Biomedicine & Pharmacotherapy 118 (2019) 109282

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

journal homepage: www.elsevier.com/locate/biopha

Review

Effects of electromagnetic fields on osteoarthritis

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ARTICLE INFO

Keywords:
PEMFs
Chondrocytes
Extracellular matrix
Subchondral bone loss
Osteoarthritis

ABSTRACT

Osteoarthritis (OA), characterized by joint malfunction and chronic disability, is the most common form of arthritis. The pathogenesis of OA is unclear, yet studies have shown that it is due to an imbalance between the synthesis and decomposition of chondrocytes, cell matrices and subchondral bone, which leads to the degeneration of articular cartilage. Currently, there are many therapies that can be used to treat OA, including the use of pulsed electromagnetic fields (PEMFs). PEMFs stimulate proliferation of chondrocytes and exert a protective effect on the catabolic environment. Furthermore, this technique is beneficial for subchondral trabecular bone microarchitecture and the prevention of subchondral bone loss, ultimately blocking the progression of OA. However, it is still unknown whether PEMFs could be used to treat OA in the clinic. Furthermore, the deeper signaling pathways underlying the mechanism by which PEMFs influence OA remain unclear.

1. Introduction

Osteoarthritis (OA) is a very common disease, estimated to affect one in eight adults, and is a major cause of chronic pain [1,2]. It is one of the leading contributors to global disability, with the knee identified as one of the most commonly affected joints [3]. The pathogenesis of OA is unclear but studies have indicated several factors which include: articular cartilage degeneration, subchondral bone thickening, osteophyte formation, synovium inflammation (synovitis), degradation of ligaments and menisci, and joint capsule hypertrophy [4]. Currently, a variety of therapies are used to treat OA, such as medication (non-steroidal anti-inflammatory drugs, intra-articular injection of corticosteroids, alcohol, etc.), non-pharmacological treatment (sports training, patient education, etc.) and surgical treatment [5]. Noninvasive therapeutic modalities such as magnetic resonance treatment [6], and pulsed electromagnetic field (PEMF) therapy have shown positive effects on OA and consequently, should be highly recommended for clinical application. It has been demonstrated that PEMF therapy has greater positive effects in treating various bone disorders, including fresh fractures, delayed and nonunion fractures, compared to drug therapy [7,8]. However, the effects of PEMFs on OA patients are still unclear at present. When properly applied, one group reported that PEMFs increased chondrocyte proliferation, synthetic activity and phenotypic maturation [9] without side effects in osteoporotic (OP) rats. Several papers have reported that PEMF stimulation may cause a significant reduction in some of the most relevant proinflammatory cytokines in human chondrocytes [10], while another group reported no change in pain between a 2-week course of PEMF therapy and a sham-treated group [11]. However, the underlying mechanism of action of PEMFs in OA are not entirely understood (Fig. 1).

In this manuscript, we summarize the influence of PEMFs on OA and the underlying mechanism, demonstrating that PEMFs are effective in preventing OA development and progression.

2. PEMFs

2.1. Characteristics

PEMFs utilize frequencies at the lower end of the electromagnetic spectrum, ranging from 6 to 500 Hz [12]. A higher rate of change (Tesla/second) is capable of stimulating biological currents in the tissue, with peculiar biological effects [13]. PEMF treatment is regarded as a noninvasive physical therapy for treating skeletal diseases. It is been demonstrated that PEMFs have advantages including rapid effect,

Abbreviations: ACLT, anterior cruciate ligament transection; ADL, activities of daily living; AIMS, Arthritis Impact Measurement Scale; CollII, type II collagenase; ECM, extracellular matrix; GAG, glycosaminoglycan; IGF1, insulin-like growth factor I; MMPs, matrix metalloproteinases; NO, nitric oxide; OA, osteoarthritis; OP, osteoporosis; OVX, ovariectomy-induced; PEMFs, pulsed electromagnetic fields; PG, proteoglycan; PGE2, prostaglandin E2; TNF-α, tumor necrosis factor-α;; VAS, visual analogue scale; WOMAC, Western Ontario and McMasters University Osteoarthritis Index; X-linked, inhibitor of apoptosis protein XIAP

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https://doi.org/10.1016/j.biopha.2019.109282
Received 30 April 2019; Received in revised form 20 July 2019; Accepted 25 July 2019

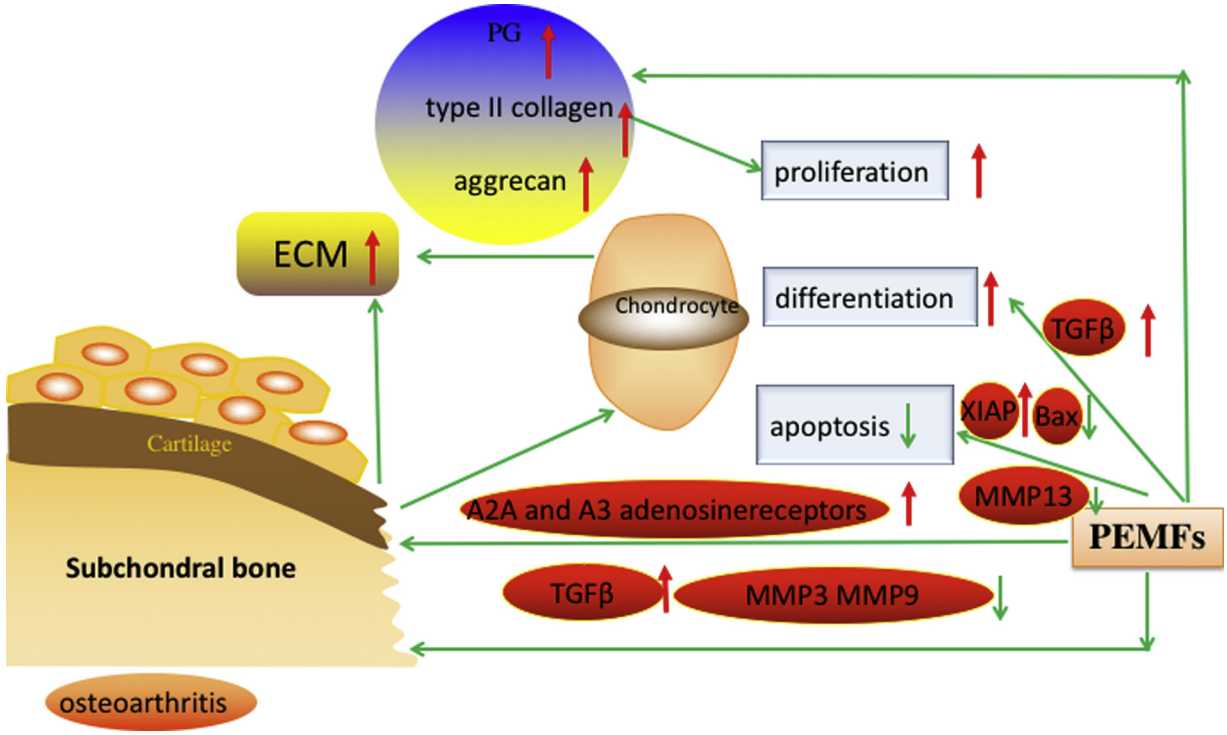

Fig. 1. PEMFs stimulate proliferation of chondrocytes and exert a protective effect on the catabolic environment through Coll II, PG aggrecan, TGFβ. PEMFs suppress chondrocyte apoptosis. PEMFs promote matrix synthesis and decrease the levels of inflammatory cytokines, resulting in a beneficial effect on tissue engineering of cartilage. Furthermore, this technique is beneficial for subchondral trabecular bone microarchitecture and the prevention of subchondral bone loss, ultimately blocking the progression of OA.
Coll II, type II collagenase; ECM, extracellular matrix; GAG, glycosaminoglycan; OA, Osteoarthritis; PEMFs, pulsed electromagnetic fields; PG, proteoglycan;

ease of operation, and lack of adverse effects and thus are suitable for widespread application [12,13].

2.2. Effects of PEMFs on OA

2.2.1. Clinical experiments

Some articles have comprehensively reviewed recent experiments regarding the effect of the clinical use of PEMFs on OA [14–16] (Table1). The effects of PEMFs on pain and functional ability have attracted attention, although controversy remains. The main outcomes of interest were pain and functional disability as recorded by validated self-reporting instruments such as the Western Ontario and McMasters University Osteoarthritis Index (WOMAC), activities of daily living (ADL), EuroQol, Arthritis Impact Measurement Scale (AIMS) or SF-36 [16]. Recently, it was shown that PEMFs eased the pain of patients suffering from OA [17]. After 6 weeks of treatment with PEMF and a 12-week follow-up, one study found significant improvements in ADL, pain and stiffness compared with control groups [18]. Another study reported that after PEMF treatment, a 50% decrease in maximum visual analogue scale (VAS) was observed, starting on day 1 and persisting to day 42 [19]. The positive effects of treatment with PEMF were demonstrated by another experiment involving 71 knee OA patients who experienced an increase in mobility and walking distance after a 6-week course of PEMF treatment [20]. The persistence of several functional and analgesic effects was documented after 4 weeks [20]. In addition, 6 weeks of PEMF therapy caused a significant improvement in WOMAC score in 75 patients suffering from knee OA [21]. Moreover, treatment with PEMF for 1 month resulted in an improvement in pain and functional performance of patients with knee OA [22].

In contrast, Ozgüçlü et al. reported that there were no statistically significant differences between a group given 2 weeks of PEMF therapy and a sham group in terms of WOMAC pain, stiffness and physical function scores [11]. Similarly, Ay and colleagues were unable to find a beneficial symptomatic effect of PEMF in the treatment of knee OA in any patients compared to a sham group after five sessions per week for 2 weeks [23].

There are various reasons that might account for these conflicting results. First, different groups used different clinical designs, different types of PEMFs and different treatment protocols. For example, two studies applied low frequency PEMF (3–50 Hz) with a long duration of treatment (3–10 h a week) [18,21], while another three studies applied high frequency (75HZ, 110HZ, 27MHZ) PEMF with shorter treatment duration [24–26]. It has been found that PEMF treatments using low frequency and long duration produced a greater trend for short-term improvement in WOMAC function score than the application of high frequency PEMF treatments or trials with a short treatment duration. Secondly, the sample sizes of these studies were too small to constitute a clinical trial.

2.2.2. Animal experiments

A variety of articles have comprehensively reviewed recent experiments regarding the effect of PEMFs in animal models of OA (Table2). In 12-month-old Dunkin–Hartley guinea pigs (an OA model), it has been reported that PEMF therapy (75 Hz, 1.6 m T, 6 h per day for 3 months) slows the progression of OA lesions in the knee of aged guinea pigs and preserves the morphology of articular cartilage [27,28]. Using 15-month-old animals, researchers observed a quantifiable progressive worsening of OA lesions, compared to animals aged 12 months. The progression of OA was significantly delayed by over 6-month exposure to PEMFs, particular in cartilage parameters. The average modified Mankin score was lower in PEMF-treated animals, in comparison with control animals. The results demonstrated that PEMFs exerted positive effects both in cartilage and bone in late-stage lesions [29]. In fact, no effects of PEMFs on subchondral and epiphyseal bone were evident, when using 12-month-old animals. It is possible that the OA was not so advanced and a stimulation time of 3 months was not sufficient to

Table 1
Effects of PEMF on osteoarthritis in clinical studies.

Refs.	Subjects	Device and treatment parameters	Treatment duration	Outcomes of function
[11]	40 patients with knee OA	50 HZ	30 min a day, 10 sessions, 2 weeks	PEMF does not have additional effect on the classical physical treatment in reducing symptoms of knee OA
[17]	60 patients with radiographic evidence of knee OA	1000 Hz, 100 μs burst width	12 h daily treatment for 1 month	PEMF therapy is effective for pain management in knee OA patients and also affects pain threshold and physical functioning
[18]	83 patients with knee OA	50 Hz	2 h a day, 30 sessions, 6 weeks	It has been demonstrated a beneficial symptomatic effect of PEMF in the treatment of knee OA in all patients.
[19]	34 patients with knee OA	6.8 MHz, 7 ms burst	15 min twice daily, 14days	The results suggest that non-thermal, non-invasive PEMF therapy can have a significant and rapid impact on pain from early knee OA
[20]	71 persons (all with a knee gap smaller than 3 mm)	10–300 Hz, 3.4–13.6 μT	16 min a day, daily, 6 weeks	Pain relief in osteoarthritis patients was confirmed by PEMF therapy
[21]	69 patients with knee OA	3–7.8 Hz	10 min 3 times a day, daily, 6 weeks	PEMF are beneficial in reducing pain and disability in patients with knee OA without significant side-effects
[22]	86 patients with OA of the knee and 81 patients with OA of the cervical spine	5–12 Hz,	30 min a day, 18 sessions, 4 weeks	PEMF has therapeutic benefit in painful OA of the knee or cervical spine
[23]	55 patients suffering from knee OA	50 Hz, 105 μT	30 min a day, 15 sessions, 3 weeks	The beneficial effect of PEMF on pain relief was demonstrated
[24]	46 patients with OA hip pain and 46 patients with OA knee pain	82 HZ	3 times a week for 15 min, over a period of 3 weeks	No evidence was found therefore for the specific effectiveness of PEMF for treatment of osteoarthritic hip or knee pain
[25]	103 patients with knee OA	300 Hz, a pulse duration of 300 μs	20 min a day, 9 sessions, 3 weeks	The findings do not demonstrate pulsed short-wave diathermy, as it is utilized in clinical settings, to be effective in the treatment of osteoarthritis of the knee
[26]	27 patients with radiographic evidence of knee osteoarthritis	400 HZ, 200 μs-400 μs, 10–20W	20 min a day, 6 sessions, 2 weeks	PEMF had little or no anti-inflammatory effect on conditions such as osteoarthritis of the knee

Table 2
Effects of PEMF on osteoarthritis in animal studies.

Refs.	Animal model	Parameters of PEMF	Phenotypes	Possible molecular mechanisms
[27]	10 Dunkin Hartley guinea pigs aged 12 months	75 Hz, 1.6 MT, 6 h a day for 3 months	PEMFs preserve the morphology of articular cartilage and retard the development of OA lesions	PEMFs increased A2a adenosine receptor numbers, suppresing inflammation
[28]	26 male 12-month old guinea pigs	1.5 Hz, 1 h/day for 6 months	PEMF treatment preserves the morphology of articular cartilage and retards the development of osteoarthritic lesions	stimulation of TGFβ may be a mechanism through which PEMF favorably affects cartilage homeostasis
[29]	15-month-old guinea pigs.	75 Hz, 1.6 mT 6 h/day for 6 months	PEMF stimulation significantly changed the progression of OA lesions in all examined knee areas	PEMFs could protect the joint against OA degeneration by diminishing cartilage damage progression and subchondral bone sclerosis
[30]	male Wistar rats (80–100 g)	5 Hz, 4 mT, 90 min/day for 28 days	PEMF therapy showed that 5 Hz4 m T90 min group was found to be effective in reducing inflammation in arthritic rats	PEMFs significantly inhibited the rate of release of b-glucuronidase from lysosomal rich and sub-cellular fractions
[31]	Healthy male Wistar rats, each weighing approximately 80–100 g	5 Hz, 4 μT, 90 min/day for 42 days	PEMF is indeed beneficial in reducing inflammation without potential side effects	The antiinflammatory effect could be partially mediated through the stabilizing action of PEMF therapy
[35]	64 New Zealand White (NZW) rabbits, 32 male and 32 female, 3 months of age	75 Hz, 8 mw/cm2, 30 min/day for 10 days	The application of PEMF for 40 min, had significant effects in improving osteoarthritis	These treatments also decreased serum tumour necrosis factor-α levels, reduced the expression of caspase-3 and caspase-8 and reduced chondrocyte apoptosis
[36]	48 female Sprague-Dawley rats (250 ± 50 g)	8 Hz, 3.8 mT, 40 min/day for 30 days	PEMF can reduce cartilage degeneration	Changes in XIAP and Bax mRNA expression might be the mechanism by which PEMF therapy affects postmenopausal osteoarthritis
[38]	48 female SPF Wistar rats	8 Hz, 3.8 mT, 40 min/day for 30 days	PEMFs can prevent and cure the knee osteoarthritis resulting from estrogen decrease.	PEMFs inhibited chondrocyte apoptosis and downregulated MMP13 expression of knee joint cartilage

contradict the complex bone remodeling process [27]. Histological studies have shown that PEMFs decrease inflammatory cell infiltration of the arthritic rat ankle joint, and reduce hyperplasia and hypertrophy of cells lining the synovial membrane induced by the adjuvant [30,31]. It has been demonstrated that TGFβ exerts positive effects in cartilage homeostasis and maintains extracellular matrix (ECM) morphology [32–34].

PEMF therapy also decreases the number of immunopositive cells to type II collagen (Coll II), matrix metalloproteinases (MMP)s and IL-1β, while increasing the number of TGFβ-1-positive cells. Enhancement of TGFβ-1 may account for the reparative mechanism of action [9]. Ciombor et al. [28] have demonstrated that PEMF therapy favorably affects cartilage homeostasis through targeting TGFβ, which is believed to upregulate gene expression for aggrecan, downregulate matrix metalloprotease and IL-1 activity, and upregulate inhibitors of matrix metalloprotease. Another study using an anterior cruciate ligament transection (ACLT) rabbit model, confirmed the down-regulation of serum tumor necrosis factor-α (TNF-α) levels, preventing cartilage degeneration after 10-day PEMF therapy (PEMFs for 30 min: 8 mw/cm^2, 75 Hz) [35]. PEMFs also increased the mRNA expression of inhibitor of apoptosis protein and decreased Bax mRNA expression in rats, inhibiting ovariectomy-induced (OVX) cartilage degeneration [36]. MMPs constitute a group of endopeptidases that degrade the extracellular matrix. Among them, five proteins—MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13—are closely related to the onset of OA. In the occurrence and development of OA, elevated levels of MMPs and decreased expression of MMP inhibitors result in the degradation of collagen, proteoglycan (PG) and elastin fibers in the ECM of articular cartilage; thus, MMPs become mediators of OA [37]. Interestingly, PEMFs are effective in exerting beneficial effects on knee cartilage via the regulation of catabolic factors, such as decreasing MMP-13 [38], and in favorably affecting cartilage homeostasis [28].

3. Cellular mechanisms involved in PEMFs-treated OA

3.1. Chondrocytes

Chondrocytes, present within the cartilage matrix [39] are able to synthesize and secrete Coll II, PG and aggrecan and produce an extensive ECM. Aggrecan is highly negatively charged and creates a hydrated matrix, conferring compressive stiffness on cartilage. In arthritis, the fibrillar network of collagen, which forms the endoskeleton, is damaged and there is loss of aggrecan, leading to joint dysfunction [40].

It has been demonstrated that PEMFs exert effects on chondrocytes [41–45]. However, the different cell sources as well as the different protocols of PEMF might result in different outcomes. Multiple experiments have used PEMF therapy to influence cultured human chondrocyte cells. In these studies, the strength of the magnetic field varied from 1 mT to 2.5 mT, the frequency ranged from 30 Hz to 75 Hz and the duty cycle was approximately 10%. Unsurprisingly, the effects of PEMFs on chondrocytes were not consistent. It has been demonstrated that PEMFs exert positive effects on PG synthesis in human OA chondrocytes [41] and promote development of the chondrocyte phenotype in monolayer cultures [42]. PEMFs increase proliferation of healthy human chondrocytes as well as human OA chondrocytes [46,47]. Exposure to PEMFs for 24 h results in higher proliferation of chondrocytes and mRNA expression of aggrecan, type I and X collagen in porcine chondrocytes, but lower glycosaminoglycan (GAG) production compared to controls [48]. In contrast, another study reported no significant change in proliferation or GAG synthesis of human OA chondrocytes when treated with PEMFs [44]. Schmidt-Rohlfing et al. did not find any effect of a PEMF on human OA chondrocytes, such as no significant differences in gene expression of Coll II and aggrecan between the treatment and control groups [43]. The deeper mechanisms are still unknown but are thought to be exerted, at least partially, through inhibition of the mitogen-activated protein kinase (MAPK) signaling pathways [49]. Nitric oxide (NO) might play an important role in the effect of PEMFs in increasing human chondrocyte proliferation [50]. Moreover, a PEMF might enhance the effects of insulin-like growth factor I (IGF1) [51], which plays an anabolic role in chondrocyte metabolism [52].

Esposito et al. reported that PEMFs enhance cell proliferation and chondrogenic differentiation from stem cells [53]. It has also been established that PEMF therapy is beneficial for chondrogenic differentiation from human umbilical cord-derived stem cells [53]. Furthermore, when human adipose-derived stem cells were exposed to a PEMF, chondrogenic differentiation was stimulated in both two-dimensional and three-dimensional cultures [54]. The upregulation of chondrogenic differentiation by PEMFs might be induced through increased TGF-β [55]. TGF-β plays a role of paramount importance in cartilage healing. It has been shown that TGFβ-1 stimulates Coll II synthesis and offsets pro-inflammatory cytokine production [56].

Apoptosis plays a significant role in the physiopathology of articular cartilage in the course of OA. It has been demonstrated that PEMFs suppress chondrocyte apoptosis and MMP-13 expression in knee cartilage of ovariectomized rats [38]. Specifically, the application of a PEMF, as well as the administration of estrogen, may inhibit the apoptosis of chondrocytes in OVX rats [38]. A PEMF can reverse cartilage degeneration caused by lower estrogen levels through modulation of relevant anti-apoptotic proteins. A PEMF can also upregulate the expression of X-linked inhibitor of apoptosis protein (XIAP) and down-regulate the expression of Bax. The signal pathways involved in this mechanism remain to be addressed [36].

3.2. Cartilage

Cartilage is a highly specialized skeletal tissue, which is responsible for flexibility and durability at sites where a semisolid architecture is needed to provide shape and form. The components Coll II, PGs and GAGs are abundant in cartilage ECM. These components are responsible for the ECM organization and provide shear and tensile properties and the ability to resist compressive loads to cartilage. Moreover, it has been reported that for normal cartilage function, extracellular adenosine levels must be quite tightly regulated since depletion results in up-regulation of GAG release and the production of MMPs such as MMP-3 and MMP-13, prostaglandin E2 (PGE2) and NO, whilst its increase may trigger chondrocyte death [57–59].

The effects of PEMFs on cartilage are still controversial. Further, PEMFs have a protective effect on the catabolic environment. For example, after 3 weeks of 2 h per day treatment with a PEMF, GAG and Coll II both increase [60]. It has been shown that PEMFs increase matrix synthesis in bovine cartilage explant cultures [61,62]. Various studies showed that GAGs, Coll II and PG production are all upregulated in human and bovine cartilage explants, with or without IL1β treatment, after stimulation [63–65]. Further, the effects of PEMFs on PG biosynthesis by articular cartilage is age dependent [61]. The negative effects of IL1β were partly counteracted by the PEMFs, but this effect was restricted to cartilage in young subjects [61]. Notably, the chondroprotective effects of PEMFs were similar to those of IGF-1 through increasing PG synthesis, particularly in the early stages of OA, and might include IRS-1 phosphorylation [51]. Moreover, the effects of PEMFs and IGF-1 on PG synthesis in human OA cartilage explants cultured in the absence or presence of IL1β are additive [51,62,66].

It has also been demonstrated that PEMFs promote matrix synthesis and decrease the levels of inflammatory cytokines, resulting in a beneficial effect on tissue engineering of cartilage [67]. Other studies have reported that PEMFs could be considered adjuvant therapy to repress progression of OA by counteracting the progression increased by high inflammatory cytokine levels [65]. A large body of evidence supports the hypothesis that adenosine is able to inhibit the up-regulation of pro-inflammatory cytokines such as TNFα and IL-1β, which are crucial in most common inflammatory diseases such as rheumatoid arthritis

[57,68]. Activation of A2A and A3 adenosine receptors seems to be associated with inhibition of TNFα, IL-6, IL-8 and elastase release by activated mononuclear phagocytes [69,70]. Interestingly, it has been reported that PEMFs up-regulate the expression of A2A and A3 adenosine receptors in bovine chondrocytes and synoviocytes, resulting in the suppression of the release of pro-inflammatory cytokines [71,72]. Furthermore, PEMFs increase the levels of TGF-β [28,73], which plays a role of paramount importance in cartilage healing [56], as well as decreasing IL-1 levels [51,65,74]. PEMF intervention for 6 months can significantly reduce MMP-3 and MMP-9 expression, suggesting that PEMFs can inhibit both cartilage degradation due to enzyme overexpression and improve the destruction of articular cartilage [28].

Importantly, these results support the positive effect of PEMFs in preventing articular cartilage degeneration.

3.3. Subchondral bone

The majority of reports regarding PEMF effects are limited to the study of chondrocytes and articular cartilage. A limited number of studies have evaluated subchondral bone by means of histological grading scales or by measuring subchondral bone thickness and epiphyseal bone trabecular volume.

It has been demonstrated that subchondral trabecular bone microarchitecture participates in changing microarchitectural properties [75,76]. The subchondral bone plate could influence cartilage degradation because it is in direct contact with the cartilage. However, no significant differences have been observed in epiphyseal trabecular bone remodeling processes, such as bone volume (BV/TV), trabecular number (Tb.N), trabecular thickness (Tb.Th) and trabecular separation (Tb.Sp) measurements between PEMF- and sham-treated animals. When extended to the study of PEMF intervention in advanced OA, the results show that PEMFs can not only reduce soft subosseous bone thickness, but also can reduce all histomorphometric indicators. Regarding health effects, PEMFs increase the Tb.Sp of most knees, and reduce BV/TV, Tb.Th and Tb.N to improve subchondral bone trabecular structure [29]. These findings mean that alterations in epiphyseal trabecular bone metabolism in OA joints seem to be quite complex, for instance, a mixture of thickening and increased porosity. One possible explanation is that a 3-month treatment duration is not sufficient to influence the complex bone-remodeling process [27]. When the effects of 75 Hz and 37 Hz PEMFs on cartilage thickness were compared, results showed that both frequencies had the ability to prevent deleterious changes in both cartilage and bone structural parameters in late-stage knee OA [77]. PEMF therapy thus mediates subchondral trabecular bone microarchitecture, at least partially, potentially through Wnt/β-catenin signaling and OPG/RANKL/RANK signaling [78].

Moreover, it has been found that preemptive PEMF treatment is more beneficial for subchondral trabecular bone microarchitecture and prevention of subchondral bone loss. Early PEMF therapy prevented changes to subchondral Tb.N and Tb.Sp, while delayed PEMF treatment maintained subchondral BV/TV, Tb.N and Tb.Sp [79]. When applying PEMF in OA treatment, it is thus crucial to apply it at the right time.

4. Discussion

4.1. Evidence for therapeutic effects

At present, various research groups are focusing on the potential therapeutic effects of PEMFs in OA, but the findings are still inconsistent. The clinical use of PEMF to treat patients with OA is controversial because studies have produced conflicting results, due to differences in study design and small sample sizes. Whether application of PEMFs with different parameters (treatment starting point and duration, daily exposure time, PEMF waveform and subject-related factors) exert positive effects on OA are still controversial. After a 6-week PEMF treatment and a 12-week follow-up, significant improvements were found in ADL, pain and stiffness compared with control groups [18]. Another study reported that there were no statistically significant differences between 2 weeks of PEMF therapy and the sham group in terms of WOMAC pain, stiffness, and physical function scores [11]. There are various possible explanations for these different outcomes. First, different clinical designs and parameters were chosen by different groups. Also, many groups used small sample sizes, which were not accurate enough for a clinical trial. For example, two groups applied low frequency PEMF (3–50 Hz) with long durations of treatment (3–10 h a week) [18,21], while another three studies applied high frequency PEMF with shorter treatment durations [24–26]. It has been found that PEMF with low frequencies and long treatment durations reflect a greater trend for short-term improvement in WOMAC function score than high frequency, low duration treatments. However, there is an equivocal lack of benefit in pain relief.

Long-term PEMF treatments have the ability to stimulate cellular proliferation and DNA synthesis through opening of voltage-sensitive calcium channels [80], while shorter therapy exerts no effect on DNA synthesis [46]. Different PEMF parameters (e.g., field intensity, frequency, exposure time) may result in controversial effects on chondrocyte activity. PEMF therapy has been demonstrated to stimulate proliferation of healthy human chondrocytes [50] as well as human OA chondrocytes [46,47]. Moreover, exposure to a PEMF for 24 h increased porcine chondrocyte proliferation and enhanced mRNA expressions of aggrecan, type I and X collagen, while decreasing GAG production [48]. It has also been reported that PEMFs increase the beneficial effect of chondrogenic differentiation from stem cells. PEMFs increase TGF-β secretion and enhance chondrogenic differentiation through the TGF-β pathway [55]. Moreover, PEMFs are known to enhance IGF-1 expression [51], which participates in chondrocyte metabolism [52]. PEMFs can suppress cartilage degeneration via the inhibition of chondrocyte apoptosis by increasing the expression of anti-apoptotic proteins.

ECM degradation is regarded as another main characteristic of OA. PEMFs increase A2A and A3 adenosine receptor expression, contributing to suppression of pro-inflammatory cytokine release, such as TNFα and IL-1, which are harmful to cartilage homeostasis [71,72]. PEMFs also stimulate matrix synthesis and, at the same time, suppress inflammatory cytokines [67]. Moreover, effects of PEMFs on ECM component synthesis, such as collagen II, have been reported [48]. Others also analyzed the effect of PEMFs on porcine chondrocytes and reported that 3 weeks of 2 h per day PEMF therapy increased the expression of GAG and Coll II [60]. The beneficial effects of PEMFs on the ECM are exerted through regulation of catabolic factors, such as MMP13. Inhibition of the MAPK signaling pathway might be involved in these effects [49].

It has been shown that various experimental parameters such as cell viability, ECM production, and cell cycle progression, result in different effects [46]. For example, several studies reported that the PEMF-induced proliferative and differentiative effects are dependent on the cell type [81,82], the differentiation stage [83], and the culture conditions [46,81,84]. Moreover, the time–response curves of PEMF biological effects were investigated [81,85–87]. Over-confluence of chondrocytes would minimize the contact inhibition which causes changes in biochemical status, resulting in dedifferentiation [81,85–87]. Thus, the longer-duration designs of PEMF therapy should utilize collagen matrix in three-dimensional cultures, and overcome the limitation of dedifferentiation.

PEMF therapy has been demonstrated to improve bone and cartilage turnover in an animal model of OA [28]. Further work is needed to study the beneficial effects of PEMF treatment in patients with knee OA. Part of the pre-clinical work is to study the PEMF parameters and exposure conditions, which optimize the effects on cartilage. Further investigation is needed to investigate the specific mechanism and identify the most effective treatment regimens for cartilage protection.

4.2. Limitations and adverse effects

The number of clinical studies on this topic is limited. Most of the trials we summarized had small sample sizes. Moreover, clinical experiments are different from animal experiments. For example, animals commonly used as naturally occurring OA models are studied by surgical methods, which cannot mimic the occurrence of slowly progressing OA in humans [88]. Moreover, the parameters of PEMFs are varied, resulting in different outcomes. Furthermore, it is challenging to ensure blinding between the treatments, which is a basic requirement in studies of PEMF treatment. Several studies have reported little information of how treatment blindness was achieved. Therefore, unblinded studies may have been included, which may have produced false results.

None of the trials reported any adverse effects. However, PEMF therapy is not recommended for patients with cardiac devices [89]. It has also been reported that magnetic fields may increase the risk of cancer in children [90,91]. However, exposure to PEMFs might impair cancer cell viability [92–94]. These controversial results might be dependent on differences in study design. Moreover, the use of electric devices, such as heating blankets, hairdryers or electric razors, causes higher risks of cancer in adults [95,96].

Overall, it has been demonstrated that PEMFs have an effective influence on oogenesis using animal models and cells. However, the role of PEMFs in OA patients is not well explored, and more reliable evidence from high-quality, randomized controlled trials, with large sample sizes and long-term follow-up is required to validate these findings. Furthermore, it will be important to take contraindications of long-term PEMFs into account in further studies.

5. Conclusions

Based on recent studies of PEMFs and their potential role in mediating OA, PEMFs might be regarded as a valuable treatment for OA. Few studies have reported adverse effects of long-term application of PEMFs because of the small number of samples, meaning that the evidence regarding usage of PEMF devices is not sufficient. Therefore, more reliable evidence from high-quality, randomized controlled trials, with large sample sizes and long-term follow-up, is needed to validate these findings and to evaluate the possible health benefits or risks of PEMF therapy. Furthermore, gene-knockout mice should be used to identify the specific target genes involved in the treatment of OA by PEMFs, such as TGF-β, which is beneficial in cartilage homeostasis and in maintaining extracellular matrix (ECM) morphology, as well as A2A and A3R receptors, which are activated in relation to inflammation.

Contributions

Chengqi He was involved in the design of the article. Tiantian Wang, Wei Xie and Wenwen Ye drafted of the article. International Science Editing assisted in revision of the review. All authors had final approval.

Funding source

All sources of funding should be acknowledged, and you should declare any extra funding you have received for academic research of this work. If there are none state ‘there are none’.

Declaration of competing interest

None.

Acknowledgments and Funding

This work was supported by Grants from National Natural Science Foundation of China (81572236 to C Q He), the Chengdu Bureau of Science and Technology (No. 2015-HM02-00042-SF to C Q He) and Sichuan science and Technology (No.2015SZ0054 to C Q He).

We thank International Science Editing (http://www.internationalscienceediting.com) for editing this manuscript.

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