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Review

Advances and Challenges of Biodegradable Implant Materials with a Focus on Magnesium-Alloys and Bacterial Infections

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Abstract: Medical implants made of biodegradable materials could be of advantage for temporary applications such mechanical support during bone-healing or as vascular stents to keep blood vessels open. After completion of the healing process the implant would disappear, avoiding long-term side effects or the need for surgical removal. Various corrodible metal alloys based on magnesium, iron or zinc have been proposed as sturdier and potentially less inflammatory alternative to degradable organic polymers, in particular for load-bearing applications. Despite the recent introduction of magnesium-based screws the remaining hurdles to routine clinical applications are still challenging, such as limiting mechanical material characteristics or unsuitable corrosion characteristics. Here, salient features and clinical prospects of currently investigated biodegradable implant materials are summarized with a main focus on magnesium alloys. A mechanism of action for the stimulation of bone growth due to the exertion of mechanical force by magnesium corrosion products is discussed. To explain divergent in vitro and in vivo effects of magnesium a novel model for bacterial biofilm infections is proposed which predicts crucial consequences antibacterial implant strategies.

Keywords: bioresorbable implants; corrosion layer; vascular stents; orthopedic implants; microbial infections

1. Introduction

For metallic implants, industrially developed, inert and long-lasting materials such as titanium (Ti) alloys, stainless steel (SS) and cobalt-chromium (CoCr) alloys are most frequently used [1-4]. The healing process duration is highly variable depending on the extent of injury, disease state, age and treatment. In general healing requires from a brief 1 month period up to 6 months in more complex cases. Frequently permanent implants are removed after completion of the healing process to avoid diverse side effects. Such long-term disadvantages are the failure to adapt to rapid growth in young children, bone degradation by stress shielding, microbial implant infections, excessive fibrosis or persistent inflammation. Novel bioresorbable metal implants could provide support during the healing process, and then disappear to avoid long-term side effects without requiring surgical removal [5, 6]. Conventionally, initial material tests are done most economically in vitro under precisely defined technical conditions. Subsequent assays are performed under increasingly complex and more costly cell culture conditions, followed by small animal experiments and eventually tested in large animals or in clinical trials. However, corrosion results obtained under simple technical conditions cannot be extrapolated to clinical circumstances. In one study, the

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corrosion rate for magnesium alloys was reported to differ four orders of magnitude between in vitro and in vivo conditions [7]. Due to inherent limitations in reproducing the complexities of living tissue in vitro, this review preferentially refers to animal models or clinical trials if available [8, 9]. For molecular genetic and economic reasons, small animal studies are most popular. However, in particular for load bearing applications, it must be kept in mind that size is an important parameter and eventually large animal experiments and clinical data are essential. Even though intense research efforts recently culminated in clinical reports, degradable metallic implants are not yet routinely applied (see section 7 for details). Compared to organic polymers, biodegradable metals can achieve higher strengths and ductility and would therefore by preferred for load bearing applications such as bone plates, screws or coronary stents [10]. Mainly three types of metal alloys have been investigated as degradable implants for biomedical applications based on magnesium, iron or zinc. The main purpose of this article is a brief and easily understandable overview of virtues and clinical hurdles of self-degrading implants as screws, plates or intramedullary rods for load-bearing orthopedic (musculoskeletal) applications or as vascular stents. In addition, a novel model for implant infections is proposed to explain divergent effects of magnesium on bacteria in vitro and in vivo.

2. Material requirements for fully bioresorbable vascular stents

Clinical requirements provide the basis for the required implant material characteristics. Age-related vascular malfunctions such as vessels clogged by a blood clot are of growing importance [11, 12]. One of the earliest effective treatments was antithrombotic therapy, but this required some time until the clot was dissolved. Then, vascular stents, used to keep blood vessels open, were shown to be superior, despite the fact that treatment had to be delayed to prevent patient deaths. Balloon angioplasty is routinely applied and requires minimal invasive surgery. A small folded stent on a balloon at the tip of a catheter is maneuvered through blood vessels until it is located at the site of the restriction. The position within the body can be monitored with the help of an x-ray camera. For this reason, an x-ray dense stent material is of advantage. Once positioned the balloon is inflated to unfold the stent. Stents are overextended to a limited degree to allow a firm anchoring in the vessel wall to prevent migration and also to compensate for the inherent elastic recoil of the stent after balloon deflation. The stent material must be sturdy to allow for thin struts, minimize the recoil and withstand the pressure of the tissue and the forces during movements of the body [13]. Clinically well established, thin, yet robust and highly ductile stainless steel or shape memory alloy stents fulfill these requirements. Nevertheless, initial stent overextension and thereafter persistent mechanical stress due to interactions with pulsing blood vessel walls stimulates smooth muscle cell proliferation in the vessel walls. In a process termed restenosis a growing mass of proliferating vascular smooth muscle-related cells eventually obstruct the stented vessel again. The blood flow may be reestablished by inserting a second stent or by a surgical bypass, leading to additional patient discomfort, risks and costs [14, 15]. In clinical applications restenosis has been successfully curbed by drug-eluting stents [16]. Thereby, unwanted cell growth is suppressed locally by clinically well-established drug-loaded polymer coated stents that gradually release immune suppressive agents like sirolimus or the antiproliferative-acting drug paclitaxel. Even though these drugs could reduce the incidence of restenosis, serious side effects were a delayed healing response, inflammation and persistent thrombosis risks [17-20]. Therefore, costly regular and prolonged antiplatelet treatments are needed and non-complying patients drastically increase the thrombosis hazard [21]. Therefore the application of drug eluting stents must be carefully considered for each patient individually depending on the restenosis risks and the treatment-associated bleeding vulnerability. As an alternative, long-term side effects could be avoided by fully biodegradable stents that provide the essential support for a few weeks during the healing process and then completely disappear [22-25]. In essence, key degradable stent material requirements are appropriate corrosion characteristics, biocompatibility, high elasticity to allow for small folded stents and sufficient strength to resist collapsing.

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3. Material requirements for degradable orthopedic implants

To allow healing, broken bones must be firmly stabilized to avoid even micro-movements under the influence of considerable forces. Since inflammation may antagonize bone repair, the implant must be highly biocompatible. Clinically, all requirements are met by sturdy plates, screws or intramedullary nails made of titanium alloys or stainless steel. Nevertheless, after completion of the healing process stress shielding implants are mostly removed since their prolonged presence can lead to bone degradation [26]. Strong, tissue friendly self-degrading implants with bone-like mechanical parameters to minimize stress-shielding and suitable degradation characteristics could reduce such side effects and would appear highly attractive to avoid second surgery for implant removal. Whereas conventional permanent implant materials are sturdy and biologically inert, resorbable polymeric materials as well as corrodible metals have distinct biological characteristics (Table 1). In the following the cardinal properties of the most intensively investigated prospective biodegradable implant materials for load-bearing applications are described.

Table 1. Basic properties of degradable implant materials

Implant material	Degradation speed	Physical and corrosion characteristics	Biological effects	References
Organic polymers	Adjustable	Potentially flexible but mostly too weak for load –bearing applications; Implant swelling in moist environments; X-ray transparent	Inflammatory acidic hydrolysis products	[27, 28]
Iron	Very slow, complete degradation may require several years	Sturdy but irregular corrosion characteristics	Accumulation of inflammatory iron hydroxide particles in various tissues	[29-31]
Zinc-based	Slow, life-time by far exceeds expected healing periods	Suboptimal strength	Non-inflammatory	[32, 33]
Magnesium - based	Rapid, danger of mechanical implant failure before the healing process is completed	Alloys with sufficient strength available; compliance can be adjusted; irregular pitting corrosion; corrosion coat formation due to slowly dissolving solid precipitates resulting in reduction of initial corrosion rates	Non-inflammatory; gas accumulation in the tissue; accumulating solid corrosion products or gaseous hydrogen may exert pressure on non-yielding bony tissue	[34-36]
Surgical steel	inert	Sturdy, suitable for load-bearing applications, allows for ductile thin vascular stent struts	Non-inflammatory, inert	[1]
Titanium	inert	Sturdy, highly suitable for load-bearing applications	Non-inflammatory, bone-friendly surface oxide layer	[1]

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4. Polymeric vascular stents

Even though they may act somewhat inflammatory compared to metals, biodegradable polymeric implants have been routinely employed as suture material and to temporarily fix tendons to bones until they eventually adhere by themselves [37, 38]. Popular hydrolysable polymers used for bioresorbable scaffolds are poly(lactic-co-glycolic) acid (PLGA), polylactic acid (PLA) or polyglycolic acid (PGA) [39]. A main research focus has been polymeric stents with several features that had to be optimized. Since polymeric materials are generally less sturdy than metals, thicker struts are required that makes the stents more difficult to direct through small vessels. Moreover, they are x-ray transparent and therefore harder to localize in the patient. Furthermore, polymers tend to swell in aqueous environments and acidic hydrolysis products act inflammatory [27]. In experimental animal models degrading polymer stents resulted in increased restenosis rates [40, 41]. A first commercially available fully absorbable polylactic acid stent (Absorb, Abbot) that dissolved in 2 to 3 years was FDA approved in 2016 but despite promising short-term results long-term side effects were negative and sales were terminated by 2017 [42, 43]. In clinical trials these polymer stents were more difficult to insert due to increased efforts required for imaging and over a 2 year period induced higher rates of in-stent thrombosis than drug eluting metal stents [44]. In summary, presently investigated resorbable polymer stents were deemed inferior to established metal stents.

5. Iron as a prospective stent material

Pure iron and iron alloys were proposed in 2001 as corrodible stent materials [45]. However, despite appropriate mechanical properties, iron implants take years to disappear. The corrosion rate is an order of magnitude too small for the implant to disappear without long-term side effects [30, 46, 47]. The immediate oxidation products (Fe^{2+}) and ferrous (Fe^{3+}) ions are essential for life and presumably non-toxic at the expected concentrations [48-52]. In pioneering animal experiments iron implants analysis revealed insoluble iron hydroxide precipitates that accumulated mainly at the site of implantation [45, 53]. Further analyses in a mouse model, revealed iron precipitates engulfed by local cells and after a few weeks such iron laden cells could be detected in various organs throughout the body [54]. In war veterans, corroding iron fragments from grenade splinters have been shown to migrate in the body and to cause chronic inflammation [55-57]. Overall, the slow degradation rate prevented a timely end to possible side effects after completion of the healing process and inflammatory precipitates impede clinical applications of iron implants.

6. Zinc alloy stents

Corrodible zinc-based implants have been introduced relatively recently in 2013 (reviewed in [58]). Even though the mechanical properties can be adjusted according to the requirements, zinc alloys with a reported yield strength up to 300 MPa do not achieve the strength of titanium or stainless steel [125]. However, zinc alloys corroded with more favorable kinetics, less rapidly than magnesium alloys and faster than iron. Zinc alloy degradation products were considered sufficiently biocompatible [59]. In a rat model after 4 months in the abdominal aorta, zinc stents were still structurally intact. The implant and the relevant degradation product Zn^{2+} appeared non-toxic and even anti-inflammatory [60]. One year after implantation of a pure zinc stent in a rabbit aorta an examination revealed artery remodeling and tissue healing without signs of inflammation, platelet aggregation or thrombosis [33]. It was therefore concluded that selected zinc alloys had promising strength and excellent biocompatibility for prospective bio-corrodible stent applications [61]. Nevertheless, it remains to be demonstrated in clinical trials that zinc alloys provide advantages over clinically established permanent metal alloys.

7. Characteristics of magnesium-based implants

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The first reported medical application of degradable magnesium alloys, as ligature wire, was investigated in humans in 1878 [62]. Side effects included the occurrence of gas pockets in the tissue and rapid, irregular pitting corrosion leading to premature implant failure. In part, pure magnesium has been experimentally used to simplify the interpretation of biological responses. In general, alloy metals such as aluminum, calcium, lithium, zirconium and rare earth elements have been employed to adjust mechanical properties such as the stiffness to bony tissue or to reduce the degradation rate. In addition, grain refinement, metallic glasses obtained by ultrafast cooling techniques and protective surface coatings resulted in improved degradation characteristics, increased material strength and bone-compatible elastic moduli [63-74].

In biological environments magnesium reacts with water molecules in a pitting type corrosion with kinetics that depend on the surrounding tissue [75-77]. In addition, irregular corrosion could lead to premature mechanical implant failure [78, 79]. The primary magnesium corrosion products, soluble magnesium ions (Mg^{2+}) and hydroxide ions (OH^-) as well as hydrogen gas (H_2), are well tolerated by the body. Mg^{2+} ions are essential for living cells by complexing with the energy carrier adenosine triphosphate and numerous enzymatic processes and excess Mg^{2+} can be excreted in the urine [80, 81]. Soluble hydroxide ions could in principle lead to toxic pH increases [75]. However, in biological environments magnesium implants appear highly biocompatible presumably due to an adequate buffering capacity of the tissue. In addition, magnesium and hydroxide ions combine in a pH neutral way, and, together with carbonic acid, phosphates and other components present in surrounding body fluids, precipitate to form a corrosion-retarding and highly biocompatible implant-tissue interface [82, 83]. However, perhaps surprisingly at first sight, during corrosion these precipitates can transiently lead to increases of the overall implant mass and volume. This is particularly critical for implants in non-yielding bony tissue. Magnesium hydroxide deposition, calcium phosphate precipitation at the tissue interface and the exertion of mechanical stress by the resulting volume increase may provide an explanation for the observed stimulation of new bone growth and calcium phosphate deposition [84-86]. 1g of Mg can generate around one liter of hydrogen gas. Hydrogen gas is non-toxic and easily diffusible but excessive corrosion can nevertheless lead to formation of undesirable gas bubbles (emphysema) in surrounding soft tissue or might build up pressure in bone enclosed cavities and may therefore also stimulate bone growth in appropriate setups [87, 88].

In orthopedic applications selected magnesium alloys could achieve mechanical properties more similar to human bone than titanium or steel, which could be favorable employed to reduce implant-associated stress shielding and bone degradation [89, 90]. In clinical trials, magnesium-based screws in bone healing in patients have been reported to be without notable side effects [91, 92]. In 2013 the first commercial magnesium screws (Magnezix, Syntellix) were available that completely disappeared 1 to 2 years after implantation [93]. More recently, an additional interference screw made of an MgYREZr-alloy was introduced in the market (Milagro; DePuy Mitek) [94]. A transient appearance of radio translucent areas around magnesium implants was reported [95]. In fact, such a phenomenon would be expected from the above proposed mechanism; an initial magnesium implant size expansion by the deposition and the subsequent resorption of solid corrosion products, leaving a temporary void space to be filled by bony tissue.

Vascular magnesium alloy stents with reduced corrosion rates have been shown to be mechanically stable for up to 6 months in animal experiments and were eventually evaluated in the clinic [96-102]. Polymer-coated drug-eluting magnesium stents (Magmaris and DREAMS; Biotronik AG, 231 Switzerland) were commercially offered and claimed to be resorbed to 95% within a year in clinical trials. Thus, they may thereby overcome long-term side effects [103-105]. Both, orthopedic and vascular magnesium implants appear promising but, with the exception of small orthopedic implants like pins or screws, the development is still in its infancy and a broader clinical applicability needs to be demonstrated [106].

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8. Magnesium implant infection susceptibility mechanism: Race for the surface versus susceptible tissue surface model

Bacterial implant infections are a difficult to treat problem in orthopedics and in particular in non-sterile environments like the oral cavity [107]. Bacteria can form recalcitrant biofilms on implant surfaces that are resistant to conventional antibiotic treatments. As a last resort, the entire implant may have to be removed to allow an efficacious antibiotic treatment before the implant can be replaced. Corroding magnesium has been shown to act antibacterial in vitro due to the generation of hydroxide ions and pH increases [108-111]. In contrast, in animal studies an enhanced susceptibility to bacterial infections has been observed [112, 113]. The reasons that could enhance the susceptibility to infection in vivo are not understood and difficult to explain. Any model must take into account that the corrosion effects are no different in vitro, where there is no such enhanced susceptibility. The proposed model is an attempt to explain this observation. Conventionally, exposed implant surfaces are thought to be susceptible to bacterial adherence in competition with host tissue adhesion [114]. To allow bacterial adhesion and survival on the freshly implanted magnesium toxic pH increases directly at the interface would have to be prevented in vivo. Unfortunately, experimental observation of the initial steps of bacterial invasion has not been accomplished so far. However, if a freshly implanted magnesium surface does act bactericidal, this scenario appears unlikely. Importantly, despite systemic antibiotic treatment bacterial biofilms on magnesium were observed, not only on the implant surface but, in addition, in the adjacent tissue (Figure 1), suggesting that bacterial adhesion to the implant may actually not be essential for biofilm formation [112].

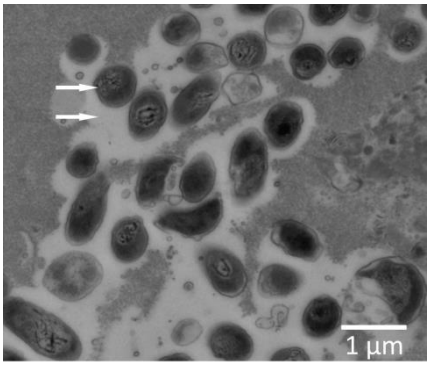

Figure 1. Bacterial biofilm in tissue pockets at a distance from the implant surface. Magnesium discs subcutaneously implanted into BAL/c mice were immediately infected with Pseudomonas aeruginosa. After one week, tissue adjacent to the implants was subjected to scanning transmission electron microscopic analysis (for a more detailed description see [112]). Bacteria (upper arrow) surrounded by clear areas (lower arrow), indicating the presence of exopolysaccharide matrix material, a typical biofilm component.

Alternatively, similar to burn wound infections or keratitis, initial bacterial invasion could occur via the wound liquid to susceptible wounded tissue surfaces (Figure 2) [115, 116]. If true for implanted materials other than magnesium, this scenario would predict dire consequences for implant infection prevention strategies.

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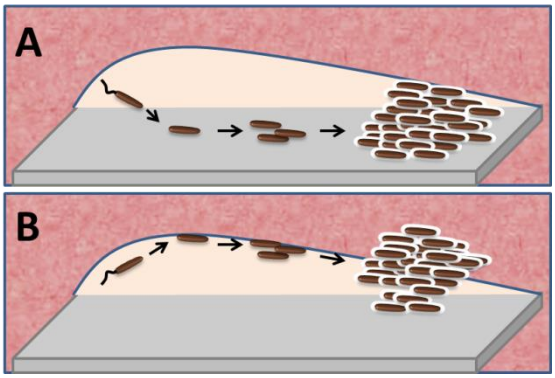

Figure 2. Model proposing tissue infection as initial key step of bacterial implant infections. A: Conventional model. Consecutive steps of biofilm infections are shown from left to right. Planktonic bacteria (brown) enter the wound-liquid-filled interspace (colorless) between implant (grey) and tissue (pink). As a crucial step towards biofilm formation, bacteria first adhere to the implant surface and form micro-colonies. After reaching a critical density bacteria switch to the biofilm mode and secrete extracellular matrix compounds. Biofilm features, such as the encapsulation in the matrix, nutrient restriction and slow growth, render the associated bacteria highly resistant to the host immune defenses and to antibiotics. Subsequently, secreted exotoxins and proteases allow bacteria to invade the adjacent host tissue. Alternatively, adhesion of host tissue to the implant acts to protect the implant surface from bacterial attachment and subsequent biofilm formation. Based on the in vitro results, in this scenario magnesium implants would be expected to act bactericidal.

B: Tissue infection model. Whereas under normal circumstances contiguous epithelial cell layers protect living tissue, wounding renders tissue highly susceptible to bacterial infections. After implant insertion the essential initial bacterial attachment occurs primarily at the susceptible injured tissue surface. Bacterial colonies growing on the tissue surface eventually switch to the biofilm mode with analogous outcomes as in the conventional model. However, whereas bacterial adhesion to the implant may occur, it plays no essential role for the course of the infection. Adhesion of host tissue to the implant would still be important to antagonize infections but predominantly to protect the wound tissue surface, and not the implant, from bacterial colonization. Despite acting bactericidal upon close contact, the observed enhanced infection susceptibility of magnesium implants is explained by interference of corroding magnesium with host tissue adhesion. Factors that prolong the wound surface exposure to bacteria could be alkaline pH immediately after implantation, and hydrogen gas evolution or eroding solid corrosion layers thereafter.

9. Implications for the design of antibacterial implants

A wide variety of anti-infective implant strategies have been investigated, mostly in vitro [117]. In the light of the proposed tissue invasion model, in order to be efficacious, antibacterial substances would need to be diffusible to reach bacteria in the vicinity of the implant. Therefore, implant nanostructures that act antiadhesive or passive coatings that act bactericidal upon contact would not be expected to curb infections in patients. In addition, implant features that affect tissue adhesion play an important, through different role than previously thought, which is to primarily prevent bacterial adhesion to the injured tissue rather than to the implant (Table 2). Even though magnesium implants could not curb bacterial infections in mice, clinical data is needed before a final conclusion can be drawn. In addition, several alternative strategies are presently investigated, such as antibiotic-releasing coatings for magnesium-based implants or the addition of antibacterial acting alloy metals like silver, copper or zinc that release cytotoxic ions [118-124]. The major challenge for such approaches appears to be the balance of achieving efficacious bactericidal ion concentrations in vivo without damaging the host tissue.

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Table 2. Implant features predicted by the tissue infection model to influence the susceptibility to infections in vivo

Ineffective coatings	Infection risks	Favorable measures
Surfaces that antagonize bacterial adhesion	Factors that hinder host tissue adhesion; convex or microporous surfaces	Surfaces favoring tissue integration; smooth, flat or concave forms;
Contact-dependent bactericidal surfaces	Relative movement of implants versus tissue	Antibacterial substance-releasing coatings

10. Conclusions

In long-term clinical trials biodegradable polymeric stents were inferior to conventional drug-eluting metal stents while recently introduced biocorrodible magnesium-based bone screws were without noticeable side effects. However, since in vitro tests and even small animal studies cannot predict the outcome in human patients, long-term clinical confirmation of the expected benefits with regard to potential risks are needed. In addition a novel model for implant infections suggests that host cell adhesion to implants is important to prevent bacterial invasion of the exposed host tissue surface and not as previously thought to prevent bacterial adhesion to the implant. The model predicts that passive antibacterial implant coating strategies would not be efficacious in vivo.

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