



Magnetic Materials in Promoting Bone Regeneration

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OPEN ACCESS

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Specialty section:

This article was submitted to
Biomaterials,
a section of the journal
Frontiers in Materials

Received: 16 July 2019

Accepted: 14 October 2019

Published: 01 November 2019

Citation:

Peng J, Zhao J, Long Y, Xie Y, Nie J
and Chen L (2019) Magnetic Materials
in Promoting Bone Regeneration.
Front. Mater. 6:268.
doi: 10.3389/fmats.2019.00268

Strategies to promote bone regeneration have been always the focus of investigations since the skeleton plays important roles like mechanical support, organ protection, and mineral homeostasis maintenance in the normal physiological activities of the human body. Magnetic fields have shown to be highly influential in the regeneration process, arousing tremendous interest in utilizing magnetic materials to enhance osteogenesis. In this work, we attempt a more comprehensive and detailed review of magnetic materials in promoting bone regeneration by including not only the mechanisms of bone regeneration, the history and basic concepts of magnetism, but also the types of magnetic materials as well as their influence parameters, designs and fabrication techniques with a focus on their usage in the field of bone regeneration like 3D printed scaffolds and implants. In addition, we provide some possible ideas on the synergistic action between magnetic and other materials on bone tissue. Finally, we propose the development trend of magnetic materials in the field of bone regeneration in the future. There is a huge demand for a more effective and less traumatic way to accelerate bone regeneration of the patients with diseases like fractures, tumors and osteoporosis that cause severe pains, bone loss, limb deformations, and restrictions of mobility. Magnetic materials have substantial potential to be manufactured into novel clinical applications with the ability to increase the bone regeneration efficiency.

Keywords: magnetic materials, bone diseases, bone regeneration, magnetic fields, influence factors, synergistic effects

INTRODUCTION

As a highly mineralized tissue, bone not only provides mechanical protection for connective tissue and soft tissue, it also actively participates in the regulation of pH and calcium levels in blood and the formation of blood cells (Porter et al., 2009). Before we explore magnetic materials, the process of bone regeneration must be understood.

“Osteogenesis” is a procedure where bone-forming cells [mainly multipotent mesenchymal stem cells (MSCs)] mature and differentiate into osteoblasts. Osteogenesis is accompanied by mineralization of the extracellular matrix by deposition of calcium hydroxyapatite (Caetano-Lopes et al., 2007). Both of the signaling molecules (e.g., cytokines, growth factors, sex hormones) and interactions with osteoclasts (cells derived from macrophages which have the opposite role to osteoblasts) (Huang et al., 2014), have an influence on proliferation, differentiation, and function of osteoblasts. The relationship between osteoblasts and osteoclasts is related mainly to the receptor activator of nuclear factor- κ B ligand (RANKL), usually on the surface of developing osteoblastic cells, which can bind with its receptor RANK, resulting in the activation, proliferation

and differentiation of pre-osteoclast cells (Khosla, 2001; Atkins et al., 2003). Osteoprotegerin (OPG) is an osteoblast-derived factor, which can bind with RANKL as a “decoy” receptor to inhibit the bone resorption (Theoleyre et al., 2004). Moreover, the secreted protein transforming growth factor (TGF)- β 1 is able to promote the aggregation, proliferation, and differentiation of osteoblast and increasing OPG expression while reducing RANKL expression (Janssens et al., 2005). The formation of osteoblasts and osteoclasts is shown schematically in **Figure 1**.

Bone defects can heal spontaneously to an extent, particularly in younger individuals (Stevens, 2008). However, they cannot cope with extensive mechanical stimuli or damage that is beyond their regeneration capacity, such as fractures, tumors, osteoporosis, and other bone disorders (Fernandez-Yague et al., 2015). Hence, there is a desperate need for more efficacious treatment. Verrier et al. reviewed the approaches to tissue engineering/regeneration from the perspective of vascularization and gene therapy (Verrier et al., 2016). In general, strategies to accelerate bone regeneration can be categorized as biological, physical, or surgical (**Table 1**).

Of the methods listed in **Table 1**, physical stimulation has been preferred to use of pharmacologic agents and surgery by clinicians and patients because it is non-invasive. Magnetic materials have caught the researchers’ attention because of their low cost and adaptability. Surgical insertion of a bone substitute directly into the bone defect would appear to be the quickest way to repair bone. However, Grado et al. summarized the most commonly used bone substitutes and pointed out a lack of angiogenesis in the center of the replacement (Fernandez de Grado et al., 2018). A review by Xia et al. (2018) introduced studies of magnetic fields and magnetic nanoparticles (MNPs) on osteogenic enhancements.

Here, we highlight use of magnetic materials in bone applications. We explain their background, factors that influence their use, as well as their design and fabrication methods. In addition, the synergistic effects of magnetic materials with other materials are also discussed.

MAGNETIC MATERIALS AND BONE REGENERATION

Basic Concepts of Magnetism

Magnetic materials usually consist of iron (Fe), cobalt (Co), or nickel (Ni). These materials can produce magnetic fields directly or indirectly. They are functional materials with a very long history and wide range of uses. Magnetic fields may also be generated by variation in an electric field. This includes a concentric magnetic field formed around a cylindrical conductive wire, which is called an electromagnetic field (EMF). EMFs can be subdivided into pulse electromagnetic fields (PEMFs), alternating magnetic field (AMFs), or rotating magnetic fields (RMFs). Static magnetic fields (SMFs) are produced by permanent magnets. Among them, SMFs and PEMFs are used most widely.

Magnetic fields have two main properties: direction and magnitude. Two objects can interact with each other even if separated by space. There are many physical quantities used to

describe the magnetic properties of materials, some of which are listed in **Table 2**.

Recent decades have witnessed the rapid development and wide application of magnetic materials in various fields. For example, “soft” magnetic materials are critical for the next generation of electrical machines to enable sustainable electricity worldwide (Silveyra et al., 2018). Moreover, some magnetic materials with coatings have been utilized to separate various molecules and cells (Kudr et al., 2017). Magnetic particles and composites can be used for drug delivery (Amiri et al., 2019), imaging-based diagnosis of cancer (Belyanina et al., 2017) and non-invasive clinical measurements (e.g., measurement of Fe levels in the liver) (Avrin and Kumar, 2007). Scientists have focused on the synthesis of materials with magnetic effects and their biological performance (Tampieri et al., 2014; Cao et al., 2018; Patel et al., 2018). A great advantage of magnetic materials is that they can deliver biological “cues” without the need for contact with tissues. Besides, magnets can be made into various appropriate formulations, making it easier to locate them at the appropriate sites to influence physiological processes.

Parameters Influencing the Magnetic Properties of Materials

The factors affecting magnetic properties must be clarified so that better use of materials can be made for research and production. For example, in biosensing, higher M_s is preferred because it provides higher sensitivity and efficiency than lower M_s (Colombo et al., 2012). Here, we focused mainly on the effects of the size, temperature, composition and preparation methods on the magnetic properties of materials because these four parameters have great practical utility and can be manipulated if appropriate methods are employed.

Magnetic materials can be blocks, membranes or even fluids. Nevertheless, it is the size of each magnetic particle not the magnetic material itself that influences the properties of the magnetic composite. A decreasing diameter can enhance H_c ; that is, the smaller the diameter, the stronger is the ability to retain magnetism. From 1962 to 1975, researchers reduced the size of a γ -Fe₂O₃ particle from 1 to 0.3 μ m, and H_c increased nearly 30-fold (Aharoni et al., 1962b; Matsui et al., 1976). If a magnetic particle is reduced to a certain size, its magnetic direction changes readily with the external magnetic field (“superparamagnetism”) (Bean and Livingston, 1959). Hence, improving the thermal stability of a magnetic particle while reducing its size could help to obtain higher H_c . Moreover, the magnitude of M_s depends upon the size of nanoparticle (NP) to some extent (Jun et al., 2008). However, Peddis et al. found that large NPs showed lower H_c compared with smaller NPs, suggesting that other factors influence their magnetic properties (Peddis et al., 2008).

In 1895, the future Nobel Prize winner Pierre Curie found that ferromagnetic materials behaved in a paramagnetic manner above a certain temperature, and named it the “Curie temperature” (T_c). There are dozens of types of magnetic materials, each with its own T_c (Oguchi et al., 1983; Mohn and

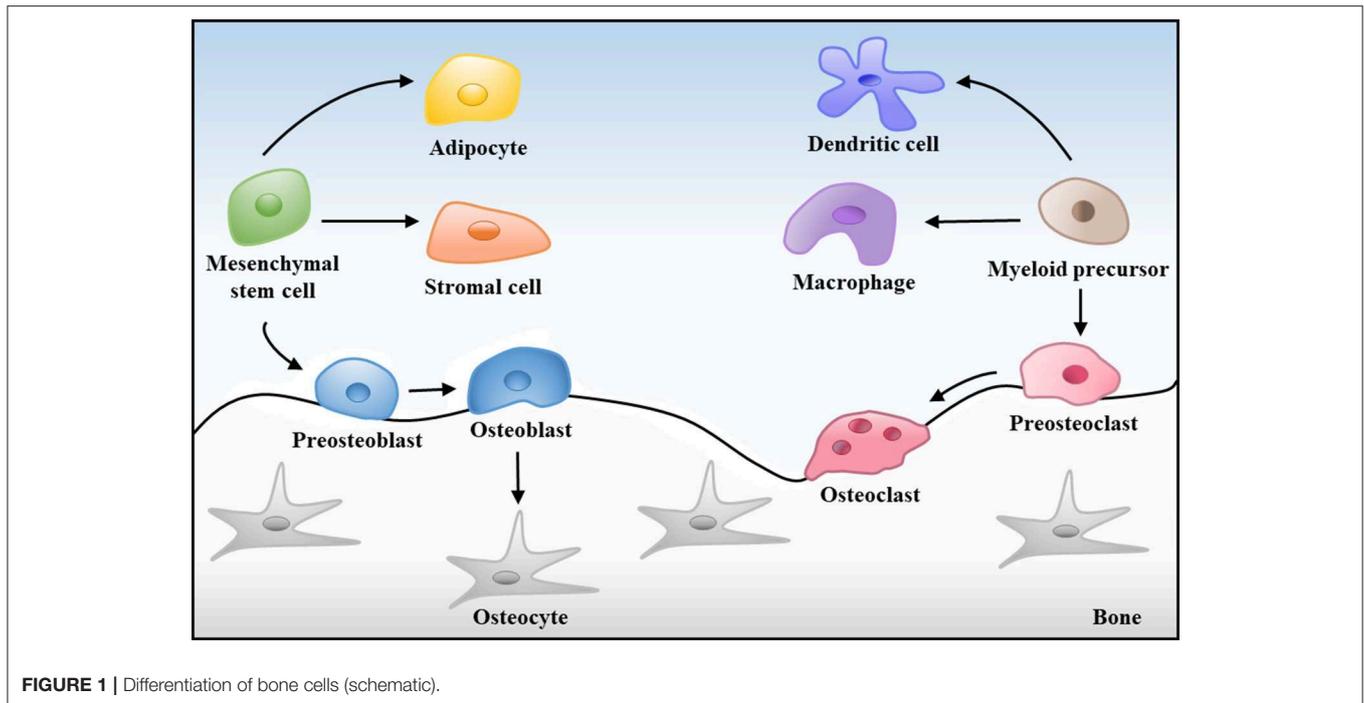


FIGURE 1 | Differentiation of bone cells (schematic).

Wohlfarth, 1987). For example, the T_c of $\alpha\text{-Fe}_2\text{O}_3$ is 725°C (Aharoni et al., 1962a).

The different compositions of magnetic materials also have considerable influence on their properties. In 1978, Uehori et al. claimed that the maximum H_c could be reached using 70% of Fe and 30% of Co (Uehori et al., 1978). In 2007, Chaubey et al. found M_s reached a maximum if the molar ratio of Fe:Co was 1.5:1 (Chaubey et al., 2007). The performances of biomedical devices can be improved by adjusting the composition of magnetic materials. But the effects of different compositions are usually detected *in vitro*, which has resulted in a lack of data for *in vivo* applications.

The preparation method also has an important impact on magnetic properties. Traditionally, magnetic powder is made by grinding, during which the grains are deformed readily, causing internal stress, which is unfavorable to the properties of the final magnetic products. In 1989, Coehoorn et al. heated a metal slowly to a certain temperature, maintained it for a sufficient time, and then cooled it at an appropriate rate. This annealing procedure eliminated the internal stress, restored the magnetism, and optimized the properties of permanent magnets. Moreover, the permeability of the magnetic material will decrease whereas the H_c will increase if appropriate annealing measures are not taken (Coehoorn et al., 1989).

The magnetic properties depend upon the synthetic method, too. For example, Clavel et al. observed that when benzyl alcohol was used, co-doped MNPs were ferromagnetic, but when an anisole/benzyl alcohol solvent system was used, the MNPs were antiferromagnetic (Clavel et al., 2007). Hence, using different solvents during the synthesis may produce materials with opposite magnetic properties.

In addition to the four main factors mentioned above, other factors are related to magnetization, such as the relative distribution of the cation in the crystal structure and the shape of magnetic materials. Comparisons of the parameters influencing magnetic properties are listed in Table 3.

The Effects of Magnetic Materials on Bone Regeneration

Magnetic materials can create magnetic fields (including SMFs and PEMFs), which are closely related to the survival and evolution of creatures on Earth because all organisms are under a geomagnetic field (Lohmann, 2010). Moreover, magnetism arises from moving electrons, but cells, tissues, and organs have magnetic fields of their own, and different magnetic fields may interact with each other. Therefore, several scientific research have paid attention to the possible health effects of magnetic materials.

Biological Effects of Magnetic Fields on the Body

The therapeutic functions of magnetic fields have attracted the attention of people for many years. The first attempt toward application of magnets was made at the Pitié-Salpêtrière Hospital in Paris (Richet, 1880). Since the twenty-first century, magnetic materials have been used more widely in medicine, such as in breast-cancer therapy (Zheng et al., 2018), treatment of bacterial infections (Xu et al., 2019), cardiovascular repair (Vosen et al., 2016b), neural regeneration (Funnell et al., 2019), and especially in the skeletal system (Thevenot et al., 2013).

There are relatively more research about the effects of magnetic fields on nervous system and skeletal

TABLE 1 | Common strategies employed to augment bone regeneration.

References	Methods	Mechanisms of actions	Advantages	Disadvantages
BIOLOGICAL APPROACH				
Carter and Schipani, 2006	Calcitonin	Direct action on osteoblasts, osteoclasts, and osteocytes.	1. Simple and easy to operate because oral administration or local injections are employed. 2. The mechanisms have been studied relatively deeply.	1. They may have an effect on the whole body with other complications. 2. The effect is not strong enough.
Boyce et al., 2003; Lombardi et al., 2011; Benson et al., 2016	Parathyroid hormone	Promoting RANKL production to stimulate osteoclast activation indirectly.		
Eells et al., 2003; Bonnet et al., 2008	Thyroid hormone	Increasing the volume of trabecular bone but the method is controversial.		
Kenny and Raisz, 2002	Sex hormones	Altering the secretion of local cytokines, prostaglandins and growth factors.		
PHYSICAL APPROACH				
Eells et al., 2003; Fujita et al., 2008; Karu, 2008	Low-level laser	Stimulating the synthesis of major matrix protein in bone and the proliferation of osteoclasts, osteoblasts, and fibroblasts.	1. They can be used in a non-invasive way, thereby decreasing the pain of patients. 2. Relatively inexpensiv.	1. Considerable uncertainty about the mechanisms. 2. The range of action is not easy to control accurately. 3. There is not a clear "gold standard" for the dose or irradiation time.
Shimizu, 1986; Nishimura et al., 2008	Vibration	Increasing RANKL expression in fibroblasts and osteoclasts.		
Saunders, 2005; Xu et al., 2011; Jing et al., 2014	Magnet	See section magnetic materials and bone regeneration for details.		
Friedenberg et al., 1970; Davidovitch et al., 1980	Electric current	Increasing expression of the genes related to osteo-differentiation, angiogenesis and collagen organization.		
SURGICAL APPROACH				
de Melo Pereira and Habibovic, 2018	Bone graft	Filling the defect directly.	1. The effect is obvious, which can shorten treatment time. 2. The site of action is accurate.	1. There are risks of immunogenic response, donor-site morbidity, and pathogen transmission. 2. The properties of the materials used in bone transplantation may not match those of natural bone.
Leucht et al., 2007	Corticotomy and osteotomy	Triggering more aggregation of cytokines and chemokines and inducing rapid demineralization of surrounding normal bone, thus accelerating bone repair (regional acceleratory phenomenon).		
Acikan et al., 2018	Distraction osteogenesis	Activating the proliferation and creation of cells.		

system. It is reported that low-frequency magnetic fields: (i) can active N-methyl-D-aspartate receptors in glutamatergic Ca^{2+} channels to promote neuronal differentiation (Ozgun et al., 2019); (ii) may improve depressant behavior and cognitive dysfunction mainly by modulating synaptic function (Yang et al., 2019). However, repeated stimulations of intracranial nerves may bring inestimable side effects, and the penetration depth is relatively limited.

SMFs has been reported to have the ability to inhibit proliferation of cancer cells by influencing the orientation of kinase domains of epidermal growth factor receptors (EGFRs) (Zhang et al., 2016a). Also, bare iron-oxide NPs are able to produce significant amounts of reactive oxygen species (ROS), which can disrupt the mitochondrial activity of tumor cells at a certain concentration (Gokduman and Gok, 2020). However, cancer treatment using magnetic materials is achieved mainly by the delivery of special anticancer drugs to cancer cells through

TABLE 2 | Several main physical quantities used to describe the magnetic properties of materials (Bozorth, 1947).

Physical quantity	Symbol	Unit	Meaning
Magnetization	M	T	The local value of its magnetic moment per unit volume.
Saturation magnetization	M_s	T	With the increase of the intensity of external magnetic field, the magnetization of a magnetic material also increases. When the external magnetic field increases to a certain intensity, the magnetization of the material reaches the maximum. This steady magnetization value is called the saturation magnetization of the substance at which all the magnetic moments are aligned.
Remanent magnetization	M_r	T	The induced magnetization remaining after an applied field is removed.
Coercivity	H_c	T	When degaussing is required, we need to apply a magnetic field in the opposite direction, the intensity of which needed to bring the magnetization to zero.
Magnetic moment	μ	emu	A vector that characterizes the magnet's overall magnetic properties, which we can use to evaluate the magnetic response of materials.
Magnetic field	B	T	The strength of the magnetic field.

T , tesla.

TABLE 3 | Parameters influencing the magnetic properties of materials.

Parameters	Main influence on the magnetic properties of materials	References
Size	<ol style="list-style-type: none"> 1. Decreasing diameter can enhance H_c; 2. if the size is too small, it will result in a zero H_c; 3. Within a certain range, the magnitude of M_s increases linearly with size. 	Bean and Livingston, 1959; Lin et al., 2006; Jun et al., 2008
Temperature	If heated to T_c , ferromagnetic materials behave paramagnetically, the magnetic field of the magnet cannot maintain stability.	Laurent et al., 2008
Composition	<ol style="list-style-type: none"> 1. Composition is the most commonly cited factor that greatly affects the magnetic properties of materials; 2. Most magnetic materials contain iron and most of others are rare-earth metals (samarium/cobalt); 3. with few exceptions (e.g., $Zn_{0.4}Fe_{2.6}O_4$ MNPs), alloyed MNPs such as FeCo generally exhibit higher M_s; 4. Careful control of low-level metallic impurities (e.g., Cu) and non-metallic impurities (e.g., oxygen) is pivotal during all processing stages, regardless of which processing route is chosen. 	Gutfleisch, 2000; Kumari et al., 2014
Preparation	<ol style="list-style-type: none"> 1. The temperature and time of annealing have a great influence on the properties of magnetic materials; 2. Different synthetic methods (including using different solvents and surface coatings) will lead to changes in performance. 	Coehoorn et al., 1989; Clavel et al., 2007; Kumari et al., 2014
Others	<ol style="list-style-type: none"> 1. The distribution of cations in octahedral and tetrahedral sites defines the type of magnetic behavior in spinel structures; 2. Cubic MNPs have higher M_s than spherical MNPs of the same volume. 	Zhen et al., 2011; Kolhatkar et al., 2013

Zn, zinc; Co, cobalt; Fe, iron; O, oxygen; Cu, copper.

MNPs (Fang et al., 2019; Gawali et al., 2019; Kim et al., 2019), rather than reliance only on the influence of magnetic fields. The reason might be due to the excessive intensity (>1 T) of the magnetic fields needed to treat tumor cells (Zhang et al., 2016a; Gokduman and Gok, 2020), which will interfere with other normal physiological activities of the body.

Complexes of lentiviral vectors and MNPs have been used to re-endothelialize and restore vascular function (Vosen et al., 2016a). Bekhite et al. found that SMFs increase cardiomyocyte differentiation of Flk-1⁺ cells derived from mouse embryonic stem cells *via* Ca²⁺ influx and ROS production (Bekhite et al., 2013). Nevertheless, excessive magnetic fields may affect the EGFR pathway (Gellrich et al., 2018).

Studies about the antibacterial properties of magnetic fields are relatively superficial. Magnetic fields can destroy bacterial biofilms to a certain extent, thereby reducing the infection prevalence after some surgical procedures (Chopra et al., 2017; Chang et al., 2018; Junka et al., 2018).

Biological Effects and Mechanisms of Magnetic Materials on Bone Regeneration

Specific drugs that can affect bone defects directly are not available, which hampers treatment of bone defects (Borrelli et al., 2003). Studies on magnetic materials that promote bone regeneration have demonstrated their efficacy.

Weak SMFs and weak PEMFs have been found to promote the proliferation, orientation, and migration of osteoblast-like cells (Yamamoto et al., 2003; Ba et al., 2011; Kim et al., 2015), and to induce osteogenic differentiation in bone marrow-derived MSCs (Schäfer et al., 2010; Kim et al., 2015; Huang et al., 2017). Histology has shown that magnetic field could enhance the activity of bone cells and activate remodeling of alveolar bone (Stark and Sinclair, 1987; Darendeliler et al., 1995).

The direction and intensity of a magnetic field has an influence on bone regeneration. Kotani et al. reported that cultured MC3T3-E1 cells (which are pre-osteoblasts from the calvarias of C57BL/6 mice) were parallel to magnetic fields after 60-h

exposure to a SMF (Kotani et al., 2002), which was the first study to show that the growth direction of adherent cells could be regulated by magnetic fields. Besides, in a certain range, as the magnetic-field intensity increases, the biological effects of a magnetic field become more obvious but, beyond a certain range, the effects will decrease and even become inhibitory (“biological window”) (Markov, 2005).

The beneficial effects of a certain intensity of a SMF on osteogenesis have been demonstrated. In 1964, Kotani et al. found that skeletal anabolic responses were enhanced upon exposure to a high-magnitude SMF *in vivo* and *in vitro* (Patel, 1964). Moreover, the SMF could accelerate fracture healing of osteoporotic rats by increasing the local bone mineral density (BMD) (Yan et al., 1998). Miyakoshi et al. described the capacity of SMF to regulate the proliferation, morphology and apoptosis of cells (Miyakoshi, 2005). In 2016, Yun et al. used SMFs with Fe NPs to promote the formation of new bone. And they found the expression of bone morphogenetic protein (BMP)-2 was upregulated and alkaline phosphatase (ALP) activity was enhanced (Yun et al., 2016). Yun and coworkers suggested that these effects may be because the Fe NPs become superparamagnetic due to the SMF, which was conducive to the adhesion and proliferation of osteoblasts. Zhang et al. also reported that SMFs improved expression of bone-associated genes such as *BMP-2* and *runt-related transcription factor 2 (RUNX2)* (Zhang et al., 2018b). Yang and coworkers found that SMFs of different intensity had different effects on osteoblast induction and, simultaneously, the concentration of Fe and mRNA expression of transferrin receptor-1 were also affected, suggesting that Fe may be involved in how a magnetic field acts on osteoblasts (Yang et al., 2018). Meanwhile, SMFs can upregulate expression of *collagen type II alpha 1 (COL2A1)* and *SOX9*, which are genes related to chondrogenic differentiation of human bone marrow-derived MSCs, and promote the synthesis and secretion of hyaluronic acid and collagen (Son et al., 2015).

EMFs can be divided into three groups: extremely-low-frequency (ELF) fields (0–300 Hz), intermediate-frequency fields (300–100 kHz), and radiofrequency fields (100 kHz to 300 GHz) (Ahlbom et al., 2008). Azadian et al. analyzed 39 articles associated with the bone tissue application of EMFs. They found the frequency spectrum of PEMFs, in general, was from 1 to 250 Hz. A frequency <75 Hz had a significant impact upon osteogenesis. The osteogenic effects induced by PEMFs were the most obvious within the range 15–35 Hz (Azadian et al., 2019).

In 1990, Tabrah et al. undertook a study in which 20 osteoporosis-prone women were exposed to a 72 Hz of a PEMF 10 h per day for 12 weeks. Data on the BMD of the radii before, during and after exposure period indicated that the appropriate application of PEMFs might have great clinical value to treat osteoporosis (Tabrah et al., 1990). In 1974, Bassett et al. promoted fracture healing with PEMFs in clinics for the first time (Bassett et al., 1974). In 1979, use of EMFs was approved by the US Food and Drug Administration (FDA) as safe and non-invasive treatment. Since then, several research has shown that PEMFs can elicit therapeutic effects against bone diseases (Bassett et al., 1982; Assiotis et al., 2012). PEMFs are also reported to promote osteogenic differentiation of MSCs by stimulating the mRNA

expressions of osteogenic related genes such as *RUNX2*, *ALP*, *BMP-2*, and *distal-less homeobox 5 (DLX5)* (Yang et al., 2010). Sollazzo et al. exposed human osteoblasts (MG-63) to PEMFs for 18 h, and found that PEMFs induced upregulation of expression of *homeobox A10 (HOXA10)* and *signal transducer and activator of transcription 3 (STAT3)*, which are important factors in bone formation (Sollazzo et al., 2010). Low-frequency PEMFs have also been shown to promote TGF- β 1 release (Li et al., 2007; Shen and Zhao, 2010).

Different types and parameters of magnetic fields may have different effects on bone cells, some of which are summarized in **Table 4**. Irrespective of whether SMFs or PEMFs are employed, the effects on bone regeneration may be related mainly to activation of Wnt/ β -catenin (Zhou et al., 2012), RANK/RANKL/OPG (Lei et al., 2017, 2018) or MAPK (mitogen-activated protein kinase) (Yong et al., 2016) signaling pathways. Moreover, bone tissue may be sensitive to low-frequency PEMFs, which may be associated with strong transmembrane potential changes and Ca^{2+} influx. Also, the capacity of SMFs to promote the proliferation and division of osteoblasts could be due to cytoskeletal changes.

Safety of Magnetic Fields

There have been concerns regarding the negative effects of magnetic fields on human health during radiography such as magnetic resonance imaging (MRI), which is the most widely used application of magnetic fields, and using between 0.15 T and 3 T (Wada et al., 2010). The International Commission on Non-Ionizing Radiation Protection published exposure guidelines for SMFs and set the limit for SMF exposure at 400 mT (International Commission On Non-ionizing Radiation, 1994).

SMFs are relatively safe because they do not emit electromagnetic radiation. It has been reported that 2-h exposure in a SMF of 3.5–23.0 T does not have serious long-term effects on mice (Tian et al., 2019). Wang and colleagues demonstrated the safety of exposure to SMFs of 2–12 T (Wang et al., 2019).

Reddy et al. found that 8-week-continuous exposure of PEMFs did not increase genetic toxicity and cytotoxicity significantly according to detection of the micronucleus and polychromatic erythrocytes in the bone marrows and blood of adult male mice (Reddy et al., 2010). The effects of ELF fields on the cardiovascular system was studied but insufficient evidence was found to indicate the side-effects according to Jauchem (1997). Azadian et al. summarized nearly one decade of studies and found scant evidence that EMFs (1–100 mT) affected early embryogenesis adversely in mammals (Azadian et al., 2019).

However, a recent study found that prolonged exposure to ELF fields could stimulate the generation of pro-inflammatory cytokines, thus affecting the immunoreaction (Hosseinabadi et al., 2019). Halgamuge showed that exposure to weak EMFs could disrupt melatonin production, which may result in long-term health impact on humans (Halgamuge, 2013). Available data on EMFs and physiological activities are insufficient

TABLE 4 | Studies on the biological effects and mechanisms of different magnetic materials on bone regeneration in the last two decades.

References	Year	Magnetic material	Type of the magnetic fields	Subjects	Exposure method	Biological effects	Mechanisms
Nagai et al., 2000	2000	SmCo	SMF, 180 mT	4-week-old male Wistar rats	Continuous exposure for 7–21 days	Formation of ectopic bone was promoted.	Purifying BMP and increasing the blood-vessel density of bone.
Yamamoto et al., 2003	2003	NdFeB	SMF, 160 mT	Calvaria cells of 21-day-old fetal Sprague-Dawley rats	Continuous exposure for 20 days	The total area, number and mean size of bone nodules, calcium content in the matrix and two markers of osteoblastic phenotype (ALP and OCN) showed a significant increase.	Promoting the differentiation and activation of osteoblasts.
Xu et al., 2011	2011	SmFeN	SMF, 180 mT	10-week-old female Wistar rats	Continuous exposure for 6 weeks	BMD values of osteoporotic lumbar vertebrae in the ovariectomized rats increased.	Improving the blood circulation within bone, resulting in an improved blood supply.
Giombor et al., 2002	2002	EBI Medical Systems	PEMF, 1.6 mT, 15 Hz	28–35-day-old male CD rats	8 h/day for 6–8 days	Chondrogenesis and endochondral calcification were accelerated.	Upregulating gene expression for proteoglycan and collagen in extracellular-matrix constituents.
Jing et al., 2011	2011	A pulsed signal generator and three Helmholtz coils	PEMF, 2.4 mT, 15 Hz	3-month-old male Sprague Dawley rats	8 h/day for 8 weeks	The maximum load, stiffness, and energy absorption of diabetic bone were increased.	Improving the cortical structure.
Jing et al., 2014	2014	A pulsed signal generator and three Helmholtz coils	PEMF, 2.4 mT, 15 Hz	3-month-old male Sprague-Dawley rats	2 h/day for 4 weeks	Levels of markers of bone formation, including OCN and P1NP, were increased.	Promoting gene expression of OPG and OCN in tibia.

SMF, static electromagnetic field; PEMF, pulsed electromagnetic field; Sm, samarium; Co, cobalt; Nd, neodymium; Fe, iron; B, boron; N, nitrogen; BMD, bone mineral density; BMP, bone morphogenetic protein; ALP, alkaline phosphatase; OCN, osteocalcin; P1NP, N-terminal propeptide of type-1 procollagen; OPG, osteoprotegerin.

to make a definitive claim about the side effects of EMFs on health.

MAGNETIC MATERIALS IN BONE REGENERATION

Design of the Magnetic Materials Used in Bone Regeneration

In recent decades, magnetic materials have been designed as films, scaffolds, and implants to meet different needs. Co-precipitation, micro-emulsions, thermal decomposition, ultrasonic irradiation, and sol-gel reactions have been described to prepare magnetic materials with stable properties and controllable shapes (Wu et al., 2016).

The relative proportion of the surface and interface of a membranous material is relatively large, and the properties related to the surface are very prominent. Hence, there are a series of physical effects related to the surface and interface. Biomagnetism scaffolds have been reported to guide the proliferation, differentiation and mineralization of bone cells, thus arousing great interest of researchers in bone healing. Compared with the membrane and the scaffold forms, the block has larger volume and density, is easier to operate, and can produce a more powerful and stable magnetic field, which can be implanted directly into the body or placed on body surface to work. Properties of the three forms of magnetic materials above are summarized in **Table 5**.

In addition to design and syntheses mentioned above, other methods can be employed. For example, by integrating superparamagnetic NPs into calcium phosphate (CaP) ceramics, in 2010, Yao et al. developed a novel CaP-MNP composite to obtain bone repair which had good biocompatibility with bone cells (Wu et al., 2010). In 2015, Qing et al. prepared magnetic nanofibers through electrospinning polylactide and ferromagnetic Fe₃O₄ NPs to learn the influence of SMFs on the differentiation of osteoblastic cells (Cai et al., 2015). Moreover, chitosan materials, with excellent biocompatibility, antibacterial, and drug-loading properties (Kassem et al., 2019; Sah et al., 2019), have also been combined with magnetic materials for bone regeneration. In 2012, Shi et al. found that chitosan-coated iron-oxide NPs had excellent biocompatibility, and increased osteoblast proliferation, and decreased damage to cell membranes (Shi et al., 2012). In 2017, Aliramaji et al. synthesized iron-oxide MNPs using reverse co-precipitation, and investigated the effects of chitosan-based magnetic scaffolds with MNPs (0, 0.5, 1, and 2%) on the cellular activity of bone tissue (Aliramaji et al., 2017). In 2018, an MNP composite layer containing collagen, chitosan, and hydroxyapatite was fabricated by Paun et al. to ensure the magnetic properties of three-dimensional biomimetic materials that could accelerate osteogenesis in SMFs (Paun et al., 2018).

Developments in biotechnology and biomedical engineering are continuing apace (Anderson, 2006) but improvements in the biological properties of magnetic materials are important. Avoidance of allogeneic reactions by controlling the adsorption of protein on the interface between the material and body is

TABLE 5 | Comparison of three common forms of magnetic materials used in bone regeneration.

Forms	Composition	Fabricating method	Biological effects	Advantages	References
FILMS					
	PVA, FeCl ₂ , and FeCl ₃	Ultrasonication and conventional co-precipitation	It is considered to be a good choose to accelerate bone regeneration at the fracture site.	1. Biocompatible. 2. Fairly uniform distribution and a 3D network. 3. More tensile strength than the solution cast films. 4. Superparamagnetism.	Chatterjee et al., 2004
	PVA, GTA, FeCl ₂ , and FeCl ₃	Chemically cross-linked and dialysis	It can be used in a novel drug delivery system that releases a cytokine like PTH to promote bone regeneration.	1. Biocompatible. 2. Good stability.	Albornoz and Jacobo, 2006
	PLA, Nha, and γ -Fe ₂ O ₃ nanoparticles	Electrospinning technique	It induces a significantly higher proliferation rate and faster differentiation of osteoblasts.	1. Absorbable and metabolizable. 2. No obvious damages so far.	Meng et al., 2010
	Fe ₃ O ₄ , chitosan and PVA	Electrospinning technique	It facilitates the osteogenesis in MG-63 human osteoblast-like cells.	Biodegradable.	Yan et al., 2011
SCAFFOLDS					
	PCL, FeCl ₂ ·4H ₂ O and FeCl ₃ ·6H ₂ O	Electrospinning technique	It can be a promising candidate scaffolds for bone regeneration.	1. Great improvement of the hydrophilicity of the nanofibers. 2. Bone-bioactive and mechanical effects.	Singh et al., 2014
	PCL matrix, FeHA nanoparticles	Rapid prototyping technique, a 3D fiber deposition technique, hydrothermal and solvothermal synthesis	It accelerates the growth of cells.	1. Biodegradable. 2. A good level of histocompatibility.	De Santis et al., 2015
	HA, collagen, biomimetic nano-apatite and ferrofluids	Dip-coating magnetization technique	It attracts more growth factors and other biomolecules.	1. Excellent biocompatibility properties. 2. Cheap and simple. 3. No aggressive chemical conditions.	De Santis et al., 2011
BLOCKS					
	NdFeB	Unknown	It promotes the pattern and rate of bone deposition and thymidine uptake.	Non-invasive.	De Santis et al., 2011
	SmCo	Unknown	It stimulates the turnover rate and synthesis of fibroblasts.	Simple and easy to operate.	McDonald, 1993

GTA, glutaraldehyde; PVA, polyvinyl alcohol; FeCl₂, ferrous chloride; FeCl₃, ferric chloride; PLA, poly (D, L-lactide); nHA, hydroxyapatite nanoparticles; PCL, poly caprolactone; MNP, magnetic nanoparticle; FeHA, iron-doped hydroxyapatite.

crucial. Therefore, carrying out in-depth study of biomaterial surfaces is important. Other crucial areas are: (i) surface modification of materials and devices in contact with blood (e.g., biological activation, anti-coagulation); (ii) surface functionalization (e.g., wear resistance of the magnetic material, selective immobilization of biomolecules); (iii) morphology and structure of implanted devices (Hench and Polak, 2002).

Applications of Magnetic Materials in Bone Regeneration

As early as 1979, it was reported that SmCo magnets implanted in tissues did not elicit side effects on blood cells (Cerny, 1979) and tissue around the implants (Cerny, 1980). In 2004, Taniguchi et al. placed rats suffering from adjuvant arthritis in a SMF for 12

weeks. The femoral BMD increased greatly compared with that of the control group (Taniguchi et al., 2004). Meng et al. suggested that magnetic films could offer potential in treatment of bone diseases (Meng et al., 2010). In 2013, Meng et al. described osteogenesis enhancement of superparamagnetic nanofibrous scaffolds *in vivo* with external SMFs by implanting the scaffolds into New Zealand white rabbits with lumbar transverse defects (Meng et al., 2013). In 2017, Bambini et al. inserted dental implants with NdFeB magnets into the tibia of New Zealand white rabbits, and found that the SMF generated by the magnetic implants strengthened bone regeneration (Bambini et al., 2017).

In 1979, PEMFs were approved by the US FDA to treat fracture non-unions. Subsequently, various non-invasive devices, such as PEMFs for osteoporotic fractures in rats (Androjna et al.,

2014) and a double-coil system to heal fresh tibial fractures of humans (Hinsenkamp et al., 1984), have been developed for clinical treatment.

The clinical applications of magnetic materials for bone regeneration are in their infancy. With technological developments, magnetic materials for clinical application may develop in three main directions. The first direction is interventional and auxiliary devices for minimally invasive or non-invasive treatment. This will involve development of biodegradable materials, micromachining of implanted instruments, surface anticoagulation, and modification of tissue proliferation. The second direction will involve combination with biologically derived materials. Collagen, sodium hyaluronate, chitosan, and silk fibroin have been used widely in the clinic, but the quality and variety of materials must be improved and expanded. Such alterations will improve the biocompatibility, quality and stability of the material to aid combination of the magnetic material with bioderived materials. The third direction is nano materials such as nano-coatings and carriers for controlled release of nano-drugs. In addition, computer-aided three-dimensional printing could provide precise machining, rapid prototyping, and customization of magnetic materials.

Although scholars have created many designs for application of magnetic materials to aid bone regeneration, their optimal dose, side effects, and long-term stability have yet to be determined.

SYNERGISTIC EFFECTS WITH OTHER MATERIALS

Another advantage of magnetic materials is that they can be combined readily with other stimuli that have effects on bone regeneration. This interaction, in which the total effect is superior to the sum of the individual effect of each stimulus, is called a “synergistic” or “cooperative” effect.

Magnetism and Electricity

Effects of electric fields and magnetic fields on biological tissues has been studied since the eighteenth century. Electrical stimulation is beneficial to osteogenesis promotion because it increases expression of the genes associated with osteogenic differentiation (Hu et al., 2018). Moreover, the electrical stimulation on tissue grafts has been found to promote formation of blood vessels and collagen tissue (Fonseca et al., 2018).

A changing electric field can produce a magnetic field. Accordingly, changing the magnetic field (e.g., EMF, PEMF) can generate electric currents in tissues. Therefore, PEMFs and EMFs combine electricity and magnetism, which promote bone regeneration.

We synthesized a flexible nanocomposite P (VDF-TrFE) membrane that can mimic the endogenous electric potential and explored its efficacy for bone-defect repair (Zhang et al., 2016b). We found that the membrane accelerated osteogenesis and bone maturity both *in vitro* and *in vivo*, thereby offering an innovative method to promote bone regeneration. In 2018, we adjusted the surface potential of the membrane (Zhang et al., 2018a). This is

a development trend for biomaterials proposed by Winkler et al. which is a new way to heal bone defects by mimicking the biology of bone healing (Winkler et al., 2018).

However, the coupling of electricity and magnetism is focused mainly on alternating current. Besides, the human body is a conductor of electricity, so the intensity of current must be calibrated very carefully to avoid causing damage to it.

Magnetism and Force

A magnet has two opposite poles: north and south. The same poles produce a repulsive force whereas different poles attract each other. Hence, two magnets can apply a force to each other without making contact. Moreover, an object placed between them is also affected by the magnetic field simultaneously.

In 1986, Jackson and Thomas used magnetic force as an aid to improve retention of osseointegration of rare-earth magnetic applications (Jackson, 1986). The combination of magnetism and force is used often in dentistry. In 1987, Kawata et al. designed the first magnetic brackets, which were made from an alloy of Fe, Co, and chrome. However, they could not provide sufficient force to move teeth, so rare-earth magnets were designed subsequently to replace them (Kawata et al., 1987). In 1995, Darendeliler et al. compared the impact on movement of orthodontic tooth of three forms of stimuli using male Hartley guinea pigs (Darendeliler et al., 1995). Groups with a SmCo magnet or PEMF stimulation combined with a coil-spring force increased the amount of new bone deposited in the tension area compared with the control group with coil-spring force alone. Two years later, they wrote a review introducing clinical applications of magnets in orthodontics and the biological implications (Darendeliler et al., 1997).

Scholars have found that the force generated by magnetic materials is more efficacious with less pathological and traumatic changes in oral environment compared with using only mechanical force to move teeth (Blechman and Smiley, 1978; Tomizuka et al., 2006). A great advantage of magnetic force is that once the magnetic material is placed in an appropriate position, it can act without contact through an external magnetic field. However, adding force to the corresponding area is easy but control is difficult because the magnitude of the force fluctuates greatly with the distance.

Magnetism and Hyperthermia

Hyperthermia can lead to enhancement of tissue perfusion, skeletal muscles relaxation, and tension reduction in soft tissue (Schmidt and Simon, 2001). In recent years, thermotherapy has also been found to have positive effects upon bone formation. Ota et al. assessed the influence of thermal stimulation on osteogenesis in rat and rabbit models. They demonstrated that a heat stimulus could facilitate bone formation, and could be promising treatment for diseases related to bone defects (Ota et al., 2017).

The main challenge of using thermotherapy against diseases is how to apply the appropriate amount of heat to the target area without interfering with other areas to prevent complications (heat has good conductivity in the human body). In recent years, scientists have discovered that magnetic materials can be used to

solve this problem. For example, Petryk et al. used alternating magnetic fields (AMFs) with Fe particles to induce hyperthermia locally because heat can be produced from the hysteresis loss of magnetic particles under AMFs (Petryk et al., 2013). Using MNPs, we achieved artificial local control of temperature within selected regions. However, this approach is used mainly for the treatment of tumors and cancers, and has been less studied in bone regeneration.

Moreover, magnetism and hyperthermia can be combined with phototherapy. Lu et al. designed SrFe₁₂O₁₉ MNP chitosan porous scaffolds (MBCSs) with excellent osteogenic capacity and antitumor function (Lu et al., 2018). Not only did the magnetic field produced by the MBCSs promote expression of osteoblast-specific genes and regeneration of new bone, it also improved photothermal conversion. Tumor cells cultured on scaffolds underwent apoptosis due to temperature increases under the irradiation of a near-infrared laser. Therefore, a combination of phototherapy with magnetic materials could be used against tumor-related bone defects.

CONCLUSIONS AND FUTURE OUTLOOK

Bone regeneration, as a highly complex physiological process, has been studied widely. Several methods have been employed to enhance bone formation preclinically and clinically. Nevertheless, reducing the duration of bone regeneration is challenging because of the uncertainties and problems of each method. For example, although bone-like calcium phosphate has been used widely, Islam et al. pointed out that some factors, such as microbial contamination and precursor-phase residues, lead to treatment failure (Islam et al., 2017).

Magnetic fields can be applied to an object without touching it, and the properties of magnetic materials are improving. However, most of the magnetic materials used to promote bone regeneration are based on body implantation, which leads to four main problems. First, postoperative infection and rejection are constant problems and may affect the pattern of bone deposition. Second, magnetic materials may affect some types of examination and treatment (e.g., MRI) because of the metal elements they contain. Third, the alloys used in magnetic materials, if not protected appropriately, are highly susceptible to corrosion by tissue fluids. The fourth problem is the possible local and systemic toxic effects of the alloys used in a magnet synthesis. Consequently, how to apply

magnetic materials in a non-invasive way will become a focus of future explorations.

In addition, even though animal models have been used widely, there are several difficulties in controlling the many variables associated with bone regeneration in humans. For example, animals from the same species can have anatomical, biochemical and gene-expression differences, and species differences can hamper data interpretation for clinical application.

Moreover, bone reconstruction is extremely complex, involving many components acting at different time steps. Hence, ascertaining the parameters of magnetic materials that produce the optimal effects (e.g., intensity of the magnetic field, shape of the material, alloy composition, preparation process) is crucial. Also, combination of magnetism with light, sound, or heat may have a stronger effect on bone regeneration than magnetism alone. Hence, clearer understanding at the cellular level of the effects of magnetic fields is important.

Wearing a device that provides magnetism for long periods of time (e.g., 6 months) may be burdensome for some patients. Also, the cost of magnetic devices is a burden. Therefore, a magnetic-material industry with the goals of low energy consumption, low environmental pollution, and low cost could be very important for treatment of bone defects in the future.

AUTHOR CONTRIBUTIONS

LC, JP, and JZ conceived of and wrote the manuscript. JP and JZ are co-first authors of the manuscript. YL, YX, and JN contributed to original draft preparation. LC critically revised the manuscript.

FUNDING

This work was supported by the National Science Fund for Distinguished Young Scholars (Grant No. 31725011) and the National Natural Science Foundation of China (Grant No. 2017YFC1104301).

ACKNOWLEDGMENTS

Financial support from the National Science Fund for Distinguished Young Scholars and the National Natural Science Foundation of China (NSFC) is gratefully acknowledged.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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