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Review

RESORBABLE Mg^{2+}-CONTAINING PHOSPHATES FOR BONE TISSUE REPAIR

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Abstract: Materials based on Mg^{2+}-containing phosphates are gaining great relevance in the field of bone tissue repair via regenerative medicine methods. Magnesium ions, together with condensed phosphate ions, play a significant role in the process of bone remodeling, affecting the early stage of bone regeneration through active participation in the process of osteosynthesis. Here we provide a comprehensive overview of the usage of biomaterials based on magnesium phosphate and magnesium calcium phosphate in bone reconstruction. The role of magnesium ions in angiogenesis, an important process associated with osteogenesis, is considered. Finally, the biological properties of magnesium phosphates for bone regeneration are summarized. They show promising results in terms of use as bone replacement material.

Keywords: whitlockite; calcium magnesium phosphates; struvite; newberrite; bone reconstruction; resorbability; bioactivity; orthopedic applications

1. Introduction

There is a great interest in bioresorbable materials for tissue engineering in modern surgery. Materials similar to native bone tissue are promising. However, in reconstructive surgery and orthopedics, titanium-based metals and their alloys or stainless steel are widely used as orthopedic implants. The main limitations in the use of these metals are due to their undesirable mechanical properties, leading to serious problems of bone remodeling [1,2]. Thus, the absence of degradation of these materials requires a second operation to remove the implant, and the release of toxic ions as a result of corrosion and microparticles due to material wear can cause inflammatory osteolysis [3–6]. With long-term use of metal implants and prostheses, there is a high concentration of prosthetic metal particles in the synovial fluid and tissue around the implant, which is the result of the continuous release of metal particles from the implant under mechanical stress [7,8]. Although non-degradable metal implants are generally considered non-toxic, some of their components can contribute to the development of neoplasms [9]. To date, cases of the development of osteosarcomas in patients after implantation of metal endoprostheses have been described [10]. Thus, there is a need to search for biomaterials for new generation implants, which, having the necessary strength characteristics, are biodegradable and do not require repeated surgical interventions for their extraction. The development of such materials will make it possible to shorten the period of restoration of working capacity, as well as to improve the quality of life of the population. In regenerative medicine, biomaterials including magnesium and its compounds are relevant and promising for the creation of resorbable biologically active materials in modern implantology [11–14]. Magnesium alloys have a wide range of properties for these purposes, such as Young's modulus close to the properties of human bone, lack of toxic effects on the body, biodegradation, in addition, magnesium is integrated into the lattice of bone tissue hydroxyapatite and takes part in the processes of cellular metabolism. When ingested, magnesium forms

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chelate-like bonds with many organic substances, thereby ensuring the participation of more than 500 enzymes in metabolic processes - creatine kinase, adenylate cyclase, phosphofructokinase, NAD + kinase, K+ -Na+ -ATPase, Ca-ATPase and many others. Thus, magnesium in the form of coenzymes directly or indirectly participates in the processes of glycolysis, the Krebs cycle, oxidative phosphorylation, protein synthesis, the cycle of urea, glucose and citric acid, metabolism of nucleic acids, lipids, etc. [15]. Therefore, the need for secondary surgery to remove the implant can be eliminated [16–18].

Due to its mechanical properties close to human bone, magnesium allows eliminating the effects of shielding stress, which contributes to improved biocompatibility of the implant with bone tissue. However, magnesium implants have low corrosion resistance in the chlorine-containing environment of the body, where later there is a premature loss of mechanical properties before the onset of complete recovery of the bone fracture. In connection with this problem, the most developing at present is a regenerative approach aimed at restoring the body's own bone structures by means of osteogenesis. It is believed that the body itself can restore lost tissues if certain conditions are created for this. Without external intervention, the cavities are overgrown with fibrous tissue, which has low strength and prevents the transport of nutrients through it, it encapsulates the area of the defect. One of the approaches to prevent the formation of fibrous tissue in the defect area is to fill it with osteoconductive material, which will be a source of phosphate and calcium ions in the defect area. Since the inorganic part of human bone consists of hydroxyapatite (HAP: $Ca_{10}(PO_4)_6(OH)_2$) and whitlockite (WH: $Ca_{18}Mg_2(HPO_4)_2(PO_4)_{12}$) [19]. Preference is given to materials based on calcium and magnesium phosphates due to their chemical proximity to the mineral component of bone tissue, lack of toxicity and biocompatibility. Due to defects in the body, there are complex forms and it is convenient to use materials to fill them, to take the form of a defect. These materials include magnesium phosphate cements (MPC), which have several advantages - ease of use during the operation, the ability to be resorbed in the body. Recent studies in the field of materials intended for reparative osteogenesis are focused, in terms of the characteristics of the research object, on porous bioceramics, which, on the one hand, is a scaffold for various cells, with biological activity (growth factors, hormones, antibacterial substances, antioxidants and etc.) that are released in the environment at a controlled rate. On the other hand, the material must be biocompatible, resorbable, have a system of pores of different modalities (these properties are related to such characteristics as osteoconductivity) and have sufficient strength throughout the entire period of functioning (implantation and integration into the bone). For the regeneration of bone tissue, ceramics with an ionic type of chemical bond based on calcium phosphates are widely used. However, despite the excellent bioavailability, these substances are not sufficiently resorbable, which does not meet the requirements of a regenerative treatment approach. The use of magnesium phosphates implies a greater solubility of the material in comparison with hydroxyapatite and tricalcium phosphate. Despite the smaller radius of the Mg^{2+} ion in comparison with Ca^{2+}, the large hydration enthalpy of the magnesium cation overlaps its contribution to the strengthening of the crystal lattice energy, thereby increasing the phosphate solubility. In addition, possessing special biological functions (suppression of proliferation, osteoclasts and the ability of proliferation and adhesion of osteoblasts), magnesium can shift the balance of bone tissue remodeling towards osteosynthesis.

The increase in the average life expectancy of the population and its growing medical needs have led to research work in search of new materials for bone tissue regeneration with qualitatively improved properties.

2. The role of magnesium in the human body and its inducing influence on bone regeneration

In the human body magnesium is distributed irregularly: 65% is an inherent part of the hydroxyapatite lattice in the inorganic bone matrix, 34% remain in the intracellular space and 1% in the extracellular space [20,21]. In cells, magnesium ions occupy the

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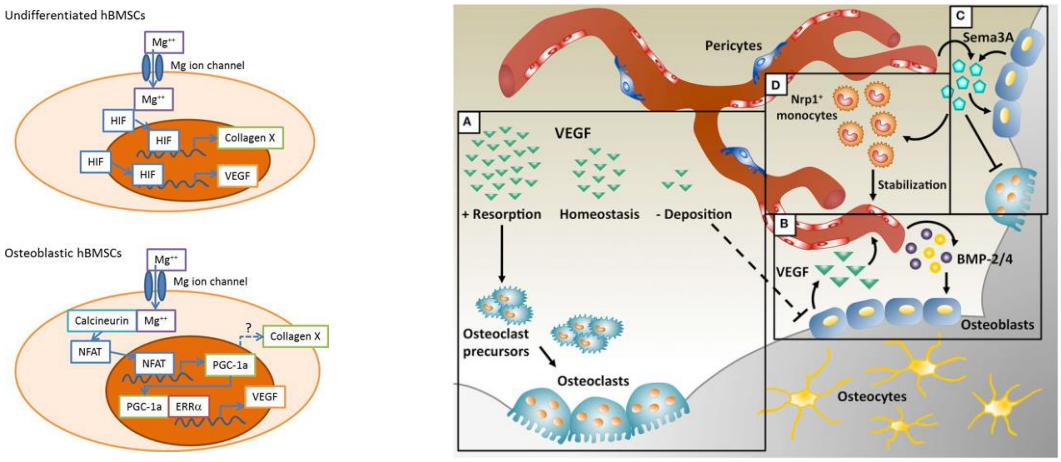
second place after potassium ions and, combining into complexes (80-90%), provide metabolic processes. They are also distributed to all cellular structures (nucleus, mitochondria, cytoplasmic reticulum, cytoplasm). The concentration of intracellular magnesium is maintained at a constant level, despite fluctuations in the ion level in the extracellular space. This is due to the relatively limited permeability of the plasma membrane for the cation and the presence of a magnesium transport system [22–25].

Magnesium is involved in the regulation of intracellular supply and excretion of calcium through calcium and magnesium-dependent ATPase. It also reduces the release of energy, which is necessary for the penetration of calcium into the cisternae, thereby causes a weakening of the interaction of the contractile proteins actin and myosin in myofibrils and their sliding along one another in the presence of ionized calcium [26]. Magnesium affects the activity of osteoblasts and osteoclasts [27], the concentration of parathyroid hormone, the active form of vitamin D [28], which are the main regulators of bone homeostasis [15]. Yoshizawa et al. [29] reported that the addition of 10×10^{-3} m of magnesium in cell cultures of human bone marrow stromal cells (hBMSC) and differentiated osteoblasts enhance mineralization of the extracellular matrix (ECM) by increasing the production of collagen-X and growth factor vascular endothelium (VEGF). They further demonstrated (Figure 1a) that Mg- increased VEGF is co-regulated by hypoxia inducible factor 2a (HIF-2a) in undifferentiated cells (hBMSCs) and peroxisome proliferator- activated receptor gamma- coactivator (PGC)-1a in differentiated (hBMSCs).



(**a**) (**b**)

Figure 1. (**a**) Schematic diagram of the putative intracellular signaling cascades upon stimulation of hBMSC with magnesium ions. The addition of a magnesium cation causes an increase in the intracellular Mg ion concentration in undifferentiated BMSCs. The HIFs then migrate to the cell nucleus and induce the production of COL10A1 and VEGF. On the other hand, in differentiated BMSCs, the Mg ion activates the production of PGC-1α (via an unknown transcription factor), which induces the production of VEGF. Adapted with permission [29]. Copyright 2014, Elsevier. (**b**) Combination of angiogenesis and osteogenesis in intramembranous ossification. (A) Physiological levels of vascular endothelial growth factor (VEGF) maintain bone homeostasis, whereas too small s VEGF interrupting w t differentiation of osteoblasts, and too much VEGF increasing w t recruitment of osteoclasts resulting in bone resorption. (B) During bone repair, VEGF is produced by osteoblasts and promotes migration and proliferation of endothelial cells. In turn, endothelial cells secrete osteogenic factors such as bone morphogenetic protein (BMP) -2 and BMP- 4, which support osteoblast differentiation. (C) VEGF dose-dependently regulates the expression of Sema 3 A in endothelial cells, while Sema 3 A from various sources inhibits osteoclast differentiation and stimulates bone deposition. (D) Sema 3 A is also responsible for a set of neuropilin-1 (Nrp 1 +) expressing monocytes that contribute to vascular stabilization [30].

On the one hand, vascular endothelial growth factor (VEGF) is a major regulator of vascular growth and is required for the effective coupling of angiogenesis and osteogenesis during postnatal bone repair [30–34]. On the other hand, VEGF also inhibits osteoblast differentiation and competes with platelet-derived growth factor (PDGF-BB) for binding with PDGF-Rs (proteins that regulate the proliferation, differentiation and growth of cells). It deteriorates the function of pericytes, which leads to formation of immature blood

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vessels and interrupts communication of angiogenesis and osteogenesis [35–39]. VEGF may have opposite effects on bone physiology under various circumstances (Figure 1b).

Recently Huang et al. [40] found that an additional 10×10^{-3} m magnesium cation can activate the canonical signaling pathway Wnt (one of the most important signaling pathways in the cell which is necessary for normal differentiation and maintenance of the phenotype of stem cells). It also can significantly increase the expression of β- catenin and it`s downstream genes (LEF1, DKK1), which, in turn, forces hBMSC to differentiate into the direction of the osteoblast lineage and causes an osteogenic effect. Also, Hamushan et al. [41] reported that the magnesium cations are enhancing the consolidation in distraction osteogenesis through regulation of PTCH protein by activating the Hedgehog (Hh) signal transduction pathway. That is an alternative Wnt signaling pathway. Magnesium derived from implants improves rats bone fracture healing by promoting neurological production of CGRP (calcitonin- associated peptide) [42,43]. Xu at al. were the first to display [44], that osteogenic effect of magnesium can directly affect bone cells, particularly osteocytes. Extracellular Mg^{2+} via magnesium transport / channels (e.g. TRPM6, TRPM7 and MAGT1) enters bone cells. That leads to a subsequent increase in the level of intracellular cAMP for ATF4-dependent Wnt / β- catenin signaling activation in bone cells (Figure 2). Mg^{2+} deficiency (approximately 0.04 – 10%) enhances osteoclastogenesis [45,46].

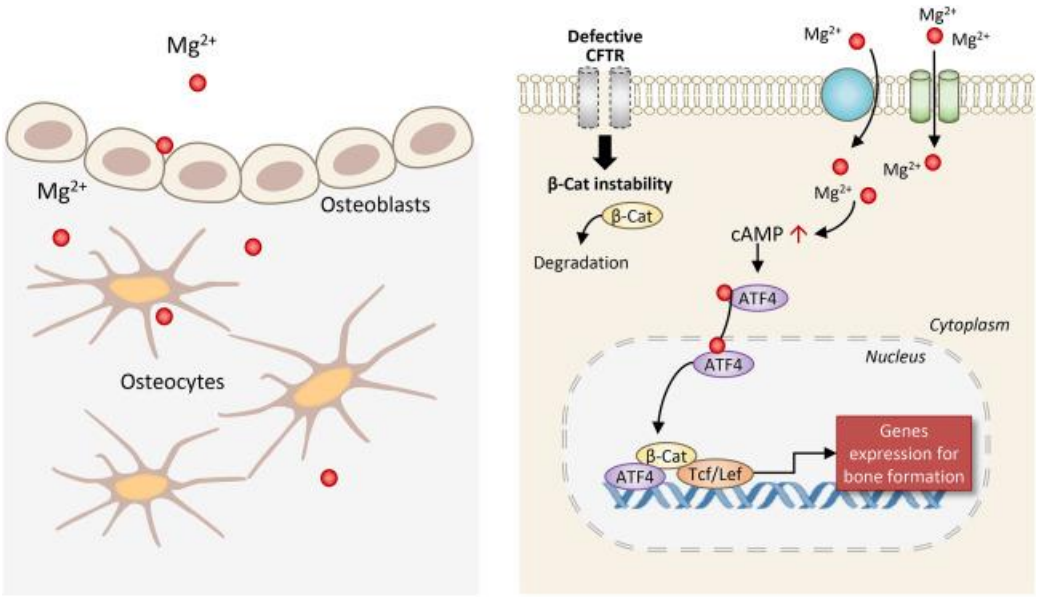

Figure 2. The effect of magnesium on bone formation with CFTR deficiency. Magnesium ions enters bone forming cells through Mg^{2+} channels or transporters. Mg^{2+} induces cAMP increase and the activation of transcription factors, ATF4 and β -catenin (β -Cat), rescuing CFTR- deficiency-impaired Wnt / β -catenin signaling to promote bone formation [44].

Zhai et al. discovered [47], that magnesium ions inhibit the differentiation of osteoclast precursors by inhibiting NF- κB and NFATc1. Mg^{2+} also involved in osteoimmunological reactions by contributing polarization of macrophages towards the M2 phase (which promotes tissue regeneration), in lieu of M1 phase (which contributes to the inflammatory response) [48–51]. Generally, magnesium takes a multifunctional role in bone growth and regeneration. Magnesium is necessary at all stages of a protein molecule synthesis; protein synthesis decreases with depletion of intracellular Mg^{2+} ions reserves. Magnesium maintains an adequate supply of pyridine and pyrimidine nucleotides what is necessary for the DNA and RNA synthesis. It acts as a physiological regulator of cell growth [52,53].

The participation of the magnesium ion in human metabolic processes is also determined by physicochemical characteristics. They include a relatively small ionic radius (0.86Å versus 1.14Å for Ca^{2+}), high mobility and charge density (so Mg^{2+} usually coordinated by 6-7 H_2O molecules), It is a hard Lewis acid and therefore has a high affinity for

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hard bases - oxygen-containing ligands such as water, carbonates, sulfates and phosphates [54]. The magnesium ion has two hydration shells, which makes the radius of the solvated ion larger than that of other cations (Ca^{2+}, Na^{+}, K^{+}). This ion has high hydration energy (≈456 kJ/mol) and a fairly stable coordination number (usually six), implying an octahedral configuration of the first coordination sphere of the ligands. Thus, magnesium, in comparison with the other, most abundant Ca^{2+} ion, wins its competition in many biological processes [23]. In addition, magnesium hydroxide is a weaker base ($K_b=2.5\cdot10^{-3}$) in comparison with calcium hydroxide ($K_b=4.3\cdot10^{-2}$) [23], which creates a less alkaline environment during the hydrolysis of the corresponding salts; this is important in case of a large release of these ions in biological fluids to overcome such a phenomenon as alkalosis.

Magnesium is an extremely light metal. With a density of 1.74 g/cm^3, magnesium is 1.6 and 4.5 times less dense than aluminum and steel, respectively [55]. Magnesium's breaking strength is higher than that of ceramic biomaterials such as hydroxyapatite, while the Young`s modulus and compressive yield strength of magnesium is closer to those of natural bone than other commonly used metal implants. Mg^{2+} affects the overall rate of crystallization of amorphous calcium phosphate and the subsequent growth of hydroxyapatite (HA) [56]. The inclusion of magnesium in hydroxyapatite structure reduces crystal size and crystal order by replacing calcium with magnesium [57], So Mg- based implants application can improve the strength of the new bone at the implantation site. Mg- substituted HAP exhibits high bioactivity and increased osteoconductivity and osseointegration, as an extracellular inorganic matrix [58–60]. During the degradation of Mg-based implants, the temporarily stored magnesium ions in the implantable bone matrix can be gradually released into the circulatory system without affecting the concentration of magnesium ions in the blood serum [57]. The concentration of magnesium in the blood serum (0.65-0.95 mmol/l) remains at a normal level for a long time, despite the deficiency of the ions in the tissues. The lack of correlation between the level of serum magnesium and the total content of magnesium in the human body is explained by the fact that ions coming from bones compensate for the decrease in the amount of magnesium [22]. Changes in plasma magnesium levels occur in case of significant long-term depletion of the ion store. Thus, magnesium is an essential element not only in the human body, but it also necessitates the development of Mg-based biomaterials, capable of mediating the controlled delivery of magnesium ions.

Around 1938, McBride conducted a large number of trials to investigate the potential clinical usage of magnesium implants. Taking into account the characteristics of magnesium, he developed several methods of work. He also indicated that Mg-based implants are more suitable for use as fixation devices for autogenous bone grafts [61]. Besides, Liu et al. [62] noted that the heat-treated magnesium alloy showed improved maintainability since the remaining defect size was smaller than that of the untreated magnesium alloy. This may be due to the improvement in the corrosion resistance of the magnesium alloy by heat treatment. Brar et al pointed out [63] that the mechanical properties of magnesium were significantly improved when the grain size of the matrix was reduced with the addition of strontium. To investigate the effect of elevated extracellular magnesium on human osteoclasts, Wu et al. exposed cultures to various concentrations of magnesium (from magnesium chloride or magnesium extract). Thereby the degradation effect of the magnesium alloy was simulated. It was found out that magnesium chloride initially promoted and then slowed down the development of proliferation and differentiation of osteoclasts, depending on the concentration, while magnesium extract, apparently, reduced the metabolic activity of osteoclasts [64]. It was showed that magnesium extract at certain concentrations has a positive effect on the formation of osteoblasts, but a suppressive effect on the differentiation of osteoclasts [27].

3. Magnesium Phosphate-based Bone Cements

Magnesium phosphate-based bone cements have a wide range of applications in medicine as synthetic bone substitutes due to outstanding properties such as self-aligning ability, high initial strength, excellent adhesion and degradability [57,58]. Besides, other

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researchers emphasize that these materials are promising as a bone replacement in accordance with the degradability and ability to regenerate bone in orthopaedic sheep implant models [65]. Despite the valuable properties of magnesium phosphates, these materials have properties that significantly affect the usage of materials such as their lack of macroporosity, poor drug release properties, poor drug delivery properties what limit their use [66]. However, there are some ways to improve the performance of magnesium phosphate cements.

Zhao et al [67]. were aimed at improving the physicochemical and biocompatible properties, biodegradation and drug release of composites through the use of varying degrees of crosslinking of gelatin microspheres into bone cements based on magnesium phosphate. In addition, composites of macroporous magnesium phosphate-based bone cements with sustained drug release, built by crosslinking with gelatin microspheres, have demonstrated excellent viability and stimulating effects on proliferation, osteogenesis differentiation, mineralization capacity and gene expression (COL I, OPN and Runx2) of MC3T cells and also showed a strong potential for promoting angiogenesis. To summarize, the addition of gelatin can provide a suitable environment for cell growth and lead to an improvement in proliferation, osteogenesis differentiation and the ability to mineralize MC3T3-E1 cells [68], [69]. It should also be noted that it was the gelatinous microspheres that accelerated the degradation of macroporous bone cements based on magnesium phosphate. While comparing samples containing different degrees of crosslinking, it is observed that the degradation rate decreases with an increase in the degree of crosslinking [70]. Through this work, it was revealed that it is possible to improve the disadvantages of macroporous magnesium phosphate-based bone cements with low porosity and poor drug release properties. According to the described results of the study, it was found that the addition of gelatin made the degradation of the pH of composites of macroporous bone cements based on magnesium phosphate more consistent with the physiological environment of humans [71].

It is believed that the most important factor affecting the rheological properties of magnesium phosphate cements is the initial hydration rate. It was found out that an increase in the interparticle film thickness increases the distance between solid particles and reduces friction between particles. As a result, the yield strength decreases, therefore the liquid state among the solid particles is the main factor for the rheological properties of magnesium phosphate cements. It was noted that the more dispersed the particles in the system, the higher the absolute value of the zeta potential, the more stable the system, but the dispersion can resist aggregation. However, an opposite phenomenon is observed, which consists in the fact that the lower the absolute value of the zeta potential, the more likely it is that the system should solidify.

Ma et al. [72] report about the influence of the Mg / P ratio in the rheological properties of magnesium phosphate cements. It was found out that the thickness of the water film decreases significantly with increasing Mg / P ratio, indicating that a higher Mg / P ratio decreases the separation distance between solid particles. Based on the presented experimental data, it can be noted that the change in the yield point and plastic viscosity lends itself to an initial decrease and then a gradual increase, depending on the increase in the Mg / P ratio from 2.5: 1 to 4.5: 1. It should also be noted that the author was able to reveal that a higher Mg / P ratio reduces the interparticle water film and its thickness and significantly accelerates the initial rate of hydration, which is responsible for changing the rheological parameters. The Mg / P ratios can also affect the zeta potential, which changes insignificantly. It can hardly explain the mechanism of the Mg / P ratio of rheological parameters. Therefore, electrostatic force is not the main factor affecting rheological properties of magnesium phosphate cements with different Mg / P ratios.

4. Whitlockite synthesis and its bone remodeling features

Hydroxyapatite is known as the most thermodynamically stable phase at near-neutral pH values [73]. Whitlockite is a biologically important phase in bone tissue. However, difficulties can appear in the synthesis of this compound, since this phase is

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thermodynamically stable in a narrow area. Whitlockite exists in biological systems and can be precipitated under acidic conditions, it can be synthesized in the form of nanoparticles below boiling point of water. It has a higher stability than hydroxyapatite at pH below 4.2. In addition, it has been suggested that the incorporation of magnesium into whitlockite may be one of the reinforcing factors. The influence of this factor has been previously studied in other Mg- doped calcium phosphate systems. For example, the adhesion, proliferation, expression of genes associated with bone mineralization, and the amount of calcium-containing mineral osteoblast deposits, grown on Mg-doped calcium phosphate compounds, increase was observed [74–77].

Jang et al. also performed research [78], which consists in studying the properties of whitlockite and assessing its biocompatibility. Due to the fact that the theoretical composition of whitlockite is in the area with a strong preference for the precipitation of hydroxyapatite, the synthesis of whitlockite in the ternary system $Ca(OH)_2$-$Mg(OH)_2$-H_3PO_4 is difficult. The method of synthesis was suggested. Whitlockite was synthesized by adding an appropriate amount of H_3PO_4 dropwise at a rate of 12.5 ml/min into solution of Ca(OH)2 and Mg(OH)2 that was prepared at the suggested ratios of hydroxides. The heat was applied between 60° -90°. According to the results of the study, pure white nanoparticles were synthesized. They show excellent biocompatibility, which was comparable to hydroxyapatite. To summarize, the better biocompatibility of whitlockite can be caused by many factors, such as nanostructure, mechanical hardness and roughness. Studies have demonstrated that cells grown on a whitlockite granule showed an even better state of proliferation than the level of cell growth on a hydroxyapatite granule.

In addition, in the process of bone remodeling, osteoclasts create an acidic environment that mobilizes pre-existing minerals with a characteristic phase similar to hydroxyapatite [79,80]. Unlike hydroxyapatite, whitlockite is relatively stable in acidic environments. It is argued that the increased content of whitlockite in adolescent bone allows to suggest that it can actively participate in the process of bone remodeling [81,82].

Kim et al. [83] reported that the dynamic phase transformation from whitlockite to hydroxyapatite contributes to the rapid regeneration of bone with a denser hierarchical nonosseous structure. Structural analysis confirms this fact. In the course of the study it was shown that whitlockite minerals have the ability to continuously release an increased level of magnesium and phosphate ions compared to hydroxyapatites under physiologically significant conditions. Improved protein adsorption on whitlockite minerals was also confirmed by the in vivo test results, which showed a higher amount of the organic bone formation matrix in whitlokite –based chondroitin sulfate gel implants, than in hydroxyapatite-based chondroitin sulfate implants. Whitlockite can induce bone regeneration through phase transformation not only quantitatively, but also qualitatively. According to the results of the study, it was obtained that whitlockite minerals stimulate bone regeneration, so they can be used for bone healing, and the contribution of inorganic minerals in the process of bone remodeling is expressed in acidic pH conditions.

Difficulties arise in the synthesis of whitlockite since hydroxyapatite easily precipitates from calcium ions and phosphate ions at neutral pH. It has been found that the pure phase of whitlockite nanoparticles can be precipitated in an acidic aqueous system where there is an excessive amount of magnesium ions. The stability of hydroxyapatite decreases under acidic conditions and Mg^{2+} ions are too small to maintain the crystal structure of hydroxyapatite, thereby preventing its precipitation [84–86]. Hydroxyapatite and whitlockite can be transformed into each other through dissolution and re-precipitation processes in the long term by controlling pH [86]. While hydroxyapatite has higher stability under physiological conditions than whitlockite, whitlockite has the superior osteogenic ability [78,83,87]. Even though whitlockite, due to its high solubility, which is greater than that of hydroxyapatite, gradually dissolves under physiological conditions, it can maintain its material phase, mass and shape for several months both in vitro and in vivo [78,83,87]. Whitlockite bioceramic implants showed a faster resorbability than hydroxyapatite bioceramic implants both in vitro and in vivo [78,83].

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Cheng et al. [19] report that whitlockite promotes the osteogenic activity of cells more than hydroxyapatite. For example, the bone-forming activity of cells was significantly higher when their microenvironment consisted of hydroxyapatite and whitlockite in a 3:1 ratio than any other ratio. When mature osteoclasts were grown on the surface of bioceramic scaffolds of whitlockite and hydroxyapatite, the resorbed area of scaffolds of whitlockite was twice that of scaffolds of hydroxyapatite [83]. In addition, when whitlockite bioceramic implants were inserted into a rat calvarial defect model, the resorption rate of whitlockite was faster than hydroxyapatite. Moreover, synthetic hydroxyapatite had a much slower resorption rate than the regeneration rate of native skeletal tissue, probably due to its high crystallinity [88]. To conclude, hydroxyapatite maintains the mechanical stability of the composite hydrogel frameworks, while whitlockite improves the osteogenic capacity of the organic/inorganic hybrid composite framework.

5. Resorbability of phosphate-based biomaterials with different Ca/Mg ratios

Partial substitution of magnesium for calcium cations in hydroxyapatite or tricalcium phosphate (up to 2.4 wt%) is characterized by a reduced degree of crystallinity, large pore size and specific surface area [89–93]. The presence of magnesium cations in the structure reduces the parameters of the crystal lattice in accordance with its smaller ionic radius (0.065 nm), which leads to an increase in the stability of the structure and a decrease in solubility [91,94]. In this case, the substitution of Mg^{2+} for Ca^{2+} ions in TCP and HAp in an amount up to 14 mol.% occurs through the formation of a solid solution [95,96]. An increase in the substitution of magnesium for calcium up to ~ 20 mol.% lead to the formation of a weakly crystalline phase. A completely amorphous phase occurs in the range 35–50 mol.% [97–106]. Consequently, TCP and HAp doped with magnesium demonstrate increased solubility. However, Gallo et al. [107] studied the resorption behaviour of bioceramics based on undoped and Mg-doped β-TCP (1 and 6 mol%). An alternative to osteoclast culture (pH 4.4) was implemented for 1 h to determine the characteristics of the stimulation of the material for resorption. It was demonstrated for the first time that crystal orientation is a discriminator between grains that resolved first and grains that resolved slower. It is possible to regulate the kinetics of resorption by dosing β-tricalcium phosphate with the ions of interest. Magnesium doping affects the β-TCP lattice parameters and, in addition, stabilizes the β-TCP phase against dissolution. Therefore, the orientations of the crystals, which were predominantly resorbed, changed, which explains the decrease in solubility. Also, Lee et al. [108] stabilized calcium phosphates, such as brushite ($CaHPO_4 \cdot 2(H_2O)$) and tricalcium phosphate ($Ca_3(PO_4)_2$), which are thermodynamically unstable under physiological conditions, by replacing the calcium cation with magnesium. The addition of magnesium successfully stabilizes brushite in an aqueous solution at pH 7.5 for 12 hours at room temperature. The conversion of brushite to apatite usually occurs at elevated pH values. As the magnesium content increases, the surface energy of the particle decreases and the particle takes on a more spherical shape. Brushite with 14% magnesium substitution still retains a lamellar morphology, but the particles are smaller and thicker. Substitution of up to 50% with magnesium completely transforms it into a spherical nanocrystalline particle (~ 100 nm). This indicates that the brushite structure becomes poorly crystalline and/or disordered and amorphous in the presence of magnesium. Thus, stabilization of the brushite phase under physiological conditions with the introduction of magnesium opens up a number of bio-functional applications. They require the synthesis of CaP phases under physiological conditions in the presence of signaling molecules, as well as cells. This is especially useful for testing the effectiveness of brushite in delivering non-viral genes. In addition, replacing Ca^{2+} with Mg^{2+} can also stabilize β-TCP at high temperatures (up to 1600°C) [109,110]. The presence of pyrophosphate ions, due to the tendency to form complexes in solution, can also contribute to the formation of amorphous precipitates [111]. The formation of amorphous mixed calcium-magnesium phosphate was also noted during the production of bio-cement by the interaction of calcium phosphate, magnesium carbonate, and phosphoric acid [112].

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The excessive magnesium content in solution with Ca^{2+} and PO_4^{3-} can lead to precipitation of brushite and whitlockite. Boistelle et al. [113] found that initially only the amorphous phase precipitates and brushes at 37°C in urine or aqueous solutions with comparable Ca^{2+} and Mg^{2+} concentrations. Later, amorphous calcium phosphates are converted to either whitlockite or apatite, depending on the composition of the solution. It has also been shown that magnesium is a potent inhibitor of evolution towards apatite. Cheng et al. [114] observed homogeneous nucleation of unstable amorphous calcium magnesium phosphate in solutions with a concentration of [Ca] = 3 mM and [PO_4] ≤ 10 mM at 37°C and then transformation into apatite, brushite, and whitlockite (and newberite) depending on the values of Mg / Ca and [PO_4].

Wu et al. [115] investigated the phenomena of bone regeneration of the left femur in white rabbits using a new calcium-magnesium phosphate cement (CMPC). The results showed that CMPC had shorter set-up times and markedly better mechanical properties than calcium phosphate (CPC) or magnesium phosphate (MPC) cements. In addition, CMPC showed significantly improved degradation compared to CPC in the simulated body fluid. It was shown by cell culture results that CMPC is biocompatible and can support cell proliferation. These results indicate that CMPC satisfies the basic requirements of bone tissue engineering and also may have a significant clinical advantage over CPC. It may have the potential for use in orthopaedic, reconstructive, and maxillofacial surgery. Klammert et al. [116] report that a significant improvement in the properties of brushite cement is achieved through the use of magnesium-substituted β-tricalcium phosphate (general formula $Mg_xCa_{3-x}(PO_4)_2$ with 0 <x <3). It has suitable biocompatibility and improved mechanical properties compared to brushite cement. The introduction of magnesium increases the setting time of the cement from 2 min for a matrix without magnesium to 8–11 min for $Mg_{2.25}Ca_{0.75}(PO_4)_2$ as a reagent. At the same time, the compressive strength of the hardened cement is doubled from 19 MPa to more than 40 MPa after 24 hours of wet storage. Magnesium ions slowed down the brushite setting reaction and also formed newberite ($MgHPO_4{\cdot}3H_2O$) as a second setting product. In other studies [117] it is observed that excessive magnesium oxide residues lead to high pH and poor biocompatibility. Goldberg et al. [118] studied the influence of [Ca+Mg]/P ratio on mechanical properties of calcium magnesium phosphates cements. It is also confirmed that presence of magnesium oxide affects the compressive strength significantly. Besides, it leads to an alkaline reaction that affects cytotoxicity. It is reported that cements with 1.67 [Ca+Mg]/P ratio demonstrate high compressive strength up to 22 ± 3 MPa. Kowalewicz et al. [119] studied in vivo degradation, osseointegration and biocompatibility of three-dimensional (3D) frameworks of calcium magnesium phosphate cements (CMPC). After 6 weeks of implantation, the Mg225 material based on $Ca_{0,75}Mg_{2,25}(PO_4)_2$ showed greater osteointegration and volume reduction compared to Mg225d based on Mg225 treated with ammonium hydrogen phosphate (DAHP). DAHP treatment results in struvite deposition. Thus, the size and overall porosity reduce, as well as pressure stability increases. All materials showed excellent biocompatibility. They were completely intersected with new bone and the remaining scaffold material was embedded in the native bone. Based on these results, Mg225 and Mg225d appear to be promising bone substitutes for a variety of loads that should be investigated further. The effectiveness of crystallization inhibitors and modifying additives depends on the reaction conditions [120,121]. Also there is another field of interest that is representing the production and study of ceramic materials from calcium and magnesium orthophosphates [122,123]. The preparation of ceramics in the quasi-binary system $Ca_3(PO_4)_2$–$Mg_2P_2O_7$ based on powders synthesized from calcium and magnesium nitrates and ammonium hydrogen phosphate at various Ca / Mg molar ratios were studied [124]. The influence of the reaction temperature, concentration and pH of the initial solutions was mainly considered [125–128]. Kitikova et al. showed [129], that the temperature of solutions, the rate of addition of reagents, and maturation of sediments have an insignificant effect on the characteristics of calcium magnesium phosphates.

6. Conclusions

Analysis of the literature data showed that, despite the promising use of Mg^{2+}-containing biomaterials, several problems impede their clinical use. It follows that the development of new Mg^{2+}-containing biomaterials with controlled biodegradation and osteoinduction has great importance for various branches of clinical medicine. It is known that a high proliferative potential of osteoblasts is preserved on smooth matrices, but osteogenic differentiation of cells is hindered. When creating volumetric implants, the main problems are resistance to mechanical stress and osteointegration with the prevention of the formation of a fibrous capsule around the implant. Randomly organized porosity using, for example, a replica method, significantly reduces the strength of the porous ceramic material against regularly organized porosity using volumetric printing techniques. The use of modern additive technologies makes it possible in the shortest possible time to obtain a physical three-dimensional object of almost any architecture from a computer model made using computer-aided design systems. The use of this approach in the preparation of resorbable Mg^{2+}-containing biomaterials will be suitable for obtaining an osteoconductive macroporous material with sufficient strength and capable of supporting the growth of newly formed bone into the implant, due to the special architecture of the framework of the interconnected pores. This development will make it possible to create bone implants for the treatment of bone tissue defects in the form of an inorganic basis for personalized bone and tissue engineering structures.

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

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