

EVALUATION OF RESORBABLE ZN-MG ALLOY BIOCOMPATIBILITY *IN VITRO* AND *IN VIVO*Gordienko II¹✉, Kornilov DO¹, Chernyi SP¹, Simarzina VM¹, Rasposienko DY², Slukina AE¹, Ivasenko MI¹, Vinokurov DE², Zornikov DL¹¹ Ural State Medical University, Yekaterinburg, Russia² Mikheev Institute of Metal Physics, Yekaterinburg, Russia

Bioabsorbable Zn–Mg alloys are considered an alternative to metallic fixators, but data on their biocompatibility at low Mg content remain insufficient. Aim — to evaluate the biocompatibility of Zn–Mg alloys containing 0.5–2 wt.% Mg *in vitro* and *in vivo*. Cytotoxicity of Zn–0.5Mg and Zn–1Mg powders (0.15–2.5 mg/mL) was assessed in direct contact with SCP-1 cells (MTT assay). *In vivo*, cylindrical implants of four compositions were placed bilaterally into the tibial metaphysis of rabbits ($n = 4$). Complete blood count was performed on day 7; computed tomography (CT) was performed at 3 and 10 months. At 2.5 mg/mL, cell viability was $12.5 \pm 1.0\%$ (Zn–0.5Mg) and $16.8 \pm 1.6\%$ (Zn–1Mg). At 1.25 mg/mL, Zn–1Mg showed no toxicity ($101.4 \pm 3.3\%$), whereas Zn–0.5Mg remained cytotoxic ($51.3 \pm 4.4\%$). Recovery to $> 80\%$ viability was observed at 0.62 mg/mL for Zn–0.5Mg and 0.31 mg/mL for Zn–1Mg. *In vivo*, all animals maintained normal activity; haematological parameters were within normal range. At 3 months, CT showed stable implants without signs of osteolysis. Cortical bone density was 647.3 ± 5.4 HU, trabecular bone density was 510.5 ± 6.4 HU, comparable to intact bone. At 10 months, implants remained visible. Zn–Mg alloys with 0.5–2 wt.% Mg exhibit dose-dependent cytotoxicity *in vitro* and satisfactory biocompatibility *in vivo* without systemic inflammatory reactions or bone resorption over 10 months. The alloy with 1% Mg has a more favourable cell viability profile.

Keywords: bioabsorbable implants, Zn–Mg alloy, biocompatibility, MTT assay, computed tomography

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Compliance with ethical standards: The study was approved by the Local Ethics Committee of the Ural State Medical University, Ministry of Health of the Russian Federation, Yekaterinburg (Protocol No. 4 dated April 19, 2024). Informed consent is not applicable because laboratory animals were used.

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ОЦЕНКА БИОСОВМЕСТИМОСТИ РЕЗОРБИРУЕМЫХ ZN-MG СПЛАВОВ *IN VITRO* И *IN VIVO*И. И. Гордиенко¹✉, Д. О. Корнилов¹, С. П. Черный¹, В. М. Симарзина¹, Д. Ю. Распосиенко², А. Е. Слукина¹, М. И. Ивасенко¹, Д. Е. Винокуров², Д. Л. Зорников¹¹ Уральский государственный медицинский университет, Екатеринбург, Россия² Институт физики металлов имени М. Н. Михеева, Екатеринбург, Россия

Биорезорбируемые сплавы Zn–Mg рассматривают как альтернативу металлическим фиксаторам, однако данные об их биосовместимости при низком содержании Mg остаются недостаточными. Цель работы — оценить биосовместимость сплавов Zn–Mg с содержанием Mg 0,5–2 мас.% *in vitro* и *in vivo*. Цитотоксичность порошков Zn–0,5Mg и Zn–1Mg (0,15–2,5 мг/мл) оценивали в прямом контакте с клетками SCP-1 (MTT-тест). *In vivo* цилиндрические импланты четырех составов устанавливали билатерально в метафиз большеберцовой кости кроликам ($n = 4$). На 7-е сутки был выполнен общий анализ крови, через 3 и 10 месяцев — компьютерная томография. При 2,5 мг/мл жизнеспособность клеток составила $12,5 \pm 1,0\%$ (Zn–0,5Mg) и $16,8 \pm 1,6\%$ (Zn–1Mg). При 1,25 мг/мл Zn–1Mg не проявлял токсичности ($101,4 \pm 3,3\%$), тогда как Zn–0,5Mg сохранял цитотоксичность ($51,3 \pm 4,4\%$). Восстановление $> 80\%$ наблюдалось при 0,62 мг/мл для Zn–0,5Mg и 0,31 мг/мл для Zn–1Mg. *In vivo* все животные сохраняли нормальную активность; гематологические показатели находились в пределах нормы. Через 3 месяца по данным КТ импланты стабилизировались, признаков остеолитической реакции не было. Плотность кортикальной кости составила $647,3 \pm 5,4$ HU, трабекулярной — $510,5 \pm 6,4$ HU, что сопоставимо с интактной костью. Через 10 месяцев импланты по-прежнему визуализировались. Сплавы Zn–Mg с 0,5–2 мас.% Mg демонстрируют дозозависимую цитотоксичность *in vitro* и удовлетворительную биосовместимость *in vivo* без системных воспалительных реакций и костной резорбции в течение 10 месяцев. Сплав с 1% Mg имеет более благоприятный профиль клеточной выживаемости.

Ключевые слова: биорезорбируемые импланты, Zn–Mg сплав, биосовместимость, MTT-тест, компьютерная томография

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In recent decades, bioresorbable implants have been considered a promising alternative to conventional metallic fixators in traumatology and orthopedics [1–3]. A key characteristic of such implants is their ability to undergo controlled degradation *in vivo*. This eliminates the need for a second surgical intervention to remove the fixation device, which is associated with additional tissue trauma, risk of infectious complications, and increased treatment costs [3, 4]. This clinical advantage has driven intensive research into both polymeric and metallic materials with tailored biodegradation parameters.

An ideal bioresorbable implant should possess mechanical properties comparable to those of human bone tissue, including a similar elastic modulus, sufficient strength, and ductility. The material degradation rate should match the recovery rate of bone mechanical strength at the fracture site [3]. Other essential requirements include high biocompatibility, absence of toxic and carcinogenic effects, and a predictable pattern of degradation products [1, 3].

Polymeric implants, mainly based on PLA (Polylactic acid) and PGA (Polyglycolic acid), are already used in clinical practice; however, their application is limited by relatively low mechanical strength [4]. Furthermore, polymer resorption is accompanied by the formation of acidic hydrolysis products, which can lead to local aseptic inflammation [5]. In contrast, metallic bioresorbable implants offer significantly higher strength, a predictable electrochemical corrosion mechanism, and no pronounced local acidosis at the implantation site [6, 7]. These properties make them potentially suitable for osteosynthesis of fractures in major weight-bearing bones under high mechanical loads.

Among the metals considered for developing bioresorbable implants, most attention has been given to magnesium (Mg), iron (Fe), and zinc (Zn) [8, 9]. Mg alloys demonstrate high biocompatibility and an elastic modulus close to that of bone tissue; however, their main drawback is an excessively high corrosion rate under physiological conditions, accompanied by hydrogen evolution and premature loss of mechanical strength [10, 11]. In contrast, despite satisfactory mechanical properties, Fe is characterized by extremely slow *in vivo* degradation, limiting its clinical applicability [9, 12]. In this context, Zn is viewed as a material with a more optimal balance between resorption rate and mechanical stability, making it a promising basis for implants with controlled degradation kinetics [13].

In addition to favorable corrosion properties, Zn is an essential trace element involved in the regulation of osteogenesis, alkaline phosphatase activity, and the expression of growth factors. *In vivo* studies have shown that Zn-based implants undergo uniform corrosion at a rate of approximately 0.17–0.22 mm/year, which corresponds to the timeline of bone repair [14]. However, pure Zn exhibits relatively low mechanical strength (ultimate tensile strength of approximately 100–150 MPa), which limits its use under significant loading [13].

One of the most effective approaches to enhancing the strength of Zn is alloying with various metals. Binary Zn–Mg alloys have attracted attention as potential materials for bioresorbable implants due to the combination of mechanical stability and moderate biodegradation rate [13, 15]. The addition of Mg promotes the formation of intermetallic phases (Mg_2Zn_{11} , $MgZn_2$) that strengthen the alloy's structure. The ultimate tensile strength of Zn–Mg alloys can reach 260–498 MPa, depending on the Mg content and processing method [16, 17]. At the same time, the corrosion rate increases moderately compared to pure Zn, remaining within limits compatible with physiological bone regeneration processes [16]. Some authors report that the addition of Mg enhances the biocompatibility of alloys compared to pure Zn [18]. However, data on the cytotoxicity

of binary Zn–Mg alloys are contradictory and depend on the Mg fraction in the alloy [15, 19]. An excessive amount of Mg in the alloy may, conversely, impair mechanical properties and excessively accelerate corrosion processes [19].

Thus, despite a substantial number of studies on Zn–Mg alloys, data on the effects of low Mg concentrations (0.5–2 wt.%) on cytotoxicity, degradation rate, and tissue response remain partially contradictory. Moreover, comprehensive studies combining *in vitro* and *in vivo* analysis for this concentration range are limited, which hinders the optimization of alloy composition for clinical applications.

The aim of this study was a comprehensive assessment of the biocompatibility of Zn–Mg alloys with Mg content (0.5–2 wt.%), including analysis of cytotoxicity on SCP cell cultures *in vitro* and evaluation of the biological response to material implantation *in vivo*.

METHODS

To achieve this aim, the study was conducted in two sequential stages. The first stage involved a screening assessment of *in vitro* cytotoxicity using powders of the investigated alloys. The powder form was chosen for a standardized direct-contact MTT assay, allowing the determination of threshold concentrations causing cell death under conditions of maximum material surface area (stress test). The second stage evaluated *in vivo* biocompatibility using compact cylindrical implants, the shape of which corresponds to potential clinical application as fixators for osteosynthesis. Direct quantitative comparison of absolute *in vitro* cell viability values and *in vivo* implant degradation rates was not performed due to differences in sample morphology.

Investigated materials

Zn Ts0 (GOST 3640-79) and Mg Mg90 (GOST 804-72) were used as starting materials. Samples were melted under two experimental regimes. A sealed quartz ampoule containing the specified composition was heated to 440 °C (20 °C above the melting point of Zn), held for 10 hours, and rapidly quenched in water.

In further studies, all investigations were conducted using the alloys in the as-cast state. The materials were characterized by a coarse-grained microstructure consisting mainly of zinc-based solid solution (Zn) grains. In alloys with a Mg content exceeding 1.5%, a degenerate eutectic ($(Zn) + Mg_2Zn_{11}$) was also found along the intergranular boundaries in the form of thin layers; its volume fraction did not exceed 5%. An increase in the Mg content led to a decrease in the average grain size from 400 to 195, 160, and 120 μm .

Powder of the required particle size was obtained by dispersion in a planetary ball mill (PM 100, Retsch GmbH, Germany). First, cast ingots were milled on a milling machine to produce metal chips. The chips were then ground using agate balls in an agate jar (200 mL) at 300 rpm (revolutions per minute) for 5 hours in a heptane medium to prevent particle agglomeration. Agate balls were used to avoid iron contamination of the finished powder; iron particles can appear on the powder surface after grinding with standard steel balls.

The mass ratio of chips to balls was 1 : 2. The ball mass was 60 g, so each run produced 30 g of powder. After milling, the powder was sieved through a 100 μm mesh to remove coarse particles. The sieved powder was thoroughly washed in an ultrasonic bath with ethanol, and the resulting suspension was filtered through filter paper. The finished powder remaining on the filter paper was dried for 24 hours in a ventilated fume hood.

Particle size distribution was characterized using an optical microscope (Neophot 32, Carl Zeiss, Jena, Germany) and a scanning electron microscope (TESCAN MIRA 2, TESCAN, Brno, Czech Republic) equipped with an energy-dispersive X-ray spectroscopy system (Oxford Instruments, UK). The powder granules had an irregular flake-like shape. The average particle size was 50 μm for Zn-0.5Mg, 65 μm for Zn-1Mg, 96 μm for Zn-1.5Mg, and 89 μm for Zn-2Mg. The fraction of particles with a minimum diameter < 20 μm did not exceed 5% in any sample.

For the *in vivo* study, blanks in the form of cylinders (diameter 1.5 mm, height 8 mm) were cut from the original ingots using an electric discharge machine. Subsequently, to remove oxides and achieve the required surface quality, the samples were mechanically polished with abrasive paper of 240, 400, and 800 grit.

In vitro cytotoxicity

Cell line and culture conditions

Immortalized human bone marrow stromal cells of the SCP-1 line, which exhibit stable adhesion to metallic surfaces, were used to assess cytotoxicity. Cells were cultured in T-25 flasks (Sarstedt, Germany) with adhesive coating in a medium containing 88% LoSera basal medium (HiMedia, India), 10% fetal bovine serum (FBS, HiMedia, India), 0.01% L-glutamine (ServiceBio, China), and 0.01% penicillin/streptomycin/amphotericin B solution (CDH, India), in a CO₂ incubator (Panasonic (Sanyo) MCO-15A, Japan) at 37 °C with 5% CO₂.

At 90–100% confluency, passaging was performed: the spent medium was removed, the cells were washed twice with Hanks' balanced salt solution (HBSS, ServiceBio, China) without Ca²⁺ and Mg²⁺ ions, then 2.5 mL of 0.25% trypsin-EDTA solution (ServiceBio, China) was added. Trypsin exposure was 10 seconds, after which the flask was placed in the CO₂ incubator for 1 minute 30 seconds. The cells were then resuspended in 10 mL of fresh medium. Cell detachment from the underlying surface was monitored using an inverted light microscope (Nexcope NIB620FL, China). The cell suspension was collected into a tube and centrifuged at 1600 rpm for 3 minutes. The supernatant was removed. The pellet was resuspended in 15 mL of medium and 5 mL was transferred to three new flasks (three-fold dilution).

The cell suspension was added to a 96-well plate (Sarstedt, Germany) at a concentration of 525,000 cells/mL and cultured for 24 hours before adding the test material.

Preparation of metal powder suspensions

Cytotoxicity was assessed by the direct contact method. Powders of Zn-Mg alloys with 0.5 and 1 wt.% Mg (Groups A and B, respectively) were used. Powders with 1.5 and 2 wt.% Mg were not tested *in vitro* because the excessively large particle size did not allow dosing of the metal powder.

The powders were sterilized by autoclaving at 121 °C for 60 minutes and then cooled to room temperature under sterile conditions. A suspension in culture medium (as described above) was prepared in 1.5 mL Eppendorf tubes at a stock concentration of 10 mg/mL. After thorough shaking on a microcentrifuge vortex, this suspension was serially diluted two-fold to working concentrations of 2.5, 1.25, 0.62, 0.31, and 0.15 mg/mL.

The culture medium was removed from the wells containing the cell culture, and 100 μL of the prepared powder suspensions were added to 72 wells according to the scheme shown in Fig. 1.

MTT assay

Powder suspensions at concentrations of 2.5–0.15 mg/mL were added to wells with cell culture. The top three rows (6 wells each) of each group contained experimental samples and the intact control. Row 4 — powder adsorption control with cells (no MTT), row 5 — powder adsorption control with MTT (no cells), row 6 — adsorption control with DMSO (no cells). The inclusion of additional controls made it possible to eliminate false-positive reactions associated with non-specific binding of powder particles to MTT assay components, which had been observed in early experiments. The exposure time was 24 hours.

The samples were analyzed using the MTT assay. For this purpose, dry MTT reagent (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide, ServiceBio, China) was dissolved at a concentration of 5 mg/mL in 1 × Phosphate-Buffered Saline (PBS, ServiceBio, China). Then, 1 mL of MTT stock solution (5 mg/mL) was mixed with 9 mL of culture medium (working MTT concentration 0.5 mg/mL). After 24 hours of exposure to the test metal powders, the medium was carefully aspirated from all wells using a vacuum aspirator, and 100 μL of working MTT solution (0.5 mg/mL) was added to each well. The plates were incubated for 2.5 hours in a CO₂ incubator. The solution was then removed using a vacuum aspirator, and 100 μL of DMSO (ServiceBio, China) was added to each well. The plates were incubated for 15 minutes on an orbital shaker (100 rpm).

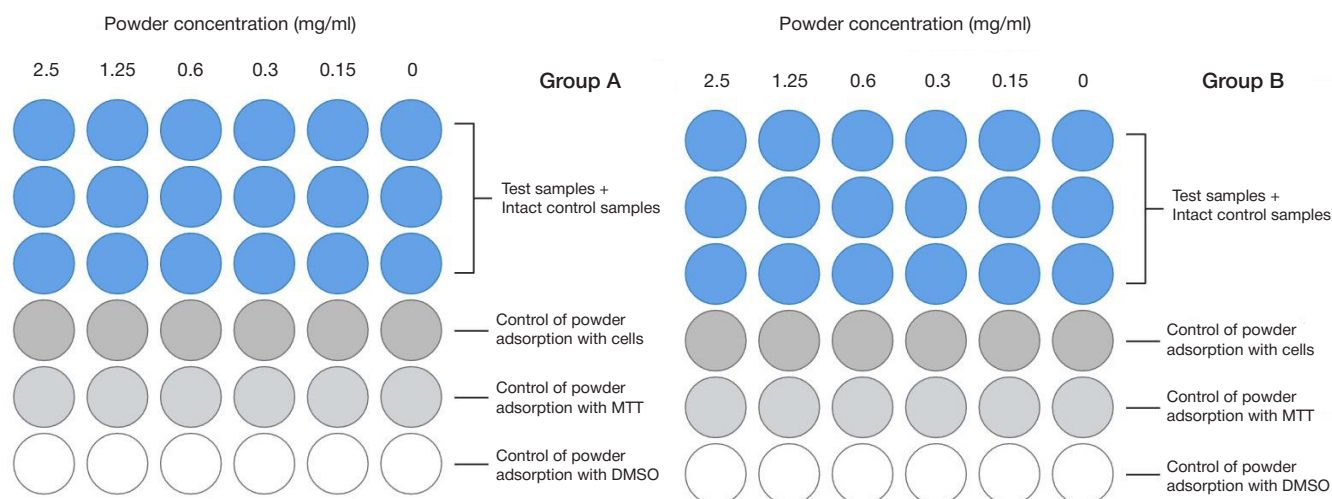


Fig. 1. Group A — samples with 0.5 wt.% Mg, all working concentrations. Group B — samples with 1 wt.% Mg, all working concentrations

Optical density of each sample was measured at 540 nm (reference wavelength 750 nm) using a microplate reader (Alsheng AMR-100, China). Viability was calculated using the formula $\%Vi = (100 \times OD_e)/ODb$, where OD_e is the optical density of the experimental samples and ODb is the mean optical density of the negative controls. Intact cells cultured under the same conditions but without the addition of metal powder were used as the negative control. Additional controls (powder adsorption control with cells without MTT, powder adsorption control with MTT without cells, adsorption control with DMSO without cells) were used to detect non-specific binding of MTT assay components to powder particles. If any of the additional controls registered an optical density exceeding 5% of the negative control values, the corresponding powder concentration was excluded from the analysis as giving a false-positive result. In all cases presented in this study, the values of the additional controls did not exceed this threshold. All measurements were performed in triplicate [20].

In vivo study

The experimental study was conducted at the animal facility of the Ural State Medical University, Ministry of Health of Russia, using four adult male Soviet Chinchilla rabbits. The study included clinically healthy animals aged 6–9 months, body weight 2.0–3.5 kg, which had undergone quarantine and veterinary examination with confirmation of normal clinical and laboratory parameters. The animals were housed in accordance with GOST 33216-2014 and FELASA recommendations. The experimental protocol was approved by the Local Ethics Committee of the Ural State Medical University (Protocol No. 4 dated April 19, 2024).

The sample size ($n = 4$) was based on the pilot nature of the study and is the minimum sufficient to assess local and systemic reactions to the implant in a given organism. To increase the number of experimental points, implants were placed bilaterally (in the right and left hind limbs of the same rabbit).

Zn–Mg implants with Mg contents of 0.5, 1, 1.5, and 2 wt.%, cylindrical in shape with a diameter of 1.5 mm and height of 8 mm, were used as test samples. Before use, the implants were sterilized in a dry-heat oven at 180 °C for 60 minutes.

Surgical procedure

Surgeries were performed under general anesthesia induced by intramuscular injection of Zoletil 100 (Virbac Sante Animale, France) at a dose of 10 mg/kg. Respiratory rate and heart rate were monitored during the procedure. The animal was fixed on the operating table in lateral recumbency (on the side of

the intervention). Hair was removed from the animal's hind limbs using an electric clipper, and the surgical site was then sequentially treated with 70% ethanol and povidone-iodine solution (Egis Pharmaceutical Plant, Hungary).

A longitudinal skin incision 3–4 cm long was made on the medial surface in the projection of the proximal tibial metaphysis. After layer-by-layer dissection of the soft tissues, the proximal metaphysis was visualized. A cortical-cancellous defect with a diameter of 1.5 mm and depth to the opposite cortical layer was created on the medial surface of the metaphysis, 6–8 mm from the joint line, using an engraver with a sterile cylindrical bur of 1 mm diameter. Drilling was performed under constant irrigation with sterile saline to prevent thermal damage to the bone tissue. The implant was inserted into the created defect until it contacted the opposite cortical layer. Tight mechanical fixation of the implant was achieved in all cases (Fig. 2).

After implant placement, the wound was closed layer-by-layer with separate interrupted sutures: the fascia with Vicryl 4-0 (Medin-N, Russia), and the skin with Prolene 3-0 (Medin-N, Russia). The suture line was treated with oxytetracycline spray (Terramycin, Zoetis, USA). No immobilization of the operated limb was performed. A similar procedure was performed on the contralateral side during the same operation.

After surgery, the animals received analgesia with ketoprofen (VIC, Russia) at 1 mg/kg intramuscularly once daily for 3–4 days; the effectiveness of analgesia was monitored using the Rabbit Grimace Scale. For prevention of infectious complications, enrofloxacin (KRKA, Slovenia) was administered at a dose of 5 mg/kg intramuscularly for 3 days. Throughout the observation period, the general condition, behavior, appetite, and postoperative wound status of the animals were monitored daily.

Hematological analysis

On the seventh postoperative day, blood was collected from the marginal ear vein for a complete blood count (CBC). Blood was analyzed using an automatic hematology analyzer (Mythic 5Vet PRO, Orphée S.A., Switzerland). Red blood cell count (RBC), hemoglobin level (HGB), white blood cell count (WBC), and leukocyte differential (GRA%, MID%, LYM%) were determined. Results were interpreted taking into account reference values for this animal species.

Computed tomography (CT)

Computed tomography was performed at 3 and 10 months after implantation using a 64-slice tomograph (Philips Tomoscan AV, Philips Healthcare, The Netherlands) with a slice thickness of 0.6 mm.



Fig. 2. Stages of surgical intervention. Implant insertion into the created bone defect. **A.** Preparation of a trephine hole in the proximal metaphysis of the tibia of experimental animals. **B.** Implantation process of a Zn-based alloy pin into the created trephine hole. **C.** Implanted pin tightly placed in the prepared trephine hole; final view

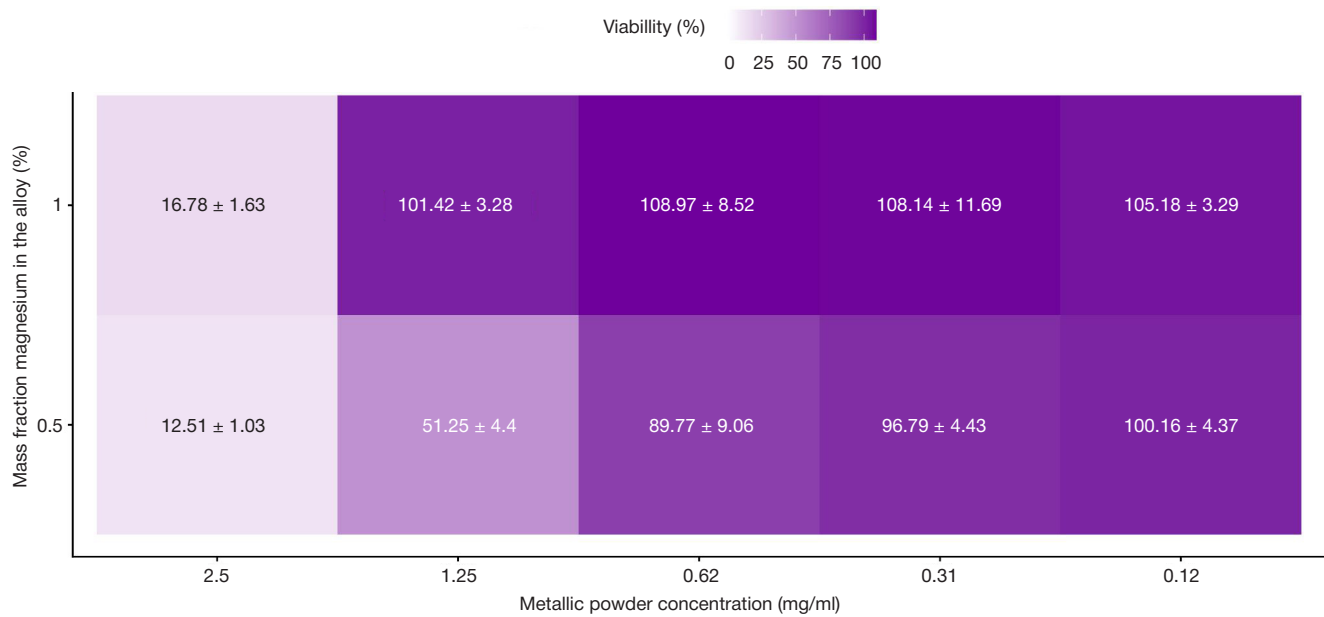


Fig. 3. Heat map of SCP-1 cell viability after exposure to bioresorbable Zn-Mg alloy powders. Color scale: cold colors — low viability, warm colors — high viability

The obtained images were analyzed using RadiAnt DICOM Viewer software (Medixant, Poland). The analysis assessed the presence of gas or fluid collections in the peri-implant zone, signs of inflammatory changes in soft tissues, as well as areas of bone destruction.

Bone density was measured in Hounsfield units (HU). For quantitative analysis, cortical bone density (CBD) was measured ventrally and dorsally relative to the implant, and trabecular bone density (TBD) was measured in the peri-implant zone.

Statistical analysis

Quantitative data were processed using Microsoft Office Excel 2020 (Microsoft, USA). Quantitative indicators are described using arithmetic means (M) and standard deviations (SD). No a priori sample size calculation was performed. No comparisons between groups using statistical tests were made due to the small sample size. Graphs were generated using R version 4.5.2 (R Foundation for Statistical Computing, Austria).

Table 1. Hematological parameters on postoperative day 7

Parameter	Zn-0.5Mg	Zn-1Mg	Zn-1.5Mg	Zn-2Mg	Reference values*
WBC (10 ⁹ /L)	5.3	8.47	9.79	7.89	5.0–12.0
LYM% (%)	44.42	45.58	52.73	48.46	30–75
LYM# (10 ⁹ /L)	2.314	3.86	5.162	3.013	2.0–8.0
MON% (%)	10.35	13.12	11.79	13.22	2–10
MON# (10 ⁹ /L)	0.866	1.111	1.154	1.043	0.1–0.9
NEU% (%)	38.41	40.52	34.4	37.96	20–60
NEU# (10 ⁹ /L)	2.037	3.434	3.369	2.996	1.0–5.5
EOS% (%)	0.8	0.76	0.92	0.32	0–7
EOS# (10 ⁹ /L)	0.042	0.064	0.09	0.025	0.1–0.5
BASO% (%)	0.02	0.02	0.16	0.04	0–3
BASO# (10 ⁹ /L)	0.001	0.001	0.015	0.003	0.1–0.5
RBC (10 ¹² /L)	6.18	7.09 (H)	6.88 (H)	6.23	4.5–7.0
HGB (g/L)	148 (H)	157 (H)	157 (H)	141 (H)	100–140

Note: * — Reference values for rabbits [21]; H — increasing the parameter.

RESULTS

Cytotoxicity Assay

Analysis of the cytotoxicity of metallic powders of bioresorbable Zn-Mg alloys on human bone marrow stromal cells of the SCP-1 line revealed a dose-dependent reduction in cell viability (Fig. 3).

At the maximum tested concentration of 2.5 mg/mL, both alloys exhibited pronounced cytotoxicity. Cell viability was 12.51 ± 1.03% for the alloy containing 0.5% magnesium and 16.78 ± 1.63% for the alloy containing 1% magnesium. Upon reducing the concentration to 1.25 mg/mL, the alloy with 0.5% magnesium retained moderate cytotoxicity (viability of 51.25 ± 4.4%), whereas the alloy with 1% magnesium showed no toxic effect (101.42 ± 3.28%).

Concentrations of 0.62 mg/mL and lower for the alloy with 1% magnesium were characterized by cell viability at or above control levels: 108.97 ± 8.52% at 0.62 mg/mL,

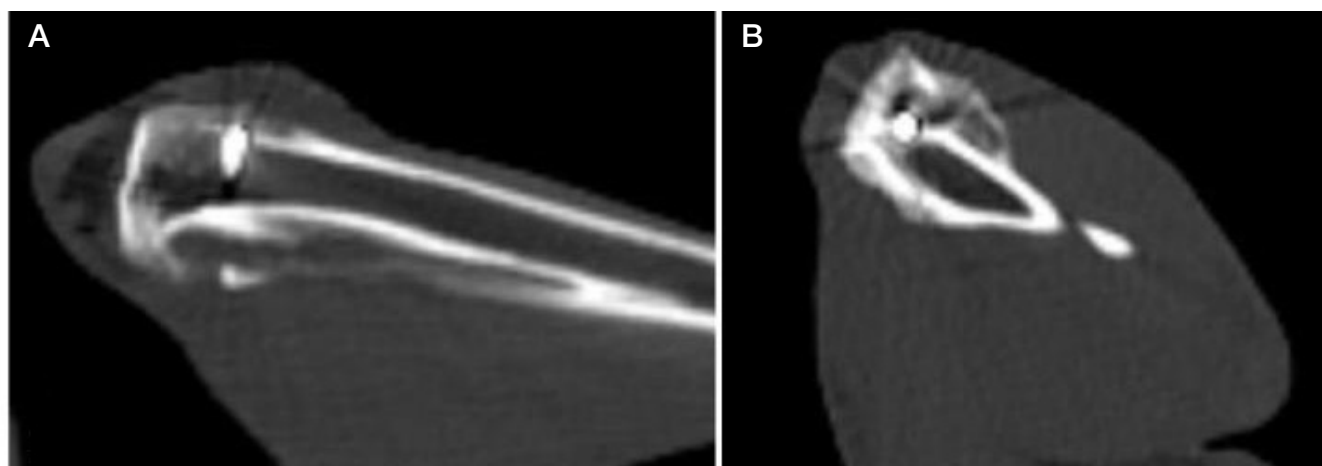


Fig. 4. Computed tomography results 3 months after surgery. The implant is visualized in the metaphyseal region of the tibia. **A.** Sagittal section including the diaphysis. **B.** Sagittal section including the epiphysis

108.14 ± 11.69% at 0.31 mg/mL, and 105.18 ± 3.29% at 0.12 mg/mL. For the alloy with 0.5% magnesium, restoration of viability to acceptable levels (> 80%) was observed starting from a concentration of 0.62 mg/mL (89.77 ± 9.06%), with a further increase to 96.79 ± 4.43% and 100.16 ± 4.37% at concentrations of 0.31 and 0.12 mg/mL, respectively.

In vivo study

Throughout the postoperative period, the general condition of the animals remained satisfactory. All rabbits maintained normal motor activity, appetite, and physiological body temperature. No clinical signs of wound inflammation or infection, nor any impairment of hind limb function, were detected.

Hematological parameters

On day 7 after surgery, the main hematological parameters were determined — red blood cell count (RBC), hemoglobin concentration (Hb), total white blood cell count (WBC), and leukocyte differential count (Table 1).

WBC counts were within the reference range ($5.0\text{--}12.0 \times 10^9/\text{L}$). Both relative and absolute values of lymphocytes (LYM) and neutrophils (NEU) corresponded to the physiological norm, while the relative monocyte count (MON) slightly exceeded the upper reference limit, ranging from 10.35% to 13.22%. EOS and BASO values were also within the reference ranges. RBC counts ranged from 6.18 to $7.09 \times 10^{12}/\text{L}$, and HGB ranged from 141 to 157 g/L, which slightly exceeded the upper reference limit.

Computed tomography

Computed tomography (CT) performed 3 months after implantation demonstrated preservation of the position of all implants

without signs of migration, indicating stable mechanical fixation and integration into the bone tissue (Fig. 4).

Analysis of bone mineral density based on CT data using RadiAnt DICOM Viewer revealed high homogeneity of cortical (CBD) and trabecular (TBD) bone density parameters in all animals (Table 2).

Eight experimental samples were examined, representing a total of 4 implant types with magnesium content ranging from 0.5% to 2% in 0.5% increments. Mean cortical bone density (CBD) values ranged from 642.5 to 655 HU depending on the Mg concentration in the implant, while trabecular bone density (TBD) ranged from 505 to 517 HU. The overall mean value for all samples was 647.25 ± 5.42 HU for CBD and 510.5 ± 6.40 HU for TBD. The normal bone density values for healthy rabbit bone average 655 HU for cortical bone density and 510 HU for trabecular bone density.

According to CT data obtained 10 months after surgery, the implant was identified at the original implantation site. Analysis of gas presence in the peri-implant zone revealed slight gas release, without spread into the bone marrow canal of the tibia of the laboratory animal.

DISCUSSION

The potential of binary Zn–Mg alloys as biodegradable medical materials was first reported in 2011 [22]. The authors found that the *in vitro* degradation rate of Zn–Mg alloys was on the order of tens of microns per year, which may be sufficient for the restoration of bone mechanical strength at the injury site. Subsequently, it was established that alloying zinc with magnesium leads to the formation of intermetallic phases (primarily $\text{Mg}_2\text{Zn}_{11}$ and MgZn_2), providing a significant increase in strength characteristics due to dispersion hardening while maintaining an elastic modulus close to that of bone tissue [16].

Table 2. Cortical (CBD) and trabecular (TBD) bone density in the peri-implant zone at 3 months

Sample	CBD, HU				TBD, HU			
	right	left	M	Reference	right	left	M	Reference
0.50%	654	656	655	655	505	505	505	510
1%	643	642	642.5		504	506	505	
1.50%	644	646	645		518	516	517	
2%	646	647	646.5		513	517	515	
Group mean (n = 4) M (SD)	647.25 (5.42)				510.5 (6.40)			

Furthermore, implants made from binary Zn alloys demonstrate better osseointegration than pure Zn, which may be associated with the stimulating effect of Mg ions on osteogenesis [15].

The results obtained in our study demonstrate a dose-dependent nature of cytotoxicity of the investigated Zn–Mg alloys and confirm their satisfactory biocompatibility profile at concentrations 1.25 mg/mL for 1 wt.% and 0.62 mg/mL for 0.5 wt.%. The most pronounced reduction in cell viability (to 12.5–16.8%) was observed at the maximum powder concentration (2.5 mg/mL), whereas dilution of the medium restored viability to values comparable to or exceeding the control (up to 109.0%). This response profile indicates that the local concentration of released metal ions is the main factor determining cell survival [8, 16].

It was demonstrated that at a concentration of 0.31 mg/mL for Zn–5Mg alloy, endothelial cell viability exceeded 100%, whereas for pure Zn under the same conditions it was about 85% [15]. In another study recorded a decrease in cell viability to 50% at a concentration of 0.75 mg/mL of Zn–3Mg alloy, but at lower concentrations cell viability gradually increased [23]. Similarly it was reported >70% viability of HOS and MG-63 cell lines when exposed to diluted extracts of Zn–1.2Mg alloy [24].

It should be noted that in most of the cited studies, cytotoxicity was assessed using the extract method, which may lead to a reduction in peak ion concentrations and, consequently, to higher cell viability values [15]. The direct contact model used in the present study is potentially closer to the conditions of local material-cell interaction, and the use of an extended control system made it possible to increase the reliability of the cytotoxicity assessment and partially eliminate the influence of non-specific powder adsorption on the MTT assay results, which has previously been noted as one of the problems of *in vitro* evaluation of metallic biomaterials [25].

Despite the absence of direct electrochemical measurements and quantitative assessment of ion release kinetics in the present study, a discussion of possible mechanisms of the observed cytotoxicity seems necessary. According to the literature, Zn^{2+} ions at concentrations comparable to those used in our work at maximum powder concentrations (2.5 mg/mL and, for Zn–0.5Mg alloy, at 1.25 mg/mL) induce apoptosis in bone-derived cells primarily through the mitochondrial pathway. It was shown that exposure to Zn^{2+} in the range of 80–160 μM leads to an increased Bax/Bcl-2 ratio, release of cytochrome c from mitochondria, activation of caspase-3 and -9, and consequent cell death [19]. An additional mechanism is the induction of oxidative stress: Zn^{2+} ions promote the generation of reactive oxygen species, causing damage to membrane lipids and DNA. In our study, the reduction in cell viability to 12–17% at 2.5 mg/mL for both alloys is in good agreement with these literature data. Interestingly, at 1.25 mg/mL, the Zn–1Mg alloy showed no toxicity (viability 101.4%), whereas Zn–0.5Mg remained cytotoxic (51.3%). This difference may be explained not only by different rates of Zn^{2+} ion release due to different proportions of $\text{Mg}_2\text{Zn}_{11}$ intermetallic phases (as discussed above), but also by a possible direct protective effect of Mg^{2+} ions [19].

In our study, the alloy with 1 wt.% Mg demonstrated a more favorable biocompatibility profile compared to the alloy containing 0.5% Mg. A critical difference was observed in the concentration range of 1.25–2.5 mg/mL, where the alloy with higher magnesium content showed significantly lower cytotoxicity. At concentrations of 0.62 mg/mL and below, both alloys demonstrated comparable cell viability values exceeding the 80% threshold. This effect may be explained by an increased proportion of intermetallic phases (primarily $\text{Mg}_2\text{Zn}_{11}$) in the Zn–1Mg alloy, which reduces the bioavailability of Zn^{2+}

ions and limits their local concentration spikes in the cellular environment [16, 26]. Furthermore, the increase in cell viability may also be due to the bioprotective effect of Mg^{2+} ions, as well as their influence on cellular metabolism and regulation of apoptosis [8].

At concentrations of 0.62 mg/mL for Zn–1Mg and 0.12 mg/mL for Zn–0.5Mg, the alloys demonstrated cell viability above 100% (up to $108.97 \pm 8.52\%$), indicating a possible stimulatory effect of subtoxic concentrations of released metal ions. A similar stimulatory effect of Zn^{2+} ions was demonstrated in *in vitro* studies on mesenchymal stem cells [19].

The results of *in vivo* hematological analysis 7 days after implantation did not reveal signs of a systemic inflammatory reaction. WBC counts ($5.30\text{--}9.79 \times 10^9/\text{L}$) were within the physiological norm, indicating the absence of a pronounced immune response and were consistent with the data of other authors, who also did not detect elevation of inflammatory markers in animals after implantation of Zn–Mg–Fe alloys [27]. The stability of RBC and HGB parameters confirms the absence of clinically significant blood loss and hemolytic effect, while a slight exceedance of the upper limit of the reference range may be explained by individual characteristics of the animals' hydration status. According to the result of another work, the hemolysis rate for Zn–1.2Mg alloys was less than 2%, which is below the limit value of 5% established by ISO 10993-4 [24, 28]. Taken together, these data confirm that Zn–Mg alloys do not cause a pronounced systemic inflammatory and toxic response *in vivo*.

CT data at 3 months demonstrated preservation of implant position and absence of signs of migration, indirectly confirming sufficient residual mechanical strength in the early post-implantation period. Bone density values (CBD 642.5–655 HU; TBD 505–517 HU) were comparable to intact bone, indicating the absence of osteolytic changes. This is consistent with literature data. In particular, with the report that a statistically significant increase in new bone area was observed in the Zn–0.8Mg group compared to pure Zn, as well as an increase in bone–implant contact, indicating improved osteoconductivity of the material [24].

At 10 months after implantation in our study, the implant was still visible at its original placement site, which is consistent with the data of other authors, who reported stable implant position for 120–360 days after surgery. The authors also described the absence of signs of implant encapsulation and peri-implant bone destruction according to micro-CT data [29]. The fact that a minimal amount of free gas was released in the peri-implant area indicates a reaction of magnesium in the alloy composition, which is a sign of the beginning of the material resorption process in the biological environment of the laboratory animal.

Study limitations

When interpreting the results of this study, a number of limitations related to the experimental design, assessment methods, and differences between the *in vitro* and *in vivo* stages must be considered.

The first and most important limitation concerns the difference in morphology and physical state of the samples used at different stages. *In vitro* cytotoxicity was assessed on Zn–0.5Mg and Zn–1Mg alloy powders with an average particle size of 50 to 65 μm , whereas *in vivo*, compact polished cylindrical samples (diameter 1.5 mm, height 8 mm) of alloys with 0.5, 1, 1.5, and 2 wt.% Mg were implanted. The powder form provides a significantly larger specific surface area

compared to the compact implant, leading to a more rapid and massive release of Zn^{2+} and Mg^{2+} ions into the culture medium. Essentially, the direct contact powder model represents a «stress test» that reveals threshold concentrations, whereas the compact implant *in vivo* degrades at a substantially lower rate. Therefore, a direct quantitative comparison of absolute *in vitro* cell viability percentages (*in vitro*) with any parameters of tissue response or resorption rate *in vivo* was not performed and would be methodologically incorrect. The *in vitro* data are used exclusively for qualitative comparison of the two compositions with each other and to demonstrate the dose-dependent nature of cytotoxicity.

A second limitation is the absence of direct measurements of metal ion concentrations in biological media. We did not determine Zn^{2+} and Mg^{2+} content either in the culture medium after incubation with the powders, or in the blood of experimental animals, or in the tissue fluid of the peri-implant zone. This does not allow us to establish a direct causal relationship between a specific ion concentration and the observed biological effect, nor to separate the contribution of direct cytotoxic action of ions, osmotic disturbances, and possible pH changes, especially under direct contact with the powder. Furthermore, without data on the kinetics of ion release, it is impossible to quantitatively explain why, at a powder concentration of 1.25 mg/mL, the Zn-1Mg alloy showed no toxicity, whereas Zn-0.5Mg remained cytotoxic.

Another important limitation is the lack of direct measurements of corrosion resistance and quantitative assessment of degradation rate. We did not perform electrochemical tests (potentiodynamic polarization, electrochemical impedance spectroscopy) in standardized media, did not measure implant mass loss after explantation, did not determine the depth of corrosion damage, and did not analyze the composition of corrosion products on the surface. Without these data, it is impossible to quantitatively link the observed biological effects (*in vitro* cytotoxicity, absence of osteolysis *in vivo*) to the actual rate of ion release. Moreover, the absence of pH measurements

in the culture medium during the MTT assay does not allow us to exclude a contribution of alkalization (characteristic of magnesium-containing alloys) to cell death. Thus, we cannot definitively establish the mechanism of cytotoxicity — whether it is a direct consequence of Zn^{2+} ion action, a result of pH change, or a combination of factors. In this work, we confine ourselves to describing the phenomenology (dose-dependent reduction in viability) and discussing possible mechanisms based on literature data. Future studies should include a full set of corrosion and mechanistic tests.

It should also be noted that systemic hematological parameters *in vivo* do not fully reflect local inflammatory changes and cellular reactions at the implantation site. The absence of histological analysis of peri-implant tissues significantly limits the possibility of detailed assessment of local inflammatory response, the nature of cellular infiltration, as well as the processes of remodeling and new bone formation at the micro level. Furthermore, this study did not evaluate the degradation rate of the implants, which does not allow us to quantitatively link the observed biological effects with the dynamics of material breakdown.

CONCLUSIONS

A two-stage evaluation of the biocompatibility of binary Zn-Mg alloys with 0.5–2 wt.% Mg was performed, including a screening cytotoxicity study on powders *in vitro* (0.5–1 wt.%) and an assessment of the tissue response to compact implants *in vivo* (0.5–2 wt.%). A dose-dependent cytotoxicity profile was established *in vitro*, with higher Mg content associated with a more favorable cell viability profile in the high-concentration range. *In vivo*, no signs of systemic inflammatory reaction were detected; hematological parameters remained within the physiological range, and computed tomography data indicated stable implant fixation and no pronounced signs of bone resorption during the observation period. Collectively, these results confirm the promise of further research into Zn-Mg alloys as a class of bioresorbable materials.

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