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REVIEW  
ОБЗОРНАЯ СТАТЬЯ

### Magnetic field application in bone tissue regeneration: issue current status and prospects for method development

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**Abstract.** *Relevance.* Magnets have long been used to treat various diseases, especially in inflammatory processes. According to existing historical data, magnetotherapy was already used in ancient times by the Chinese, Egyptians and Greeks. Different magnetic field strengths affect cells in different ways, with medium-strength magnetic fields being the most widely used. The review presents a brief history and current state of the issue of using a magnetic field in bone tissue regeneration. Modern knowledge about the mechanisms of physiological and reparative regeneration, restoration of bone tissue is clarified, and modern areas of bone tissue engineering are considered, taking into account the characteristics of microcirculation and the effect of a magnetic field on the physiology of bone tissue and reparative regeneration. One of the key findings of the review is that the magnetic field improves bone tissue repair by influencing the metabolic behavior of cells. Studies show that magnetotherapy promotes the activation of cellular processes, accelerates the formation of new bone tissue and improves its quality. It is also noted that the magnetic field has a positive effect on microcirculation, improving the blood supply to tissues and facilitating a better supply of nutrients to the site of injury. This contributes to faster wound healing and early rehabilitation of patients. *Conclusion.* Magnetotherapy is one of the effective physical and rehabilitation methods of treatment that will become increasingly important in modern medicine. However, further research is needed to better understand the mechanisms of action of a magnetic field on bone tissue and to determine the optimal parameters for its application.

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## Introduction

The effect of a magnetic field (MF) on human health has been of interest to researchers since the beginning of the New Time. The English physicist and physician William Gilbert, who went down in the history of science as a scientist who was the first to find an explanation for the operation of the magnetic needle of a compass and suggested the existence of the Earth's magnetic poles, and also as the author of the first London Pharmacopoeia, suggested that magnets can cause mental disorders, leading even to death, but also restore beauty and health to girls suffering from pallor and bad complexion, due to the fact that they dry and tighten strongly without causing harm [1]. That is, the discoverers of the magnetic field have already pointed out its versatile effect on the human body. The Russian scientist Alexander Middendorf was the first scientist who started a fundamental study of the influence of a magnetic field on the organisms of living beings. In particular, he discovered that the ability of migratory birds to navigate in space is similar in nature to the orientation of a magnetic compass needle to the magnetic pole of the Earth [2].

The use of electricity and electromagnetism in medicine began in the 18th century. However, all these attempts can be compared with medieval magic, which has nothing to do with traditional and even more evidence-based medicine.

So, in the 1750s, German doctors applied permanent magnets to various parts of the body, hoping for their positive effect on the body in the treatment of various diseases [3].

In 1774, Anton Franz Mesmer, a Viennese doctor, gave patients to drink a liquid with a suspension of iron and then drove permanent magnets through the body. He believed that in this way he affects «animal magnetism», which in turn is the basis of the life of any living organism. He also healed people with his own biomagnetism. In 1784, in Paris, a commission of the Academy of Sciences and the Academy of Medical Sciences in a series of «blind» experiments studied Mesmer's method — *mesmerism*. The conclusions of the commission refuted the effectiveness of the method and recognized it as a «figment of the imagination» and charlatanism.

After the discovery by the Italian physician, physicist and physiologist Luigi Galvani of «animal

electricity» («Treatise on the Forces of Electricity in Muscular Movement», 1791) in 1796, the American physician Elisha Perkins patented and actively used metal sticks made of copper and steel, called pullers, for the treatment of any disease: from pain to rheumatism. In 1798–1799, as a result of placebo-controlled studies conducted by the British physician John Highgart, the action of pullers was recognized as an ineffective medical remedy, having in some cases only a placebo effect [4].

### **Reparative regeneration of bone tissue and modern trends in bone tissue engineering**

Recent studies have led to a clear understanding that the successful healing of fractures, as well as bone defects, is based on carefully coordinated cross-talk between inflammatory and bone-forming cells [5]. Bone tissue renewal is a complex mechanism based on the interaction of angiogenic and osteogenic processes that can lead to its formation. The process of bone regeneration is focused on the primary role of the occurrence of vascularization, in particular, the turning point is the ability to vascularize volumetric scaffolds in order to deliver enough nutrients, growth factors, oxygen for its restoration [6].

The supply of oxygen and nutrients is limited to a size of no more than 200 microns due to diffusion. The cells will not survive and new bone formation will be hampered in the center of a bone defect without a vasculature [7]. It is necessary to take into account the important fact in which macrophages play inflammatory cells that contribute to the recruitment and regulation of mesenchymal stem cell (MSC) differentiation during bone regeneration. Indeed, animal studies have comprehensively demonstrated that fractures do not heal without the direct involvement of macrophages [5, 8].

To this day, the standard clinical methods for bone restoration are the use of autografts and allografts. However, there are some limitations in the use of these techniques, manifested in a limited amount of bone, complications at donor sites, the risk of disease transmission, etc. [9, 10].

Bone engineering goes beyond the limitations of traditional methods. An actively developing and promising direction striving to overcome these limitations, which attracts a lot of attention from researchers [11–13]. The main goal of tissue engineering is to imitate natural processes, in particular, remodeling and regeneration, by creating scaffolds that can send regenerative signals to cells [14–16].

The nanostructure of bone and the interaction between organic components play a key role in the creation of a biomaterial with properties similar to natural bone tissue [17].

Numerous types of materials are currently in use, which generally have good biocompatibility and mechanical properties. In this process, natural or synthetic scaffolds, cells, and growth factors combine to form a construct that is structurally, functionally, and mechanically similar to native tissue that requires repair [18].

However, these materials cannot be artificially controlled after implantation, which can lead to poor recovery efficiency [19]. Currently, tissue engineering strategies have demonstrated a completely new promising direction in bone tissue regeneration associated with biophysical stimulation of osteogenesis processes generated by a magnetic field [20].

### **Physicochemical and biological mechanisms of magnetic field action**

In modern medicine, electricity is used in various forms: direct exposure to currents (microcurrents), electrophoresis, electromagnetic induction, magnetic fields, etc. The purpose of this article is to review modern methods of exposure to constant and variable magnetic fields on bone tissue and its regeneration.

Magnetic fields are an integral part of the electric field, changing in the process of its change in time. In addition, magnetic fields can be created by charged particles, either by the current of electrons (a non-permanent magnet), or by the magnetic moment of electrons. The main characteristic of a magnetic field is its strength, which is determined by the magnetic induction vector.

Under the action of a magnetic field, the liquid crystal structures (lipoproteins, membrane mitochondria, etc.) that are part of tissues can orient themselves relative to the magnetic induction vector due to the anisotropy of their properties. As a result of this orientational shift and the interaction of the arising own magnetic field with the external one, reversible structural changes occur in cell membranes, their permeability, intensity and direction of biochemical reactions change. The movement of charged particles through membranes changes. The magnetic field induces an induction electromotive force in conductive tissues [21].

Special magnetic receptors, except for particles of biomagnetin, do not exist in living organisms. Therefore, it is important to know how magnetic field signals are transformed in response to biological signals.

Primary processes of interaction of a MF with particles of matter is a purely physical process [21]. The action of the MF field on any charged bodies, including living objects, is described in the classical approximation by means of the Lorentz force. The Lorentz force is the force with which the electromagnetic field, according to classical (non-quantum) electrodynamics, acts on a point charged particle [22, 23]. The Lorentz effect in a living organism is accompanied by structural and functional changes at all levels where there are charged particles (ions and molecules) and elementary and bioelectrical processes occur [24].

The magnetic moments of atoms and molecules are mediators in the transmission of magnetic field signals to the biochemical level. The fine regulation of protein activity, carried out by biophysical mechanisms involving magnetically sensitive intermediates, leads to a shift in metabolic processes. Starting from this level, one can observe the effect of MF on changing the concentration of metabolic products [21]. Also, the interaction of magnetic fields with biological systems can be carried out due to ion parametric resonance [25].

Another possible mechanism is the influence of the magnetic field on the intermediate singlet-triplet (S-T) state of the reacting radicals and, consequently, on the reaction yield. Singlet-triplet transitions can occur in pairs of radicals that are in a spin-correlated state, which is precisely magnetically sensitive. They

occur as intermediates in chemical reactions involving free radicals, such as many enzyme-substrate reactions. The MF, modulating the singlet-triplet transformation, thereby changes the yield of free radicals, which changes the parameters of the reaction.

Through such mechanisms of nonspecific transformation of physical stimuli caused by the action of a magnetic field into biochemical stimuli, a number of processes in the cell can change: the rate of enzymatic reactions, ion current in channels, membrane permeability, expression of various proteins, and changes in gene regulation. However, the specific mechanisms of the implementation of the effects of a magnetic field on living cells and tissues are still poorly understood, because in such experimental studies, it is very difficult to achieve reproducibility of results due to the significant influence of a large number of side factors, such as temperature, electric fields, humidity, pressure, lighting, as well as chemical, physiological, and genotypic factors [26].

### **The influence of the magnetic field on the physiology of bone tissue and reparative regeneration**

Biophysical stimulation is a non-invasive manipulation aimed at increasing and enhancing the reparative and anabolic activity of tissues. Clinical biophysics forms the basis of the «new pharmacology», which uses physical stimuli to treat various human diseases. The complexity of the interaction between physical agents and biological systems especially complicated the work of researchers, but contributed to the discovery of new directions [7].

Many human tissues (bone, cartilage, skin and ligament tissues) have piezoelectric properties, i. e. the ability to generate an electric field in response to mechanical deformation of the material. It is known that the human body, when moving, can generate microcurrents and, thus, an electric field, which creates a potential gradient in the range from  $-10$  to  $-90$  mV along the cell membrane. Even small electrical fields and potentials can affect the migration, proliferation and phenotype of various cell types (e.g., epithelial

and endothelial cells), as well as induce tissue regeneration (e.g., nerve fibers, bones, ligaments) or directly affect electrically sensitive tissues (nerves, cardiac myocardium, smooth muscle layer of blood vessels) [27, 28].

Electromagnetic and magnetic fields are widely used in orthopedic clinical practice to accelerate bone healing processes. In a study by Fukada E. et al. piezoelectric properties of bone have been demonstrated. Bone tissue has a piezoelectric constant of about 7–8 pC/N [29], and the piezoelectric properties of bone tissue play a crucial role in its regeneration and restructuring in response to mechanical loads [27, 28]. Thus, a study by Fukada et al. showed that in areas of compression, the bone is electronegative and causes bone resorption, while areas of tension are electropositive and form bone [30].

In cellular engineering of musculoskeletal tissue, physical stimuli induce MSC proliferation, modulate their behavior, and maintain their differentiation by modulating their intracellular signaling pathways. This suggests that the use of such stimuli may be a promising strategy to improve bone fracture healing and cartilage regeneration. To date, some physical manipulations have already been introduced into clinical use for bone and cartilage regeneration [18].

Piezoelectric effects that occur in bone tissue under load [31], the presence of mechanotransduction [32], and molecular mechanosensors in osteocytes [33, 34] suggest that an external electromagnetic or magnetic effect will also have a physiological effect on metabolic processes in bone tissue.

In clinical practice, pulsed electromagnetic fields (PEMFs) are widely used to accelerate bone healing [7]. Over the past decades, substantial and growing evidence has emerged showing that PEMF therapy as an alternative non-invasive method is able to provide a satisfactory therapeutic effect in a wide range of bone diseases. The basic principle of the pulsed magnetic field is to influence cell differentiation and proliferation by influencing various metabolic pathways, stimulate angiogenesis and bone formation, and thus promote fracture healing [35]. Stimulation of PEMFs has been shown to promote the proliferation and

mineralization of osteoblasts in vitro, as well as to inhibit osteoclastogenesis. Stimulation of PEMFs has also been demonstrated to be capable of stimulating osteoblast functions in vitro [36].

For example, in a study by Umiatin U. et al. presented the results of a histological analysis of the results of fracture healing in vivo after stimulation with PEMFs. The study showed that the bone cartilage in the PEMFs group of laboratory animals was higher than in the control group throughout the entire observation period. In addition, the PEMFs group had less fibrous tissue at the onset of healing [37]. These results indicate that stimulation of PEMFs has an effect on the induction of osteogenesis during fracture healing and reduces the risk of delayed union.

Inductive coupling is the basis for the application of PEMFs. PEMFs consist of a coil of wire through which a current flow and a pulsed magnetic field is generated. Pulsed magnetic fields are inductive in bone tissue, which leads to a change in the secondary electric field. Secondary electric fields depend on pulsed magnetic fields and tissue properties.

Magnetic fields ranging from 0.1 to 20 Hz are commonly used to generate electrical fields in the range of 1 mV/cm to 100 mV/cm in bone. The PEMFs device generates a time-varying electrical field to mimic the normal physiological response of bone cells to mechanical stress. This electric field initiates enhanced bioeffects of bone growth and remodeling. A systematic review and meta-analysis show the potential impact of PEMF on several human cell types, including bone marrow mesenchymal stem cells. However, mesenchymal stem cells from human adipose tissue are less sensitive to PEMF. Studies also indicate that frequencies above 100 Hz with a flux density of 1 to 10 mT and long-term exposure over 10 days are more effective in achieving cellular response when using PEMF [38].

Studies have shown that magnetic fields affect the intracellular calcium concentration, which in turn activates cellular processes that promote bone tissue regeneration. A special role in this process is played by voltage-gated calcium channels (VGCC), which are activated under the influence of magnetic fields. This leads to accelerated

osteogenic differentiation of MSC, increased expression of osteogenic markers, and extracellular calcium deposition. All these facts point to the important role of calcium signaling in the process of bone tissue repair under the influence of magnetic fields [39].

In a study by Zhai M. et al. 2016 studied the effects and potential molecular signaling mechanisms of PEMFs on osteoblasts *in vitro*. Osteoblast-like MC3T3-E1 cells were exposed to PEMFs (0.5, 1, 2 or 6 h/day) at a frequency of 15.38 Hz at different intensities (5 G (0.5 mT), 10 G (1 mT) or 20 G (2 mT)) for 3 consecutive days. PEMF stimulation at 20 G (2 mT) for 2 hours per day showed the most prominent stimulatory effects on osteoblast proliferation when analyzed with Cell Counting Kit-8. Exposure to PEMFs induced a well-organized cytoskeleton and contributed to the formation of extracellular matrix mineralization nodes.

After stimulation with PEMFs, including Ccnd 1 and Ccne 1, there was a significant increase in the expression of genes associated with proliferation. Moreover, PEMFs increased gene and protein expression of collagen type 1, transcription factor 2 associated with Runt, and Wnt/ $\beta$ -catenin signaling during the proliferation and differentiation phases. Taken together, these results highlight that PEMFs stimulated osteoblast function through a mechanism associated with Wnt/ $\beta$ -catenin signaling and therefore regulates the expression of genes/proteins associated with osteogenesis [40].

Numerous studies have demonstrated the effect of strong MFs (up to 0.6 T) on osteoblast differentiation, orientation of cells or matrix proteins. However, the influence of weak MFs (with amplitudes of 0–200  $\mu$ T) on the orientation of bone formation has not been sufficiently studied and is the subject of numerous discussions. So, in the study by Okada R. et al. assessed the effect of low MF on osteoblast differentiation, bone formation, and orientation of both cells and newly formed bone. An apparatus was prepared with two magnets (190 mT) aligned in parallel to create a parallel MF. *In vitro*, rat bone marrow stromal cells were used to evaluate the effect of low MF on cell orientation, osteoblast differentiation, and mineralization. A model of ectopic bone induced by bone morphogenetic protein (BMP-2) was used to elucidate the effect of low MT

on microstructural indices, trabecular orientation, and orientation of newly formed bone apatite crystals.

Low MF led to an increase in the proportion of cells oriented perpendicular to the direction of the MF and contributed to the differentiation of osteoblasts *in vitro*. Moreover, *in vivo* analysis has shown that low MFs promote bone formation and change the orientation of trabeculae and apatite crystals in a direction perpendicular to the MF. These changes led to an increase in the mechanical strength of the bone induced by BMP-2. These results suggest that the use of low MF can promote bone regeneration with sufficient mechanical strength by controlling the orientation of the newly formed bone [41].

In another study by Kamei N. et al. demonstrated the effectiveness of magnetic targeting of bone marrow MSCs using a rabbit forelimb bone defect model. In this study, a rabbit forelimb bone defect was occluded with artificial bone having interlocking porous hydroxyapatite. The magnetic effect on bone marrow MSCs enhanced MSC infiltration into artificial bone and bone formation. Magnetically labeled bone marrow MSCs were injected into the site of a bone fracture in the presence or absence of a magnetic field. As observed using *in vivo*, magnetic targeting was found to enhance the proliferation and survival of transplanted MSCs. Radiographic and histological evaluations showed that magnetic targeting improved bone repair at four and eight weeks after treatment [42].

Despite a large amount of data on the use of MFs to influence bone regeneration, a number of meta-analyses of the literature on this topic provide mixed results. The effect of PEMF on bone healing remains uncertain and has not been established as a standardized treatment.

The aim of the systematic review and meta-analysis by Peng L. et al. there was an evaluation of the effect of PEMF on bone healing in patients with fractures; a pooling of 14 studies ( $n = 1,131$  patients) showed a healing rate of 79.7 % (443/556 patients) in the PEMF group and 64.3 % (370/575); PEMF increased healing rate by Mantel — Haenssel analysis (RR = 1.22; 95 % confidence interval [CI] = 1.10–1.35; I<sup>2</sup> = 48 %) and relieved pain by inverse analysis of variance (standardized mean difference [SMD] = -0.49,

95 % CI = - 0.88, I2 = 60 %). 0.10; I2 = 60 %) and accelerated healing time by inverse analysis of variance (SMD = -1.01; 95 % CI = -2.01 to -0.00; I2 = 90 %). Moderate-quality evidence indicates that PEMF s increase the healing rate and relieve fracture pain, while very low-quality evidence indicates that PEMF s accelerate healing time. Therefore, larger, high-quality randomized controlled trials and preclinical studies of optimal frequency, amplitude, and duration parameters are needed [43].

There is currently no clear understanding of the effect of PEMF on bone healing. This is likely due to the different parameter settings used. In addition, a different reaction of cells involved in the process of bone healing was recorded. As is known, the biological effects caused by PEMF can vary depending on many parameters, including frequency, duration of continuous exposure, amplitude, and even directionality [44]. However, the available data show the possible efficacy of PEMF as a non-invasive, inexpensive, and safe method of improving bone healing. But success rates for PEMF vary greatly between published trials for the treatment of both acute and delayed or non-consolidated fractures, as well as other clinical conditions. Different animal models consider heterogeneous settings and different outcome measures [45].

The positive effect of a permanent MF on the regeneration and remodeling of bone tissue has been demonstrated in many works [46–49], while a smaller number of studies have also shown the beneficial effect of a low-frequency rotating magnetic field on bone tissue [50–52]. For example, in 2006 Zhang et al. demonstrated that treatment with a rotating magnetic field with a frequency of 8 Hz and an induction of 400 mT for 30 days for 30 minutes. per day in combination with the introduction of calcium preparations contributed to an increase in the effectiveness of treatment by increasing the density of the bone tissue of the femur, increasing its strength properties, as well as elasticity and elasticity in the model of osteoporosis in ovariectomized rats. In addition, it was shown that the activity of alkaline phosphatase and the content of phosphate and calcium in the blood serum were higher in the experimental group of rats exposed to MF compared with control rats

without treatment. Moreover, even after a cycle of MF therapy in rats, bone density and the level of calcium ions in the blood serum continued to gradually increase compared to the control group, which may indicate a delayed effect of MF exposure on bone tissue [50].

Other authors have shown that a rotating MF with a frequency of 8–10 Hz and an induction of 320–600 mT, when exposed to it 2 hours a day for 1–2 months, significantly accelerates the regeneration of tissues of the femoral head in rats in a model of steroid-induced osteonecrosis. At the same time, there was a decrease in blood viscosity, cholesterol levels in blood serum, there was also a drop in triglyceride levels and a decrease in pressure in the cavity of the hip joint [51].

It was also shown that exposure to a rotating MF with a frequency of 7.5 Hz and an induction of 400 mT 2 hours a day for 15–21 days suppresses the differentiation of MSC along the adipogenic pathway through the JNK/Wnt/PPAR $\gamma$ 2 signaling pathway, but MF does not affect osteogenic differentiation of MSC [52]. However, other researchers have not found a noticeable effect of a rotating MF with similar parameters on the processes of regeneration and remodeling of bone tissue [53]. In the case of using a rotating magnetic field as a therapy, its parameters, such as frequency and induction, as well as pathophysiological features of an experimental model of a disease or bone defect in animals or a clinical case, are of great importance, which requires additional preclinical and clinical studies.

### Microvasculature and magnetic fields

As it turned out, the process of bone regeneration is focused on the primary role of the occurrence of vascularization, which is called the angiomesenchymal phase [54, 55]. In the angiomesenchymal phase, Vascular Endothelial Growth Factor (VEGF) regulates the process of angiogenesis, which is closely related to osteogenesis. The VEGF pathway is a key regulator of vascular regeneration.

Both osteoblasts and hypertrophied chondrocytes have been shown to express high levels of VEGF, thereby promoting invasion into blood vessels and transformation of the avascular cartilage matrix into

vascularized bone. VEGF promotes both vasculogenesis, promoting aggregation and proliferation of endothelial mesenchymal stem cells into the choroid plexus, and angiogenesis, stimulating the growth of new vessels from existing ones. Therefore, VEGF plays a critical role in neoangiogenesis and revascularization at the fracture site. It is noted that the presence of VEGF promotes fracture healing, and the blocking of VEGF receptors leads to a delay or interruption of regenerative processes. Many studies have suggested that PEMFs have a stimulating effect not only on osteogenesis, but also on angiogenesis, in various cellular models in both physiological and pathological conditions [56, 57].

PEMF can promote bone repair by inducing the activation of various signaling pathways that enhance both osteogenesis and angiogenesis. The Fibroblast Growth Factor (FGF) and VEGF signaling pathways have been shown to be involved in the regulation of osteoblast proliferation and differentiation and in the angiogenesis required for bone formation. The study showed that in the human umbilical vein after exposure of endothelial cells to PEMFs, there was a 150 % increase in FGF-2 mRNA and a 5-fold increase in protein, a molecular shift responsible for the increase in endothelial cells, cell proliferation and tubulization, key steps in the formation of new vessels [58].

In a study by Hyldahl F. et al. demonstrated the effect of PEMFs on VEGF by microglial transmitters. They generated electromagnetic fields using PEMFs, identical to those that appear outside neurons when action potentials propagate. As a result, PEMFs increased mRNA synthesis for VEGF. The authors of the study found that PEMFs enhance the secretion of VEGF proteins from microglia, which have angiogenic and proliferative profiles [59].

In another study by Peng L. et al. studied the effects and associated mechanisms of PEMFs in mice with myocardial infarction. Mice with myocardial infarction were treated with PEMFs (15 Hz, 1.5 mT or 30 Hz, 3.0 mT) for 45 minutes per day for 2 weeks. In addition, an *in vivo* matrigel assay was used to monitor the effect of PEMFs in stimulating angiogenesis. Compared to the sham PEMFs group, treatment with 30 Hz 3.0 mT PEMFs significantly improved cardiac function.

Treatment with PEMFs at 15 Hz 1.5 mT and 30 Hz 3.0 mT increased capillary density, decreased infarct size, increased expression of VEGF protein and S1177, phosphorylated endothelial nitric oxide synthase, as well as increased levels of VEGF mRNA and hypoxia inducible factor 1-alpha (HIF-1 $\alpha$ ) in the border zone of the infarction. In addition, treatment with 30 Hz 3.0 mT also increased the level of FGF2 protein and mRNA and the level of  $\beta$ 1 integrin protein and showed a stronger therapeutic effect [60].

Thus, PEMFs contribute to the regulation of angiogenesis by VEGF, which enhances vascularization, which is an integral part of reparative regeneration.

### **Osteoplastic materials with magnetically sensitive nanoparticles**

Nanoparticles (NPs) are particles that have at least one dimension in the range of nanometer sizes up to  $\approx$  100 nm. Such nanostructures are classified by their high surface area to volume ratio and are therefore particularly strong, versatile and reactive compared to the bulk state. These specific properties open up new and interesting optimization possibilities among the optical, mechanical, and magnetic properties of NPs [61].

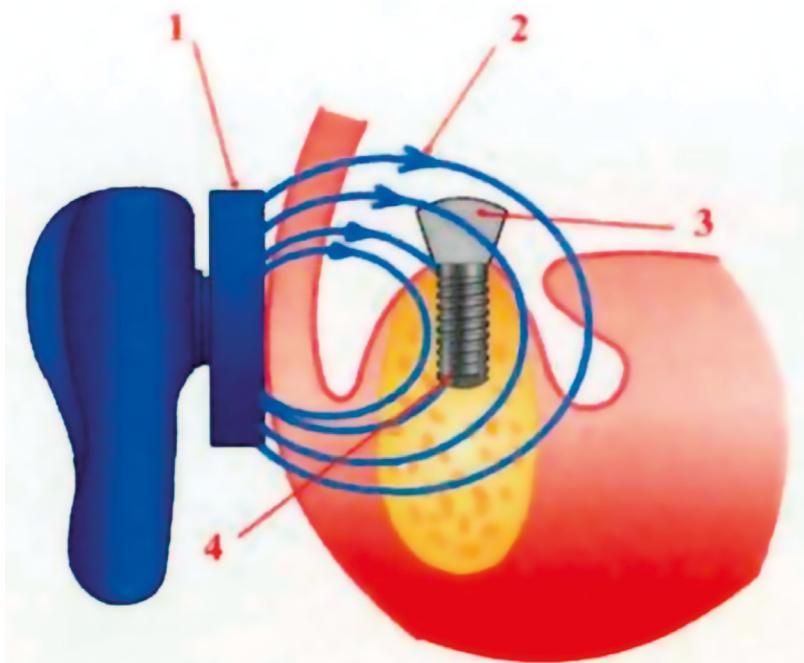
A special class is made up of nanoparticles with electromagnetic properties — magnetic nanoparticles (MNPs), an important class of nanoparticles made from pure metals or mixtures of metals and polymers [62]. MNPs are an advanced tool in medicine, since they can be simultaneously functionalized and controlled by a magnetic field [63]. MNPs are widely used in the biomedical field, including magnetic resonance imaging (MRI), cancer therapy, tissue engineering, biosensors, etc.

In maxillofacial surgery and surgical dentistry, therapeutic devices are actively used that have an electromagnetic effect on soft and hard tissues, as well as have anti-inflammatory and reparative effects [64, 65]. The scheme of the electromagnetic device's effect on the processes of reparative osteogenesis and osseointegration of a dental implant is shown in figure 1.

MNPs have unique physicochemical properties that differ significantly from those of conventional materials. One of these properties is the «surface effect». Due

to their influence, nanoparticles exhibit much greater chemical activity compared to macroparticles and, therefore, bind to a particular compound much more efficiently. Another property is magnetism. Magnetic

nanoparticles consist of ferromagnets with a magnetic permeability much higher than unity, and they are capable of being magnetized in the absence of an external magnetic field [66, 67].



**Fig. 1.** Schematic representation of an external therapeutic electromagnetic inductor in the buccal region, the propagation of electromagnetic waves and their effect on soft tissues, bone tissues and dental implants. 1 – external inductor, 2 – magnetic flux, 3 – healing abutment, 4 – dental implant

In recent years, much attention has been paid to the interaction between MNPs and cells, which indicates that MNPs can promote cell growth due to their ability to reduce intracellular  $H_2O_2$  through internal peroxidase-like activity and accelerate the progression of the cell cycle. In addition, MNPs can respond to magnetic fields, which makes them suitable for, for example, targeting drugs and separating molecules and cells. The forces generated by magnetic nanoparticles in a magnetic field can significantly affect the behavior of cells. The magnetic force generated by the magnetic field together with MNPs can affect the microenvironment around materials and thus cause a number of changes in cell behavior [68, 69].

Based on these data, in the field of tissue engineering, the inclusion of MNPs in bone scaffolds for the manufacture of magnetic scaffolds is being actively studied. This is advantageous because MNPs can become

an integral component of the scaffold, allowing them to generate a large amount of miniature magnetic forces in the scaffold under the action of an external magnetic field to continuously stimulate osteogenic cell proliferation and extracellular matrix secretion [70].

The most interesting molecules in terms of binding magnetic nanoparticles to target cells are aptamers, synthetic single-stranded RNA or DNA molecules that can specifically bind to any molecular and cellular targets, proteins, small organic molecules, viral particles, bacteria, antibodies, whole cells, cell lysates. and even tissues [71].

The appearance of the material with a magnetic response allows the frameworks to have the appropriate ability to interact with an external magnetic field. In a magnetic field, a material with a magnetic response can provide targeted drug release, improve scaffold performance, and further have a positive effect on bone

formation. The combination of magnetic field treatments will bring significant advances in regenerative medicine and help improve the treatment of bone defects and promote bone repair.

For the effective treatment of extensive bone defects, the development and fabrication of multifunctional biomaterials remains a significant challenge. In a study and Lu J.W. et al. 2018, using the example of a bone tissue defect caused by a tumor process, bone tissue regeneration with antitumor activity was demonstrated. The study used magnetic nanoparticles of modified mesoporous bioglass included in porous scaffolds. The radiated magnetic field from the porous scaffold promoted the expression of genes associated with osteogeny and new bone regeneration due to the activated BMP-2/Smad/Runx2 pathway. Moreover, the magnetic nanoparticles in the porous framework improved the photothermal conversion property. When irradiated with a near-infrared laser, the increased temperature of tumors co-cultivated with the scaffold triggered apoptosis and tumor ablation. Thus, magnetic nanoparticles in the scaffold not only accelerated stem cell proliferation, osteogenic differentiation, and new bone regeneration, but also increased the efficiency of photothermal therapy in bone tumors [72]. Research by Qing Li. et al. showed that a magnetic nanoparticle coated with n-HA is a promising biomagnetic material for future applications [73]. The response of cells and tissues to PEMF in the presence of titanium devices for orthopedic or dental use has been investigated using a wide range of PEMF approaches and settings. The most recent studies narrow their focus to 15 Hz PRF PEMF stimulation or 75 Hz trapezoidal stimuli with higher intensity, around 1–2 mT [74].

## Conclusion

Bone tissue regeneration is a complex multi-stage process. Despite the ability of bone to self-heal, the presence of non-standard situations in clinical practice, as well as the growing need for the use of bone materials, determines the strategic search for new methods of its restoration. These new directions include the creation of magnetically

sensitive osteoplastic materials that stimulate osteogenesis and improve the healing of fractures and bone defects.

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## Применение магнитного поля в регенерации костной ткани: современное состояние вопроса и перспективы развития метода

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**Аннотация.** *Актуальность.* Магниты с давних времен использовались для лечения различных заболеваний, особенно при воспалительных процессах. Согласно существующим историческим данным, магнитотерапию применяли уже в древности китайцы, египтяне и греки. Разная сила магнитного поля по-разному влияет на клетки, при этом наиболее широко используются магнитные поля средней силы. В настоящем обзоре литературы представлены краткая история и современное состояние вопроса применения магнитного поля в регенерации костной ткани. Уточнены современные знания о механизмах физиологической и репаративной регенерации, восстановления костной ткани, а также рассмотрены современные направления инженерии костной ткани с учетом особенностей микроциркуляции и влияние магнитного поля на физиологию костной ткани и репаративную регенерацию. Одним из ключевых выводов обзора является то, что магнитное поле улучшает восстановление костной ткани, влияя на метаболическое поведение клеток. Исследования показывают, что магнитотерапия способствует активации клеточных процессов, ускоряет образование новой костной ткани и повышает ее качество. Также отмечается, что магнитное поле оказывает положительное влияние на микроциркуляцию, улучшая кровоснабжение тканей и способствуя лучшему поступлению питательных веществ к месту повреждения. Это способствует более быстрому заживлению ран и ранней реабилитации пациентов. *Выводы.* Магнитотерапия является одним из эффективных физических и реабилитационных методов лечения, которые будут приобретать все большее значение в современной медицине. Однако необходимо проводить дальнейшие исследования для более полного понимания механизмов действия магнитного поля на костную ткань и определения оптимальных параметров его применения.

**Ключевые слова:** магнитное поле, костная ткань, регенерация, магнитотерапия, импульсивные электромагнитные поля

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