface, to improve corrosion and microbiology, has received wide attention. Several techniques for coating inorganic material on metallic implants have been proposed, including thermal spraying, plasma spraying, biomimetic coating, sol–gel dip coating, pulsed laser deposition, and EPD. All these methods have their own advantages/disadvantages that should be weighed up before biomedical application (Besra & Liu, 2007).

To date, EPD allows for cheap and quick coating of various materials with conductive substrates by immersing them in a suspension containing particles of the material and applying an electric field. For successful coating, several parameters related to EPD processes need to be optimized before using metallic implants coated with HA to combat antibacterial and antifungal properties, and currently, EPD is the most frequently applied technique to produce coatings, using ions, such as selenium, copper, and others incorporated in HA.

Finally, although the fabrication and biocompatibility of the various biomaterials, in terms of geometry, dimension, porosity, photoactivity, and surface chemistry, which generate less toxic biological responses have been unique over the years. Their successful development for theranostic therapies, that is, translation into a clinical setting remains largely unexplored mainly due to long-term biocompatibility uncertainties. Therefore, future in vitro and in vivo studies of functionalized biomaterial need to be carried out to improve biological responses and to diminish side effects before these can be translated into routine clinical settings (Kafshgari & Goldmann, 2020) and (Tesler et al., 2021; Maqbool et al., 2021).

ACKNOWLEDGMENTS

The author thanks Prof. A. R. Boccaccini for his encouraging feedback and Prof. J. Ballarre for her support as well as Celia Marshall (MA) for proofreading and editing the manuscript. This study was supported by the DFG (FA 336/13-1) and European Union Horizon 2020 program (Phys2BioMed, Grant: 812772).

Note in press: Relevant patents entitled "Bone morphogenetic protein-conjugated monoclonal antibodies against hapten-dope metal scaffolds for prosthesis implants", and "Silicone- or fluorosilicone-coated solid substrates and process for their preparation" were filed in 1992 by Dr. J.L. Alonso in Spain and in 2021 with the EPO (application No. EP21166558) by Dr. A.B. Tesler and Dr. W.H. Goldmann et al., respectively.

DATA AVAILABILITY STATEMENT

Data are openly available in a public repository that issues data sets with DOIs.

ORCID

Wolfgang H. Goldmann http://orcid.org/0000-0003-0738-2665

REFERENCES

Alshemary, A. Z., Akram, M., Goh, Y., Tariq, U., Butt, F. K., Abdolahi, A., & Hussain, R. (2015). Synthesis, characterization, in vitro bioactivity antimicrobial activity of magnesium and nickel-doped silicate hydroxyapatite. *Ceramics International*, *41*, 11886–11898.

Anthony, P. P., Gie, G. A., Howie, C. R., & Ling, R. S. (1990). Localised endosteal bone lysis in relation to the femoral components of cemented total hip arthroplasties. *The Journal of Bone and Joint Surgery*, *72*, 971–979.

Arciola, C. R., Campoccia, D., Speziale, P., Montanaro, L., & Costerton, J. W. (2012). Biofilm formation in *Staphylococcus* implant infections. A review of molecular mechanisms and implications for biofilm-resistant materials. *Biomaterials*, *33*, 5967–5982.

Aydemir, T., Liverani, L., Pastoreb, J. I., Cere', S. M., Goldmann, W. H., Boccaccini, A. R., & Ballarre, J. (2020). Functional behavior of chitosan/gelatin/silica-gentamicin coatings by electrophoretic deposition on surgical grade stainless steel. *Materials Science & Engineering C*, *115*, 111062.

Baino, F., Ferraris, S., Miola, M., Perero, S., Verne, E., Coggiola, E., Dolcino, D., & Ferraris, M. (2016). Novel antibacterial ocular prostheses: Proof of concept and physico-chemical characterization. *Materials Science & Engineering, C: Materials for Biological Applications*, *60*, 467–474.

Ballarre, J., Aydemir, T., Liverani, L., Röther, J. A., Goldmann, W. H., & Boccaccini, A. R. (2020). Versatile bioactive and antibacterial coating system based on silica, gentamicin, and chitosan: Improving early stage performance of titanium implants. *Surface & Coatings Technology*, *381*, 125138.

Barbosa, M. A. (2016). Corrosion of metallic implants, W. Murphy J. Black & G. Hastings. *Handbook of biomaterial properties* (2nd ed., pp. 509–548). New York: Springer Science+Business Media.

Besra, L., & Liu, M. (2007). A review of fundamentals and applications of electrophoretic deposition (EPD). *Progress in Materials Science*, *52*, 1–61.

Boccaccini, A. R., Keim, S., Ma, R., Li, Y., & Zhitomirsky, I. (2010). Electrophoretic deposition of biomaterials. *Journal of the Royal Society Interface*, *7*, S581–S613.

Boccaccini, A. R., Peters, C., Roether, C. A., Eifler, D., Misra, S. K., & Minay, E. J. (2006). Electrophoretic deposition of polyetheretherketone (PEEK) and

PEEK/Bioglass® coatings on NiTi shape memory alloy wires. *Journal of Materials Science*, *41*, 8152–8159.

Cacciotti, I. (2016). Cationic and anionic substitutions in hydroxyapatite, *Handbook of Bioceramics and Biocomposites* (pp. 145–211). Cham: Springer.

Campoccia, D., Montanaro, L., & Arciola, C. R. (2013). A review of the biomaterials technologies for infection-resistant surfaces. *Biomaterials*, *34*, 8533–8554.

Chen, Q., Cabanas-Polo, S., Goudouri, O. M., & Boccaccini, A. R. (2014). Electrophoretic co-deposition of polyvinyl alcohol (PVA) reinforced alginate-Bioglass® composite coating on stainless steel: Mechanical properties and in-vitro bioactivity assessment. *Materials Science & Engineering, C: Materials for Biological Applications*, *40*, 55–64.

Choi, A. H., Ben-Nissan, B., Conway, R. C., & Macha, I. J. (2014). Advances in calcium phosphate nanocoatings and nanocomposites. In B. Ben-Nissan (Ed.), *Advances in calcium phosphate biomaterials* (pp. 485–509). Springer.

Ciraldo, F. E., Arango-Ospina, M., Goldmann, W. H., Beltran, A. M., Detsch, R., Grünewald, A., Röther, J. A., & Boccaccini, A. R. (2020). Fabrication and characterization of Ag and Ga-doped mesoporous glass-coated scaffolds with improved mechanical properties based on natural marine sponges. *Journal of Biomedical Materials Research Part A*, 1–19. https://doi.org/10.1002/jbm.a.37123.

Ciraldo, F. E., Liverani, L., Gritsch, L., Goldmann, W. H., & Boccaccini, A. R. (2018). Synthesis and characterization of silver-doped mesoporous bioactive glass and its applications in conjunction with electrospinning. *Materials*, *11*, 692.

Ciraldo, F. E., Schnepf, K., Goldmann, W. H., & Boccaccini, A. R. (2019). Development and characterization of bioactive glass containing composite coatings with ion releasing function for antibiotic-free antibacterial surgical sutures. *Materials*, *12*, 423.

Cordero-Arias, L., & Boccaccini, A. R. (2017). Electrophoretic deposition of chondroitin sulfate-chitosan/bioactive glass composite coatings with multilayer design. *Surface & Coatings Technology*, *315*, 417–425.

Czekanska, E. M., Stoddart, M. J., Ralphs, J. R., Richards, R. G., & Hayes, J. S. (2014). A phenotypic comparison of cells lines versus human primary osteoblasts for biomaterials testing. *Journal of Biomedical Materials Research. Part A*, *102*, 2636–2643.

Deligianni, D., Korovessis, P., Porte-Derrieu, M., & Amedee, J. (2005). Fibronectin preadsorbed on hydroxyapatite together with rough surface structure increases osteoblasts' adhesion in vitro. *Journal of Spinal Disorder & Techniques*, *18*, 257–262.

Dorozhkin, S. V. (2013). Calcium orthophosphate-based bioceramics. *Materials*, *6*, 3840–3942.

Duan, K., & Wang, R. (2006). Surface modifications of bone implants through wet chemistry. *Journal of Materials Chemistry*, *16*, 2309–2321.

Eliaz, N., & Metoki, N. (2017). Calcium phosphate bio-ceramics: A review of their history, structure, properties, coating technologies, and biomedical applications. *Materials*, *10*, 334.

El-Rashidy, A. A., Waly, G., Gad, A., Hashem, A. A., Balasubramanian, P., Kaya, S., Boccaccini, A. R., & Sami, I. (2018). Preparation and in vitro characterization of silver-doped bioactive glass nanoparticles fabricated using a sol-gel process and modified Stöber method. *Journal of Non-Crystalline Solids*, *483*, 26–36.

El-Rashidy, A. A., Waly, G., Gad, A., Röther, J. A., Hum, J., Yang, Y., Detsch, R., Hashem, A. A., Sami, I., Goldmann, W. H., & Boccaccini, A. R. (2018). Antibacterial activity and biocompatibility of zein scaffolds containing silver-doped bioactive glass. *Biomedical Materials*, *13*, 065006.

Ferraris, M., Balagna, C., Perero, S., Miola, M., Ferraris, S., Baino, F., Battiato, A., Manfredotti, C., Vittone, E., & Vern, E. (2012). Silver nanocluster/silica composite coatings obtained by sputtering for antibacterial applications. *IOP Conference Series: Materials Science and Engineering*, *40*, 1–6.

Ferraris, M., Perero, S., Ferraris, S., Miola, M., Vernè, E., Skoglund, S., Blomberg, E., & Wallinder, I. O. (2017). Antibacterial silver nanocluster/silica composite coatings on stainless steel. *Applied Surface Science*, *396*, 1546–1555.

Ferraris, M., Perero, S., Miola, M., Ferraris, S., Gautier, G., Maina, G., Fucale, G., & Verne, E. (2010). Chemical, mechanical, and antibacterial properties of silver nanocluster-silica composite coatings obtained by sputtering. *Advanced Engineering Materials*, *12*, 276–282.

Geetha, M., Singh, A. K., Asokamani, R., & Gogia, A. K. (2009). Ti-based biomaterials, the ultimate choice for orthopaedic implants—A review. *Progress in Materials Science*, *54*, 397–425.

Gritsch, L., Lovell, C., Goldmann, W. H., & Boccaccini, A. R. (2018a). Fabrication and characterization of copper(II)-chitosan complexes as antibiotic-free antibacterial biomaterial. *Carbohydrate Polymers*, *179*, 370–378.

Gritsch, L., Lovell, C., Goldmann, W. H., & Boccaccini, A. R. (2018b). Do bioresorbable polyesters have antimicrobial properties? *Journal of Materials Science: Materials in Medicine*, *29*, 18.

Gurappa, I. (2002). Characterization of different materials for corrosion resistance under simulated body fluid conditions. *Materials Characterization*, *49*, 73–79.

Gutierrez, A., Holler, E., Zapater, P., Sempere, L., Jover, R., Perez-Mateo, M., Schmoelmerich, J., Such, J., Wiest, R., & Frances, R. (2011). Antimicrobial peptide response to blood translocation of bacterial DNA in Crohn's disease is affected by NOD2/CARD15 genotype. *Inflammatory Bowel Diseases*, *17*, 1641–1650.

Hanawa, T. (2004). Metal ion release from metal implants. *Materials Science & Engineering, C: Materials for Biological Applications*, *24*, 745–752.

Hench, L. L. (1991). Bioceramics: From concept to clinic. *Journal of the American Ceramic Society*, *74*, 1487–1510.

Hench, L. L. (2006). The story of Bioglass®. *Journal of Materials Science: Materials in Medicine*, *17*, 967–978.

Hench, L. L., & Jones, J. R. (2015). Bioactive glasses: Frontiers and challenges. *Frontiers in Bioengineering and Biotechnology*, *3*, 1–12.

Hench, L. L., & Thompson, I. (2010). Twenty-first century challenges for biomaterials. *Journal of the Royal Society Interface*, *7*, S379–S391.

Huang, Y., Hao, M., Nian, X., Qiao, H., Zhang, X., Zhang, X., Song, G., Guo, J., Pang, X., & Zhang, H. (2016). Strontium and copper co-substituted hydroxyapatite-based coatings with improved antibacterial activity and cytocompatibility fabricated by electrodeposition. *Ceramics International*, *42*, 11876–11888.

Jones, J. R. (2013). Review of bioactive glass: from Hench to hybrids. *Acta Biomaterialia*, *9*, 4457–4486.

Kafshgari, M. H., & Goldmann, W. H. (2020). Insights into theranostic properties of titanium dioxide for nanomedicine. *Nano-Micro Letters*, *12*, 22.

Kamachimudali, U., Sridhar, T. M., & Raj, B. (2003). Corrosion of bioimplants. *Sadhana*, *22*, 601–637.

Karthika, A., Kavitha, L., Surendiran, M., Kannan, S., & Gopi, D. (2015). Fabrication of divalent ion substituted hydroxyapatite/gelatin nanocomposite coating on electron beam treated titanium: Mechanical, anticorrosive, antibacterial and bioactive evaluations. *RSC Advances*, *5*, 47341–47352.

Kaya, S., Cresswell, M., & Boccaccini, A. R. (2018). Mesoporous silica-based bioactive glasses for antibiotic-free antibacterial applications. *Materials Science & Engineering, C: Materials for Biological Applications*, *83*, 99–107.

Kim, J. S., Kuk, E., Yu, K. N., Kim, J. H., Park, S. J., Lee, H. J., Kim, S. H., Park, Y. K., Park, S. H., Hwang, C. Y., Kim, Y. K., Lee, Y. S., Jeong, D. H., & Cho, M. H. (2007). Antimicrobial effects of silver nanoparticles. *Nanomedicine: Nanotechnology, Biology and Medicine*, *3*, 95–101.

Kim, T. S., Cha, J. R., & Gong, M. S. (2017). Investigation of the antimicrobial and wound healing properties of silver nanoparticle-loaded cotton prepared using silver carbamate. *Textile Research Journal*, *88*, 766–776.

Kitsugi, T., Nakamura, T., Oka, M., Yan, W. Q., Goto, T., Shibuya, T., Kokubo, T., & Miyaji, S. (1996). Bone bonding behavior of titanium and its alloys when coated with titanium oxide (TiO_2) and titanium silicate (Ti_5Si_3). *Journal of Biomedical Materials Research*, *32*, 149–156.

Kumar, A., Murugavel, S., Aditya, A., & Boccaccini, A. R. (2017). Mesoporous 45S5 bioactive glass: Synthesis, *in vitro* dissolution and biomineralization behavior. *Journal of Materials Chemistry B: Materials for Biology and Medicine*, *5*, 8786–8798.

Łapa, A., Cresswell, M., Campbell, I., Jackson, P., Goldmann, W. H., Detsch, R., & Boccaccini, A. R. (2020). Gallium- and cerium-doped phosphate glasses with antibacterial properties for medical applications. *Advanced Engineering Materials*, *22*, 1901577.

Łapa, A., Cresswell, M., Campbell, I., Jackson, P., Goldmann, W. H., Detsch, R., Parsons, A., Ahmed, I., & Boccaccini, A. R. (2019). Ga and Ce ion-doped phosphate glass fibres with antibacterial properties and their composite for wound healing applications. *Journal of Materials Chemistry B: Materials for Biology and Medicine*, *7*, 6981–6993.

Lertcumfu, N., Jaita, P., Manotham, S., Jarupoom, P., Eitssayeam, S., Pengpat, K., & Rujijanagul, G. (2016). Properties of calcium phosphates ceramic composites derived from natural materials. *Ceramics International*, *42*, 10638–16644.

Li, B., & Webster, T. J. (2018). Bacteria antibiotic resistance: New challenges and opportunities for implant-associated orthopedic infections. *Journal of Orthopaedic Research*, *36*, 22–32.

Maloney, W. J., Jasty, M., Rosenberg, A., & Harris, W. H. (1990). Bone lysis in well-fixed cemented femoral components. *The Journal of Bone and Joint Surgery*, *72*, 966–970.

Manivasagam, G., Dhinasekaran, D., & Rajamanickam, A. (2010). Biomedical Implants: Corrosion and its prevention—A Review. *Recent Patents on Corrosion Science*, *2*, 40–54.

Maqbool, M., Nawaz, Q., Rehman, M. A. U., Cresswell, M., Jackson, P., Hurle, K., Detsch, R., Goldmann, W. H., Shah, A. T., & Boccaccini, A. R. (2021). Synthesis, characterization, antibacterial properties, and in-vitro studies of selenium and strontium Co-substituted hydroxyapatite. *International Journal of Molecular Sciences*, in press.

Maráková, N., Humpolíček, P., Kašpárková, V., Capáková, Z., Martinková, L., Bober, P., Trchová, M., & Stejskal, J. (2017). Antimicrobial activity and cytotoxicity of cotton fabric coated with conducting polymers, polyaniline or polypyrrole, and with deposited silver nanoparticles. *Applied Surface Science*, *396*, 169–176.

Mehdipour, M., & Afshar, A. (2012). A study of the electrophoretic deposition of bioactive glass-chitosan composite coating. *Ceramics International*, *38*, 471–476.

Mohanty, A. K., Misra, M., & Drzal, L. T. (2005). *Natural fibers, biopolymers, and biocomposites* (pp. 1–896). CRC Press.

Mokhena, T. C., & Luyt, A. S. (2017). Electrospun alginate nanofibres impregnated with silver nanoparticles: Preparation, morphology and antibacterial properties. *Carbohydrate Polymers*, *165*, 304–312.

Mondal, S., Dorozhkin, S. V., & Pal, U. (2017). Recent progress on fabrication and drug delivery applications of nanostructured hydroxyapatite. *Wiley Interdisciplinary Reviews: Nanomedicine and Nanobiotechnology*, *10*, e1504.

Navarro, J. M. P., Michiardi, A., Castaño, O., Navarro, O. C. M., Michiardi, A., & Planell, J. A. (2008). Biomaterials in orthopedics. *Journal of the Royal Society Interface*, *5*, 1137–1158.

Ouyang, L., Zhao, Y., Jin, G., Lu, T., Li, J., Qiao, Y., Ning, C., Zhang, X., Chu, P. K., & Liu, X. (2016). Influence of sulfur content on bone formation and antibacterial ability of sulfonated PEEK. *Biomaterials*, *83*, 115–126.

Pishbin, F., Mouriño, V., Flor, S., Kreppel, S., Salih, V., Ryan, M. P., & Boccaccini, A. R. (2014). Electrophoretic deposition of gentamicin-loaded bioactive glass/chitosan composite coatings for orthopedic implants. *ACS Applied Materials & Interfaces*, *6*, 8796–8806.

Pishbin, F., Mouriño, V., Gilchrist, J. B., McComb, D. W., Kreppel, S., Salih, V., Ryan, M. P., & Boccaccini, A. R. (2013). Single-step electrochemical deposition of antimicrobial orthopaedic coatings based on a bioactive glass/chitosan/nano-silver composite system. *Acta Biomaterialia*, *9*, 7469–7479.

Purdue, P. E., Koulouvaris, P., Nestor, B. J., & Sculco, T. P. (2006). The central role of wear debris in periprosthetic osteolysis. *HSS Journal*, *2*, 102–113.

Radda'a, N. S., Goldmann, W. H., Detsch, R., Roether, J. A., Cordero-Arias, L., Virtanen, S., Moskalewicz, T., & Boccaccini, A. R. (2017). Electrophoretic deposition of tetracycline hydrochloride loaded halloysite nanotubes chitosan/bioactive glass composite coatings for orthopedic implants. *Surface & Coatings Technology*, *327*, 146–157.

Ratnayake, J. T. B., Mucalo, M., & Dias, G. J. (2017). Substituted hydroxyapatite for bone regeneration: a review of current trends. *Journal of Biomedical Materials Research Part B: Applied Biomaterials*, *105*, 1285–1299.

Rehman, M. A. U., Bastan, F. E., Haider, B., & Boccaccini, A. R. (2017). Electrophoretic deposition of PEEK/bioactive glass composite coatings for orthopedic implants: A design of orthopedic implants: A design of experiments (DoE) study. *Material & Design*, *130*, 223–230.

Rehman, M. A. U., Bastan, F. E., Nawaz, Q., Goldmann, W. H., Maqbool, M., Virtanen, S., & Boccaccini, A. R. (2018). Electrophoretic deposition of lawsone loaded bioactive glass (BG)/chitosan composite on polyetheretherketone (PEEK)/BG layers as antibacterial and bioactive coating. *Journal of Biomedical Materials Research, Part A*, *106A*, 3111–3122.

Rehman, M. A. U., Ferraris, S., Goldmann, W. H., Perero, S., Bastan, F. E., Nawaz, Q., di di Confiengo, G. G., Ferraris, M., & Boccaccini, A. R. (2017). Antibacterial and bioactive coatings based on radio frequency co-sputtering of silver nanocluster-silica coatings on PEEK/bioactive glass layers obtained by electrophoretic deposition. *ACS Applied Materials & Interfaces*, *9*, 32489–32497.

Rondelli, G., & Vicentini, B. (1999). Localized corrosion behaviour in simulated human body fluids of commercial Ni-Ti orthodontic wires. *Biomaterials*, *20*, 785–792.

Seuss, S., Heinloth, M., & Boccaccini, A. R. (2015). Development of bioactive composite coatings based on combination of PEEK, bioactive glass and Ag nanoparticles with antibacterial properties. *Surface & Coatings Technology*, *301*, 100–105.

Sobczak-Kupiec, A., Pluta, K., Malina, D., & Tyliszczak, B. (2017). Studies on bone-derived calcium phosphate materials. *Journal of Renewable Materials*, *5*, 3.

Sivakumar, M., & Rajeswari, S. (1992). Investigations of failures in stainless orthopedic implant devices: Pit induced stress corrosion cracking. *Journal of Materials Science*, *11*, 1039–1042.

Goodman, S. B., Yao, Z., & Keeney, M. (2013). The future of biologic coatings for orthopaedic implants. *Biomaterials*, *34*, 3174–3183.

Sumita, M. (1997). Present status and future trend of metallic materials used in orthopedics. *Orthopaedic Audio-Synopsis Continuing Medical Education*, *48*, 927–934.

Sun, F., Sask, K. N., Brash, J. L., & Zhitomirsky, I. (2008). Surface modifications of nitinol for biomedical applications. *Colloids Surfaces B Biointerfaces*, *67*, 132–139.

Supova, M. (2015). Substituted hydroxyapatites for biomedical applications: A review. *Ceramics*, *41*, 9203–9231.

Tejido-Rastrilla, R., Ferraris, S., Goldmann, W. H., Grünewald, A., Detsch, R., Baldi, G., Spriano, S., & Boccaccini, A. R. (2019). Studies on cell compatibility, antibacterial behavior, and zeta potential of

Ag-containing polydopamine-coated bioactive glass-ceramic. *Materials*, *12*, 500.

Tesler, A. B., Prado, L. H., Khusniyarov, M. M., Thievessen, I., Mazare, A., Fischer, L., Virtanen, S., Goldmann, W. H., & Schmuki, P. (2021). A one-pot universal approach to fabricate lubricant-infused slippery surfaces on solid substrates. *Advanced Functional Materials*, in press.

Thamaraiselvi, T. V., & Rajeswari, S. (2004). Biological evaluation of bioceramic materials. *Trends in Biomaterials and Artificial Organs*, *18*, 9–17.

Tite, T., Popa, A. C., Balescu, L. M., Bogdan, I. M., Pasuk, I., Ferreira, J. M. F., & Stan, G. E. (2018). Cationic substitutions in hydroxyapatite: Current status of the derived biofunction and in their in vitro interrogation methods. *Materials*, *11*, 2081.

Torkaman, R., Darvishi, S., Jokar, M., Kharaziha, M., & Karbasi, M. (2017). Electrochemical and in vitro bioactivity of nanocomposite gelatin-forsterite coatings on AISI 316 L stainless steel. *Progress in Organic Coatings*, *103*, 40–47.

Unalan, I., Endlein, S. J., Slavik, B., Büttner, A., Goldmann, W. H., Detsch, R., & Boccaccini, A. R. (2019). Evaluation of electrospun poly(e-caprolactone)/gelatin nanofiber mats containing clove essential oil for antibacterial wound dressing. *Pharmaceutics*, *11*, 570.

Unalan, I., Slavik, B., Büttner, A., Goldmann, W. H., Frank, G., & Boccaccini, A. R. (2019). Physical and antibacterial properties of peppermint essential oil loaded poly(e-caprolactone) (PCL) electrospun fiber mats for wound healing. *Bioengineering & Biotechnology*, *7*, 346.

Valiev, R. Z., Semenova, I. P., Latysh, V. V., Rack, H., Lowe, T. C., Petruzelka, J., Dluhos, L., Hrusak, D., & Sochova, J. (2008). Nanostructured titanium for biomedical applications. *Advanced Engineering Materials*, *10*, 815–817.

Virk, R. S., Rehman, M. A. U., Munawar, M. A., Schubert, D. W., Goldmann, W. H., Dusza, J., & Boccaccini, A. R. (2019). Curcumin-containing orthopedic implant coatings deposited on poly-ether-ether-ketone/bioactive glass/hexagonal boron nitride layers by electrophoretic deposition. *Coatings*, *9*, 572.

Wajda, A., Goldmann, W. H., Detsch, R., Boccaccini, A. R., & Sitarza, M. (2019). Influence of zinc ions on structure, bioactivity, biocompatibility and antibacterial potential of melt-derived and gel-derived glasses from CaO-SiO_2 system. *Journal of Non-Crystalline Solids*, *511*, 86–99.

Wajda, A., Goldmann, W. H., Detsch, R., Grünewald, A., Boccaccini, A. R., & Sitarz, M. (2018). Structural characterization and evaluation of antibacterial and angiogenic potential of gallium-containing melt-derived and gel-derived glasses from CaO-SiO_2 system. *Ceramics International*, *44*, 22698–22709.

Wijnhoven, S. W. P., Peijnenburg, W. J. G. M., Herberts, C. A., Hagens, W. I., Oomen, A. G., Heugens, E. H. W., Roszek, B., Bisschops, J., Gosens, I., Van De Meent, D., Dekkers, S., De Jong, W. H., van Zijverden, M., Sips, A. J. A. M., & Geertsma, R. E. (2009). Nano-silver: A review of available data and knowledge gaps in human and environmental risk assessment. *Nanotoxicology*, *3*, 109–138.

Williams, D. F. (1987). Tissue-biomaterial interactions. *Journal of Materials Science*, *22*, 3421–3445.

Winkler, T., Sass, F. A., Duda, G. N., & Schmidt-Bleek, K. (2018). A review of biomaterials in bone defect healing, remaining shortcomings and future opportunities for bone tissue engineering. *Bone & Joint Research*, *7*, 232–243.

Xu, Z., Liu, C., Wie, J., & Sun, J. (2012). Effects of four types of hydroxyapatite nanoparticles with different nanocrystal morphologies and sizes on apoptosis in rat osteoblasts. *Journal of Applied Toxicology*, *32*, 429–435.

Yang, Y., Zheng, K., Liang, Mainka, A., Taccardi, N., Roether, J. A., Detsch, R., Goldmann, W. H., Virtanen, S., & Boccaccini, A. R. (2018). Cu-releasing bioactive glass/polycaprolactone coating on Mg with antibacterial and anticorrosive properties for bone tissue engineering. *Biomedical Materials*, *13*, 015001.

Zhitomirsky, D., Roether, J. A., Boccaccini, A. R., & Zhitomirsky, I. (2009). Electrophoretic deposition of bioactive glass/polymer composite coatings with and without HA nanoparticle inclusions for biomedical applications. *Journal of Materials Processing Technology*, *209*, 1853–1860.

How to cite this article: Goldmann, W. H. (2021). Biosensitive and antibacterial coatings on metallic material for medical applications. *Cell Biol Int*, 45, 1624–1632.
https://doi.org/10.1002/cbin.11604