Magnesium-based implants: a mini-review

Bérengère J.C. Luthringer, Frank Feyerabend, Regine Willumeit-Römer

Institute of Materials Research, Department for Structural Research on Macromolecules, Helmholtz-Zentrum Geesthacht (HZG), Geesthacht, Germany

Correspondence: Bérengère Luthringer. Institute of Materials Research, Department for Structural Research on Macromolecules, Helmholtz-Zentrum Geesthacht (HZG), Geesthacht, Germany <berengere.luthringer@hzg.de>

ABSTRACT. The goal of this review is to bring to the attention of the readership of Magnesium Research another facet of the importance of magnesium, i.e. magnesium-based biomaterials. A concise history of biomaterials and magnesium are thus presented. In addition, historical and current, clinical magnesium-based applications are presented.

Key words: biomaterial, clinical applications, implant, magnesium

Brief history of biomaterial

The first implanted biomaterial can be traced back to 3000 years BC, where gold and silver were employed to repair trephination [1]. The oldest western European implants date back to 2300 BC, where iron, wood, and ivory were combined to produce an artificial tooth [2]. However, it wasn’t until the late 18th/early 19th century, and particularly after the Second World War, that the science of implantology took off.

The field of biomaterials is constantly expanding and evolving, therefore defining the term “biomaterial” is not a simple task. In the ’80s, the American National Institute of Health (NIH) proposed the following definition: “any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments, or replaces any tissue, organ, or function of the body” [3]. However, this definition includes neither surgical instruments/apparatus nor orthodontics, or dento-facial orthopaedics, and described biomaterials as inert or not interacting with surrounding tissue. A decade later, a broader definition of biomaterial was proposed: “a biomaterial is a substance that has been engineered to take a form which, alone or as part of a complex system, is used to direct, by control of interactions with components of living systems, the course of any therapeutic or diagnostic procedure, in human or veterinary medicine” [4].

The evolution of the definition of ‘biomaterial’ is closely linked to the development of biomaterials themselves. The first generation of biomaterials were mainly designed to match the mechanical, chemical, and physical requirements of their applications, with minimal toxic responses [5]. However, biomaterials are sensu stricto not inert, and increased understanding of material toxicity led to the demand for greater biocompatibility. For example, titanium and its alloys are one of the most commonly used biomaterials for orthopaedic applications. Due to the fact that they are generally much stronger than bone, they can induce a stress-shielding effect [6]. Moreover, during the lifetime of the implant wear debris is produced [7], which could induce osteolysis, a major cause of orthopaedic-implant aseptic loosening. Alloys have been developed and a wide variety of surface treatments have been employed to overcome these inconveniences. Furthermore, the notion of “foreign body reaction” (late stage of inflammation and wound healing reactions leading to implant encapsulation [8]), as well as the concept of osseointegration or osteoinduction, emphasised the need for a deeper understanding of the
interaction between biomaterials and surrounding/living tissues. Combined research efforts led to the development of a second generation of biomaterials that can be divided into two classes: (1) “resorbable”, meaning that they should be able to maintain mechanic integrity until the tissue regains its own stability, thereafter being absorbed by the body, and (2) “bioactive” i.e., able to elicit a specific tissue response or to strengthen the intimate contact between the implant and the osseous tissue. Bioactive glass or calcium phosphates (e.g., hydroxyapatite) as ceramics or as metal coatings [9], grafting of peptides [10] or phospholipids [11] onto metal surfaces or porous structures, and the development of resorbable polymers such as chitosan and polylactide [12] are some of the strategies which were/are used. The newest, third generation of biomaterials (“smart” materials) combine bioactivity and biodegradability, and should elicit specific cellular responses at the molecular level). Polymer-, bioglass-, and metal-based scaffolds, which carry and release bioactive agents, such as drugs and growth factors, are being developed [13-15]. Magnesium-based implants are bioresorbable, and accumulating evidence supports their osteoinductivity [16-18]; they can therefore be classified as bioactive materials.

Magnesium

Magnesium is the second most abundant, intracellular, divalent cation. Magnesium and its corrosion products exhibit high biocompatibility [19-21]. It has a structural role in the cell membrane and in chromosomes, and is involved in various mechanisms, e.g. as a cofactor for over 300 enzymes and in metabolic pathways [22, 23]. Bone contains approximately 67% of the body’s magnesium, 30% of this being exchangeable due to its presence on the surface of bone, thus providing a dynamic store for the maintenance of magnesium homeostasis [24, 25].

In contrast to calcium, the clinical importance of which being undisputed, the significance of Mg is frequently underestimated. This might be due to the fact that magnesium is often described as a calcium antagonist (e.g., in muscle contraction/relaxation, in action potential conduction in nodal tissue, and in neurotransmitter release) [26]. Furthermore, the action of these elements as a “chronic regulator” (Mg) or “acute regulator” (Ca) remains a debated question [27]. Nonetheless, their roles and fates are interwoven. Under hypomagnesaemia (cellular magnesium deficiency) conditions, potassium levels are altered. As magnesium is needed to activate sodium/potassium pumps, sodium and potassium gradients will not be maintained, leading to passive, intracellular loss of potassium and increases in intracellular sodium and hydrogen ions [28]. Subsequently, intracellular calcium overload will come into play, as calcium transport is magnesium-dependent, and sodium inhibits sodium/calcium exchange. This general electrolyte imbalance will lead to decreases in cell activity and vitality, as well as electrical instability, which in turn leads to cardiac arrhythmia. Generally, magnesium supplementation alone is sufficient to restore electrolyte homeostasis [29]. As the kidney can respond rapidly to an elevated serum level of magnesium, hypermagnesaemia is rare and is mainly due to advanced chronic kidney disease and iatrogenic artefacts, e.g., laxatives and anti-acids [30-32]. Therefore it seemed less important to study the effects of high magnesium concentrations at a cellular level.

A brief history of magnesium and magnesium as a biomaterial

The positive therapeutic effect of magnesium as magnesia Alba (white magnesia/magnesium carbonate) has been well-known since antiquity, and due to its antacid and mildly cathartic properties, it became one of the favourite remedies of the 18th century for improving digestion. In a process to characterise it chemically and increase its purity, Friedrich Hoffman (1660-1742) and, notably, Joseph Black (1728-1799) were able to distinguish magnesia from lime, leading to the recognition of magnesium as an element in 1754 [33]. However, it was only in 1808 that Humphrey Davy (1778-1829) was able to isolate the metal (not pure), and proposed the name “mangnium” as magnesium was the name previously applied to metallic manganese. Nonetheless, the term magnesium was preferred [34]. The first pure magnesium was produced in 1828 by Antoine Bussy (1794-1882) by heating magnesium chloride and potassium in a glass tube. In 1833, the electrolysis of magnesium chloride was achieved by Michael Faraday (1791-1867). In the middle
of the 19th century, magnesium production using the Deville-Caron process, involving the reduction of magnesium chloride with potassium in a heated, closed container began in France and England. Later, in 1886, Germany started the commercial production using a more efficient process based on the electrolysis of molten carnallite, and became the main producer of magnesium metal until the beginning of the First World War. Moreover, most of the initial knowledge concerning alloying and processing accumulated during this time, leading to the term “the German metal”.

The increased availability of magnesium led to its widespread use. The first reported use of a magnesium-based material in medicine dates back to 1878 when magnesium wires were successfully employed as blood vessel ligatures by Edward C. Huse [35]. In the following years, several applications were tested, which were found to be more or less effective. Among them, (I) connectors or tubes to treat vessel, intestinal, and nerve anastomoses [36, 37], (II) plates, sheets, and screws used in arthroplasty or fractures [38, 39], and (III) to treat haemangioma cavernosum [40]. Such haemangioma was also rather positively treated in 1981 [41]. For a more extensive review, please refer to [42].

During this period lasting about two decades, some important considerations were raised such as extensive, post-operative subcutaneous gas cavities (mostly not painful), the difficulty to obtain high magnesium purity, and material machining (i.e., a broad term used to describe the removal of material from a workpiece). These obstacles may explain the gradual decline in interest in magnesium and its alloys that followed. Nowadays, magnesium is mainly produced in two ways: (1) fused salt electrolysis of melted magnesium chloride in a heated iron crucibles that are heated from below, and (2) thermal reduction of magnesium oxide (Pidgeon process). However, the availability of ultra-high purity magnesium and recent advances in material science and engineering have enabled corrosion rates and mechanical properties to be precisely controlled [43]. Additionally, increasing life expectancy and other reasons such as complications associated with the long-term presence of implants have increased the interest in degradable materials for bone substitution [44]. This situation has led to a renaissance of magnesium as a base for alloys for cardiovascular and orthopaedic applications.

Overview of current in vitro investigations of magnesium-based biomaterials

As already mentioned, the main concern of using magnesium is or was mainly its inherent property to produce gas while degrading, leading to the formation of gas cavities in vivo. Nowadays, degradation rates as well as mechanical properties can be tailored by combining different factors such as magnesium purity, the choice of alloying elements, the metal microstructure, and the material processing route.

To increase the mechanical and corrosion properties of magnesium alloys, rare earth elements (such as yttrium and gadolinium), zirconium, manganese, zinc, calcium, lithium, and strontium, among others are used [21, 45]. Even though the biocompatibility of the rare earths remains a question of debate, the main fact that has to be considered is that the toxicity of any element is always a question of concentration [46].

Most material science magnesium-related publications involve investigation of mechanical properties, nano/micro-structures, and corrosion rates. The corrosion rate is regarded one of the most important properties as regards biocompatibility. Certainly, too high a degradation rate will lead to possible deleterious increased osmolality, an altered pH environment, and gas production. Already here the conditions chosen (e.g., corrosion buffer, temperature, cell culture condition, static or dynamic conditions, and the methodology employed to measure corrosion rates, have a huge impact on the results and need to be addressed. If the corrosion rate is to be used as a measure to predict behaviour in vivo, conditions as similar as possible to those found in vivo have to be selected [47].

The second step is to evaluate the in vitro compatibility of the materials. Generally, this measurement can be performed by a direct contact assay, where cells are directly cultured on the material surface, or indirectly using extracts prepared according to EN ISO standards 10993:5 [48] and 10993:12 [49]. Various methods can be selected to measure cell viability (e.g., live-dead staining and cell counting). However, here again methods have to be carefully chosen to avoid pitfalls. For example, one of the most common tests used, the colorimetric assay MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) is based on
The method has to be carefully selected and/or adapted [51]. Furthermore, the choice of cell type, either a cell line or primary cells, has also to be considered. The preferred and often-used cell lines are probably not the optimal choice [52]. As previously stated, investigations that closely mimic the in vivo conditions are to be preferred, and even more complex culture types such as co-culture, 3D cell culture, and the use of bioreactor systems should be considered. Moreover, highly targeted strategies, following the changing characteristics of the materials during degradation, have to be established. Further development of the in vitro tests will be necessary due to the planned European Union directive to abolish animal testing.

In vivo investigations are mainly performed in rats, rabbits, and guinea pigs, involving different implantation sites that can greatly influence corrosion behaviour and rate. It is easy to understand that any material placed subcutaneously, intramedullary or within blood flow, will react differently. Therefore, the in vivo implantation site needs be chosen according to the desired future application of the material. Several in vivo studies have reported the beneficial effect of magnesium-based coatings [53, 54] or magnesium-bulk material [18, 55-57] on implant anchorage in host bone, mineral apposition rates, and bone mass. Histomorphometry, and histochemical and immunohistochemical techniques are the major methodologies used to study the interfacial healing response. Even if quantitative or semi-quantitative results are possible, they are difficult to achieve, so these methods remain mainly qualitative. However, with methods such as dual energy X-ray absorptiometry (DXA) and microfocus computed tomography (μCT), at least mineral content and mass and density of the new bone can be measured quantitatively.

Whether quantitative or qualitative, these methods describe osseous tissue reparation only phenotypically. The mechanisms as to why or how magnesium-based alloys influence bone remodelling are not addressed, and are probably very difficult to assess in vivo. Additionally, the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) encourage the mechanistic understanding of clinical pharmacokinetics and drug–drug interactions before the introduction of new compounds to the market. Albeit restricted to clinical drug development, it is reasonable to think that this recommendation will be extended to other medical products, particularly degradable materials such as magnesium-based devices.

Nonetheless, because of the interwoven functions of magnesium, even if attention were to be restricted to bone metabolism, elucidation of the mechanism(s) by which magnesium-based implants increase osteoinduction or osseointegration is not an easy task. Therefore, efforts have to be made to establish realistic in vitro models, and to create bridges between the different disciplines dealing with magnesium (e.g., biochemistry, biology, and material science).

Current human applications of magnesium-based biomaterials

Cardiovascular applications

Atherosclerosis is defined by the accumulation of fatty substances, collagen, and elastin in areas of high shear stress in the artery. Such thickening of the vessel wall may lead to narrowing of the lumen or stenosis. Ischaemic heart disease is predicted to be the major cause of disability and death worldwide by the year 2020 [58]. Historically, the first treatment applied has been the mechanical widening of the narrowed or obstructed arteries by inflating a balloon, with or without placement of a permanent stent (angioplasty). The consequent biological cascade of events leads to vessel remodelling, but with a potential risk of decreased cellularisation and increased extra-cellular matrix accumulation, which, in turn, could lead to restenosis. This negative remodelling is reduced by the presence of a stent, but the incidence of restenosis remains considerable (25%) [58]. Furthermore, a permanent stent can provoke physical irritation, long-term endothelial/vascularisation dysfunction, chronic inflammatory reactions, thrombosis, abolition of the vasomotor component at the implantation site, and impaired adjacent vessel segment behaviour; the non-adaptability of stent size to child growth, and the restriction of further chirurgical interventions are also important considerations [59-61]. These drawbacks have been partially reduced by the development of drug-eluting stents (DES), which are usually coated with anti proliferative drugs[62]; however, the risk of very late,
stent thrombosis remains [63]. The next steps involved the introduction of polymer- (e.g., polylactic and glycolic acid; [64] and metal- (iron and magnesium) based, temporary scaffolding and combination with the drug-eluting feature. However, metals have superior mechanical properties compared to polymers, and were therefore developed faster. Iron is essential to metabolism, but both excess and deficiency can be toxic [65], however, toxicity should not be a hindrance considering the small quantities involved, (about 40mg), and the low corrosion rate of iron-based, absorbable metal stents (AMS) [66, 67]. However, for stent application, a faster degradation rate is preferred. Therefore, magnesium-based AMS are advantageous. Furthermore, as magnesium is essential to metabolism, and excess is generally excreted very quickly, the question of toxicity is eluded.

With a special focus on magnesium-based stents (figure 1), the first reported cases of implantation date from 2005. In the first case, a bare, resorbable magnesium-stent was implanted into the left pulmonary artery of a preterm baby [68]. The implantation was successful not only because the size of the implant- adapted to growth of the patient, there was the possibility of implant renewal. Then, two other publications referred to the successful implantations of resorbable, bare metal stent (BMS) from BIOTRONIK (Berlin, Germany; made of 93% magnesium and 7% rare-earth metals): (1) in a coronary artery within the scope of the first, in-human clinical trial (Clinical Performance and Angiographic Results of Coronary Stenting with Absorbable Metal Stents or PROGRESS-AMS) [69], and (2) in an infrapopliteal artery of patient with critical limb ischaemia [70]. The authors stated that the implanted stents had great potential and mechanical properties, comparable to those of conventional, stainless steel ones, were reabsorbed within approximately two months, and were compatible with non-invasive follow-up by magnetic resonance imaging (MRI). The PROGRESS-AMS study was a prospective, multicentre study (first-in-man (FIM) trial involving 63 patients), designed to evaluate the clinical safety and feasibility of the AMS for the treatment of lesions in a coronary artery. Follow-up included coronary angiography and intravascular ultrasound (IVUS) at four, 12, and 28 months, and clinical assessment at six months and 12 months [71, 72]. The device success rate and procedural success rate were both 100%. After four months, the AMS were nearly completely degraded and were well-embedded in the intima. However, restenosis was also observed after four months due to negative remodelling (increased neointima or scar tissue), and early recoil. These drawbacks were linked to the AMS degradation kinetics and weakening of the radial force. The authors were rather enthusiastic, and suggested increasing the radial support duration by either tailoring of the alloy composition, surface passivation (i.e., treatment to reduce the material’s surface chemical reactivity), modification of the stent design, or combination with a drugelution strategy.

The second generation of BIOTRONIK AMS (Drug-Eluting Absorbable Metal Scaffold or DREAMS) was developed to elute Paclitaxel, originally used in cancer therapy as an antiproliferative drug, with a poly(lactic-co-glycolic acid) carrier. The stent scaffold was changed as well as the magnesium-alloy composition. Furthermore,

Figure 1. Magnesium, absorbable-drug eluting stent. Courtesy of BIOTRONIK, Berlin, Germany.
radiopaque markers were added to the pre-mounted scaffold to facilitate its visualisation and positioning [73]. DREAMS was clinically tested in a prospective, multicentre, FIM trial, which included 46 patients with de novo coronary artery lesion (BIOSOLVE-I study). The bioabsorption time-lapse was increased. Furthermore, the AMS had a good safety profile, and promising clinical and angiographic performance results (target lesion revascularisation and target-lesion failure) up to 12 months with vasomotion. However, the late lumen-loss remained high compared to other drug-eluting stents [73, 74].

Development of the BIOTRONIK AMS was furthered by adding tantalum radiopaque end-markers and replacing Paclitaxel with Sirolimus (DREAMS 2 AMS). The second generation DREAM is currently recruiting (BIOSOLVE-II; [75]).

### Orthopaedic applications

For orthopaedic applications steel, titanium, and their alloys are the preferred metal implant materials. However, their mechanical properties are generally poorly matched with those of bones. This can lead to rupture of the implant due to dislocation (irregularity within the implant’s crystal structure [76]; or to aseptic loosening (osteolysis secondary to wear and corrosion products [77]. Furthermore, polymers generally do not offer sufficient mechanical strength for such applications and are often associated with “foreign body reaction” [78]. Additionally, polymers degrade by hydrolysis, and an acidic pH environment can be created which may enhance osteoclastogenesis to the detriment of osteoblastogenesis [79]. Again, a possible alternative can be biodegradable magnesium-based implants, which have

### Table 1. Mechanical properties of different materials (n/a: not applicable).

<table>
<thead>
<tr>
<th>Material Type</th>
<th>Tensile Strength [MPa]</th>
<th>Young’s Modulus [GPa]</th>
<th>Density [g/cm³]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue [88]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortical bone</td>
<td>35 - 283</td>
<td>5 - 23</td>
<td>1.8 - 2.0</td>
</tr>
<tr>
<td>Cancellous bone</td>
<td>1.5 - 38</td>
<td>0.01 - 1.57</td>
<td>1.0 - 1.4</td>
</tr>
<tr>
<td>Polymers [89-92]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyglycolide (PGA)</td>
<td>60 - 99.7</td>
<td>6 - 7</td>
<td>1.5 - 1.707</td>
</tr>
<tr>
<td>Polylactide (PLA)</td>
<td>32.2</td>
<td>0.35 - 3.5</td>
<td>1.21 - 1.25</td>
</tr>
<tr>
<td>Poly-L-lactide (PLLA)</td>
<td>45 - 70</td>
<td>2.7 - 4.14</td>
<td>1.24 - 1.30</td>
</tr>
<tr>
<td>Polycaprolactone (PCL)</td>
<td>23</td>
<td>0.21 - 0.44</td>
<td>1.11 - 1.146</td>
</tr>
<tr>
<td>Chitosan</td>
<td>34 - 44</td>
<td>1.1 - 1.4</td>
<td>n/a</td>
</tr>
<tr>
<td>Calcium Phosphates [88, 93]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-Tri-calcium phosphate (β-TCP)</td>
<td>18 - 130</td>
<td>23.4 - 84.8</td>
<td>3.14</td>
</tr>
<tr>
<td>Hydroxyapatite (HA)</td>
<td>40 - 200</td>
<td>70 - 120</td>
<td>3.05 - 3.15</td>
</tr>
<tr>
<td>Bulk metallic glasses [94]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bioglass (45S5)</td>
<td>42</td>
<td>35</td>
<td>2.2 - 2.8</td>
</tr>
<tr>
<td>Mg67Zn28Ca5</td>
<td>675 - 894</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>Metals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Titanium alloys [95, 96]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ti6Al4V</td>
<td>895 - 930</td>
<td>110 - 114</td>
<td>4.43</td>
</tr>
<tr>
<td>Ti6Al7Nb</td>
<td>900 - 1050</td>
<td>114.00</td>
<td>4.51</td>
</tr>
<tr>
<td>Ti13Nb13Zr</td>
<td>973 - 1037</td>
<td>79 - 84</td>
<td>4.66</td>
</tr>
<tr>
<td>Iron alloys [97, 98]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure Iron (electroformed)</td>
<td>160 - 435</td>
<td>211</td>
<td>7.86</td>
</tr>
<tr>
<td>Fe35Mn</td>
<td>235</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Magnesium alloys [21, 88, 99-101]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pure Mg</td>
<td>90</td>
<td>44</td>
<td>1.74</td>
</tr>
<tr>
<td>AZ91E</td>
<td>165 - 457</td>
<td>45</td>
<td>1.81</td>
</tr>
<tr>
<td>WE43</td>
<td>250 - 277</td>
<td>44 - 46</td>
<td>1.84</td>
</tr>
<tr>
<td>Mg10Gd</td>
<td>69.1 - 85.4</td>
<td>-</td>
<td>1.88</td>
</tr>
<tr>
<td>Mg6Zn</td>
<td>277 - 281</td>
<td>42.3</td>
<td>1.84</td>
</tr>
<tr>
<td>Mg1Ca</td>
<td>75 - 240</td>
<td>-</td>
<td>1.73</td>
</tr>
</tbody>
</table>
mechanical properties more similar to those of bones (table 1). Their main benefits are (1) avoidance of second or revision surgery, therefore decreased patient morbidity, the risk of new symptoms developing, and health care costs, (2) temporary support during tissue recovery, and (3) possible inherent repair (i.e., osteoinduction [16-18]).

Magnesium alloy MgYREZr (magnesium-yttrium-rare earth-zirconium alloy) has been reported to have good compatibility, osteoconductive properties [80], appropriate tissue reactivity in terms of inflammation, and no allergic reactions were found [81]. Therefore, this alloy was selected as a substitute for titanium screws (figure 2) for fixation during corrective surgery in patients with a mild hallux valgus (i.e., deformity characterised by lateral deviation of the big toe).

The study was a prospective, monocentre study, involving 26 patients, to determine if MAGNEZIX compression screws (Syntellix AG, Hannover, Germany) were equivalent to standard titanium screws [82]. Range of motion (ROM) of the first metatarsophalangeal joint (MTPJ), the American Orthopaedic Foot and Ankle Society (AOFAS) score for hallux, pain level according to the visual analogue scale (VAS), satisfaction rate (very satisfied, satisfied, or unsatisfied with the results), and identification of any complications were determined preoperatively and up to six months post-operatively (in total, eight study visits). Follow-up also included magnesium and standard electrolyte levels in the blood and urine, and renal (e.g., urea and creatinine) and liver (specific enzyme activities) assessment preoperatively and at eight days. Biomechanical analyses revealed no significant differences between the two groups and no increased magnesium levels in blood. Successful implantations and subsequent benefits were observed in both groups without significant differences between them. Furthermore, no negative effects such as complications, pain or allergic reactions were observed. The production of gas inherent to magnesium degradation generated neither bone erosion nor necrosis. The independent authors concluded that there was an equivalent clinical outcome between both types of screw, and recommended a larger and longer follow-up study.

Figure 2. Screws used to correct mild hallux valgus [82]: left: titanium screw (fracture compressing screw, Königsee Implantate GmbH, Allendorf, Germany), and right: MAGNEZIX compression screw. Courtesy of Syntellix AG, Hannover, Germany.
In 2007, Manfré et al. presented a new, injectable, osteoinductive, bioceramic composed of magnesium and hydroxyapatite (Mg-HA) during the annual symposium of the American Society of Spine Radiology (ASSR) [83]. In patients with a bone mineral density lower than normal induced by osteopenia and osteoporosis, the prevalence of vertebral compression fractures, with or without trauma, is increased. Such fractures are generally treated via percutaneous vertebroplasty by injecting cement into the damaged area. However, the incidence of secondary vertebral fractures remains high [84]. Therefore, the authors suggested preventive percutaneous vertebroplasty to reduce the risks. They injected the Mg-HA cement into five non-fractured vertebrae in three patients. Follow-up included computer tomography (CT) and MRI after one, 15, 30, and 60 days. Sclerosis (or bone growth) increased at the injection site over the 60 days, and the authors stated that prophylactic treatment such as this could be efficient, but it needed to be studied in a larger target group.

MaioRegen (Fin-Ceramica Faenza S.p.A., Faenza, Italy) is a multilayered scaffold composed of Type I equine collagen and Mg-HA, mimicking osteocartilage tissue (figure 3). This osteochondral scaffold is supposed to promote tissue regeneration in cases of large and severe chondral/osteochondral lesions. Previous in vivo human studies [85, 86] have underlined the ease of the surgical procedure and its good outcome. Therefore, MaioRegen is currently under clinical investigation (phase 4) for the treatment of knee chondral and osteochondral lesions: the study should be completed by July 2015 (clinicalTrials.gov Identifier NCT01282034). The clinical trial is multicentre, prospective, randomized, controlled, two-armed, and single-blinded, and involves eleven European centres and 150 patients. Follow-up will include MRI after six, 12, and 24 months.

Figure 3. MaioRegen three-dimensional matrix. This multilayer scaffold mimics the entire osteocartilaginous tissue: cartilage, tide-mark, and sub-chondral bone. Courtesy of Fin-Ceramica Faenza S.p.A., Faenza, Italy.
Other applications

Velox CD (Transluminal Technologies LLC, Syracuse, USA) is a complete device for wound closure of arteriotomies (figure 4). The implant is made from a biocompatible and fully bioabsorbable magnesium alloy (containing magnesium, aluminium, and iron). After placement, the intravascular part dissolves after 24h, whereas the extracellular part dissolves after two weeks. The device has been tested in 42 patients who received anticoagulants, achieving immediate haemostasis following percutaneous femoral procedures [87].

Conclusion and outlook

Magnesium and magnesium-based alloys in biomaterial applications have shifted again into the focus of the biomedical industry. Thanks to the first CE mark approvals of magnesium-based implants interest will increase further, as the hurdles for approval by e.g. the FDA have been lowered. One important aspect is the understanding/improvement of the production processes of the materials, and their quality. The other, even more important aspect is a deeper understanding of the underlying biological cell and tissue mechanisms in the targeted tissues, which is a prerequisite for facilitating future regulatory applications. Therefore, it is of the utmost importance to establish the correlations between the biological, biochemical, mechanical and microstructural properties of magnesium-based implants. This demands a highly interdisciplinary approach, requiring specialist input from each discipline.

Disclosure


References

Magnesium-based implants


39. Verbrugge J. L'utilisation du magnésium dans le
traitement chirurgical des fractures. Bull Mem Soc
Nat Cir 1937; 59: 813-23.
40. Payr E. Zur Technik der Behandlung kavernöser
41. Wilflingseder P, Martin R, Papp C. Magnesium
seeds in the treatment of lymph- and haeman-
giomata - Revival of an old method. Chir Plast
1981; 6: 105-16.
42. Witte F. The history of biodegradable magnesium
43. Staiger MP, Pietak AM, Huadmai J, Dias G. Mag-
nesium and its alloys as orthopedic biomaterials: a
review. Biomaterials 2006; 27: 1728-34.
44. Zhang Z, Egaña JT, Reckhenrich AK, et al. Cell-
based resorption assays for bone graft substi-
45. Zhang LN, Hou ZT, Ye X, Xu ZB, Bai XL, Shang
P. The effect of selected alloying element additions
on properties of Mg-based alloy as bioimplants:
A literature review. Front Mater Sci 2013; 7:
227-36.
factors of rare earth and other elements
used in magnesium alloys on primary cells and cell
47. Martinez Sanchez AH, Luthringer BJC, Feyer-
abend F, Willumeit-Römer R. Mg and Mg alloys:
How comparable are in vitro and in vivo corrosion
48. 10993-5: 2009 I. Biological evaluation of medical
49. 10993-12: 2012 I. Biological evaluation of medical
devices – Part 12: Sample preparation and reference
materials. 2012.
R, Feyerabend F. Interference of magnesium cor-
rrosion with tetrazolium-based cytotoxicity assays.
51. Fischer J, Pröfrock D, Hort N, Willumeit R,
Feyerabend F. Improved cytotoxicity testing of
magnesium materials. Mater Sci Eng 2011; 176:
830-4.
52. Burmester A, Luthringer B, Willumeit R, Feyer-
abend F. Comparison of the reaction of bone-
derived cells to enhanced MgCl2-salt concentra-
tions. Biomatter 2014: 00-10.
53. Park JW, An CH, Jeong SH, Suh JY. Osseoint-
egration of commercial microstructured titanium
implants incorporating magnesium: a histomorpho-
metric study in rabbit cancellous bone. Clin Oral
54. Zhao SF, Jiang QH, Peel S, Wang XX, He FM.
Effects of magnesium-substituted nanohydroxyap-
attite coating on implant osseointegration. Clin Oral
55. Kraus T, Fischerauer SF, Hanzi AC, Uggowitzer
PJ, Loffler JF, Weinberg AM. Magnesium alloys for
temporary implants in osteosynthesis: in vivo stud-
ies of their degradation and interaction with bone.
Comparative biomechanical and radiological char-
acterization of osseointegration of a biodegradable
magnesium alloy pin and a copolymeric control
for osteosynthesis. J Mech Behav Biomed Mater
57. Ragamouni S, Kumar JM, Mushahary D, Nemani
H, Pande G. Histological analysis of cells and matrix
mineralization of new bone tissue induced in rabbit
femur bones by Mg-Zr based biodegradable
58. Murray CJL, Lopez AD. Mortality by cause for
eight regions of the world: Global Burden of Disease
Study. Lancet 1997; 349: 1269-76.
59. Erne P, Schier M, Resink TJ. The road to
bioabsorbable stents: reaching clinical reality? Card-
60. Migliavacca F, Petrini L, Massarotti P, Schievano S,
Auricchio F, Dubini G. Stainless and shape memory
alloy coronary stents: a computational study on the
interaction with the vascular wall. Biomech Model
61. Hofma SH, van der Giessen WJ, van Dalen BM,
et al. Indication of long-term endothelial dysfunc-
tion after sirolimus-eluting stent implantation. Eur
Heart J 2006; 27: 166-70.
62. Farooq V, Gogas BD, Serruys PW. Restenosis: delin-
eating the numerous causes of drug-eluting stent
restenosis. Circ Cardiovasc Intervent 2011; 4: 195-
205.
everolimus-eluting stent on stent thrombosis: a
meta-analysis of 13 randomized trials. J Am Coll
Cardiol 2011; 58: 1569-77.
64. Lam MK, Sen H, Tandjung K, et al. Comparison of 3
biodegradable polymer and durable polymer-based
drug-eluting stents in all-comers (BIO-RESORT):
rationale and study design of the randomized TWENTE III multicenter trial. Am
65. Andrews NC, Schmidt PJ. Iron homeostasis. Annu
66. Peuster M, Hesse C, Schloo T, Fink C, Beerbaum
P, von Schnaupenburg C. Long-term biocompatibility


