REVIEW ARTICLE

CONTENTS

Prospects of osteosynthesis with fixators based on magnesium alloys, mechanical and physiological properties. The state of the problem at the current stage

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ABSTRACT

Aim: The aim of this work is to analyze the available scientific information regarding to the prospects of metal-osteosynthesis with biodegradable fixators based on magnesium alloys.

Materials and Methods: A set of general and special methods of scientific knowledge are used in the article. Search and analysis of full-text articles and scientific publications - carried out in databases of systematic reviews of MEDLINE, PubMed, Web of Science, Google Scholar, Scopus.

Conclusions: Magnesium-based implants contribute to a tissue regeneration and healing during degradation and do not require removal. This allows you to avoid the second surgical intervention and reduces treatment costs. That is why the development and implementation of biodegradable fixators for osteosynthesis is of great importance.

KEY WORDS: magnesium alloy, bioresorbable fixators, magnesium fixators, bioresorbable alloy, biodegradable screws

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INTRODUCTION

Traditionally, metal implants are made of rust resistant steel, titanium (Ti) and cobalt-chromium (Co–Cr) alloys. Although these metals have demonstrated good biocompatibility, high wear resistance, and sufficient mechanical strength, but they have critical limitations [1].

Firstly, they are often incompatible with the physiological properties of natural bone, wear out mechanically and can cause inflammation and metallosis due to corrosion. Their use requires the second surgical intervention to remove fixators that have fulfilled their goal. In the place of implantation, tension is created due to the high Young's modulus, which is characteristic of traditional fixators for osteosynthesis. Reduction of peripheral bone density and loss of mechanical strength due to the presence of an implant increases the risk of secondary fracture. In order to overcome the large number of disadvantages of traditional implants at the present time, the leading countries of the world (USA, South Korea and Germany) are developing and clinically implementing implants made of bioresorbable materials, including metal implants based on magnesium alloys [2].

Magnesium-based implants are of particular interest because it is proved that they promote osteogenesis, angiogenesis, and neuroregeneration while oppressing osteoclast activity and inflammation [3]. Magnesium-based implants promote bone regeneration and remodeling. However, it is still unclear how magnesium affects metabolism and bone remodeling.

Magnesium is the fourth most popular cation in organism equal to approximately 1 mole (24 g) in an adult and more than 60% is accumulated in bones and teeth. Most of the magnesium that accumulates in bone tissue is concentrated on the hydrated surface layers of apatite crystals, which is promising in the development of fixators for osteosynthesis [4]. This ensures a rapid exchange of magnesium between the blood and the extracellular liquid, which leads to ion homeostasis. Magnesium has been found to be a cofactor for various enzymatic reactions related to energy metabolism, protein and nucleic acid synthesis, functional support of the parathyroid glands, and vitamin D metabolism, which are directly related to bone formation [5] . Several researchers who have studied the effects of a magnesium-depleted diet on rats have shown a decrease in

systemic bone density. Suppression of the growth of the proximal end of the tibia and even the development of osteoporosis in this group was noted [6]. In these studies, increased magnesium intake has been proven to prevent a decrease in bone mineral density (BMD) in patients with osteoporosis. It is not reported about symptoms of toxicity caused by excess magnesium, as magnesium concentration is strictly mediated by the kidneys through urinary excretion [7].

AIM

The aim of this work is to analyze the available scientific information regarding to the prospects of metal-osteosynthesis with biodegradable fixators based on magnesium alloys.

MATERIALS AND METHODS

A set of general and special methods of scientific knowledge are used in the article.Search and analysis of full-text articles and scientific publications - carried out in databases of systematic reviews of MEDLINE, PubMed, Web of Science, Google Scholar, Scopus.

REVIEW AND DISCUSSION

Studies [8] have shown that when the concentration of magnesium ions reaches the appropriate range (it means, 50–100 parts per million), it is able to enhance the viability of osteoblasts. It was found that the specific activity of alkaline phosphatase (AL) of osteoblasts cultivated on environments supplemented with Mg ions was significantly higher compared to the control. Real-time RT-PCR research also demonstrated higher expression levels of ALP and transcription factor - 2 (Runx2) after stimulation with appropriate amounts of Mg ions. The highest expression levels of collagen type I (Colla 1) and osteopontin (Opn) were detected on the third day in cells cultured in conditioned medium [9].

In other studies, magnesium was added to different types of materials, including hydroxyapatite and tricalcium phosphate, and then the biological activity of these materials was investigated and compared to a control. When apatite in collagen was completely replaced by magnesium, a toxic effect was observed in the form of inhibition of the extracellular matrix [10]. However, when the amount of magnesium fluctuated in the appropriate range, the formation of the osteogenic matrix, as well as the attachment to cells of osteoblasts, on the background of the synthesis of alkaline phosphatase, increased. An increase in osteogenic activity in vivo was also recorded [11].

Although the mechanism of influence of magnesium ions on fracture healing has not yet been fully investigated, the understanding of this mechanism has been significantly deepened in recent works. In particular, in the studies conducted by Yoshizawa etc. [12]it is suggested that the osteoregenerative effect of magnesium on undifferentiated stromal cells of human bone marrow (hBMSC) and osteogenic hBMSC is probably connected with the following organized reactions: 1) activation of hypoxia-inducible factor 2 a (HIF-2 a) and peroxisomes ; 2) gamma coactivation of the proliferator-activated receptor (PGC)-1a, accordingly.

Zhang et al. has found that rat bone marrow stem cells (BSCs) show significantly reinforced expression of integrin-a-5-b-1 when cultured with 5% calcium phosphate cement which contains magnesium (5MCFC), and accordingly promote osteogenic differentiation, whereas this effect was not observed when cultured with 10MCFC and 20MCFC. More recently, Zhang et al. demonstrated that magnesium ions can stimulate calcitonin-induced accumulation of neuronal polypeptide (CGRP) in both the peripheral cortex of the femur and the ipsilateral dorsal root ganglia (DRG), thus promoting fracture healing in a rat animal model [13].

This study revealed an uncertain role for Mg-2þ in CGRP-mediated osteogenic differentiation. In another study devoted to the long-term mechanism of magnesium alloy degradation in vivo, Makkar P. et al. found that the use of biodegradable fixators based on magnesium can promote the crystallization of calcium phosphate in a rabbit femoral condyle fracture model [14]. All these reports have emphasized one more time the importance of magnesium for fracture healing and indicate its therapeutic potential in bone fracture regeneration in orthopedic clinics.

Bone metabolism includes both the formation of bone tissue and its destruction. It is the dynamic balance of osteoblasts and osteoclasts that supports the stability of bone tissue regeneration. Currently, the factors that mainly affect osteoclast differentiation and osteoresorption are PI3K-Akt and OPG-RANK-RANKL signaling. Recent studies have shown that inhibition of PI3K-Akt signaling activity reduces osteoclast resorption [15]. While different concentrations of magnesium ions can regulate PI3K-Akt signaling in osteoblasts [16]. However, the OPG-RANKL-RANK signaling pathway promotes bone resorption. Gene transcription for osteoclast differentiation requires M-CSF and RANKL, which are released by osteoblasts. This indicates that a certain degree of differentiation and functional activity of osteoblasts contributes to the activity of osteoclasts [17].

Magnesium-based implants release its ions, which leads to an increase in local concentrations. When the appropriate concentration is reached, the PI3K-Akt signaling pathway is activated to promote osteogenic differentiation. Osteoblast differentiation leads to the secretion of RANK and M-CSF to induce osteoclast differentiation, which explains the coexistence of bone formation and bone resorption in the early stages after implantation of magnesium-based fixators. However, additional experiments are still needed to confirm this assumption. There is an opinion that simultaneous bone formation and bone resorption accelerates remodeling and promotes bone formation, which allows to increase the rate of callus formation [18].

Magnesium-based implants promote tissue recovery and regeneration during degradation and do not require removal. This allows to avoid the second surgical intervention and reduces treatment costs. It has been proven that magnesium can promote osteogenesis, angiogenesis, and neuroregeneration while inhibiting osteoclast activity and inflammation [19].

Most of the clinical researches are focused on the benefits of uses of magnesium, such as the stimulation of osteogenesis and angiogenesis. For example, Wang Z, et al. used magnesium-based implants in an experimental rat osteonecrosis model. The regenerative potential of implants based on magnesium alloys was proven [20]. Some investigators have attempted to use magnesium-based screws in anterior cruciate ligament reconstruction, but the strength of magnesium-based screws in such injuries remains questionable.

Lee J.W. et al. analyzed the voltage in the screw head and successfully improved its construction, which solved the key point of the clinical use of screws based on magnesium alloys [21]. Magnesium-based metal implants also show benefits in restoring bone fracture healing in elderly patients and in osteoporosis. Lin etc. added magnesium particles to clinically used polymethyl methacrylate (PMMA) bone cement to give it osseointegration, angiogenic, and anti-infective properties [22].

Bioactive magnesium metal powder has also been included into a composite of bioactive carcass that is made to repair large bone defects [23]. Recent studies have shown that, due to surface modification, corrosion properties decrease and biocompatibility of magnesium alloy implants increases [24]. One of the approaches is to significantly increase the corrosion resistance of magnesium alloys due to sol-helium and polyester-based synthetic coatings. For example, Zhang et al. developed a new double-crosslinked hydrogel with Mg ions by photocrosslinking gelatin methacryloyl (GelMA), thiolated chitosan (TCS) and modified polyhedral oligomeric silsesquioxane (POSS) nanoparticles with subsequent inclusion of magnesium ions through MgS coordination connections [25]. Researchers have used more than two approaches to successfully improve the corrosion properties and biocompatibility of magnesium-based implants, opening a new way to prepare biodegradable fixators [26].

Li et al. modified the inner layer of Mg(OH)2 with a nanocoating by introducing stearic acid (SA), which improved the adhesion strength between the outer and inner layers, avoiding the penetration of corrosive environment [27]. In a similar way, to improve the corrosion resistance and biocompatibility of magnesium alloys, Cheng et al. tested a Mg-Al layered double hydroxide (LDH) coating on the surface of pure magnesium and demonstrated not only greater corrosion resistance, but also improved osteogenic, angiogenic, and anti-inflammatory activity and better osseointegration in vivo than pure magnesium [28].

The use of other nanocoatings to improve the biocompatibility and degradation resistance of magnesium alloy was reported in another work [29]. Lin et al. used TiO2/Mg2TiO4 nanocoating on the outer layer of magnesium alloy to improve its biocompatibility and resistance to bacterial infections [30]. Also Liu et al. found that a lithium-bound nanoporous coating provides a magnesium alloy with increased corrosion resistance, and also promotes angiogenesis and bone formation [31].

Gao et al. used calcium phosphate to improve the biocompatibility and stability of the magnesium alloy [32]. Razavi et al. extended this approach using a new bioceramic nanocomposite coating that resulted to reducing corrosion rate and improved new bone formation while reducing inflammation at the border of implants and surrounding tissue [33]. Other authors achieved an increase of resistance to degradation and bactericidal activity by inputing graphene nanoparticles into a magnesium alloy [34]. Numerical studies also emphasize the improvement of corrosion characteristics of natural polymer coatings due to the inclusion of synthetic polymers. In addition, sol-gel and synthetic polyester coatings have demonstrated the ability to act as local drug delivery platforms [35]. Chen et al. produced a coating filled with zoledronate on the surface of an AZ31 magnesium alloy. The results showed that it has better corrosion resistance, and zoledronate may also play a role, confirming the possibility of its easy and effective use in the clinic [36]. It should be noted that researches in this field are very limited. In addition, there were attempts to make alloys in metallic glass to improve corrosion resistance [37]. With the development of materials science, more and more researchers used

nanocomposites to increase the corrosion resistance and biocompatibility of magnesium alloys [38]. The key problem, however, remains the dynamic balance between the rate of degradation and recovery of bone tissue.

The mechanical strength, corrosion resistance, and biocompatibility of magnesium alloys have also been shown to be improved by surface modification. However, cytotoxicity tests were not included in most known studies [39]. Based on the analysis of available sources, it was found that, unlike an inert metal, there is no unified standard for assessing metals for cytotoxicity in biodegradable fixators. Observation of tissue changes in the place of installation of implants requires further investigation.

In general, magnesium and its alloys have excellent biocompatibility with bone tissue. As a result, magnesium has become widely used in the field of biomaterials as a biodegradable and bioabsorbable material for medical usage. There are various methods of controlling the corrosion of magnesium, such as cleaning, anodizing, alloying (fusing) metals, and coating the surface with various materials. Studies have shown that magnesium purification significantly reduces corrosion [40]. But chemically pure magnesium has weak mechanical properties, it is very brittle and not strong in breaking. Magnesium alloys with different elements offer the opportunity to increase the mechanical strength of pure magnesium, but the alloying elements must be carefully selected to maintain biocompatibility and increase the corrosion resistance of magnesium.

CONCLUSIONS

The use of fixators made of magnesium alloys during osteosynthesis of bone fractures does not require the second surgical intervention with regard to remove the fixators, which have fulfilled their goal. Magnesium alloys are light and have one-third the density of titanium fasteners. Magnesium-based implants contribute to osteogenesis, angiogenesis, neuroregeneration, regeneration and remodeling of bones at the same time inhibiting osteoclast activity and inflammation. Magnesium and its alloys have excellent biocompatibility with bone tissue. Magnesium-based implants contribute to a tissue regeneration and healing during degradation and do not require removal. This allows you to avoid the second surgical intervention and reduces treatment costs. That is why the development and implementation of biodegradable fixators for osteosynthesis is of great importance.

Overall, several challenges remain to be resolved for the clinical usage of magnesium-based biodegradable osteosynthesis fixators.

Firstly, it is necessary to control the degradation rate of magnesium fixators and maintain the desired mechanical properties throughout the treatment period to support tissue healing.

Secondly, in vivo animal limb experiments still can not reproduce the assessment of workload required for interventions in patients. In the future, it is likely that experiments on primates will be necessary to obtain better evaluation data.

Thirdly, the question of reducing gas formation of magnesium-based implants in vivo still needs further researches.

Fourthly, there is still no appropriate system for biological assessment of in vitro and in vivo effects on cells for biodegradable alloys.

That is, the issue of efficiency and safety of magnesium alloys has been considered in a number of studies in recent years. The use of magnesium alloys in fixators for bone osteosynthesis provides an economical improvement and a possible solution for the consolidation of bone fractures.

When the therapeutic effect and mechanism of action of biodegradable fixators are clearly understood, then the development of clinical protocols will be possible. That is why the search for components and the study of the effect on the regeneration of bone tissue with the use of implants based on magnesium alloys is quite relevant.

However, the clinical usage of magnesium-based implants is still in the research and development stage. The metabolism of magnesium ions in bones is not fully understood and therefore requires further research. In particular, there is currently no clear system for the biological assessment of biodegradable fixators. Therefore, the use of magnesium alloy in the clinic remains promising, but not sufficiently studied and requires further researches.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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