We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Rare Earth Metals as Alloying Components in Magnesium Implants for Orthopaedic Applications

Nina Angrisani¹, Janin Reifenrath¹,
Jan-Marten Seitz² and Andrea Meyer-Lindenberg³

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/48335>

1. Introduction

During the last decade magnesium and magnesium alloys (MA) were the centre of a large number of studies especially in Europe [1-3] and Asia [4-6]. The main focus of these studies was to evaluate the use of magnesium and MA as basic material for clinical applications.

For the treatment of bone fractures, orthopaedic implants made of surgical steel or titanium are used when weight bearing bones are affected. The major disadvantage of these materials is that they need to be removed in a second surgery due to implant loosening or intolerance after longer implantation times resulting in higher costs and stress for the patient. Therefore resorbable implant materials are needed which complementarily provide sufficient stability for weight bearing applications.

Magnesium is a light metal which is known to corrode in aqueous solution. Its density is 1.74 g/cm³ at room temperature and therewith 1.6 fold resp. 4.5 fold lower than aluminium or steel [7]. With prospect of orthopaedic use, its advantages are its appropriate compressive and tensile strengths as well as its Young's Modulus (41-45 GPa), which is considerably closer to cortical bone compared to other metallic implant materials [7-9]. The corrosion rate ranges between aluminium and unalloyed steel [10].

Magnesium as a mineral occurs naturally in the body and is eliminated through the kidneys [11,12]. Due to their high excretion ability hypermagnesaemia is rare [13]. Severe symptoms like arrhythmia, feeling of faintness up to paralyses and/or cardiac or respiratory arrest are only seen in the course of therapeutical intravenous application [11,14].

Therefore, magnesium and MA are intensively investigated to develop a basic material for the production of degradable osteosynthesis implants e.g. plates, screws or intramedullary nails.

Alloying with other elements such as lithium, aluminium, zinc or rare earth metals aims to adjust the corrosion resistance and mechanical properties of magnesium [9,15-18]. In engineering applications **Aluminium** (Al) as another light metal is often used as alloying component in MA for its beneficial effect of strength, hardness and castability improvement [19]. For an optimum balance between strength and ductility the authors claim a content of 6 wt %. Contents between 1-9 wt% are classified as corrosion protective, whereof the higher the content the better the protection [8]. Many groups investigated MA containing Al [20-27], despite its questionable biocompatibility [28]. High concentrations are considered to be neurotoxic and implicated in pathologies such as dementia, senile dementia and Alzheimer's Disease [29]. However according to reference [30] the uptake of even high amounts of Al results in physiological neutral behaviour and exceptional low quantities are absorbed. Formerly, different groups reported on high corrosion rates of Mg-Al-alloys [20-22], but recently a decrease in corrosion rate could be shown in comparison to pure Mg or other MA, especially when further elements e.g. zinc [26,27] or Rare Earth Metals [23,31] are added.

Besides aluminium, **Lithium** (Li) could be added to increase the ductility and the corrosion resistance with a simultaneous decrease in strength [8,19,32]. However, the engineering application is limited [19]. In medicine, Li is therapeutically used for the treatment of manic-depressive disorders. However, a correlation with teratogenicity, nephrotoxicity and mania is discussed [33].

Zinc is often used in combination with aluminium to improve strength at room temperature [19]. In combination with zirconium or rare earths it is used to produce MA hardenable by precipitations and with superior strength. Regarding the corrosion behaviour, zinc lowers the corrosive effect of iron and nickel impurities [19]. In the body zinc belongs to the essential trace elements and is excreted mainly via the faeces. It plays an important role in numerous processes e.g. protein synthesis, nucleic acids synthesis, carbohydrate and lipid metabolism [34]. Zinc deficiency is associated with an increase in bone mass and osteoblast DNA synthesis [35,36].

The main reason for the addition of **Zirconium** to MA is the purpose of grain refinement. Although it is a powerful grain refiner it cannot be used in Al-containing MAs because it is removed from solid solution due to the formation of stable compounds [19]. Such compounds are also formed with elements like manganese, iron, silicon, carbon, nitrogen, oxygen or hydrogen when they are present within the melt [19]. Hence, the amount of soluble zirconium is the important factor rather than the total amount. Zirconia implants have excellent resistance to corrosion and wear, good biocompatibility and high bending strength and fracture toughness [37].

The usual addition of **Rare Earths** (RE) in engineering applications is performed as mischmetal or didymium, whereof the mischmetal contains 50 wt% cerium and the rest principally neodymium and lanthanum [19]. REs aim to increase the strength of MA and to

decrease weld cracking and porosity during the casting procedure [19]. Regarding the development of a resorbable implant material it is important, that the addition of RE can achieve an increase of the corrosion resistance [23,38-40]. However, this also depends on the other alloying elements. In reference [41] was reported on a decrease of the corrosion resistance *in vitro* after combining Al and Neodymium with Mg as main alloying component.

There are controversial reports about the effect and toxicity of REs. Especially high concentrations are considered to have toxic effects [42-45]. On the other hand a bone-protective effect and an increase in bone density could be shown after a six months feeding trial [46]. Low amounts of REs in MA were appraised as well tolerable in reference [28]. In reference [45] the short-term effect of REs *in vitro* was evaluated. The authors assessed the responses of different cell lines after the addition of the single RE elements and found differences between light (Lanthanum (La), Cerium (Ce), Praseodymium (Pr)) and medium to heavy (Neodymium (Nd), Europium (Eu), Gadolinium (Ga) and Dysprosium (Dy)) RE elements: light RE elements showed toxic effects at lower concentrations [45]. They concluded that La and Ce should be used only when absolutely necessary. Most of the contemporarily published *in vivo* examinations used MA with low amounts of REs, which were added as mischmetal [2,9,40,47-50]. This mischmetal can actually differ depending on the time and/or date of purchase. For example, [45] determined the RE mixture of WE43 to be mainly Nd, Gd and Dy whereas in the most commercially available RE composition metals Ce, Nd and La form the major fraction [44,51]. In *in vivo* examinations, LAE442, a MA with 4 wt% lithium, 4 wt% aluminium and 2 wt% REs showed generally good biocompatibility with slow and homogeneous degradation properties [1,2,23,47]. Nevertheless, in reference [3] was pointed out, that from a medical point of view the addition of such a content-varying mixture has to be seen very critically since reproducibility is one of the main requirements for medical devices. Hence, they examined the *in vivo* degradation behaviour of this repeatedly used MA LAE442 in comparison to LACe442 which replaced the RE mixture by the single RE element Cerium. The outcome of this *in vivo* study supported the simultaneously performed examinations described in reference [45] as this replacement led to a severe increase of the degradation rate with subsequent tissue reactions. Therefore the authors concluded that Ce could not supersede the RE composition. So far unknown regulative effects between the different RE elements seem to exist.

But despite the good results of LAE442, the effort to replace the mixture by a single element is still reasonable to achieve a most accurate implant device.

Since in reference [45] Nd was classified as suitable, referring to LAE442, LANd442 was developed as well as Nd2 and their *in vitro* corrosion behaviour was assessed [41]. They showed that the corrosion rate for Nd2 was lower than for LANd442. However, the application of a MgF₂-coating lowered the corrosion rate of LANd442. After these positive results, LANd442 was introduced into *in vivo* experiments. Parts of this study will be included in the next subchapter.

Some groups reported on the fact that *in vitro* and *in vivo* degradation properties could differ considerably [6,24]. Thus, besides profound *in vitro* tests like bending tests, corrosion

tests or microstructure characterisation to identify and adjust the material properties, the *in vivo* degradation behaviour and biocompatibility has to be investigated thoroughly.

Besides other animal models e.g. rats and sheep, the rabbit is a well established laboratory animal in orthopaedic research [52-54].

2. *In vivo* experiments

To investigate the clinical applicability of different RE containing MA the rabbit (female New Zealand White rabbits, body weight > 3 kg) was chosen as animal model. Partially, the results of the following data have already been published or submitted [55-57]. Extruded, cylindrical pins (length 25 mm, diameter 2.5 mm) were produced and washed in acetone for eliminating fabrication residues. Sterilization was carried out by gamma irradiation. Ten implants of three different RE containing MA were produced: LAE442, LANd442 and ZEK100. These cylinders were randomly implanted into the middle third of the tibial medullary cavity (Fig 1), one in each hind leg. The follow up period was six months. Clinical examinations were performed regularly to assess the clinical tolerance of the implants.

Figure 1. X-ray depiction of an implanted MA-pin with marked μ -CT scan area.

μ -Computed tomography is a non-destructive analysing method to assess changes within the structure of either engineering components or medical implants [2,40,58,59]. It can also be used to evaluate the reactions of the surrounding tissue to implanted orthopaedic devices after *in vivo* examinations [57,60,61]. However, the laboratory animals have to be sacrificed for these investigations. To evaluate the proceeding degradation and to perform a proper initial-to-end-value comparison *in vivo* μ -computed tomography scans have been introduced recently [50,55,57,60,62]. Further they allow for a reduction of laboratory animals as the results after different implantation periods could be gained from the same animal.

For the presented study an XtremeCT (Fa. Scanco Medical, Zurich, Switzerland) was used. The animals were scanned in general anaesthesia and in supine position (Fig.2). The scan was performed from the knee joint space up to approx. 5 mm beneath the implant (Fig.1) with a resolution of 41 μ m, 1000 projections at 0-180° and an integration time of 100 ms. The

electron energy used was 60 kVp and the intensity was 900 μ A. In the first eight weeks the rabbits were scanned biweekly, afterwards every four weeks.

Figure 2. μ -computed tomography of the rabbit tibia under general anaesthesia.

The μ -computed tomography evaluation **included three parts**: First, the implant itself was assessed (changes in structure and volume of the pins as well as their corrosion morphology). For each implant material a specific threshold was determined which represented the pin most accurately (LAE42 and LANd442: 138, ZEK100: 127). The implants were subsequently manually outlined and measured by means of the software μ CT evaluation program V6.1 (XtremeCT, Fa. Scanco Medical, Zurich, Switzerland). To further quantify the corrosion rate and the corrosion morphology, the direct 3D thickness of the volumes of interest (VOIs) was calculated. Therefore, the structure was filled with overlapping spheres of maximal diameter. The diameter of the spheres at each location denotes the local thickness. The average thickness was determined by averaging over the whole structure resulting in histograms of bin sizes with an average 3D thickness and a standard deviation for each implant. A low average bin size with a low standard deviation indicates a high degree of uniform corrosion. A high standard deviation of the histogram is caused by an irregular shape of the remaining implant and therefore it is an indicator for the extent of pitting corrosion [55].

Second the gas which emerged during the degradation process of magnesium implants was assessed. The corrosion mechanism of pure Mg and MA consists of two electrochemical parts: the anodic partial reaction forms Mg^{2+} and 2e^- , whereas the cathodic partial reaction evolves hydrogen and 2OH^- from the reaction of water with the 2e^- [10,63,64]. In vitro corrosion tests of MA which quantify the amount of emerging gas utilize this mechanism [41]. Many in vivo studies reported on the emergence of gas during the course of MA-implant degradation either as diffuse accumulation or palpable and non-palpable gas bubbles un-

derneath the skin [23,55,58,65]. It is a continuous discussion, if these bubbles actually contain hydrogen. Hence, as a supplementary investigation a gas-tight syringe was used to gather the emerged gas (approx. 0.5 ml) out of a large subcutaneous gas bubble. It was sent to the Institute of Organic Chemistry, Technical University Braunschweig, and analyzed. However, it was not possible to verify pure hydrogen. The most likely explanation is that the highly volatile gas undergoes rapid exchange with the surrounding tissue. From the authors' point of view there is no need to doubt that the degrading magnesium implants are the source of the gas independent on the actual composition in the bubbles as faster degrading alloys subjectively generate higher amounts of gas. This leads to the matter of quantifying the gas volume. So far, no method has been described to report on the quantity of gas emerged particularly over the course of time. So within this second part of the μ CT evaluation a method for quantifying the gas volume using the XtremeCT was established. Within the 2D-slices of the μ CT-scans of the LAE442 group, the occurring gas was manually outlined and measured by means of the software μ CT evaluation program V6.1. The threshold of the grey values was determined to be between -1000 and 25.

With proceeding degradation the corrosion products influence the surrounding tissue. The smaller the impact of the implant the better is its biocompatibility. On the one hand it could be generally said, that an implant is biocompatible when its functionality is achieved without inducing a foreign body reaction [66]. On the other hand, according to the Conference 1984 of the European Society for Biomaterials, biocompatibility is the ability of a material to fulfil its purpose for a specific application with an appropriate host response [67]. This definition includes the fact that every inserted implant actually could/will influence the surrounding tissue in one or another way and emphasize on the adequacy. The reactions which are described are either foreign body reactions ([3,57,60,65] or structural changes of the bone [2,57,61]. To assess cellular reactions histological examinations have to be carried out. However, μ CT is a well-established tool to evaluate structural changes of the bone. Thus, as a third part of the μ CT evaluation the impact of the degrading implant on the adjacent bone was evaluated by a quantitative determination of the bone density (in mg HA/cm³), the bone volume (in mm³/slice) and the bone porosity (in percent). The bone volume which was included into the evaluation was defined by choosing those slices in which also the implant was seen. Hence, the bone directly adjacent to the implant was manually outlined. The threshold value for the subsequent evaluations was determined to be 160 and the same software was used as for the implant and gas evaluation. Due to internal processing, the latest investigation time for ZEK100 was week 20.

2.1. Pin degradation

The density is given in the unit mg HA/mm³ (milligram hydroxyapatite per cubic millimetre) which is the unit the XtremeCT gives for the density of mineralized tissue such as bone. Therefore, the indicated density values do not correspond to common used alloy density values but allow for a comparison of the three alloys investigated among each other. Their density differed from the beginning of the implantation period. LAE442 density was higher than LANd442. ZEK100 showed the lowest density (Fig. 3). Besides the varying alloying

components different grain sizes of the alloy could influence the density [68] and therefore cause the detected differences. During the course of degradation LAE442 showed only a slight decrease in density with a very low standard deviation. Also the density of LANd442 implants diminished slightly, however the standard deviation was obviously higher implying a more inhomogeneous procedure. ZEK100 implants showed the highest loss in density.

The initial volume of all alloys ranged in similar values. According to the density, LAE442 implants showed only a minor decrease over the implantation period and demonstrated again a low standard deviation. The changes of volume in LANd442 implants also matched the results of the density. A slight decrease could be found with a higher standard deviation in comparison to LAE442. ZEK100 pins demonstrated an obvious loss of volume particularly from the 12th week on with an exceptional high standard deviation in the later scan weeks (Fig. 3).

Figure 3. Volume and density changes of LAE442, LANd442 and ZEK100 implants over the implantation duration of 24 weeks.

These results indicate a slow and uniform degradation of LAE442 implants. LANd442 pins also degraded slowly but less uniformly. ZEK100 showed an equally slow degradation within the first weeks of implantation. This process accelerated distinctly resulting in inhomogeneous pin geometries.

The examination of the true 3D-thickness confirmed these findings (Fig. 4). Corresponding to the volume and density changes, the average diameter of the spheres and thus the true 3D-thickness of LAE442 implants underlay only minor changes in the course of degradation. The low and uniform variance of diameter is a sign for a very homogeneous degradation. LANd442 implants showed a slight decrease of the true 3D-thickness. The variance of diameter increased in the course of implantation moderately. Taken together both results it could be said that LANd442 pins degraded slowly but faster and more inhomogeneous than LAE442. ZEK100 displayed the most obvious changes. From the 8th week on the average diameter of the spheres decreased continuously while the variance of diameters showed a profound increase. Consequently, ZEK100 implants degraded fast and irregularly.

Figure 4. True 3D-thickness and variance of diameter as indicator for homogeneous or heterogeneous degradation of the implanted LAE442, LANd442 and ZEK100 pins, respectively.

The colour mapping of the degraded implants after six months implantation duration in comparison to an undegraded implant visualized the differences of the pin geometry (Fig. 5).

2.2. Gas volume

In outlining and evaluating the occurring gas within the marrow cavity it was possible to quantify the gas volume during the course of degradation.

It is noteworthy that a distinct proceeding decrease in volume was found until week 12 followed by a continuous increase. This could be explained by the fact that a certain amount of gas was brought into the marrow cavity due to the surgical procedure. This gas volume is reabsorbed by the organism in the subsequent time. Corresponding to the beginning degradation of the implant, which is represented by the volume and density changes (Fig. 6 and 7), the amount of gas which is emerged exceeded the absorption capacity of the organism resulting in the increase of gas volume.

Figure 5. depiction and colour mapping of a MA-cylinder before implantation and of MA-cylinders (alloys: LAE442, LANd442 and ZEK100) after six months implantation period in the rabbit tibia.

Fig. 8 shows a 3D-evaluation of the bone (transparent) with implanted MA-cylinder (blue) and surrounding gas (brown).

For further examinations, this method can be used to compare the gas volume with possible occurring changes of the surrounding tissue.

Figure 6. Quantity of gas volume and pin density of LAE442 cylinders over six months implantation duration measured by μ -computed tomography (XtremeCT, Scanco medical).

Figure 7. Quantity of gas volume and pin volume of LAE442 cylinders over six months implantation duration measured by μ -computed tomography (XtremeCT, Scanco medical).

Figure 8. depiction of an implanted MA-cylinder (blue) within the tibia diaphysis (yellow-transparent) surrounded by gas (brown-red).

2.3. Changes in bone structure

The bone adjacent to all three types of implanted MA pins lost density during the course of degradation (Fig. 9). For LAE442 implants the decrease in density was more pronounced in the first weeks of implantation and slowed down in the following period. From week 12 on only a negligible further decrease could be seen. LANd442 also showed a moderate decrease in bone density up to week 12 followed by an increase in the next four weeks and subsequent steady state until week 24. Due to the lower number of investigations the density course of ZEK100 implants appeared to be different. They induced a proceeding reduction of the bone density over the total investigation period. However, a higher number of investigations could reveal a similar pattern as for LAE442 and LANd442.

The bone volume (specified per slice) increased over the investigated time period.

No distinct differences could be found for the different MA cylinders (Fig. 10).

In contrast to the aforementioned results the changes in porosity of the bone showed no regular pattern (Fig. 11). The bone porosity adjacent to LAE442 implants first increased up to week 4, followed by a decrease up to week 12. Afterwards the bone porosity again increased up to the end of the investigation period but slower than in the beginning. LANd442 implants showed only minor changes within the first 12 weeks. After that the porosity increased first moderately up to week 16 and from then on intensely till the end of investigation. However this increase in the LANd442 mean value is particularly caused by one implant which degraded severely faster than all other implants of the same group without any obvious explanation. The high standard deviation for the scans in week 16 and 24 illustrated this fact. If this cylinder would be excluded from the evaluation the mean porosity of the LANd442 pins would steadily decrease from week 8 on up to week 24. After the implantation of ZEK100 cylinders a distinct increase in bone porosity could be seen in the first eight weeks followed by a moderate decrease up to week 20.

Figure 9. Bone density adjacent to implanted LAE442-, LANd442- and ZEK100-cylinders in the course of implantation over up to 24 weeks.

Figure 10. Bone volume/slice adjacent to implanted LAE442-, LANd442- and ZEK100-cylinders in the course of im-plantation over up to 24 weeks.

Figure 11. Bone porosity adjacent to implanted LAE442-, LANd442- and ZEK100-cylinders in the course of implantation over up to 24 weeks.

Taken into account all gathered results the μ -computed tomography evaluation of the bone structure illustrated the bone remodelling processes well. The increase in bone volume indicated endosteal and periosteal new bone growth. The simultaneous decrease in bone density can be explained by the fact that this newly formed bone is not as dense as the mature bone. The varying porosity depends on two different factors. On the one hand the state of the bone remodelling process influences this value. The newly formed bone is not as much structured as the mature bone and therefore shows a higher porosity. Since the bone of LAE442 implants showed a higher increase in bone volume accompanied by the most distinct decrease in density particularly in the first weeks of implantation the ascending porosity at this time could be explained. On the other hand the two-dimensional evaluation which was not included here showed that the faster degrading ZEK100 implants induced more bone cavities than the slower degrading alloys [65]. This is probably the cause for the initial increase in porosity. To which extend the decreasing density influences the computation of the porosity remains to be shown as the further degrading ZEK100 cylinders should continuously increase the porosity instead of the determined however slight decrease.

3. Conclusions

After considering both the accessible literature and the presented results, REs seem useful and maybe even necessary alloying components in MA basis material for the production of orthopaedic implants.

It could be shown that the addition of REs lead to mostly biocompatible, degradable implants with however different degradation characteristics.

LAE442 proved to be the slowest degrading alloy with the lowest influence on the surrounding tissue. The replacement of the RE composition metal by the single element Nd did not result in improvement of the biocompatibility nor of the degradation behaviour. Contrary, these LANd442 implants showed a less regular corrosion process than LAE442 cylinders. Therefore LAE442 implants should be favoured over LANd442. Therewith, two alloys which aimed to replace the RE composition by a single element (LANd442, LACe442 [3]) failed in exceeding the good degradation behaviour and biocompatibility of LAE442.

ZEK100 as a completely different approach to develop an alloy for orthopaedic implant production clearly showed inferior results by degrading inhomogeneously and causing significant structural changes in the adjacent bone and tissue [55].

In principal, a slow degrading MA should be developed as a faster degradation is correlated with a reduced clinical tolerance and an increased impact on the adjacent bone: the implant in the right leg of one LANd442 rabbit degraded significantly faster than the other implants. The animal showed a moderate to severe lameness of the affected leg and an obvious increase in bone porosity. Also in reference[3] was reported on the poor biocompatibility of LACer442 which degraded very fast.

Altogether, the perfect composition of a degradable MA implant material has not been developed yet. Regarding the biocompatibility, Li-Al-RE-containing MA turned out to be very promising. However, to satisfy the high standards for the production of medical devices efforts to replace the RE composition metal by one or even a couple of the single RE elements should not be abandoned with further focus on a slow and homogenous degradation behaviour.

Acknowledgement

The authors thank Dr. Ulli Papke from the Institute of Organic Chemistry (TU Braunschweig) for analyzing the gas out of the gas-tight syringe.

The presented results are part of the collaborative research centre (CRC599, Medical University of Hannover, University of Veterinary Medicine Hannover and University of Hannover), which is sponsored by the German Research Foundation (DFG).

Author details

Nina Angrisani¹, Janin Reifenrath¹, Jan-Marten Seitz² and Andrea Meyer-Lindenberg³

Clinic for Small Animals, University of Veterinary Medicine, Hannover,, Germany

Institute of Materials Science, Leibniz University Hannover, Garbsen,, Germany

Clinic for Small Animal Surgery and Reproduction, Centre of Clinical Veterinary Medicine, Faculty of Veterinary Medicine, Ludwig-Maximilians-University Munich, Munich,, Germany

References

- [1] Witte, F., Ulrich, H., Rudert, M., & Willbold, E. (2007). Biodegradable magnesium scaffolds: Part 1: appropriate inflammatory responseJ Biomed Mater Res A , 81, 748-756.
- [2] Thomann, M., Krause, C., Bormann, D., Höh, N., von der, Windhagen. H., & Meyer-Lindenberg, A. (2009). Comparison of the resorbable magnesium alloys LAE442 und MgCa0.8 concerning their mechanical properties, their progress of degradation and the bone-implant-contact after 12 months implantation duration in a rabbit model- Mat Sci Eng Tech , 40, 82-87.
- [3] Reifenrath, J., Krause, A., Bormann, D., Rechenberg, B., von, Windhagen. H., & Meyer-Lindenberg, A. (2010). Profound differences in the in-vivo-degradation and biocompatibility of two very similar rare-earth containing Mg-alloys in a rabbit model Mat.-wiss. u. Werkstofftech. , 41, 1054-1061.
- [4] Xu, L., Yu, G., Zhang, E., Pan, F., & Yang, K. (2007). In vivo corrosion behavior of Mg-Mn-Zn alloy for bone implant application J Biomed Mater Res A , 83, 703-711.
- [5] Li, Z., Gu, X., Lou, S., & Zheng, Y. (2008). The development of binary Mg-Ca alloys for use as biodegradable materials within bone Biomaterials , 29, 1329-1344.
- [6] Zhang, S., Zhang, X., Zhao, C., Li, J., Song, Y., Xie, C., Tao, H., Zhang, Y., He, Y., Jiang, Y., & Bian, Y. (2010). Research on an Mg-Zn alloy as a degradable biomaterial Acta Biomater , 6, 626-640.
- [7] Catrin Kammer(2000). Magnesium-Taschenbuch. Düsseldorf: Aluminium-Verlag.
- [8] Volker Kaese(2002). Beitrag zum korrosionsschützenden Legieren von Magnesiumwerkstoffen. Düsseldorf: VDI.
- [9] Staiger, M. P., Pietak, A. M., Huadmai, J., & Dias, G. (2006). Magnesium and its alloys as orthopedic biomaterials: a review Biomaterials , 27, 1728-1734.

- [10] Song, G., & Atrens, A. (1999). Corrosion mechanisms of magnesium alloys *Adv Eng Mater* , 1, 11-33.
- [11] Hermans, C., Lefebvre, C., Devogelaer, J. P., & Lambert, M. (1996). Hypocalcaemia and chronic alcohol intoxication: transient hypoparathyroidism secondary to magnesium deficiency *Clin Rheumatol* , 15, 193-196.
- [12] Hartwig, A. (2001). Role of magnesium in genomic stability *Mutation research* , 475, 113-121.
- [13] Tinsley, R., Harrison, Anthony. S., & Fauci, . (1998). *Harrison's principles of internal medicine*. New York: McGraw-Hill Health Professions Div.
- [14] Knochel, J. (1998). Disorders of magnesium metabolism. In: Harrison TR, Fauci AS, editors. *Harrison's principles of internal medicine*. New York: McGraw-Hill Health Professions Div. , 2263-2266.
- [15] Drynda, A., Deinet, N., Braun, N., & Peuster, M. (2009). Rare earth metals used in biodegradable magnesium-based stents do not interfere with proliferation of smooth muscle cells but do induce the upregulation of inflammatory genes *J Biomed Mater Res A* , 91, 360-369.
- [16] Gu, X., Zheng, Y., Cheng, Y., Zhong, S., & Xi, T. (2009). In vitro corrosion and biocompatibility of binary magnesium alloys *Biomaterials* , 30, 484-498.
- [17] Zberg, B., Uggowitzer, P. J., & Löffler, J. F. (2009). MgZnCa glasses without clinically observable hydrogen evolution for biodegradable implants *Nat Mater* , 8, 887-891.
- [18] Yang, Y., & Li, X. (2010). Influence of neodymium on high cycle fatigue behavior of die cast AZ91D magnesium alloy *Journal of Rare Earths* , 28, 456-460.
- [19] Polmear IJ(1999). *Grades and Alloys* In: Avedesian MM; Baker H, editors. *Magnesium and Magnesium Alloys*. Materials Park, OH: ASM International. , 12-23.
- [20] Verbrugge, J. (1934). Le matériel métallique résorbable en chirurgie osseuse *La Press Med* , 23, 460-465.
- [21] McBride ED(1938). Absorbable metal in bone surgery *J Am Med Assoc* , 111, 2464-2467.
- [22] Znamenskii MS(1945). Metallic osteosynthesis by means of an apparatus made of resorbing metal *Khirurgiya* , 12, 60-63.
- [23] Elinor Switzer(2005). *Resorbierbares metallisches Osteosynthesematerial*. Available: http://elib.tiho-hannover.de/dissertations/switzere_ss05.pdf
- [24] Witte, F., Fischer, J., Nellesen, J., Crostack, H. A., Kaese, V., Pisch, A., Beckmann, F., & Windhagen, H. (2006). In vitro and in vivo corrosion measurements of magnesium alloys *Biomaterials* , 27, 1013-1018.

- [25] Witte, F., Reifenrath, J., Müller, P. P., Crostack, H. A., Nellesen, J., Bach-W, F., Bormann, D., & Rudert, M. (2006). Cartilage repair on magnesium scaffolds used as a subchondral bone replacement *Mat.-wiss. u. Werkstofftech.* , 37, 504-508.
- [26] Huang, J., Ren, Y., Jiang, Y., Zhang, B., & Yang, K. (2007). In vivo study of degradable magnesium and magnesium alloy as bone implant *Front. Mater. Sci. China* , 1, 405-409.
- [27] Pardo, A., Merino, M. C., Coy, A. E., Arrabal, R., Viejo, F., & Matykina, E. (2008). Corrosion behaviour of magnesium/aluminium alloys in 3.5 wt.% NaCl *Corros Sci* , 50, 823-834.
- [28] Song, G. (2007). Control of biodegradation of biocompatible magnesium alloys *Corros Sci* , 49, 1696-1701.
- [29] El-Rahman SS(2003). Neuropathology of aluminum toxicity in rats (glutamate and GABA impairment). *Pharmacol Res* , 47, 189-194.
- [30] Ungethüm, M., & Winkler-Gniewek, W. (1984). Toxikologie der Metalle und Biokompatibilität metallischer Implantatwerkstoffe *Z Orthop Ihre Grenzgeb* , 122, 99-105.
- [31] Krause, C., Bormann, D., Hassel, T., Bach-W, F., Windhagen, H., Krause, A., & Hackenbroich, Chr. (2006). Mechanical properties of degradable magnesium implants in dependence of the implantation duration. In: *Proceedings of the international symposium on magnesium technology in the global age:* , 329-343.
- [32] Haferkamp, H., Kaese, V. N. M., Philipp, K., Phan-Tan, T. H. B., & Rohde, R. (2001). Untersuchungen an magnesiumbasierten Legierungen als neue Materialien in der Implantologie *Mat.-wiss. u. Werkstofftech.* , 32, 116-120.
- [33] McIntyre, R. S., Mancini, D. A., Parikh, S., & Kennedy, S. H. (2001). Lithium revisited *Can J Psychiatry* , 46, 322-327.
- [34] Islam, Du., & Loots, T. (2007). Diabetes, metallothionein, and zinc interactions: a review *Biofactors* , 29, 203-212.
- [35] Litchfield, T. M., Ishikawa, Y., Wu, L. N., Wuthier, R. E., & Sauer, G. R. (1998). Effect of metal ions on calcifying growth plate cartilage chondrocytes *Calcif. Tissue Int.* , 62, 341-349.
- [36] Lutz, W., Burritt, M. F., Nixon, D. E., Kao, P. C., & Kumar, R. (2000). Zinc increases the activity of vitamin D-dependent promoters in osteoblasts *Biochem. Biophys. Res. Commun.* , 271, 1-7.
- [37] Rocchietta, I., Fontana, F., Addis, A., Schupbach, P., & Simion, M. (2009). Surface-modified zirconia implants: tissue response in rabbits *Clin Oral Implants Res* , 20, 844-850.
- [38] Wu, G., Fan, H., Zhai, C., & Zhou, Y. P. (2005). The effect of Ca and rare earth elements on the microstructure, mechanical properties and corrosion behaviour of AZ91D *Mater Sci Eng A* , 408, 255-263.

- [39] Kannan MB, Raman RKS(2008). In vitro degradation and mechanical integrity of calcium-containing magnesium alloys in modified-simulated body fluid *Biomaterials* , 29, 2306-2314.
- [40] Krause, A., Höh, N., von der, Bormann. D., Krause, C., Bach, F., Windhagen, H., & Meyer-Lindenberg, A. (2010). Degradation behaviour and mechanical properties of magnesium implants in rabbit tibiae *J Mater Sci* , 45, 624-632.
- [41] Seitz, J., Collier, K., Wulf, E., Bormann, D., & Bach, F. (2011). Comparison of the corrosion behavior of coated and uncoated magnesium alloys in an in vitro corrosion environment *Adv. Eng. Mater.* 13: BB323., 313.
- [42] Jha AM, Singh AC(1994). Clastogenicity of lanthanides--induction of micronuclei in root tips of *Vicia faba* *Mutat. Res.* , 322, 169-172.
- [43] Hirano, S., & Suzuki, K. T. (1996). Exposure, metabolism, and toxicity of rare earths and related compounds *Environ. Health Perspect.* , 104, 85-95.
- [44] Wells, W. H., & Wells, V. (2001). The Lanthanides, Rare Earth Metals. In: Bingham E, editor. *Metals and metal compounds, compounds of inorganic nitrogen, carbon, oxygen, and halogens*. New York: Wiley. , 423-458.
- [45] Feyerabend, F., Fischer, J., Holtz, J., Witte, F., Willumeit, R., Drücker, H., Vogt, C., & Hort, N. (2010). Evaluation of short-term effects of rare earth and other elements used in magnesium alloys on primary cells and cell lines *Acta Biomater* , 6, 1834-1842.
- [46] Alexander Feldhaus(2006). Wirkung von Seltenen Erden auf den osteoporotisch veränderten Knochen im Tiermodell der ovariectomierten Ratte. Available: http://edoc.ub.uni-muenchen.de/6361/1/Feldhaus_Alexander.pdf
- [47] Witte, F., Kaese, V., Haferkamp, H., Switzer, E., Meyer-Lindenberg, A., Wirth, C. J., & Windhagen, H. (2005). In vivo corrosion of four magnesium alloys and the associated bone response *Biomaterials* , 26, 3557-3563.
- [48] Erne, P., Schier, M., & Resink, T. J. (2006). The road to bioabsorbable stents: reaching clinical reality? *Cardiovascular and interventional radiology* , 29, 11-16.
- [49] Tschegg, E., Lindtner, R. A., Doblhoff-Dier, V., Stanzl-Tschegg, S. E., Holzlechner, G., Catellani, C., Imwinkelried, T., & Weinberg, A. (2010). Characterization methods of bone-implant-interfaces of bioresorbable and titanium implants by fracture mechanical means *J Mech Behav Biomed Mater* , 4, 766-75.
- [50] Castellani, C., Lindtner, R. A., Hausbrandt, P., Tschegg, E., Stanzl-Tschegg, S. E., Zannoni, G., Beck, S., & Weinberg-M, A. (2011). Bone-implant interface strength and osseointegration: Biodegradable magnesium alloy versus standard titanium control *Acta Biomater* , 7, 432-440.
- [51] Lazar Leonovich Rokhlin(2003). *Magnesium Alloys Containing Rare-earth Metals*. London: Taylor & Francis Ltd.

- [52] Abdel, M. P., Morrey, Grill. D. E., Kolbert-N, An. K., Steinmann, S. P., Sanchez-Sotelo, J., & Morrey, B. F. (2012). Effects of joint contracture on the contralateral unoperated limb in a rabbit knee contracture model: A biomechanical and genetic study J Orthop Res doi:10.1002/jor.22106
- [53] Reifenrath, J., Gottschalk, D., Angrisani, N., Besdo, S., & Meyer-Lindenberg, A. (2012). Axial forces and bending moments in the loaded rabbit tibia in vivo *Acta veterinaria Scandinavica* 54: 21.
- [54] Zhang, W., Wang, W., Chen-Y, Q., Lin-Q, Z., Cheng-W, S., Kou-Q, D., Ying-Z, X., Shen, Y., Cheng-J, X., Nie-F, P., Li-C, X., Rompis, F., Huang, H., Zhang, H., Mu-L, Z., & Peng, L. (2012). Effect of calcium citrate on bone integration in a rabbit femur defect model *Asian Pac J Trop Med* , 5, 310-314.
- [55] Huehnerschulte, T. A., Angrisani, N., Rittershaus, D., Bormann, D., Windhagen, H., & Meyer-Lindenberg, A. (2011). In vivo corrosion of two novel magnesium alloys ZEK100 and AX30 and their mechanical suitability as biodegradable implants *Materials* , 4, 1144-1167.
- [56] Ullmann, B., Reifenrath, J., Dziuba, D., Seitz, J., Bormann, D., & Meyer-Lindenberg, A. (2011). In vivo degradation behaviour of the magnesium alloy LANd442 in rabbit tibiae *Materials* , 4, 2197-2218.
- [57] Hampp, C., Ullmann, B., Reifenrath, J., Angrisani, N., Dziuba, D., Bormann, D., Seitz-M, J., & Meyer-Lindenberg, A. (2012). Research on the biocompatibility of the new magnesium alloy LANdan in vivo study in the rabbit tibia over 26 weeks *Adv. Eng. Mater.* 14: B28-B37., 442.
- [58] Höh, N., von der, Bormann. D., Lucas, A., Denkena, B., Hackenbroich, C., & Meyer-Lindenberg, A. (2009). Influence of different surface machining treatments of magnesium-based resorbable implants on the degradation behavior in rabbits *Adv Eng Mater* 11: BB54., 47.
- [59] Happel, C. M., Klose, C., Witton, G., Angrisani, G. L., Wienecke, S., Groos, S., Bach-W, F., Bormann, D., Männer, J., & Yelbuz, T. M. (2010). Non-destructive, high-resolution dimensional visualization of a cardiac defect in the chick embryo resembling complex heart defect in humans using micro-computed tomography: double outlet right ventricle with left juxtaposition of atrial appendages *Circulation* 122: e561-4., 3.
- [60] Lalk, M., Reifenrath, J., Rittershaus, D., Bormann, D., & Meyer-Lindenberg, A. (2010). Biocompatibility and degradation behaviour of degradable magnesium sponges coated with bioglass- method establishment within the framework of a pilot study *Mat Sci Eng Tech* , 41, 1025-1034.
- [61] Kraus, T., Fischerauer, S. F., Hänzi, A. C., Uggowitzer, P. J., Löffler, J. F., & Weinberg, A. M. (2012). Magnesium alloys for temporary implants in osteosynthesis: In vivo studies of their degradation and interaction with bone *Acta Biomater* , 8, 1230-1238.

- [62] Vecchio, K. S., Zhang, X., Massie, J. B., Wang, M., & Kim, C. W. (2007). Conversion of sea urchin spines to Mg-substituted tricalcium phosphate for bone implants *Acta Biomater* , 3, 785-793.
- [63] Song, G., & Atrens, A. (2003). Understanding Magnesium Corrosion- A Framework for Improved Alloy Performance *Adv Eng Mater* , 5, 837-858.
- [64] Song, G. (2005). Recent progress in corrosion and protection of magnesium alloys *Adv Eng Mater* , 7, 563-586.
- [65] Huehnerschulte, T. A., Reifendrath, J., Rechenberg, B., von, Dziuba. D., Seitz-M, J., Bormann, D., Windhagen, H., & Meyer-Lindenberg, A. (2012). In vivo assessment of the host reactions to the biodegradation of the two novel magnesium alloys ZEK100 and AX30 in an animal model *Biomedical engineering online* , 11, 14-42.
- [66] Niinomi, M. (2008). Metallic biomaterials *J Artif Organs* , 11, 105-110.
- [67] Romani, A. M., & Scarpa, A. (2000). Regulation of cellular magnesium *Front Biosci* 5: d, 720-734.
- [68]