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REVIEW ARTICLE

Pulsed electromagnetic field applications: A corporate perspective

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Summary Corporate establishment of US Food & Drug Administration approved pulsed electromagnetic fields (PEMFs) for clinical applications has been achieved. However, optimization of PEMFs for improvement in efficacy for current indications, in addition to the expansion into new indications, is not trivial. Moving directly into a clinical trial can be costly and carries little guarantee for success, necessitating the need for preclinical studies as supported by this review of the extensive corporate preclinical experience by Orthofix, Inc.

The Translational Potential of this Article: This review illustrates the need to gain enough *in vitro*/*in vivo* knowledge of specific PEMF signals and its target tissue interaction to enable a high success rate in clinical trials.

Introduction and background

Contemporary development of magnetic and electromagnetic field applications as therapeutic modalities started immediately after World War II with designing and manufacturing of various types of electromagnetic signals [1]. During these years, it was established that symmetrical waveforms are less effective than asymmetrical or pulsed signals [2]. These pulsed electromagnetic field (PEMF) signals are inductively coupled to the treatment site and therefore noninvasive [2,3]. The PEMF signals contain a wide range of spectral components allowing for potential coupling to a variety of possible biochemical signalling pathways [4].

The possibility of treatment using electromagnetic fields for various disorders drew corporate interest, in part due to the ability to noninvasively induce an electric current in the target tissue. While electromagnetic studies have included disorders such as major depressive disorder (using transcranial magnetic stimulation) [5], fibromyalgia [6], and osteoarthritis of the knee [7], the only Class III electromagnetic field devices approved by the US Food & Drug Administration (FDA) have been within the category of bone growth simulation/ostegenesis stimulation. Within this category, Orthofix Inc. (Lewisville, TX, USA) originally

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developed three PEMF devices for osteogenesis stimulation: Physio-Stim®, Spinal-Stim® and Cervical-Stim®. Each of these devices incorporates a specific set of triangular shaped PEMF signals (Figure 1). The particular set of signals takes advantage of having its polarization and depolarization within the positive magnetic field range as signals within both the negative and positive part have been found to be less effective [2,8]. While PEMF signals can be varied through alterations of their pulse period, burst period, amplitude, and number of pulses/burst, the specific parameters for the three devices were selected based on preliminary preclinical studies (unpublished data) combined with PEMF field parameter limitations due to engineering considerations such as battery life and device portability.

As mentioned, common for all the approved commercial electromagnetic field devices for osteogenesis stimulation is their classification by the FDA as a Class III device (Table 1). A Class III device requires the establishment of safety and effectiveness of the device through valid scientific evidence before approval by the FDA can be achieved. This is done through the initial FDA approval of an investigational device exemption (IDE) allowing for the device to be used in a clinical study collecting safety and effectiveness data. This data is required to support a premarket approval (PMA) application which upon approval, enables the device to enter the market. This process ensures that safety issues such as hardware failure, inadvertent exposure of incorrect target tissues, incorrect exposure (amplitude, duration etc.), and unanticipated adverse events etc. are considered and evaluated.

The first Orthofix device to receive FDA approval was the Physio-Stim device (Figure 2), which was designed for the treatment of an established nonunion acquired secondary to trauma, excluding vertebrae and all flat bones, where the width of the nonunion defect is less than half the width of the bone to be treated. Note that a nonunion is considered to be established when the fracture site shows no

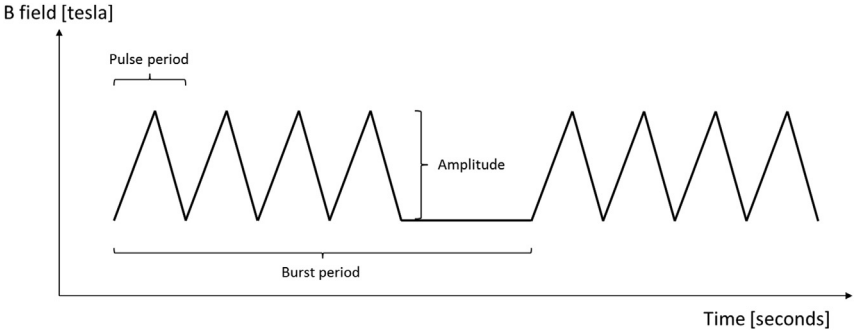

Figure 1 Representation of the Orthofix Pulsed electromagnetic field signal.

Table 1 US Food & Drug Administration (FDA) approved commercial electromagnetic field devices for osteogenesis stimulation.

EMF Device	Manufacturer	Indication	Description
Physio-Stim	Orthofix, Inc.	Treatment of nonunion acquired secondary to trauma, excluding vertebrae and all flat bones	A series of 5 different EMF single coils for various skeletal locations.
Spinal-Stim	Orthofix, Inc.	Adjunct treatment to spinal fusion and as a nonoperative treatment for salvage of failed spinal fusion	Dual coil (coils placed anterior and posterior to spine) acting as a Helmholtz coil at the lumbar spine
Cervical-Stim	Orthofix, Inc.	Adjunct treatment for cervical spine fusion surgery in patients at high risk for nonfusion	Single coil placed posteriorly to the cervical spine
CMF SpinaLogic	DJO, LLC	Adjunctive treatment to primary lumbar spinal fusion surgery for one or two levels	Single coil worn posteriorly at the lumbar spine
CMF OL1000	DJO, LLC	Treatment of nonunion fractures acquired secondary to trauma, excluding all vertebrae and flat bones	A series of 5 different EMF coils (single or dual coil) for various skeletal locations.
EBI Bone Healing System	Zimmer Biomet, Inc.	Treatment of fracture nonunions, failed fusions, and congenital pseudarthrosis in the appendicular system	A series of 12 different EMF single coils for various skeletal locations.

EMF = electromagnetic field.

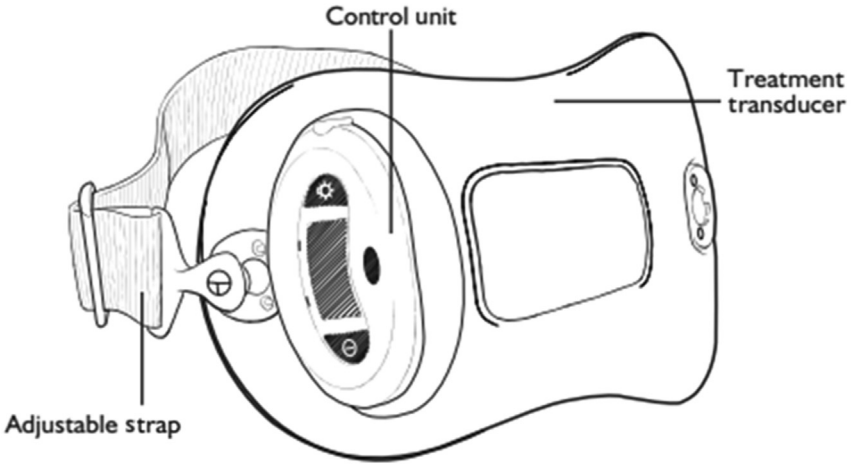

Figure 2 Physio-Stim pulsed electromagnetic field (PEMF) device.

radiographically progressive signs of healing for at least 90 days. Five different Physio-Stim device models were developed to treat nonunions at different anatomical sites: tibia, ulna/radius, humeral head, hip, and the clavicle. The PEMF signal for the Physio-Stim device is characterized by a fundamental (burst) frequency of 15 Hz, a pulse frequency of 3.85 kHz, and magnetic field amplitude of 1.19 mT.

For the FDA approval of the Physio-Stim device, an IDE clinical study was performed investigating the long-term follow-up of fracture nonunions treated with PEMF [9]. Specifically, established nonunions (no evidence of healing after 9 months) for 181 individuals (193 fractures) were treated with PEMF for a minimum of 8 hours per day for 6 months or until union. A cohort of 139 patients (149 fractures) completed their treatment. Patients treated with PEMF less than 3 hours/day only had a success rate of 36%, whereas treatment of more than 3 hours/day led to a significantly higher success rate of 80%. The treatment success was unaffected by long bone versus short bone, open fractures versus closed fractures, or duration of nonunion prior to surgery. Long-term follow-up at 4 years of patients treated with PEMF for more than 3 hours/day showed no significant change in success rate. In addition, it was concluded that the Physio-Stim device was deemed safe, based on the reported adverse events.

The second device, Spinal-Stim (Figure 3), is a noninvasive electromagnetic bone growth stimulator indicated as an adjunct to spinal fusion to increase the probability of fusion success and as a nonoperative treatment for salvage of failed spinal fusion, where a minimum of 9 months has elapsed since the last surgery. The PEMF signal for the Spinal-Stim device is characterized by a fundamental (burst) frequency of 1.5 Hz, a pulse frequency of 3.85 kHz, and magnetic field amplitude of 0.68 mT.

A randomized double-blind prospective IDE study of PEMF (Spinal-Stim) as an adjunct to lumbar fusion was performed for patients ($n = 195$) undergoing initial lumbar fusion surgery [10]. Following surgery, patients were instructed to wear the PEMF device for 8 hours daily until a successful fusion or nonunion was determined by the physician and an independent radiographic reviewer. For the active PEMF group, the success rate was 83%, which was statistically significant compared to the placebo-treated group (65%). In addition, stratification of consistent users

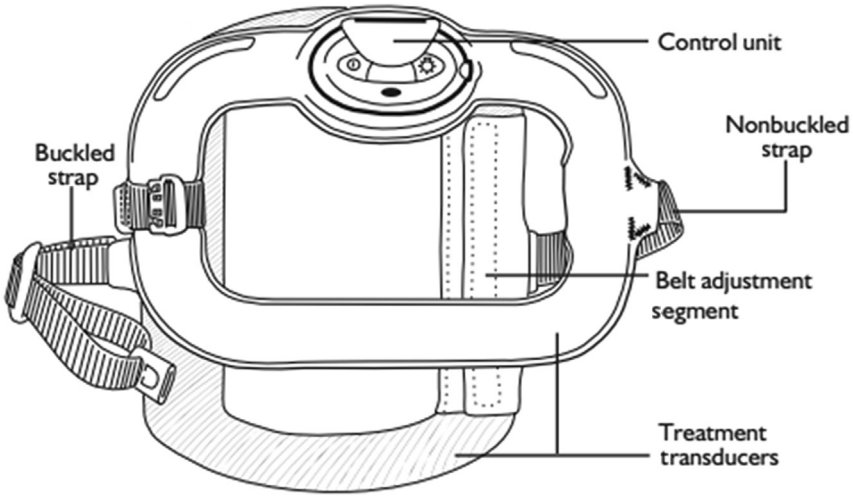

Figure 3 Spinal-Stim pulsed electromagnetic field (PEMF) device.

(i.e., more than 2 hours/day of PEMF treatment) revealed a success rate of 92% versus 68% (placebo), while non-consistent PEMF users (< 2 hours/day) show similar fusion rates as the placebo (65% vs. 61%) [11].

A second clinical study, conducted using the Spinal-Stim PEMF device on 100 patients, showed that PEMF was also an effective treatment specifically for chronic pseudoarthrosis following lumbar fusion [12]. Specifically, patients with chronic pseudoarthrosis after lumbar fusion who underwent 2 hour daily PEMF treatment for at least 90 days showed a 67% fusion success rate which was comparable to reoperation rates for pseudoarthrosis [12].

The last device developed was the Cervical-Stim device (Figure 4); the only osteogenesis stimulator approved by the FDA as a noninvasive, adjunct treatment option for cervical spine fusion surgery in patients at high risk for nonfusion. The PEMF signal for the Cervical-Stim device is characterized by a fundamental (burst) frequency of 15 Hz, a pulse frequency of 3.85 kHz and magnetic field amplitude of 1.19 mT.

The safety and efficacy of the Cervical-Stim device as an adjunct to arthrodesis after anterior cervical discectomy and fusion was examined in a randomized, controlled, prospective multicentre IDE clinical study. The study involved 300 patients with risk factors for nonunion [13]. Radiographic evidence showed that PEMF stimulation increased fusion rates at 6 months (84% vs. 69%), which was statistically significant. The fusion rates at 12 months, however, were not different, and the authors conclude that detailed analysis of subgroups was ongoing. Based on anticipated and unanticipated adverse events, Cervical-Stim was also determined to be safe.

With the establishment of three FDA approved signals for osteogenesis stimulation, Orthofix, like many other companies within the electromagnetic corporate community, has been looking to optimize the PEMF signals for improvements in efficacy for the current indications in addition to expanding the types of applications that PEMF can be utilized for. Moving directly into a clinical trial can be costly and carries little guarantee for success without additional knowledge of how a target tissue reacts to a specific PEMF. The investigative challenge lies in determining the full range of tissue and cellular states normally present during the healing process of the target tissue. Each pathological stage may require different PEMF parameters for optimal dosage and may even vary widely between different tissues.

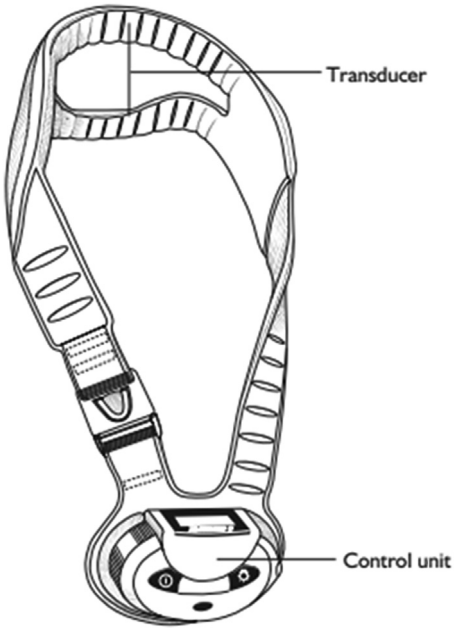

Figure 4 Cervical-Stim pulsed electromagnetic field (PEMF) device.

Thus, in order to progress the clinical field of PEMF applications, it has been necessary to take a step back and examine a variety of target tissues for various PEMF configurations. Specifically, osteogenesis has been studied extensively both *in vitro* and *in vivo* for fracture healing, signalling pathway determinations, osteoporosis treatment, and anabolic/catabolic effects. Recently tenogenesis, myogenesis, and *in vivo* tendon repair have also been examined in relation to potential PEMF applications for rotator cuff repair. Back pain and the associated intervertebral disc inflammation have also been targeted for PEMF application and research. In another approach, several finite element models for PEMF exposure have been developed to determine the variations and application of PEMF at various spinal targets. Further, in this review of corporate PEMF research activities, we will describe some specifics of these studies both for needs of clinical application and for search of mechanisms of action.

Osteogenic experiments

In vitro signalling pathways

A series of studies have been performed in search of basic science evidence for the potential mechanism(s) of action of PEMF. Specifically, Patterson et al [14] reported that PEMF (Physio-Stim, 10 hours/day for 2 days and 10 minutes, 30 minutes, and 60 minutes of single exposure) exposure of murine preosteoblasts (MC3T3-E1) might function in a similar manner to soluble growth factors through the activation of specific signalling pathways including the PI-3 kinases/mTOR pathway within minutes of PEMF exposure (Figure 5) [14].

In a mature osteoblast-like cell line (UMR106-01), it was also found that the anabolic effects of PEMF (Physio-Stim; 2.5—30 minutes exposure) might be mediated by activation of the proteins, insulin receptor substrate-1, the S6 ribosomal subunit kinase, and endothelial nitric oxide synthase [15]. The activation of similar proteins was found for the anabolic peptide parathyroid hormone (PTH) [15], indicating that PEMF might act through a similar signalling pathway.

Performing microarray analyses of PEMF stimulated (Cervical-Stim, 4 hours/day) human bone marrow stromal cells, Partridge et al [16] showed significant regulation during proliferation (131 genes), the differentiation phase (37 genes) and the mineralization phase (173 genes). In the proliferation and differentiation phase, PEMF regulated osteoblast gene expression predominantly involved upregulation of cell adhesion and binding proteins (matrix

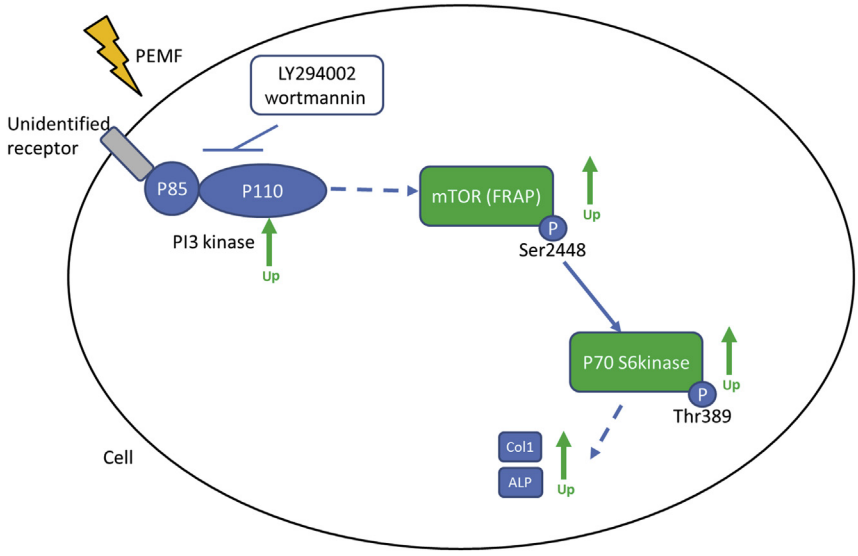

Figure 5 Model of mTOR pathway activation following short-term PEMF exposure (minutes) and immediate examinations. Adapted from Patterson et al [14]. mTOR — mechanistic target of rapamycin; PEMF — pulsed electromagnetic field; PI3 kinase — phosphatidylinositide 3-kinase; P85 — regulatory subunit of PI3 kinase; P110 — catalytic subunit of PI3 kinase; LY294002 — specific reversible inhibitor of PI3 kinase; Wortmannin — specific irreversible inhibitor of PI3 kinase; mTOR (FRAP) — mechanistic target of rapamycin (FKBP12—rapamycin-associated protein); Ser2448 — phospho-mTOR; P70 S6kinase — ribosomal protein S6 kinase beta-1; Thr389 — phospho-p70 S6 kinase; Col1 — collagen-1; ALP — alkaline phosphatase.

metalloproteinase-1 (MMP1), protein regulator of cytokinesis 1 (PRC1), and actin-related protein 2/3 complex subunit 5 (ARCP5)) and transcriptional regulators (microRNA21 (MIR21) and cyclin dependent kinase inhibitor 3 (CDKN3)). For the mineralization phase, the effect was mainly seen through downregulation of transcriptional regulators (MIR21), proteases (plasminogen activator inhibitor-1 (SERPINE1), and BCL2 associated athanogene 2 (BAG2)), cell adhesion and binding proteins in addition to cytoskeletal and structural proteins (collagen, type I, alpha 2 (COL1A2), fibronectin 1 (FN1), vimentin (VIM)). Of the genes that were upregulated, in particular the transforming growth factor beta (TGF-β) signalling pathway was affected by PEMF with TGF-β2 upregulated during differentiation and mineralization and TGF-β1 upregulated during differentiation.

Furthermore, Affymetrix microarray analysis of human bone marrow stromal cells showed that PEMF increases phosphorylation of Smad2 in the differentiation phase, but not as much in the mineralization phase [17—19]. No Smad3 phosphorylation due to PEMF was found for either phase. This was supported by pan-TGF-β antibody blocking the PEMF-induced Smad2 effect. In addition, the authors found, similar to their previous studies, that microRNA21 (an osteogenic miRNA) was increased by PEMF in differentiating human bone marrow stromal cells, indicating that PEMF affects bone metabolism through regulation of microRNA21 leading to a decrease in Smad7 in order to activate the TGF-β pathway, which in turn regulates Runx2 mRNA expression (Figure 6) [19].

In vitro anabolic and catabolic proliferation and differentiation

In isolated rat primary osteoblast cells it was found that both BMP-2 and PEMF (Spinal-Stim, 4 hours daily) increased cell proliferation, differentiation, and mineralization (using assays for alkaline phosphatase, procollagen-1, and osteocalcin), which was additive when both BMP-2 and PEMF were used [20]. This suggests that BMP-2 and PEMF may work through different pathways.

PEMF (Physio-Stim, 4 hours daily) has also been shown to significantly stimulate extracellular signal—regulated kinase (ERK) activation and proliferation of preosteoblasts in young women (< 33 years old) with less of an effect of cells from older women (> 33 years old) [21—24]. However, interestingly it was shown that PEMF had a significant inhibitory effect on osteoclast formation and gene expression (cathepsin-K, nuclear factor of activated T-cells (NFAT), and tartrate-resistant acid phosphatase (TRAP)) for older women, which was even greater than the inhibitory effect for young women. Through RNA sequencing, the inhibitory effects were further found to potentially be indirectly regulated through action on osteoblast lineage cells [24].

Osteotomies/fracture repair

Ibiwoye et al [25] reported that bone was preserved in a critical-sized osteotomy exposed 3 hours daily to PEMF (Physio-Stim) for 10 weeks [25]. Specifically, bilateral, mid-diaphyseal fibular osteotomies were performed in aged rats that achieved a nonunion status within 3—4 weeks which was followed by PEMF exposure. Unilateral PEMF exposure preserved the fibulae bone mass as measured by micro-computed tomography (micro-CT) relative to the contralateral control fibulae bone.

In another study by the same group, PEMF (Physio-Stim) was shown to enhance healing of fibular osteotomies in a rat model, where unilateral PEMF exposure was done for 3 hours daily for 5 weeks following noncritical sized (0.2 mm)

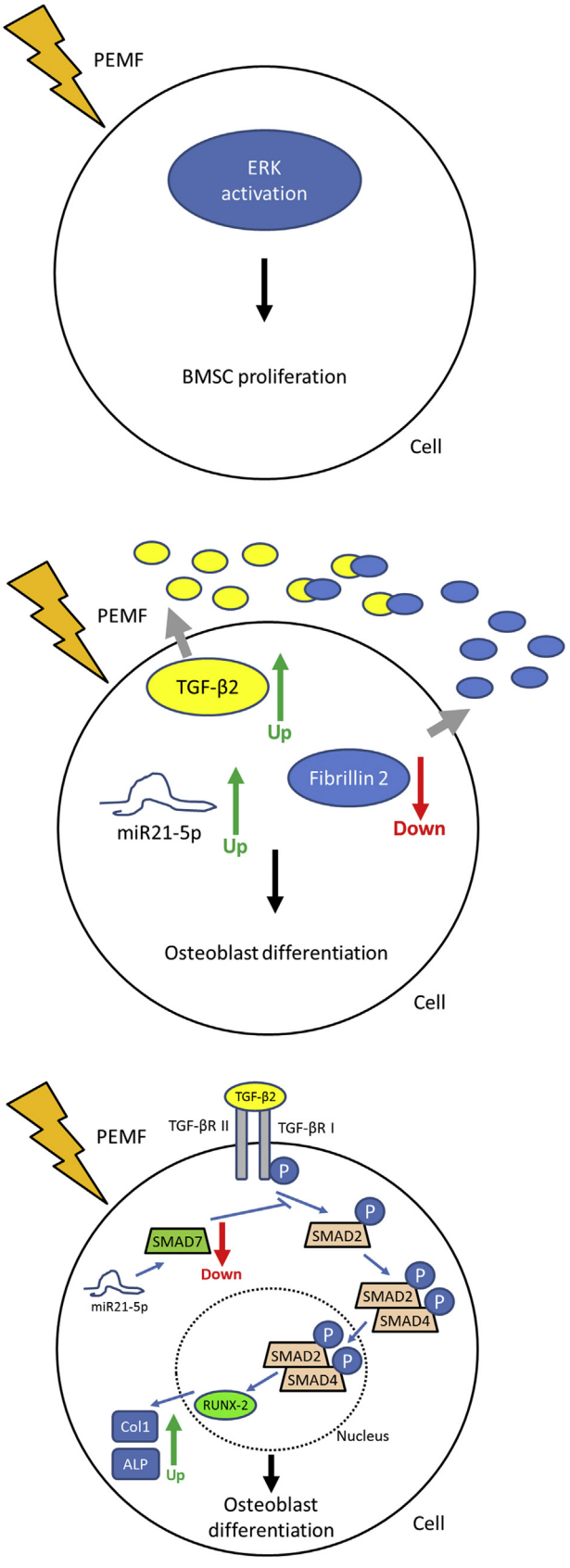

Figure 6 Model of TGF-β pathway activation following long-term PEMF exposure (days). Adapted from Selvamurugan et al [19]. TGF-β — transforming growth factor beta; PEMF — pulsed electromagnetic field; ERK — extracellular signal—regulated kinase; BMSC — bone marrow stromal cells; TGF-β2 — transforming growth factor beta 2; miR21-5p — microRNA21-5p; TGF-βR I — transforming growth factor β receptor-I; TGF-βR II — transforming growth factor β receptor-II; TGF-β2 — transforming growth factor β2; SMAD2 — mothers against decapentaplegic homolog 2; SMAD4 — mothers against decapentaplegic homolog 4; SMAD7 — mothers against decapentaplegic homolog 7; P — phosphorylation; RUNX-2 — runt-related transcription factor 2; Col1 — collagen-1; ALP — alkaline phosphatase.

osteotomies [26]. It was shown with mechanical testing that hard callus formation was increased two-fold revealing that the apparent modulus of the osteotomies approached that of unoperated fibulae (80%). While using a similar exposure protocol with another PEMF signal with a higher pulse frequency (63.00 kHz vs. 3.85 kHz), and lower fundamental frequency (1.5 kHz vs. 15 Hz) and magnetic field amplitude (0.02 mT vs. 1.19 mT), no effect in osteotomy healing was found, indicating that the biological outcome is dependent on the specificity of PEMF waveform parameters.

Similarly, it was shown that PEMF (Physio-Stim) enhanced healing of fibular osteotomies in a rat model for osteoporosis [27]. Specifically, full body PEMF exposure (Physio-Stim) for 3 hours daily for 6 weeks was done following noncritical sized osteotomies (0.2 mm). It was shown that the hard callus elastic modulus for the ovariectomized group was normalized using PEMF as compared to sham controls. These results indicate the potential benefit of using PEMF as a treatment modality for osteoporotic patients following fractures.

Osteoporosis

In an osteoporosis prevention rodent model, rats were ovariectomized and underwent 3 hours daily PEMF exposure (Physio-Stim) within 3 days of ovariectomy and followed for 6 weeks, 12 weeks, 18 weeks, and 24 weeks [28,29]. Other groups received bisphosphonate treatment instead [alendronate (Fosamax); 3 subcutaneous injections per week; 10 μg/kg body weight]. Micro-CT showed significantly more trabecular bone remaining at the L4 vertebrae for the PEMF group relative to the sham (30% more, relatively). However, the alendronate alone and alendronate+PEMF-treated groups had similar bone preservation with significantly more bone than both of these groups.

In another study, an osteoporosis reversal rodent model was used where rats were ovariectomized followed by 4 weeks of estrogen deficiency bone loss [30,31]. Subsequently, they underwent 3 hours daily PEMF exposure (Physio-Stim at various slew rates, 10 T/s to 300 T/s) for 6 weeks. The positive control group received bisphosphonate treatment instead [alendronate (Fosamax); 3 subcutaneous injections per week; 10 μg/kg body weight]. Micro-CT showed significantly more trabecular bone at the proximal tibia for specific PEMF slew rates (30 T/s) relative to any other PEMF group. In addition, the 30 T/s signals ability to mitigate the bone loss was similar to the alendronate group, indicating that the application of PEMF to various tissues is waveform specific.

Tenogenic and myogenic experiments

In vitro differentiation and proliferation

The effects of PEMF (Physio-Stim) on tenocyte and myocyte proliferation and differentiation have been studied *in vitro* using human rotator cuff tenocytes and C2C12 murine myoblasts, respectively [32]. Three hours of PEMF exposure daily for 2 weeks enhanced gene expression of growth factors in human rotator cuff tenocytes (COL1, TGFβ-1, PDGFβ, BMP12 and TIMP4) and myocytes (MyoD) under inflammatory conditions [10 ng/mL interleukin-1 (IL-1)] but not under normal conditions. In addition, it was found that myotube formation was increased under both normal and inflammatory conditions (10 ng/mL IL-1). The implications from these results may be the potential use of PEMF as a nonoperative treatment to improve clinical outcomes following rotator-cuff repair.

In vivo tendon healing

Daily PEMF exposure (3 hours of Physio-Stim) has been shown to improve tendon-to-bone healing in an acute rotator cuff repair model in rats [33]. Specifically, the tendon modulus increased significantly at early time periods (100% and 60% at 4 weeks and 8 weeks, respectively) with increased maximum stress (4 weeks) and subsequent improved bone quality at 16 weeks (increased bone volume fraction, trabecular thickness, and bone mineral density). This may indicate a potential new usage for PEMF as an adjunct treatment to surgical rotator cuff repair to prevent post-operative re-tears. Further investigations [34] revealed that using PEMFs with varying fundamental frequencies (3.85—40 kHz) or exposure durations (1 hours/day, 3 hours/day, or 6 hours/day) led to improvements in tendon properties for both types of PEMF and all exposure durations. However early (4 weeks) improvements in tendon modulus was only found for PEMFs at lower fundamental frequencies (for all exposure durations).

Intervertebral disc experiments

In vitro anti-inflammation

The effect of PEMF (Physio-Stim) on intervertebral disc (IVD) biology was examined by Miller et al [35] who studied the effect of PEMF on IVD gene expression in normal and inflammatory conditions. Human annulus fibrosus (AF) and nucleus pulposus (NP) cells were exposed to IL-1a and stimulated with PEMF for 4 hours daily for up to 7 days. Results indicated that PEMF lessened the IL-1a-induced inflammatory effects (25% IL-6 decrease in NP cells; 26% MMP-13 decrease in AF cells). PEMF was also found to significantly decrease IL-1a-induced gene expression of IL-17A (33%) and MMP2 in NP cells and nuclear factor kappa B (NF-κB) (11%) in AF cells. The results indicate that PEMF does have an effect on inflammatory disc cells which could potentially be helpful for patients with IVD degeneration.

In human annulus fibrosus cells a GFP-tagged MS2 reporter system was also used to visualize and quantify dynamic changes of IL-6 mRNA transcription in response to inflammation and PEMF (Physio-Stim) stimulation [36,37]. The novel cellular model showed that the reduction in IL-1 induced IL-6 expression could be observed in real-time within the initial 4 hours of PEMF exposure. Further work [38] has shown that the reduction in IL-6 and other inflammatory genes in the disc cells by PEMF (Physio-Stim) is mediated by NF-κB, a key proinflammatory signalling pathway.

In an acute inflammation rat IVD model (single disc stab of the Co6-7, Co7-8, and Co8-9 vertebral levels and observed 4 and 7 days later) it was found that PEMF (Physio-Stim) reduces IL-6 and IL-1b at the gene and protein levels [39,40]. This indicates that PEMF may have an anti-inflammatory effect in disc degeneration; however accompanying histologic results did not reveal any significant differences between PEMF and sham treatment. The authors concluded that, although the results are promising, further long-term studies using a long-term inflammation animal model should be examined.

Finite element modelling

Power attenuation in tissues

Experimental examinations of power attenuation of different types of PEMF (Physio-Stim, Spinal-Stim) for transverse magnetic or electric field have previously been done by Zborowski et al [41]. It was found that the observed 1 dB power attenuation of the exposed tissue is comparable to the threshold of body sensitivity to sound. In addition, it was found that the transverse magnetic field leads to higher energy absorption which may be used to optimize the PEMF targeting through manipulation of PEMF coil geometry.

Field visualization and strength comparisons

Electromagnetic field visualization has previously been performed for FDA approved PEMF for lumbar fusion (Spinal-Stim) [42]. Specifically, two-dimensional field line calculations and field magnitude contour plots were compared to three-dimensional field isosurfaces, which in turn were verified through experimentally measured field strength values within the treatment zone of the PEMF device. The agreement between the models and the experimental measurements allows for future field visualizations of custom PEMF fields.

Finite element modelling of two FDA approved magnetic stimulation devices for lumbar fusion (SpinaLogic, DJO (Vista, California, USA), and Spinal-Stim, Orthofix) has also been performed using a three-dimensional toroidal shell model [43]. The electric field and current densities were calculated at the target tissue (lumbar vertebrae) and compared to an FDA approved electric stimulation device (SpinalPak, Biomet (Warsaw, Indiana, USA)). The local maximum electric field and current density generated at the virtual vertebrae were found to be twice as high for the SpinalPak device relative to the Spinal-Stim device, which in turn was several orders of magnitude higher than the SpinaLogic device. However the Spinal-Stim device exposure was shown to be more uniform radially across the individual vertebrae in addition to being the only device

exposing the vertebrae to a magnetoacoustic pressure which was calculated to be within the audible range.

Conclusions and recommendations

PEMF therapy has been shown to be safe and effective in a clinical setting as an adjunct to lumbar and cervical intervertebral fusion and for long bone nonunions. However, the success of optimizing PEMF signals for current indications or applying PEMF for new indications hinges on a significant amount of research involving the careful use of both virtual (finite element modelling), *in vitro* and *in vivo* models prior to moving into a clinical trial. While practically all existing therapeutic PEMF devices have been empirically designed, recently, the analytical approach for new devices has been proposed [44]. Any clinical application should start with the correct diagnosis and clinical estimates of the parameters of PEMF needed to treat the specific pathology/injury which would be followed by extensive preclinical research of the desired PEMF. This is particularly important since, as the review illustrates, specific optimal PEMF waveform parameters exist which may not carry over between target tissues. In addition, although initial signalling pathway models have been proposed for short- and long-term PEMF applications for osteogenesis (Figures 5 and 6, respectively) the specific pathways are not complete and no specific PEMF receptor(s) have been identified. Thus, the degree and specificity of which PEMF may act is not completely understood. In addition, pathways may differ between target cell types, further underscoring the importance of thorough preclinical research into the desired target cell/tissue type. It is thus advisable to gain enough *in vitro* and *in vivo* knowledge of the specific PEMF signal and its target tissue interaction to enable a high success rate in a clinical trial. Finally, considerations should also be given to the engineering challenges of designing a device that may have to be portable or fit a certain anatomy while enabling the exposure of a specific PEMF waveform.

Conflicts of interest

EIW, NZ and JTR are employed by and own stock in Orthofix, Inc.

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