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Review Article

Low frequency pulsed electromagnetic field — A viable alternative therapy for arthritis

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Arthritis refers to more than 100 disorders of the musculoskeletal system. The existing pharmacological interventions for arthritis offer only symptomatic relief and they are not definitive and curative. Magnetic healing has been known from antiquity and it is evolved to the present times with the advent of electromagnetism. The original basis for the trial of this form of therapy is the interaction between the biological systems with the natural magnetic fields. Optimization of the physical window comprising the electromagnetic field generator and signal properties (frequency, intensity, duration, waveform) with the biological window, inclusive of the experimental model, age and stimulus has helped in achieving consistent beneficial results. Low frequency pulsed electromagnetic field (PEMF) can provide noninvasive, safe and easy to apply method to treat pain, inflammation and dysfunctions associated with rheumatoid arthritis (RA) and osteoarthritis (OA) and PEMF has a long term record of safety. This review focusses on the therapeutic application of PEMF in the treatment of these forms of arthritis. The analysis of various studies (animal models of arthritis, cell culture systems and clinical trials) reporting the use of PEMF for arthritis cure has conclusively shown that PEMF not only alleviates the pain in the arthritis condition but it also affords chondroprotection, exerts antiinflammatory action and helps in bone remodeling and this could be developed as a viable alternative for arthritis therapy.

Keywords: Arthritis, Bone, Chondroprotection, Inflammation, Osteoblasts, PEMF

Introduction

Rheumatoid arthritis (RA) and osteoarthritis (OA) are the two most common forms of arthritis. In the management of RA, nonsteroidal antiinflammatory drugs (NSAIDs) are often used for extended periods of time and are frequently combined with disease modifying antirheumatic drugs (DMARDs) and corticosteroids. OA is a chronic noninflammatory condition in which the main therapeutic end point is pain control with simple analgesics. NSAIDs are associated with upper gastrointestinal side effects, ranging from mild dyspepsia to more severe complications such as gastric hemorrhage[1]. Long term studies have shown significant morbidity and mortality up to 90% for RA patients treated with DMARDs[2].

Use of complementary therapies in RA and OA have gained acceptance and much work is being carried out to put it on a scientific footing. Some of the complementary therapies used in arthritis treatment are: (i) dietary supplementation, (ii) hydrotherapy, (iii) siddha, (iv) homeopathy, (v) ayurveda, (vi) acupuncture, (vii) electric stimulation and (viii) magnetic therapy. Physical medicine in general and magnetobiology in particular can provide noninvasive, safe and easy to apply methods to directly treat the site of injury or the source of pain, inflammation and dysfunction[3]. As observed earlier, low frequency PEMF has a detailed, long term record of safety, backed by clinical, animal and tissue culture studies over a period of 20 years[4]. This review focusses on the positive effects in applying magnetic component of the electromagnetic field (EMF) in the treatment of arthritis.

Historical perspective

Ancient Indian work, Atharva veda (a scholarly treatise which has formed the basis for Ayurveda) includes a number of *mantras* in Chapters 1 to 4, which detail the usage of magnets. Greek scholars like

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Plato, Homer and Aristotle have dwelt upon the healing properties of magnet in their masterly works. During the renaissance period (1493-1542), Paracelsus used magnets to control inflammation[5]. The first scientific approach on the study of earth's natural magnetism was given by William Gilbert, physician to Queen Elizabeth I of England, through his celebrated treatise 'De magnete' (comprehensive book on magnetism) published during 17th century[6]. The subject of magnetic fields caused by electric currents began with Hans Christian Oersted. Ampere's discovery and Faraday's laws of electromagnetic induction in 1831, showed that electricity and magnetism were not distinct, separate phenomena, but they interacted when there were time-varying electric or magnetic fields. Galvani and Volta demonstrated that electric currents elicited biological stimulus. One of the earliest observations on the effect of time-varying magnetic field was by d'Arsonval. He reported subjects seeing bright spots, called magneto-phosphenes, in the visual field when exposed to pulsating magnetic field[7]. Though history is replete with magnetic healing, it was considered as a justifiable part of medicine only from 20th century.

Interaction of magnetic fields with biological systems

Life has evolved in the natural Geomagnetic Field (GMF) environment and right from the primeval stages of amoebae, it has sustained in this environment. Also, the micorpulsations of the GMF have shown to be vital components affecting life process[8]. Thus, the role of GMF in general and magnetic field in particular, on living organisms has necessitated a critical examination of many of the views in biology.

The influence of magnetic field on biological system is broadly classified as internal and external. The external is further sub-classified as environmental and man-made. The internal magnetic environment of man is made up of magnetic fields generated by the time varying electrical activity of the brain and heart within the body[9]. Robin Baker *et. al*[10] have reported that bones from the region of the sphenoid/ethmoid sinus complex of humans are magnetic and contain deposits of ferric iron. The static magnetic fields exhibited by certain organs in the body, like the liver, are due to iron present in molecular form. Thus, the influence of magnetic field has played a vital role in the evolution and sustenance of life[11]. Theoretically, the biological effects of a constant magnetic field can be due to the orientation of paramagnetic and diamagnetic molecules. Such effects are possible only if the energy of the magnetic field, calculated per molecule, exceeds kT, where k is the Boltzmann's constant and T is the absolute temperature. For this, the intensity of the field must be at least 10,000 times greater than the geomagnetic field. In theory, the weak EMF is incapable of producing biological effects. But, investigations have shown that biological systems are sensitive to a constant magnetic field and EMF of different frequencies with energy much less than the theoretically estimated effective level[12] .

Exposure systems

The exposure system has three components :

1. The signal generator, which produces input voltage signal of a particular waveform and frequency; 2. the amplifier, which produces electric current output supplying the electromagnetic field generator and 3. the electromagnetic field generator, viz, coils of copper wire produce magnetic field and the field intensity can be varied by altering the amplifier.

Kairu *et.al*[13] have reported that the stimulation effect of the induced electric field in the coil (circular, square, double circular and square, and quadruple square) depends on coil size, waveform and duration. The major field parameters are frequency, waveform, intensity of the field and duration of exposure. The delivery of induced electric field at the site of stimulation is very important. For this reason, it has been recognized that coil shape and size are important parameters for effective stimulation. Coils shaped differently induce electric fields with different characteristics. Coils are designed for focal stimulation as well as for uniform field. The common coil types used are shown in Fig.1. In order to elicit specific site response, several authors have employed different techniques on the coil design to deliver focal magnetic stimulation[14]. One major drawback in magnetic field stimulation is that it does not confine to a small target region and as a result, the precise site of stimulation is difficult to predict. When broad areas are to be stimulated, it is necessary for the field to be uniform over the area. In such conditions, it is desirable to have a coil system (like the Helmholtz's and Ruben's) which provides a uniform magnetic field over a considerable volume and which is also easily accessible from outside the coil[15].

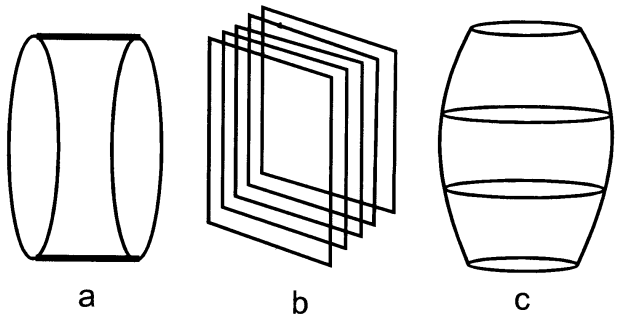

Fig. 1 — Magnetic coils commonly used in PEMF therapy (a: Helmholtz coil, b: Ruben's coil, c: Fransleau-Braunbeck coil)

Magnetic stimulus

Therapy using PEMF stimulation can broadly be divided into two frequency bands: radiofrequency band operating in the MHz region that uses either capacitative or inductive coupling of the energy to the tissue, and the low-frequency magnetic field is in 1 Hz - 10 kHz range. There are two methods by which PEMF stimulation can be non-invasively applied to biological systems: capacitative and inductive coupling. Capacitative coupling does require the placement of opposing electrodes in direct contact with the skin surface surrounding the tissue of interest[16]. In contrast, inductive coupling does not require the electrodes to be in direct contact with the skin. Rather, the time-varying magnetic field of the PEMF induces an electric field, which in turn, produces a current in the body's conductive tissue.

The pattern of induced electric fields and eddy currents depend on the geometric positions of anatomical features, waveform and the direction and spatial distribution of the incident magnetic field. When compared with electrical stimulation, magnetic stimulation has been shown to be advantageous for the following reasons: (i) no direct contact of electrodes, (ii) non-invasive in nature, (iii) minimum discomfort to the subject, (iv) easy penetrability and (v) low attenuation[17].

Signal properties

Frequency — Electromagnetic fields, waves and impulses which occupy the frequency band between 3Hz and 3 KHz have been termed extremely low frequency (ELF)[18]. Very low frequency or VLF (3 KHz to 30 KHz) and ultra low frequency or ULF (< 3Hz) phenomena occupy adjacent wavebands. Persinger *et. al*[19], from a more psychophysiological reference point, have indicated time-varying magnetic and electric fields and electromagnetic waves between 0.01-100 Hz within the ELF band.

Intensity — From the health and safety point of view, the World Health Organization have brought out safety guidelines on the magnetic flux density that would produce potentially hazardous current densities in tissue[20]. From the available data on human exposure to time-varying magnetic fields, in the range of 10-100 mA/m^2 (from fields higher than 5-50 mT at 50-60 Hz), various stimulation of thresholds are exceeded leading to health hazards.

Duration — Persinger[21] has observed that exposure length is an important control factor in experiments with magnetic field for the effect to be significant and that long term exposures are associated with more positive results. Treatment times range from 20 min to 8-10 h per day, depending on the condition to be treated and the field parameters used[22].

Waveform — Waveform means the shape and form of a signal. Waveforms are generally categorised as — sinusoidal and nonsinusoidal. The amplitude of the sinusoidal waves follows a trigonometric sine function with respect to time. The nonsinusoidal waveforms commonly used are: saw tooth, square and triangle, which are based on the resemblance of the shape of the wave.

Biological response to PEMF

One of the important observations that has been drawn is that there exists in nature electromagnetic phenomena whose time varying properties overlap with the fundamental electromagnetic frequencies generated by living organisms. Since the frequencies and intensities of the ELF electromagnetic fields are within the range of fields generated by living organisms, they may be important biological stimuli. The frequency of the applied field would be theoretically important in understanding the effect, for at lower ELF regions (below 20Hz), there is probably a change over in nature from dominance of the electromagnetic to the magnetic component[23]. This band has been shown to include the majority of important bioelectrical-behavioral correlation. If the applied ELF field influences biological structure with similar biofrequencies, then different applied frequencies would influence different structures[24].

The locus and the biophysical mechanisms of EMF detection are not known in humans, but in animals, experiments have shown presence of a sensory detector. Migratory birds have been shown to possess miniature magnetic compass needles made of magnetite which are used in the migration from north to south and backward[25]. In humans, evidence and

analysis suggest that this mechanism occurs in the nervous system[26]. One of the hypotheses in the mechanism of detection is that the ionic permeability of membrane-channel proteins may be increased during application of EMFs, resulting in the initiation of second messengers that ultimately lead to biological effects[27].

The response of biological systems to potentially effective EMF depends on its state of physiological equilibrium[28]. Putative infected animals constitute systems in a transition state and thus may be responsive to the EMF exposure, whereas healthy animals would act as relatively stable systems, exhibiting less or no sensitivity to the same field parameters[29]. This is evidenced in studies[30] on adjuvant induced arthritis in rats wherein arthritic animals exposed to PEMF are noticed to have decreased levels of inflammatory markers and enhanced antioxidant status, whereas, normal rats exposed to the same field parameters have not shown any changes in the studied parameters. The same observation has also been reported earlier by Eraslan *et. al*[31].

Optimization of physical and biological window

The physical window constitutes the field parameters viz., frequency, intensity, duration, waveform, geometry of exposure while the biological window includes the experimental model or cell type used, stimulus, age and period of study. Reproducibility of experiments can be expected only if these major variables are taken into account. Different results will be obtained by different combinations of given physical and, or biological variables[32].

Pulsing electromagnetic field (PEMF) therapy may be a viable form of complementary and alternative medicine. Clinical applications include the treatment of fractures, wounds, and heart disease and recent applications involve treatment of recurrent headache disorders[33]. PEMF has been reported for the management of therapeutically resistant problems of musculoskeletal system[34]. PEMF therapy is shown to be effective for chronic knee arthritis[35] and multiple sclerosis[36]. Previous studies[37,38,30] have conclusively shown that optimization of the frequency, intensity and duration could help in attaining consistent beneficial results in experimental arthritis in rats.

Effect of PEMF in arthritis

The results obtained from various *in vivo* models along with various cell culture systems have provided an insight into the mechanism by which PEMF exerts its effects on degenerated connective tissue in arthritis. In this review, results are illustrated under three major classifications viz., chondroprotection, antiinflammatory effects and bone remodeling.

Chondroprotection through PEMF — Cartilage is a highly specialized skeletal tissue that is elaborated at sites where a semisolid architecture is required to provide shape and form, yet ensures flexibility and durability. The chondrocytes synthesize and secrete type II collagen and aggrecan and elaborate extensive extracellular matrix (ECM). Aggrecan is highly negatively charged and creates a hydrated matrix thereby contributing to the compressive stiffness of the cartilage. In arthritis, the fibrillar network of collagen, which forms the endoskeleton, is damaged and there is loss of aggrecan, leading to joint dysfunction[39]. Different experimental cell culture and *in vivo* models of endochondral ossification have demonstrated the effect of PEMF on increasing chondrocyte proliferation and synthesis of ECM. Studies on electrical phenomena in cartilage have suggested that when cartilage is mechanically compressed, there is movement of fluids and electrolytes, leaving neutralized negative charges in the proteoglycan and collagen in the cartilage matrix. These streaming potentials could work in cartilage and transduce mechanical stress to an electrical (or electromagnetic) phenomenon capable of stimulating chondrocyte synthesis of matrix components[40].

In vivo models:

In Dunkin Hartley guinea pigs (OA model), PEMF treatment (pulse burst of 30ms duration, energy below 75HZ) is shown to significantly reduce the number of immunopositive cells to collagenase type II, stromeolysin and IL-1β, while the number of TGFβ-1 cells is significantly increased. Stimulation of TGFβ-1 may be responsible for the reparative mechanism of action[41]. Fini *et. al*[42] have reported that PEMF (75Hz, 1.6mT, 6h per day for 3 months) preserves the morphology of articular cartilage and retards the development of OA lesions in the knee of aged guinea pigs. Histology of adjuvant induced arthritic rat ankle joint has shown extensive subchondral and surface erosion due to arthritis and it has revealed almost normal architecture of articular cartilage after treatment with PEMF at 5Hz, 4μT for 90 min[38,30].

Aaron and Ciombor[43] have used an experimental model of decalcified bone matrix induced

endochondral ossification to examine the effects of PEMF. A quantitative increase in sulphate incorporation, glycosaminoglycan (GAG) content and calcification is noticed due to an increase in ECM synthesis triggered by the enhanced differentiation of mesenchymal stem cells. In another study using the same model, Ciombor *et. al*[44] have proved accelerated chondrogenesis with an applied magnetic field of a pulse-burst of 4.5ms duration repeated at 15 burst/s. This study also confirms the upregulation of gene expression for the synthesis of aggrecan and type II collagen and greater immunoreactivity of 3B3 and 5D4 suggesting an increase in the rate of differentiation of chondrocytes and enhanced phenotypic maturation.

In vitro studies:

An array of *in vitro* investigations on chondrocytes have conclusively demonstrated the ability of PEMF to stimulate the synthesis of extracellular matrix components and promote chondrocyte proliferation[45-49]. De Mattei *et. al*[48] have demonstrated that a range of exposure length (1, 4, 9 and 24h), different frequencies (2, 37, 75, 110HZ) and magnitudes (0.5, 1, 1.5, 2mT) could stimulate anabolic activities in cartilage explants.

Antiinflammatory effects of PEMF —The basic mechanism of low frequency fields is the forced vibration of all the free ions on the surface of a cell's plasma membrane caused by an external oscillating field. Irregular gating of ion channels, caused by the forced vibration of free ions, under the influence of an external oscillating EMF, can certainly upset the electrochemical balance of the plasma membrane and consequently disrupt the cell's function[50]. Such manipulations distort transmembrane proteins (ion channels) and thus lead to intracellular signaling of the cytoskeleton[51].

Membrane mediated calcium signaling:

Interaction between the cell membrane and PEMF modulates critical events in signal transduction mechanisms such as Ca^{2+} influx and mobilization, surface receptor redistribution and protein kinase C activity. Cellular production of cAMP in response to parathyroid hormone and osteoclast activating factor in cultures of osteoblast-like mouse bone cell line MMB-1 is significantly reduced by two different PEMF stimulations; one generating continuous pulse trains (75Hz) and the other generating recurrent bursts (15Hz) of shorter pulses for 72 h. The field effects are mediated at plasma membrane of osteoblasts[52]. It is proposed that membrane-mediated calcium signaling processes are involved in the mediation of field effects on the immune system[53]. Electromagnetic fields alter calcium ion flux and thereby influence subsequent cellular events in the signal transduction cascade such as gene activation[54]. Human lymphoid cells exposed to ELF magnetic field (50Hz, 2mT, 72 h) produce a modification of membrane cytoskeleton organization, together with an alteration of protein kinases activity, without affecting cell proliferation and this confirms that EMF can modify plasma membrane structure and interfere with initiation of signal cascade pathway[55]. Selvam *et. al*[30] have shown that, in adjuvant induced arthritis in rats, low frequency (5Hz) and low intensity (4μT) PEMF applied for 90 min per day for 52 days exerts its antiinflammatory effect through restoration of plasma membrane calcium ATPase activity of lymphocytes.

Direct effects on inflammatory markers:

An antiinflammatory mechanism of action is also hypothesized based on *in vitro* capability of PEMF to increase the number of A_{2A} adenosine receptors in human neutrophils[56]. In an earlier report, a decrease in lysosomal enzyme activities has been shown consequent to PEMF exposure of arthritic rats[38] and this finding corroborates with the observations of report on synovial fibroblasts[57]. Chang *et. al*[58] have shown reduction in the levels of TNF-α and IL-6 in ovariectomised rats exposed for 7 days with different intensities of electric field (4.8, 8.7, and 1.2mv/cm). Antioxidant effects and decrease in the level of inflammatory mediator PGE_2 on the application of PEMF therapy are noticed in adjuvant induced arthritis in rats. A more significant observation is that no significant changes are seen in normal rats exposed to PEMF[30].

PEMF and bone remodelling — With aging and in inflammation, bone formation does not keep pace with bone resorption and the bone mass is gradually lost throughout entire skeleton. With this loss of bone mass, there is a disproportionately greater decrease in bone strength[59]. The original basis for PEMF therapy is the observation that physical stress on bone causes the appearance of tiny electric currents (piezoelectric potentials) that are thought to be responsible for the transduction of the physical stress into a signal that promotes bone formation[60].

Recent reports suggests that short daily electromagnetic stimulation appears to be a promising

treatment for acceleration of both bone-healing and peri-implant bone formation[61].

Osteoblast proliferation and differentiation:

Weak, pulsating EMF has the ability to stimulate bone healing. DNA synthesis in Chinese Hamster V79 cells is significantly enhanced when they are exposed to weak PEMF generated by specific combinations of the pulse width (25μs), frequency (10, 100 Hz) and intensity (2×10^{-5}, 8×10^{-5}T). But, DNA synthesis of cells in the fields at 4×10^{-4}T is repressed to 80% to that of control not exposed to PEMF[62]. It is consistently shown that electromagnetic stimulation promotes osteogenesis and this is mostly found to result from the effects of EMFs on osteoblasts[63-65]. PEMF stimulation is reported to enhance the osteoblast differentiation[66,67] and to increase bone formation[66,67]. Different transduction pathways through which PEMF effects osteoblast proliferation have been reported. A recent study reports that PEMF induces osteoblast proliferation partially through protein kinase A, protein kinase C or protein kinase G pathways[68]. Induction of osteogenesis by PEMF is also speculated to be achieved through upregulation of bone morphogenetic proteins. PEMF exposure in a human osteoblastic cell line has resulted in the transcriptional upregulation of BMP-4, 5 and 7[69]. Exposure of osteoblasts to PEMF has shown induction of osteogenesis through increase in the levels of BMP-2 and 4 mRNA[70]. PEMF stimulatory effects on the proliferation and differentiation of osteoblasts are also shown to be mediated by the increase in the NO synthesis[71]. The clinically beneficial effect of low frequency pulsed electromagnetic fields (ELF-PEMF) on bone healing has been described through osteoblasts stimulated with pulsed electromagnetic fields as shown by increase in human umbilical vein endothelial cells (HUVEC) proliferation[72]. Effects of low frequency (7.5Hz) PEMF on osteoblasts culture has demonstrated osteoblast growth, stimulation of TGF-β and increase in alkaline phosphatase activity[73].

Effects on osteoclasts:

PEMF could enhance osteoblast activity but causes significant reduction in osteoclast formation[74]. Treatment with PEMF could shift the balance towards osteogenesis. Chang *et. al*[58] have found that osteoclast formation is significantly reduced in bone marrow cells from ovariectomised rats treated with PEMF compared with cells isolated from sham-operated rats.

The pulsed electromagnetic fields (PEMFs) applied for the integration of osteochondral autografts in sheep limit the bone resorption in subchondral bone; furthermore, reduction in the cytokine profile in the synovial fluid indicated a more favorable articular environment for the graft[75].

Effects on mesenchymal stem cells:

Human mesenchymal stem cells (hMSCs) are a promising cell type for both regenerative medicine and tissue engineering applications by virtue of their capacity for self-renewal and multipotent differentiation. Modulation of osteogenesis in human mesenchymal stem cells by specific pulsed electromagnetic field stimulation is reported[76]. It is also suggested that PEMF exposure could enhance the proliferation of bone marrow stem cells in culture during the exponential phase[77].

Clinical trials for arthritis using PEMF

There are clinical trials reporting beneficial effects with PEMF therapy but it is not consistent. A randomized double-blind clinical trial on patients with primary knee OA has been reported by Trock *et. al*[34]. Patients have been treated with PEMFs (frequency <30Hz, intensity 10-20G {1G = 10^{-4}T}, 67ms pulse phase duration) 30 min/day, 3-5 treatments per week for a total 18 treatments in 1 month. The waveform is quasirectangular, with abruptly rising and deteriorating, with a pulse burst duty cycle of 0.8 sec. Pain level, joint motion and tenderness have improved by 47% after 1 month of treatment. Trock *et. al*[60] have again performed a similar study on the effect of PEMFs in the treatment of patients with knee and cervical spine OA. In this trial, the field is energized in a step-wise fashion as follows: 5Hz, 10-15G for 10min, 10Hz, 15-25G for 10min, then 12Hz, 15-25Hz for 10min. Treatments are given for 30 min and 3-5 sessions are given per week for a total of 18 treatments extending for a month. The treatment has resulted in pain reduction by 37%. Nickolakis *et. al*[78] have reported that PEMF stimulation is safe, reduces impairment in activities of daily life and improves knee function with chronic pain due to OA.

Ganguly *et. al*[79] have conducted a study investigating the effectiveness of PEMF stimulation in reducing pain, tenderness, swelling, joint functional disability and joint spasm with deformity in patients suffering from rheumatoid polyarthritis. Patients in this study have been assessed according to their

serological grouping. Results indicate that those individuals lacking the rheumatoid factor show much earlier improvement for pain, tenderness and joint functional disability relative to serological-positive individuals.

A systematic review of the literature from 1966 to 2005 has provided evidence that PEMF has little value in the management of knee osteoarthritis[80]. In another clinical trial, PEMF could not demonstrate a beneficial symptomatic effect in the treatment of knee OA in all patients though there is statistically significant improvement in morning stiffness and activities of daily living activities compared to placebo[81].

Genotoxic effects

Earlier reports have demonstrated that EMF does not produce genotoxic effects[82-84]. EMF exposures do not increase spontaneous levels of cytokines or induce an active state in normal peripheral blood mononuclear cells[85].

Exposure of human lymphocyte cultures to a pulsing electromagnetic field (PEMF; 50 Hz, 1.05 mT) for various durations (24, 48 and 72 h) has resulted in a statistically significant suppression of mitotic activity and a higher incidence of chromosomal aberrations[86].The reasons for these discrepancies could be due to the type of field used and the duration of exposure. Hence, an international effort must be made to strictly standardize the exposure system used[87].

Looking ahead

As shown by *in* vivo studies, PEMF therapy has the potential to regenerate the damaged tissue through stimulation of matrix component synthesis and upregulation of osteogenesis apart from alleviating inflammation and pain. In addition, *in vitro* studies conclusively demonstrate the beneficial effects of PEMF in different cell types (Table 1). There are no systemic effects as PEMF could directly be applied to the site of injury. In spite of the reports of beneficial

Table 1— Beneficial effects of PEMF therapy in different cell types

Cells	PEMF effects	Mechanism of action	Exposure parameters	References
Lymphocytes	Antiinflammation	Modification of membrane and cytoskeletal organization together with an alteration of protein kinase activity.	50Hz, 2mT, 72 h	55
		Stabilizes membrane and restores Ca-ATPase activity	5Hz,4μT, 90min for 52days	30
	Cytotoxicity	Absence of spontaneous proliferation. No induction of chromosomal alteration in normal and B- CLL lymphocytes	50Hz for 24, 48 and 72h	88
Neutrophils	Antiinflammation	Increases the expression and functionality of A2a adenosine receptors	75Hz,0.2 to 3.5mT for 30-120min	56
Fibroblasts	ECM synthesis	Collagen production though modification of cAMP metabolism	Pulse burst of 4.8ms duration repeated at 15Hz for 12h per day for 6 days and 1 day	89
Chondrocytes	Regeneration of chondrocytes	Increases chondrocyte proliferation of human articular chondrocytes at low and high densities	75Hz, 2.3mTfor 1,6, 9 & 18h for 3 & 6 days	48
		Human OA chondrocytes cultured in alginate gel has increased concentration of proteoglycan in culture medium	<30Hz,10-20G,3h per day for 72h	49
	ECM synthesis	Bovine articular chondrocyte monolayers had increased PG synthesis	75Hz, 1.5mT, 24h	47
		Increase in viability of human chondrocytes	21.2MHz period of 15ms for 72h	92
Osteoclasts	osteogenesis	Significant reduction in osteoclast formation	60Hz electric fields at 9.6μV/cm	71
Osteoblasts	Osteogenesis through proliferation	Increase in the level of BMP- 2 and 4 mRNA	4.5ms bursts, repeating at 15Hz 75Hz, impulse width of 0.3ms for 2h, induced electric field of 2mV/cm	69
		Enhance osteoblast activity by PKA, PKC pathways		67
		Enhanced osteoblast proliferation by increasing NO synthesis.	15Hz, 0.6mT for 15 days	70

effect of magnetic field in the treatment of arthritis, we remain only half way through explaining the mechanism by which PEMF reinforces the regenerative capabilities of injured tissue and only part way towards the selection of optimal stimulation method[90]. There are reports, which hold that PEMF is not beneficial. This could be due to lack of standardization of the exposure systems and biological conditions. It is important to understand accurately the internal current and electric field induced within the body and the non-homogeneous and anisotropic conductivity of body tissue and to develop models that will take into account the spatial distribution of the magnetic field and its waveform[91]. Optimization of exposure conditions and standardization of its interaction with biological window would help in developing this potential therapy as a viable alternative for treatment of cartilage and bone disorders.

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