



Review

Promising application of Pulsed Electromagnetic Fields (PEMFs) in musculoskeletal disorders

Hongzhi Hu^{a,c,1}, Wenbo Yang^{a,1}, Qianwen Zeng^{b,1}, Wei Chen^c, YanBin Zhu^c, Weijian Liu^a, Shangyu Wang^a, Baichuan Wang^{a,**}, Zengwu Shao^{a,**}, Yingze Zhang^{a,c,*}

^a Department of Orthopaedics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China

^b Department of Pediatrics, Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology, Wuhan 430030, China

^c Department of Orthopaedic Surgery, The Third Hospital of Hebei Medical University, Shijiazhuang, 050051, China



ARTICLE INFO

Keywords:

Pulsed electromagnetic fields

Musculoskeletal disorders

Application

Therapy

Mechanism

ABSTRACT

Increasing evidence suggests that an exogenous electromagnetic field might be involved in many biologic processes which are of great importance for therapeutic interventions. Pulsed electromagnetic fields (PEMFs) are known to be a noninvasive, safe and effective therapy agent without apparent side effects. Numerous studies have shown that PEMFs possess the potential to become a stand-alone or adjunctive treatment modality for treating musculoskeletal disorders. However, several issues remain unresolved. Prior to their widely clinical application, further researches from well-designed, high-quality studies are still required to standardize the treatment parameters and derive the optimal protocol for health-care decision making. In this review, we aim to provide current evidence on the mechanism of action, clinical applications, and controversies of PEMFs in musculoskeletal disorders.

1. Introduction

After the design and manufacture of various types of electromagnetic signals during World War II, magnetic and electromagnetic field began to serve as therapeutic modalities [1]. In the 1950s, Yasuda et al. [2] demonstrated the existence of electric potentials in bones, including steady-state potential and stress-induced potential. Since then, researchers have generated interest in the efficacy of the electricity on bone growth and fracture repair [3–6]. Various devices have been developed to generate electromagnetic fields for osteogenesis stimulation [7]. In 1964, Bassett et al. [8] demonstrated the effects of electric currents on new bone growth in vivo and then reported the therapeutic use of pulsed electromagnetic fields (PEMFs) in humans congenital and acquired pseudarthroses and non-unions in 1977 [9]. Then PEMF stimulation was approved by US Food and Drug Administration (FDA) to treat nonunion fractures in 1979 [10]. Subsequently, there was an abundance in the literature of reports describing the effects of PEMF

therapy on bone fracture repair [11–14].

PEMF, one of electromagnetic field therapeutic modalities, is low frequency fields with specific waveforms and amplitudes, ranging between 6 and 500 Hz [15]. It is characterized by a high rate of change (Tesla/s) that induces bioelectric currents in tissues, producing special biological effects [16]. Of note, low frequency fields have been shown to be nonionizing and nonthermal [17]. The frequency of electromagnetic fields used in clinical treatment is usually less than 100 Hz and the magnetic flux density is between 0.1 mT and 30 mT [18]. The existing PEMF has different types of waveforms including asymmetrical, biphasic, sinusoidal, quasi-rectangular, and trapezoidal [15,19]. Among them, quasi-rectangular and quasi-triangular PEMF were approved by FDA as the safe and effective treatment for fractures and their sequelae [15]. In clinical applications, Bassett's sawtooth signal is one of the most famous pulsed magnetic field shapes, whose magnetic field changes rapidly. The rapid changes in signal strength can cause large currents in the tissue [20].

* Corresponding author at: Department of Orthopaedics, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430022, China.

** Corresponding authors.

E-mail addresses: 13720105746@163.com (H. Hu), yangwenbo@hust.edu.cn (W. Yang), 779549578@qq.com (Q. Zeng), wangbaichuan-112@163.com (B. Wang), szwpro@163.com (Z. Shao), yzling_liu@163.com (Y. Zhang).

¹ Equally contribution.

<https://doi.org/10.1016/j.bioph.2020.110767>

Received 2 June 2020; Received in revised form 6 September 2020; Accepted 17 September 2020

Available online 23 September 2020

0753-3322/© 2020 Published by Elsevier Masson SAS. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

More recently, increasing evidence suggests that this noninvasive, safe and effective therapy might be as a promising adjuvant for treating various musculoskeletal disorders [21–26]. However, the exact mechanism of action of PEMF at cellular and molecular level is still ongoing debate [22,27,28]. In addition, there is no standardized treatment protocols or rationale for parameter selection [29]. Therefore, extensive clinical trials and validation are still needed prior to their widely clinical application. In this review, we aim to provide current evidence on the mechanism of action (Fig. 1), clinical applications, and controversies of PEMFs in musculoskeletal disorders.

2. Mechanism of action

Over the past several decades, a collection of studies were focused on the mechanisms underlying the effects of PEMFs on biological organisms [30–36]. Since the currently used PEMFs are too weak to depolarize cell membranes, the biological activity of PEMFs might be associated with the amplification mechanisms that occur during transmembrane coupling [6]. The transmembrane receptors are probably sites of amplification. PEMFs were reported to affect ligand binding and distribution as well as activity of several membrane receptors including PTH [37–40], insulin [41], IL-2 [42], IGF-2 [43], LDL [44], calcitonin [45], thereby modulating transmembrane signaling. More recently, Varani et al. also demonstrated the PEMFs exerted a strong anti-inflammatory effect on the joint environment via acting as agonist of A_{2A} and A₃ adenosine receptors [46,47]. The receptor activation can

reduce the release of prostaglandin E₂ (PGE₂) and pro-inflammatory cytokines IL-6 and IL-8, as well as inhibit the activation of the transcription factor NF- κ B [48].

A recent review summarized the underlying signaling pathways of PEMFs, including Ca²⁺, Wnt/ β -catenin, mitogen-activated protein kinase (MAPK), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF), transforming growth factor (TGF)- β / bone morphogenetic proteins (BMP), insulin-like growth factor (IGF), Notch, and cAMP/protein kinase A (PKA), in bone repair [49]. Furthermore, the mammalian target of rapamycin (mTOR) pathway has also been demonstrated to be the underlying signaling pathway of PEMFs involved in bone formation [50]. Of note, PEMF exposure also affected the synthesis of growth factors such as IGF [51], BMP [52], TGF- β [53], and PGE₂ [54], promoting the synthesis of extra-cellular matrix (ECM) proteins and facilitating tissue repair [6].

To date, PEMFs are still an empirically based treatment. Despite intense research, the conclusively defined mechanism of action of PEMFs remains, to a wide extent, not well elucidated. Therefore, there is still a need for further research on the underlying mechanism of action of PEMF.

3. Main clinical applications of PEMFs

3.1. Delayed union or nonunion fractures

It was reported that 5–10 % of fractures may develop delayed union

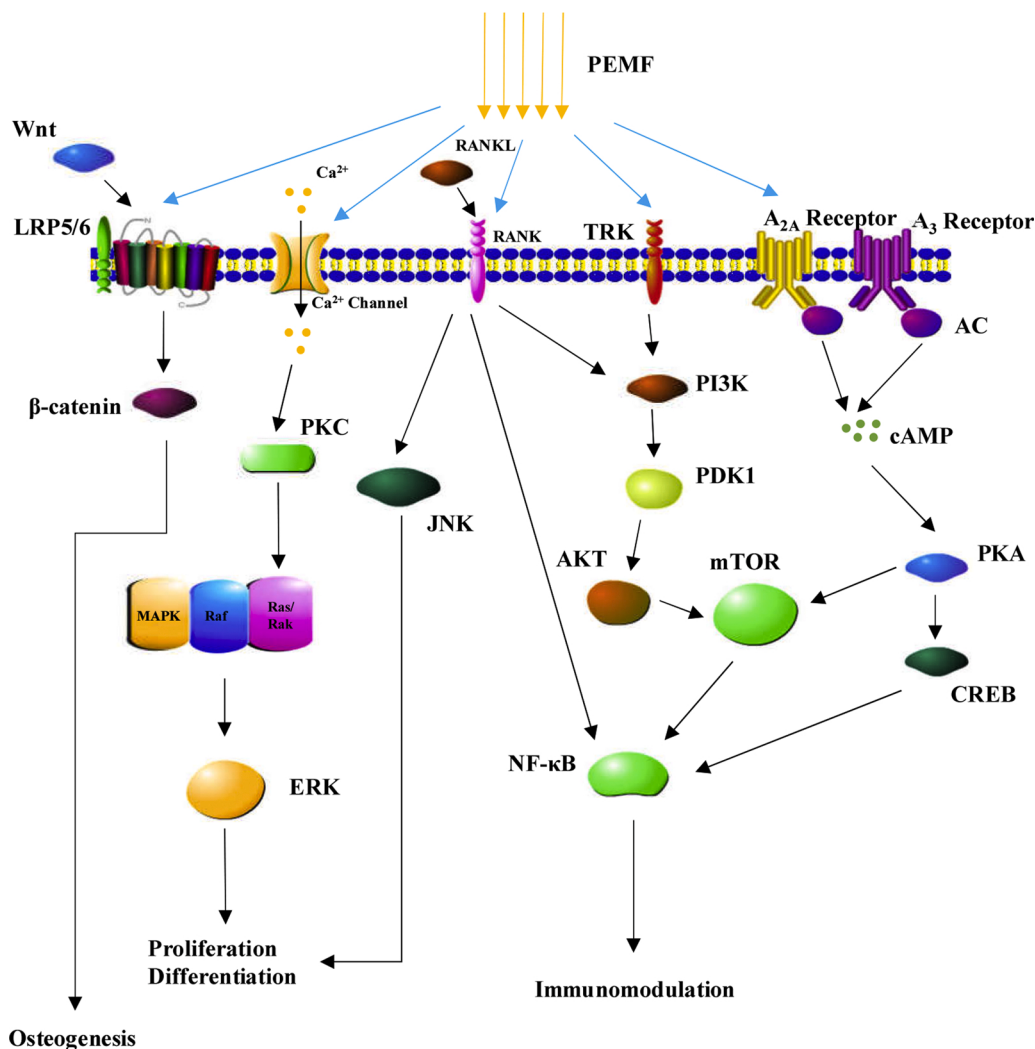


Fig. 1. The underlying molecular mechanisms of biological effects induced by PEMFs. PEMF stimulation is involved in the regulation of cell proliferation and differentiation as well as immune modulation and inflammation response through a variety of underlying molecular mechanisms.

Abbreviation: PEMFs Pulsed electromagnetic fields; PKC Protein kinase C; MAPK Mitogen-activated protein kinase; ERK Extracellular signal-regulated kinases; RANKL Receptor activator of nuclear factor kappa-B ligand; RANK Receptor activator of nuclear factor kappa-B; JNK c-Jun N-terminal kinase; TRK Tyrosine kinase receptor; PI3K Phosphatidylinositol 3-kinases; PDK1 Phosphoinositide dependent protein kinase-1; AKT Protein kinase B; mTOR mechanistic target of rapamycin; AC Adenylyl cyclase; cAMP cyclic adenosine monophosphate; PKA Protein kinase A; CREB cAMP response element-binding protein; NF- κ B Nuclear factor-kappa B.

or nonunion under the usual treatment [3,55]. These non-union bone fractures will not only bring along prolonged pain and disability for the patients, but also result in heavy social and economic burden [3,56]. Surgery is currently the preferred treatment for the delayed unions and nonunion fractures, but probably may bring about serious complications, such as neurovascular damage, infection, or implant-related problems [23,57,58]. As an alternative, PEMF therapy, which has attracted the attention of clinicians in recent years, has the potential to reduce the risk of these complications [22,59,60].

After PEMF therapy gain approval by the US FDA, numerous studies have reported its efficacy in treating nonunion fractures, with the overall healing rate ranging from 68 % to 90 % [13,60–70]. Previous in vitro and in vivo studies demonstrated that the application of PEMF therapy improved the local environment and increased expression of growth factors to facilitate the bone healing process [54,71,72]. However, indications and strategies for the treatment of nonunion fractures with PEMF vary in the literature [59,73,74]. In the opinion of most investigators, PEMF therapy would not be used until an established nonunion is diagnosed [74,75]. And other investigators used the late delayed union stage (over 6 months after fracture) as an indication for the use of PEMF [73,76]. However, a prospective randomized controlled study [59] concluded that the early application of PEMF treatment (Orthopulse® II, OSSATEC, Uden, The Netherlands, 8 h/day) can significantly improve the fracture healing rate. The average success rate in the PEMF treatment group was 77.4 % (the average duration of PEMF treatment was 4.8 months), which was much higher than that of control group (48.1 %, the average duration of sham treatment was 4.4 months). Accordingly, PEMF treatment should be considered and initiated as early as possible after diagnosis of a delayed union (at about 16 weeks after fracture).

Of note, few studies have specifically investigated effect of treatment “dose” of PEMF stimulation (The Biomet® EBI Bone Healing System (EBI, LLC (a Zimmer Biomet company), Parsippany, NJ, USA)) on the healing times of nonunion fractures. A recent study followed 1382 patients treated with PEMF stimulation and demonstrated that the average healing time was reduced by 6 days for each additional hour of daily PEMF treatment [60]. And the survival analysis showed that the median healing time of patients treated with PEMF for an average of 10 h was 35 %–60 % less than that of patients treated with PEMF for an average of 1 h per day. In addition, the study also showed that patients treated with PEMF for 9 or more hours a day healed on average 76 days earlier than those treated with PEMF for 3 or less hours a day. All these findings supported that an increase in the average daily “dose” of PEMF stimulation was associated with an acceleration in the rate of fracture healing.

3.2. Osteoarthritis (OA)

OA is one of the most common diseases of the elderly and seriously affect the patients' life quality [77,78]. Knee is the most commonly affected joints and knee OA is a leading contributor to disability in the elderly [79,80]. Numerous therapies are available to treat knee OA, including anti-inflammatory medications, non-pharmacological treatment, and ultimately total knee replacement for advanced OA [81,82]. Current treatment is designed to alleviate pain, minimize disability and delay the progression of joint damage progression [83]. However, there are few truly effective treatments available [84].

Nowadays, various studies are focusing on the potential therapeutic effects of PEMF therapy on preventing OA development and progression, but the findings are still controversial [27,85–88]. PEMF therapy has been demonstrated to promote stem cell proliferation and chondrogenic differentiation [89–92]. A pre-clinical study reported that PEMFs treatment (6 h a day for 6 months), in Dunkin Hartley guinea pigs, was able to halt the progression of OA, to limit cartilage surface clefts and fibrillation, to preserve cartilage thickness and to prevent sclerosis of the subchondral bone [93]. Similarly, numerous in vitro and animal trials have shown PEMFs are beneficial for cartilage homeostasis,

which contributes to preventing articular cartilage degeneration [94–96]. Furthermore, many randomized trials have demonstrated the potential of PEMFs to improve the symptoms of OA [97,98]. Nevertheless, a randomized, placebo-controlled study suggested that ten sessions of PEMFs (50 Hz, 30-G intensity, 90-s interval, and 30-min duration in each session) over 2 weeks had little value in reducing symptoms of knee OA [85]. In addition, one review concluded that PEMFs had no obvious effects on the management of knee OA [86]. The conflicting results might due to different study design and small sample sizes, which were not reliable enough for clinical trials [27]. Although the effect of PEMFs on knee OA remains controversial, recent studies support PEMFs as a useful complementary treatment option for knee OA [25–27,88]. A recent meta-analysis conducted by Viganò M. and colleagues demonstrated that PEMF treatment is effective in alleviating the symptoms of knee OA in the short term, but it seems not significantly better than other conservative therapies, such as physiotherapy [99]. More reliable evidence, therefore, is still warranted to validate the efficacy of PEMF in the management of knee OA.

3.3. Osteoporosis (OP)

OP is a well-defined chronic metabolic bone disease characterized by low bone mass deteriorating microarchitecture, and increased bone fragility [28,100]. With aging of the population and longer life in worldwide, the prevalence of OP increases dramatically and results in a huge financial burden to all the countries [100]. The researchers estimated that in the future, nearly half of people over the age of 60 in developed countries will suffer from OP, 80 % of whom are postmenopausal women [101,102]. Under certain pathological conditions, the imbalance between bone resorption and bone formation leads to the abnormal bone remodeling, which contributes to various types of OP [103].

Currently, various antiosteoporosis drugs have been proven to be effective in maintaining healthy bone mass and strength [102,104,105]. However, long term use of these drugs may lead to various potential adverse and side effects [106], such as osteonecrosis of the jaw [107], infections [108], hypocalcemia [109], increased risk of certain cancers [110], atrial fibrillation [111], and atypical femoral fractures [112]. In recent years, physical therapy for this kind of disease has got increased attention besides pharmacotherapy [113]. PEMFs, as an efficient physical therapy for various bone disorders [114,115], have been demonstrated to have the potential value in treating OP [24,28,115]. A randomized, active-controlled clinical trial [115] demonstrated that the treatment of postmenopausal OP with PEMFs at specific parameters (8 Hz, 3.82 m T, 40 min/day, and 6 times/week) and alendronate (70 mg/week) achieved the same therapeutic effect for within 24 weeks.

A previous review has confirmed that PEMFs can significantly alleviate pain and improve quality of life in patients with primary OP [116]. Furthermore, PEMFs can not only significantly upregulate biomarkers associated with bone formation but also downregulate biomarkers associated with bone resorption [117]. However, the effects of PEMFs on bone mineral density (BMD) in patients with OP also remain controversial [117–119]. Garland et al. [120] showed that the BMD of patients with OP increased significantly after 3 months in the stimulated knees compared with the control group. Nevertheless, a randomized controlled single blind study suggested that no significant increase in BMD was observed after the PEMF treatment (100-Hz, 60 min per day, 3 times a week for 3 months). [119]. Similarly, Tabrah et al. [121] found no further beneficial effects of PEMFs (72 Hz, 10 h of each day of the 12 week) on BMD over an 8-year follow-up. These conflicting results might contribute to different clinical designs and parameters used by different groups [28].

3.4. Osteonecrosis (ON)

ON is considered to be a devastating disease which often involves the

hip joint (femoral head) [122,123]. The most often cited risk factor for ON is high-dose corticoid administration [124,125]. In order to prevent collapse, several surgical treatments are available, such as core decompression [126], vascularized fibular grafting [127], non-vascularized bone grafting [128], osteotomy [129], and joint arthroplasty [130]. Although the surgical treatments are effective, the costs and complications of the surgery should arouse more attention [131]. If the femoral head collapses, the treatment of ON usually requires total hip arthroplasty [131,132]. Furthermore, long-term results of joint replacement in the relatively young population seem not always optimistic [133]. Therefore, prevention of ON is of great importance in patients requiring high doses of corticosteroid therapy, but there is no effective strategy to delay the progression of ON [132].

PEMFs were firstly applied by Bassett and colleagues to treat 118 patients with ON of the femoral head, which obtained the satisfactory curative effect [134]. Since then, PEMF treatment has been considered as a safe and effective treatment for patients with ON [133,135]. Massari et al. [133] performed a retrospective analysis to analyze the effects of PEMFs on patients with ON of the femoral head and concluded that PEMFs might be indicated in the early stages of this disease (Ficat stages I and II). Ishida et al. [132] used a rabbit model to evaluate and confirm the preventative value of PEMFs on steroid-induced ON. Similarly, Ding et al. [131] concluded that PEMF stimulation (15 Hz, 4 h each day for 1–8 weeks) can prevent steroid-induced ON in rats and showed the decreased serum lipid levels and increased expression of TGF- β 1 might be the underlying mechanisms. In addition, Ikegami et al. [136] suggested that the underlying mechanisms of PEMF stimulation might be associated with restraint of the decreased blood flow that appears early after steroid administration.

3.5. Tendon disorders

Tendon disorders, which include both acute tendon injuries and chronic tendinopathies, are one of the most common musculoskeletal conditions and are responsible for pain and disability [137]. Generally, non-operative management is considered to be the first-line treatment, including non-steroidal anti-inflammatory drugs, ultrasound, and physiotherapy [138]. The rehabilitation times from the tendon pathologies might be extensive and the outcomes are often unsatisfactory [99]. This is partly due to the complex architecture structure of the ECM, very few of low activity tendon-resident cells, as well as the avascular nature of tendons [139]. In addition, our incomplete understanding of the molecular and cellular events underlying tendinopathy hamper the development of new and effective treatment strategies [140].

There are still a lot of disputes about the roles of inflammation in the pathogenesis of tendinopathy [138,140,141]. However, recent evidence convincingly showed that a cascade of inflammatory events, such as secretion of inflammatory mediators, infiltration of lymphocyte and macrophage, and activation of matrix metalloproteinase (MMP), exert a paramount role in the etiology of tendinopathies [142–144]. Among various cytokines, interleukin-1 β can promote tendinopathy by activating matrix metalloproteinases (MMPs), ultimately triggering catabolic degradation of ECM. Therefore, targeting the inflammatory cascade and reducing the abnormal ECM remodeling, appears to be a promising treatment for tendinopathy. Previous studies have demonstrated that PEMFs could be used to control articular tissue inflammation and stimulate anabolic pathways, that eventually lead to tissue repair [35,145]. More recently, the feasibility to use PEMFs for the management of tendon disorders has been evaluated by many studies [140,146,147]. Gehwolf et al. [140] provided evidence that in vitro treatment of tendon-derived cells with PEMFs might limit their catabolic effects of a pro-inflammatory stimulus by IL-1 β , thereby resulting a more tissue reparative state. Other study at cellular level has also shown that PEMFs might be effective in the modulation of gene expression, cell proliferation and cytokine production in human tendon cells [148]. Interestingly, PEMF was found to have no effect on gene expression of

tenocytes in standard culture medium, however, it has a positive role in enhancing their gene expressions under an inflammatory condition [149]. This evidence suggests that PEMF might be suitable to treat tendon disorders associated with inflammation. Girolamo et al. [147] evaluated different biological effects exerted by different PEMF intensity, duration and length of exposure, and concluded that repeated 1.5 mT-PEMF treatment showed the best biological effects.

Moreover, the failure of tendon healing may also be attributed to the incomplete restoration of tendon body and lack of osteointegration at the level of the enthesis [150]. Therefore, the enhancement of tenogenic process during tendon regeneration and the improvement of enthesis reconstruction are effective methods to improve tendon repair. Previous studies showed that PEMF exposure on human tendon increased the expression of collagen type I, as well as production of IL-10 and VEGF, which can promote the healing process of tendon [147,148]. Of note, the application of mesenchymal stem cells (MSCs) in tendon healing and regeneration is still a debate but novel therapies [150,151]. A controlled laboratory study demonstrated that PEMFs have little effects on the proliferation of human tendon stem cells (hTSCs) but enhance the expression of stem cell marker [151]. Therefore, the application of PEMFs might open up new perspectives for tendon regeneration.

3.6. Other conditions

Including the main applications mentioned above, PEMFs have also been shown to be beneficial in the treatment of lateral epicondylitis [152,153], fibromyalgia [154,155], degenerative disc disease [156–158], musculoskeletal chronic pain [21,159], and nerve regeneration [160,161]. As can be seen, the indications for PEMFs in the treatment of musculoskeletal disorders will continue to expand with time and experience.

3.7. Limitations and adverse effects

Although PEMFs show satisfactory therapeutic effect on various musculoskeletal conditions, there still several issues remain unresolved. Firstly, numerous studies have focused on the underlying mechanism of action of PEMFs, but deeper mechanisms are still unknown [27,28,72,94,132,162]. Secondly, there are no standardized clinical protocols or rationale for parameter selection. Different parameters of PEMF, such as frequency, intensity and exposure time, were manipulated in different clinical and experimental studies [27,28]. For one specific disease, the optimal parameters of PEMF therapy are still not known. As is the case with dosage of medicines, the correct physical parameters of PEMF should be found in each specific clinical case. In addition, the small samples sizes used in many studies remains as a limitation [59,88,163]. So, it is necessary that rigorously designed high quality, large-scale randomized controlled trials with long-term follow-up are warranted to confirm the effects of PEMFs on patients with musculoskeletal disorders.

PEMFs are generally considered to be a safe and effective technique for patients and study participants if appropriate precautions are taken [164]. However, it is still necessary to assess whether PEMFs pose any risks to the health of operators and patients in routine clinical use. Numerous safety exposure guidelines and expert opinions from competent authorities and expert groups have provided that exposure to electromagnetic fields might have potential adverse effects on the brain and peripheral nervous system, cardiovascular system, cognitive and vestibular function [165–167]. Moreover, previous studies have reported that electromagnetic fields exposure were associated with depression and suicide and neurodegenerative diseases among utility workers [168–171]. Of note, recent studies demonstrated that long-term exposure to man-made electromagnetic fields may lead to DNA damage, which is associated with an increased risk of seizures, syncope, cancer, neurodegenerative diseases, reproductive declines, etc. [171–173]. For the sake of security, therefore, high attention must be paid to the

potential adverse effects of long-term PEMFs in further studies.

4. Conclusion

Based on the currently positive findings of the emerging published studies, PEMFs show great potential to become a stand-alone or adjunctive treatment modality for treating musculoskeletal disorders, due to their noninvasiveness, safety and efficacy. Considerable studies have explored the underlying cellular and subcellular mechanisms of PEMF stimulation on various musculoskeletal diseases, providing a molecular basis for extending its clinical application. However, several issues remain unresolved, such as the unknown deeper mechanisms and optimal parameter selection. Accordingly, prior to their widely clinical application, further researches from well-designed, high-quality studies are still required to clarify the deeper mechanisms, standardize the treatment parameters and derive the optimal protocol for health-care decision making. In summary, with adequate patient selection, appropriate indications, and homogeneous therapeutic strategies, PEMFs could exert a potent role for treating certain musculoskeletal disorders in the future.

Author contributions

HZH, WBY and QWZ wrote the manuscript. WC, YBZ and WJL revised the full paper. BCW, ZWS and YZZ reviewed and edited the paper. All authors read and approved the paper.

Ethics approval and consent to participate

None.

Consent to publish

None.

Data availability

Not applicable.

Funding information

None.

Declaration of Competing Interest

The authors report no declarations of interest.

References

- [1] M.S. Markov, Pulsed electromagnetic field therapy history, state of the art and future, *Environmentalist* 27 (4) (2007) 465–475.
- [2] The classic: Fundamental aspects of fracture treatment by Iwao Yasuda, reprinted from *J. Kyoto Med. Soc.*, 4:395–406, 1953, *Clin. Orthop. Relat. Res.* (124) (1977) 5–8.
- [3] G. Victoria, B. Petrisor, B. Drew, D. Dick, Bone stimulation for fracture healing: What's all the fuss? *Indian J. Orthop.* 43 (2) (2009) 117–120.
- [4] C.T. Brighton, Z.B. Friedenberg, E.I. Mitchell, R.E. Booth, Treatment of nonunion with constant direct current, *Clin. Orthop. Relat. Res.* (124) (1977) 106–123.
- [5] S.F. Dealler, Electrical phenomena associated with bones and fractures and the therapeutic use of electricity in fracture healing, *J. Med. Eng. Technol.* 5 (2) (1981) 73–79.
- [6] D.M. Ciombor, R.K. Aaron, The role of electrical stimulation in bone repair, *Foot Ankle Clin.* 10 (4) (2005) 579–593, vii.
- [7] E.I. Waldorff, N. Zhang, J.T. Ryaby, Pulsed electromagnetic field applications: a corporate perspective, *J. Orthop. Translat.* 9 (2017) 60–68.
- [8] C.A. Bassett, R.J. Pawluk, R.O. Becker, Effects of electric currents on bone in vivo, *Nature* 204 (1964) 652–654.
- [9] C.A. Bassett, A.A. Pilla, R.J. Pawluk, A non-operative salvage of surgically-resistant pseudarthroses and non-unions by pulsing electromagnetic fields. A preliminary report, *Clin. Orthop. Relat. Res.* (124) (1977) 128–143 (Accessed 19 August 2016).
- [10] C. Daish, R. Blanchard, K. Fox, P. Pivonka, E. Pirogova, The application of Pulsed Electromagnetic Fields (PEMFs) for bone fracture repair: past and perspective findings, *Ann. Biomed. Eng.* 46 (4) (2018) 525–542.
- [11] S. Adie, I.A. Harris, J.M. Naylor, H. Rae, A. Dao, S. Yong, V. Ying, Pulsed electromagnetic field stimulation for acute tibial shaft fractures: a multicenter, double-blind, randomized trial, *J. Bone Joint Surg. Am.* 93 (17) (2011) 1569–1576.
- [12] C.A. Bassett, S.N. Mitchell, S.R. Gaston, Treatment of ununited tibial diaphyseal fractures with pulsing electromagnetic fields, *J. Bone Jt. Surg.* 63 (4) (1981) 511–523. American volume.
- [13] C. Androjna, B. Fort, M. Zborowski, R.J. Midura, Pulsed electromagnetic field treatment enhances healing callus biomechanical properties in an animal model of osteoporotic fracture, *Bioelectromagnetics* 35 (6) (2014) 396–405.
- [14] C.A. Bassett, Fundamental and practical aspects of therapeutic uses of pulsed electromagnetic fields (PEMFs), *Crit. Rev. Biomed. Eng.* 17 (5) (1989) 451–529.
- [15] J. Juutilainen, S. Lang, Genotoxic, carcinogenic and teratogenic effects of electromagnetic fields. Introduction and overview, *Mutat. Res.* 387 (3) (1997) 165–171.
- [16] B. Rubik, Bioelectromagnetics & the future of medicine, *Adm. Radiol. J.* 16 (8) (1997) 38–46.
- [17] J. Pasek, T. Pasek, K. Sieron-Stoltny, G. Cieslar, A. Sieron, Electromagnetic fields in medicine – the state of art, *Electromagn. Biol. Med.* 35 (2) (2016) 170–175.
- [18] M.S. Markov, Expanding use of pulsed electromagnetic field therapies, *Electromagn. Biol. Med.* 26 (3) (2007) 257–274.
- [19] N. Bachl, G. Ruoff, B. Wessner, H. Tschann, Electromagnetic interventions in musculoskeletal disorders, *Clin. Sports Med.* 27 (1) (2008) 87–105, viii.
- [20] A.M. Elshawi, H.A. Hamada, D. Mosaad, I.M.A. Ragab, G.M. Koura, S. M. Alrawaili, Effect of pulsed electromagnetic field on nonspecific low back pain patients: a randomized controlled trial, *Braz. J. Phys. Ther.* 23 (3) (2019) 244–249.
- [21] A. Assiotis, N.P. Sachinis, B.E. Chalidis, Pulsed electromagnetic fields for the treatment of tibial delayed unions and nonunions. A prospective clinical study and review of the literature, *J. Orthop. Surg. Res.* 7 (2012) 24.
- [22] H.-f. Shi, J. Xiong, Y.-x. Chen, J.-f. Wang, X.-s. Qiu, Y.-h. Wang, Y. Qiu, Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study, *BMC Musculoskelet. Disord.* 14 (2013) 35.
- [23] H.F. Liu, H.C. He, L. Yang, Z.Y. Yang, K. Yao, Y.C. Wu, X.B. Yang, C.Q. He, Pulsed electromagnetic fields for postmenopausal osteoporosis and concomitant lumbar osteoarthritis in southwest China using proximal femur bone mineral density as the primary endpoint: study protocol for a randomized controlled trial, *Trials* 16 (2015) 265.
- [24] S. Ryang We, Y.H. Koog, K.I. Jeong, H. Wi, Effects of pulsed electromagnetic field on knee osteoarthritis: a systematic review, *Rheumatology* 52 (5) (2013) 815–824.
- [25] X. Yang, H. He, Y. Zhou, Y. Zhou, Q. Gao, P. Wang, C. He, Pulsed electromagnetic field at different stages of knee osteoarthritis in rats induced by low-dose monosodium iodoacetate: effect on subchondral trabecular bone microarchitecture and cartilage degradation, *Bioelectromagnetics* 38 (3) (2017) 227–238.
- [26] T. Wang, W. Xie, W. Ye, C. He, Effects of electromagnetic fields on osteoarthritis, *Biomed. Pharmacother.* 118 (2019) 109282.
- [27] T. Wang, L. Yang, J. Jiang, Y. Liu, Z. Fan, C. Zhong, C. He, Pulsed electromagnetic fields: promising treatment for osteoporosis, *Osteoporos. Int.* 30 (2) (2019) 267–276.
- [28] Y.Y. Wang, X.Y. Pu, W.G. Shi, Q.Q. Fang, X.R. Chen, H.R. Xi, Y.H. Gao, J. Zhou, C. J. Xian, K.M. Chen, Pulsed electromagnetic fields promote bone formation by activating the sAC-cAMP-PKA-CREB signaling pathway, *J. Cell. Physiol.* 234 (3) (2019) 2807–2821.
- [29] R.K. Aaron, B.D. Boyan, D.M. Ciombor, Z. Schwartz, B.J. Simon, Stimulation of growth factor synthesis by electric and electromagnetic fields, *Clin. Orthop. Relat. Res.* (419) (2004) 30–37.
- [30] T. Goto, M. Fujioka, M. Ishida, M. Kuribayashi, K. Ueshima, T. Kubo, Noninvasive up-regulation of angiopoietin-2 and fibroblast growth factor-2 in bone marrow by pulsed electromagnetic field therapy, *J. Orthop. Sci.* 15 (5) (2010) 661–665.
- [31] J. Zhou, H. He, L. Yang, S. Chen, H. Guo, L. Xia, H. Liu, Y. Qin, C. Liu, X. Wei, Y. Zhou, C. He, Effects of pulsed electromagnetic fields on bone mass and Wnt/beta-catenin signaling pathway in ovariectomized rats, *Arch. Med. Res.* 43 (4) (2012) 274–282.
- [32] D. Jing, M. Zhai, S. Tong, F. Xu, J. Cai, G. Shen, Y. Wu, X. Li, K. Xie, J. Liu, Q. Xu, E. Luo, Pulsed electromagnetic fields promote osteogenesis and osseointegration of porous titanium implants in bone defect repair through a Wnt/beta-catenin signaling-associated mechanism, *Sci. Rep.* 6 (2016) 32045.
- [33] J. Tong, L. Sun, B. Zhu, Y. Fan, X. Ma, L. Yu, J. Zhang, Pulsed electromagnetic fields promote the proliferation and differentiation of osteoblasts by reinforcing intracellular calcium transients, *Bioelectromagnetics* 38 (7) (2017) 541–549.
- [34] M. De Mattei, M. Pasello, A. Pellati, G. Stabellini, L. Massari, D. Gemmati, A. Caruso, Effects of electromagnetic fields on proteoglycan metabolism of bovine articular cartilage explants, *Connect. Tissue Res.* 44 (3–4) (2003) 154–159.
- [35] G. Vicenti, D. Bizzoca, V.S. Nappi, F. Moretti, M. Carrozzo, V. Belviso, B. Moretti, Biophysical stimulation of the knee with PEMFs: from bench to bedside, *J. Biol. Regul. Homeost. Agents* 32 (6 Suppl. 1) (2018) 23–28.
- [36] C.T. Brighton, W.P. McCluskey, Response of cultured bone cells to a capacitively coupled electric field: inhibition of cAMP response to parathyroid hormone, *J. Orthop. Res.* 6 (4) (1988) 567–571.

- [37] Y. Hiraki, N. Endo, M. Takigawa, A. Asada, H. Takahashi, F. Suzuki, Enhanced responsiveness to parathyroid hormone and induction of functional differentiation of cultured rabbit costal chondrocytes by a pulsed electromagnetic field, *Biochim. Biophys. Acta* 931 (1) (1987) 94–100.
- [38] C.D. Cain, W.R. Adey, R.A. Luben, Evidence that pulsed electromagnetic fields inhibit coupling of adenylate cyclase by parathyroid hormone in bone cells, *J. Bone Miner. Res.* 2 (5) (1987) 437–441.
- [39] R.A. Luben, C.D. Cain, M.C. Chen, D.M. Rosen, W.R. Adey, Effects of electromagnetic stimuli on bone and bone cells in vitro: inhibition of responses to parathyroid hormone by low-energy low-frequency fields, *Proc. Natl. Acad. Sci. U. S. A.* 79 (13) (1982) 4180–4184.
- [40] G.J. Bourguignon, W. Jy, L.Y. Bourguignon, Electric stimulation of human fibroblasts causes an increase in Ca^{2+} influx and the exposure of additional insulin receptors, *J. Cell. Physiol.* 140 (2) (1989) 379–385.
- [41] A. Cossarizza, D. Monti, F. Bersani, R. Paganelli, G. Montagnani, R. Cadossi, M. Cantini, C. Franceschi, Extremely low frequency pulsed electromagnetic fields increase interleukin-2 (IL-2) utilization and IL-2 receptor expression in mitogen-stimulated human lymphocytes from old subjects, *FEBS Lett.* 248 (1–2) (1989) 141–144.
- [42] R.J. Fitzsimmons, J.T. Ryaby, F.P. Magee, D.J. Baylink, IGF-II receptor number is increased in TE-85 osteosarcoma cells by combined magnetic fields, *J. Bone Miner. Res.* 10 (5) (1995) 812–819.
- [43] M.R. Cho, H.S. Thatté, R.C. Lee, D.E. Golan, Induced redistribution of cell surface receptors by alternating current electric fields, *FASEB J.* 8 (10) (1994) 771–776.
- [44] V.S. Shankar, B.J. Simon, C.M. Bax, M. Pazianas, B.S. Moonga, O.A. Adebajo, M. Zaidi, Effects of electromagnetic stimulation on the functional responsiveness of isolated rat osteoclasts, *J. Cell. Physiol.* 176 (3) (1998) 537–544.
- [45] K. Varani, S. Gessi, S. Merighi, V. Iannotta, E. Cattabriga, S. Spisani, R. Cadossi, P. A. Borea, Effect of low frequency electromagnetic fields on A2A adenosine receptors in human neutrophils, *Br. J. Pharmacol.* 136 (1) (2002) 57–66.
- [46] K. Varani, F. Vincenzi, A. Ravani, S. Pasquini, S. Merighi, S. Gessi, S. Setti, M. Cadossi, P.A. Borea, R. Cadossi, Adenosine receptors as a biological pathway for the anti-inflammatory and beneficial effects of low frequency low energy pulsed electromagnetic fields, *Mediators Inflamm.* 2017 (2017), 2740963.
- [47] F. Vincenzi, M. Targa, C. Corciulo, S. Gessi, S. Merighi, S. Setti, R. Cadossi, M. B. Goldring, P.A. Borea, K. Varani, Pulsed electromagnetic fields increased the anti-inflammatory effect of A2A and A2B adenosine receptors in human T/C-28a2 chondrocytes and hFOB 1.19 osteoblasts, *PLoS One* 8 (5) (2013) e65561.
- [48] J. Yuan, F. Xin, W. Jiang, Underlying signaling pathways and therapeutic applications of pulsed electromagnetic fields in bone repair, *Cell. Physiol. Biochem.* 46 (4) (2018) 1581–1594.
- [49] H. Miyamoto, Y. Sawaji, T. Iwaki, T. Masaoka, E. Fukada, M. Date, K. Yamamoto, Intermittent pulsed electromagnetic field stimulation activates the mTOR pathway and stimulates the proliferation of osteoblast-like cells, *Bioelectromagnetics* 40 (6) (2019) 412–421.
- [50] R.J. Fitzsimmons, D.D. Strong, S. Mohan, D.J. Baylink, Low-amplitude, low-frequency electric field-stimulated bone cell proliferation may in part be mediated by increased IGF-II release, *J. Cell. Physiol.* 150 (1) (1992) 84–89.
- [51] M. Nagai, M. Ota, Pulsating electromagnetic field stimulates mRNA expression of bone morphogenetic protein-2 and -4, *J. Dent. Res.* 73 (10) (1994) 1601–1605.
- [52] R.K. Aaron, S. Wang, D.M. Ciombor, Upregulation of basal TGF β 1 levels by EMF coincident with chondrogenesis—implications for skeletal repair and tissue engineering, *J. Orthop. Res.* 20 (2) (2002) 233–240.
- [53] C.H. Lohmann, Z. Schwartz, Y. Liu, Z. Li, B.J. Simon, V.L. Sylvia, D.D. Dean, L. F. Bonewald, H.J. Donahue, B.D. Boyan, Pulsed electromagnetic fields affect phenotype and connexin 43 protein expression in MLO-Y4 osteocyte-like cells and ROS 17/2.8 osteoblast-like cells, *J. Orthop. Res.* 21 (2) (2003) 326–334.
- [54] D. Holmes, Non-union bone fracture: a quicker fix, *Nature* 550 (7677) (2017) S193.
- [55] P.C. Schottel, D.P. O'Connor, M.R. Brinker, Time trade-off as a measure of health-related quality of life: long bone nonunions have a devastating impact, *J. Bone Jt. Surg.* 97 (17) (2015) 1406–1410. American volume.
- [56] R.M. Peters, F.M. Claessen, J.N. Doornberg, G.P. Kolovich, R.L. Diercks, M.P. van den Bekerom, Union rate after operative treatment of humeral shaft nonunion—a systematic review, *Injury* 46 (12) (2015) 2314–2324.
- [57] M. El Haj, A. Khoury, R. Mosheiff, M. Liebergall, Y.A. Weil, Orthogonal double plate fixation for long bone fracture nonunion, *Acta Chir. Orthop. Traumatol. Cech.* 80 (2) (2013) 131–137.
- [58] H.F. Shi, J. Xiong, Y.X. Chen, J.F. Wang, X.S. Qiu, Y.H. Wang, Y. Qiu, Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study, *BMC Musculoskelet. Disord.* 14 (2013) 35.
- [59] H.B. Murray, B.A. Pethica, A follow-up study of the in-practice results of pulsed electromagnetic field therapy in the management of nonunion fractures, *Orthop. Res. Rev.* 8 (2016) 67–72.
- [60] B.D. Adams, G.K. Frykman, J. Taleisnik, Treatment of scaphoid nonunion with casting and pulsed electromagnetic fields: a study continuation, *J. Hand Surg.* 17 (5) (1992) 910–914.
- [61] C.A. Bassett, S.N. Mitchell, M.M. Schink, Treatment of therapeutically resistant non-unions with bone grafts and pulsing electromagnetic fields, *J. Bone Jt. Surg.* 64 (8) (1982) 1214–1220. American volume.
- [62] C.A. Bassett, S.N. Mitchell, S.R. Gaston, Pulsing electromagnetic field treatment in ununited fractures and failed arthrodeses, *Jama* 247 (5) (1982) 623–628.
- [63] A.W. Dunn, G.A. Rush, 3rd, Electrical stimulation in treatment of delayed union and nonunion of fractures and osteotomies, *South. Med. J.* 77 (12) (1984) 1530–1534.
- [64] G.K. Frykman, J. Taleisnik, G. Peters, R. Kaufman, B. Helal, V.E. Wood, R. S. Unsell, Treatment of nonunited scaphoid fractures by pulsed electromagnetic field and cast, *J. Hand Surg.* 11 (3) (1986) 344–349.
- [65] M. Marcer, G. Musatti, C.A. Bassett, Results of pulsed electromagnetic fields (PEMFs) in ununited fractures after external skeletal fixation, *Clin. Orthop. Relat. Res.* (190) (1984) 260–265.
- [66] M.W. Meskens, J.A. Stuyck, H. Feys, J.C. Mulier, Treatment of nonunion using pulsed electromagnetic fields: a retrospective follow-up study, *Acta Orthop. Belg.* 56 (2) (1990) 483–488.
- [67] W.J. Sharrard, A double-blind trial of pulsed electromagnetic fields for delayed union of tibial fractures, *J. Bone Jt. Surg.* 72 (3) (1990) 347–355. British volume.
- [68] W.J. Sharrard, M.L. Sutcliffe, M.J. Robson, A.G. Maceachern, The treatment of fibrous non-union of fractures by pulsing electromagnetic stimulation, *J. Bone Jt. Surg.* 64 (2) (1982) 189–193. British volume.
- [69] G.B. Holmes Jr., Treatment of delayed unions and nonunions of the proximal fifth metatarsal with pulsed electromagnetic fields, *Foot Ankle Int.* 15 (10) (1994) 552–556.
- [70] O.M. Tepper, M.J. Callaghan, E.I. Chang, R.D. Galiano, K.A. Bhatt, S. Baharestani, J. Gan, B. Simon, R.A. Hopper, J.P. Levine, G.C. Gurtner, Electromagnetic fields increase in vitro and in vivo angiogenesis through endothelial release of FGF-2, *FASEB J.* 18 (11) (2004) 1231–1233.
- [71] A. Streit, B.C. Watson, J.D. Granata, T.M. Philbin, H.N. Lin, J.P. O'Connor, S. Lin, Effect on clinical outcome and growth factor synthesis with adjunctive use of pulsed electromagnetic fields for fifth metatarsal nonunion fracture: a double-blind randomized study, *Foot Ankle Int.* 37 (9) (2016) 919–923.
- [72] W.G. de Haas, A. Beaupre, H. Cameron, E. English, The Canadian experience with pulsed magnetic fields in the treatment of ununited tibial fractures, *Clin. Orthop. Relat. Res.* (208) (1986) 55–58.
- [73] R.B. Simonis, E.J. Parnell, P.S. Ray, J.L. Peacock, Electrical treatment of tibial non-union: a prospective, randomised, double-blind trial, *Injury* 34 (5) (2003) 357–362.
- [74] A.T. Barker, R.A. Dixon, W.J. Sharrard, M.L. Sutcliffe, Pulsed magnetic field therapy for tibial non-union. Interim results of a double-blind trial, *Lancet* 1 (8384) (1984) 994–996.
- [75] M.W. Meskens, J.A. Stuyck, J.C. Mulier, Treatment of delayed union and nonunion of the tibia by pulsed electromagnetic fields. A retrospective follow-up, *Bull. Hosp. Dis. Orthop. Inst.* 48 (2) (1988) 170–175.
- [76] J.V. Henderson, C.M. Harrison, H.C. Britt, C.F. Bayram, G.C. Miller, Prevalence, causes, severity, impact, and management of chronic pain in Australian general practice patients, *Pain Med.* 14 (9) (2013) 1346–1361.
- [77] A.A. Guccione, D.T. Felson, J.J. Anderson, J.M. Anthony, Y. Zhang, P.W. Wilson, M. Kelly-Hayes, P.A. Wolf, B.E. Kreger, W.B. Kannel, The effects of specific medical conditions on the functional limitations of elders in the Framingham Study, *Am. J. Public Health* 84 (3) (1994) 351–358.
- [78] M. Cross, E. Smith, D. Hoy, S. Nolte, I. Ackerman, M. Fransen, L. Bridgett, S. Williams, F. Guillemin, C.L. Hill, L.L. Laslett, G. Jones, F. Cicuttini, R. Osborne, T. Vos, R. Buchbinder, A. Woolf, L. March, The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study, *Ann. Rheum. Dis.* 73 (7) (2014) 1323–1330.
- [79] M.J. Elders, The increasing impact of arthritis on public health, the Journal of rheumatology, Supplement 60 (2000) 6–8.
- [80] V. Pavone, F. Boettner, S. Fickert, T.P. Sculco, Total condylar knee arthroplasty: a long-term followup, *Clin. Orthop. Relat. Res.* (388) (2001) 18–25.
- [81] M.C. Hochberg, R.D. Altman, K.T. April, M. Benkhalti, G. Guyatt, J. McGowan, T. Towheed, V. Welch, G. Wells, P. Tugwell, R. American College of, American College of Rheumatology, Recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee, *Arthritis Care Res.* 64 (4) (2012) 465–474.
- [82] W. Zhang, R.W. Moskowitz, G. Nuki, S. Abramson, R.D. Altman, N. Arden, S. Bierma-Zeinstra, K.D. Brandt, P. Croft, M. Doherty, M. Dougados, M. Hochberg, D.J. Hunter, K. Kwok, L.S. Lohmander, P. Tugwell, OARSI recommendations for the management of hip and knee osteoarthritis, Part II: OARSI evidence-based, expert consensus guidelines, *Osteoarthritis Cartil.* 16 (2) (2008) 137–162.
- [83] G.H. Lo, M.G. Merchant, J.B. Driban, J. Duryea, L.L. Price, C.B. Eaton, T. E. McAlindon, Knee alignment is quantitatively related to periarthral bone morphometry and density, especially in patients with osteoarthritis, *Arthritis Rheumatol.* 70 (2) (2018) 212–221.
- [84] E. Ozgucul, A. Cetin, M. Cetin, E. Calp, Additional effect of pulsed electromagnetic field therapy on knee osteoarthritis treatment: a randomized, placebo-controlled study, *Clin. Rheumatol.* 29 (8) (2010) 927–931.
- [85] C. McCarthy, M. Callaghan, J. Oldham, Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: a systematic review, *BMC Musculoskelet. Disord.* 7 (2006) 51.
- [86] G. Thamsborg, A. Florescu, P. Oturai, E. Fallentin, K. Tritsaridis, S. Dissing, Treatment of knee osteoarthritis with pulsed electromagnetic fields: a randomized, double-blind, placebo-controlled study, *Osteoarthritis Cartil.* 13 (7) (2005) 575–581.
- [87] H. Wuschech, U. von Hehn, E. Mikus, R.H. Funk, Effects of PEMF on patients with osteoarthritis: results of a prospective, placebo-controlled, double-blind study, *Bioelectromagnetics* 36 (8) (2015) 576–585.
- [88] M. Esposito, A. Lucariello, C. Costanzo, A. Fiumarella, A. Giannini, G. Riccardi, I. Riccio, Differentiation of human umbilical cord-derived mesenchymal stem cells, WJ-MSCs, into chondrogenic cells in the presence of pulsed electromagnetic fields, *In Vivo* 27 (4) (2013) 495–500.

- [89] M. De Mattei, A. Caruso, F. Pezzetti, A. Pellati, G. Stabellini, V. Sollazzo, G. C. Traina, Effects of pulsed electromagnetic fields on human articular chondrocyte proliferation, *Connect. Tissue Res.* 42 (4) (2001) 269–279.
- [90] S. Anbarasan, U. Baranedarhan, S.F. Paul, H. Kaur, S. Rangaswami, E. Bhaskar, Low dose short duration pulsed electromagnetic field effects on cultured human chondrocytes: an experimental study, *Indian J. Orthop.* 50 (1) (2016) 87–93.
- [91] R.J. Fitzsimmons, S.L. Gordon, J. Kronberg, T. Ganey, A.A. Pilla, A pulsing electric field (PEF) increases human chondrocyte proliferation through a transduction pathway involving nitric oxide signaling, *J. Orthop. Res.* 26 (6) (2008) 854–859.
- [92] M. Fini, P. Torricelli, G. Giavaresi, N.N. Aldini, F. Cavani, S. Setti, A. Nicolini, A. Carpi, R. Giardino, Effect of pulsed electromagnetic field stimulation on knee cartilage, subchondral and epiphyseal trabecular bone of aged Dunkin Hartley guinea pigs, *Biomed. Pharmacother.* 62 (10) (2008) 709–715.
- [93] D.M. Ciombor, R.K. Aaron, S. Wang, B. Simon, Modification of osteoarthritis by pulsed electromagnetic field—a morphological study, *Osteoarthr. Cartil.* 11 (6) (2003) 455–462.
- [94] K. Varani, M. De Mattei, F. Vincenzi, S. Gessi, S. Merighi, A. Pellati, A. Ongaro, A. Caruso, R. Cadossi, P.A. Borea, Characterization of adenosine receptors in bovine chondrocytes and fibroblast-like synoviocytes exposed to low frequency low energy pulsed electromagnetic fields, *Osteoarthr. Cartil.* 16 (3) (2008) 292–304.
- [95] M. De Mattei, M. Fini, S. Setti, A. Ongaro, D. Gemmati, G. Stabellini, A. Pellati, A. Caruso, Proteoglycan synthesis in bovine articular cartilage explants exposed to different low-frequency low-energy pulsed electromagnetic fields, *Osteoarthr. Cartil.* 15 (2) (2007) 163–168.
- [96] D.H. Trock, A.J. Bollet, R.H. Dyer Jr., L.P. Fielding, W.K. Miner, R. Markoll, A double-blind trial of the clinical effects of pulsed electromagnetic fields in osteoarthritis, *J. Rheumatol.* 20 (3) (1993) 456–460.
- [97] D.H. Trock, A.J. Bollet, R. Markoll, The effect of pulsed electromagnetic fields in the treatment of osteoarthritis of the knee and cervical spine. Report of randomized, double blind, placebo controlled trials, *J. Rheumatol.* 21 (10) (1994) 1903–1911.
- [98] M. Viganò, C. Perucca Orfei, E. Ragni, A. Colombini, L. de Girolamo, Pain and functional scores in patients affected by knee OA after treatment with pulsed electromagnetic and magnetic fields: a meta-analysis, *Cartilage* (2020), 1947603520931168.
- [99] I. Macias, N. Alcorta-Sevillano, C.I. Rodriguez, A. Infante, Osteoporosis and the potential of cell-based therapeutic strategies, *Int. J. Mol. Sci.* 21 (5) (2020).
- [100] S.R. Cummings, L.J. Melton, Epidemiology and outcomes of osteoporotic fractures, *Lancet* 359 (9319) (2002) 1761–1767.
- [101] N.B. Watts, J.P. Bilezikian, P.M. Camacho, S.L. Greenspan, S.T. Harris, S. F. Hodgson, M. Kleerekoper, M.M. Luckey, M.R. McClung, R.P. Pollack, S. M. Petak, A.O.T. Force, American association of clinical endocrinologists medical guidelines for clinical practice for the diagnosis and treatment of postmenopausal osteoporosis, *Endocr. Pract.* 16 (Suppl. 3) (2010) 1–37.
- [102] Y. Tanaka, T. Ohira, Mechanisms and therapeutic targets for bone damage in rheumatoid arthritis, in particular the RANK-RANKL system, *Curr. Opin. Pharmacol.* 40 (2018) 110–119.
- [103] J.A. Kanis, C. Cooper, R. Rizzoli, J.Y. Reginster, C. Scientific Advisory Board of the European Society for, O. Economic Aspects of, A. the Committees of Scientific, F. National Societies of the International Osteoporosis, European guidance for the diagnosis and management of osteoporosis in postmenopausal women, *Osteoporos. Int.* 30 (1) (2019) 3–44.
- [104] J. Compston, C. Bowring, A. Cooper, C. Cooper, C. Davies, R. Francis, J.A. Kanis, D. Marsh, E.V. McCloskey, D.M. Reid, P. Selby, G. National Osteoporosis Guideline, Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013, *Maturitas* 75 (4) (2013) 392–396.
- [105] J.Y. Reginster, F. Pelousse, O. Bruyere, Safety concerns with the long-term management of osteoporosis, *Expert Opin. Drug Saf.* 12 (4) (2013) 507–522.
- [106] W.Y. Chiu, J.J. Lee, K.S. Tsai, Atypical femoral fractures shortly after osteonecrosis of the jaw in a postmenopausal woman taking alendronate for osteoporosis, *J. Clin. Endocrinol. Metab.* 98 (4) (2013) E723–6.
- [107] A.D. Anastasilakis, K.A. Toulis, D.G. Goulis, S.A. Polyzos, S. Delaroudis, A. Gionisi, E. Terpos, Efficacy and safety of denosumab in postmenopausal women with osteopenia or osteoporosis: a systematic review and a meta-analysis, *Horm. Metab. Res.* 41 (10) (2009) 721–729.
- [108] S. Papapoulos, R. Chapurlat, C. Libanati, M.L. Brandi, J.P. Brown, E. Czerwinski, M.A. Krieg, Z. Man, D. Mellstrom, S.C. Radominski, J.Y. Reginster, H. Resch, J. A. Roman Ivorra, C. Roux, E. Vittinghoff, M. Austin, N. Daizadeh, M.N. Bradley, A. Grauer, S.R. Cummings, H.G. Bone, Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension, *J. Bone Miner. Res.* 27 (3) (2012) 694–701.
- [109] J.J. Body, P. Bergmann, S. Boonen, J.P. Devogelaer, E. Gielen, S. Goemaere, J. M. Kaufman, S. Rozenberg, J.Y. Reginster, Extraskelatal benefits and risks of calcium, vitamin D and anti-osteoporosis medications, *Osteoporos. Int.* 23 (Suppl. 1) (2012) S1–23.
- [110] S.R. Cummings, A.V. Schwartz, D.M. Black, Alendronate and atrial fibrillation, *N. Engl. J. Med.* 356 (18) (2007) 1895–1896.
- [111] B. Ettinger, D.B. Burr, R.O. Ritchie, Proposed pathogenesis for atypical femoral fractures: lessons from materials research, *Bone* 55 (2) (2013) 495–500.
- [112] P.M. Camacho, S.M. Petak, N. Binkley, B.L. Clarke, S.T. Harris, D.L. Hurley, M. Kleerekoper, E.M. Lewiecki, P.D. Miller, H.S. Narula, R. Pessah-Pollack, V. Tangpricha, S.J. Wimalawansa, N.B. Watts, American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis - 2016, *Endocr. Pract.* 22 (Suppl. 4) (2016) 1–42.
- [113] H. Liu, J. Zhou, L. Gu, Y. Zuo, The change of HCN1/HCN2 mRNA expression in peripheral nerve after chronic constriction injury induced neuropathy followed by pulsed electromagnetic field therapy, *Oncotarget* 8 (1) (2017) 1110–1116.
- [114] H.F. Liu, L. Yang, H.C. He, J. Zhou, Y. Liu, C.Y. Wang, Y.C. Wu, C.Q. He, Pulsed electromagnetic fields on postmenopausal osteoporosis in Southwest China: a randomized, active-controlled clinical trial, *Bioelectromagnetics* 34 (4) (2013) 323–332.
- [115] L.Q. Huang, H.C. He, C.Q. He, J. Chen, L. Yang, Clinical update of pulsed electromagnetic fields on osteoporosis, *Chin. Med. J.* 121 (20) (2008) 2095–2099.
- [116] J.A. Spadaro, W.H. Short, P.R. Sheehy, R.M. Hickman, D.H. Feiglin, Electromagnetic effects on forearm disuse osteopenia: a randomized, double-blind, sham-controlled study, *Bioelectromagnetics* 32 (4) (2011) 273–282.
- [117] N. Roozbeh, F. Abdi, A. Amraee, Z. Atarodi Kashani, L. Darvish, Influence of radiofrequency electromagnetic fields on the fertility system: protocol for a systematic review and meta-analysis, *JMIR Res. Protoc.* 7 (2) (2018) e33.
- [118] N. Giordano, E. Battisti, S. Geraci, M. Fortunato, C. Santacroce, M. Rigato, L. Gennari, C. Gennari, Effect of electromagnetic fields on bone mineral density and biochemical markers of bone turnover in osteoporosis: a single-blind, randomized pilot study, *Curr. Ther. Res.* 62 (3) (2001) 187–193.
- [119] D.E. Garland, R.H. Adkins, N.N. Matsuno, C.A. Stewart, The effect of pulsed electromagnetic fields on osteoporosis at the knee in individuals with spinal cord injury, *J. Spinal Cord Med.* 22 (4) (1999) 239–245.
- [120] F.L. Tabrah, P. Ross, M. Hoffmeier, F. Gilbert Jr., Clinical report on long-term bone density after short-term EMF application, *Bioelectromagnetics* 19 (2) (1998) 75–78.
- [121] D. Petek, D. Hannouche, D. Suva, Osteonecrosis of the femoral head: pathophysiology and current concepts of treatment, *EFORT Open Rev.* 4 (3) (2019) 85–97.
- [122] M. Leo, F. Milena, C. Ruggero, S. Stefania, T. Giancarlo, Biophysical stimulation in osteonecrosis of the femoral head, *Indian J. Orthop.* 43 (1) (2009) 17–21.
- [123] M.A. Mont, L.C. Jones, D.S. Hungerford, Nontraumatic osteonecrosis of the femoral head: ten years later, *J. Bone Jt. Surg.* 88 (5) (2006) 1117–1132. American volume.
- [124] T. Kubo, K. Ueshima, M. Saito, M. Ishida, Y. Arai, H. Fujiwara, Clinical and basic research on steroid-induced osteonecrosis of the femoral head in Japan, *J. Orthop. Sci.* 21 (4) (2016) 407–413.
- [125] V. Gangji, J.P. Hauzeur, C. Matos, V. De Maertelaer, M. Toungouz, M. Lambermont, Treatment of osteonecrosis of the femoral head with implantation of autologous bone-marrow cells. A pilot study, *J. Bone Jt. Surg.* 86 (6) (2004) 1153–1160. American volume.
- [126] A.V. Korompilias, A.E. Beris, M.G. Lykissas, I.P. Kostas-Agnantis, P.N. Soucacos, Femoral head osteonecrosis: why choose free vascularized fibula grafting, *Microsurgery* 31 (3) (2011) 223–228.
- [127] S.B. Keizer, N.B. Kock, P.D. Dijkstra, A.H. Taminiau, R.G. Nelissen, Treatment of avascular necrosis of the hip by a non-vascularised cortical graft, *J. Bone Joint Surg.* 88 (4) (2006) 460–466. British volume.
- [128] B.D. Shannon, R.T. Trousdale, Femoral osteotomies for avascular necrosis of the femoral head, *Clin. Orthop. Relat. Res.* (418) (2004) 34–40.
- [129] T. Siguier, M. Siguier, T. Judet, G. Charnley, B. Brumpt, Partial resurfacing arthroplasty of the femoral head in avascular necrosis. Methods, indications, and results, *Clin. Orthop. Relat. Res.* (386) (2001) 85–92.
- [130] S. Ding, H. Peng, H.S. Fang, J.L. Zhou, Z. Wang, Pulsed electromagnetic fields stimulation prevents steroid-induced osteonecrosis in rats, *BMC Musculoskelet. Disord.* 12 (2011) 215.
- [131] M. Ishida, M. Fujioka, K.A. Takahashi, Y. Arai, T. Kubo, Electromagnetic fields: a novel prophylaxis for steroid-induced osteonecrosis, *Clin. Orthop. Relat. Res.* 466 (5) (2008) 1068–1073.
- [132] L. Massari, M. Fini, R. Cadossi, S. Setti, G.C. Traina, Biophysical stimulation with pulsed electromagnetic fields in osteonecrosis of the femoral head, *J. Bone Jt. Surg.* 88 (Suppl. 3) (2006) 56–60. American volume.
- [133] C.A. Bassett, M. Schink-Ascani, S.M. Lewis, Effects of pulsed electromagnetic fields on Steinberg ratings of femoral head osteonecrosis, *Clin. Orthop. Relat. Res.* (246) (1989) 172–185.
- [134] G.M. Marcheggiani Muccioli, A. Grassi, S. Setti, G. Filardo, L. Zambelli, T. Bonanzinga, E. Rimondi, M. Busacca, S. Zaffagnini, Conservative treatment of spontaneous osteonecrosis of the knee in the early stage: pulsed electromagnetic fields therapy, *Eur. J. Radiol.* 82 (3) (2013) 530–537.
- [135] A. Ikegami, K. Ueshima, M. Saito, K. Ikoma, M. Fujioka, S. Hayashi, M. Ishida, H. Fujiwara, O. Mazda, T. Kubo, Femoral perfusion after pulsed electromagnetic field stimulation in a steroid-induced osteonecrosis model, *Bioelectromagnetics* 36 (5) (2015) 349–357.
- [136] F. Rosso, D.E. Bonasia, A. Marmotti, U. Cottino, R. Rossi, Mechanical stimulation (pulsed electromagnetic fields “PEMF”) and extracorporeal shock wave therapy “ESWT”) and tendon regeneration: a possible alternative, *Front. Aging Neurosci.* 7 (2015) 211.
- [137] B.M. Andres, G.A.C. Murrell, Treatment of tendinopathy: what works, what does not, and what is on the horizon, *Clin. Orthop. Relat. Res.* 466 (7) (2008) 1539–1554.
- [138] H. Tempfer, C. Lehner, M. Grütz, R. Gehwolf, A. Traweger, Biological augmentation for tendon repair: lessons to be learned from development, disease, and tendon, *Stem Cell Res.* (2017) 1–31.
- [139] R. Gehwolf, B. Schwemmer, M. Jessen, S. Korntrner, A. Wagner, C. Lehner, N. Weissenbacher, H. Tempfer, A. Traweger, Global responses of IL-1 β -primed 3D

- tendon constructs to treatment with pulsed electromagnetic fields, *Cells* 8 (5) (2019).
- [140] M. Abate, K.G. Silbernagel, C. Siljeholm, A. Di Iorio, D. De Amicis, V. Salini, S. Werner, R. Paganelli, Pathogenesis of tendinopathies: inflammation or degeneration? *Arthritis Res. Ther.* 11 (3) (2009) 235.
- [141] N.L. Millar, G.A. Murrell, I.B. McInnes, Inflammatory mechanisms in tendinopathy - towards translation, *Nat. Rev. Rheumatol.* 13 (2) (2017) 110–122.
- [142] B.J. Dean, P. Gettings, S.G. Dakin, A.J. Carr, Are inflammatory cells increased in painful human tendinopathy? A systematic review, *Br. J. Sports Med.* 50 (4) (2016) 216–220.
- [143] G. Schulze-Tanzil, O. Al-Sadi, E. Wiegand, W. Ertel, C. Busch, B. Kohl, T. Pufe, The role of pro-inflammatory and immunoregulatory cytokines in tendon healing and rupture: new insights, *Scand. J. Med. Sci. Sports* 21 (3) (2011) 337–351.
- [144] F. Benazzo, M. Cadossi, F. Cavani, M. Fini, G. Giavaresi, S. Setti, R. Cadossi, R. Giardino, Cartilage repair with osteochondral autografts in sheep: effect of biophysical stimulation with pulsed electromagnetic fields, *J. Orthop. Res.* 26 (5) (2008) 631–642.
- [145] L. Osti, A.D. Buono, N. Maffulli, Pulsed electromagnetic fields after rotator cuff repair: a randomized, controlled study, *Orthopedics* 38 (3) (2015) e223–8.
- [146] L. de Girolamo, M. Viganò, E. Galliera, D. Stanco, S. Setti, M.G. Marazzi, G. Thiebat, M.M. Corsi Romanelli, V. Sansone, In vitro functional response of human tendon cells to different dosages of low-frequency pulsed electromagnetic field, *Knee Surg. Sport. Traumatol. Arthrosc.* 23 (11) (2015) 3443–3453.
- [147] L. de Girolamo, D. Stanco, E. Galliera, M. Viganò, A. Colombini, S. Setti, E. Vianello, M.M. Corsi Romanelli, V. Sansone, Low frequency pulsed electromagnetic field affects proliferation, tissue-specific gene expression, and cytokines release of human tendon cells, *Cell Biochem. Biophys.* 66 (3) (2013) 697–708.
- [148] M. Liu, C. Lee, D. Laron, N. Zhang, E.I. Waldorff, J.T. Ryaby, B. Feeley, X. Liu, Role of pulsed electromagnetic fields (PEMF) on tenocytes and myoblasts-potential application for treating rotator cuff tears, *J. Orthop. Res.* 35 (5) (2017) 956–964.
- [149] A. Marmotti, G.M. Peretti, S. Mattia, L. Mangiavini, L. de Girolamo, M. Viganò, S. Setti, D.E. Bonasia, D. Blonna, E. Bellato, G. Ferrero, F. Castoldi, Pulsed electromagnetic fields improve tenogenic commitment of umbilical cord-derived mesenchymal stem cells: a potential strategy for tendon repair-an in vitro study, *Stem Cells Int.* 2018 (2018), 9048237.
- [150] P. Randelli, A. Menon, V. Ragone, P. Creo, U. Alfieri Montrasio, C. Perucca Orfei, G. Banfi, P. Cabitza, G. Tettamanti, L. Anastasia, Effects of the pulsed electromagnetic field PST® on human tendon stem cells: a controlled laboratory study, *BMC Complement. Altern. Med.* 16 (2016) 293.
- [151] K. Uzunca, M. Birtane, N. Tastekin, Effectiveness of pulsed electromagnetic field therapy in lateral epicondylitis, *Clin. Rheumatol.* 26 (1) (2007) 69–74.
- [152] M.D. Devereaux, B.L. Hazleman, P.P. Thomas, Chronic lateral humeral epicondylitis—a double-blind controlled assessment of pulsed electromagnetic field therapy, *Clin. Exp. Rheumatol.* 3 (4) (1985) 333–336.
- [153] S.T. Sutbeyaz, N. Sezer, F. Koseoglu, S. Kibar, Low-frequency pulsed electromagnetic field therapy in fibromyalgia: a randomized, double-blind, sham-controlled clinical study, *Clin. J. Pain* 25 (8) (2009) 722–728.
- [154] C. Maestu, M. Blanco, A. Nevado, J. Romero, P. Rodríguez-Rubio, J. Galindo, J. Bautista Lorite, F. de las Morenas, P. Fernandez-Arguelles, Reduction of pain thresholds in fibromyalgia after very low-intensity magnetic stimulation: a double-blinded, randomized placebo-controlled clinical trial, *Pain Res. Manag.* 18 (6) (2013) e101–6.
- [155] H.M. Lee, U.H. Kwon, H. Kim, H.J. Kim, B. Kim, J.O. Park, E.S. Moon, S.H. Moon, Pulsed electromagnetic field stimulates cellular proliferation in human intervertebral disc cells, *Yonsei Med. J.* 51 (6) (2010) 954–959.
- [156] S.L. Miller, D.G. Coughlin, E.I. Waldorff, J.T. Ryaby, J.C. Lotz, Pulsed electromagnetic field (PEMF) treatment reduces expression of genes associated with disc degeneration in human intervertebral disc cells, *Spine J.* 16 (6) (2016) 770–776.
- [157] E. Hattapoglu, I. Batmaz, B. Dilek, M. Karakoc, S. Em, R. Cevik, Efficiency of pulsed electromagnetic fields on pain, disability, anxiety, depression, and quality of life in patients with cervical disc herniation: a randomized controlled study, *Turk. J. Med. Sci.* 49 (4) (2019) 1095–1101.
- [158] A.W. Thomas, K. Graham, F.S. Prato, J. McKay, P.M. Forster, D.E. Moulin, S. Chari, A randomized, double-blind, placebo-controlled clinical trial using a low-frequency magnetic field in the treatment of musculoskeletal chronic pain, *Pain Res. Manag.* 12 (4) (2007) 249–258.
- [159] N. Seo, S.H. Lee, K.W. Ju, J. Woo, B. Kim, S. Kim, J.W. Jahng, J.H. Lee, Low-frequency pulsed electromagnetic field pretreated bone marrow-derived mesenchymal stem cells promote the regeneration of crush-injured rat mental nerve, *Neural Regen. Res.* 13 (1) (2018) 145–153.
- [160] S. Zhu, J. Ge, Z. Liu, L. Liu, D. Jing, M. Ran, M. Wang, L. Huang, Y. Yang, J. Huang, Z. Luo, Circadian rhythm influences the promoting role of pulsed electromagnetic fields on sciatic nerve regeneration in rats, *Front. Neurol.* 8 (2017) 101.
- [161] J. Zhou, Y. Liao, H. Xie, Y. Liao, H. Liu, Y. Zeng, N. Li, Pulsed electromagnetic field ameliorates cartilage degeneration by inhibiting mitogen-activated protein kinases in a rat model of osteoarthritis, *Phys. Ther. Sport.* 24 (2017) 32–38.
- [162] F.R. Nelson, R. Zvirbulis, A.A. Pilla, Non-invasive electromagnetic field therapy produces rapid and substantial pain reduction in early knee osteoarthritis: a randomized double-blind pilot study, *Rheumatol. Int.* 33 (8) (2013) 2169–2173.
- [163] G. Rutherford, B. Lithgow, Z. Moussavi, Transcranial magnetic stimulation safety from operator exposure perspective, *Med. Biol. Eng. Comput.* 58 (2) (2020) 249–256.
- [164] M. Shuvy, S. Abedat, R. Beeri, M. Valitzki, Y. Stein, K. Meir, C. Lotan, Electromagnetic fields promote severe and unique vascular calcification in an animal model of ectopic calcification, *Exp. Toxicol. Pathol.* 66 (7) (2014) 345–350.
- [165] J.F. Schenck, C.L. Dumoulin, R.W. Redington, H.Y. Kressel, R.T. Elliott, I. L. McDougall, Human exposure to 4.0-Tesla magnetic fields in a whole-body scanner, *Med. Phys.* 19 (4) (1992) 1089–1098.
- [166] W.H. Bailey, S.H. Su, T.D. Bracken, R. Kavet, Summary and evaluation of guidelines for occupational exposure to power frequency electric and magnetic fields, *Health Phys.* 73 (3) (1997) 433–453.
- [167] E. van Wijngaarden, D.A. Savitz, R.C. Kleckner, J. Cai, D. Loomis, Exposure to electromagnetic fields and suicide among electric utility workers: a nested case-control study, *West. J. Med.* 173 (2) (2000).
- [168] D. Baris, B.G. Armstrong, J. Deadman, G. Thériault, A case cohort study of suicide in relation to exposure to electric and magnetic fields among electrical utility workers, *Occup. Environ. Med.* 53 (1) (1996) 17–24.
- [169] W.H. Bailey, Health effects relevant to the setting of EMF exposure limits, *Health Phys.* 83 (3) (2002) 376–386.
- [170] S. Rossi, M. Hallett, P.M. Rossini, A. Pascual-Leone, Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research, *Clin. Neurophysiol.* 120 (12) (2009) 2008–2039.
- [171] L. Kheifets, A. Ahlbom, C.M. Crespi, G. Draper, J. Hagihara, R.M. Lowenthal, G. Mezei, S. Oksuzyan, J. Schuz, J. Swanson, A. Tittarelli, M. Vinceti, V. Wunsch Filho, Pooled analysis of recent studies on magnetic fields and childhood leukaemia, *Br. J. Cancer* 103 (7) (2010) 1128–1135.
- [172] M. Bagheri Hosseinabadi, N. Khanjani, M. Mirzaii, P. Norouzi, A. Atashi, DNA damage from long-term occupational exposure to extremely low frequency electromagnetic fields among power plant workers, *Mutat. Res.* 846 (2019), 403079.
- [173] D.J. Panagopoulos, Comparing DNA damage induced by mobile telephony and other types of man-made electromagnetic fields, *Mutat. Res.* 781 (2019) 53–62.