Review

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Resorbable implants in pediatric fracture treatment

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Abstract: Pediatric osteosynthesis has developed over the last 20 years, thereby reducing medical and economic burden, including long and expensive hospitalization. Currently, conventional and rigid alloying systems such as titanium are used for stabilization of bone fractures in children. In many cases, implants must be removed, as otherwise growth would be impeded. Biodegradable implant materials exhibit beneficial properties and would make a second removal surgery unnecessary. In the following article, we will give an overview of implant materials that are currently used in pediatric traumatology with a focus on Mg-based implants. Furthermore, we will discuss current scientific knowledge on resorbable implants, including results from pre-clinics and clinics.

Keywords: bone fracture; pediatric surgery; resorbable implants.

Introduction

Over the past decade, the need for implants in pediatric trauma has increased, although previously pediatric bone fractures were only rarely treated by osteosynthesis or not at all. The main reason for this is the exceptional ability of children's bodies to heal and correct misalignments. However, over the last 20 years, surgical treatment of pediatric fractures has become more common and state of the art, in particular for long bone fractures. Analysis of efficiency and effort in terms of hospitalization costs and psychological effects on children have shown osteosynthesis to be the more attractive option. Furthermore, surgical tools and techniques have been adapted according to children's requirements. Treatment of long bone fractures in children relies on a novel, not particularly rigid fixation procedure, termed elastic stable intramedullary nailing/flexible intramedullary nailing, which optimally supports fracture healing in children.

Conventional alloying systems such as titanium (Ti) are commonly used for bone fracture fixation in children. Given that conventional implants must always be removed, involving considerable effort for children and parents, the following question is frequently raised: could conventional, non-resorbable implants be replaced by resorbable implants?

While conservative methods require only a single anesthesia treatment, the antagonist of conservative methods needs two surgical interventions, meaning two anesthesia treatments. However, another important aspect is the percentage of re-reposition maneuvers that must also be taken into account regarding conservative procedures. Therefore, the major advantages of a resorbable implant are the single surgical procedure with definitive fixation of the fracture, a single anesthesia treatment, and minimized re-reposition maneuvers, compared to conservative treatment.

First, the article will give an overview of implant materials that are currently used in certain indications with a focus on magnesium-based implants. In a second part, the article will discuss current scientific knowledge on resorbable implants investigated in pre-clinical and clinical studies.

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Resorbable and biocompatible materials

In general, biomaterials are used to support or even replace organs and tissues by taking over their functions. Non-resorbable and resorbable materials are currently used as implants and inlays in dental, cardiac, neuro-, and orthopedic surgery [1–3]. Especially in orthopedics and traumatology, resorbable biomaterials are well suited to support fracture healing. The optimal material should exhibit the required yield strength, good biocompatibility, and homogenous degradation, as well as functional properties to support or induce bone formation by releasing beneficial degradation products. The following section will focus on different types of resorbable biomaterials, including their advantages and disadvantages, in fracture treatment in children:

1. Polymers
   The most prominent polymers are poly-L-lactic acid (PLLA) and poly-lactic-co-glycolic acid (PLGA), which are widely considered for use as osteosynthesis and bone grafts [4, 5]. Polymer-based implants are made of sugar derivatives such as PLLA and PLGA, with poor osteoconductivity and mechanical properties (low strength and stiffness, high brittleness). Depending on the polymer, the degradation rate varies between weeks to years. For example, poly-glycolic acid shows weak mechanical properties due to bulk degradation and induces tissue damage because of degradation-induced increase of glycolic acid concentration [6, 7]. To overcome the shortcomings associated with polymer-based implant degradation, the following issues would need to be addressed:
   i. Enzymes are needed to degrade slow polymer-based materials, which are limited *in vivo*.
   ii. The monomer degradation rates must be controlled in fast copolymers.
   iii. Polymer-based implants can only be used in non-load-bearing regions, due to their brittleness and low E-modulus.
   iv. Because of the slow degradation rate, inflammatory cascades might be activated, inducing a fibrotic capsule and so-called “creeping” of the polymer-based system [8].

   Polyhydroxybutyrate (PHB) can serve as an alternative polymer. As PHB is produced by microorganisms, especially bacteria, this might cause toxicological problems. Recently, the toxicity of PHB has been dramatically reduced, thereby raising its medical potential [9]. However, concerns about the limited access of PHB-degrading enzymes are still present. Therefore, researchers are currently focused on attaching enzymes to guarantee adequate degradation of polymer- or PHB-based implants. Moreover, functional properties (i.e. osteoinductivity or osteoconductivity) of polymer-based materials have yet to be discovered.
2. Ceramics
   Ceramics are characterized as synthetic bone replacement materials with good biocompatibility, osteoconductivity, osseointegration, and non-immunogenic properties. Ceramics are composed of hydroxyapatite (HA), or α- and β-tricalciumphosphates (TCPs). Either pure HA or a two-phase combination of HA and β-TCP are frequently used. Ceramics made of pure HA show chemically identical properties compared to naturally occurring HA, by releasing calcium and phosphate, as well as supporting osteogenesis. Nevertheless, pure HA and HA-based ceramics remain in the body for several years because of the slow degradation rate [10]. Moreover, ceramics do not constitute optimal implant materials for osteosynthesis due to their lack of load-bearing capacity.

   Two-phase ceramics include a slow (HA) and a fast (β-TCP) degradation source, which support bone formation and stability. A major disadvantage of TCPs, however, is that their biomechanical properties result in brittleness and low yield strength (6–10 MPa), and they tend to break apart [11]. In pediatric trauma care, ceramics are used to fill bone cysts.
3. Biodegradable metals
   Biodegradable metals including iron (Fe), zinc (Zn), and magnesium (Mg) are more tensile, stable, and load bearing [12, 13], respectively, compared to polymers and ceramics. The low melting point of Fe constitutes an interesting property for processing Fe-based alloys. However, studies in our group revealed that limited access to oxygen was associated with slow degradation rates [14]. Therefore, Fe is currently not a suitable material for biodegradable metal implants, especially in children [15]. In contrast, Zn displays several disadvantages: low rigidity and deformability, as well as corrosion inhibition, which are the most important. Therefore, Zn is likely more suited as an alloying element in combination with other materials. Apart from good biocompatibility, Mg also shows favorable biomechanical properties, as already demonstrated by push-out tests *ex vivo*. Other studies have demonstrated the functional properties of Mg-based implants, especially their ability to support bone fracture healing [16–18].

Magnesium-based implants

In pediatric trauma surgery, it is of utmost importance to use resorbable implants without short-term and especially without long-term adverse effects. For instance, studies have demonstrated that intermetallic phases of alloying elements are traceable for several years. The effect on the growing skeleton was not investigated in any of those works [19, 20]. However, over the last decade, several studies have focused on Mg-based implants alloyed with rare-earth elements (REEs), such as yttrium or gadolinium [19, 21–23], which slow down the degradation rate and increase implant stability. Initial experiments with Mg-based alloying systems including REEs (WE43; Mg-Y-Nd-HRE) showed improved bone-implant interfaces and osseointegration compared to conventional Ti in a growing rat model. In our study, we suggested that bone formation was supported by the Mg-based WE43, which is fundamental for its application in osteosynthesis [24]. In another study, we demonstrated a slow degradation rate of the Mg-based implant WZ21 (Mg-1 wt% Zn-0.25 wt% Ca-0.15 wt% Mn-2 wt% Y). WZ21 did not induce any inflammatory response, neither immediately after implantation nor over a time period of 24 weeks. Additionally, micro-computed tomography (μCT) showed enhanced, new bone formation between 4 and 8 weeks after WZ21 implantation [25].

However, REEs have been described to be mildly toxic, without causing severe reactions in the body. These elements (REEs including gadolinium, yttrium, etc.) do not normally occur in the human body, and their harmful or beneficial effects on the growing skeleton have not been elucidated. As a result, the aim was set to develop a resorbable metallic implant based on elements occurring naturally within the body and avoiding the use of REEs, such as gadolinium or yttrium. Different research groups focused on producing implants from high-purity Mg (>99.99 wt%), which were further evaluated *in vivo*. Wang et al. demonstrated enhanced recruitment of stromal stem cells isolated from the bone marrow after using Mg-based interference screws in a rabbit tendon graft model that underwent anterior cruciate ligament reconstruction (ACLR) [26]. Another study showed that the corrosion of high-purity Mg is accelerated when co-implanted with Ti screws, depending on the distance between the two alloying systems. This group suggested that in close proximity, Mg-based and Ti screws might form a galvanic-like cell, which enhances Mg corrosion *in vivo* [27]. To investigate the shortcomings of pure Mg alloys, such as rapid gas formation, Lim et al. compared uncoated and HA-coated Mg plates by inserting these above the frontal bone of Sprague-Dawley rats. While uncoated Mg plates showed gas formation 2 weeks after insertion, HA-coated Mg plates only showed gas formation after 12 weeks [28].

A collaboration between the Medical University of Graz and the ETH Zurich developed appropriate REE-free Mg-based implants, which were evaluated *in vitro* and *in vivo*. Apart from the good biocompatibility, the biomechanical properties and controlled degradation rate were comparable with WZ21 and WE43. To develop the optimal Mg-based implant, different compositions of Mg, Zn, and Ca were investigated, especially in growing organisms.

In a first study, μCT analysis revealed extremely rapid degradation rates of ZX50 (Mg-5 wt% Zn-0.25 wt% Ca-0.15 wt% Mn) in growing rats. It is important to note that the regulation of degradation rates play a major role in bone formation. At the desired implant degradation rate, an adequate concentration of magnesium hydroxide [$Mg(OH)_2$] and hydrogen gas develops because of pit corrosion. The insoluble $Mg(OH)_2$ forms a protective layer around the implant surface and when the chloride level in the body rises, Mg is released from $Mg(OH)_2$ to bind chloride and form $MgCl_2$. This product is soluble and can therefore be transported or degraded [29]. However, fast degradation rates result in increased gas formation, which negatively influence bone formation by suppressing bone and, at worst, destroying the physis [30]. In contrast, slow degradation rates can result in chronic, inflammatory immune responses, as seen with slow polymer-based materials. Therefore, regulating degradation rates of Mg-based implants is a challenge that will determine how these implants are used not only in pediatrics but also in orthopedics and traumatology in adults.

In further studies, the Zn content was reduced and high-purity Mg was used for implant fabrication (ZX10 and ZX20). The degradation rate of ZX10 was significantly lower compared to ZX20 (manuscript in preparation). As a result, animals implanted with ZX10 showed improved bone in-growth and osseointegration. Furthermore, bone healing via callus formation was demonstrated, which has been proven to be the necessary support for fracture healing.

To simulate bone fracture fixation in children and adolescents, initial experiments were performed with Mg-based screws (ZX00) in a growing sheep model. ZX00 (Mg-0.45 wt% Zn-0.45 wt% Ca) was transcortically implanted into the ovine tibia and compared to conventional Ti screws. The ZX00 alloying system revealed optimal biomechanical properties and controlled degradation rates *in vivo*. Moreover, good biocompatibility, osteoconductivity, and adequate support of callus formation

were observed in the ovine model. Twelve weeks after ZX00 implantation, new bone formation and a stable bone-implant interface was demonstrated. In contrast, weaker bone formation beneath the implant was observed with Ti screws (because the load is carried over the screw and the bone degrades), which might also result in re-fracture after implant removal.

Current scientific knowledge on resorbable implants: results from pre-clinics and clinics

Therefore, pre-clinical *in vivo* studies in large animal models are needed to answer fundamental questions on resorbable implants in growing skeletons, based on the growing potential of children:

1. Are there any short- or long-term adverse effects on growth associated with the implant? Long-term studies that continue until complete resorption of the implant (12–24 months) are needed.
2. Does the implant support bone bridging and, in consequence, lead to growth arrest and bone deviation? This question could be answered only by surveillance over at least 2 years, as this period is used in pediatric trauma to judge how the implant affects a phenomenon such as growth arrest.
3. Are there differences in the inflammatory reaction compared to adult bone?

The remaining part of this article focuses on the literature addressing the above questions. We examined *in vivo* studies using large immature animal models and clinical trials performed on children. Most *in vivo* studies use large mature or adult animals. However, *in vivo* studies in mature sheep showed sequestration of PLLA implants within new bone, 3 months after implantation. One year after PLLA implantation, a further tissue reaction associated with structural disintegration was observed. However, the reduced PLLA mass was subsequently replaced by avascular fibrous tissue including macrophages and multinucleated cells on the PLLA surface. Observations after 3 years displayed isolated polymer fragments indicating the longevity of this resorbable implant material [31]. Another study showed an increase in mechanical strength of polylactide carbonate (PLC) and PLLA, 6 and 12 weeks after ACLR in sheep. Interestingly, the PLC screw was entirely replaced by new bone after 52 weeks, whereas PLLA screws were not resorbed and surrounded by a fibrous layer, thereby suggesting satisfactory mechanical and osteoconductive properties of PLC [32]. One of the longest studies concerning resorbable implants in large animal models was published in 2002 by Jukkala-Partio et al. Two self-reinforced PLLA screws were used to fix subcapital femoral osteotomies in young adult sheep. The follow-up periods comprised 12 weeks, 1 year, and 3 years, as well as 7 years and 4 months (n = 1). Three years after fixation, implant areas were replaced by new bone and connective tissue with some implant remnants. Tight bone was observed >7 years later, thereby indicating good mechanical properties and biocompatibility but very slow degradation rates [33]. Interestingly, Thormann et al. utilized interference screws made of the Mg alloy W4, which were coated with polyethylene glycol and implanted in the femur condyle of a sheep model. Compared to Ti, W4 screws showed enormous gas formation and a consequential bone defect after 6 and 12 weeks, and even 1 year after implantation. Moreover, W4 screws were not fully integrated in the surrounding bone tissue compared to PLLA and Ti [34]. To the best of our knowledge, Magarelli et al. were the only group to use growing sheep to investigate the biocompatibility of HA- and β-TCP-coated PLLA screws implanted into the femurs [35]. The studies described above used mature or adult ovine models or did not mention maturation status; other studies with large growing animal models focused on maxillofacial or calvarian surgery [36]. We did not find any research on the impact of resorbable implants on the growth plate.

Similar to *in vivo* studies using large animal models, clinical trials have especially focused on PLLA. A thorough search of the literature yielded only one clinical trial using Mg-based implants in children. However, in 2013, a new minimally invasive treatment for pediatric, diaphyseal forearm fracture was published. Conventional open reduction and internal fixation using plates was compared to this minimally invasive method. Therefore, ultra-high-strength, resorbable intramedullary nails of poly(lactide-*co*-glycolide) were used in 5–15-year-old children. Follow-up patients showed good union in the fractured bones and acceptable alignment. However, one re-fracture occurred due to high-energy trauma. To determine long-term outcomes, a randomized multicenter study was conducted [37]. Poircuitte et al. published a prospective monocentric study with 24 patients who had a fracture that was amenable to osteosynthesis by small-diameter screws. Some of the screws (d = 2.8 mm) were made of poly-L-lactide-poly-D-lactide acid and trimethylene carbonate. Every month,

patients were clinically and radiographically monitored until the end of the follow-up protocol (1 year). No instability, secondary displacement, growth disturbances, or osteolysis were observed. All fractures healed without complications [38]. Another study aimed to compare the efficacy of the open reduction and resorbable poly-D,L-lactic acid (PDLLA) pin fixation method with the closed reduction and lateral external fixation method in irreducible delayed displaced supracondylar humeral fractures (SHFs) in children. A total of 124 consecutive patients with irreducible delayed Gartland type III SHF were recruited. While 64 patients of group 1 underwent PDLLA pin fixation after open reduction, 60 patients of group 2 were treated by lateral external fixation after closed reduction. Within 8–12 weeks, all fractures healed without Volkmann contracture, non-union, infection, or myositis ossificans. Functional and cosmetic results were comparable between the two groups, indicating that both PDLLA pin fixation and lateral external fixation are reliable and safe alternatives for irreducible delayed SHF [39].

In 2015, Yu et al. presented a new technique to treat avascular necrosis of the femoral head and non-union using biodegradable Mg screws. In this study, 19 young adult patients with displaced femoral neck fractures were recruited and treated with this new technique: the fracture was fixed with Ti and pure Mg screws, and combined with the implantation of vascularized iliac grafting. Of the 19 cases, 18 showed hip union after an average duration of 4.1 months, whereas only 1 non-union was observed. The Harris hip score revealed 1 poor, 3 fair, and 14 excellent results, and avascular necrosis of the femoral head was not observed in any patient [40].

Although the authors may not have covered all publications, there have only been a few studies that focus on resorbable implants to treat pediatric fractures. To generate well-founded knowledge, research must answer the open questions on pediatric bone fractures and their treatment, in large growing animals or in clinical studies. The knowledge created so far is insufficient to recommend application and requires further investigation.

In summary, it can be said that the development of resorbable material implants constitutes a milestone in improving treatment of pediatric bone fractures.

Author Statement

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Author Contributions

Annelie-Martina Weinberg: conceptualization; supervision; validation; writing – original draft; writing – review and editing. Nicole Gabriele Grün: data curation; investigation; methodology; project administration; writing – original draft. Patrick Lukas Holweg: investigation; methodology; software; writing – original draft. Nicholas Donohue: investigation; software; visualization; writing – review and editing. Thomas Klestil: conceptualization; formal analysis; supervision; writing – review and editing.

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Reviewer Assessment

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Reviewers' Comments to Original Submission

Reviewer 1: Lucas M. Wessel

Feb 07, 2018

Reviewer Recommendation Term:	Accept with Minor Revision
Overall Reviewer Manuscript Rating:	N/A

Custom Review Questions	**Response**
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	5 - High/Yes
Does the abstract clearly reflect the paper's content?	5 - High/Yes
Do the keywords clearly reflect the paper's content?	5 - High/Yes
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	5 - High/Yes
How comprehensive and up-to-date is the subject matter presented?	4
How adequate is the data presentation?	4
Are units and terminology used correctly?	3
Is the number of cases adequate?	5 - High/Yes
Are the experimental methods/clinical studies adequate?	5 - High/Yes
Is the length appropriate in relation to the content?	5 - High/Yes
Does the reader get new insights from the article?	5 - High/Yes
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	5 - High/Yes
Please rate the statistical evaluation and quality control.	4
Please rate the appropriateness of the figures and tables.	N/A
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	4
Please judge the overall scientific quality of the manuscript.	5 - High/Yes
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

This is a very nice review concerning absorbable implants for osteosynthesis in children and describes also the history of absorbable implants used until now. The manuscript is very understandable and well investigated. However a lot of abbreviations are used and not all of them are explained or elucidated. In some of these abbreviations the reader will miss the meaning of it. Short explanations would be appropriate. Congratulations to the authors for a very good job in summarizing the state of the art.

Reviewer 2: Dirk W. Sommerfeldt

Feb 13, 2018

Reviewer Recommendation Term:	Revise with Major Modification
Overall Reviewer Manuscript Rating:	50

Custom Review Questions	**Response**
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	2
Does the abstract clearly reflect the paper's content?	2
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	3
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	3
Are units and terminology used correctly?	5 - High/Yes
Is the number of cases adequate?	3
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	3
Does the reader get new insights from the article?	4
Please rate the practical significance.	4
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	3
Please rate the appropriateness of the figures and tables.	2
Please rate the appropriateness of the references.	4
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	2
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:

This is a difficult paper to review, the reason being that from my point of view it comprises two manuscripts put into one.
The first paper would be a non-biased, objective review of all resorbable implants currently being put into use in children.
The second paper would be a scientifically thorough evaluation of the author‘s quest to identify optimum resorption kinetics in magnesium-alloy-based implants.
However, this manuscript throws these two very different aims together to produce something I would call “not fish nor flesh”.
Both, the review part together with the thorough literature review as well as the more basic scientific paper dealing with resorption kinetics optimization in magnesium-based implants will have their merit, audience, and are well worth being published in my opinion.
Therefore, as a reviewer, I can only recommend to take this submitted manuscript apart, to write two separate papers as outlined above, and finally, to resubmit one or the other or both papers to this journal‘s review process.

Editors' Comments to Original Submission

Feb 14, 2018

Re-format manuscript regarding structure. Clearly separate into two sections and clearly state in the introduction that the manuscript comprises two parts,

1. overview of what is beeing used and
2. what is the current state of scientific knowledge and development

Authors' Response to Reviewer Comments

Apr 19, 2018

Point-to-point revision

Reviewer #1:
This is a very nice review concerning absorbable implants for osteosynthesis in children and describes also the history of absorbable implants used until now. The manuscript is very understandable and well investigated. However a lot of abbreviations are used and not all of them are explained or elucidated. In some of these abbreviations the reader will miss the meaning of it. Short explanations would be appropriate. Congratulations to the authors for a very good job in summarizing the state of the art.
We thank Reviewer #1 for drawing our attention to abbreviations. We checked again the manuscript for abbreviations and missing explanations and added the explanation if necessary (e.g. page 10 polyethyleneglycol).

Reviewer #2:
This paper comprises two manuscripts put into one. The first paper would be a non-biased, objective review of all resorbable implants currently being put into use in children. The second paper would be a scientifically thorough evaluation of the author's quest to identify optimum resorption kinetics in magnesium-alloy-based implants.
However, this manuscript throws these two very different aims together. Both, the review part together with the thorough literature review as well as the more basic scientific paper dealing with resorption kinetics optimization in magnesium-based implants will have their merit, audience, and are well worth being published in my opinion. Therefore, as a reviewer, I can only recommend to take this submitted manuscript apart, to write two separate papers as outlined above, and finally, to resubmit one or the other or both papers to this journal's review process.

Editor's suggestion:
Re-format manuscript regarding structure. Clearly separate into two sections and clearly state in the introduction that the manuscript comprises two parts,
1. overview of what is being used and
2. what is the current state of scientific knowledge and development

We thank **Reviewer #2** for his comments and suggestion on manuscript's structure. According to the comments and **suggestions of the editors** the manuscript was slightly changed in structure as follows:
Abstract: we included the following part "...we will give an overview of implant materials that are currently used in pediatric traumatology with a focus on Mg based implants. Furthermore we will discuss current scientific knowledge on resorbable implants including results from pre-clinics and clinics."
Page 3: we included the following statement on manuscript's structure "First, the article will give an overview of implant materials that are currently used in certain indications with a focus on Magnesium-based implants. In a second part the article will discuss current scientific knowledge on resorbable implants investigated in pre-clinical and clinical studies."
Page 5: we also included the title "Magnesium-based implants" to improve the structure and rearranged the first two paragraphs to improve readability of the manuscript.
We also included some details on polymers in page 3 and 4 highlighted with track changes.

Reviewers' Comments to Revision

Reviewer 2: Dirk W. Sommerfeldt

May 07, 2018

Reviewer Recommendation Term:	Accept
Overall Reviewer Manuscript Rating:	N/A

Custom Review Questions	**Response**
Is the subject area appropriate for you?	5 - High/Yes
Does the title clearly reflect the paper's content?	4
Does the abstract clearly reflect the paper's content?	4
Do the keywords clearly reflect the paper's content?	4
Does the introduction present the problem clearly?	4
Are the results/conclusions justified?	4
How comprehensive and up-to-date is the subject matter presented?	5 - High/Yes
How adequate is the data presentation?	4
Are units and terminology used correctly?	4
Is the number of cases adequate?	3
Are the experimental methods/clinical studies adequate?	4
Is the length appropriate in relation to the content?	4
Does the reader get new insights from the article?	4
Please rate the practical significance.	5 - High/Yes
Please rate the accuracy of methods.	4
Please rate the statistical evaluation and quality control.	3
Please rate the appropriateness of the figures and tables.	3
Please rate the appropriateness of the references.	5 - High/Yes
Please evaluate the writing style and use of language.	5 - High/Yes
Please judge the overall scientific quality of the manuscript.	3
Are you willing to review the revision of this manuscript?	Yes

Comments to Authors:
I like the manuscript better now in the second pass. However, I still believe that it is not the best idea to mix the objective and full-scope review part together with the elaborate and detailed story about the development of Mg-based implants in the author‘s working group.