Abstract. Background and aim of the work: Magnesium (Mg) is a metal physiologically present in bone tissue and essential for bone health. Mg-based alloys exhibit mechanical properties, namely density and strength, similar to human cortical bone. These features have been exploited for the development of osteosynthesis devices in biodegradable Mg-based alloys. Accordingly, the aim of this study is to rank the effectiveness and safety of Mg-based alloys applied in bone surgery in comparison to other suitable metals, focusing in particular on Mg superior biocompatibility and biodegradability. Methods: a systematic review of the literature was conducted including only primary research studies dealing with patients suffering from fractured or osteotomized bones fixed using Mg-based osteosynthesis devices. Results: literature revision suggested Mg-alloys holding comparable properties and side effects in comparison with titanium (Ti) screws, thus showing similar efficacy and safety. Particularly, the gas formation in the carpal bones was identified as the main side effect of the Mg-alloys, during the corrosion/degradation phase of Mg. Conclusions: according to the literature, the main advantages exploiting Mg-alloys for bone implants are related to their biocompatibility, bio-absorbability/-degradability, the lack of surgical removal, osteoconductivity and antibacterial activity. On the opposite, the main limitation of Mg-alloys is due to the poor mechanical resistance of small devices that lack of sufficient strength to withstand high forces. Therefore, an important future prospect could rely in the development of innovative hybrid systems aimed at fixing high load-bearing fractures, as well as in regenerative medicine by developing new Mg-based engineered scaffolds. (www.actabiomedica.it)

Key words: Magnesium; Mg alloy; absorbable metal; osteosynthesis; fracture; screw; hallux valgus; orthopedic surgery; bone fixation; implant.

Introduction

Magnesium (Mg) is a metal physiologically joining the native bone tissue that is involved in the absorption and metabolism of calcium (Ca) (1,2). It is the lightest among all the commonly applied structural metals, displaying a density of about 2/3 that of aluminum (Al) and 1/4 that of steels (3). The properties of Mg-alloys can be influenced by the composition as well as by the processing technologies (3). As a consequence, four parameters can be mainly considered to rank Mg-alloys performances: strength (absolute or specific), corrosion resistance, formability and creep resistance, all of them still representing a challenge for the common Mg-alloys (3).

To date, Mg finds applications in bone repair by the exploitation of Mg and Mg-alloys based biodegradable osteosynthesis materials due to their favorable mechanical properties, density, Young’s modulus and compressive strength, all of them comparable to those of the natural bone (4). Particularly, Mg has shown mechanical strength similar to human cortical...
bone, thus making it an ideal candidate for different medical devices development, such as bone substitutes, bone temporary pro-regenerative scaffolds, and osteosyntheses plates and screws (5).

The mechanical properties of Mg can be exploited in combination with other metals with the aim of forming superior alloys with high stability degree at room temperature.

Mg-alloys are divided into two main groups: the first includes those incorporating Al with traces of zinc (Zn) and manganese (Mn), while the second encloses alloys incorporating Rare Earth (RE) elements in combination with zirconium (Zr) and yttrium (Y) or silver (Ag) and small amount of Zr (6). Al can improve the mechanical properties as well as the corrosion resistance, while Mn increases Mg ductility and RE elements enhance the creep resistance of Mg-alloys at high temperatures (7,8). In vitro and in vivo experiments regarding the combination Mg-Al and Mg-RE alloy systems showed promising results, although some concerns regarding the reduction of the metal’s biocompatibility after implant degradation were pointed out (9). Nowadays, Mg RE-based alloys hold the most promising resistance towards high-strength despite the rapid development of RE-free Mg-alloys reaching a comparable mechanical resistance (3).

An additional issue relying on Mg-based implants pertains to the release of high amount of hydrogen in conjunction with the degradation process: the resulting toxic effect is due to ability of the body to accumulate hydrogen bubbles within the implant site thus negatively affecting its stability (10). A general alkalization of the physiological environment in correspondence to the implant site has been also demonstrated by Mg corrosion studies evaluating the pH increase of neutral buffered solutions in less than 24 hours (11,12), suggesting that Mg-based implants can overcome the buffer capacity of the environment leading to a local alkalization (13). In order to reduce the Mg corrosion rate and the consequent release of hydrogen bubbles, different strategies have been developed. First of all, it is important to reduce the presence of impure elements in pure Mg-based implants such as iron (Fe), nickel (Ni) or copper (Cu) due to the evidence that Mg corrosion resistance is directly dependent by the purity rate, as demonstrated by high purity Mg evolution (14). However, High Purity (HP) Mg implants hold lower mechanical properties than commercial purity ones; thus, the development of alloys represents a good compromise to reduce the corrosion rate while maintaining the same high mechanical strength (10). As an example of promising devices, Mg-Ca and Mg-Zn alloys demonstrated a gradual degradation, being able to maintain proper mechanical resistance and release lower hydrogen volumes than pure Mg. The size of the Mg implants represents one more issue: Witte et al. demonstrated that the incomplete absorption and the increase of hydrogen release following bulky metallic plates implantation were associated with pH increases and osteolysis in an in vivo study involving rabbits and dogs (13).

The use of polymeric coating onto the Mg-based alloy’s surface represents a promising strategy to reduce osteolysis and to improve cytocompatibility, cellular growth and adhesion (14). In vitro tests using SaOS-2 human osteoblasts-like cells cultivated directly onto AZ91 alloys (Al 9% - Zn 1%) coated with PolyCaprolactone (PCL) membranes showed improved cytocompatibility (15). Similarly, SaOS-2 cells adhesion and growth were shown to be increased onto Mg implants coated by PolyLactic Acid (PLLA) and PCL in comparison to the pure Mg; moreover, following surface coating the alloys were more resistant to corrosion, thus achieving a higher pH stability and reducing the Mg release rate (16). The comparison between uncoated AZ91 implants and PCL membrane/AZ91 hybrid implants further demonstrated the advantage of coating in terms of reduction of corrosion, bone repair and new bone formation without inflammation, necrosis and hydrogen accumulation in a rabbit model (15). However, such in vitro studies were performed at a very short term time-points, so it is possible to speculate that polymeric coating is able to enhance the cytocompatibility of the Mg-based alloy at early stages of degradation (15-17), but that at later stages the coating could undergo to a faster degradation rate in comparison to the bare alloy (18,19).

Thus, further studies are needed to assess the advantage of applying Mg-alloys over other suitable materials for osteosynthesis.

The first use of Mg as biomaterial in orthopedic surgery was in the early 1900s (20,21). Due to the
fact that first implants were composed of pure Mg, its rapid degradation caused a rapid loss of the biomechanical properties leading to the release of a large amount degradation products within tissues, and in particular to accumulation of gas (21). Therefore, in 2013 entered the market a new generation of Mg-alloys known as “smart implants”, that were developed with the specific aim of fast degrade just after they completed their function of bone fragments fixation until fracture healing. These compression screws were clinically approved and obtained the European (CE) Mark certificate (21).

Mg-based implants have been tested for their fixation ability for fractures or bone flaps in Germany, China and Korea (22-24). Germany was the first country reporting promising clinical outcomes relying on MgYReZr alloy screws in hallux valgus surgery. The same screws were also used in Ireland for the treatment of Madelung deformity and in Iran for scaphoid fractures (20). In China, HP-Mg screws were used to fix vascularized bone flaps for the treatment of the femoral head's osteonecrosis (ONFH) obtaining satisfactory therapeutic results (20,22). These promising outcomes encouraged for the use of HP-Mg screws also for femoral neck and metatarsal fractures and diaphyseal and acetabular defects. In Korea, other promising results were obtained by the exploitation of Mg-Ca-Zn screws in radius fractures (23), contributing to the approval for clinical use by the Korea Food and Drug Administration in 2015 (20).

Since Mg-based implants are replaced by new bone through the physiological self-healing process, there is no need of a secondary surgery aimed to their removal. This is a relevant advantage of the Mg devices use, carrying to a significative reduction of the hospitalizations costs as well as decreasing psychological stress in patients (20).

However, given the recent increasing of the clinical use of such devices in humans, a systematic review can be very helpful to gather and compare the results coming from the studies available in literature.

Based on these premises, the aim of this systematic review was to evaluate the effectiveness and safety of Mg-based osteosynthesis devices in comparison to other fixation metals, focusing on the Mg promising properties in terms of biocompatibility and biodegradability. A better understanding of the potentialities of these biomaterials will help for the optimizing of their applications in the clinical practice.

Methods

A systematic review (SR) was conducted following the guidelines provided by the Preferred Reporting Items for Systematic reviews and the Meta-Analyses (PRISMA) statement (25).

Elegibility criteria

Inclusion and exclusion criteria are described in Table 1.

Search strategy

Articles’ survey was performed from May 15th, 2020 to June 5th, 2020 using the following databases: MedLine (PubMed), Scopus (Elsevier), Web of Science (Clarivate Analytics) and Google (for grey literature).

Firstly, an explorative search was done using the keywords “Mg”, “Mg-alloy”, “MgYReZr”, “human”, “osteosynthesis”, “bone”, “bioabsorbable screw”, “bio-degradable implants” in combination with the Boolean operators “OR” and “AND”. No limitations in terms of language and time were applied in order not to lose potential articles inherent to the PICOS (Population, Intervention, Control, Outcome, Study design) search tool.

Afterwards, a definitive literature survey was performed typing the search string “magnesium AND (bone fixation OR osteosynthesis) NOT in vitro NOT animal” in the above mentioned databases.

Research strategy is reported in the flow diagram (Figure 1) according to PRISMA guidelines (25).

Risk assessment of bias

Bias risk assessment in the case-control studies was examined using the Newcastle–Ottawa Scale (NOS) (26), which explores three key domains of the studies: selection, comparability and outcome.
We analyzed the RCTs with the Jadad Scale (27), often used to assess the methodological quality of controlled trials. Studies were scored according to the presence of three key methodological features of clinical trials: specifically randomization, masking, and accountability of all patients, including withdrawals.

Results

A total of 25 full text articles responding to eligibility criteria were found regarding Mg alloy osteosynthesis devices and selected for qualitative analysis (Figure 1).

Eight articles reported about surgical treatment of the hallux valgus, while 5 dealt with ankle fractures (three for the medial malleolus and two for the lateral malleolus). The remaining 12 studies dealt with different conditions in the following anatomical sites: wrist for distal radius (two studies), wrist for carpus (two), mandible (two), hip for proximal femur (three), elbow for distal humerus (two) and knee for proximal tibia intercondylar eminence fracture (one) (Table 2).

The survey counted a total number of 646 patients treated with Mg devices for bone fixation.

Table 1: Eligibility criteria.

| Inclusion criteria | Exclusion criteria |
|--------------------|--------------------|
| **Population**     | • *In vivo* studies performed in animals |
| People with fractured or osteotomized bones without limitation in age and sex | • *In vitro* studies |
| **Intervention**   | • Secondary reviews |
| Osteosynthesis by Mg alloy devices (screw) | • Studies regarding bone cement or other materials |
| **Control group**  | • Mathematical simulation studies |
| Other osteosynthesis material fixation i.e itanium alloy | |
| **Outcomes**       | |
| • healing and union of the fracture (versus mal-union and non-union) | |
| • re-operation due to failure of the fixation | |
| • restoration of function postoperatively | |
| • presence of lasting pain | |
| • toxicity | |
| • screw’s biodegradability / resorbability | |
| **Study design**   | |
| • Primary research studies | |
| • RCT | |
| • case series | |
| • case reports | |
| • retrospective and prospective studies | |
| • English, French and German language | |
| • all clinical studies without any publication date limit | |
Table 2. Summary of the general characteristics of the included studies.

| Author and year of publication | Type of study | Database indexing | Intervention | Country | Anatomical site | EBM Level |
|--------------------------------|--------------|--------------------|--------------|---------|----------------|-----------|
| Windhagen et al., 2013 (24)   | RCT          | PubMed             | Mg screw for hallux valgus surgery | Hannover, Germany | Hallux | 1b |
| Yu et al., 2015 (28)          | Case series  | PubMed             | Vascularized iliac grafting | China | Femoral neck | 4 |
| Modrejewski et al., 2015 (29) | Case series  | Google             | Distal metatarsal osteotomies | Germany | Hallux | 4 |
| Wichelhaus et al., 2016 (30)  | Case report  | PubMed             | Use of Mg implant for partial wrist fusion | Rostock, Germany | Wrist | 4 |
| Biber et al., 2016 (31)       | Case report  | Google             | Intraarticular fracture fixation | Nuremberg, Germany | Humeral capitulum | 4 |
| Zhao et al., 2016 (22)        | RCT          | PubMed             | Vascularized bone grafting | Dalian, Hong Kong, Shenyang, Dongguan China | Femoral head | 1b |
| Plaass et al., 2016 (32)      | Case series  | PubMed             | Chevron osteotomy | Hannover, Germany | Hallux | 4 |
| Leonhardt et al., 2017 (33)   | Case series  | PubMed/Scopus      | Fixation of the fracture with Mg screw | UK | Jaw | 4 |
| Meier et al., 2017 (34)       | Case series  | PubMed             | Use of resorbable MgYREZr compression screw in unstable scaphoid fractures | Germany | Scaphoid | 4 |
| Grieve et al., 2017 (35)      | Case report  | Google             | Carpal fracture fixation | Dublin, Ireland | Scaphoid | 4 |
| Biber et al., 2017 (36)       | Case report  | PubMed             | Use of bioabsorbable metal screws in traumatology | Germany | Lateral malleolus | 4 |
| Gigante et al., 2018 (37)     | Case series  | PubMed             | Tibial spine | Ancona, Italy | Knee | 4 |
| Kose et al., 2018 (38)        | Case series  | PubMed             | Fixation of medial malleolar fractures | Antalya, Turkey | Medial malleolus | 4 |
| Acar et al., 2018 (39)        | Case-Control | PubMed             | Distal chevron osteotomy in hallux valgus | Antalya, Turkey | Hallux | 3 |
| Aktan et al., 2018 (40)       | Case report  | PubMed             | Fixation of Small Osteochondral Fragments in a Commminuted Distal Humerus Fracture | Antalya, Turkey | Distal humerus | 4 |
| Plaass et al., 2018 (41)      | Case series  | PubMed             | Fixation of distal metatarsal osteotomies | Hannover, Germany | Hallux | 4 |
| Acar et al., 2018 (42)        | Case report  | Google             | Use of Mg screw for isolated lateral malleolar fracture | Antalya, Turkey | Lateral malleolus | 4 |
| Lingling et al., 2019 (43)    | Case report  | PubMed             | Iliac bone flap | Guangzhou, China | Femur fracture | 4 |
| Klauser et al., 2019 (44)     | Case-Control | Pubmed/Scopus      | Distal metatarsal osteotomies | Hanover, Germany | Hallux | 3 |
| Atkinson et al., 2019 (45)    | Case-Control | PubMed             | Scarf osteotomy | London, UK | Hallux | 3 |
| Choo et al., 2019 (46)        | Case-Control | PubMed             | Mg screw for hallux valgus surgery | Singapore | Hallux | 3 |
| Leonhardt et al., 2020 (47)   | Case series  | PubMed/Scopus      | Osteosynthesis of the mandibular condyle | Germany | Jaw | 4 |
| Turan et al., 2020 (48)       | Case report  | Google             | Fixation of radial styloid fractures | Antalya, Turkey | Radial styloid | 4 |
| May et al., 2020 (49)         | Case-Control | PubMed             | Fixation of medial malleolar fracture | Antalya, Turkey | Medial malleolus | 3 |
| Acar et al., 2020 (50)        | Case-Control | Google             | Biplane chevron medial malleol osteotomy | Antalya, Turkey | Medial malleolus fracture | 3 |
Examined studies were classified for author, country, title, journal, type of study, database indexing, intervention, anatomical site and Evidence Based Medicine (EBM) Level (51) as reported in Table 2.

Study design included 2 Randomized Clinical Trials (RCTs), 6 case control, 9 case series, 8 case reports (Table 2).

All the patients were operated by using Mg based screws.

Clinical outcomes, rate of implant removal (4 cases) and complications are reported in the tables below (Tables 3-10).

Mg devices in hallux valgus surgery provided good functional and radiological outcomes comparable to the control titanium groups with only one exception where complications were reported (Table 3).

Similarly, excellent functional results were found for fracture fixation in the ankle, mandible, humerus, knee and femur (Tables 4-9).

| Table 3. Summary of the results found in the studies on hallux valgus. |
|---------------------------------------------------------------|
| **Author** | **Patients** | **Outcome measures** | **Clinical outcomes** | **Type of device** | **Control group** | **Significance** | **Follow up** | **Rate of implant removal** | **Complications** |
|------------|--------------|----------------------|----------------------|-------------------|------------------|-----------------|---------------|--------------------------|------------------|
| Windhagen et al., 2013 (24) | 26 (13/13) | AOFAS-MTP-IP | Both groups were similar regarding AOFAS and VAS | Magnezix® MgYREZr screw | Titanium screw | p>0.05 | 6 months | 1 in Ti group | None |
| Modrejeski et al., 2015 (29) | 4 | Clinical findings | Not excellent clinical results | Magnezix® MgYREZr screw | / | 3-6-12-36 months after surgery | None, good Mg implant degradation | Bone marrow oedema |
| Plaass et al., 2016 (32) | 45 | AOFAS-MTP-IP NRS FAAM SF-36 | Improvement in AOFAS, FAAM and VAS | Magnezix® MgYREZr screw | / | p>0.05 | n: 39, 6 weeks n: 23, 12 weeks n: 8, >26 weeks | None | 1 relapse 1 hallux varus |
| Acar et al., 2018 (39) | 31 (16/15) | AOFAS-MTP-IP VAS | Excellent | Magnezix® MgYREZr screw 2.7 mm | Titanium screw | p>0.05 | 17.6 months | 1 in Ti group | Prolonged swelling 1 vs 0 |
| Klauser et al., 2018 (44) | 200 (100/100) | Clinical findings | Both groups were similar regarding complications | Magnezix® MgYREZr screw | Titanium screw | p>0.05 | 12.2 weeks (Mg groups) 11.7 weeks (Ti groups) | None | Soft tissue irritation; delayed wound healing; deep infection; screw fracture |
| Plaass et al., 2018 (41) | 26 (13/13) | AOFAS-MTP-IP VAS FAAM SF-36 | Both groups were similar regarding outcome measures | Magnezix® MgYREZr screw 3.2 mm | Titanium screw | p<0.05 | 3 years | 1 in Ti group | None |
| Choo et al., 2018 (46) | 93 (24/69) | Clinical findings | Similar functional outcomes | MgYREZr bioabsorbable screw | Titanium screw | p<0.05 | 12 months | None in magnesium group | None |
| Atkinson et al., 2019 (45) | 36 (11/25) | MOXFQ FAOI EQ-5D-3L | Both groups were similar regarding MOXFQ, FAOI and EQ-5D-3L | Magnezix® MgYREZr screw | Titanium screw | p<0.05 | 19 months | None | None |
### Table 4. Summary of the results found in the studies on malleolar fracture and osteotomy.

| Author                  | Patients | Outcome measures | Clinical outcomes | Type of device | Control group | Significance | Follow up | Rate of implant removal | Complications |
|-------------------------|----------|------------------|-------------------|----------------|---------------|--------------|-----------|--------------------------|----------------|
| Biber et al., 2017 (36) | 1 (43 years patient) | Clinical findings | Excellent         | Magnezix® MgYREZr screw 3.2 mm | /             | /            | 17 months | Mg screw removal 8 months post-implant for radiolucency | No pain, swelling or other deficits were observed |
| Kose et al., 2018 (38)  | 11 (20-78 years patients) | AOFAS and VAS | Excellent          | Magnezix® MgYREZr screw 3.2 mm | /             | p>0.05       | 17 months | None | None |
| Acar et al., 2018 (42)  | 1 (19 years patient) | AOFAS | Excellent with return to preinjury level of activity | Magnezix® MgYREZr screw 3.2 mm | /             | /            | 2 years | None | None |
| Acar et al., 2020 (50)  | 22 (12M; 10F) 18-56 years | AOFAS and VAS | Similar to control | Magnezix® MgYREZr screw 3.2 mm | Titanium screw | p<0.05 | 1 year | 1 in Ti group | Pain and irritation |
| May et al., 2020 (49)   | 48 (23/25 years patients) | AOFAS and KL in both | Similar to AOFAS and KL in both | Magnezix® MgYREZr screw 3.2 mm | Titanium screw | p<0.05 | 1 year | 5 in Ti group | None |

### Table 5. Summary of the results found in the studies on mandible fracture.

| Author                  | Patients | Outcome measures | Clinical outcomes | Type of device | Control group | Significance | Follow up | Rate of implant removal | Complications |
|-------------------------|----------|------------------|-------------------|----------------|---------------|--------------|-----------|--------------------------|----------------|
| Leonhardt et al., 2017 (33) | 5 | Changes in jaw movements, occlusion | Excellent with satisfactory occlusion | Magnezix® MgYREZr screw 2.7 mm | /             | /            | 3 months | 1 | One screw fracture, revised with Mg screw in a second operation |
| Leonhardt et al., 2020 (47) | 6 | Changes in jaw movements over time and occlusion | Improvement in mouth opening, right and left laterotrusion and protrusion distances | Magnezix® MgYREZr screw | /             | /            | 1 year | / | / |

### Table 6. Summary of the results found in the included studies on humeral fracture (elbow).

| Author                  | Patients | Outcome measures | Clinical outcomes | Type of device | Control group | Significance | Follow up | Rate of implant removal | Complications |
|-------------------------|----------|------------------|-------------------|----------------|---------------|--------------|-----------|--------------------------|----------------|
| Biber et al., 2016 (31) | 1 | ROM | Excellent with unrestricted ROM | Magnezix® MgYREZr screw 3.2 mm | /             | /            | 24 months | None | None |
| Aktan et al., 2018 (40) | 1 | ROM, Mayo elbow performance score | Excellent | Magnezix® MgYREZr screw 2.7 mm | /             | /            | 4 months | None | None |
Table 7. Summary of the results of included studies on carpus.

| Author                  | Patients n | Outcome measures | Clinical outcomes | Type of device | Control group | Follow up | Rate of implant removal | Complications                                      |
|-------------------------|------------|------------------|-------------------|----------------|---------------|-----------|------------------------|---------------------------------------------------|
| Meier et al., 2016 (34) | 5          | ROM, gross grip strength and VAS | Excellent | Magnesium alloy MgYREZr | /             | 24 months | None | Extensive resorption cysts in 3 patients, delayed consolidation |
| Grieve et al., 2017 (35)| 6          | Clinical findings | Good results | Magnezix® MgYREZr screw 3.2 mm | /             | 6-18 months | 1 case of fixation failure | None |

Table 8. Summary of the results found in included study on knee intercondylar tibial eminence fracture.

| Author                  | Patients n | Outcome measure | Clinical outcomes | Type of device | Control group | Follow up | Rate of implant removal | Complications |
|-------------------------|------------|-----------------|-------------------|----------------|---------------|-----------|------------------------|---------------|
| Gigante et al., 2018 (37)| 7          | Lysholm and KDC scores | Excellent with the formation of new bone at the end of follow up | Magnezix® MgYREZr screw 3.2-3.5 mm | /             | 12 months | None | None |

Table 9. Summary of the results found in the included studies on femoral fracture (hip).

| Authors                  | Patients n | Outcome measure | Clinical outcome | Type of device | Control group | Significance | Follow up | Rate of implant removal | Complications                                      |
|--------------------------|------------|-----------------|------------------|----------------|---------------|--------------|-----------|------------------------|---------------------------------------------------|
| Yu et al., 2015 (28)     | 19         | Harris hip score (HHS) and avascular necrosis of femoral head | Non union: 1 Satisfactory union: 17 14: excellent results (HHS ≥ 90) 3: fair results (HHS 80-90) 1: poor results (HHS < 80) | Pure Mg screw 4 mm | /             | p<0.0125 | 16 months | 1 case | Low rate of non union |
| Lingling et al., 2016 (43)| 1          | Harris hip score (HHS) | Improvement in patient hip functions; good biodegradability of Mg screw | Pure Mg screw | /             | /           | 2 years | None | None |
| Zhao et al., 2016 (22)   | 48 (Mg vs Ti groups randomly distributed) | Harris hip score (HHS) | Mg group showed improved HHS (95.7%) compared to Ti a purity of group (84%) | Pure Mg Titanium fixation screw 4 mm with p<0.05 | 12 months | None | Mg group n: 2 femoral head collapse Ti group n: 6 femoral head collapse n: 3 prolapsed bone flaps n: 7 bone flap displacement | None |
However, another case of Mg implant failure, was found in distal radius fracture: due to the poor functional results, there was a need for implant revision caused by osteolysis and paresthesia (Table 10).

The methodological quality of the analysed papers was good for all the 6 case control studies with a low risk of bias, while both the included RCTs resulted in a high risk of bias with low quality of method (Table 11 and 12). 17 out of the 25 papers were even case series or case reports with EBM level 4 (Tab.2).

| Author                  | Patients | Outcome measures | Clinical outcomes | Type of device | Control group | Significance | Follow up | Rate of implant removal | Complications                                     |
|-------------------------|----------|------------------|-------------------|----------------|---------------|--------------|-----------|-------------------------|---------------------------------------------------|
| Wichelhaus et al., 2016 | 1        | Fracture union   | Poor              | Magnezix® MgYREZr screw | /             | /            | 6 weeks  | None                    | Revision following loosening and backing out of the screw, pain and paresthesia, osteolysis |
| Turan et al., 2020      | 2        | Fracture union   | Excellent         | Magnezix® MgYREZr screw 2.7 mm | /             | p<0.05       | 27 months | None                    | None                                              |

| Study                  | Selection | Comparability | Exposure | Score |
|------------------------|-----------|---------------|----------|-------|
|                        | Case definition | Cases representativeness | Selection of controls | Definition of controls | Comparability of cases and controls on the basis of the design or analysis | Ascertainment of exposure | Same method of ascertainment for cases and controls | Non-response rate |       |
| Acar et al (39)        | *         | *             | *        | *    | *    | *           | *         | *         | 7 (good)          |
| Klauser et al (44)     | *         | *             | *        | *    | *    | *           | *         | *         | 9 (good)          |
| May et al (49)         | *         | *             | *        | *    | *    | *           | *         | *         | 9 (good)          |
| Atkinson et al (45)    | *         | *             | *        | *    | *    | *           | *         | *         | 8 (good)          |
| Choo et al (46)        | *         | *             | *        | *    | *    | *           | *         | *         | 8 (good)          |
| Acar et al (50)        | *         | *             | *        | *    | *    | *           | *         | *         | 8 (good)          |

| Study                  | Randomization? | Double blinding? | Withdrawals and dropouts described? | Appropriate randomization? | Appropriate blinding? | Total Score |
|------------------------|-----------------|------------------|--------------------------------------|---------------------------|-----------------------|-------------|
| Zhao et al (22)        | 1               | 0                | 0                                    | +1                        | -1                    | 1           |
| Windhagen et al (24)   | 1               | 0                | 0                                    | +1                        | -1                    | 1           |
Discussion

Mg-based alloy bioabsorbable screw is a novel smart tool for bone fixation showing very promising results thanks to its high resorbability, good osteoconductive properties and antibacterial properties (21). We systematically reviewed the existing literature on the clinical application of Mg implants for bone fixation, comparing Mg-based versus Ti screws in several surgical uses. Clinical and radiological outcomes were considered for each study, as well as the complications and the need for implant removal were reported.

One of the first applications of Mg screws was for the surgical treatment of hallux valgus (21). In a retrospective study, Acar et al. reported the results achieved in two groups of patients treated with Mg or Ti screws for the fixation of a modified chevron osteotomy: the clinical and radiographic outcomes were comparable for both the groups (26). The results achieved with the use of Magnezix® screws were comparable where different studies were considered with patients reporting no long-term pain, no surgical infections, no loss of fixation position and a high level of satisfaction (24,41, 44, 45).

Unfortunately, only few studies compared Magnezix® bone screws with Ti screws for hallux valgus using RCTs. However, patients’ homogeneity in terms of preoperative demographic and clinical characteristics, as well as the adequate duration of follow up, represent the strengths of these studies.

One of the major issues related to Mg screw is its corrosion rate, that is due to electron exchange with water that leads to the production of gaseous hydrogen, divalent magnesium cations and hydroxide ions. Since hydrogen gas is poorly soluble in biological fluids it rapidly diffuses within the surgical site and the neighbor tissues (52). This evidence explains the gas propagation to the soft tissues that may be observed in the early post-operative radiographs, appearing as a radiolucent zone around the screw that might be confused with an anaerobic bacterial infection (21). Acar et al. reported a continuous radiolucency from 6 to 12 months after surgery due to Mg implant degradation, without any interference on bone union (39). Corrosion process completes within 2-3 years (7, 21). Thus, a future promising strategy ameliorating the Mg-alloys performance can rely on the coupling with other metals aimed at countering the corrosion thus better controlling the rate of biodegradation in Mg biomaterials.

Mg screws seem to offer protection against infection, probably due to the fact that the corrosion products coming from the Mg devices determine an increase of the environmental pH leading to a general alkalization able to inhibit bacterial proliferation (50). Acar et al did not find any superficial or deep infection in their clinical series (39) and this observation is in line with other studies on hallux valgus (24,38, 39, 41, 45).

Importantly, only a few patients of the Mg groups required implant removal in contrast to those of the Ti groups. Indeed, the implant removal procedure represents a severe burden from an economical point affecting the public health as well as the several side effects can be observed in patients such as re-fracture, infections and neurovascular injury (53).

Malleolar fractures are common injuries representing about 9% of all fractures (54). The goal of the surgical treatment aims at the reduction and the fixation of bone fragments until tissue consolidation. Considering that the soft tissues surrounding the fractured malleolus are frequently injured, complications such as wound dehiscence and infection can occur, thus requiring for metallic implant removal (36). Although many surgical devices are available for this purpose, Mg-based screws represent a promising improvement. Kose et al. reported that Mg bioabsorbable screws provided good fixation, with union of medial malleolus fractures in all patients displaying good clinical outcomes; their only side effect was related to the notice of a radiolucent zone in the soft tissues around the screw that however disappeared in the following 12 months (38). Even though this study lacks the control group, it offers preliminary encouraging results about the use of Mg screw for medial malleolar fracture fixation. Similar results were found in the retrospective case series of patients treated with Mg or Ti screws: clinical and radiological outcomes were similar in both groups (38). No malunion, non union or other complications were observed, suggesting that Mg and Ti based screws were equally effective in enhancing the bone healing (38, 49, 50). Successful results were also obtained in the treatment of isolated lateral malleolar fractures with Mg screw: in both cases presented
by Acar et al. (42) and by Biber et al. (36), successful clinical and radiological outcomes were reached, displaying a positive fracture healing after eight weeks and three months, respectively.

The mandible represents a particular type of bone since it consists of a thin cortical layer adjusted on a large amount of cancellous bone; so, the use of a Ti based screw for mandibular condyle fracture could lead to the perforation of the condylar surface (55). Also, in this case the use of Mg implant could be beneficial relying on its degradation process. Leonhardt retrospectively analyzed some cases of patients treated with Mg screw for fracture of the condylar head observing good clinical results, including complete restoration of mandibular function and implant degradation without side effects and no need for implant removal (47). However, it must be considered that further studies on a larger cohort of patients are needed to study in detail the remodeling processes of mandibular condyle.

As regards to the radius treatment, Turan et al. (48) reported two cases of radial styloid fractures treated with Mg resorbable screws. In accordance with the previous studies, in both patients the fracture healing was achieved without any complication and the radiolucent area around the screw did not interfere with the fracture union. Moreover, the density measurement of the screw and the cortical bone were identical, suggesting that Mg screws successfully turned into cortical bone.

Biber et al. (31) described the application of Mg screw for osteochondral fracture fixation of capitulum humeri, observing an uneventful healing progression, with clinical recovery and radiographic bone union, lacking evidence of any harmful effect due to the degradation products. This was in line with the study of Windhagen et al. relative to bone consolidation without radiological abnormalities in chevron osteotomies (24). Moreover, MRI after 36 months revealed implant replacement with bone tissue following Mg-device degradation, confirming the results of Modrewjeski et al. on distal metatarsal osteotomies (29). Another interesting study on this field was performed by Ak- tan et al., who reported the case of a patient with an intrarticular fracture of the distal humerus (40) which healed uneventfully with an excellent clinical and radiographic outcome and no further complications. Previous in vivo and in vitro experimental studies showed that the degradation products of Mg screws did not harm the surrounding cartilage (37).

Recently, Gigante et al. reported their experience in the fixation of avulsion fractures of the tibial intercondylar eminence with Mg screws reporting good results without any surrounding articular cartilage deterioration of the knee (37). Although the small number of patients and short follow-up period, these successful results suggested that Mg bioabsorbable screws can be safely applied for the fixation of articular fractures.

Besides these promising results, negative outcomes were reported in two studies by Wichelhaus et al. (30) and Meier et al. (34) regarding applications in the carpal bones. In the first study, the Scapho-Trapezio-Trapezoid (STT) fusion was performed using Mg screws in a patient with scaphoid fracture and STT arthritis. Extensive gas and cysts formation in carpal bones were observed in the early phase, requiring revision surgery using a titanium screw that successfully provided osseous consolidation of the fusion. It could be speculated that the poor osteointegration and the resulting mechanical instability was caused by the Mg screw itself, thus confirming the results found in a previous in vivo study (56). In the study published by Meier et al. (34), conflicting results were reported after scaphoid fracture fixation with Mg screw in a cohort of 5 patients. Similarly to the former study, gas formation and osteolysis around the screw were observed early after surgery in 3 patients. However, clinical outcome was excellent at the final follow up, with good recovery of wrist function and fracture union. Nevertheless, according to the results reported in these studies, Mg screw for scaphoid fracture should be used with caution, due to the risk of bone resorption and delayed healing.

The mean level of methodological quality of the 25 analysed papers is quite poor being good only for the 6 case control studies and considering that 17 were case series or case reports.

Most of the studies included in this review consist of limited cohorts or case reports, and it must also be clarified that for many of them the follow up is too short for detecting long term complications related to Mg implants. Despite these described limitations affecting the general final considerations, the homogeneity of pathologies in the evaluated populations rep-
resent a significative result of this survey allowing for a critical overview about the use of Mg or Mg-alloys-based materials for the clinical practice.

Authors believe that the novelty of the present review consists in the illustration of the clinical outcome of the use of Mg screws by anatomical site, as summarized in the specific tables and discussed in subparagraphs, in order to highlight the differences for a better and more specific clinical application. Moreover, authors think that the further inclusion of grey literature can give a more complete view of the state of the art.

Indeed, authors’ systematic review complements the one by Sukotjo et al. (57) which mostly focuses on complications also through a metaanalysis.

Mg screws are a relatively new biomaterial that has been used in fracture and osteotomy fixation in a variety of indications over the past decade. Most of the studies included in this review focus on elective foot surgery, but there are limited clinical data about the use of Mg bioabsorbable screws in trauma surgery, particularly on larger bones or joints. Mg screws seem to be appropriate candidates for an alternative fracture fixation method. However, further clinical trials on larger number of patients are needed for this special indication. As a matter of fact, most of the described articles include a small number of patients (with a maximum of 200 patients for hallux valgus articles), and the interventional group sample size is often small if compared to the control group size. It should also be highlighted that many of the studies have a too short follow-up for detecting long term complications related to Mg implants, with a maximum period of follow-up of 3 years (only 2 of them). Finally, most of the articles included consist of case reports or case series (EBM level of 4) and only 2 RCTs are evaluated. Despite these limits, the homogeneity of pathologies in the studied populations increases their strength.

The main limitation of this review resides in the non-quantitative nature of the analysis.

Conclusions

Bone surgery has improved in the last years due to the introduction of new implant biomaterials and new surgical techniques.

Most of the studies included in this systematic review reveal similar functional outcomes between Ti and Mg devices, although the rate of implant removal and complications seems to be reduced by the use of Mg. According to the current literature, Mg-based alloy screws seem to be comparable to the traditional osteosynthesis implants in terms of efficacy and safety. Indeed, the effectiveness of a Mg screw in stabilizing fractures does not seem to be inferior to that of Ti. A point in favor of the indirect safety of Mg relies on its biodegradability, that avoids the need of further surgery for implant removal. Another advantage of Mg devices besides biocompatibility, relies in their osteoconductivity allowing to a full replacement of the autologous bone once they are resorbed. A final important advantage of Mg is represented by its potential antibacterial activity.

Nowadays, the use of Mg-based alloys is still limited to small implants, that are used to fix bone fragments avoiding high mechanical stresses.

As a future perspective, improvements should be addressed to develop innovative hybrid implants containing Mg-based alloys and traditional metal alloys, in order to increase the mechanical strength of these devices thus allowing fixation of weight-bearing sites. This challenging goal, that requires material research, biological evaluation, clinical assessment and product registration, needs a cooperation between universities, industries and hospitals to encourage further development of Mg implants (20).

An additional valuable future prospect, alongside the study of new resorbable metal alloys, could rely on regenerative medicine and surgery by developing new Mg-based engineered scaffolds for personalized treatments in precision medicine.

Conflict of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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