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Review Article

The effects and mechanisms of electromagnetic fields on bone remodeling: From clinical to laboratory

Junyu Liu [a,b,c], Weihao Ren [a,b,c], Shenghang Wang [d,e], Jiancheng Yang [f], Hao Zhang [e], Yuhong Zeng [f], Dachuan Yin [b,c], Peng Shang [a,b,c,*]

[a] Research & Development Institute of Northwestern Polytechnical University in Shenzhen, Shenzhen, 518057, China
[b] School of Life Science, Northwestern Polytechnical University, Xi'an, 710072, China
[c] Key Laboratory for Space Bioscience and Biotechnology, Institute of Special Environment Biophysics, Northwestern Polytechnical University, Xi'an, 710072, China
[d] Law Sau Fai Institute for Advancing Translational Medicine in Bone and Joint Diseases (TMBJ), School of Chinese Medicine, Hong Kong Baptist University, Hong Kong SAR, China
[e] Department of Spine Surgery, People's Hospital of Longhua, Affiliated Hospital of Southern Medical University, Shenzhen, 518109, China
[f] Department of Osteoporosis, Honghui Hospital, Xi'an Jiaotong University, Xi'an, 710054, China

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ABSTRACT

Electromagnetic fields (EMFs) are physical fields generated by electrically charged objects, and play a vital role in the growth and development of living organisms. Bone is a highly dynamic structure that undergoes a constant remodeling process. From 1962 to 1977, Bassett discovered the piezoelectric effect in bone tissue and found that EMFs accelerated osteogenesis, promoted tibial fracture healing in dogs, and had positive effects in clinical trials. Since then, EMFs have been increasingly studied in bone remodeling disorders as a non-invasive physical therapy. This review summarizes clinical trials and laboratory studies on EMF interventions in bone remodeling disorders over the past few decades, outlining the effects of EMFs on various bone cells and their underlying molecular mechanisms. In addition, we propose issues in current studies and give an outlook on the research and application of EMFs as a non-invasive physical therapy.

The translational potential of this article: This article systematically reviews the research ranging from biological and physical mechanisms to medical applications of EMFs on bone remodeling and related diseases, identifies key challenges in future basic research, and proposes new strategies for developing novel medical equipment and advancing clinical applications in this field. These insights contribute to the advancement of non-invasive physical therapies in orthopedics.

1. Introduction

The skeleton provides mechanical support for stature and locomotion, protects vital organs, and controls mineral homeostasis. A healthy skeleton must be maintained by constant bone modeling to carry out these crucial functions throughout life. Bone is composed of organic materials such as collagen and inorganic materials such as hydroxyapatite, mostly consisting of a hard cortical component and a "spongy" cancellous or trabecular component, which has mechanical properties that protect and support the skeleton as well as aid in movement. Bone remodeling is a process in which osteoclasts remove old bone and osteoblasts form new bone, which maintains bone health [1,2]. In order to accomplish normal physiological bone remodeling, the correct coupling of bone formation and bone resorption requires direct communication among different bone cells, including osteoblast lineage (osteoblasts, osteocytes, and bone-lining cells) and bone-resorbing cells (osteoclasts) and their precursor cells. The remodeling cycle is composed of five sequential phases: activation, resorption, reversal, formation, and quiescence [3]. Beginning with the first phase of osteoclast activation, resorption by osteoclasts and osteogenesis by osteoblasts proceed successively, eventually returning to the quiescent phase (Fig. 1).

The imbalance of bone remodeling caused by a variety of external physical, chemical, and biological factors is the biological basis for the development of associated bone diseases. The major types of them are

* Corresponding author. Research & Development Institute of Northwestern Polytechnical University in Shenzhen, No. 45, Gaoxin South 9th Road, Nanshan District, Shenzhen, China.
E-mail address: shangpeng@nwpu.edu.cn (P. Shang).

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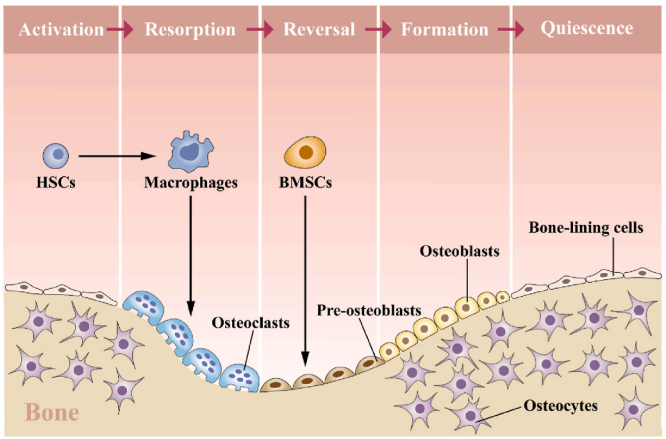

Fig. 1. Bone remodeling. In the activation phase, HSCs differentiate into macrophages, subsequently generating osteoclast precursors, and preparing for the subsequent stages; in the resorption phase, osteoblasts respond to signals produced by osteocytes, recruiting osteoclast precursors to the remodeling site, these precursors come into contact, fuse, and differentiate into osteoclasts, initiating bone resorption and forming individual resorption pits; in the reversal phase, osteoclasts on the surface of the bone gradually disappear and are replaced by pre-osteoblasts; in the formation phase, osteoblasts appear one after another on the surface of the pits and proliferate, differentiate, and form new bone; as the resorption pits approach filling, osteoblasts lose their bone-forming activity, becoming bone-lining cells on the surface, and then entering the quiescence phase. (HSCs: hematopoietic stem cells; BMSCs: bone marrow mesenchymal stem cells.)

fractures, nonunion, and osteoporosis. Fracture refers to the complete or partial disruption of the continuity of bone structure, typically occurring as a single-site fracture, with a minority presenting as multiple fractures. When there was no imaging progression of healing nine months after the fracture and no changes in the bone calluses were observed in the last three months, we refer to this condition as nonunion. Osteoporosis is a systemic metabolic bone disease characterized by reduced bone mass and degradation of bone microarchitecture, resulting in increased bone fragility and fracture risk, which is divided into primary osteoporosis and secondary osteoporosis [4].

Currently, conservative treatments such as cast fixation are widely used for the treatment of fractures, while pharmacological interventions are predominant in the prevention and treatment of osteoporosis. However, pharmaceutical treatments often come with various side effects, and over time, they may lead to the development of drug resistance. Therefore, electromagnetic field therapy, as a non-invasive physical treatment method, is gaining increasing prominence in research and applications for various diseases.

An increasing number of clinical studies have demonstrated that EMFs of specific parameters have preventive and curative effects on bone remodeling disorders, promoting fracture healing, relieving pain, and promoting higher bone mineral density (BMD) in patients with osteoporosis, which has also been observed in animal models studied in the laboratory. Also, cellular experimental studies have shown that the specific parameter EMFs promote the differentiation of bone marrow mesenchymal stem cells and osteoblasts, facilitate the proliferation of osteocytes, and inhibit osteoclastogenesis, which modulates the effects on bone remodeling.

This review mainly summarizes several aspects of EMFs, including the discovery of EMFs, the classification of EMFs, the treatment of EMFs on bone remodeling disorders, and the mechanisms of EMFs on bone. Furthermore, current questions and challenges are also pointed out, which provide a reference for the non-invasive treatment of EMFs.

2. Discovery and development of electromagnetic fields in bone remodeling disorders

The geomagnetic field (GMF) is the magnetic field in space from the center of the earth to the top of the magnetosphere. It was proposed by Gilbert in 1600 [5]. Through his experiments, Gilbert came to an amazing conclusion that the earth is magnetic, which is the reason why the compass points to the north. It was from Gilbert that the modern development of electricity and magnetism truly started.

The research of electromagnetics originated in the 19th century, and many of these scientists are well known to us. In 1820, Ørsted accidentally observed that the compass was deflected with the current and discovered the relationship between magnetism and electricity [6]. In the same year, Ampere developed electromagnets and made outstanding contributions [7]. In 1831, Faraday demonstrated that electric charges could be transferred by electromagnetism, which was later called electromagnetic induction [8]. A few decades later, in 1881, Tesla invented a high-frequency, high-voltage transformer, the “Tesla coil”, and in 1882 he proposed the idea of a two-circuit alternating current [9,10]. In 1898, he published an article on the use of high frequency oscillators in electrotherapy [11]. Afterward, electromagnetic fields were gradually applied to the treatment of various diseases.

In 1892, Julius Wolff and others realized that mechanical loads could affect bone architecture in living beings, and when bone receives external pressure for a long time, the density will increase and it will become harder, this regularity was summarized as Wolff’s Law [12]. This relationship between mechanical forces and living organisms was summarized as the stress-growth law, by the father of biomechanics, Yuancheng Fung. As a mechanical receptor organ, the piezoelectricity of bone was also discovered. In 1962, Bassett of Columbia University found that when bones were subjected to mechanical stress, negative potentials were formed in the compressed area, generating an electrical potential [13]. This discovery is similar to that of Japanese scientists Fukada and Yasuda, and is known as the piezoelectric effect on bone [14]. In 1964, Bassett found that electrical currents generated by electrodes implanted in vivo were able to promote new bone growth with significant bone formation in negatively charged areas [15]. He proposed that the magnitude of the electrical potential generated by mechanical stress depended on the rate and magnitude of bone deformation, while the polarity depended on the direction of bone bending. He gave a detailed overview of these results in 1965 [16], and systematically discussed the biological significance of piezoelectricity in 1968 [17].

However, for the clinical translation of bone-related disease

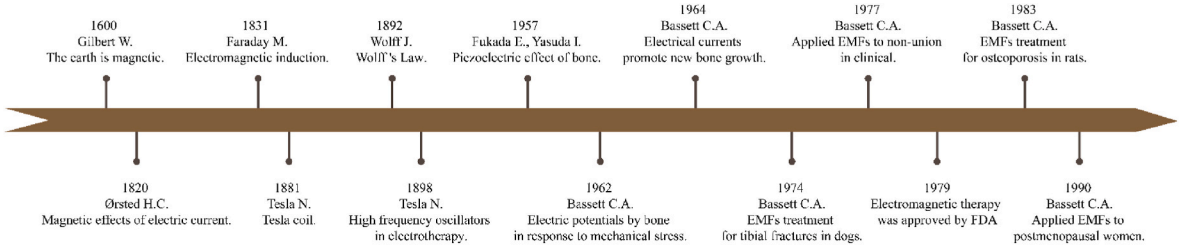

Fig. 2. The discovery of EMFs as physical therapy in bone remodeling disorders.

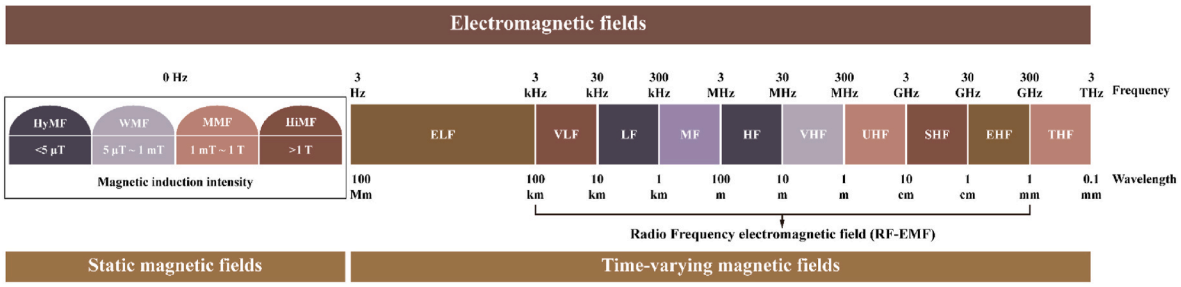

Fig. 3. Classification of electromagnetic fields.

treatment, electrical stimulation has a surgically invasive effect, which increases the risk of infection during the surgery, and electrodes may have harmful electrolytic effects when releasing current. Therefore, people have turned their attention to non-invasive treatment options.

In 1974, Bassett et al. proposed a non-invasive surgical method using EMF to treat bone remodeling disorders [18]. He proved that the 1 Hz PEMF could accelerate the bone formation of the dog's tibia at 28 days after "fracture" [19]. In 1977, he applied electromagnetic therapy to the clinic for the first time and demonstrated that the success rate of the treatment of surgically-resistant pseudarthroses and non-unions by ELF-PEMF was 70 % [20]. In 1979, this physical therapy was approved by the Food and Drug Administration (FDA) [21]. Since then, Bassett has done a number of studies related to the therapeutic effects of pulsed electromagnetic fields on fractures, non-union of bones, and congenital pseudarthrosis [21–24]. In 1983, he conducted a study on PEMFs for the treatment of osteoporosis in rats [25], and in 1990, he measured the effect of PEMFs on BMD in postmenopausal women [26]. These studies have opened a new door for the application of magnetic fields to the treatment of bone remodeling disorders (Fig. 2).

Since then, EMFs have been widely used as a non-invasive treatment in bone remodeling disorders. In recent years, numerous studies on the use of EMFs in treating bone remodeling disorders have emerged, along with a growing interest in the mechanisms of bone remodeling by EMFs.

3. Classification of electromagnetic fields and bone growth stimulators

The electromagnetic fields (EMFs) are the unity and general term of internally connected and interdependent electric and magnetic fields. Under specific conditions, an electric field can generate a magnetic field, and a magnetic field can also generate an electric field. The two are mutual cause and effect, forming an electromagnetic field. In 1865, Maxwell perfected his equation [27]. This system of equations directly derives the wave equations of electric and magnetic fields. So far, electromagnetic waves have been thoroughly confirmed. According to whether the current changes, electromagnetic fields can be roughly divided into static magnetic fields (SMFs) and time-varying magnetic fields. According to the way the current changes, time-varying magnetic fields can be divided into sinusoidal electromagnetic fields (SEMFs) and pulsed electromagnetic fields (PEMFs) [28].

According to the intensity of magnetic flux density, SMFs can be divided into Hypomagnetic Field (HyMF), Weak Magnetic Field (WMF), Moderate Magnetic Field (MMF), and High Magnetic Field (HiMF) [29]. Magnetic fields generated in the form of electromagnetic waves, such as PEMFs, are usually divided by the frequency of electromagnetic waves. According to the relevant literature and the radio frequency band regulations of the International Telecommunication Union (ITU), we divide this kind of magnetic field into 10 frequency bands, including Extremely Low Frequency (ELF), Very Low Frequency (VLF), Low Frequency (LF), Medium Frequency (MF), High Frequency (HF), Very High Frequency (VHF), Ultra High Frequency (UHF), Super High Frequency (SHF), Extremely High Frequency (EHF), Tremendously High Frequency (THF) [30]. The specific parameters are shown in Fig. 3.

Table 1
The modalities of BGSs.

Modalities	Device Description	Product and Application Holder
Capacitive Coupling (CC)	A pair of electrodes are placed on the skin such that a current can be driven across that target site.	OrthoPak SpinalPak (Zimmer Biomet)
Pulsed Electromagnetic Field (PEMF)	A modulated electromagnetic field is generated near the treatment site through an external coil.	EBI Bone Healing System (Zimmer Biomet) Physio-Stim™ I & II SpinalStim (Orthofix, Inc.) Cervical Stim (Orthofix, Inc.)
Combined Magnetic Fields (CMF)	A coil generates a combination of a static and pulsed magnetic fields near the treatment site.	OL1000 BGS SpinaLogic (DJO, LLC)
Low Intensity Pulsed Ultrasound (LIPUS)	Pulsed ultrasonic signals are generated using ultrasonic transducers.	Exogen Ultrasound BGS (Bioventus, LLC) AccelStim Bone Growth Stimulator (Orthofix, Inc.)

According to the regulations of the FDA, EMF devices used in clinical bone healing are currently classified as non-invasive bone growth stimulators (BGSs), which typically utilize a generator and transducer to non-invasively deliver either an electrical, magnetic or mechanical waveform to the fracture site to augment bone healing. As shown in Table 1, BGSs are usually classified into 4 modalities depending on the physical stimuli used: capacitive coupling (CC), pulsed electromagnetic field (PEMF), combined magnetic fields (CMF), and low intensity pulsed ultrasound (LIPUS).

It can be seen that existing EMF-BGSs usually use PEMFs, and the parameters used are all low-frequency with 1 Hz–50 kHz. This leads us to ask some questions, what are the trials performed in the clinical setting? How effective are low-frequency EMFs for bone remodeling? What is the effect of medium/high-frequency EMFs on bone remodeling? What are the mechanisms of EMFs acting on bone remodeling? To clarify these questions, we conducted a literature search, which is summarized in the follow-up content.

4. Clinical applications of EMFs in bone remodeling disorders

4.1. Fracture and nonunion

Although fractures can heal spontaneously, there are still many reasons leading to delayed healing or nonunion of fractures, especially for people with low bone mass, where the risk of delayed healing after a fracture is extremely high, therefore electromagnetic fields as a physical therapy can alleviate this phenomenon.

4.1.1. Static magnetic fields (SMFs)

SMFs accelerate bone formation, which was first discovered by

Russian scientists in 1971 [31]. Since then, this type of physical therapy has been progressively studied.

Limited clinical trials have demonstrated the accelerating effect of SMFs on fracture healing. Costantino et al. inserted NdFeB magnets in each of the plaster casts to produce a SMF exposure to the hand or wrist fracture site and showed that SMF (1.2 T) resulted in the formation of bone callus with a mean time 35 % shorter than the "standard" time [32]. In a randomized controlled trial (RCT) reported in Chinese, patients with Colles fractures were immobilized with or without magnetic splints (80 mT/150 mT), and after 2 months of treatment, the results showed that patients in the magnetic splint group had significantly lower swelling reduction time, pain resolution time, and clinical healing time than those in the non-magnetic group [33]. It was also shown that magnetic splinting (0.13 T–0.15 T) combined with heat therapy could significantly shorten the time to swelling and scab formation in patients with tibiofibular fractures, with a significant treatment effect in 88.46 % of patients [34]. In another RCT reported in Chinese, patients with tibiofibular fractures were fixed with either a permanent magnetic external fixator (0.12 T) or a normal fixator, and the healing rate was significantly higher and the healing time was significantly shorter in the magnetic external fixator group than in the normal external fixator group [35].

These clinical trials showed that SMFs can promote fracture healing. However, there are still fewer clinical studies of SMFs on fracture or nonunion worldwide, and more rigorous RCTs are needed to support their role in the future.

4.1.2. Pulsed electromagnetic fields (PEMFs)

As mentioned earlier, in 1977, Bassett first applied PEMFs in the clinical treatment of bone diseases, and demonstrated a success rate of 70 % in the treatment of non-unions and pseudarthroses with ELF-PEMF, which highlighted its efficacy. Until now, PEMFs have been one of the most widely used physiotherapy treatments for bone diseases and have been used in a wide range of bone remodeling disorders.

For patients with long bone fractures, Shi et al. proposed early use of PEMF (15 Hz, 50 mV) treatment could promote the early healing rate of fracture patients and reduce the pain time of patients [36]. For middle-aged and elderly people, Ziegler et al. proposed ELF-PEMF (16 Hz, 2–282 μT) treatment had a tendency to accelerate bone consolidation after high tibial osteotomy, this effect was stronger and more significant for people older than 50 [37]. Cheing et al. found that PEMF (50 Hz, 9.9 mT) had the ability to improve joint range of motion and alleviate pain in patients with distal radius fractures six weeks after fixation. Additionally, its effectiveness was demonstrated to be superior when combined with ice therapy to either PEMF or ice alone [38]. Abdelrahim et al. found that for closed reduction treatment of mandibular fractures, there was no significant change in BMD 15 days after PEMF (72 Hz) treatment. However, after 30 days of treatment, there was a significant increase in the percentage change of BMD [39]. The OL1000 series of magnetic field devices developed by DJO (USA) accelerated the healing time and reduced the risk of infection in patients with fractures [40].

In summary, as one of the most commonly used physical therapies, PEMFs with specific parameters have the capability to reduce the healing time of fractures, alleviate pain, induce an increase in BMD, and concurrently reduce the risk of nonunion. Additionally, they are beneficial in promoting healing for patients with nonunion fractures and have a promising application.

4.2. Osteoporosis

At present, global population aging is one of the significant social issues. With the increasing aging population, the attention to the health of the elderly is gradually deepening. Osteoporosis, as a major health concern, affects many individuals. The reduction in bone mass and the deterioration of bone microstructure intensify the risk of fractures, which is particularly concerning for osteoporotic patients, especially the elderly. Therefore, the research on EMFs as a non-invasive physical therapy method for osteoporosis is gaining considerable attention.

4.2.1. Static magnetic fields (SMFs)

Until now, there has been a lack of articles specifically addressing the clinical application of SMFs in osteoporosis. There is only one article on clinical applications related to postmenopausal vertebral deformities and back pain, published by Mészáros et al. They found that placing a NdFeB magnetic particle array plate (192 mT) on the back of women with postmenopausal vertebral deformities and back pain did not result in significant changes in back pain perception, and the bone turnover markers remained stable [41].

It is worth noting that there are few clinical studies on static magnetic fields for osteoporosis, which may be due to poor patient compliance caused by the lack of portability of the static magnetic fields and the long duration of operation. We are currently conducting a clinical trial titled "Intervention Study of Moderate Magnetic Fields on Women with Postmenopausal Osteoporosis" (Registration Number: ChiCTR2100048604, www.chictr.org.cn). This study aims to elucidate the impact of MMFs on osteoporosis, contributing valuable insights to the medical translation of magnetic field therapy.

4.2.2. Pulsed electromagnetic fields (PEMFs)

For osteoporosis, some of the earliest clinicians to apply PEMF therapy were also Bassett and Tabrah et al., In 1990, they confirmed that PEMF (72 Hz, 2.85 mT) could induce an increase in BMD in the trabecular region of susceptible women with osteoporosis, indicating a certain preventive effect on osteoporosis [26].

Since then, an increasing number of studies have focused on the role of PEMFs in the prevention and treatment of osteoporosis. Liu et al. proposed that PEMF (8 Hz, 3.82 mT) had a therapeutic effect on postmenopausal osteoporosis, and the therapeutic effect of PEMF with specific parameters was the same as alendronate [42]. Xiang et al. found that PEMF (20 Hz, 0.2 mT–1 mT) treated senile osteoporosis disease and could alleviate subjective signs efficiently, and BMD has also been raised [43]. Catalano et al. investigated the mechanisms of magnetic fields on postmenopausal women with osteoporosis. They found that PEMF (16/18/20/22 Hz, 3/3.2/3.4/3.6 mT) could promote an increase in serum BSAP levels and induce a decrease in CTX concentration. Meanwhile, the RANKL/OPG ratio and DKK-1 concentration significantly decreased, and β-catenin concentration increased. This suggests that PEMFs influence bone remodeling by regulating the RANKL/OPG and Wnt/β-Catenin signaling pathways [44]. Eid et al. found that PEMF (33 Hz, 5 mT) could improve BMD in women with osteoporosis after thyroidectomy, and the combined treatment with physical exercise yielded even better results [45]. Elsisi et al. reported that twelve weeks of PEMF (100 Hz, 8.5 mT) therapy could significantly increase BMD and mineral content in the lumbar vertebrae, femur, and tibia of postmenopausal women. This indicates that PEMF treatment is an effective means of preventing osteoporosis [46]. Shanb et al. found that PEMF (100 Hz, 8.5 mT) could significantly increase BMD in elderly patients with osteoporosis, and its combination with alendronate sodium yielded even better results [47].

It can be seen that PEMFs have the potential to improve the microstructural changes in bones caused by osteoporosis, enhance BMD, and exhibit promising prospects in the prevention and treatment of bone remodeling disorders.

5. Laboratory studies of EMFs in bone remodeling disorders

In recent years, there has been a growing number of laboratory studies aimed at exploring the role of EMFs in bone remodeling disorders. Common animal models for fractures include dogs, rabbits, and rats, while common animal models for osteoporosis involve rats and mice. The following section reviews some of the research on various EMFs in animal experiments.

5.1. Static magnetic fields (SMFs)

SMFs, as the electromagnetic field with a frequency of 0 Hz, are often used in bone-remodeling studies to explore the effects of different intensity fields on bone tissues.

For fracture, Bruce et al. reported that the magnetic intramedullary nails (0.022 T–0.026 T) improved the mechanical properties of rabbit fractured radius [48], increased BMD and promoted femur fracture healing in fractured New Zealand rabbits [49]. Saifzadeh et al. found that SMF (0.1 T) exposure for 8 weeks promoted fracture healing in dogs with an osteotomy of the midshaft radius [50]. Wang et al. reported that SMF (0.05 T–0.5 T) increased BMD, bone volume per tissue volume (BV/TV), mechanical properties, and proportion of mineralized bone matrix of the callus during fracture healing in mice [51].

For osteoporosis, Zhang et al. found that SMF (4 mT) exposure for 16 weeks inhibited the structural deterioration and mechanical strength reduction of trabecular bone and cortical bone in T1DM rats. And it also inhibited the reduction of bone formation in T1DM rats, thereby preventing the deterioration of bone structure and strength [52]. Yang et al. found that SMF (0.2 T–0.4 T) could improve hindlimb unloading-induced reduction in BMD and bone mineral content (BMC), and stop the bone microstructure deterioration [53]. They also found that the expression of marker proteins in the femur and concentrations of biochemical indicators in serum involved in bone formation were elevated and bone resorption was reduced under SMF (2 T–4 T) [54]. Zhen et al. reported that SMF (0.2 T–0.4 T) improved the bone mass, microstructure and biomechanical properties of lumbar vertebrae in $HAMP^{-/-}$ mice [55]. Lv et al. reported that SMF (0.4 T–0.7 T) increased BMD and BMC of femur, improved biomechanical strength with higher ultimate stress, stiffness and elastic modulus, and ameliorated the impaired bone microarchitecture in type 1 diabetic mice and enhanced bone turnover by increasing the level of markers for bone formation (OCN and Collagen I) as well as bone resorption (CTSK and NFAT2) [56]. Zhang et al. reported that SMF (1 T–2 T) combined with iron oxide nanoparticles (IONPs) could prevent the destruction of bone microstructure, improve the mechanical properties, and reduce the number of osteoclasts in unloaded mice [57]. Kotani et al. reported that SMF (7.84 T–8.20 T) could promote bone formation in both in vitro and in vivo models, and had the effect of regulating the direction of bone formation [58].

As we mentioned, SMFs can promote fracture healing, alleviate pain, and improve BMD and mechanical properties, as well as improve the level of bone turnover in osteoporosis patients, improve BMD and mechanical properties. However, the current studies on SMFs are still relatively few, and the range of intensity is limited, so the following research still needs to be strengthened.

5.2. Pulsed electromagnetic fields (PEMFs)

Since Bassett first pioneered PEMFs in animal models in 1974 [19], more and more studies of PEMFs on bone remodeling disorders have been conducted in experimental animals.

For fracture, Umiatin et al. reported that PEMF (50 Hz, 1.6 mT) induced more cartilage tissue and less fibrous tissue in the left femur of fractured rats, reducing their risk of delayed healing [59]. Bilgin found that PEMF (50 Hz, 1.5 mT) promoted tibial healing tissue formation and fracture healing in fractured rats [60]. Androjna et al. reported that PEMF (15 Hz, 0.52 mT) improved the elastic modulus of hard callus at the fibula fracture site in ovariectomized rats, thereby improving its mechanical properties and reducing the risk of fracture nonunion [61].

For osteoporosis, Topal et al. found that PEMF (7.3 Hz, 0.8 ± 0.2 mT) promoted the healing of right femur defects in osteoporotic rats by decreasing their CTx levels and increasing the area of new bone [62]. They also found that PEMF (15 Hz) with a specific magnetic field strength could reduce trabecular bone loss in osteoporotic rats [63]. Lei et al. reported that long-term stimulation of PEMF (15 Hz, 1.6 mT) alleviated lumbar spine osteoporosis in postmenopausal mice by increasing bone formation and inhibiting bone resorption [64]. Cai et al. reported that PEMF (15 Hz, 2 mT) maintained bone structure and mechanical properties by promoting bone anabolism in type 1 diabetic rabbits [65]. They also found that the combined effect of PEMF (15 Hz, 2 mT) and WBV mainly inhibited bone loss in aged rats by improving the activity of osteoblasts and bone cells, but had no effect on bone resorption [66]. Another study showed that PEMF (15 Hz, 2 mT) was able to modify radiation-induced bone loss by regulating osteoblasts [67]. Immediately after, Shao et al. proposed that PEMF (15 Hz, 2.4 mT) could alleviate bone fragility in type 2 diabetic mice through Wnt/β-catenin signaling pathway [68]. Jing et al. proposed that PEMF (15 Hz, 2.4 mT) could partially prevent the deterioration of bone strength and structure in diabetic rats induced by streptozotocin, and improve the formation of damaged bone [69]. They also found that PEMF (15 Hz, 2.4 mT) could alleviate disuse bone loss by promoting bone anabolism [70]. Wyszkowska et al. reported that low-frequency MF (50 Hz, 7 mT) exposure could obviously increase the plasma inflammatory parameters in rats, and other types of MFs contributed to the anti-inflammatory and tissue repair processes [71,72].

The same as SMFs, PEMFs with specific parameters can also promote fracture healing, prevent fracture nonunion, improve bone microstructure and mechanical properties, and alleviate osteoporosis. However, the parameters used are essentially the same, and new parameters remain to be developed.

5.3. Other magnetic fields

5.3.1. Sinusoidal electromagnetic fields (SEMFs)

Compared with PEMF, SEMFs have not been applied to clinical trials of bone remodeling disorders, and have less research in animal experiments.

Sert et al. reported that SEMF (50 Hz, 1 mT) induced an increase in tibial cortical bone thickness and elevated blood levels of ALP in ovariectomized rats [73]. Zhou et al. reported that SEMF (50 Hz, 1.8 mT) promoted the bone formation of rat femur tissue in vitro, and inhibited its bone resorption at the same time [74]. Immediately afterward, he discovered the SEMF (50 Hz, 1.8 mT) increased the peak bone mass of growing rats by promoting osteoblast differentiation, which was mediated to a certain extent by the activation of Wnt10b of primary cilia and subsequent Wnt/β-catenin signaling [75].

5.3.2. Rotating magnetic fields (RMFs)

RMFs are a class of time-varying magnetic fields with low frequency and high intensity. Although much of the research on it has focused on nerve diseases and tumor therapy [76], a few experiments have been conducted on bone remodeling disorders.

Zhang et al. reported that RMF (8 Hz, 0.4 T) combined with calcium supplement improved bone mechanical properties and induced elevated BMD ovariectomized rats [77]. Pan et al. reported that RMF (8 Hz–10 Hz, 0.32 T–0.6 T) was able to accelerate the recovery of femoral head osteonecrosis in rats, and the regeneration of damaged bone tissue was significantly increased [78].

5.3.3. Combined magnetic fields (CMFs)

Based on various electromagnetic field experiments, researchers have boldly carried out research on combined magnetic fields. Due to many factors, there is not much current research on combined magnetic fields.

Fitzsimmons et al. reported that short-term exposure to CMF (15.3 Hz) which consisted of the coils with 5.3 mA AC and 7.5 Ma DC, promoted an increase in the number of IGF-II receptors and affected calcium flux in the TE-85 human osteosarcoma cell line [79,80]. Bao et al. reported that NdFeB (40 ± 5 mT) intramedullary implants combined with PEMFs (20 Hz, 8 mT–10 mT) could accelerate the repair of rabbit ankle bone defects [81].

It has been shown that EMFs with specific parameters can promote fracture healing, reduce inflammation and pain, and shorten healing time. They also can alleviate the bone loss induced by various conditions, enhance the microstructure and mechanical properties of bone, and are one of the widely used and promising physiotherapy methods.

6. Biological mechanisms of EMFs on bone

6.1. Effects of EMFs on bone cells

During bone remodeling, a variety of bone cells are involved, including osteocytes, osteoblasts, osteoclasts and bone marrow mesenchymal stem cells. Osteocytes are differentiated from mature osteoblasts that produce mineralized nodules, embedded in the bone that can modify the surrounding extracellular matrix through specific molecular mechanisms, and communicate with osteoclasts and osteoblasts through signal pathways such as RankL/OPG pathway and Sost/Dkk1/Wnt pathway [82]. Osteoblasts are a special type of bone-forming cells that can express parathyroid hormone receptors, produce bone matrix proteins, and participate in the process of bone mineralization, thereby playing a role in bone formation [83]. Osteoclasts are differentiated from mononuclear phagocytes and have the ability to remove mineralized bone matrix. These cells are multinucleated cells with obvious morphological characteristics and express characteristic proteins such as tartrate-resistant acid phosphatase and calcitonin receptor [84]. Bone marrow mesenchymal stem cells are precursor cells with multiple differentiation potentials, which can differentiate into bone, cartilage, and adipose tissue. They are important regulatory factors for bone modeling, bone remodeling, and bone repair [85].

In order to examine the mechanism of EMFs on bone remodeling, a series of studies have been carried out to explore the effects of different parameters of EMFs on bone cells.

6.1.1. Bone marrow mesenchymal stem cells (BMSCs)

Several studies have shown that EMFs can promote osteogenic and chondrogenic differentiation of BMSCs and promote bone formation.

For SMFs, Kim et al. discovered that SMFs (3/15/50 mT) promoted cell proliferation, ALP activity, calcium release, and mineralized nodule formation in human bone marrow mesenchymal stem cells, and increased the expression of osteogenic marker genes in a dose- and time-dependent manner [86]. Amin et al. reported that SMF (0.4 T) promoted the cartilage differentiation of human bone marrow mesenchymal stem cells [87]. Chen et al. found that SMFs (0.2 T–0.6 T) inhibited the adipogenic differentiation of BMSCs and promoted their osteogenic differentiation in an intensity-dependent manner, with the SMF (0.6 T) increasing the RUNX2-mediated gene transcription in BMSCs [88].

For time-varying magnetic fields, Chen et al. reported that PEMF (16 Hz, 6 μT–282 μT) protected the primary cilia integrity of osteoprogenitor cells and protected them from cigarette smoke extracts [89]. Ehnert et al. reported that in the case of co-culture with osteoblasts, low-frequency PEMF (26 Hz, 6 μT–282 μT) could promote the osteogenic differentiation of adipose-derived mesenchymal stem cells [90]. Bagheri et al. reported that PEMF (75 Hz, 1.5 mT) activated the Notch pathway and promoted the osteogenic differentiation of human mesenchymal stem cells [91]. Martini et al. reported that PEMF (75 Hz, 1.5 mT) promoted the osteogenic differentiation of human bone marrow mesenchymal stem cells by regulating the bone morphogenetic protein-2 signaling pathway [92]. Yang et al. reported that SEMF (15 Hz, 1 mT) promoted the osteogenic differentiation of mesenchymal stem cells, inhibited the formation of adipocytes, and could intervene in the direction of their differentiation [93]. At the same time, Liu et al. found that the viability and differentiation ability of human bone marrow mesenchymal stem cells changed with the frequency of 1 mT SEMF (10/30/50/70 Hz) [94]. Then, Song et al. reported that SEMF (15 Hz, 1 mT) promoted the proliferation and differentiation of rat mesenchymal stem cells in a time-dependent manner [95].

6.1.2. Osteoblasts

Similarly to BMSCs, EMFs are important in promoting maturation and differentiation, increasing the ALP activity, and promoting mineralized nodule production for osteoblasts.

For SMFs, Yamamoto et al. reported that when the SMF (160 mT) was present, the total area, number, and average size of bone nodules produced by the mineralization of rat osteoblasts increased [96]. Imaizumi et al. discovered that exposure to SMF (250 mT) increased mineralized nodule formation in mouse osteoblastic MC3T3-E1 cells [97]. Yang et al. found that SMF (2 T–4 T) promoted the ALP activity and mineralized nodule formation [54], and the SMF (16 T) had no obvious toxic effect on MC3T3-E1 osteoblasts, while increasing cellular proliferation, ALP activity, calcium content, and bone nodule formation [98].

For time-varying magnetic fields, Barnaba et al. reported that the alkaline phosphatase-specific activity of PEMF-exposed (14.9 Hz, 0.4 mT) osteoblast cultures showed a statistically significant increase when compared with the control group after 7 and 10 days of exposure [99]. Esmail et al. found that PEMF (15 Hz, 4 mT) and dexamethasone respectively increased and decreased the proliferation of MC3T3-E1 osteoblasts, meanwhile, PEMF eliminated the effect of dexamethasone on MC3T3-E1 osteoblasts [100]. Wei et al. showed that exposure to PEMF (48 Hz, 1.55 mT) promoted proliferation (increased number of cells in S and G(2)M phase) of primary rat calvaria cells but not of MC3T3-E1 cells [101]. Yan et al. found that PEMF (50 Hz, 0.6 mT) could significantly promote the proliferation and differentiation of osteoblasts, among which primary cilia played an indispensable role [102]. Then, Xie et al. reported that PEMF (50 Hz, 0.6 mT) induced osteoblast differentiation and maturation by up-regulating the expression of BMPRII at the base of the primary cilia [103]. Lin et al. showed that PEMF-exposed (75 Hz, 1.5 mT) osteoblasts had enhanced cell proliferation (23 %), viability (36 %), and Collagen I mRNA expression (3.4-fold) compared to the controls [104]. Cheng et al. reported that SEMF (50 Hz, 1.8 mT) promoted rat osteoblast differentiation and mineralization through NO–cGMP–PKG pathway, when the pathway was blocked, its effect was weakened [105].

6.1.3. Osteoclasts

For osteoclasts, which are important in bone remodeling, EMFs with specific parameters can inhibit osteoclast differentiation.

For SMFs, Zhang et al. reported that SMFs (500 nT, 0.2 T) promoted osteoclast differentiation, formation, and resorption, while 16 T SMF exerted an inhibitory effect by disrupting actin formation [29]. Zhang et al. reported that SMF (1 T–2 T) combined with iron oxide nanoparticles (IONPs) decreased oxidative stress levels in osteoclast differentiation and inhibited the expression of NF-κB and MAPK signaling pathways during osteoclastogenesis [57]. Yang et al. found that SMF (2 T–4 T) inhibited osteoclast differentiation [54]. Dong et al. observed that in the process of osteoclast differentiation, SMF (16 T) significantly inhibited the formation of osteoclasts and reduced their resorption capacity [106].

For time-varying magnetic fields, Barnaba et al. reported that the SMF-exposed (0.9 μT) cells showed a more differentiated phenotype and a significantly higher TRAP activity after 7 and 10 days of treatment with respect to sham control, while the PEMF-exposed (50 Hz, 0.4 mT) cells exhibited a less-differentiated phenotype after 7 days of exposure compared with the relative sham control, while the activity of tartrate resistant acid phosphatase showed no statistically significant differences between exposed and control cells at any observation time [107]. He et al. found that PEMF (8 Hz, 3.8 mT) substantially reduced the number of osteoclast-like cells in the culture with macrophage colony-stimulating factor and receptor activator of nuclear factor-κB ligand, suggesting that it might modulate the process of osteoclastogenesis and subsequent bone resorption, at least partially, through nuclear factor of activated T cells 1 and receptor activator of nuclear factor-κB [108]. Wang et al. demonstrated that PEMFs (15 Hz, 0.5/3 mT) of different intensities regulated osteoclasts in different ways, bone

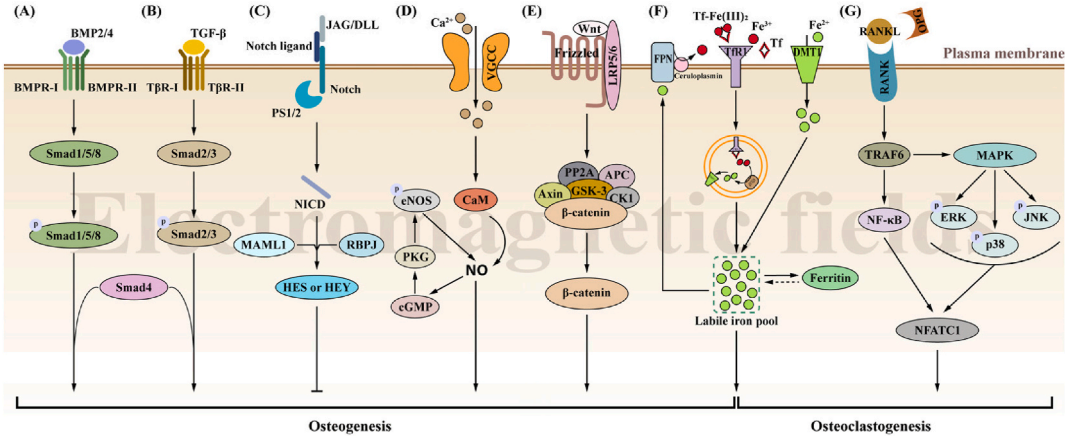

Fig. 4. Signaling pathways of EMFs on bone remodeling. EMFs affect the osteogenesis of BMSCs, osteoblasts, and osteocytes by influencing the BMP/Smad pathway, TGF-β/Smad pathway, Notch pathway, Wnt/β-catenin pathway, calcium intake, NO-cGMP-PKG pathway, and iron transport. Additionally, EMFs impact the osteoclastogenesis of osteoclasts by influencing iron transport, RANK/RANKL/OPG pathway, and MAPK pathway.

resorbing capacity was significantly decreased by 0.5 mT PEMF, primarily through inhibiting osteoclast formation and maturation, but was enhanced at 3 mT by promoting osteoclast apoptosis [109]. He et al. found that PEMF (15 Hz) could significantly inhibit osteoclast formation and gene expression, and reduce osteoclast activity [110].

6.1.4. Osteocytes

For osteocytes, even though it is important for bone remodeling, the number of studies on EMFs on osteocytes is relatively poor, as described below.

Yang et al. showed that SMF (16 T) promoted cellular viability, decreased apoptosis, increased the fractal dimension of the cytoskeleton, altered the secretion of cytokines, and increased iron levels in osteocytes [111]. Subsequently, Zhang et al. found that magnetic force loading of SMF (12 T) in the same direction as that of gravity promoted the proliferation and inhibited apoptosis of MLO-Y4 osteocytes [112]. Wang et al. found that PEMF (15 Hz, 0.5/3 mT) could inhibit osteocyte apoptosis, and can also inhibit osteocyte-mediated osteoclast production [113].

Up to now, there have been few studies on the EMFs of osteocytes. We believe that there are two main reasons, one is that osteocytes are buried in the hard tissues of bones, which makes it difficult to extract them, and the other is that people have thought that osteocytes are not active and play a minor role. However, with the emergence of various experimental techniques in recent years, people have gradually realized that osteocytes also play an important role in bone remodeling. Therefore, the effect of EMFs on the function of osteocytes might become the focus of future research with deep significance.

In summary, EMFs with specific parameters can promote the proliferation of BMSCs, promote their osteogenic and chondrogenic differentiation; they can promote the proliferation and differentiation of osteoblasts and increase ALP activity; they can inhibit apoptosis of osteocytes, promote their proliferation, and inhibit the osteoclastogenesis they mediate; and they can inhibit osteoclastogenesis by disrupting actin formation and promoting cell apoptosis. These results suggest that EMFs affect the process of bone remodeling by acting on various bone cells. At the same time, since the EMFs only work at specific parameters, the effects of different intensities are different, suggesting that the EMFs have a window effect which is multi-targeted.

6.2. The signaling pathways of EMFs acting on bone remodeling

As the effects of EMFs on bone remodeling are multi-targeted, we summarize the multiple pathways of EMF action covered in the above studies and introduce these pathways in a summarized manner to make it easier for the readers to understand the cascading effects involved (Fig. 4).

BMP/Smad pathway: EMFs affect the osteogenesis by BMP/Smad pathway. Bone morphogenetic protein (BMP2/4) binds to BMP receptor (BMPR) and leads to the phosphorylation of the Smad vertebrate homologues of mothers against decapentaplegic (Smad1/5/8). They form a complex with Smad4 and then enter the nucleus to control gene expression.

TGF-β/Smad pathway: EMFs influence the osteogenesis by TGF-β/Smad pathway. Transforming growth factor-β (TGF-β) is the prototype of a superfamily of multifunctional proteins which includes activins and BMPs. TGF-β binds to TGF-β receptor (TβR) and leads to the phosphorylation of Smad2/3. They form a complex with Smad4 and then enter the nucleus to control gene expression.

Notch pathway: EMFs affect the osteogenesis by Notch pathway. Notch signaling is a negative regulator of osteoblast differentiation, which requires direct cell-to-cell contact. The Notch receptors expressed on the cell surface bind with Jagged (JAG) or Delta-like protein (DLL). Assisted by presenilin 1/2 (PS1/2), Notch intracellular domain (NCID) is released. This domain translocates to the cell nucleus, interacts with the recombination signal-binding protein for immunoglobulin kappa J region (RBPJ), a member of the hairless LAG-2 family, and initiates the mastermind-like protein 1 (MAML1) activator complex. The activator complex induces the expression of Notch target genes, including those encoding hairy and enhancer of split (HES) and HES-related with YRPW motif (HEY) genes, thereby influencing osteogenesis.

NO-cGMP-PKG pathway: EMFs regulate the osteogenesis by NO-cGMP-PKG pathway. Nitric oxide (NO) is an important molecule involved in the behavior of bone cells. A low level of NO promotes osteoblast proliferation, but NO at high concentration inhibits the proliferation and differentiation of osteoblasts. The activation of the NO pathway is possibly caused by the high level of Ca^{2+} within cells. Following cellular uptake of Ca^{2+}, it binds to calmodulin (CaM), which stimulates nitric oxide synthase (NOS) to catalyze the oxidation of arginine to form citrulline and the release of NO. NO activates the NO receptor, which has guanylate cyclase activity, and stimulates the production of the second messenger cyclic guanosine monophosphate (cGMP). This cGMP binds to the cGMP-binding structural domain of protein kinase G (PKG) and activates the catalytic structural domain of PKG. This induction leads to the phosphorylation of endothelial nitric oxide synthase (eNOS), resulting in more NO production, which affects osteogenesis.

Wnt/β-catenin pathway: EMFs influence the osteogenesis by Wnt/β-catenin pathway. The canonical Wnt pathway, as a positive regulator of osteoblast differentiation, communicates by binding to cell surface

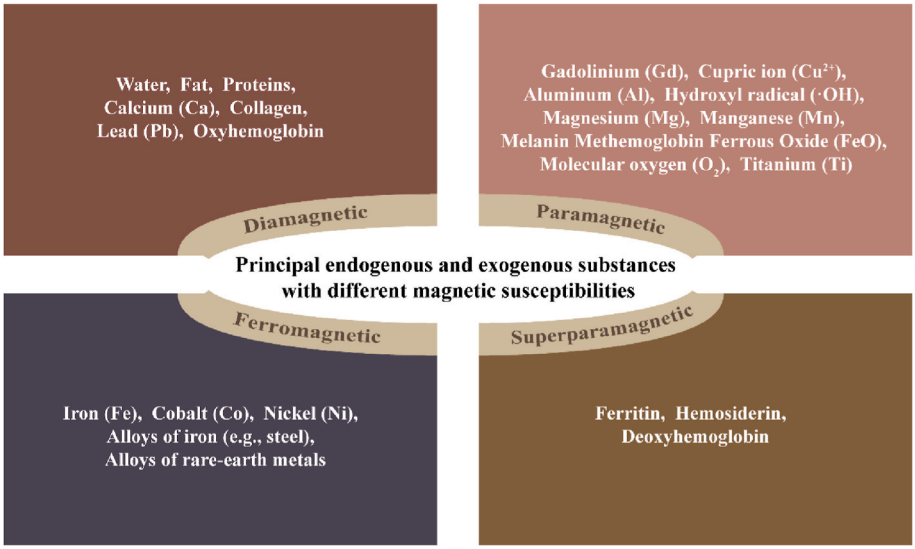

Fig. 5. Magnetism of endogenous/exogenous substances in organisms.

receptors, triggering intracellular signal cascades. In the absence of the Wnt ligand, β-catenin does not accumulate in the cytoplasm. It forms a complex with Axin, Glycogen Synthase Kinase 3 (GSK3), Protein Phosphatase 2A (PP2A), Adenomatous Polyposis Coli (APC), and Casein Kinase 1 (CK1), leading to its degradation. When the Wnt ligand is present, it binds to the Wnt receptor complex on the cell surface, consisting of Frizzled and low-density lipoprotein receptor-related protein 5/6 (LRP5/6). This interaction prevents the degradation of β-catenin by the Axin-GSK3 complex, allowing β-catenin to translocate into the cell nucleus and initiate downstream gene transcription.

Iron transport: EMFs affect the osteogenesis and osteoclastogenesis by changing iron transport. Iron is an essential trace element in cellular growth and metabolism, and EMFs can influence its transport. Extracellular Fe^{2+} directly enters the labile iron pool through divalent metal transport 1 (DMT1) on the cell membrane, while Fe^{3+} binds to transferrin (Tf) and enters the cell through transferrin receptor protein 1 (TfR1). Inside the cell, Fe^{3+} converted to Fe^{2+} by the six-transmembrane epithelial antigen of prostate 3 (STEAP3) and then enters the labile iron pool through DMT1. Some iron is stored in the form of ferritin, and excess iron is transported out of the cell via ferroportin (FPN).

RANKL/NF-κB pathway and RANKL/MAPK pathway: EMFs regulate the osteoclastogenesis by RANKL/NF-κB pathway and RANKL/MAPK pathway. Receptor activator for nuclear factor-κB ligand (RANKL) is a bone remodeling secreted factor secreted by osteocytes or osteoblasts that can induce osteoclast differentiation. During bone resorption, RANKL binds to the receptor activator for nuclear factor-κB (RANK) on the surface of osteoclasts and their precursor cells to induce osteoclast differentiation and formation; during bone formation, osteoprotegerin (OPG), another secreted factor, inhibits RANKL/RANK binding, thereby inhibiting osteoclast differentiation. Multiple RANKL-related pathways require tumor necrosis factor receptor associated factor 6 (TRAF6), which is triggered when RANKL binds to RANK, subsequently, the NF-κB pathway and MAPK pathway were induced in the cells.

In summary, electromagnetic fields act on bone through multiple pathways, and these pathways also interact with each other to regulate bone remodeling.

Moreover, at both the cellular and animal levels, more and more studies have identified genes and drugs that regulate bone remodeling other than the previously mentioned signaling pathways [114–116]. These findings provide new insights into the clinical applications of EMFs, such as their combination with inhibitors or drugs, and offer new perspectives for investigating the biological mechanisms underlying the effects of EMFs on bone remodeling.

7. Physical mechanisms of EMFs on bone

In the study of the effects and mechanisms of EMFs on bone remodeling, in addition to biological mechanisms, the exploration of physical mechanisms is also essential. From the source, the physical mechanisms are even more fundamental. The following discussion begins with the magnetism and dielectric properties of living organisms, introduces the physical stimuli of electromagnetic fields acting on biological tissues, and proposes hypotheses about the physical mechanisms.

7.1. The magnetism and dielectric properties of organisms

7.1.1. The magnetism

All substances, including human tissues, possess specific forms of magnetism [117]. In electromagnetism, magnetic susceptibility (χ) is a quantitative parameter that reflects the magnetization strength of materials when an external magnetic field is applied. This parameter is commonly used to characterize the magnetic properties of the material [118]. The magnetic properties of materials can also be characterized using magnetic permeability (μ), measured in units of henries per meter (H/m). This parameter represents the resistance to the generation of magnetic flux when a current flows through a coil in space or in the core space. It also reflects the ability of the material to conduct magnetic field lines in a magnetic field.

Based on the various interactions between magnetic fields and substances, substances can be divided into four types: diamagnetic materials, paramagnetic materials, superparamagnetic materials, and ferromagnetic materials. Diamagnetic materials exhibit repulsion when exposed to a magnetic field, and their χ is negative, while the remaining three materials tend to be attracted by a magnetic field, and their χ is characterized by positive values [119].

Due to the diamagnetic properties of water, biological tissues are predominantly diamagnetic on a macroscopic scale. However, on a microscopic scale, the magnetism of biological organisms is more complex. Gaeta M. summarized the main substance components with different magnetic properties commonly found in magnetic resonance imaging, including diamagnetic, paramagnetic, superparamagnetic, and ferromagnetic materials [119], as shown in Fig. 5.

7.1.2. The dielectric properties

In addition to magnetism, biological organisms also have dielectric

Table 2
Linear correlation coefficients between compositional parameters and densities and electrical parameters of human trabecular bone at 1.2 MHz (BMDvol: volumetric bone mineral density; GAG: glycosaminoglycan).

	Relative permittivity	Conductivity	Specific impedance
Wet density	0.60	−0.59	0.48
Dry density	0.41	−0.77	0.69
BMD_{vol}	0.67	−0.50	0.49
Fat content	−0.85	0.10	−0.11
Water content	−0.07	0.79	−0.76
Collagen content	0.64	−0.43	0.40
GAG content	0.22	−0.25	0.31

properties. The composition of living organisms, whether it is large molecules such as proteins and nucleic acids that make up living organisms or some inorganic ions in living organisms such as potassium ions, sodium ions, iron ions, etc., all carry charges. The movement and interaction of these charges give living organisms dielectric properties.

The electrical characteristics of living organisms are typically characterized by physical parameters such as permittivity (ε), conductivity (σ), impedance (Z), and others. Permittivity (ε) is a major parameter that reflects the dielectric or polarization properties of a dielectric under the influence of an electric field. Conductivity (σ), also known as electrical conductivity, is used to characterize the ease with which electric charge can flow through a dielectric and is measured in siemens per meter (S/m). And the impedance (Z) represents the resistance of the dielectric to the flow of electric current, and its unit is ohms (Ω). Impedance can be divided into capacitive reactance and inductive reactance, which respectively characterize the hindrance caused by capacitance and inductance to alternating current in a circuit.

For biological tissues, different tissues have different dielectric properties. More importantly, even the same type of tissue with varying compositions can exhibit different dielectric properties. A study has shown that for human trabecular bone, the content of different components (fat, water, collagen, glycosaminoglycan, etc.) can significantly affect the dielectric properties of bone, as shown in Table 2 [120]. This also brings us the revelation that by detecting the dielectric properties of different bone tissues, we can judge the component content and health status of the bone, which provides a new idea for medical detection.

7.2. Physical stimuli to bone from EMFs

7.2.1. Force stimuli

Since organisms have magnetic properties, when biological tissues are placed in a magnetic field, they are subjected to magnetic forces [112], and the calculation formula is as follows:

$$\boldsymbol{F} = -\frac{\chi_p}{\mu_0}\boldsymbol{B}\frac{d\boldsymbol{B}}{dz} \tag{1}$$

Where $\boldsymbol{F}$ denotes the magnetic forces with unit in newton (N), χ_p represents the volume magnetic susceptibility, μ_0 is the magnetic permeability of vacuum ($=4\pi \times 10^{-7}$ H/m), $\boldsymbol{B}$ is the magnetic flux density with unit in tesla (T), $\frac{d\boldsymbol{B}}{dz}$ is the vertical field gradient with unit in tesla per meter (T/m).

In addition to the magnetic force, due to the dielectric properties of biological tissues, when they are in a magnetic field, charged particles within the tissues experience the action of the Lorentz force, calculated as follows:

$$\boldsymbol{F}_e = q\boldsymbol{E} \tag{2}$$

$$\boldsymbol{F}_m = q(\boldsymbol{v} \times \boldsymbol{B}) \tag{3}$$

Where $\boldsymbol{F}_e$ denotes the Lorentz force in an electric field with unit in newton (N), $\boldsymbol{F}_m$ denotes the Lorentz force in a magnetic field, q represents the charge of the charged particle, measured in coulomb (C), $\boldsymbol{E}$ represents the electric field strength, measured in volts per meter (V/m) or newtons per coulomb (N/C), $\boldsymbol{v}$ is the velocity of the charged particle with its unit in meters per second (m/s), $\boldsymbol{B}$ is the magnetic flux density with unit in tesla (T). Under the influence of the Lorentz force, charged particles experience momentary tiny displacements, resulting in the generation of acoustic wave vibrations, which can have effects on biological tissues. When the acoustic vibrations propagate to the surface of the dielectric, they can be detected by an external acoustic sensor, and by analyzing the acoustic signals, information such as the sample's geometric shape and conductivity distribution can be obtained. This is the fundamental principle of magnetoacoustic imaging.

In summary, different molecules in organisms have different bioelectromagnetic properties, leading to different magnetic forces and Lorentz forces acting on them in a magnetic field. This can result in alterations in the physiological functions of the organism, which may be one of the reasons why magnetic fields can have an impact on living organisms.

7.2.2. Electrical stimuli

Since biological tissues have dielectric properties, when they act as conductors in a magnetic field, currents are induced within the tissues. This phenomenon is commonly referred to as electromagnetic induction, and the resulting current is known as induced current [30]. The calculation formula is as follows:

$$\boldsymbol{J} = \pi\sigma r\boldsymbol{B}f \tag{4}$$

Here, $\boldsymbol{J}$ represents the induced current density, measured in amperes per square meter (A/m^2), σ represents the conductivity with unit in siemens per meter (S/m), r stands for the radius of the induced current loop with unit in meter (m), $\boldsymbol{B}$ is the magnetic flux density with unit in tesla (T), and f denotes the frequency, measured in hertz (Hz). The formula for the induced electric field generated within a biological organism is as follows:

$$\boldsymbol{E} = \frac{\boldsymbol{J}}{\sigma + j\omega\varepsilon_o\varepsilon_r} \tag{5}$$

Where $\boldsymbol{E}$ represents the electric field strength, measured in volts per meter (V/m) or newtons per coulomb (N/C), $\boldsymbol{J}$ represents the induced current density, measured in amperes per square meter (A/m^2), σ represents the conductivity with unit in siemens per meter (S/m), j is imaginary unit, ω is the angular velocity with unit in radians per second (rad/s), ε_r stands for the relative permittivity of the material with unit in farads per meter (F/m), and ε_o is the vacuum permittivity, approximately equal to 8.85×10^{-12} F/m.

In conclusion, when a biological organism is exposed to a constant or varying magnetic field, it can generate internal induced currents or electric potentials. This may also be one of the reasons why magnetic fields can have an impact on biological systems.

7.2.3. Thermal stimuli

Electromagnetic fields acting on living organisms not only induce mechanical and electrical effects but also lead to thermal effects.

Absorption is the process of converting electromagnetic energy into another form, such as heat, which is then transferred to the surrounding medium. There are two methods for determining electromagnetic thermal dosages: Specific Absorption Rate (SAR) is used for frequencies below 10 GHz, while Power Density (PD) is used for frequencies above 10 GHz [30]. Specific Absorption Rate (SAR) is the rate at which energy is absorbed in human tissue and is measured in W/kg. It is calculated using the following formula:

$$SAR = \frac{\sigma|\boldsymbol{E}|^2}{\rho} = c\frac{dT}{dt} \tag{6}$$

Where σ represents the conductivity with unit in siemens per meter (S/

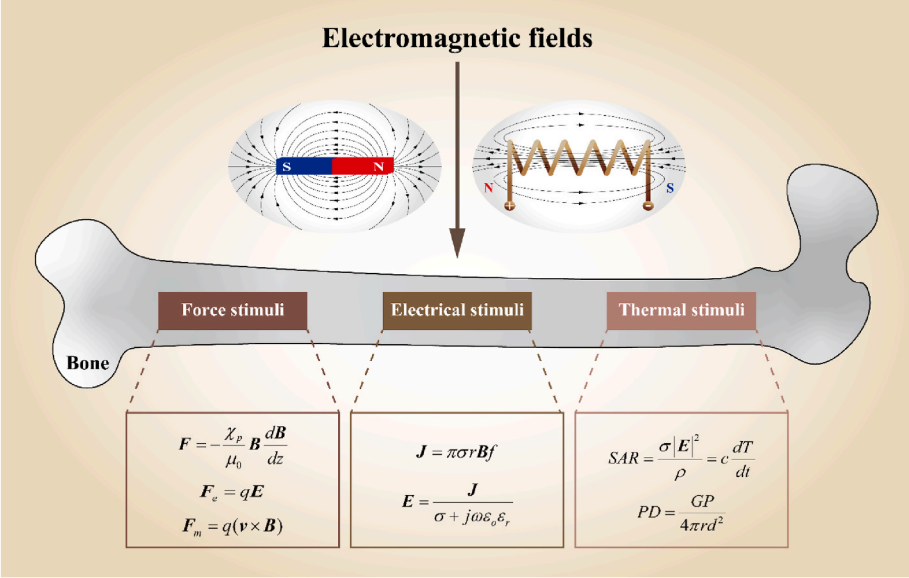

Fig. 6. Physical mechanisms of electromagnetic fields on bone.

m), $\boldsymbol{E}$ represents the electric field strength, measured in volts per meter (V/m) or newtons per coulomb (N/C), ρ is the mass density, measured in kilograms per cubic meter (kg/m^3), c denotes the specific heat capacity with unit in joules per kilogram per kelvin (J·kg^{-1}·K^{-1}), and $\frac{dT}{dt}$ is the time derivative of temperature, measured in kelvin per second (K/s).

Power density (PD) refers to the rate at which electromagnetic energy flows through a unit area perpendicular to the direction of wave propagation, measured in watts per square meter (W/m^2). It can be calculated using the following formula:

$$PD = \frac{GP}{4\pi r d^2} \tag{7}$$

Here, G denotes the linear gain of the transmitting antenna, P is the total power of the antenna in watt (W), r is the radius of the induced current loop in meter (m), and d represents the distance between the biological tissue and the radiation source in meter (m).

In summary, when a biological organism is exposed to a constant or changing magnetic field, it generates induced currents or potentials internally. The biological organism is influenced by forces, and then leading to thermal effects. These effects are likely part of the electromagnetic physics mechanisms through which magnetic fields can affect biological organisms. The analysis of thermal effects is closely related to the safety assessment of electromagnetic field exposure on biological entities (Fig. 6).

8. Conclusion

This review based on the existing literature, summarizes the role of the EMFs with different parameters in the treatment of bone remodeling disorders, including clinical application and laboratory research. At the same time, starting from the biophysical mechanism of the effect of EMFs on bone, the effect of EMFs on bone cells was reviewed. The characterization of bioelectromagnetic properties was summarized, and the possible biophysical mechanism of EMFs on bone was assumed based on various physical parameters.

Currently, as one of the non-invasive physical therapies, EMFs are widely used in the clinical treatment of bone remodeling disorders. As summarized, we speculate that EMFs induce various biological signals accordingly by delivering physical stimuli such as electrical, mechanical, and thermal cues into the bone cells. These stimuli trigger various biological signals, ultimately regulating bone cell activity and function. However, there are still several critical research gaps in the current studies. Since EMFs generate multiple physical stimuli in bone and exert multi-targeted effects on bone remodeling, their bioelectromagnetic mechanisms still require further investigation. A key challenge is to distinguish the individual and combined contributions of different physical factors. For this reason, we propose the concept of "Electro-Magnetic Fields Multi-Physical Stimuli (EMMPhS)", which emphasizes that EMFs can generate multiple physical quantities such as magnetic, electric, force, acoustic, and thermal stimuli within biological tissues. Investigating how these factors interact and contribute to bone remodeling will be essential for optimizing EMF-based therapies. Additionally, current therapeutic devices primarily utilize low-frequency EMFs, while the effects of medium/high-frequency EMFs on bone remodeling are still largely unknown. Since the window effect of EMFs, determining more effective and safer treatment parameters remains an urgent priority, which is of great significance for the development of safer, more effective, and cost-efficient clinical devices.

In conclusion, the treatment of bone remodeling disorders with EMFs has good application prospects, the exploration of its bioelectromagnetic mechanisms, new physical parameters, and the development of new equipment still need to be further researched, which will be a worthy subject for in-depth study.

Author contributions

JL and PS conceived this review, JL drafted the manuscript and drew illustrations, WR, SW, JY, HZ, YZ and DY performed the literature search and analysis, and all authors revised the manuscript. All authors approved the final version of the manuscript.

Declaration of competing interest

No potential conflict of interest was reported by the authors.

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