# *RF and Pulsed Magnetic Fields; Achieving and Maintaining Consistent Temperature In-Vivo*

*James Lacey, MD, Ottawa, Canada*

Since the first uses of cosmetic radio frequency (RF), devices have proven the efficacy of this energy when treating rhytides, laxity, focal fat and cellulite. Inconsistencies in temperature and maintaining goal therapeutic temperatures have proven to be the main challenge with traditional radio frequency devices. Pulsed Magnetic Fields (PMF) have proven to accelerate angiogenesis, heal cutaneous wounds, decrease post-surgical pain, reduce edema, negatively influence bacterial and tumour cell growth and repair both bone and nerves, but little has been known of its application in cosmetic medicine until now. . The blending of these two energies has produced a synergistic thermal and non-thermal action inducing long term collagen remodelling and adipose tissue reshaping. Venus Freeze is the first device to deliver a unique algorithm of multi pole RF, allowing the maximum amount of energy to be released while the patient experiences no discomfort due to this deep heating matrix. Each electrode has the potential to be both positive and negative and the rotational system allowing this change to occur one million times per second allows for the treatment to be comfortable and tolerable for patients. The non-thermal PMF energy is emitted simultaneously and continuously throughout the treatment.

Therapeutic threshold is defined as 39 to 41 degrees centigrade on the face or neck and 42 to 45 degrees centigrade on the body. When the tissue is heated to the proposed therapeutic temperature this increases fat cell metabolism and accelerated triglycerides egress from the cell. Increased tissue temperature increases vascular perfusion, which further enhances lipid turnover.[1] Reduction of the convex distension is also partly due to shrinkage of the tissue. Immediate collagen contraction is achieved by the denaturisation of the collagen fibril which subsequently leads to neocollagenesis. The new collagen produces tighter tissue leading to more appreciable measurements.

With the Venus Freeze we have reached the ideal external (epidermal) temperature of 41-43°C, and a sub dermal temperature of 45 - 47°C required for optimal skin tightening. It is possible that the non invasive Venus Freeze can externally achieve the same temperatures as its predeceasing and more invasive energy assisted counterparts.[2]

## METHOD

Three patients were selected to participate (women between the ages of 30 – 50 with skin type II

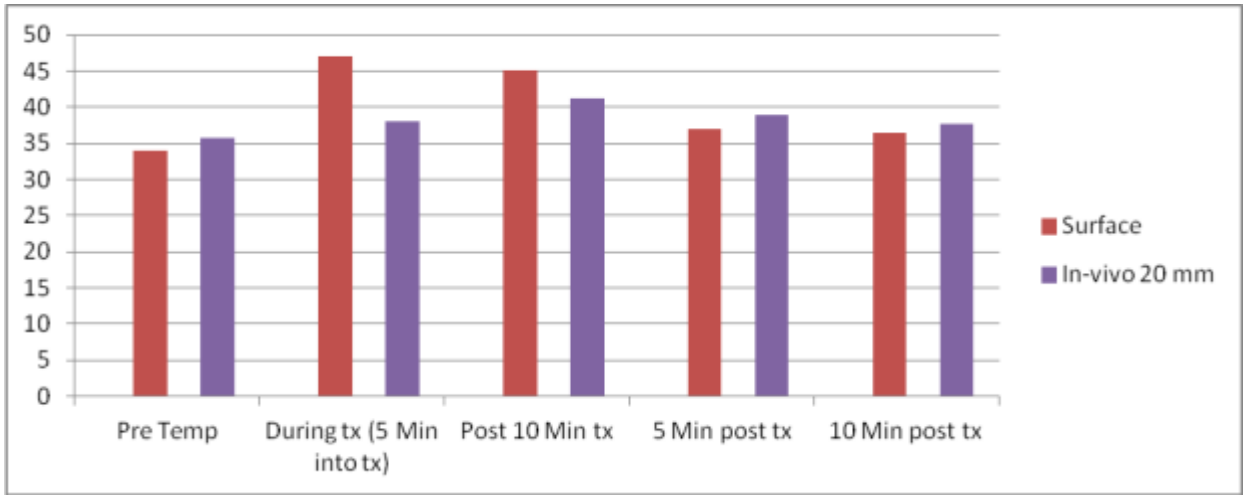
would undergo a Venus Freeze 10 minutes treatment to the abdomen prior to their abdomenoplasty or liposuction surgery. Internal and external temperature was monitored throughout and recorded at set intervals; before the treatment, after 5 minutes during treatment, 5 minutes post treatment and 10 minutes post treatment. The depth of internal monitoring was 20mm. Once the patient is under general anesthetic the abdomen program was selected with the preset values being 80% RF, continuous PEMF and the Octipolar hand piece. The treatment area was cleansed and glycerine was applied. The Octipolar applicator was applied to the skin and treatment commenced using irregular movement s on the skin to cover the area homogenously with heat. After 1 minute the device was placed on pause and the temperature on the surface of the skin was taken using a Fluke 62 mini IR thermometer and the information is recorded. The treatment is then resumed for 4 more minutes. After 4 more minutes the device is placed on pause and the external temperate and the internal temperature were measured using the Fluke Digital Thermometer for the external temperature and the Thermalert TH-8 monitoring thermometer with an MT-23/3 hypodermic needle microprobe at 20 mm depth. The treatment would resume for another 5 minutes. Once the last 5 minutes was complete the temperature was taken again in the same fashion with the same devices at the same depth. After 5 minutes and 10 minutes post treatment, the same temperatures were taken and recorded using the same devices and same depth.

## RESULTS

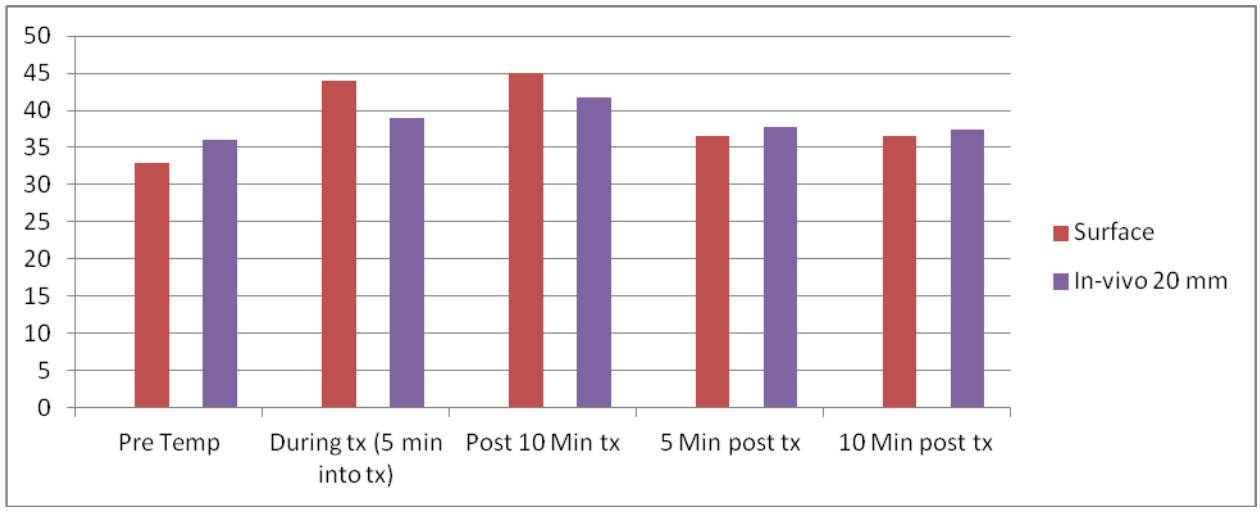
The patients had consistent heating on the surface with no negative responses such as burns, blisters or bruises. All patients reached therapeutic temperature in the first minute of treatment. All patients were able to achieve and maintain higher internal temperatures for the duration of the study which was 10 minutes post treatment. Each of the participants was able to maintain higher therapeutic internal temperatures in comparison to the external temperatures at 5 and 10 minutes post treatment. (see charts)

## SUMMARY

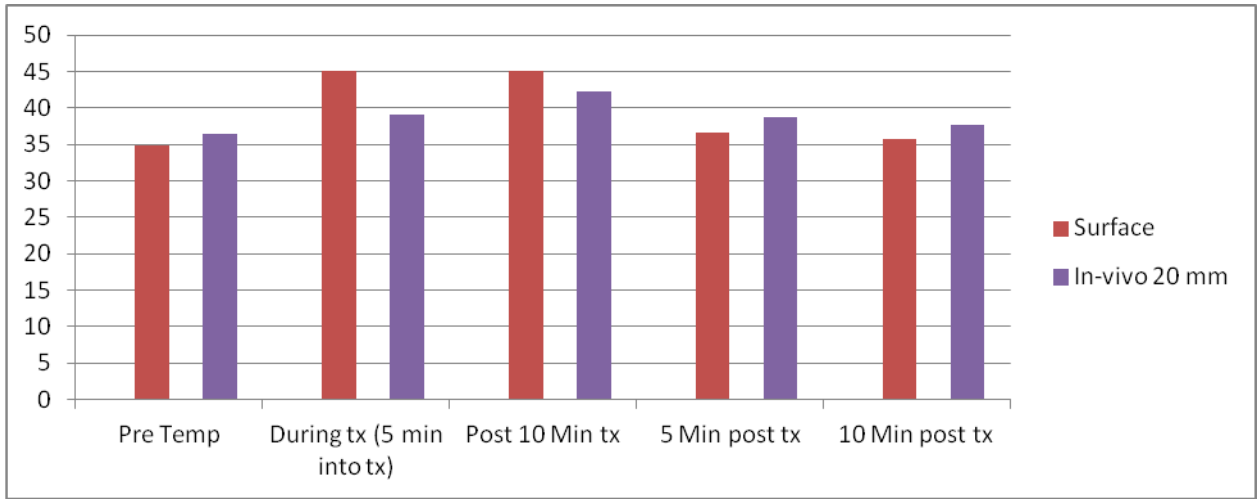
While RF and PEMF are both energies which have a achieved success in the area of focal fat, collagen regeneration and tissue tightening, it has been challenging to deliver them with consistency and without pain. The Venus Freeze multipolar system delivers consistent and homogenous heating. This extensive heating effect will aid in achieving reliable and predictable results.




PT 2




PT 3




## REFERENCES

1. Mulholland, Malcom, Chalfoun; Non-invasive Body Contouring with Radio Frequency, Ultrasound, Cryolypolysis and Low Level Laser Therapy. Clinics in Plastic Surgery 2011;July – Volume 38: Number 3.
2. Ajaka; Comparative study of the temperatures reached at the surface, 10mm and 20mm depths when performing the non invasive Venus Freeze® on the lower abdomen.

**Leonardo Marini, MD**
**SDC The Skin Doctors' Center, Triest, Italy**
**Via Bonomo 5/a ▪ I-34126 Triest ▪ Tel. +39-040- 5199 674 ▪ Fax +39-040-5199671**
**Leonardo.marini@skindoctors.it**

# THERMO-MAGNETIC REJUVENATION

## Aging and anti-aging strategies

The skin and subcutaneous fatty layer are constantly exposed to a series of naturally occurring mechanical, chemical, and electromagnetic energies whose biological influence is responsible for a highly complex adaptation response of living cells. Cellular response to environmental stress progressively deteriorate with time providing clinically evident signs, universally known as aging. **(Fig.1)** Two main aging processes have been identified: chrono-aging and extrinsic-aging. Chrono-aging is an intrinsic process affecting all cells, tissues, organs, and individuals leading to a progressive decrease in the efficiency of biological homeostasis. Extrinsic aging is characterized by a progressive, random accumulation of functional alterations within cells, lading to an increasing probability of biological malfunction, disease, and death. (14,17,30) When chrono- and extrinsic aging are working together premature aging occurs. Many theories have been proposed to explain the extremely complex mechanisms of aging. One of them focus on the progressive depletion and loss of function of adult stem cells. Adult stem cells have been found in most tissues of adult human organisms. Their role is to provide a constantly active biological source able to guarantee tissue repair and regeneration. Adult stem cells differ from embryonic stem cells which have pluri-potent differentiation capabilities, since they can differentiate into limited lines of cells. They normally reside within specific micro-environments or "niche". Many "niches" have been identified in humans within bone marrow, skeletal muscle, adipose tissue, hair follicle, peripheral circulation, intestinal epithelium, myocardium, lungs, breast, kidney, and brain. Somatic cells have a finite lifespan. They constant loss is compensated by the production of new "daughter" cells originating from adult stem cells. It has been speculated that the acquisition of adult stem cells during evolution in more complex organisms has resulted in a major extension of organismal lifespan – therefore the role of adult stem cells lies primarily in the rejuvenation of aging somatic tissues. Aging of an organism could be linked to a gradual loss of function of adult stem cells leading to a progressive increase of senescent cell population. Chronic environmental insults, inflammatory alterations, oxidative stress, and telomere shortening progressively lead to stem cells dysfunction and/or reduction via senescence or apoptotic death with advancing age. Senescent fibroblasts have been found to secrete matrix metallo proteinases (MMPs) , inflammatory cytokines, epithelial growth factors. Type I collagen is the major structural protein of the body. Collagen destruction, along with other important structural components of the skin, like elastic and reticular fibers, occur over decades. These intrinsic structural alterations are thought to be mainly responsible for the characteristic appearance of aged skin and the additional changes that result from chronic sun exposure. (35) Collagen degradation is due, at least in part, to activation of matrix metallo-proteinases (MMPs) released from epidermal keratinocytes and dermal fibroblasts after UV irradiation. (9,33,34) Heat shock response (HSR) has been proven to effectively protect living cells from progressive cumulative extrinsic- and intrisic-related alterations. Proteins, the functional "bricks" of life, are very sensitive to temperature which strongly influence their performance within and outside living cells. One of the key homeostatic responses involved in maintaining cellular longevity is the induction of a properly efficient heat shock protein (HSPs) response. HSP response is a highly conserved reaction, transversally present in all living cells. This innate cellular reaction must be considered one of the most efficient, primordial, intracellular defence mechanisms against stressful conditions. HSPs can be viewed as "molecular chaperones" synthesized when cells are exposed to potential protein damage. Exposure of cells and organisms to various forms of stress, such as high temperatures, caloric restriction, exercise, oxidative and osmotic stress, heavy metals, proteasome inhibitors, amino-acids analogues, ethanol, glutathione depletion, calcium ionophoresis and metabolic poisons, induce them to preferentially transcribe and translate HSPs. These proteins protect the proteome by folding denatured polypeptides and promoting degradation of severely damaged proteins. In addition to mediating protein quality and functional control, some HSPs such as Hsp27 and Hsp70 directly protect cells against damage-induced entry into death pathways. Optimal HSPs response, in terms of synthesis and activity is essential for cell survival. In contrast,

altered or inefficient HSPs response has been implicated in abnormal growth and development, aging and cellular apoptosis.(5) Triggering controlled, sequential heat-shock responses with subsequent up-regulation of HSPs and extracellular-intracellular signal regulating kinases (ERK; p38 SAPK-2 Stress Activated Protein Kinase; JNK cc-Jun Terminal Kinase SAPK-1) can protect adult stem cells within dermal niches leading to a prolonged "healthy skin aging". (23)
Recently it has been shown that repetitive, controlled pulsed heat exposures can stimulate an increased synthesis of pro-collagen I and pro-collagen III by fibroblasts in vitro. (7) Two seconds heat shocks exposures to 45°C were able to induce fibroblasts to produce pro-collagen I and III with a peak synthesis at 35 days, slowly decreasing after 90 days. Repetitive mild thermal stress has proven effective in providing an hormetic tool to be used in skin rejuvenation, maintaining a good intracellular stress protein profile responsible for reducing accumulation of oxidatively and glyco-oxidatively damaged proteins while stimulating proteasomal activities aiming to degrade damaged proteins and improving cellular resistance to other stressful conditions. Hormesis is a term derived from homotoxicology describing the possibility for potentially noxious events delivered to living cells to actually stimulate cellular function when administered at sub-noxious levels.(26, 27)

**Current Anti-Aging Strategies**

Overall life expectancy has considerably increased with time along with a paralleled demand for more prolonged social, intellectual and physical activities – future estimate for anti-aging market is enormously increased. Effective rejuvenating procedures should target dermal-epidermal layers as well as subcutaneous tissue with the aim of harmonizing body volumes and overlying external structures. Many rejuvenating procedures have been proposed to slow down or partially reverse skin aging with variable degrees of success. **(Fig. 2)** The majority of patients seeking medical advise to improve their skin prefer to choose from non invasive or minimally invasive treatment strategies associated with minimal side-effects and short recovery time over more aggressive, yet potentially more effective, but riskier procedures. Modern trends tend to take advantage of combination treatments where multiple procedures and energy sources are sequentially or simultaneously combined to produce balanced, three dimensional skin and subcutaneous fat rejuvenation. **(Fig.3)** Personalized rejuvenation strategies should always follow precise patient clinical evaluation in order to provide best possible clinical improvements. Well designed rejuvenating strategies should always take into account the need for a global anti-aging approach. Facial mio-remodelling with BTX-A, bio-volumization with autologous or non-permanent, non-autologous, tissue-compatible fillers, bio-stimulation with PRP and other regenerative strategies have provided a consistent contribution to skin rejuvenation and should be always considered when a balanced 3D skin rejuvenation proposal is to be discussed. Chemical peels, ablative and non ablative full surface or fractional lasers, high intensity polychromatic pulsed light, LED, focused ultrasound, monopolar, bipolar, and multipolar radiofrequency, PDT, subcutaneous fat remodeling have all a definite place in modern anti-aging medicine. (13, 15, 21) Most chemical peels and laser-assisted rejuvenating procedures are associated with variably prolonged down-time and obvious side effects.
Frenetic, highly irregular life style, wrong alimentary habits, and genetic predisposition lead to formation of cellulite and modifications of body fat distribution, mostly associated with localized adiposities.
Unfortunately aging is an ongoing, unstoppable process and clinical improvements obtained with rejuvenating procedures gradually return to baseline after a variable amount of time. Preparing patients before more complex rejuvenating procedures and providing effective maintenance treatments to prolong rejuvenating effects should be always an integral part of a well thought rejuvenating plan.

**Thermo-magnetic rejuvenation with Multi-Polar RF and Magnetic Pulses**

Monopolar, bi-polar, and multipolar RF have proven effective in stimulating collagen synthesis with clinically evident skin tightening effects. (1,4,8,37,38) Properly spaced electrodes allowing deeper RF penetration are able to induce subcutaneous fat remodelling and cellulite improvements. (2, 24) Recently a simultaneous combination of multipolar RF and pulsed magnetic fields has been proposed to induce a three-dimensional thermo-magnetic rejuvenation. **(Fig.4)**
RF passing through living tissue induce a controlled thermal surge along its path going from an active electrode to a return electrode. Water-rich tissue offer less resistance to electricity and warm more slowly than water-poor tissue, like fat, that warm faster and more efficiently. Adipocytes are highly sensitive to

temperature and their survival was recently found reduced after time-dependent thermal exposures. (10,11,20) **(Fig.5)** RF tissue penetration depends on the distance between electrodes positioned on treatment handpieces. The larger the distance the deeper the penetration. Penetration depth corresponds to half of the distance measured between two electrodes touching the skin. RF is able to produce efficient, controlled three dimensional volumetric tissue heating independently from intrinsic distribution of light-absorbing molecules (chromophores) on which laser-assisted photo-thermal effects depend. Only IR-A (760-1400nm) laser wavelengths can be used to produce a controlled volumetric heating since they are positioned within the so called "skin optical window" where main skin chromophores are not absorbing light. IR-A wavelengths are absorbed at epidermal level by 38%, at dermal level by 48%, and sub-dermal level by 17%. Properly efficient surface cooling systems are needed to prevent excessive epidermal heating when IR-A lasers are used in order to reduce treatment pain, possible burns and post-inflammatory hyperpigmentation.
RF technology can be performed on any skin phototypes and does not require epidermal cooling systems.(16) Monopolar and bi-polar RF devices need to deliver electric energy in a relatively long pulses to obtain properly effective electro-thermal tissue effects. Thermal surge is felt by patients as a relatively painful experience. Maintaining tissue temperature within controlled range of values is quite difficult when larger areas are to be treated since active electrodes and inter-electrode distance are quite small in most monopolar and bipolar devices. (25) Treatment time is proportional to the size of anatomical areas to be exposed to RF and is considerably long when small handpieces are used. Perfect contact of full electrode surfaces with the skin is needed during each electric burst in order to evenly distribute RF penetration. Reducing electrode contact surface may generate thermal burns due to excessive concentration of electricity in smaller areas. Poor electrode contact can also produce an "arching" effect responsible for localized epidermal thermal damage. In order to optimize RF treatments delivered to larger anatomical areas multipolar technology was developed. Multipolar RF handpieces are equipped with multiple electrodes positioned at variable distance among them. Electrodes are spaced far apart allowing deeper penetration. Electrodes are sequentially activated according to a pre-set pattern to produce a gradual temperature increase within exposed tissues enormously reducing risk of burns. Temperature can be easily maintained within an effective treatment range without hyper-thermic bursts. Electric paths follow different depths within tissue, depending on the distance between sequentially activated electrodes.$MP_2$ technology employed by Venus Freeze implemented all previously described RF technical solutions in its octipolar and tetrapolar handpieces working at 1MHz. **(Fig. 6)** Measuring tissue temperature during RF treatments is not easy. Infrared thermometers can be used to instantaneously measure surface skin temperature during RF applications. Surface temperatures are usually 4°C-to-6°C less than intradermal and subdermal temperatures as was recently confirmed by a precise thermo-couple study performed by Dr. Joseph Ajaka (unpublished data). He inserted thermo-couple needles at fixed depths (10mm and 20mm) and found a baseline difference of +2°C in deeper layers followed by a thermal surge of +4°C during RF treatment and a more pronounced thermal difference (+5.5°C – +6°C) during post-treatment resting phase at 5min, 10min, and 15min. **(Fig. 7)**

The idea of combining RF with pulsed magnetic fields is absolutely new and is based on a solid clinical background. We, and the earth where we live, are constantly surrounded by magnetic fields. Earth magnetism, solar storms, weather changes, human-built electric and electronic devices produce magnetic fields. **(Fig. 8)** Even the human body produces weak magnetic fields generated by chemical reactions within cells and ionic currents in nervous tissue. Electromagnetic fields (EMF) consist of electric and magnetic energies. Electric fields are generated by the presence of charged particles i.e. electrons. Magnetic fields are generated by the movement of charged particles. The human body consists of 50 trillion cells harmoniously working together. Should small energy perturbations arise within isolated cell groups, functional energetic imbalance involving the entire body may ensue. When energetic imbalance lasts longer enough, they may lead to a disease state, chronic illnesses, and premature aging. All living cells need a functional membrane to survive and perform their functions. Cell membrane potential is usually 70-90mV. 50% of cellular energy is used to keep this electric potential within normal range.
Using magnetic fields to influence the course of human diseases is not new. A Swiss physician, Paracelsus, used naturally magnetized magnetite to treat epilepsy, diarrhoea and control hemorrhagic states. He believed in the ability of magnets to attract diseases to eliminate them from the body. Mesmer, an Austrian physicians used magnets to improve body healing capabilities. In 1812 magnetic fields were reported to heal tibial non-unions. Magnetic ointments wee developed to treat headache, inflammatory bowel diseases, burns, fever sores, gout, rheumatic diseases. The advent of modern medicine saw considerable interest in magnetic fields. Fukada and Yasuda discovered piezoelectricity and described electric potential of bone tissue in the 1950s.

Basset used specific bi-phasic low frequency signals to treat non-union and delayed healing fractures in in 1964. Non invasive devices using pulsed electro-magnetic fields (PEMF)obtained FDA approval to stimulate bone growth in 1979. The same treatment was subsequently approved in 1991 to treat post-operative pain and soft-tissue edema. Since then PEMF was successfully used in many different fields of medicine and surgery. Orthopedic surgeons use them to reduce post-op pain, stimulate bone formation, and treat non-healing fractures.(18, 29) Plastic surgeons use PEMF to reduce post-op edema and ecchimoses. (19, 22,31) Traumatologists use them to reduce muscular-skeletal pain. Dermatologists prescribe them to treat chronic and diabetic ulcers since PEMF induce vasodilatation and angiogenesis.(6,12) Neurologists use PEMF to treat degenerative and post-traumatic neuropathies, depression, dystonia, migranes. PEMF produces eddy currents within treated tissues. Eddy current is an electrical current generated in conducting systems by changing magnetic fields. These currents oppose the direction of magnetic field responsible or their generation. PEMF uses electrical energy to deliver magnetic pulses through living tissue. Each magnetic pulse induces an electric signal that stimulate cellular activity through a positive interaction with cellular membrane function. (3) Intra-membrane protein distribution was found modified in cellular cultures by 50Hz PEMF, positively influencing trans-membrane ion channels, enzyme production, and receptors. Cultured fibroblasts were found to be stimulated to produce new collagen when exposed to low-frequency PEMFs. Cultured endothelial cells exposed to PEMFs were able to increase their secretion of Fibroblast Growth Factor-2 (FGF-2) three folds, and cultured medium applied to wounds has proven to considerably speed up healing processes. In vitro and in vivo PEMF-related angiogenesis was found to be dependent on endothelial release of FGF-2. Angiogenesis is a biological process consisting of sprouting of new vessels from already existing vascular structures to provide higher oxygen supply to low perfusion anatomical regions. (28,32,36) PEMFs have been considered safe after extensive studies challenging single and repeated exposures using clinical and supra-clinical doses. No cytotoxic or mutagenic activities were detected.

**Thermo-magnetic rejuvenation: a time-dependent technique**

We had the impression, from preliminary observations, that thermo-magnetic rejuvenating effects were directly proportional to RF+PEMF application time. We therefore studied a group of 16 female patients (age 42-68 – mean 53) affected by premature facial aging performing a different duration split-face RF+PEMF treatment limited to their cheek regions. The study were conducted in accordance with the ethical principles from the Declaration of Helsinki and Good Clinical Practices. After obtaining properly detailed informed consent and pre-treating all patients with the same skin-care regime, the same RF and PEMF parameters were used on both cheeks. Right cheeks were treated first, for a duration of 7 min. and left cheeks later, for a duration of 5 min. Venus Freeze (Venus Concept, Canada) and a tetra-polar MP2 handpiece were used on all patients. PEMF parameters were pre-set by the system at 15Hz, 15 Gauss (1.5 mTesla), 5ms pulse duration. A total of 10 treatment sessions were performed on all patients scheduling 2 sessions per week for five weeks. Clinical images were taken with a Visia Complexion Analysis standardized photographic system with Visia 5 software (Canfield Imaging System – Canfield Scientific, Inc. 253 Passaic Avenue, Fairfield, NJ, USA). Skin erythema was measured using a ColorMeter II (Cortex Technology, Plastvaenget 9, 9560 Hadsund, Denmark). Elastometry values were measured using a Dermacheck Multi Skin Center MC750 (Courage-Khazaka Electronic GmbH Koln, Germany). All measurements were taken on standardized facial anatomical landmarks immediately before treatment (T-1), 60 days (T-2), 90 days (T-3) and 120 days (T-4) after treatment. Subjective assessment was evaluated by analyzing treatment and immediately post-treatment acceptability questionnaires. The majority of patients confirmed an acceptable intra-treatment tolerability grading their experience as good (47%) and fair (47%) while only 6% regarded treatment as barely tolerable. Post-treatment tolerability was reported progressively increasing with time, at one, two, and three hours. No unacceptable tolerability levels were reported. Effective treatment working temperature, measured on skin surface, was set at 40.8 °C ± 0.5°C – corresponding to a dermal-hypodermal temperature of 44.5 ± 0.5 °C according to data provided by Dr. Joseph Ajaka. Surface temperature was measured with a dual laser targeting, non-contact infrared thermometer ZI-9688 (ZicoTech, Kadima, Israel). A pre-warming interval of 61-79 seconds (mean 70 sec.) was necessary to reach an effective working temperature on the right cheek. The left cheek required a pre-warming interval of 50-67 seconds (mean 56 sec.) confirming the induction of contiguous vasoactive reaction deriving from the previously PM2 treated right cheek. Average surface working temperature was 40.72 °C (40.20 – 41.30°C) on the left cheek, and 40.62 °C (40.20-41.00 °C) on the right cheek. **(Fig. 9)** Erythema, interpreted as an indirect sign of increased tissue vascular perfusion, was found more pronounced at T-2 on both cheeks: + 5.58% on the left cheek, and +3.16% on the right cheek.

Subsequent measurements revealed a progressive decrease at T-3 and T-4. Melanin readings revealed increased values at T-2: +9.60% on the right cheek and + 11.13% on the left cheek. Values progressively decreased at T-3 and T-4 confirming a moderate activation of temperature-related melanogenesis. Elastometry values decreased at T2 and progressively increased at T-3 and T-4 reaching +5.79% on the R cheek and + 2.87% on the L cheek. **( Fig. 10)** Textural variations revealed a slight increase at T-2 followed by a decrease at T-3 and an upward swing at T-4. Wrinkle count showed a moderate increase at T-2 followed by a progressive decrease at T-3 and T-4. Right cheek revealed a more significant decrease (-4.29%) than the left cheek (-3.45%). **(Fig. 11)** Data analysis of our split-face study confirmed the effectiveness of MP2 technology in rejuvenating prematurely aged skin. Treatment was well tolerated. No down-time, side effects, and complications were reported except for an isolated case of previously unreported temporo-mandibular-joint syndrome which worsened after the first application of MP2. Treatment was stopped and patient was replaced by another subject. Our study demonstrated also the importance of stretching treatment time to obtain better and more durable results concerning both wrinkle reduction and elasticity.
After our first pilot study confirming the time-dependent long-term effectiveness of thermo-magnetic technology, new treatment schedules have been proposed with the aim of optimizing cellular and tissue response according to their natural biological rhythms. Our present treatment formula consists in one seven-minute treatment per 15 $cm^2$ body area per week for a total of 6-8 sessions followed by a maintenance treatment scheduled every 30-45 days.

**Combination treatments with thermo-magnetic technology**

Thermo-magnetic technology has been successfully used also in combination with liposuction surgery preparing surgical areas before procedures and helping treated areas to smoothly recover during post-op time. MP2 technology has been effectively used in fibrotic and fibro-edematous cellulite either alone or in combination with mesotherapy. Bio-stimulation with hyaluronic acid and multivitamins has been improved pre-treating skin with MP2 technology. This technology may also temporarily increase specific light absorption by difficult-to-treat vascular targets like resistant port-wine-stains (PWS) immediately before selective laser micro-coagulation. It can be used to optimize photo-dynamic therapy (PDT) either before the application of photosensitizer precursors or immediately before specific light irradiation.

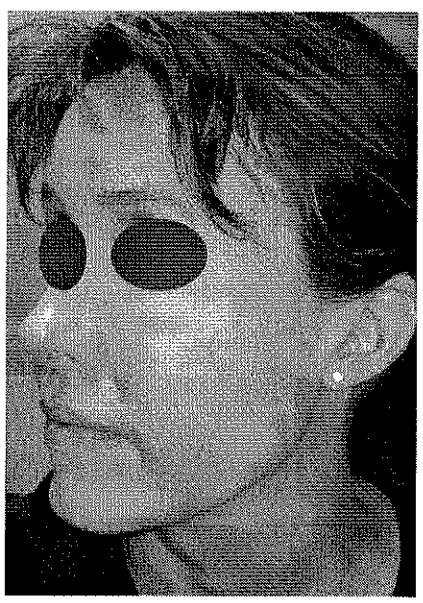
**Conclusions**

Aging is a highly complex, integrated biological process progressively affecting all cells and living tissues. Anti aging strategies have become more efficient after modern research allowed a better understanding of some of the mechanisms responsible for natural and induced cellular degeneration. Today non-invasive and micro-invasive procedures are widely preferred by the majority of patients seeking medical advice. Thermo-magnetic rejuvenation with MP2 technology has shown to induce collagen synthesis following fibroblastic activation by endothelial FGF-2, optimise collagen remodelling and extracellular matrix functional activities, increase tissue perfusion, activate effective heat shock protein thermal response able to induce a hormetic rejuvenation when periodic thermal treatments are performed. Treatment is safe and extremely easy to perform. Patient acceptability is high both during treatment sessions and immediately after. Biological response to thermo-magnetic technology is slow and considerable time is required to observe improvements. This is due to the physiologic cellular behaviour induced by sub-lethal stressful conditions which will ultimately contribute to improve their long-term endurance.

**Bibliography**

1.Alexiades-Armenakas M, Dover JS, Arndt KA. Unipolar versus bipolar radiofrequency treatment of rhytides and laxity using a mobile painless delivery method. Laser Surg Med 2008.40:446-453
2.Alexiades-Armenakas M, Dover JS, Arndt KA. Unipolar radiofrequency treatment to improve the appearance of cellulite. J Cosmet Laser Ther 2008; 10: 148–153.
3.Bersani F. et al. Intramembrane protein distribution in cell cultures is affected by 50 Hz pulsed magnetic fields. Bioelectromagnetics. 1997;18(7):463-469.
4.Biesman BS, Baker SS, Carruthers J, Silva HL, Holloman EL. Monopolar radiofrequency treatment of human eyelids: e prospective, multicenter, efficacy trial. Laser Surg Med 2006.38:890-898
5.Calderwood SK, Murshid A, Prince T. The Shock of Aging: Molecular Chaperones and the Heat Shock Response in Longevity and Aging–A Mini-Review Gerontology 2009; 55:550-558
6.Callaghan MJ, Chang El, Seiser N, Aarabi S, Ghali S, Kinnucan ER, Simon BJ, Gurtner GC. pulsed electomagnetic fields and diabetic wound healing by increasing endogenous FGF-2 release. Plast. Reconstr. Surg. 2007; 121:130-141
7.Dams SD, de Liefde-van Beest M, Nuijs AM, Oomens CWJ, Baaijens FPT. Pulsed heat shocks enhance procollageb type I and procollagen type III expression in human dermal fibroblasts. Skin Res Techn 2010; 16: 354-364
8.Fisher GH, Jacobson LG, Bernstein LJ, Kim KH, Geronemus RJ. Nonablative radiofrequency treatment of facial laxity. Dermatol Surg 2005;31:1237–1241
9.Fligiel SEG, Varani J, Datta SC, Kang S, Fisher GJ, and Voorhees JJ Collagen: Degradation in aged/photodamaged skin in vivo and after exposure to matrix metalloproteinase-1 in vitro. J Invest Dermatol 2003; 120:842-848
10.Franco W, Kothare A, Goldberg DJ. Controlled volumetric heating of subcutaneous adipose tissue using a novel radiofrequency technology. Laser Surg Med 2009.41:745-750
11.Franco W, Kothare A, Ronan SJ, Grekin RC, Timothy H. McCalmont TH. Hyperthermic injury to adipocyte cells by selective heating of subcutaneous fat with a novel radiofrequency device: Feasibility Studies. Laser Surg Med 2010.42:361-370
12.Goudarzi I, Hajizadeh S, Salmani ME, Abrari K. Pulsed magnetic fields accelerate wound healing in the skin of diabetic rats. Bioelectromagnetics. 2010 May;31(4):318-23.
13.Key DJ. Single-Treatment Skin Tightening By Radiofrequency and Long-Pulsed, 1064-nm Nd: YAG Laser Compared. Lasers Surg Med 2007;39:169–175
14.Kligman AM. Early destructive effect of sunlight on human skin. J Am Med Ass 1969;210:2377
15.Kohl E, Torezan LAR, Landthaler M, Szeimies RM Aesthetic effects of topical photodynamic therapy J Eur Acad Dermatol 2010; 24: 1261-1269
16.Kushikata N, Negishi K, Tezuka Y, Takeuchi K, Wakamatsu S. Non-Ablative Skin Tightening With Radiofrequency in Asian Skin. Lasers Surg Med 2005;36:92–97
17.Lavi R, Shainberg A, Shneyvays V, Hochauser E, Isaac A, Zinman T, Friedmann H, Lubart L. Detailed analysis of reactive oxygen species induced by visible light in various cell types. Lasers Surg Med 2010; 42:473–480
18.Lin HY, Lin YJ. In vitro effects of low frequency electromagnetic fields on osteoblast proliferation and maturation in an inflammatory environment. Bioelectromagnetics. 2011 Oct;32(7):552-60.
19.Man D, Man B, Plosker H. The influence of permanent magnetic field therapy on wound healing in suction lipectomy patients: A double blind study. Plast. Reconstr. Surg. 1999; 104(7):2261-2266
20.Manuskiatti W, Wachirakaphan C, Lektrakul N, Varothai S. Circumference reduction and cellulite treatment with a TriPollar radiofrequency device: a pilot study. J Eur Acad Dermatol 2009;23: 820-827
21.Marini L SPF-RR sequential photothermal fractional resurfacing and remodelling with the variable pulsed Er:YAG laser and scanner-assited Nd:YAG laser J Cosm Laser Ther 2009; 4:202-211
22.Mc Kinney B. The influence of permanent magnetic field therapy on wound healing in suction lipectomy patients: A double blind study. Discussion. Plast. Reconstr. Surg. 1999; 104(7):2267-2268
23.Mimeault M, Batra SK. Recent advances on skin-resident stem/progenitor cell functions in skin

regeneration, aging and cancers and novel anti-aging and cancer therapies J Cell Mol Med 2010; 14(1-2):116-134
24.Mlosek RK, Wozniak W, Malinowska S, Lewandowski M, Nowicki A. The effectiveness of anticellulite treatment using tripolar radiofrequency monitored by classic and high-frequency ultrasound. J Eur Acad Dermatol 2011;25: doi: 10.1111/j.1468-3083.2011.04148.x
25.Narins R, Tope WD, Pope K, Ross EV. Overtreatment effects associated with a radiofrequency tissue tightening device: rare, preventable, and correctable with subcision and autologous fat transfer. Dermatol Surg 2006;32: 115-124
26.Rattan SIS, Eskildsen-Helmond YEG, Beedholm R. Molecular mechanisms of anti-aging hormetic effects of mild heat stress on human cells. Nonlinearity Biol Toxicol Med 2004; 2: 105-116
27.Rattan SIS, Gonzalez-Dosal R, Nielsen ER, Kraft DC, Weibel J, Kahns S. Slowing down aging from within: mechanistic aspects of anti-aging hormetic effects of mild heat stress on human cells. Acta Biochim Pol 2004; 51(2):481-492
28.Roland D, Ferder M, Kothuru R, Faierman T, Strauch B. Effects of pulsed magnetic energy on a microsurgically transferred vessel. Plast. Reconstr. Surg. 2000; 105(4):1371-1374
29.Ryaby JT Clinical effects of electromagnetic and electric fields on fracture healing. Clin. Ortop. Relat. Res. 1998; 355(suppl.): S205
30.Sellheyer K. Pathogenesis of solar elastosis: synthesis or degradation? J Cutan Pathol 2003; 30:123-127
31.Strauch B, Herman C, Dabb R, Ignarro LJ, Pilla AA. Evidence-based use of pulsed electromagnetic field therapy in clinical plastic surgery. Aesthet Surg J. 2009 Mar-Apr;29(2):135-143.
32.Tepper OM, Callahan MJ, Chang EI, et al. Electomagnetic fields increase in vitro and in vivo angiogenesis through endothelial release of FGF-2. F.A.S.E.B. J. 2004; 18:1231
33.Varani JJ, Dame MK, Rittie L, Fligiel SEG, Kang S, Fisher GJ, Voorhees JJ. Decreased collagen production in chronologically aged skin: roles of age-dependent alteration in fibroblast function and defective mechanical stimulation. Am J Pathol 2006; 168 (6): 1861-1868
34.Varani JJ, Schuger L, Dame MK, Leonard C,Fligiel SEG, Kang S, Fisher GJ, Voorheesz JJ. Reduced fibroblast interaction with intact collagen as a mechanism for depressed collagen synthesis in photodamaged Skin. J Invest Dermatol 2004; 122:1471–1479
35.Warren R, Garstein V et al. Age, sunlight, and facial skin. A histologic and quantitative study. J Am Acad Dermatol 1991; 25: 751
36.Weber RV, Navarro A, Wu JK, Yu HL, Strauch B. Pulsed magnetic fields applied to a transferred arterial loop support the rat groin composite flap. Plast. Reconstr. Surg. 2004; 114(5):1185-1189
37.Weiss RA, Weiss MA, Munavalli G, Beassley KL. Monopolar radiofrequency facial tightening: A retrospective analysis of efficacy and safety in over 600 treatments. J Drug Dermatol 2006;5(8): 707-712
38.Willey A, Kilmer S, Newman J, Renton B, Hantash B, Krishna S, McGill S, Berube D. Elastometry and clinical results after bipolar radiofrequency treatment of skin. Dermatol Surg 2010; 36: 877-884



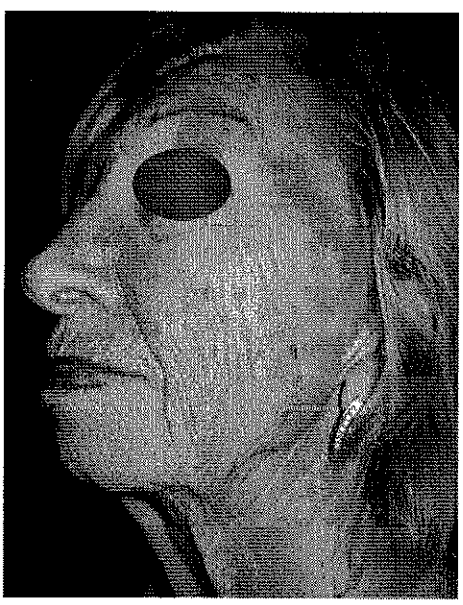


**Fig. 1** Fitzpatrick phototype 1-2 young, functionally active skin (left) and deteriorated chrono- + photo-aged skin (right)

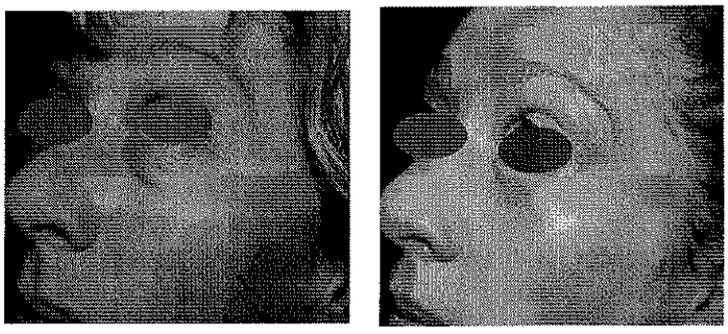


**Fig. 2** Full face conventional $CO_2$ laser resurfacing: pre-op clinical image (left) and post-op clinical result at 120 days (right)

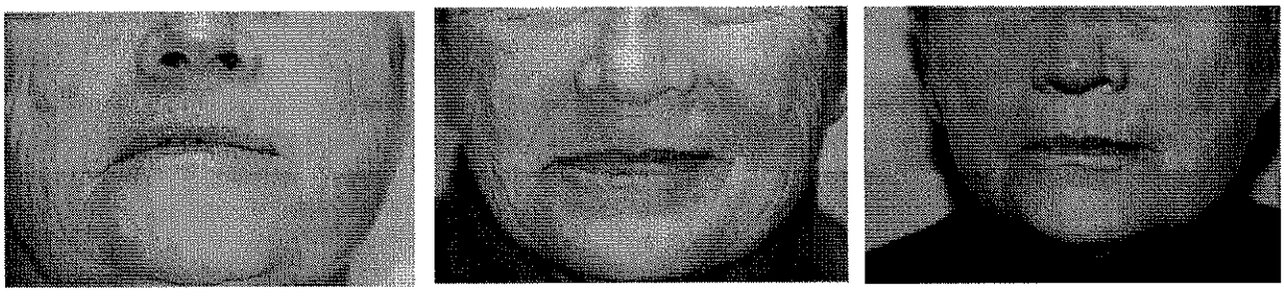


**Fig. 3** Single photo-thermal rejuvenation treatment with sequentially combined multiple laser wavelengths according to SPF-RR technique: 1064nm short and long pulse volumetric heating followed by 2940nm Er:YAG fractional resurfacing. Pre-op image (left) and post-op clinical results at 30 days (center), and 90 days (right)

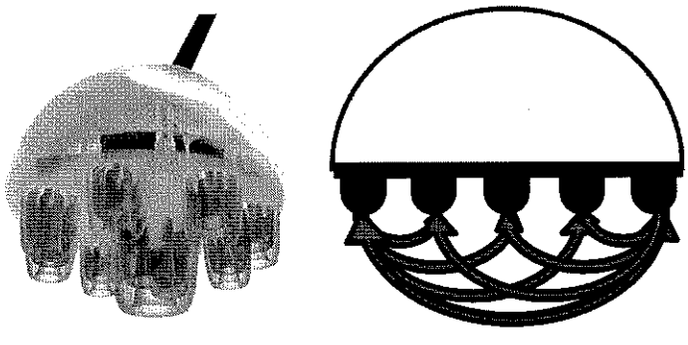


**Fig. 4** Multipolar combination of pulsed magnetic fields (left) and matrix-pattern RF (right) within the same effector handpiece as proposed by $MP_2$ technology. Multipolar electrode array is able to induce a smooth, highly tolerable, three-dimensional volumetric tissue heating.

**Typical Sources of Electromagnetic Fields**

| Frequency range | Frequencies | Some examples of exposure sources |
|---|---|---|
| **static** | 0 Hz | VDU (video displays); MRI and other diagnostic/scientific intrumentation; Industrial electrolysis; Welding devices |
| **ELF** | 0 - 300 Hz | Powerlines; Domestic distribution lines, Domestic appliances; Electric engines in cars, train, and tramway; welding devices |
| **IF** | 300 Hz – 100 kHz | VDU; Anti theft device in shops, hand free access control systems, card readers, and metal detectors; MRI; Welding devices |
| **RF** | 100 kHz – 300 GHz | Mobile telephony; Broadcasting and TV; Microwave oven; Radar, portable and stationary radio transceivers, personal mobile radio, MRI |

**Fig. 8** Table illustrating some commonly encountered electromagnetic fields induced by modern technologies

Time-Dependent Reduction in Adipocyte Viability

| Exposuretime (minutes) | Temperature (°C) | | | | |
|---|---|---|---|---|---|
| | 45 | 50 | 55 | 60 | 65 |
| 1 | 89 ± 9 | 20 ± 3 | 15 ± 1 | 17 ± 2 | |
| 2 | | 16 ± 2 | 16 ± 1 | 17 ± 2 | 11 ± 4 |
| 3 | 40 ± 19 | | 13 ± 2 | | 7 ± 7 |

**Fig. 5** Table illustrating time-dependent, in-vitro adipocyte viability response to thermal exposures 72 hours post-treatment.. Deep, trans-epidermal RF volumetric heating (working range of 45-50 °C) can remodel subcutaneous localized adiposities by selectively decreasing adipocyte mass and number. Modified from: Franco *et al.* **Hyperthermic Injury to Adipocyte Cells by Selective Heating of Subcutaneous Fat With a Novel Radiofrequency Device: Feasibility Studies.** *Laser Surg Med.*2010; 42:361-370

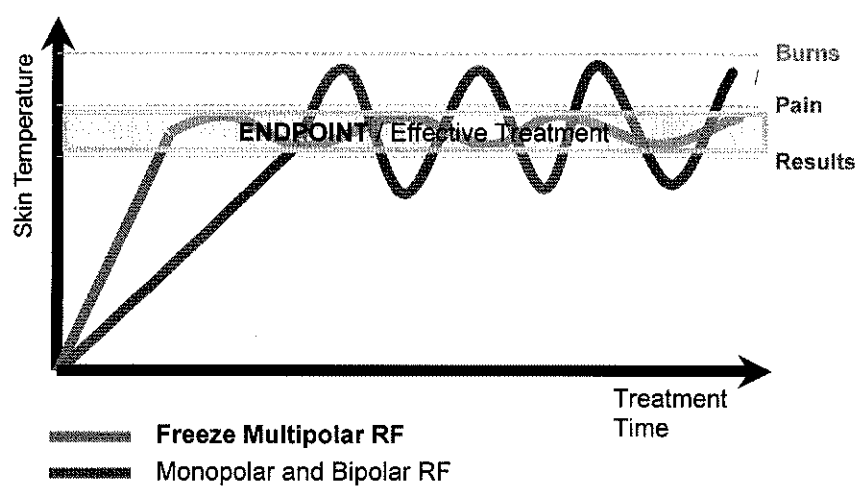


**Fig. 6** Graphic scheme illustrating different RF-induced skin temperature variations produced by different RF technologies. Multipolar RF with matrix pattern polar activation is able to reach effective volumetric treatment temperatures faster than monopolar and bipolar technologies. Multipolar RF can keep tissue temperature within effective treatment range more constantly than other RF technologies avoiding excessive and insufficient thermal variations during energy delivery.

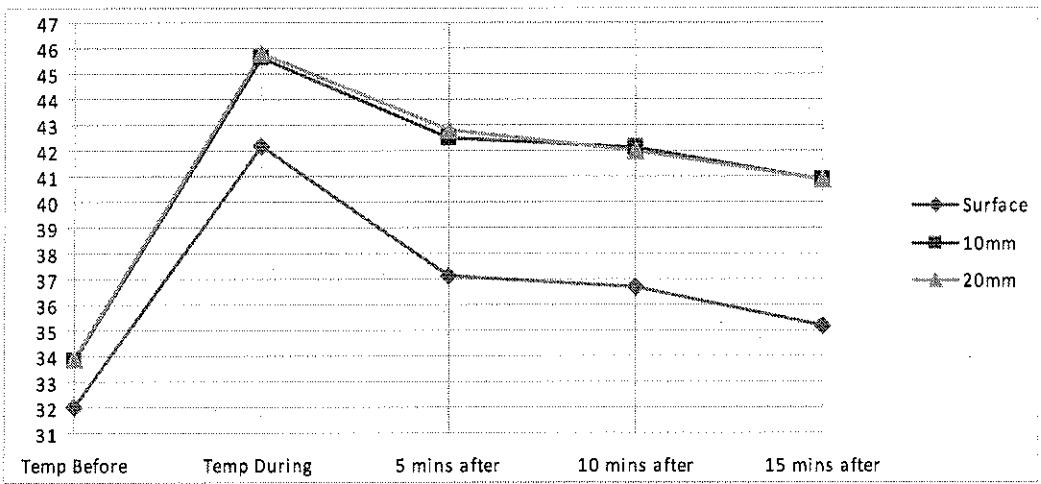



**Fig. 7** Surface and sub-surface skin tissue temperature readings during, and immediately after trans-epidermal multipolar RF treatment at 5, 10, and 15 minutes. Thermocouple needles were positioned at 10 and 20mm of depth. Courtesy of Joseph Ajaka, MD

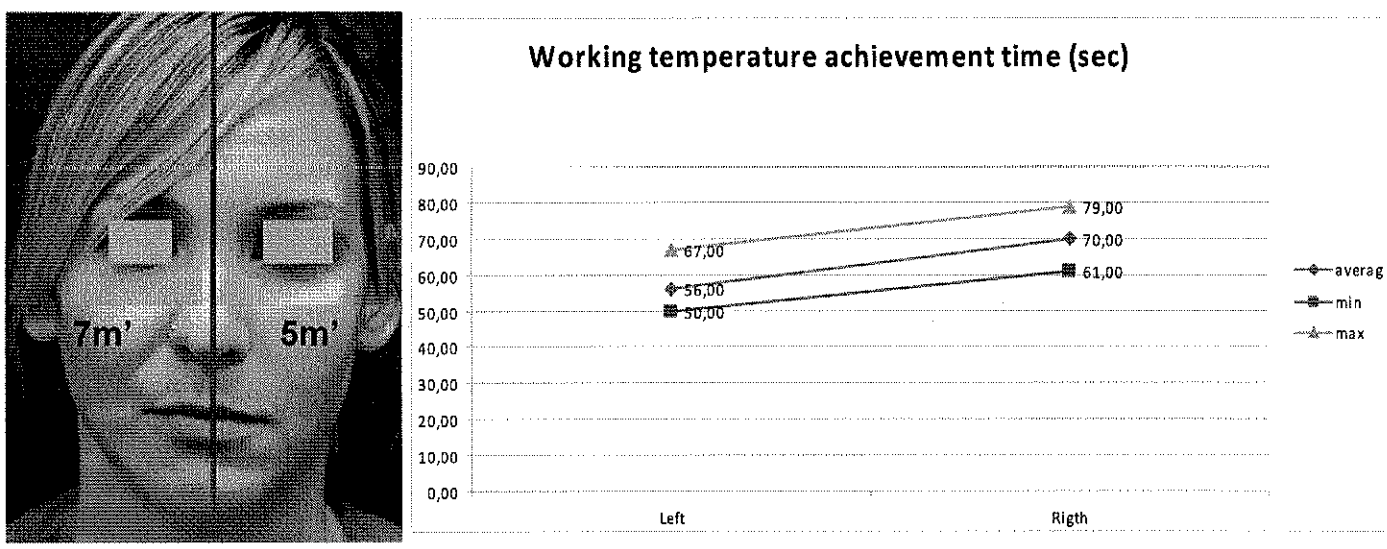



**Fig. 9** Split face study with different $MP_2$ technology treatment times. Effective working temperatures (40.8 ± 0.5 °C) measured by non-contact skin surface IR thermometry was maintained for 7 minutes on the R cheek and 5 minutes on the L cheek. Working temperature achievement time since beginning of MP2 tissue delivery (right)

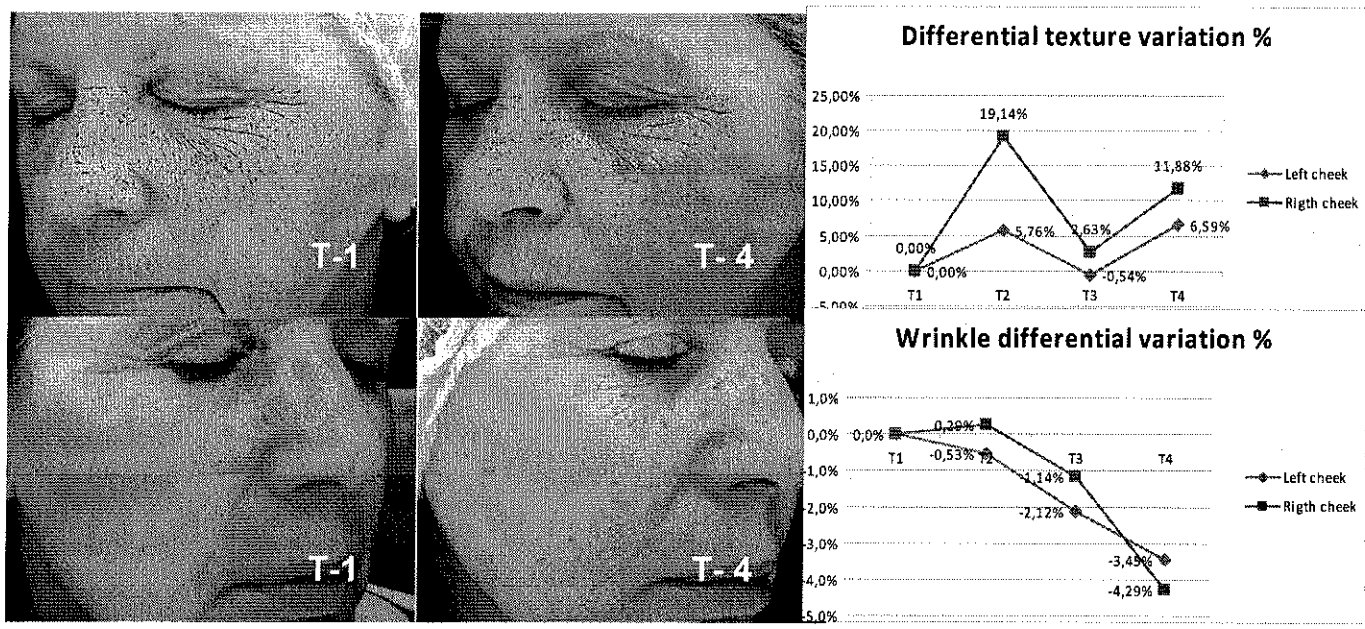



**Fig. 11** Computerized analysis of texture irregularities and wrinkle count by Visia Facial Complexion Analysis and corresponding graphs indicating a consistently significant major improvement of R treated cheek where MP2 working energy was applied two minutes longer than L cheek

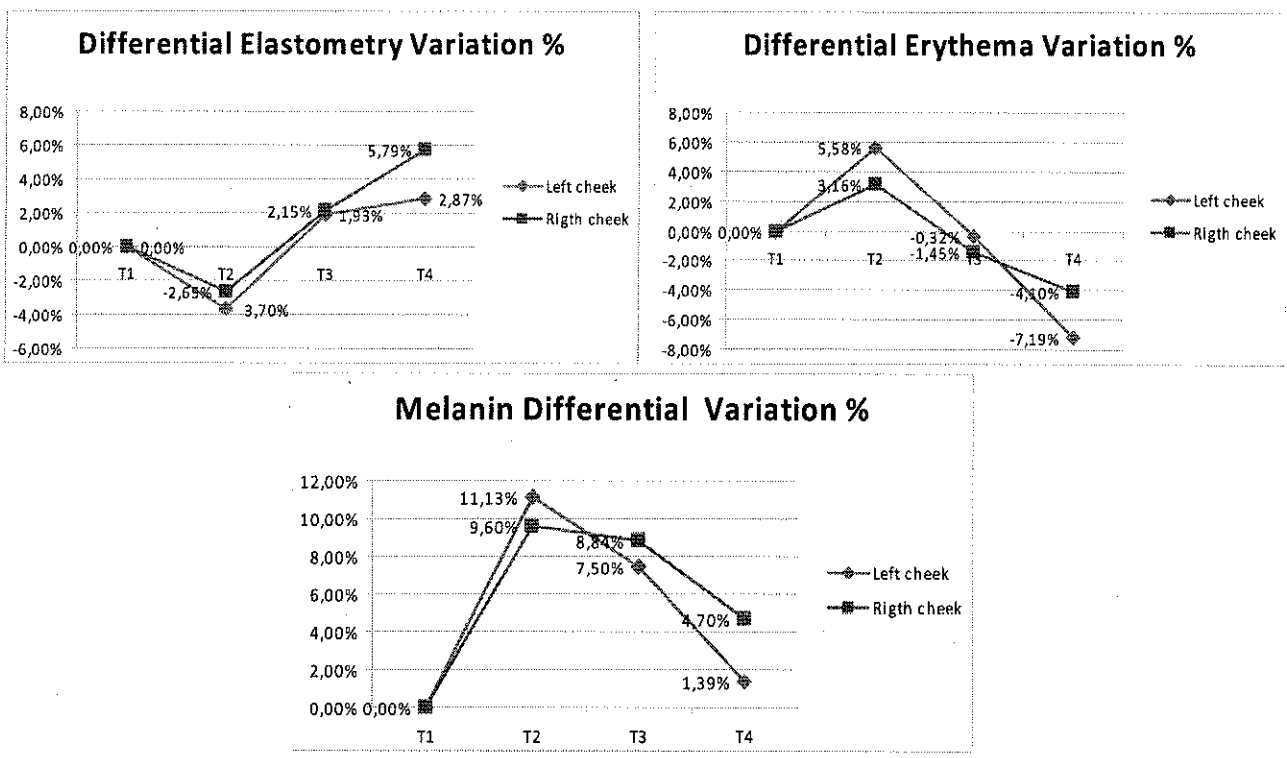



**Fig. 10** Elastometry (top left), erythema (top right), and melanin variations (center) measured on treated areas after $MP_2$ treatment. Elastometry values decreased at T-2 and progressively increased at T-3 and T-4, predominantly on the R cheek where 7 min continuous thermo-magnetic treatment was performed . Erythema and melanin values increased at T-2 and progressively decreased at T-3 and T-4 with slightly more persistence on R cheeks.

Journal of Orthopaedic Translation (2017) 9, 60—68

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: http://ees.elsevier.com/jot

REVIEW ARTICLE

# Pulsed electromagnetic field applications: A corporate perspective

**Erik I. Waldorff, Nianli Zhang, James T. Ryaby***

*Orthofix Inc., Lewisville, TX, USA*

Received 1 February 2017; received in revised form 24 February 2017; accepted 27 February 2017
Available online 31 March 2017

**KEYWORDS**
electromagnetic field;
electromagnetic wave;
magnetic field therapies

**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

* Corresponding author. Orthofix Incorporated, 3451 Plano Parkway, Lewisville, TX 75056, USA.
*E-mail address:* jamesryaby@orthofix.com (J.T. Ryaby).

http://dx.doi.org/10.1016/j.jot.2017.02.006

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

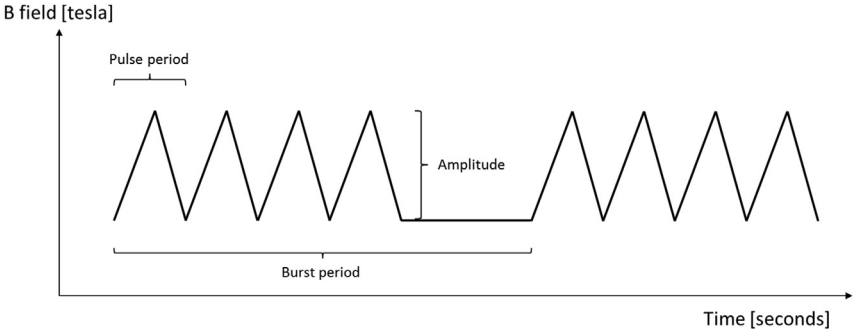



**Figure 1** Representation of the Orthofix Pulsed electromagnetic field signal.

**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.

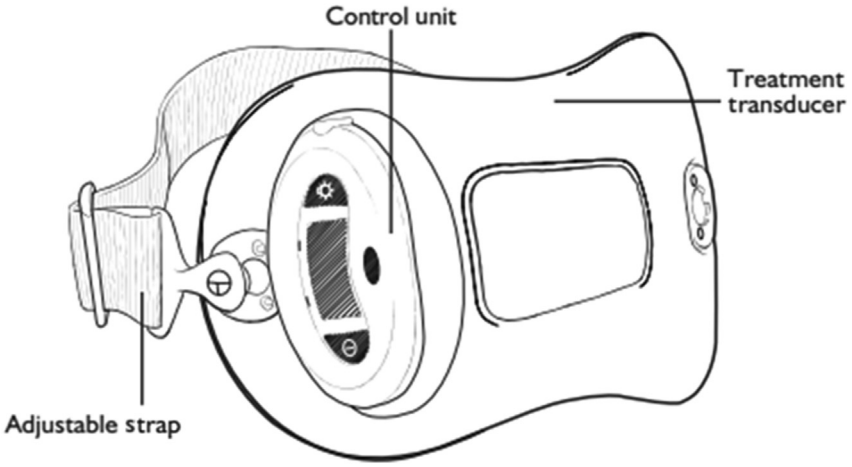



**Figure 2** Physio-Stim pulsed electromagnetic field (PEMF) device.

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

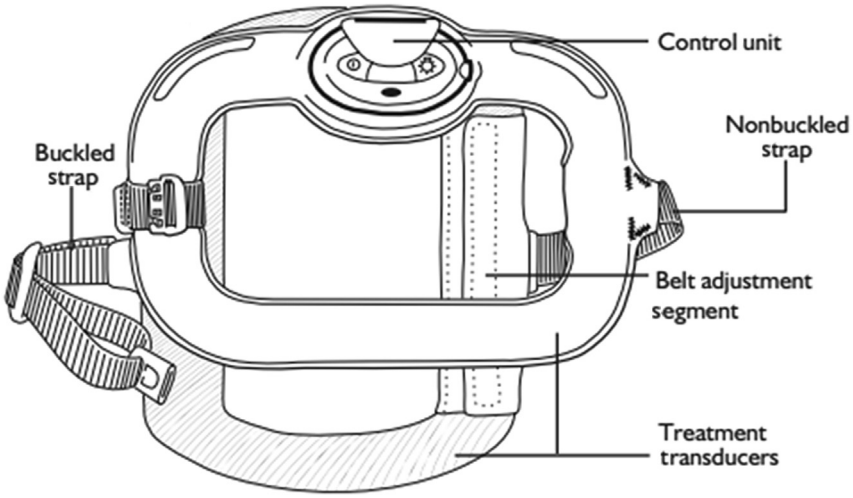



**Figure 3** Spinal-Stim pulsed electromagnetic field (PEMF) device.

(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.

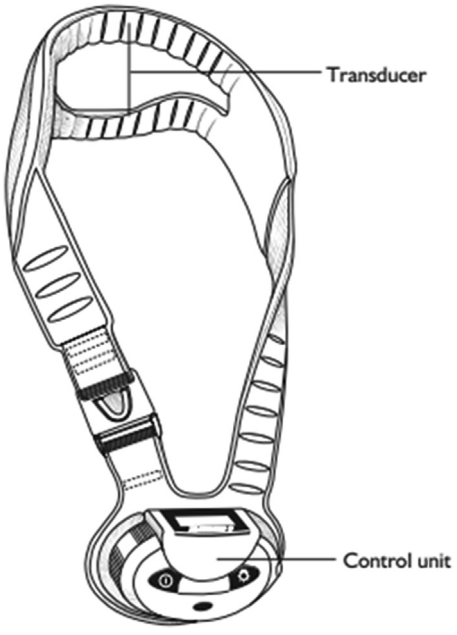



**Figure 4** Cervical-Stim pulsed electromagnetic field (PEMF) device.

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

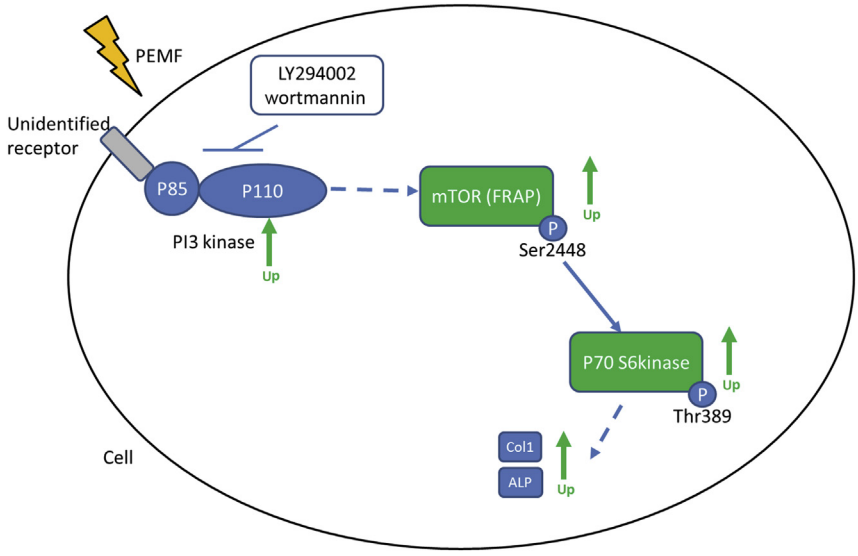



**Figure 5** Model of mTOR pathway activation following short-term PEMF exposure (minutes) and immediate examinations. Adapted from Patterson et al [14]. mTOR — mechanistic target of rapamycin; PEMF — pulsed electromagnetic field; PI3 kinase — phosphatidylinositide 3-kinase; P85 — regulatory subunit 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)

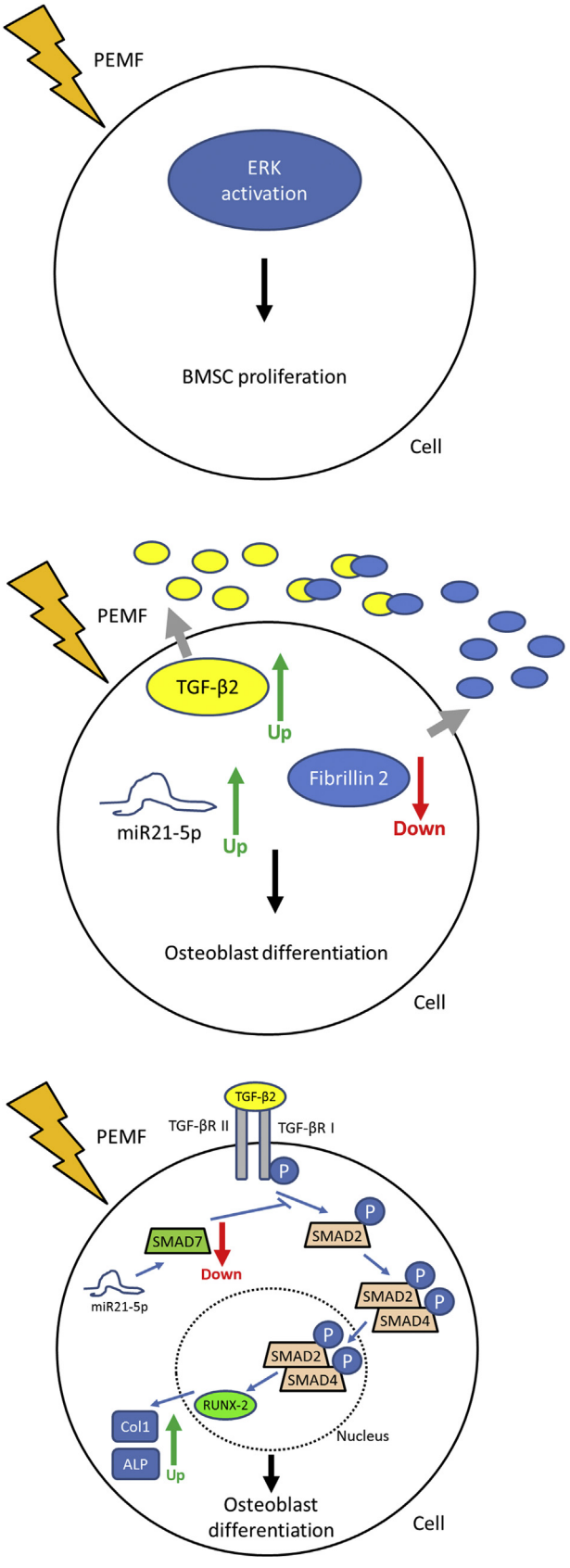



**Figure 6** Model of TGF-β pathway activation following long-term PEMF exposure (days). Adapted from Selvamurugan et al [19]. TGF-β — transforming growth factor beta; PEMF — pulsed electromagnetic field; ERK — extracellular signal—regulated kinase; BMSC — bone marrow stromal cells; TGF-β2 — transforming 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.

## References


[1] Markov MS. Pulsed electromagnetic field therapy: history, state of the art and future. Environmentalist 2007;27:465—74.

[2] Markov MS. Magnetic and electromagnetic field therapy: basic principles of application for pain relief. In: Rosch PJ, Markov MS, editors. Bioelectromagnetic medicine. New York: Marcel Dekker; 2004. p. 251—64.

[3] Bassett CA. Fundamental and practical aspects of therapeutic uses of pulsed electromagnetic fields (PEMFs). Critical Rev Biomed Eng 1989;17:451—529.

[4] Pilla AA. Pulsed electromagnetic fields: From signaling to healing. In: Markov M, editor. Electromagnetic fields in biology and medicine. Boca Raton, Florida, USA: CRC Press; 2015. p. 29—47.

[5] Carpenter LL, Janicak PG, Aaronson ST, Boyadjis T, Brock DG, Cook IA, et al. Transcranial magnetic stimulation (TMS) for major depression: a multisite, naturalistic, observational study of acute treatment outcomes in clinical practice. Depress Anxiety 2012;29:587—96.

[6] Thomas AW, Graham K, Prato FS, McKay J, Forster PM, Moulin DE, et al. A randomized, double-blind, placebo-controlled clinical trial using a low-frequency magnetic field in the treatment of musculoskeletal chronic pain. Pain Res Manag 2007;12:249—58.

[7] Nicolakis P, Kollmitzer J, Crevenna R, Bittner C, Erdogmus CB, Nicolakis J. Pulsed magnetic field therapy for osteoarthritis of the knee—a double-blind sham-controlled trial. Wien Klin Wochenschr 2002;114:678—84.

[8] Markov MS. Benefit and hazard of electromagnetic fields. In: Markov M, editor. Electromagnetic fields in biology and medicine. Boca Raton, Florida, USA: CRC Press; 2015. p. 15—28.

[9] Garland DE, Moses B, Salyer W. Long-term follow-up of fracture nonunions treated with PEMFs. Contemp Orthop 1991;22:295—302.

[10] Mooney V. A randomized double-blind prospective study of the efficacy of pulsed electromagnetic fields for interbody lumbar fusions. Spine 1990;15:708—12.

[11] Mooney V. Pulsed electromagnetic fields: an adjunct to interbody spinal fusion surgery in the high risk patient. Surg Technol Int 1993;2:405—10.

[12] Simmons Jr JW, Mooney V, Thacker I. Pseudarthrosis after lumbar spine fusion: nonoperative salvage with pulsed electromagnetic fields. Am J Orthop 2004;33:27—30.

[13] Foley KT, Mroz TE, Arnold PM, Chandler Jr HC, Dixon RA, Girasole GJ, et al. Randomized, prospective, and controlled clinical trial of pulsed electromagnetic field stimulation for cervical fusion. Spine J 2008;8:436—42.

[14] Patterson TE, Sakai Y, Grabiner MD, Ibiwoye M, Midura RJ, Zborowski M, et al. Exposure of murine cells to pulsed electromagnetic fields rapidly activates the mTOR signaling pathway. Bioelectromagnetics 2006;27:535—44.

[15] Schnoke M, Midura RJ. Pulsed electromagnetic fields rapidly modulate intracellular signaling events in osteoblastic cells: comparison to parathyroid hormone and insulin. J Orthop Res 2007;25:933—40.

[16] Partridge NC, He Z, Selvamurugan N. Microarray analysis of pulsed electromagnetic field (PEMF) stimulatory effects on human bone marrow stromal cells. Houston, TX, USA: The American Society for Bone and Mineral Research (ASBMR); September 12—15, 2014.

[17] He Z, Selvamurugan N, Nakatani T, Waldorff EI, Zhang N, Ryaby JT, et al. Pulsed electromagnetic fields (PEMF) enhance osteoblastic differentiation of human bone marrow stromal cells by activation of microRNA21 expression and the TGF-β signaling pathway. Seattle, WA, USA: The American Society for Bone and Mineral Research (ASBMR); 2015.

[18] He Z, Selvamurugan N, Siddiqui J, Waldorff EI, Ryaby JT, Partridge N. Pulsed electromagnetic field regulation of TGF-beta pathway and microRNA21 in differentiating human bone marrow stromal cell towards osteoblasts. Las Vegas, NV, USA: Orthopaedic Research Society (ORS); 2015.

[19] Selvamurugan N, He Z, Rifkin D, Dabovic B, Partridge NC. Pulsed electromagnetic field regulates MicroRNA21 expression to activate TGF-ß signaling in human bone marrow stromal cells to enhance osteoblast differentiation. Stem Cells Int 2017 (manuscript 2450327, accepted for publication on February 12, 2017).

[20] Selvamurugan N, Kwok S, Vasilov A, Jefcoat SC, Partridge NC. Effects of BMP-2 and pulsed electromagnetic field (PEMF) on rat primary osteoblastic cell proliferation and gene expression. J Orthop Res 2007;25:1213—20.

[21] Partridge N. Pulsed electromagnetic field stimulates human osteoblastic cells and inhibits human osteoclastic cells. New Orleans, LA, USA: North American Spine Society (NASS); 2013.

[22] Partridge N, He Z, Wang X, Selvamurugan N. Pulsed electromagnetic field stimulates human osteoblastic cells and inhibits human osteoclastic cells. Hong Kong, China: Global Spine Congress (GSC); 2013.
[23] Partridge N, He Z. Pulsed electromagnetic field stimulates human osteoblastic cells and inhibits human osteoclastic cells. Baltimore, MD, USA: American Society for Bone and Mineral Research (ASBMR); 2013.
[24] He Z, Selvamurugan N, Zhang N, Waldorff EI, Ryaby JT, Partridge N. RNA-Seq analysis reveals regulation of human osteoclastogenesis by pulsed electromagnetic field. Orlando, FL, USA: Orthopaedic Research Society (ORS); 2016.
[25] Ibiwoye MO, Powell KA, Grabiner MD, Patterson TE, Sakai Y, Zborowski M, et al. Bone mass is preserved in a critical-sized osteotomy by low energy pulsed electromagnetic fields as quantitated by in vivo micro-computed tomography. J Orthop Res 2004;22:1086—93.
[26] Midura RJ, Ibiwoye MO, Powell KA, Sakai Y, Doehring T, Grabiner MD, et al. Pulsed electromagnetic field treatments enhance the healing of fibular osteotomies. J Orthop Res 2005;23:1035—46.
[27] Androjna C, Fort B, Zborowski M, Midura RJ. Pulsed electromagnetic field treatment enhances healing callus biomechanical properties in an animal model of osteoporotic fracture. Bioelectromagnetics 2014;35:396—405.
[28] Midura RJ, Androjna C, Zborowski M. The effects of bone growth stimulator treatments on vertebral bone mass in an osteoporosis model. New Orleans, LA, USA: North American Spine Society (NASS); 2013.
[29] Androjna C, Waldorff EI, Ryaby JT, Zborowski M, Midura RJ. The effects of pulsed electromagnetic field (PEMF) and/or bisphosphonate treatments on vertebral bone mass in a long-term osteoporosis model. Houston, TX, USA: American Society for Bone and Mineral Research (ASBMR); 2014.
[30] Androjna C, Waldorff EI, Zhang N, Ryaby JT, Zborowski M, Midura RJ. Optimizing pulsed electromagnetic field (PEMF) signals to reduce bone loss in the ovariectomized (OVX) Rat. Seattle, WA, USA: American Society for Bone and Mineral Research (ASBMR); 2015.
[31] Androjna C, Waldorff EI, Ryaby JT, Zborowski M, Midura RJ. Optimizing pulsed electromagnetic field (PEMF) signals to reduce bone loss associated with osteoporosis. San Diego, CA, USA: Orthopaedic Research Society (ORS); 2017.
[32] Liu M, Lee C, Laron D, Zhang N, Waldorff EI, Ryaby JT, et al. Role of pulsed electromagnetic fields (PEMF) on tenocytes and myoblasts—potential application for treating rotator cuff tears. J Orthop Res 2016. http://dx.doi.org/10.1002/jor.23278.
[33] Tucker JJ, Cirone JM, Morris TR, Nuss CA, Huegel J, Waldorff EI, et al. Pulsed electromagnetic field therapy improves tendon-to-bone healing in a rat rotator cuff repair model. J Orthop Res 2016. http://dx.doi.org/10.1002/jor.23333.
[34] Huegel J, Choi D, Nuss CA, Minnig MC, Tucker JJ, Hillin CD, et al. Effects of pulsed electromagnetic field therapy at different frequencies and durations on rotator cuff tendon-to-bone healing in a rat model. San Diego, CA: Orthopaedic Research Society (ORS); 2017.
[35] Miller SL, Coughlin DG, Waldorff EI, Ryaby JT, Lotz JC. Pulsed electromagnetic field (PEMF) treatment reduces expression of genes associated with disc degeneration in human intervertebral disc cells. Spine J 2016;16:770—6.
[36] Tang X, Coughlin DG, Waldorff EI, Ryaby JT, Alliston T, Lotz JC. Dynamic imaging demonstrates the effect of pulsed electromagnetic fields (PEMF) treatment on IL-6 transcription in bovine nucleus pulposus cells. San Francisco, CA, USA: The International Society for the Study of the Lumbar Spine (ISSLS); 2015.
[37] Tang X, Coughlin DG, Waldorff EI, Ryaby JT, Alliston T, Lotz JC. Dynamic tracking of IL-6 transcription in nucleus pulposus cells in vitro. Las Vegas, NV, USA: Orthopaedic Research Society (ORS); 2015.
[38] Tang X, Coughlin DG, Waldorff EI, Zhang N, Ryaby JT, Alliston T, et al. NF-kB involved in PEMF treatment effects on pro-inflammatory cytokine IL-6 expression in nucleus pulposus. San Diego, CA: Orthopaedic Research Society (ORS); 2017.
[39] Tang X, Coughlin DG, Ouyang A, Liebenbeng E, Dudli S, Waldorff EI, et al. Pulsed electromagnetic fields (PEMF) reduce acute inflammation in the injured rat intervertebral disc. San Diego, CA: Orthopaedic Research Society; 2017.
[40] Tang X, Coughlin DG, Ouyang A, Liebenbeng E, Dudli S, Waldorff EI, et al. Anti-inflammatory effects of pulsed electromagnetic fields (PEMF) treatment in rat intervertebral disc degeneration model. Xian, China: International Combined Orthopaedic Research Societies (ICORS); 2016.
[41] Zborowski M, Kligman B, Midura RJ, Wolfman A, Patterson TE, Ibiwoye M, et al. Decibel attenuation of pulsed electromagnetic field (PEMF) in blood and cortical bone determined experimentally and from the theory of ohmic losses. Ann Biomed Eng 2006;34:1030—41.
[42] Zborowski M, Midura RJ, Wolfman A, Patterson T, Ibiwoye M, Sakai Y, et al. Magnetic field visualization in applications to pulsed electromagnetic field stimulation of tissues. Ann Biomed Eng 2003;31:195—206.
[43] Zborowski M, Androjna C, Waldorff EI, Midura AJ. Comparison of therapeutic magnetic stimulation with electric stimulation of spinal column vertebrae. IEEE Trans Magn 2015;51:5001009.
[44] Parker R, Markov M. An analytical design techniques for magnetic field therapy devices. Environmentalist 2011;31:155—60.

Cochrane Library

Cochrane Database of Systematic Reviews

# Electromagnetic fields for treating osteoarthritis

Cochrane Systematic Review - **Intervention** | Version published: 14 December 2013 see what's new
https://doi.org/10.1002/14651858.CD003523.pub2

New search


Used in 3 guidelines View article information

Shasha Li | Bo Yu | Dong Zhou | Chengqi He | Qi Zhuo | Jennifer M Hulme
View authors' declarations of interest

Collapse all Expand all

## Abstract

*Available in* English | Español | 日本語 | 한국어

### Background

This is an update of a Cochrane review first published in 2002. Osteoarthritis is a disease that affects the synovial joints, causing degeneration and destruction of hyaline cartilage and subchondral bone. Electromagnetic field therapy is currently used by physiotherapists and may promote growth and repair of bone and cartilage. It is based on principles of physics which include Wolff's law, the piezoelectric effect and the concept of streaming potentials.

### Objectives

To assess the benefits and harms of electromagnetic fields for the treatment of osteoarthritis as compared to placebo or sham.

### Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 9), PreMEDLINE for trials published before 1966, MEDLINE from 1966 to October 2013, CINAHL and PEDro up to and including October 2013. Electronic searches were complemented by handsearches.

### Selection criteria

Randomised controlled trials of electromagnetic fields in osteoarthritis, with four or more weeks treatment duration. We included papers in any language.

## Data collection and analysis

Two review authors independently assessed studies for inclusion in the review and resolved differences by consensus with a third review author. We extracted data using pre-developed data extraction forms. The same review authors assessed the risk of bias of the trials independently using the Cochrane 'Risk of bias' tool. We extracted outcomes for osteoarthritis from the publications according to Outcome Measures in Rheumatology Clinical Trials (OMERACT) guidelines. We expressed results for continuous outcome measures as mean difference (MD) or standardised mean difference (SMD) with 95% confidence interval (CI). We pooled dichotomous outcome measures using risk ratio (RR) and calculated the number needed to treat (NNT).

## Main results

Nine studies with a total of 636 participants with osteoarthritis were included, six of which were added in this update of the review. Selective outcome reporting was unclear in all nine included studies due to inadequate reporting of study design and conduct, and there was high risk of bias for incomplete outcome data in three studies. The overall risk of bias across the nine studies was low for the other domains.

Participants who were randomised to electromagnetic field treatment rated their pain relief 15.10 points more on a scale of 0 to 100 (MD 15.10, 95% CI 9.08 to 21.13; absolute improvement 15%) after 4 to 26 weeks' treatment compared with placebo. Electromagnetic field treatment had no statistically significant effect on physical function (MD 4.55, 95% CI -2.23 to 11.32; absolute improvement 4.55%) based on the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scale from 0 to 100 after 12 to 26 weeks' treatment. We also found no statistically significant difference in quality of life on a scale from 0 to 100 (SMD 0.09, 95% CI -0.36 to 0.54; absolute improvement 0.09%) after four to six weeks' treatment, based on the SF-36. No data were available for analysis of radiographic changes. Safety was evaluated in four trials including up to 288 participants: there was no difference in the experience of any adverse event after 4 to 12 weeks of treatment compared with placebo (RR 1.17, 95% CI 0.72 to 1.92). There was no difference in participants who withdrew because of adverse events (measured in one trial) after four weeks of treatment (RR 0.90, 95% CI 0.06 to 13.92). No participants experienced any serious adverse events.

## Authors' conclusions

Current evidence suggests that electromagnetic field treatment may provide moderate benefit for osteoarthritis sufferers in terms of pain relief. Further studies are required to confirm whether this treatment confers clinically important benefits in terms of physical function and quality of life. Our conclusions are unchanged from the previous review conducted in 2002.

# Plain language summary

*Available in* **English** | Español | Hrvatski | 日本語 | 한국어 | தமிழ்

**Electromagnetic fields for the treatment of osteoarthritis**

**Review question**

We conducted a review of the effect of electromagnetic fields on osteoarthritis. We found nine studies with 636 people.

**Background: what is osteoarthritis and what are electromagnetic fields?**

Osteoarthritis is the most common form of arthritis that can affect the hands, hips, shoulders and knees. In osteoarthritis, the cartilage that protects the ends of the bones breaks down and causes pain and swelling.

An electromagnetic field is the invisible force that attracts things to magnets. This invisible attraction can be created using an electrical current that may affect the cartilage around the joints. In osteoarthritis, electromagnetic fields are a kind of therapy using electrical currents applied to the skin around the joints. Small machines or mats can be used to deliver electromagnetic fields to the whole body or to certain joints. A doctor or physiotherapist can perform the therapy and some machines can be used at home.

**Study characteristics**

After searching for all relevant studies up to October 2013, we found nine studies that reviewed the effect of electromagnetic field treatment compared to a sham or fake treatment in 636 adults with osteoarthritis for a duration of 4 to 26 weeks.

**Key results**

**Pain (on a 0 to 100 scale; higher scores mean worse or more severe pain)**

- Electromagnetic fields probably relieve pain in osteoarthritis.

- People who received electromagnetic field treatment experienced pain relief of 15 points more compared with people who received fake treatment (15% improvement).

- People who received electromagnetic field treatment rated their pain to be 26 points lower on a scale of 0 to 100.

- People who received fake treatment rated their pain to be 11 points lower on a scale of 0 to 100.

**Physical function**

- Electromagnetic fields may improve physical function but this may have happened by chance.

**Overall health and well-being**

- Electromagnetic fields probably make no difference to overall health and well-being.

**Side effects**

- Electromagnetic fields probably make no difference to whether people have side effects or stop taking the treatment because of side effects, but this may have happened by chance.

We do not have precise information about side effects and complications. This is particularly true for rare but serious side effects. Possible side effects could include skin rash and aggravated pain.

**X-ray changes**

There was no information available on whether electromagnetic fields show any improvement to a joint with osteoarthritis on an X-ray.

**Quality of the evidence**

- Electromagnetic fields probably improve pain and make no difference to overall health and well-being and side effects. This may change with further research.

- Electromagnetic fields may improve physical function. This is very likely to change with further research.

## Authors' conclusions

### Implications for practice

The current, limited evidence shows a moderate clinically important benefit of electromagnetic field treatment for the relief of pain in the treatment of knee or cervical osteoarthritis.

### Implications for research

More trials are needed in this field. New trials should compare different treatments and provide an accurate description of the length of treatment, dosage and the frequency of the applications. Larger trials are needed to confirm whether the statistically significant results shown in the trials included in this review confer clinically important benefits.

## Summary of findings

**Open in table viewer**

**Summary of findings for the main comparison.** Electromagnetic field treatment compared to placebo for the treatment of osteoarthritis

**Electromagnetic field treatment compared to placebo for the treatment of osteoarthritis**

**Patient or population:** patients with osteoarthritis
**Settings:** out-patients recruited from healthcare facilities in Australia, Denmark, UK and the US
**Intervention:** electromagnetic field treatment
**Comparison:** placebo

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | No of participants (studies) | Quality of the evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Placebo | Electromagnetic field treatment | | | | |
| **Pain**<br>100 mm VAS<br><br>Scale from: 0 to 100<br><br>(Higher scores mean worse pain)<br>Follow-up: mean 6 weeks | The mean change in pain in the control groups was 10.7 | The mean change in pain in the intervention groups was 15.10**lower** (9.08 to 21.13 lower) | | 434<br>(6 studies) | ⊕⊕⊕⊖<br>**moderate**[1] | MD 15.10 (95% CI 9.08 to 21.13)<br><br>Absolute risk difference: 15% (95% CI 9.08% to 21.13%)<br><br>Relative per cent change: 21.03% (95% CI 12.65% to 29.43%)<br><br>NNT: 2 (95% CI 1 to 6) |
| **Physical function**<br><br>WOMAC function<br><br>Scale from: 0 to 100<br><br>(Higher scores mean more severe limitation)<br>Follow-up: mean 3 months | The mean change in physical function in the control groups was **1.7** | The mean change in physical function in the intervention groups was 4.55**lower** (2.23 lower to 11.32 higher) | | 197<br>(3 studies) | ⊕⊕⊖⊖<br>**low**[2] | MD 4.55 (95% CI -2.23 to 11.32)<br><br>Absolute risk difference: 4.55% (95% CI -2.23% to 11.32%)<br><br>Relative per cent change: 268% (95% CI -131% to 666%)<br><br>NNT: not statistically significant |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Quality of life**<br><br>SF-36 item<br><br>Scale from: 0 to 100<br><br>(Lower scores mean worse quality)<br><br>Follow-up: mean 16 weeks | The mean change in quality of life in the control groups was 2.4 | The mean change in quality of life in the intervention groups was 0.09 **lower** (0.36 lower to 0.54 higher) | | 145 (2 studies) | ⊕⊕⊕⊖ **moderate**[3] | SMD 0.09 (95% CI -0.36 to 0.54)<br><br>Absolute risk difference: 1% (95% CI -2.92% to 4.37%)<br><br>Relative per cent change: 30.38% (95% CI -121.5% to 182.25%)<br><br>NNT: not statistically significant |
| **Radiographic progression**<br><br>Bone scintigraphic examinations<br><br>Follow-up: mean 2.5 months | See comment | See comment | Not estimable | 78 (1 study) | See comment | No related data were available |
| **Number of patients experiencing any adverse event**<br><br>Follow-up: mean 1 month | **167 per 1000** | **195 per 1000** (120 to 320) | **RR 1.17** (0.72 to 1.92) | 288 (4 studies) | ⊕⊕⊕⊖ **moderate**[4] | Absolute risk difference: 3% (95% CI -6% to 12%)<br><br>Relative per cent change:<br><br>17% (95% CI -28% to 92%)<br><br>NNT: not statistically significant |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Number of patients who withdrew because of adverse events**<br><br>Follow-up: mean 6 months | **27 per 1000** | **24 per 1000**<br><br>(2 to 376) | **RR 0.90**<br><br>(0.06 to 13.92) | 78<br>(1 study) | ⊕⊕⊖⊖<br>**low**[5] | Only 1 study: 1 participant withdrew from each group because of adverse skin reactions unrelated to the therapy |

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
**CI:** confidence interval; **MD:** mean difference; **NNT:** number needed to treat; **RR:** risk ratio; **VAS:** visual analogue scale;**WOMAC:** Western Ontario and McMaster Universities osteoarthritis index

GRADE Working Group grades of evidence
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[1]Downgraded for moderate heterogeneity ($I^2$ = 55%); unclear risk for random sequence generation (Zizic 1995), allocation concealment (Zizic 1995), blinding of outcome assessors (Fary 2011; Nelson 2013; Zizic 1995), selective reporting (all six studies) and high risk for incomplete outcome data (Zizic 1995).
[2]Downgraded for considerable heterogeneity ($I^2$ = 84%); Zizic 1995: unclear risk for random sequence generation, allocation concealment, blinding of outcome assessors, selective reporting and high risk for incomplete outcome data. Fary 2011: unclear risk for blinding of outcome assessors and selective reporting. Garland 2007: unclear risk for selective reporting.
[3]Fary 2011: unclear risk for blinding of outcome assessors and selective reporting. Pipitone 2001: high risk for incomplete outcome data.
[4]Unclear risk for random sequence generation (Thamsborg 2005; Zizic 1995), allocation concealment (Zizic 1995), blinding of outcome assessors (Thamsborg 2005; Zizic 1995), selective reporting (all four studies) and high risk for incomplete outcome data (Garland 2007; Thamsborg 2005; Zizic 1995).
[5]Only Zizic 1995 reported this outcome. Downgraded for imprecision (wide confidence interval and few events); unclear risk for random sequence generation, allocation concealment, blinding of outcome assessors and selective reporting and high risk for incomplete outcome data.

# Background

## Description of the condition

Osteoarthritis is a progressive rheumatic disease which occurs most commonly in older populations. It is becoming increasingly common due to the ageing population in many societies. The degeneration and eventual loss of articular cartilage causes changes in periarticular bone, synovial tissue and other periarticular soft tissue structures such as ligaments and muscles. This causes the pain, swelling, tenderness and stiffness that characterise osteoarthritis, especially in the weight-bearing joints of the lower extremities.

## Description of the intervention

Current osteoarthritis treatment options include pharmacological and non-pharmacological procedures to decrease progression and treat the pain associated with this condition. They include:

1. oral pharmacological medications: analgesics such as acetaminophen, aspirin, non-steroidal anti-inflammatory drugs (NSAIDs); symptomatic slow-acting drugs for osteoarthritis (SYSADOA) such as glucosamine sulphate (Towheed 2005), diacerein (Fidelix 2006) and the non-saponifiable oils of avocado and soya; and the newer disease-modifying osteoarthritis drugs (DMOAD);
2. topical therapies (applied as gels or creams), including NSAIDs and capsaicin;
3. intra-articular therapies, including corticosteroid and hyaluronic acid injections (Bellamy 2006a; Bellamy 2006b);
4. non-pharmacological therapies, including aquatic exercise therapy (Bartels 2007), balneotherapy (Verhagen 2007), physical therapy (Rutjes 2010), occupational therapy, strengthening exercises (Fransen 2008; Fransen 2009), wedged insoles and braces and orthoses (Brouwer 2005); and
5. surgical treatment: joint replacement (Singh 2013a; Singh 2013b) and arthroscopic debridement (Laupattarakasem 2008) of the affected joint.

Management of osteoarthritis of the knee aims to relieve pain, maintain or improve mobility, and minimise disability. However, these goals are seldom achieved through drug therapy alone, as many treatments are ineffective or lead to serious adverse effects, including the potentially lethal complications encountered with selective NSAIDS (Blower 1996). Different modalities in physiotherapy have been shown to help improve clinical symptoms and function in knee osteoarthritis, generally with fewer adverse effects than medical treatment (Brosseau 2003; Rutjes 2010). Electromagnetic fields are among these non-invasive therapies, already considered a proven adjunct therapy for delayed union fractures (Bassett 1974). Interest in electromagnetic field stimulation began after observing that physical stress on bone causes the appearance of tiny electric currents called piezoelectric potentials that are thought to act as the transduction signals to promote bone formation. In vitro studies showed that chondrocyte proliferation and

matrix synthesis are significantly enhanced by pulsed electromagnetic field stimulation (De Mattei 2001; De Mattei 2003; De Mattei 2004; Fioravanti 2002; Pezzetti 1999). A number of multicentric randomised and double-blind clinical trials have been carried out with promising results (Fini 2005).

Electromagnetic fields can be delivered to biological systems by the direct placement of an electrode or non-invasively by two means:

- capacitive coupling, in which opposing electrodes are placed within a conducting medium, that is, in contact with the skin surface overlying a target tissue (e.g. bone, joint, wound);
- inductive coupling, in which a time-varying pulsed electromagnetic field induces an electrical current in the target tissue. This technique does not require direct contact with the skin or biological system.

Although the former relies on direct application of an electrical field rather than creating induced current through magnetic impulses, they act by the same mechanism. Thus both pulsed electromagnetic fields and pulsed electrical stimulation are considered electromagnetic field interventions in this update.

## How the intervention might work

Three basic principles of physics are proposed to explain how electromagnetic fields may promote the growth and repair of bone and cartilage: Wolff's Law, the piezoelectric effect and the concept of streaming potentials (Shupak 2003).

Electromagnetic field stimulation first garnered interest as treatment for osteoarthritis following the discovery of evidence that stimulation of chondrocytes increased the synthesis of the major component of the cartilage matrix, known as proteoglycans (Aaron 1993). Experimental studies suggest that electromagnetic fields may interact with ligands on the chondrocyte cell surface membrane, potentially leading to changes in internal calcium concentrations which trigger proteoglycan synthesis (Graziana 1990; Lee 1993).

Electromagnetic field treatments might also help to preserve extracellular matrix integrity in the early stages of osteoarthritis by down-regulating proteoglycan production and degradation (Ciombor 2001; Liu 1997) and by increasing chondrocyte DNA replication and cell proliferation (Pezzetti 1999; Rodan 1978).

Through these improvements in bone and cartilage maintenance and repair, pulsed electromagnetic field stimulation could influence the osteoarthritic disease process by decreasing inflammation and providing temporary relief from pain (Darendeliler 1997; Lee 1997; Trock 2000).

## Why it is important to do this review

Electromagnetic field therapy is already being widely used for the management of joint pain associated with osteoarthritis and has a promising theoretical basis for clinical application. Clinical trials evaluating its therapeutic effectiveness have been conducted recently, but with inconsistent results. A 2002 Cochrane

review suggested that pulsed electromagnetic field therapy led to improvements in all measurements for knee osteoarthritis, but concluded that further studies were required to confirm whether the statistically significant results shown in these trials conferred important benefits to patients (Hulme 2002). The optimal frequency, duration and intensity of electromagnetic fields for osteoarthritis were also yet to be determined. This update of the 2002 review will include new clinical studies which have since been published.

# Objectives

To assess the benefits and harms of electromagnetic fields for the treatment of osteoarthritis as compared to placebo or sham.

# Methods

## Criteria for considering studies for this review

### Types of studies

Randomised controlled trials or quasi-randomised trials which examined the effects of electromagnetic fields for treating osteoarthritis, with four or more weeks treatment duration.

### Types of participants

Participants over 18 years of age, with clinical or radiological confirmation of the diagnosis (or both) were considered. The diagnosis of osteoarthritis was defined using the American College of Rheumatology (ACR) criteria for classification of osteoarthritis (Altman 1986; Altman 1997). We excluded trials where participants had received any previous surgical intervention for the treatment of osteoarthritis.

### Types of interventions

All types of pulsed electromagnetic fields and pulsed electrical stimulation were included. Trials that compared the intervention group using electromagnetic fields to usual care were included, as well as placebo-controlled studies.

### Types of outcome measures

The primary measure of effectiveness was pain relief, as suggested by the third Outcome Measures in Rheumatology (OMERACT) conference (Bellamy 1997). We included the other outcomes from this conference for analysis. According to OMERACT 3 (Bellamy 1997) (last reviewed in OMERACT 6) (Pham 2003) standardised, validated instruments, such as visual analogue scales (VAS) (Carlsson 1983) and the Western Ontario and McMaster Universities osteoarthritis index (WOMAC) scale for pain (Bellamy 1988) and the Lequesne Functional Severity Index (Lequesne 1987), should be used to evaluate these outcomes.

### Major outcomes

1. Pain
2. Physical function
3. Health-related quality of life measure
4. Radiographic joint structure changes
5. Number of patients experiencing any adverse event
6. Patients who withdrew because of adverse events
7. Patients experiencing any serious adverse event

## Search methods for identification of studies

## Electronic searches

We identified relevant studies by searching the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2013, Issue 9), PreMEDLINE for trials published before 1966, MEDLINE from 1966 to October 2013, CINAHL and PEDro up to and including October 2013. We used the search strategies recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Details of the search strategy can be found in the following appendices: MEDLINE (Appendix 1), CINAHL (Appendix 2), EMBASE (Appendix 3), CENTRAL (Appendix 4) and PEDro (Appendix 5).

## Searching other resources

We complemented the electronic searches with handsearching:

- bibliographic references; and
- abstracts published in special issues of specialised journals or in conference proceedings (American Orthopaedic Physicians Annual Meeting; Asia-Pacific Orthopedic Society for Sports Medicine Meeting).

We contacted the Trial Search Co-ordinators of the Cochrane Rehabilitation and Related Therapies Field and the Cochrane Musculoskeletal Group.

We manually searched conference proceedings, used the Science Citation Index to retrieve reports citing relevant articles, contacted content experts and trialists, and screened the references of all articles obtained, including related reviews. We did not use abstracts if additional data could not be obtained.

Finally, we searched several clinical trial registries (www.clinicaltrials.gov, http://www.controlled-trials.com, http://www.anzctr.org.au/, www.umin.ac.jp/ctr) to identify ongoing trials.

The last update of the manual search was conducted on 3 October 2013.

# Data collection and analysis

## Selection of studies

Two review authors (SL and BY) independently screened the abstract, keywords and publication type of all publications obtained from the searches described. We obtained all studies which might be eligible RCTs, or quasi-RCTs, in full and independently assessed these. The two review authors independently selected trials according to the selection criteria.

When necessary, we sought information from the authors of the primary studies.

## Data extraction and management

Two review authors (SL, BY) extracted data using a standard, pre-developed form that we pilot-tested. We extracted details of trial design, patient characteristics, treatment duration and the mechanics of the electromagnetic field device used, and established baseline and end of study outcomes. We resolved differences in data extraction by referring back to the original article and by establishing consensus. A third review author (CH or JH) was consulted to help resolve differences. Where the method of randomisation or allocation concealment was not clearly described, or where data were missing, we contacted the authors of the study to clarify the issues.

## Assessment of risk of bias in included studies

The review authors assessed the risk of bias in the included studies using The Cochrane Collaboration 'Risk of bias' tool (Higgins 2011). We considered six domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessors, selective outcome reporting and incomplete outcome reporting. We expressed the judgements simply as 'low risk', 'high risk' or 'unclear risk' of bias.

We assessed two components of randomisation: generation of allocation sequence and concealment of allocation. We considered the generation of sequence adequate if it resulted in an unpredictable allocation schedule; mechanisms considered adequate included random number tables, computer-generated random numbers, minimisation, coin tossing, shuffling cards and drawing lots. We considered trials using an

unpredictable allocation sequence to be randomised. We considered trials using potentially predictable allocation mechanisms, such as alternation or the allocation of patients according to date of birth, to be quasi-randomised.

We considered concealment of allocation adequate if both the patients and the investigators responsible for patient selection were unable to predict allocation to treatment or placebo groups. Adequate concealment included central randomisation and sequentially numbered, sealed, opaque envelopes.

Since the primary measure of effectiveness was patient-reported pain relief, we considered blinding of patients adequate if experimental and control preparations were explicitly described as indistinguishable or if a double-dummy technique was used.

We considered analyses adequate if all randomised patients were included in the analysis according to the intention-to-treat principle. We further assessed the reporting of major outcomes.

## Measures of treatment effect

For continuous data, we presented results as a mean difference (MD). However, where different scales were used to measure the same concept or outcome, we used standardised mean difference (SMD). For dichotomous data, we used risk ratio (RR) (Hennekens 1987; Petitti 2000). Only if a comparison resulted in a statistically significant difference and baseline values were reported did we calculate the clinical relevance, i.e. the number need to treat to benefit (NNTB) or harm (NNTH).

## Unit of analysis issues

If we identified cross-over trials presenting continuous outcome data which precluded paired analysis, we did not plan to include these data in a meta-analysis to avoid unit of analysis error. Where carry-over effects were thought to exist, and sufficient data existed, we planned to include only data from the first period in the analysis (Higgins 2011).

## Dealing with missing data

We contacted the study investigators for missing data via email. Where possible, the analyses were based on intention-to-treat data from individual clinical trials.

## Assessment of heterogeneity

We assessed statistical heterogeneity by examining the $I^2$ statistic (Higgins 2011), a quantity that describes approximately the proportion of variation in point estimates due to heterogeneity rather than sampling error. If considerable between-group statistical heterogeneity was detected (i.e. an $I^2$ value of more than

75%), we explored the causes of heterogeneity (Higgins 2011). In addition, we employed the $Chi^2$ test of homogeneity to determine the strength of evidence that the heterogeneity is genuine. We considered heterogeneity significant when the probability (P value) was < 0.10.

## Assessment of reporting biases

We planned to assess reporting bias by screening the clinical trials register at the International Clinical Trials Registry Platform of the World Health Organization (http://apps.who.int/trialsearch/) (De Angelis 2004) to determine whether the protocol for each RCT was published before recruitment of patients for the study was started. Furthermore, we planned a comparison between the fixed-effect estimate and the random-effects estimate, as well as a funnel plot if data were available, in order to assess for the possible presence of small sample bias and reporting bias, respectively.

## Data synthesis

We planned to pool clinically homogeneous studies using the fixed-effect model for meta-analysis. When there was important heterogeneity ($I^2$ > 25%), we pooled studies using the random-effects model for meta-analysis.

## Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analysis to examine the efficacy of electromagnetic fields with different application methods and modalities, including frequency, length of treatment and different techniques, if data were available.

## Sensitivity analysis

We conducted a sensitivity analysis based on the methodological quality of each trial. We undertook sensitivity analyses to explore the impact of studies with poor ratings for domains described in the 'Risk of bias' table. We planned a priori sensitivity analyses for:

1. concealment of allocation;
2. blinding of outcome assessors;
3. extent of drop-outs (we considered 20% as a cut-point).

### 'Summary of findings' table

We presented key findings in a 'Summary of findings' table. These included the magnitude of effect of the interventions examined, the sum of available data on the main outcomes and the quality of the evidence.

For dichotomous outcomes, we calculated the absolute risk difference using the risk difference (RD) statistic in RevMan (RevMan 2012) (RR - 1 calculated the weighted relative per cent change). We calculated the number needed to treat to benefit (NNTB) or to harm (NNTH) from the control group event rate (unless the population event rate was known) and the risk ratio using the Visual Rx NNT calculator (Cates 2004).

For continuous outcomes, we calculated the absolute benefit as the improvement in the treatment group (follow-up mean minus baseline mean) less the improvement in the control group (follow-up mean minus baseline mean). We calculated the relative difference in the change from baseline as the absolute benefit divided by the baseline mean of the control group. We calculated NNTB or NNTH using the Wells calculator software available at the CMSG editorial office. We determined the minimal clinically important difference (MCID) for each outcome for input into the calculator.

We used GRADE to describe the quality of the overall body of evidence (Guyatt 2008; Higgins 2011), defined as the extent of confidence in the estimates of treatment benefits and harms. The GRADE approach specifies four levels of quality (high, moderate, low and very low).

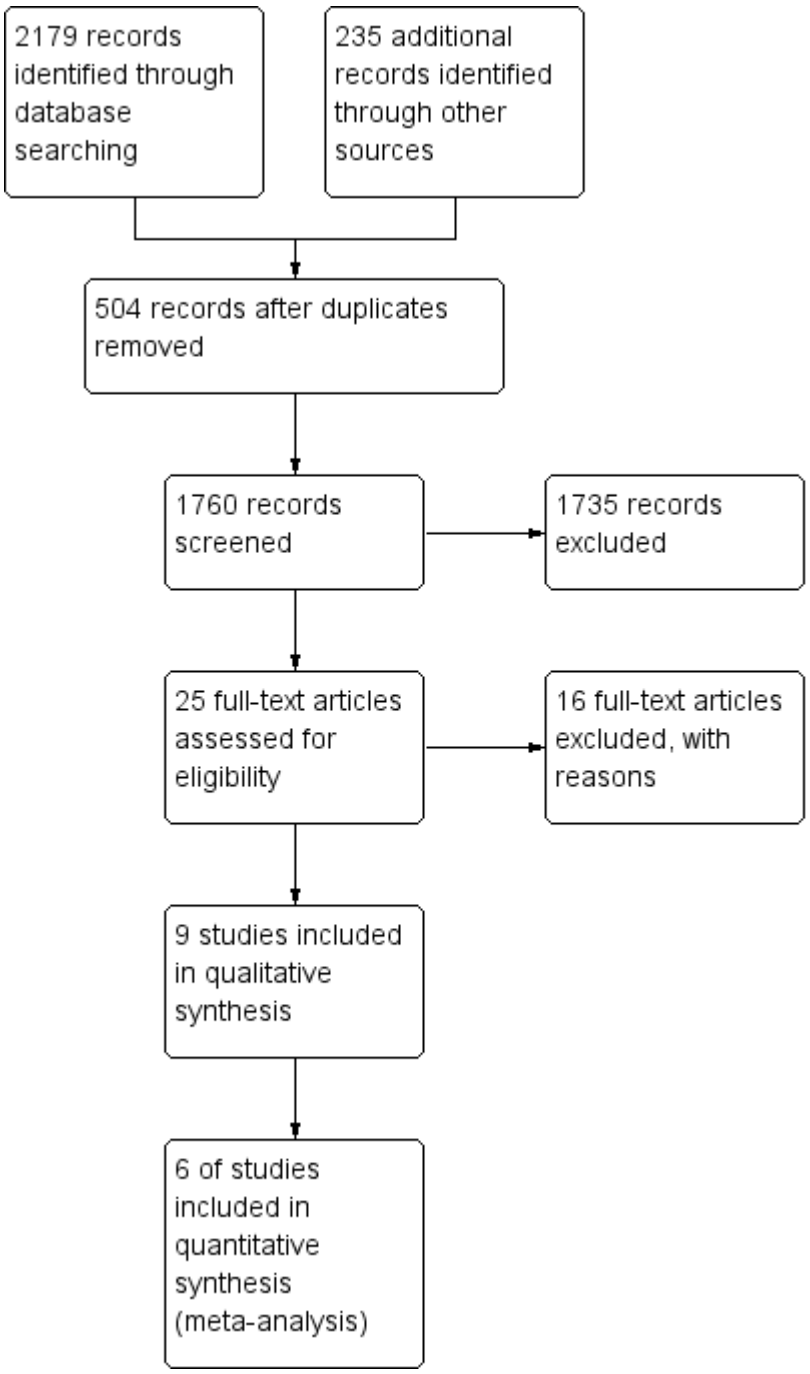
# Results

## Description of studies

### Results of the search

The search strategies retrieved 2037 articles (Figure 1). The literature search identified 25 potentially relevant articles. Of these, only nine studies met the inclusion criteria (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994; Zizic 1995) (see Characteristics of included studies table). Sixteen studies were excluded for the reasons given in the Characteristics of excluded studies table (Alcidi 2007; Ay 2009; Battisti 2004; Danao-Camara 2001; Fischer 2005; Fischer 2006; Hinman 2002; Jack 2006; Jacobson 2001; Kulcu 2009; Liu 2004; Ozgüçlü 2010; Pavlović 2012; Rigato 2002; Sutbeyaz 2006; Tomruk 2007).

**Figure 1** **Open in figure viewer** | **Download as PowerPoint**




Study flow diagram.

## Included studies

The eligible RCTs collectively involved 327 participants in active electromagnetic field treatment groups and 309 participants in placebo groups.

Six trials used pulsed electromagnetic fields (Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994) while three studies (Fary 2011; Garland 2007; Zizic 1995) used pulsed electrical stimulation.

One study used a pulsed electromagnetic field signal consisting of a 7 ms burst of 6.8 MHz sinusoidal waves repeating at one burst/s and delivering a peak induced electrical field of 34 ± 8 V/m in the knee from a portable battery-operated device (Palermo, Ivivi Health Sciences, LLC, San Francisco, CA). Patients were treated for 15 minutes twice daily for 42 days (Nelson 2013).

Another study reviewed a pulsed electromagnetic field device (Medicur) that generates pulses of magnetic energy via a soft iron core treated with 62 trace elements. Pulses are selected at base frequencies of 3 Hz, 7.8 Hz and 20 Hz and have a rise time of 1 μs, a low magnetic output (< 0.5 gauss) and a range of activity of up to 30 cm around the unit. The Medicur device runs on batteries, requires no wires or electrodes, and only needs to be held close to the area to be treated. Patients were treated for 30 minutes per session three times a day for six weeks (Pipitone 2001).

In one study a pulsed electromagnetic field was administered to the whole body using a mat which produced a field from 1 Hz to 3000 Hz with a mean intensity of 40 μT (wave ranger professional, program 12, Mediscan GmbH, Bad Haller Straße34, 4500 Kremsmünster, Austria). The frequency of the pulsed electromagnetic field ranged from 1 Hz to 3000 Hz. Patients lay on the mat for 30 minutes per session twice a day for six weeks (Nicolakis 2002).

A fourth study measured the effect of a pulse generator that yields G50V in 50 Hz pulses, changing voltage at 3 ms intervals. This results in a maximal electrical gradient of 1 to 100 mV/cm as sensed by charged particles in the tissue, depending on the distance from the coils. As a result of this current, the coils become slightly warmer than the surroundings after 30 minutes (28 to 35 °C). Treatment was given for two hours daily, five days per week for six weeks (Thamsborg 2005).

Two other trials used a non-contact device that delivered three signals in a stepwise fashion, ranging from 5 Hz to 12 Hz frequency at 10 G to 25 G of magnetic energy (Trock 1993; Trock 1994). These studies exposed the affected knee to nine hours of stimulation over a one-month period.

In one study a commercially available TENS stimulator (Metron Digi-10s) was modified by a biomedical engineer to deliver pulsed electrical stimulation current parameters as follows: pulsed, asymmetrically biphasic, exponentially decreasing waveform with a frequency of 100 Hz and pulse width of 4 ms. Current was delivered via 120 mm x 80 mm multiple-use conductive silicone electrodes inserted into larger calico pockets. The participants were asked to wear the device seven hours daily, preferably overnight, for 26 weeks (Fary 2011).

Two other pulsed electrical stimulation studies used a pulsed electrical device to deliver a 100 Hz low-amplitude signal to the knee joint via skin surface electrodes. The patients were exposed for 6 to 14 hours a day for three months and 6 to 10 hours a day for four weeks, respectively (Garland 2007; Zizic 1995).

All studies reported on patients with knee osteoarthritis and Trock 1994 also included patients with cervical osteoarthritis, with their results reported separately. The main outcome measures related to pain (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994; Zizic 1995). The major outcomes were assessed using the WOMAC osteoarthritis index: severity of joint pain, stiffness and limitation of physical function (Garland 2007; Nicolakis 2002; Pipitone 2001; Thamsborg 2005), ability to conduct activities of daily living (ADL) in terms of pain or difficulty (Trock 1993; Trock 1994), joint pain on motion (Trock 1993; Trock 1994), patient's overall assessment (Garland 2007; Trock 1994), patient evaluation of function (Zizic 1995) and physician's global assessment (Trock 1993; Trock 1994; Zizic 1995). The UK 36-item short form of the Medical Outcomes Study (SF-36) and the EuroQol (Euro-Quality of Life, EQ-5D) were also considered (Pipitone 2001).

## Excluded studies

We excluded nine RCTs with a shorter duration than four weeks since this time frame may be too short to assess harms and benefits based on biological plausibility (Alcidi 2007; Ay 2009; Battisti 2004; Jacobson 2001; Kulcu 2009; Liu 2004; Ozgüçlü 2010; Pavlović 2012; Sutbeyaz 2006;Tomruk 2007). We excluded one RCT because it included patients with cervical spondylosis and shoulder periarthritis without separately reporting results and we could not extract data on cervical osteoarthritis (Rigato 2002). We excluded four other studies because they were not RCTs (Danao-Camara 2001; Fischer 2005; Fischer 2006; Jack 2006). We excluded one study because the aim of the study was to assess the effect of static magnetic fields for chronic knee pain but not specifically for osteoarthritis (Hinman 2002). We excluded one study because the treatment period was only 10 days (Pavlović 2012).

## Risk of bias in included studies

Two review authors (SL, BY) assessed risk of bias independently. Differences were resolved by consensus with a third review author (DZ).

The overall assessment of the methodological quality of the trials in this review was as follows: we judged seven studies (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Trock 1993; Trock 1994) to be at a low risk of bias for random sequence generation, and two studies omitted a description of the randomisation process (Thamsborg 2005; Zizic 1995).

Nine of the included studies met the allocation concealment criterion (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994).

Seven trials (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Pipitone 2001; Trock 1993; Zizic 1995) had appropriate, well-described placebo treatments and we assessed them as low risk of bias for blinding.

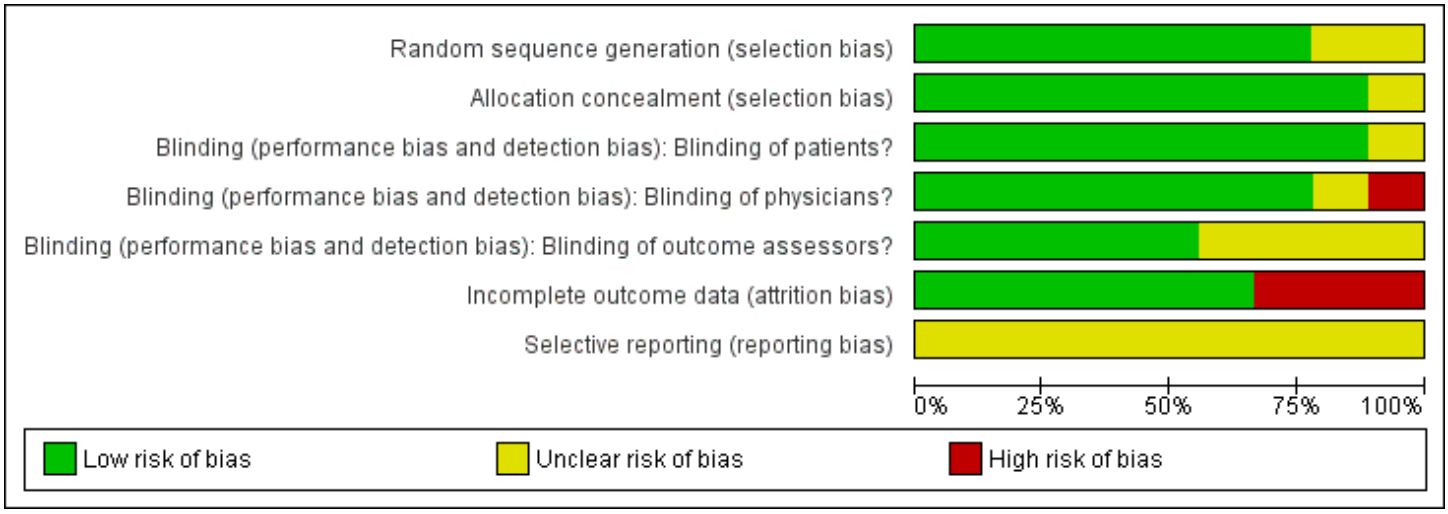
We assessed seven studies (Fary 2011; Garland 2007; Nelson 2013; Nicolakis 2002; Thamsborg 2005; Trock 1994; Zizic 1995) as low risk of bias for incomplete outcome data; six trials reported loss to follow-up ranging from 5% to 20% (Garland 2007; Nicolakis 2002; Thamsborg 2005; Trock 1993; Trock 1994; Zizic 1995), balanced across compared groups, while one trial did not report the loss to follow-up (Pipitone 2001).

No information on selective outcome reporting was found in any study.

See the 'Risk of bias' graph (Figure 2) and 'Risk of bias' summary (Figure 3).

**Figure 2**

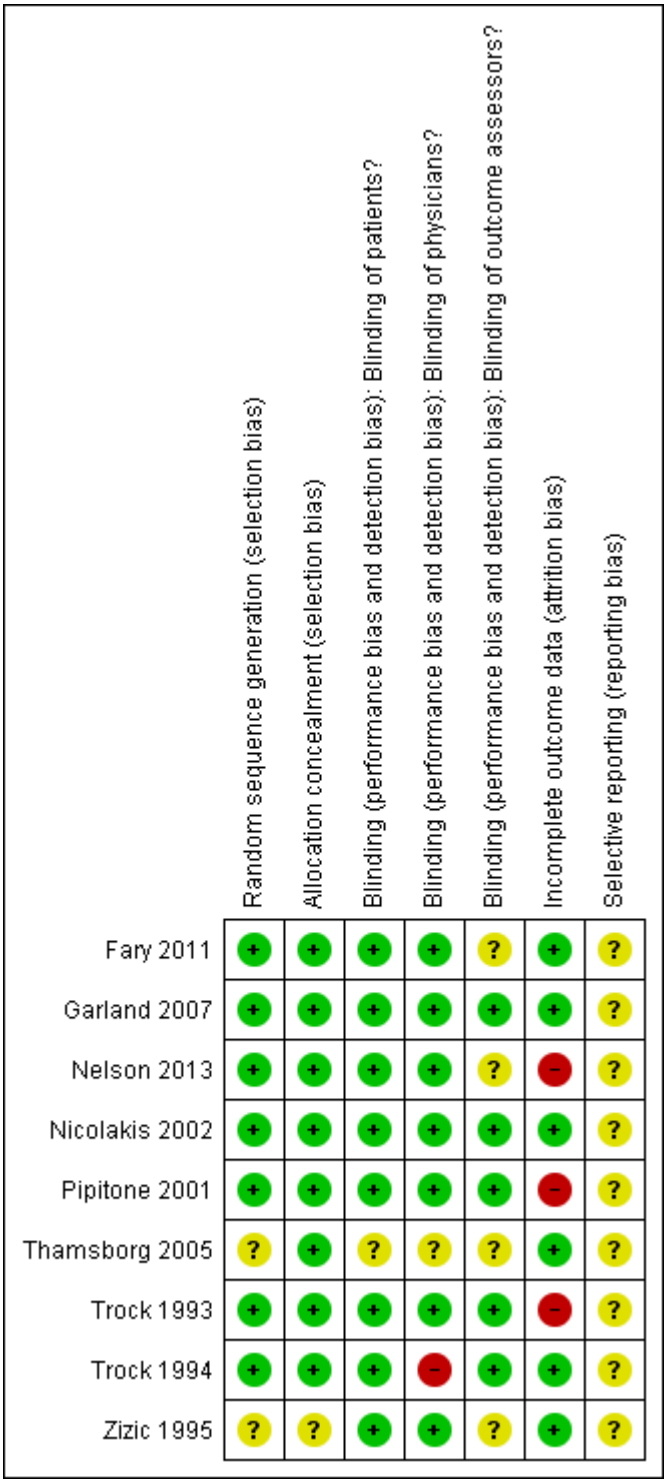
**Open in figure viewer** | **Download as PowerPoint**




'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

**Figure 3**

**Open in figure viewer** | **Download as PowerPoint**




'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

# Effects of interventions

See: **Summary of findings for the main comparison** Electromagnetic field treatment compared to placebo for the treatment of osteoarthritis

In the nine controlled trials included in the analysis, a total of 636 participants were randomised: 327 participants to electromagnetic field treatment and 309 to a placebo device. The pulsed electromagnetic field treatment trials lasted approximately four to six weeks, with treatment duration ranging from 27 hours to 60 hours (Nelson 2013; Nicolakis 2002; Pipitone 2001; Thamsborg 2005; Trock 1993; Trock 1994). The treatments in three other pulsed electrical stimulation trials were more intensive, involving 26 weeks of seven hours treatment daily (Fary 2011), four weeks of six hours per day treatment (Zizic 1995) and three months of 6 to 14 hours per day, respectively (Garland 2007). These trials did not provide the statistical details required for inclusion in meta-analysis, therefore the analysis of the relative effects of treatment times, frequencies and modes of treatment delivery was limited (see summary of findings Table for the main comparison).

## Electromagnetic field treatment versus placebo for osteoarthritis

### Pain

The combined results from the six included studies of electromagnetic field treatment which measured pain as an outcome (Fary 2011; Garland 2007; Nelson 2013; Trock 1993; Trock 1994; Zizic 1995) showed a statistically significant beneficial effect for patient pain relief (mean difference (MD) 15.10, 95% confidence interval (CI) 9.08 to 21.13). People who received electromagnetic field treatment rated their pain to be 15.10 points lower on a scale of 0 to 100 (15.10% absolute improvement and 21.03% relative improvement) (Analysis 1.1).

### Physical function

Three studies including 107 patients in the electromagnetic field treatment group and 90 patients in the placebo group measured function as an outcome (Fary 2011; Garland 2007; Pipitone 2001). Improvement of function was not statistically significant in electromagnetic field-treated patients compared to control group patients (MD 4.55, 95% CI -2.33 to 11.32; 4.55% absolute effect and 10.13% relative effect) (Analysis 1.2).

### Health-related quality of life measure

Two studies including 68 patients in the electromagnetic field treatment group and 71 patients in the placebo group measured quality of life as an outcome (Fary 2011). Improvement in quality of life was not statistically significant in electromagnetic field-treated patients compared to control group patients (SMD 0.09, 95% CI -0.36 to 0.54; 9% absolute effect and 100.8% relative effect) (Analysis 1.3).

### Radiographic joint structure changes

Only two studies (Thamsborg 2005; Trock 1993) mentioned radiographic joint structure change but no data were available.

### Number of patients experiencing any adverse event

Adverse events were presented in four studies with 156 participants in the intervention group and 132 participants in the control group (Garland 2007; Pipitone 2001; Thamsborg 2005; Zizic 1995), although specific definitions of adverse events were not provided in any study. The total number of adverse events was not statistically significantly increased in electromagnetic field-treated patients (19.9%) compared to 16.7% of placebo-treated patients, after six weeks (RR 1.17, 95% CI 0.72 to 1.92) (Analysis 1.4).

### Patients who withdrew because of adverse events

Specific reasons for withdrawals were unrelated to the therapy except in the case of adverse skin reactions which were encountered in Zizic 1995 and occurred in patients receiving both placebo and active electrical stimulation treatment. There was no significant difference between groups (RR 0.90, 95% CI 0.06 to 13.92) (Analysis 1.5), suggesting that there is no difference between the active treatment and placebo in terms of adverse effects.

### Patients experiencing any serious adverse event

No study reported any serious adverse events.

### Subgroup analyses

We did not conduct the pre-planned subgroup analyses of the most effective means of delivering therapy due to the small number of trials and insufficient data.

### Sensitivity analyses

We undertook sensitivity analyses to explore the impact of studies with poor ratings for concealment of allocation, blinding of outcome asessors and extent of drop-out and there was no change in the direction and significance of the effect sizes (results not shown).

## Discussion

## Summary of main results

Osteoarthritis is the most common of the rheumatic diseases. With an estimated 40,000 new cases of osteoarthritis diagnosed each year, it is the third leading cause of life-years lost due to disability and is associated with high morbidity and healthcare utilisation (March 2004; Towheed 2004). The range of treatments for osteoarthritis is continually increasing as conventional therapies, such as pharmaceutical management, physiotherapy and joint replacement surgery, are coupled with emerging and established complementary therapies.

Osteoarthritis results from a failure of chondrocytes within the joint to synthesise a good-quality matrix and to maintain a balance between synthesis and degradation of the extracellular matrix. The change in the quality of the matrix is mainly the result of dedifferentiation of chondrocytes, whereas the imbalance between synthesis and degradation of the extracellular matrix is caused by increased synthesis of proteinases and decreased anabolic effects of growth factors, mainly from chondrocytes but also from synovial tissue and subchondral bone. The biochemical reasoning behind the electrical stimulation of cartilage has been clearly demonstrated in vitro; its value in the treatment of delayed union fracture has been proven over two decades of use and it has been established as a standard of care (Aaron 1989; Baker 1974; Bassett 1974). The question remains as to whether it provides a financially accessible, clinically significant alternative to current therapies for osteoarthritis. The purpose of this systematic review was to evaluate the effectiveness of electrical stimulation treatment. However, its major limitation is the small number of contributing studies that could be included; this also prevented the planned subgroup analysis of variations in treatment.

All of the studies' participants had osteoarthritis of one or both knees, or cervical osteoarthritis, diagnosed by clinical symptoms and radiographic evidence, and the osteoarthritis was painful despite medical treatment.

The protocols for pulsed electrical stimulation or pulsed electromagnetic field device setting and application varied widely between studies, as did the outcome measures. Some pulsed electrical stimulation devices delivered a low-frequency (100 Hz), low-amplitude, voltage sourced (mean = 6.2 peak volts), monophasic, spiked signal to the knee via skin surface electrodes (Fary 2011; Garland 2007; Zizic 1995). In Nelson 2013 a pulsed electromagnetic field signal consisting of a 7 ms burst of 6.8 MHz sinusoidal waves repeating at one burst/s delivered a peak induced electrical field of 34 ± 8 V/m to the knee from a portable battery-operated device. Other devices used in the included trials generated a pulsating electromagnetic field with a mean intensity of 40 μT (the frequency of the pulsed magnetic field ranged: 1 Hz to 3000 Hz) (Nicolakis 2002); or generated pulses of magnetic energy via a soft iron core with base frequencies (3 Hz, 7.8 Hz and 20 Hz) (Pipitone 2001), G50V in 50 Hz pulses changing voltage in 3 ms intervals (Thamsborg 2005) and extremely low-frequency pulsed waves at 5 Hz, 10 to 15 gauss for 10 minutes, 10 Hz 15 to 25 gauss for 10 minutes and 12 Hz 15 to 25 gauss for 10 minutes (Trock 1993; Trock 1994). Characteristics of the devices, such as electromagnetic field modes, and application characteristics, such as duration, could not be evaluated in this systematic review due to the small number of trials.

Pain relief was measured using visual analogue scales (VAS). We pooled this outcome from six trials and found a significant difference between the electromagnetic field and placebo-treated groups (Fary 2011; Garland 2007; Nelson 2013; Trock 1993; Trock 1994; Zizic 1995). All were randomised controlled trials with appropriate blinding and they had appropriate, well-described placebo treatments (see Characteristics of included studies). There was moderate heterogeneity in the results. The intervention and its duration also differed between the studies.

The improvement in physical function in patients with knee osteoarthritis treated with pulsed electromagnetic fields was not statistically significant (Fary 2011; Garland 2007; Pipitone 2001). There was high heterogeneity in the results. This might be due to the different measurement tools used in the included studies. Two studies (Fary 2011; Garland 2007) used WOMAC physical function (on a 100 mm VAS) to measure the efficacy variable, while one study (Pipitone 2001) used the WOMAC disability score on a 20 cm VAS of the EuroQol. The intervention duration also differed among these studies.

Quality of life was not statistically significantly different between the treatment and placebo groups (Fary 2011; Pipitone 2001). This might be explained by the small sample sizes of the included studies measuring these outcomes, the wide variation in electromagnetic field devices and application protocols, or the inadequate intervention periods.

There were no life-threatening events reported among participants exposed to electromagnetic fields.

## Overall completeness and applicability of evidence

A comprehensive search of the literature revealed a number of studies of electromagnetic field interventions for osteoarthritis. Although the studies presented differences between placebo and active treatment for osteoarthritis for some outcomes, these effects did not meet the generally accepted criteria for clinical importance. There are currently insufficient data to draw conclusions about the efficacy of electromagnetic field interventions in the management of osteoarthritis, thus highlighting the need for larger independent studies that focus on the OMERACT core outcomes with complete documentation of results.

In summary, electromagnetic field treatment has a moderate benefit for patients' pain relief. There is inconclusive evidence that electromagnetic field treatment improves physical function, quality of life or radiographic joint structure. No serious adverse effects of electromagnetic field treatment were reported in the included trials. This might be because of the relative safety of electromagnetic fields compared to physiotherapy, which could be an advantage. This meta-analysis did not reveal clinically important results overall and the analysis was limited by the paucity of literature on electromagnetic fields for osteoarthritis. However, the statistically significant benefits seen here do support the undertaking of further large-scale studies to allow definite conclusions to be drawn.

## Quality of the evidence

The quality of the evidence of all included trials was moderate or low. Six trials described generation of allocation sequence or concealment of allocation, or reported whether primary outcomes were specified a priori. All trials described double-blinding of patients and physicians or assessors. Four of the trials were analysed according to the intention-to-treat principle. We also downgraded for heterogeneity and imprecision.

## Potential biases in the review process

We believe that we identified all relevant studies. We devised a thorough search strategy and searched all major databases for relevant studies, and we applied no language restrictions. Two review authors independently assessed the trials for inclusion in the review and for risk of bias, with a third review author adjudicating if there was any discrepancy. The biggest limitation of the review process was the heterogeneity between the trials and the lack of data in a form that could be extracted for meta-analysis.

## Agreements and disagreements with other studies or reviews

A systematic review has assessed the effectiveness of pulsed electromagnetic fields compared with placebo in the management of osteoarthritis of the knee (Vavken 2009). Nine studies, including 483 patients, were pooled. They reported that pulsed electromagnetic field treatment improved clinical scores and function in patients with osteoarthritis of the knee and that it should be considered as an adjuvant therapy in the management of these patients. However, there is still equipoise regarding the evidence in the literature for an effect on pain.

Porto Biomed. J. 2016;1(5):156–163

PORTO BIOMEDICAL JOURNAL
WHERE SCIENCE MEETS KNOWLEDGE

Porto Biomedical Journal

http://www.portobiomedicaljournal.com/

Review article

# Pulsed electromagnetic field therapy effectiveness in low back pain: A systematic review of randomized controlled trials

Renato Andrade[a,b,c], Hugo Duarte[d], Rogério Pereira[e,b,c], Isabel Lopes[f,b], Hélder Pereira[g,h,i,j,c], Rui Rocha[k,b], João Espregueira-Mendes[b,c,h,i,l,*]

[a] *Faculty of Sports, University of Porto, Porto, Portugal*
[b] *Clínica do Dragão, Espregueira-Mendes Sports Centre – FIFA Medical Centre of Excellence, Porto, Portugal*
[c] *Dom Henrique Research Centre, Porto, Portugal*
[d] *Faculty of Medicine, University of Porto, Porto, Portugal*
[e] *Faculty of Health Sciences, University of Fernando Pessoa, Porto, Portugal*
[f] *Physical Medicine and Rehabilitation Department, Centro Hospitalar São João EPE, Porto, Portugal*
[g] *Orthopaedic Department, Centro Hospitalar Póvoa de Varzim, Vila do Conde, Portugal*
[h] *3B's Research Group – Biomaterials, Biodegradables and Biomimetics, University of Minho, Headquarters of the European Institute of Excellence on Tissue Engineering and Regenerative Medicine, AvePark, Parque de Ciência e Tecnologia, Zona Industrial da Gandra, Barco, Guimarães, Portugal*
[i] *ICVS/3B's – PT Government Associate Laboratory, Braga/Guimarães, Portugal*
[j] *Ripoll y De Prado Sports Clinic FIFA Medical Centre of Excellence, Murcia-Madrid, Spain*
[k] *Orthopaedic Department, Centro Hospitalar Vila Nova de Gaia/Espinho, Portugal*
[l] *Orthopaedics Department of Minho University, Minho, Portugal*

ARTICLE INFO

*Article history:*
Received 24 July 2016
Accepted 23 September 2016

*Keywords:*
Pulsed electromagnetic fields
Low back pain
Musculoskeletal
Therapy

ABSTRACT

*Background:* Low back pain is a worldwide prevalent musculoskeletal condition in the general population. In this sense, the pulsed electromagnetic fields (PEMF) therapy has shown significant clinical benefits in several musculoskeletal conditions.
*Objective:* To assess the effectiveness of the PEMF therapy in reducing pain and clinical symptomatology in patients with low back pathological conditions.
*Methods:* It was performed a comprehensive database search using Pubmed, Scopus, Cochrane Library and PEDro databases to assess the effectiveness of the PEMF therapy in reducing pain and clinical symptomatology in patients with low back pathological conditions. The search was performed from January 2005 to August 2015 and conducted by two independent investigators, which scrutinize the reference list of most relevant studies. The methodological quality was assessed by the PEDro scale and the level of evidence was set according Oxford Center for Evidence-Based Medicine scale.
*Results:* Six studies were eligible inclusion on the qualitative analysis and five into the quantitative analysis, scoring an overall 6.8 points according the PEDro scale. The studies showed heterogeneity concerning the intervention protocols. Nevertheless, the effect sizes' indicated a clear tendency to reduction of the pain intensity favoring the PEMF groups, reaching a minimal clinically important difference.
*Conclusion:* PEMF therapy seems to be able to relieve the pain intensity and improve functionality in individuals with low back pain conditions. Further research is needed regarding PEMF effects on the different conditions of low back pain, with standardized protocols, larger samples and adjustment for low back pain confounders in order to achieve stronger conclusions.



*Abbreviations:* PEMF, pulsed electromagnetic field; NSAIDs, non-steroidal anti-inflammatory drugs; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PEDro, Physiotherapy Evidence Database; CI, confidence intervals; CEBM, Center for Evidence-Based Medicine; MCID, minimal clinically important difference.

* Corresponding author.
*E-mail address:* espregueira@dhresearchcentre.com (J. Espregueira-Mendes).

http://dx.doi.org/10.1016/j.pbj.2016.09.001

## Introduction

Low back pain is a very common health problem in general population and one of the major reasons for medical treatment seeking. It is expected that between 60 and 80% of the world population will experience low back pain during lifetime,[1] with 65% being recurrent and longstanding episodes. Low back pain can be caused by different etiologies, such as muscle or ligament strains, herniated discs, arthritis, alteration in the curvature of the spine or osteoporosis related fractures but, the majority of the patients do not have a clinically identified problem.[2] Despite the variety of treatments available, no modality or therapeutic approach has stand out as a definitive solution.[3] Thus, there is still a demand for new approaches, less invasive and free of side effects.

The risk/benefit ratio in pharmacotherapy for low back pain conditions often does not have strength enough to persist with the drugs usage. Moreover, the risk of pharmacologic addition, potential side-effects and adverse events, as well as long-term toxicity may weaken the potential benefit of the pharmacotherapy approach.[4,5] In this sense, the pulsed electromagnetic fields (PEMF) therapy can play an important role in the pain relief since is a drug-free, non-thermal, with low risk that works to enhance cellular activity healing and repair.[3] Therefore, it could be an option to the non-steroidal anti-inflammatory drugs (NSAIDs) medication, avoiding several potential side-effects from chronic NSAIDs usage.

The PEMF therapy is based in low frequency signal, with a wide range of frequencies, which will produce membrane disturbances and activation of multiple intracellular pathways.[6,7]

It has been reported that PEMF therapy yields several benefits into the bone unification, acute pain relief, wound healing, edema and inflammation control, as well as, chronic pain associated with connective tissue (cartilage, tendon, ligaments and bone) injury and joint-associated soft tissue injury, osteoarthritis, fibromyalgia, osteoporosis, skin ulcers and further potential applications.[8–11] Along this line, many reviews have been performed to assess the PEMF effectiveness in several conditions. In this sense, the PEMF showed moderate[7] or no benefits in knee osteoarthritis,[12] a beneficial tendency on the bone growth stimulation in acute fractures[13] and efficient in relieving pain and enhancing bone formation in osteoporosis.[14]

Although the use of PEMF therapy in low back pain is growing and there is substantial investigation on this topic, a systematization of its effects on the low back pain is still lacking. Therefore, this study aims to search for randomized controlled trials that assessed the effectiveness of the PEMF therapy in reducing pain symptomatology in patients with low back pathological conditions.

## Methods

### *Search strategy*

The systematic review was conducted according the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, which aims to improve the standard of reporting of systematic reviews and meta-analyses.[15] Additionally, the protocol for this review was à *priori* registered in the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/prospero/; ID: CRD42015025308).

It was conducted a comprehensive database search using Pubmed, Scopus, Cochrane Library and PEDro, searching for relevant studies that assessed the efficacy of the PEMF therapy on reducing pain on individuals with low back pain. The search was performed according the following key-words: pulsed electromagnetic field therapy; back; spine; spinal; lumbar; and further combined with the Boolean operators (AND; OR). An example of the search can be seen in Table 1. The reference list of most relevant studies was scanned for additional studies in order to achieve the greatest number of available studies on the scientific literature. All searches were comprised to the period of January 2005 to August 2015 and were conducted by two independent investigators (R.A., H.D.), which confronted both results to check for overlapping; any disagreements were discussed by until consensus was reached.

**Table 1**
Example of search strategy for Pubmed database.

| Search | Search term(s) | Results |
|---|---|---|
| #1 | Search **pulsed electromagnetic field therapy** | 342 |
| #2 | Search **back** | 86,722 |
| #3 | Search **spine** | 82,093 |
| #4 | Search **spinal** | 120,484 |
| #5 | Search **lumbar** | 43,342 |
| #6 | Search **(#2 OR #3 OR #4 OR #5)** | 237,516 |
| #7 | Search **(#1 AND #6)** | 32 |

### *Study selection*

All titles and abstracts from the selected databases were screened. After, the potential relevant studies were selected and retrieved, full texts were read in order to apply the eligibility according the following inclusion criteria: (1) assessment of pain outcome; (2) use of pulsed electromagnetic field therapy; (3) prospective design; (4) randomized controlled trials; (5) English language studies. For exclusion criteria it was determined: (i) other reviews or meta-analyses; (ii) clinical commentaries or expert opinions; (iii) case series; (iv) non-randomized controlled trials; (v) animal studies; (vi) skeletally immature population.

### *Data collection and extraction*

Two independent investigators (R.A., H.D.) retrieved all the information and matched for consensus. The main outcome of interest was the quantification of intensity of pain overtime. Thus, after the application of the eligibility criteria and the included studies were determined, the studies were analyzed based on sample demographics, study's aim, statement of conflict of interest, study duration and follow-up (period of time and percentage), PEMF devices used, treatment window, intervention protocol, parameters assessed (clinical and functional) and most significant results.

In addition, the figures of pain intensity and the Oswestry Disability Index were assessed based on their means and standard deviation values and calculated their mean differences, i.e., difference between the study's end-point and baseline values. Additionally, the Cohen's effect size, within the 95% confidence intervals (CI) was calculated. The effect sizes were computed by subtracting the experimental group mean to the control group mean and further divided by the pooled standard deviations of both groups.[16,17] Thus, a positive effect reflects a greater decrease on the pain intensity toward the experimental group. The 95% CI provides information concerning the variability of the observed effect size, its precision, as well as the accuracy with which the interval contains the population parameter (i.e., the true value). The standardized Cohen effect sizes were interpreted according to the guidelines established by Cohen[17] in which values <0.20 are trivial or not substantial, 0.20 and 0.49 are small but substantial, 0.50 and 0.79 are moderate, and ≥0.80 are large. In case of missing values (means and/or standard deviations), the authors from the respective studies were contacted in order to obtain them.

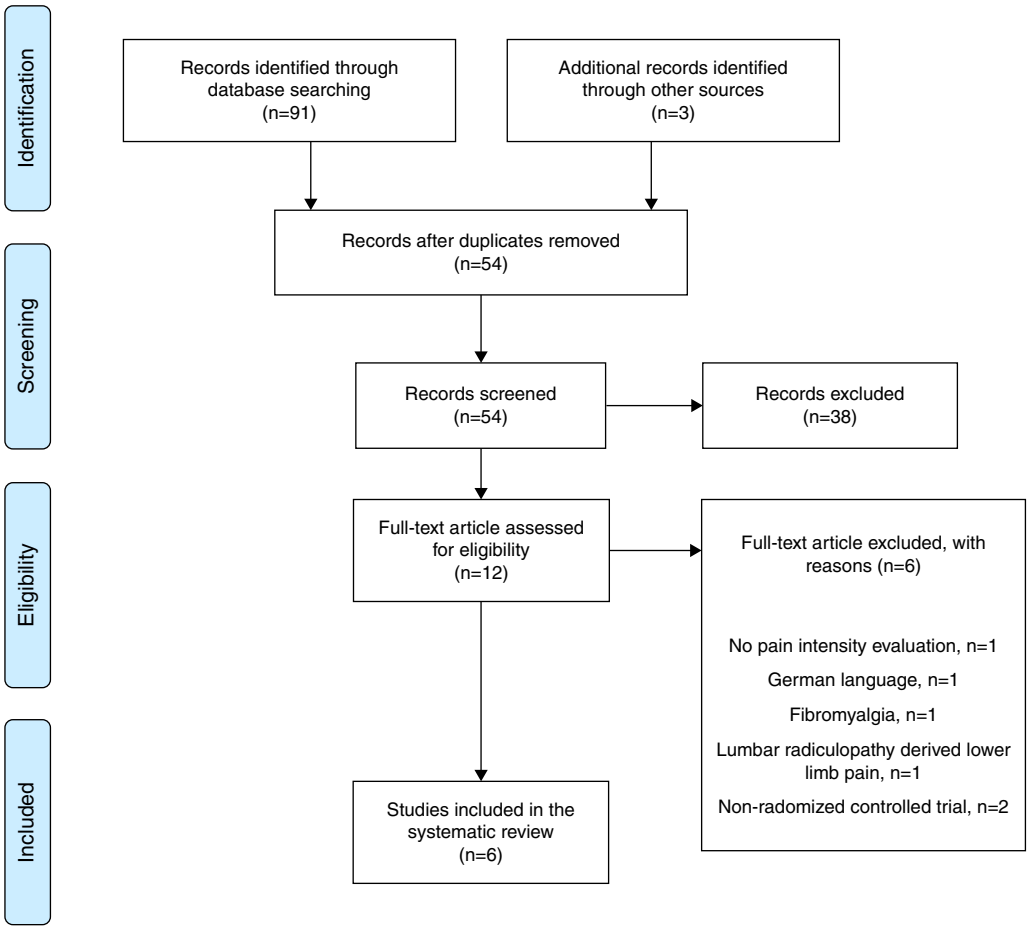



**Fig. 1.** PRISMA flow diagram of the eligibility process.

*Methodologic quality assessment*

The PEDro scale in order to assess the methodological quality (external validity, internal validity and statistical reporting) and the level of evidence was set according the Oxford Center for Evidence-Based Medicine (CEBM) scale.[18] PEDro scale has been reported to be a valid and reliable tool to measure the methodological quality of interventional clinical trials.[19,20] These parameters were independently assessed by two authors (R.A., H.D.) and all disagreement were resolved until consensus was reached.

## Results

*Study selection*

The database and hand search yielded 91 titles, which were reduced after duplicates removal and title/abstract reading to 12 full-text articles that were screened for eligibility. After screening, 6 studies were excluded[21–26] which the reasons for exclusion are highlighted in the PRISMA flow chart (Fig. 1). The remaining 6 studies were eligible inclusion on the qualitative analysis and 5 into the quantitative analysis.

*Description of studies*

In Table 2 are presented the characteristics of the 6 included original studies. Overall, the studies included a total of 210 participants (90 men and 120 women), with an overall mean age of 43.3 years old. All the included participants reported complains of low back pain, however with different etiologies: generalized low back pain[27]; acute non-specific low back pain[3]; discogenic lumbar radiculopathy[28]; failed back surgery syndrome pain[26]; chronic low back pain.[4,29]

The inclusion criteria varied across the studies. Nonetheless, across the included studies some similarities were found. All of the studies were performed in adult populations with clinically evaluated low back pain. A visual analogue scale above 5 points and a numeric rating scale above 4 points were also considered in Park, Sun, Lee, Kang, Lee, Hwang and Cha[30] and Lee, Kim, Lim, Lee, Choi, Park, Lee and Lee[29] studies, respectively. The presence of a cardiac pacemaker or other electronic implants were the only exclusion criteria enclosed in all studies. Other exclusion criteria were study-specific related comorbidities.

Generally, the studies enrolled the use of different devices, however with the same objectives and principles of PEMF therapy application. Their description can be seen in Table 3. The PEMF therapy was often compared with placebo interventions (comprising sham devices) or analgesic medication. Moreover, the studies showed heterogeneity concerning the PEMF therapy protocols, where the duration of the application ranged from 5 days to 3 weeks, and the frequency of the application from 4 times a day to just twice a week. The follow-up period also showed heterogeneity, ranging from 3 to 7 weeks,[3,4,29,30] or in some cases it was not reported.[27,28] The follow-up percentage was very satisfactory, being above the 85%, excepting Oke and Umebese[27] study which did not report the follow-up.

**Table 2**
Characteristics and main results of the included studies.

| References | Demographics | Aim | Duration/ follow-up | Intervention protocol | Treatment window | Parameters assessed | Results | Follow-up (%) |
|---|---|---|---|---|---|---|---|---|
| Krammer et al.[3] | $n = 40$<br>20M/20F<br>33 y.o. | Explore the additional benefits of PEME used as an adjunct to physiotherapy in treatment of acute non-specific low back pain | 1 weeks<br>4 weeks | Experimental group: physiotherapy and PEME<br>Control group: physiotherapy and placebo<br>7 days of PEME and physiotherapy 2×/week for 4 weeks | During 7 days | ODI; NPRS; Patient Specific Functional Scale; Level of Function | Both groups showed improvements on ODI, Patient Specific Functional Scale and NPRS scores over both follow-up periods ($p < 0.05$); however, without any significant differences between them ($p > 0.05$) | 100 |
| Park et al.[30] | $n = 38$<br>11M/27F<br>32 y.o. | Investigate the efficacy of PEMF on the lumbar myalgia | 2 weeks<br>3 weeks | Experimental group: PEMF<br>Control: sham device<br>6 times, 3×/week for 2 weeks | 10 min day, 3 days a week, during 2 weeks | VASB; VASP; Korean version of: ODI; SF-36; EQ-5D; BDI; RMDQ | Significant decrease of VASB ($p < 0.007$), VASP ($p < 0.015$) and RMDQ in PEMF group in comparison to the control group | 100 |
| Oke et al.[27] | $n = 16$<br>9M/7F<br>42.8 y.o. | Assess the therapeutic efficacy of PEMF in treatment of back pain | 5–9 days<br>N.R. | Experimental group: analgesics + NSAIDs and PEMF<br>Control group: analgesics<br>Both groups received soft tissue manipulation with an analgesic gel<br>4×/day (2 h) | 4 times a day during 2 h (Min 5 days and Max 9 days of treatment) | NPRS; Modified version of Functional Activity Scale | Significant differences on experimental group on pain rating scores ($p > 0.061$) and functional activity score ($p > 0.000$) | N.R. |
| Omar et al.[28] | $n = 40$<br>11M/29F<br>38.8 y.o. | Evaluate the effect of PEMF in patients with discogenic lumbar radiculopathy | 3 weeks<br>N.R. | Experimental group: PEMF every day for 3 weeks<br>Control group: standard medical treatment and placebo | 20 min day, during 3 weeks | VAS; ODI; Radiological evaluation; Somatosensory evoked potentials | Significant reduction in pain severity ($p < 0.024$)<br>Significant improvement in modified OSW ($p < 0.001$)<br>Improvement of SSEPs ($p < 0.05$) | 100 |
| Harden et al.[4] | $n = 40$<br>20M/20F<br>40.3 y.o. | Evaluate the TEMF on chronic low back pain | 2 weeks<br>6 weeks | Experimental group: TEMF<br>Control: sham device | 40 min session, 10 sessions in 3 weeks | VAS; MPQ-SF; BDI; STAI; QPDI; Physical performance tests | Although both groups improved over time ($p < 0.05$), the experimental group improved significantly over sham treatment during the 2-week follow-up period (20.5% reduction in pain, $p = 0.003$) | 100 |
| Lee et al.[29] | $n = 36$<br>19M/17F<br>75 y.o. | Study the effect of PEMT in patients with chronic low back pain | 3 weeks<br>7 weeks | Experimental group: active PEMT<br>Control group: placebo<br>3×/week for 3 weeks | The 15-min treatment 3 times a week for 3 weeks | NPRS; Revised ODI | PEMT reduced pain and disability in patients with chronic low back pain ($p < 0.05$) | 100 |

PEME – Pulsed Electromagnetic Energy; PEMF – pulsed electromagnetic fields; TEMF – Therapeutic Electromagnetic Fields; ODI – Oswestry Disability Index; NPRS – Numeric Pain Rating Scale; M – Male; F – Female; y.o. – years old; N.R. – not reported; VAS – visual analogue scale; VASB – visual analogue scale for discomfort for low back pain; VASP – visual analogue scale for pain intensity; SF-36 – Short-Form 36; EQ-5D – EuroQol-5 Dimension (Korean adapted); BDI – Beck's Depression Inventory (Korean adapted); RMDQ – Roland-Morris Disability Questionnaire (Korean adapted); NSAIDs – nonsteroidal anti-inflammatory drugs; IL-4/IL-6 – interleukins 4 and 6; MPQ-SF – McGill Pain Questionnaire – Short Form; BDI – Beck Depression Inventory; STAI – State-Trait Anxiety Inventory; QPDI – Quebec Pain and Disability Index.

**Table 3**
PEMF devices used across the included original studies and its reported characteristics.

| References | Devices | Additional reported information |
|---|---|---|
| Krammer et al.[3] | RecoveryRx (BioElectronics Corp) | Carrier frequency of this device is 27.12 MHz. Pulse rate of 1000 pulses p/s and a 100 μs burst width. Magnetic flux density or field strength of the device is 0.03 mT |
| Harper et al.[26] | Provant Therapy System Model 4201 (Regenesis Biomedical Inc., Scottsdale, AZ, USA) | Carrier frequency of this device is 27.12 MHz. Pulse durations are 42 ± 4 μs repeated every 1000 ± 25 μs |
| Park et al.[30] | NUGA MRT-II (NUGA MEDICAL, Wonju, Korea) | The maximum strength of PEMF was 820 mT with pulse frequency of 8.56 kHz |
| Oke et al.[27] | EMpulse, Model 301 (EM-Probe Technologies, USA) | Non reported |
| Omar et al.[28] | NR | Field strengths ranged from 5 to 15 Gauss (G) and the frequency ranged from 7 Hz to 4 kHz |
| Saggini et al.[24] | NR | Electromagnetic fields of low intensity with inferior frequencies at 100 kHz |
| Lee et al.[29] | CR-3000 system (CR Technology Co., Kyungki-do, Korea) | Carrier frequency of this device range from 1 to 50 MHz. The magnetic pulse produced is biphasic and has a pulse width of 270 μs. Maximum output amplitude of 2 T |

**Table 4**
Quantification of pain intensity and effect sizes by group.

| Reference | Control | | Experimental | | Effect size (95% CI) |
|---|---|---|---|---|---|
| | Mean ± SD | Mean difference | Mean ± SD | Mean difference | |
| Krammer et al.[3 b] | 0.77 ± 1.19 | −4.14 | 0.91 ± 0.81 | −4.09 | −0.14 (−0.76, 0.49) |
| Park et al.[30 a] | 6.29 ± 1.33 | −0.53 | 4.53 ± 2.29 | −2.1 | 0.94 (0.25, 1.59) |
| Oke et al.[27 b] | 1.63 ± 0.74 | −6.62 | 1.38 ± 1.51 | −6.37 | 0.21 (−0.78, 1.18) |
| Omar et al.[28 a] | 5.8 ± 2.7 | −1.2 | 3.6 ± 1.5 | −3.5 | 1.01 (0.33, 1.64) |
| Lee et al.[29 c] | 5.4 ± 1.2 | −1.1 | 4.5 ± 1.2 | −2.2 | 0.48 (−0.19, 1.14) |

[a] Visual analogue scale.
[b] Numeric Pain Rating Scale.
[c] 11-Point numerical rating scale.

*Outcomes of interest*

The main outcome of interest was the quantification of the intensity of low back pain. All studies reported reduction on the pain intensity, at least, on the experimental group. When assessing the mean difference on pain intensity from baseline to the end-point, it was found a reduction on the pain intensity from 2.1 to 6.4 points out of 10 on the visual analogue scale or on the numerical rating pain scale (Table 4); however, when analyzing the effect sizes, two studies showed a small effect size[27,29] and two studies showed a large effect size.[28,30]

Regarding the functionality assessment, several scales and indexes were used to quantify the participant's function: Oswestry Disability Index[3,28–30]; Patient Specific Functional Scale[3]; Korean version of Roland-Morris Disability Questionnaire[30]; Modified version of Functional Activity Scale[27]; Quebec Pain and Disability Index.[4] When focusing the Oswestry Disability Index alone, which was the most commonly reported scale for measuring the functionality, despite its large mean differences from baseline to end-points (Table 5), the effect sizes were small (<0.20). The study of Omar, Awadalla and El-Latif[28] was an exception, achieving a large effect size (>0.80), however using an adapted Oswestry Disability Index.

*Methodological quality*

The mean score of methodological quality of the included studies was 6.8 ± 1.9 (range 4–9) out of 10 points according PEDro scale and the level of evidence was 1b in all studies (Table 6).

The most common methodological limitation across the studies was the lack of "intention-to-treat" analysis, which was only performed by Park, Sun, Lee, Kang, Lee, Hwang and Cha.[30] Another major methodological issue was the concealment of the randomization, which also only performed in two studies.[3,30] Lack of subjects and the assessors blinding was also a methodological limitation across the studies, especially when concerning the therapist, once only two studies blinded the therapists.[3,29]

## Discussion

The main finding of this systematic review is that PEMF therapy seems to reduce the pain intensity and enhance better functionality in individuals with low back pain.

When used alone, the PEMF seem to have great effect in reducing the pain intensity in low back patients, independently of the low back pain condition.[28–30] However, when added to other standard

**Table 5**
Oswestry Disability Index and effect sizes by group.

| Reference | Control | | Experimental | | Effect size (95% CI) |
|---|---|---|---|---|---|
| | Mean ± SD | Mean difference | Mean ± SD | Mean difference | |
| Krammer et al.[3] | 6.5 ± 9.08 | −28.7 | 5.7 ± 6.03 | −29.9 | 0.10 (−0.52, 0.72) |
| Park et al.[30 a] | 16.06 ± 8.79 | −13.83 | 14.47 ± 12.39 | −13.37 | 0.15 (−0.49,0.78) |
| Omar et al.[28 b] | 48.2 ± 10.09 | −25.60 | 33.4 ± 9.04 | −42 | 1.54 (0.81, 2.21) |

[a] Used Korean version of Oswestry Disability Index.
[b] Used Modified Oswestry Low Back Pain Disability Questionnaire and presented the results in percentages.

**Table 6**
Methodological quality of the included studies.

| References | Study design | PEDro | | | | | | | | | | | Oxford CEBM | Conflict of interest |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | E | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | Total | Level of evidence | |
| Krammer et al.[3] | Randomized, double-blind, placebo-controlled trial | + | + | + | + | + | + | + | + | – | + | – | 8 | 1b | None |
| Park et al.[30] | Randomized, double-blind, placebo-controlled trial | + | + | + | + | + | – | + | + | + | + | + | 9 | 1b | Corporations funding |
| Oke et al.[27] | Randomized controlled trial | + | + | – | + | – | – | – | – | – | + | + | 4 | 1b | Missing |
| Omar et al.[28] | Randomized controlled trial | + | + | – | + | – | – | – | + | – | + | + | 5 | 1b | None |
| Harden et al.[4] | Randomized, single-blind, placebo-controlled trial | + | + | – | + | + | – | + | + | – | + | + | 7 | 1b | Missing |
| Lee et al.[29] | Randomized, double-blind, placebo-controlled trial | + | + | – | + | + | + | + | + | – | + | + | 8 | 1b | None |

E: eligibility criteria (this item is not used to calculate the total score); 2: random allocation; 3: concealed allocation; 4: baseline comparability; 5: participant blinding; 6: therapist blinding; 7: assessor blinding; 8: <15% dropout; 9: intention-to-treat analysis; 10: between-group statistical comparisons; 11: point estimate and variability statistical measures.

therapies (such as, standard physiotherapy[3] or analgesic therapy[27]) seems to do not add additional effect to the standard therapy.

Measuring the intensity of pain related to the different low back conditions plays a key role in following up the patient's recovery. However, because of the subjective nature of pain, clinical importance is not always easy to determine.[31] In an effort to overcome this variability, measures of improvement usually adjust for the individual's baseline by calculating raw change or percent change.[32]

The PEMF therapy has been pointed out as an effective and relatively safe tool for conservatively treat the low back pain.[4,27–30] Furthermore, it has a high potential of compliance due to its low risk of side-effects and high tolerance.[29] In fact, when analyzing the pain intensity alone, the included studies effect sizes indicate a tendency to a greater reduction on pain intensity for the PEMF groups. Nevertheless, when compared to standard therapies (such as, physiotherapy[3] or analgesic therapy[27]) seemed to produce a low effect or no effect at all. Considering the minimal clinically important difference (MCID) – minimal change in an outcome score that is clinical meaningful for the patients – all studies showed that the PEMF was able to produce a clinical meaningful pain reduction since the mean differences were higher than the minimum 2-point suggested by Childs, Piva and Fritz.[33]

Several scoring systems are frequently used in the clinical environment in order to measure the disability related to the low back conditions, which should be reliable, valid and sensitive to clinically relevant changes, taken into account both patients' and physicians' perspective and is short and practical to use.[34–37] Although, impairments such as decreased range of movement or reduced straight leg raise can be clinically observed by physiotherapists, the direct observation of activity restriction is not sufficient. Therefore, the physiotherapists have the need to rely on the patient's self-report assessment to measure the impact of low back pain on daily activities.[34]

Several studies have been demonstrating the PEMF effectiveness in reducing the disability related to the low back pain.[27–30] Regarding the studies included in this systematic review, the disability assessment was mostly made by the Oswestry Disability Index,[38] showing improvements after application of PEMF therapy, however with small effect sizes. Nevertheless, the MCID's were above the minimum recommended by Ostelo, Deyo, Stratford, Waddell, Croft, Von Korff, Bouter and de Vet[39] – between 6–10 points or 12–20 percent – indicating a meaningful improvement on the patient's functionality. On the other hand, Omar, Awadalla and El-Latif[28] showed a large effect size toward the PEMF group ($d = 1.54$, 95% CI: 0.81, 2.21) using the Modified Oswestry Low Back Pain Disability Questionnaire, obtaining a 42% mean reduction after daily applications of PEMF therapy for 3 weeks. Still, some caution should be taken when considered this study since they used an adapted score.

Other usual subjective scores – generic and disease-specific – to evaluate the low back functionality have already been explored during the last decades and are currently available for orthopedic clinical and research practice.[35] In this sense, beneficial results were reported in the included studies using different scores: Patient Specific Functional Scale[3]; Korean version of Roland-Morris Disability Questionnaire[30]; Modified version of Functional Activity Scale[27]; Quebec Pain and Disability Index.[4] Although the studies showed improvements from the baseline to the study's end-point, two studies did not achieved significant improvements toward the PEMF group when compared to the control group.[3,4]

Due to the comprehensiveness and complexity within the low back pain umbrella and allied to its associated multiple etiologies, specific attention should be directed to the characteristics of subgroups of responders.[4] In this line, the studies included in our systematic review explored the PEMF therapy effectiveness in different conditions of low back pain: generalized low back pain[27]; acute non-specific low back pain[3]; discogenic lumbar radiculopathy[28]; lumbar myalgia[30]; chronic low back pain.[4,29] Due to the high heterogeneity of the different low back pain conditions of the original studies included in this systematic review, and the small sample sizes (ranging from $n = 16$ to $n = 40$), no strong recommendations can be drawn regarding the non-specific low back pain or its several conditions.

Moreover, it was found high heterogeneity between the protocols of PEMF therapy of the different studies, differing in the devices used and its parameters (frequency, pulse rate and width, magnetic flux density, among others), duration and frequency of application (4 times a day until 3 times a week) and type of application. Hence, considerable caution should be taken when comparing the results from the different studies, highlighting the importance in achieve the most effective dosage and standardized protocol parameters. In this line, future studies should shift their focus on analyzing the different mechanisms of action (e.g., myofascial, radiculopathic, among others) and subgrouping (acute or chronic, specific or generalized, mechanical or idiopathic) the individuals with low back pain in order to evaluate the effects of PEMF therapy in these different groups of low back pain and identify the responsiveness of each specific group. Thus, it will be possible to achieve the most effective PEMF protocol to the most suitable subgroup of patients.

Generally, the studies showed a good methodological quality according the PEDro scale, with a mean of 6.3 points out of 10 possible, which is above the recommended by.[40] The studies showed a good methodological quality, i.e., good external and internal validity, providing sound interpretation of the data. However, precisely in the internal validity, some limitations were found across the

studies that could provide additional bias to the results: lack of "intention-to-treat" analysis; lack of randomization concealment; lack of blinding of subjects, therapists and assessors. Moreover, another important limitation was the statement of conflict of interest, where only three studies stated that had no conflict of interest at all. Two other studies did not make any statement about conflict of interest whatsoever and two studies reported funding upon the study's conduction.

*Study limitations*

To the best of our knowledge, no other systematic review has investigated the therapeutic effects of PEMF specifically on low back pain. Moreover, it was used 2 independent reviewers for screening and critical appraisal and registered our protocol which could have reduced the bias within the systematic review. Still, there are some limitations that are needed to be pointed out. Firstly, the low number of studies available on the scientific literature that investigates the effectiveness of PEMF on low back pain is scarce, and even fewer if we consider de low back pain subgroups. Another limitation is the small size of the studies samples, which should be larger in order to provide power to the conclusion taken from the results. Also, the lack of data (means and standard deviation values) was a limitation in some studies, and the wide range of devices and low back pain conditions, precluded the systematization of the quantitative data. The search was restricted to English language studies; however, previous work demonstrated that the restriction to English language studies on systematic reviews does not provide additional bias.[41–44] Furthermore, the studies did not made an adjustment for confounders (e.g., volume of analgesic medication consumption or psychosocial variables), which could lead to further biased results. These confounders may mix with the primary exposure or outcome and bias the true relationship of interest.[45]

## Conclusion

In conclusion, the evidence within this systematic review demonstrates that the PEMF therapy seems to be able to relieve the pain and improve functionality in individuals with different low back pain conditions. However, when added to a standard therapy, it seems to do not add any beneficial effect. Nonetheless, due to the low risk associated, it can be a potential alternative to the conventional pharmacological therapy. The lack of studies in this theme warrants further research on PEMF effects on the different conditions of low back pain, with standardized protocols, larger samples and adjustment for low back pain confounders in order to achieve stronger conclusions.

## Disclosure

We certify that no party having a direct interest in the results of the research supporting this article has or will confer a benefit on us or on any organization with which we are associated. All authors have read and approved the final manuscript.

## Conflicts of interest

The authors declare no conflicts of interest.

## References


1. Airaksinen O, Brox J, Cedraschi C, Hildebrandt J, Klaber-Moffett J, Kovacs F, et al. Chapter 4: European guidelines for the management of chronic nonspecific low back pain. Eur Spine J. 2006;15:s192–300.
2. Amirdelfan K, McRoberts P, Deer TR. The differential diagnosis of low back pain: a primer on the evolving paradigm. Neuromodulation. 2014;17:11–7.
3. Krammer A, Horton S, Tumilty S. Pulsed electromagnetic energy as an adjunct to physiotherapy for the treatment of acute low back pain: a randomised controlled trial. N Z J Physiother. 2015;43:16–22.
4. Harden R, Remble T, Houle T, Long J, Markov M, Gallizzi M. Prospective, randomized, single-blind, sham treatment-controlled study of the safety and efficacy of an electromagnetic field device for the treatment of chronic low back pain: a pilot study. Pain Pract. 2007;7:248–55.
5. Volkow N. America's addiction to opioids: heroin and prescription drug abuse; 2014 [cited 15.07.15].
6. Bassett C, Pilla A, Pawluk R. A non-operative salvage of surgically-resistant pseudarthroses and non-unions by pulsing electromagnetic fields: a preliminary report. Clin Orthop Relat Res. 1977;124:128–43.
7. Li S, Yu B, Zhou D, He C, Zhuo Q, Hulme JM. Electromagnetic fields for treating osteoarthritis. Cochrane Database Syst Rev. 2013, http://dx.doi.org/10.1002/14651858.CD003523.pub2.
8. Hazlewood C, Markov M, Kostarakis P. Magnetic fields for relief of myofascial and/or low back pain through trigger points. In: Proceedings of the forth international workshop biological effects of electromagnetic fields. 2006. p. 475–83.
9. Markov MS. Pulsed electromagnetic field therapy history, state of the art and future. Environmentalist. 2007;27:465–75.
10. Fini M, Giavaresi G, Carpi A, Nicolini A, Setti S, Giardino R. Effects of pulsed electromagnetic fields on articular hyaline cartilage: review of experimental and clinical studies. Biomed Pharmacother. 2005;59:388–94.
11. Ieran M, Zaffuto S, Bagnacani M, Annovi M, Moratti A, Cadossi R. Effect of low frequency pulsing electromagnetic fields on skin ulcers of venous origin in humans: a double-blind study. J Orthop Res. 1990;8:276–82.
12. McCarthy CJ, Callaghan MJ, Oldham JA. Pulsed electromagnetic energy treatment offers no clinical benefit in reducing the pain of knee osteoarthritis: a systematic review. BMC Musculoskelet Disord. 2006;7:51.
13. Hannemann P, Mommers E, Schots J, Brink P, Poeze M. The effects of low-intensity pulsed ultrasound and pulsed electromagnetic fields bone growth stimulation in acute fractures: a systematic review and meta-analysis of randomized controlled trials. Arch Orthop Trauma Surg. 2014;134:1093–106.
14. Huang L-Q, He H-C, He C-Q, Chen J, Yang L. Clinical update of pulsed electromagnetic fields on osteoporosis. Chin Med J. 2008;121:2095–9.
15. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med. 2009;151. W-65–94.
16. Becker BJ. Synthesizing standardized mean-change measures. Br J Math Stat Psychol. 1988;41:257–78.
17. Cohen J. Statistical power analysis for the behavioral sciences. Lawrence Erlbaum Associates, Inc.; 1977.
18. Wright JG, Swiontkowski MF, Heckman JD. Introducing levels of evidence to the journal. J Bone Jt Surg. 2003;85:1–3.
19. de Morton NA. The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study. Aust J Physiother. 2009;55:129–33.
20. Maher CG, Sherrington C, Herbert RD, Moseley AM, Elkins M. Reliability of the PEDro scale for rating quality of randomized controlled trials. Phys Ther. 2003;83:713–21.
21. Khoromi S, Blackman MR, Kingman A, Patsalides A, Matheny LA, Adams S, et al. Low intensity permanent magnets in the treatment of chronic lumbar radicular pain. J Pain Symptom Manag. 2007;34:434–45.
22. Sutbeyaz ST, Sezer N, Koseoglu F, Kibar S. Low-frequency pulsed electromagnetic field therapy in fibromyalgia: a randomized, double-blind, sham-controlled clinical study. Clin J Pain. 2009;25:722–8.
23. Liu HF, Yang L, He HC, Zhou J, Liu Y, Wang CY, et al. Pulsed electromagnetic fields on postmenopausal osteoporosis in southwest China: a randomized, active-controlled clinical trial. Bioelectromagnetics. 2013;34:323–32.
24. Saggini R, Bellomo R, Saggini A, Iodice P, Toniato E. Rehabilitative treatment for low back pain with external pulsed electromagnetic fields. Int J Immunopathol Pharmacol. 2009;22:25–8.
25. Biering-Sorensen F, Hansen B, Lee BS. Non-pharmacological treatment and prevention of bone loss after spinal cord injury: a systematic review. Spinal Cord. 2009;47:508–18.
26. Harper WL, Schmidt WK, Kubat NJ, Isenberg RA. An open-label pilot study of pulsed electromagnetic field therapy in the treatment of failed back surgery syndrome pain. Int Med Case Rep J. 2015;8:13.
27. Oke K, Umebese P. Evaluation of the efficacy of pulsed electromagnetic therapy in the treatment of back pain: a randomized controlled trial in a tertiary hospital in Nigeria. West Indian Med J. 2013;62:205–9.
28. Omar AS, Awadalla MA, El-Latif MA. Evaluation of pulsed electromagnetic field therapy in the management of patients with discogenic lumbar radiculopathy. Int J Rheum Dis. 2012;15:e101–8.
29. Lee P, Kim Y, Lim Y, Lee C, Choi S, Park S, et al. Efficacy of pulsed electromagnetic therapy for chronic lower back pain: a randomized, double-blind, placebo-controlled study. J Int Med Res. 2006;34:160–7.
30. Park W-h, Sun S-h, Lee S-g, Kang B-k, Lee J-s, Hwang D-g, et al. Effect of pulsed electromagnetic field treatment on alleviation of lumbar myalgia. J Magn. 2014;19:161–9.
31. Farrar JT, Portenoy RK, Berlin JA, Kinman JL, Strom BL. Defining the clinically important difference in pain outcome measures. Pain. 2000;88:287–94.
32. Farrar JT, Young JP, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. Pain. 2001;94:149–58.

33. Childs JD, Piva SR, Fritz JM. Responsiveness of the numeric pain rating scale in patients with low back pain. Spine. 2005;30:1331–4.
34. Davidson M, Keating JL. A comparison of five low back disability questionnaires: reliability and responsiveness. Phys Ther. 2002;82:8–24.
35. Longo UG, Loppini M, Denaro L, Maffulli N, Denaro V. Rating scales for low back pain. Br Med Bull. 2010;94:81–144.
36. Deyo R. Measuring the functional status of patients with low back pain. Arch Phys Med Rehabil. 1988;69:1044–53.
37. Kopec JA. Measuring functional outcomes in persons with back pain: a review of back-specific questionnaires. Spine. 2000;25:3110–4.
38. Fairbank JC, Couper J, Davies JB, O'Brien JP. The Oswestry low back pain disability questionnaire. Physiotherapy. 1980;66:271–3.
39. Ostelo RW, Deyo RA, Stratford P, Waddell G, Croft P, Von Korff M, et al. Interpreting change scores for pain and functional status in low back pain: towards international consensus regarding minimal important change. Spine. 2008;33:90–4.
40. Jewell DV. Guide to evidence-based physical therapist practice. Jones & Bartlett Publishers; 2014.
41. Moher D, Fortin P, Jadad AR, Jüni P, Klassen T, Le Lorier J, et al. Completeness of reporting of trials published in languages other than English: implications for conduct and reporting of systematic reviews. Lancet. 1996;347:363–6.
42. Moher D, Pham B, Lawson M, Klassen T. The inclusion of reports of randomised trials published in languages other than English in systematic reviews. Health Technol Assess. 2003;7:1.
43. Morrison A, Polisena J, Husereau D, Moulton K, Clark M, Fiander M, et al. The effect of English-language restriction on systematic review-based meta-analyses: a systematic review of empirical studies. Int J Technol Assess Health Care. 2012;28:138–44.
44. Sutton AJ, Duval S, Tweedie R, Abrams KR, Jones DR. Empirical assessment of effect of publication bias on meta-analyses. BMJ. 2000;320:1574–7.
45. Goode A, Cook C, Brown C, Isaacs R, Roman M, Richardson W. Differences in comorbidities on low back pain and low back related leg pain. Pain Pract. 2011;11:42–7.

BMC Musculoskeletal Disorders

RESEARCH ARTICLE Open Access

# Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study

Hong-fei Shi, Jin Xiong*, Yi-xin Chen*, Jun-fei Wang, Xu-sheng Qiu, Yin-he Wang and Yong Qiu

## Abstract

**Background:** Pulsed electromagnetic field (PEMF) is reported to be an effective adjunct for the management of nonunion long-bone fractures. Most studies implement PEMF treatment after 6 months or longer of delayed union or nonunion following fracture treatment. Despite these variations in treatment, the early application of PEMF following a diagnosis of a postoperative delayed union has not been specifically analyzed. In this study, the outcomes of postoperative delayed union of long-bone fractures treated with an early application of PEMF were evaluated as compared with a sham-treated control group.

**Methods:** In this prospective, randomized controlled study, a total of 58 long-bone fracture patients, who presented with delayed union of between 16 weeks and 6 months, were randomly split into two groups and subjected to an early application of PEMF or sham treatment. Clinical and radiological assessments were performed to evaluate the healing status. Treatment efficacy was assessed at three month intervals.

**Results:** Patients in the PEMF group showed a higher rate of union than those in the control group after the first three months of treatment, but this difference failed to achieve statistical significance. At the end of the study, PEMF treatment conducted for an average of 4.8 months led to a success rate of 77.4%. This was significantly higher than the control, which had an average duration of 4.4 months and a success rate of 48.1%. The total time from operation to the end of the study was a mean of 9.6 months for patients in the PEMF group.

**Conclusions:** Fracture patients treated with an early application of PEMF achieved a significantly increased rate of union and an overall reduced suffering time compared with patients that receive PEMF after the 6 months or more of delayed union, as described by others.

**Keywords:** Electromagnetic field, Delayed union, Fracture healing, Long-bone fracture

## Background

Despite recent improvements in fracture management, delayed union and nonunion remain as intractable complications following surgical reduction and fixation of long-bone fractures. It is estimated that 5–10% of all fractures show impaired healing [1]. Surgical management is usually preferred in the treatment of an established nonunion, especially in those fractures that are accompanied by infection, deformity, shortening or bony defect. Otherwise, nonsurgical methods are considered for delayed union to facilitate osteogenesis, osteoinduction, as well as osteoconduction and thus stimulate the healing process [2,3]. Among the reported therapeutic methods, the use of biophysical interventions, such as pulsed electromagnetic field (PEMF) therapy, has attracted the attention of clinicians in the past decades, because of their noninvasive characteristics [4,5].

PEMF was introduced in the mid-1970s as a beneficial tool for fracture healing [6]. Although the mechanism remains poorly understood, PEMF provides an effective

* Correspondence: dr.xiongjin@gmail.com; dr.chenyixin@gmail.com
Department of Orthopaedics, Nanjing Drum Tower Hospital, The Affiliated Hospital of Nanjing University Medical School, No. 321 Zhongshan Road, Nanjing, China

adjunct for the management of un-united long-bone fractures [7-10]. However, the indication and treatment strategies for the use of PEMF vary within the literature. The majority of investigators do not start PEMF treatment until an established nonunion is diagnosed [11-14], and others consider a late stage of delayed union (over 6 months after fracture) as the indication for its use [15-17]. Very few studies have addressed the early application of PEMF immediately after diagnosis of a delayed union (at about 16 weeks after fracture) [18], and no reports have specifically investigated the efficacy of the early application of PEMF.

Long-bone fracture healing has been recognized as an orchestration of prompt hematoma formation, inflammatory response, cell proliferation and differentiation, followed by a long-term process of ossification and remodeling [19]. Since the healing process is not considered to be accomplished in the case of a delayed union in orthopaedic terms, the early intervention of PEMF possesses the theoretical advantage of reactivating the biological process of bone repair, thereby facilitating fracture healing and possibly shortening the treatment duration. In the present study, the authors aimed to evaluate the efficacy of early-applied PEMF on postoperative delayed union of long-bone fractures. We hypothesized that the early application of PEMF in patients with delayed union might lead to an increased rate of fracture union compared with sham-treated patients. The outcomes of postoperative delayed union of long-bone fractures in patients treated with an early application of PEMF after the delayed union diagnosis were evaluated and compared with the placebo-treated controls.

## Methods

### Patients

This prospective study was approved by the Medical Ethics Committee of Nanjing Drum Tower Hospital (Ref. No. 070321). A flowchart of the study is presented in Figure 1. Between April 2007 and September 2010, patients with postoperative delayed union of long-bone fracture were recruited from the outpatient clinic. During the baseline assessment, anteroposterior and lateral radiographs were taken to address the fracture healing status and the fixation method. Data on the demographic characteristics, comorbidity, medication history, lifestyle habits, fracture type, soft tissue condition were collected, as was information on the surgery and postoperative rehabilitation. Delayed union was defined as a failure to heal after at least 16 weeks and not more than 9 months following surgical reduction and fixation of the fracture [12,18]. Radiographically, healing failure was identified when callus bridging was not observed in more than three cortices on biplane radiographs. The exclusion criteria consisted of implant loosening or failure, infection, established nonunion (healing failure after more than 9 months, without any clinical or radiographic sign of progression to union within the last 3 months) [20], a fracture gap greater than 5 mm, and the presence of the implant within the fracture gap [11]. Patients with metabolic disorders were excluded as were those patients who received medications that could affect fracture healing [18,20].

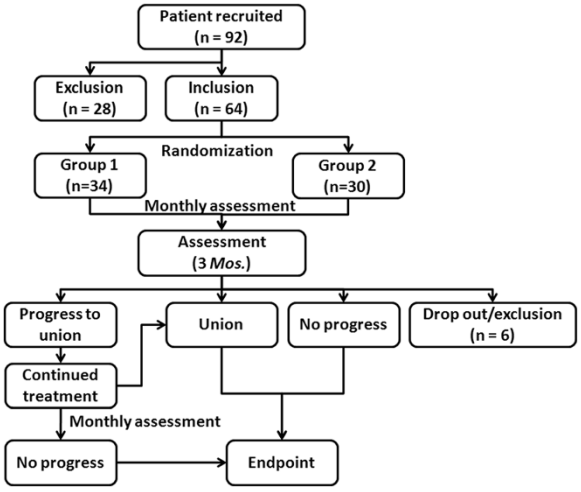



**Figure 1 Flowchart of the study.**

The authors had intended to initiate intervention 16 weeks after fracture for each patient, but not all patients were referred to the clinic in time. Therefore, patients were included in the study if they were enrolled between 16 weeks and 6 months postoperatively. A power analysis was conducted to estimate the sample size, with reference to a previously reported randomized controlled trial that achieved a union rate of 89% in PEMF-treated tibial nonunion cases compared with a 50% union rate in the sham-treated controls [13]. To detect the similar change in union rate with 80% power in our study, we required more than 48 patients.

### Interventions

Once included in the study, the patient was blindly assigned into the PEMF treatment group (Group 1) or the control group (Group 2) according to randomly generated numbers. In Group 1, PEMF treatment commenced immediately after enrollment. An electromagnetic field was delivered through a coil (Orthopulse® II, OSSATEC, Uden, The Netherlands) centered over the fracture site for 8 h/day (Figure 2), with the signal specification adjusted according to Punt's study [14]. In Group 2, the coil was applied for 8 h/day with a sham signal generator from the same manufacturer. Therefore, patients were blinded to the treatment. Protected weight

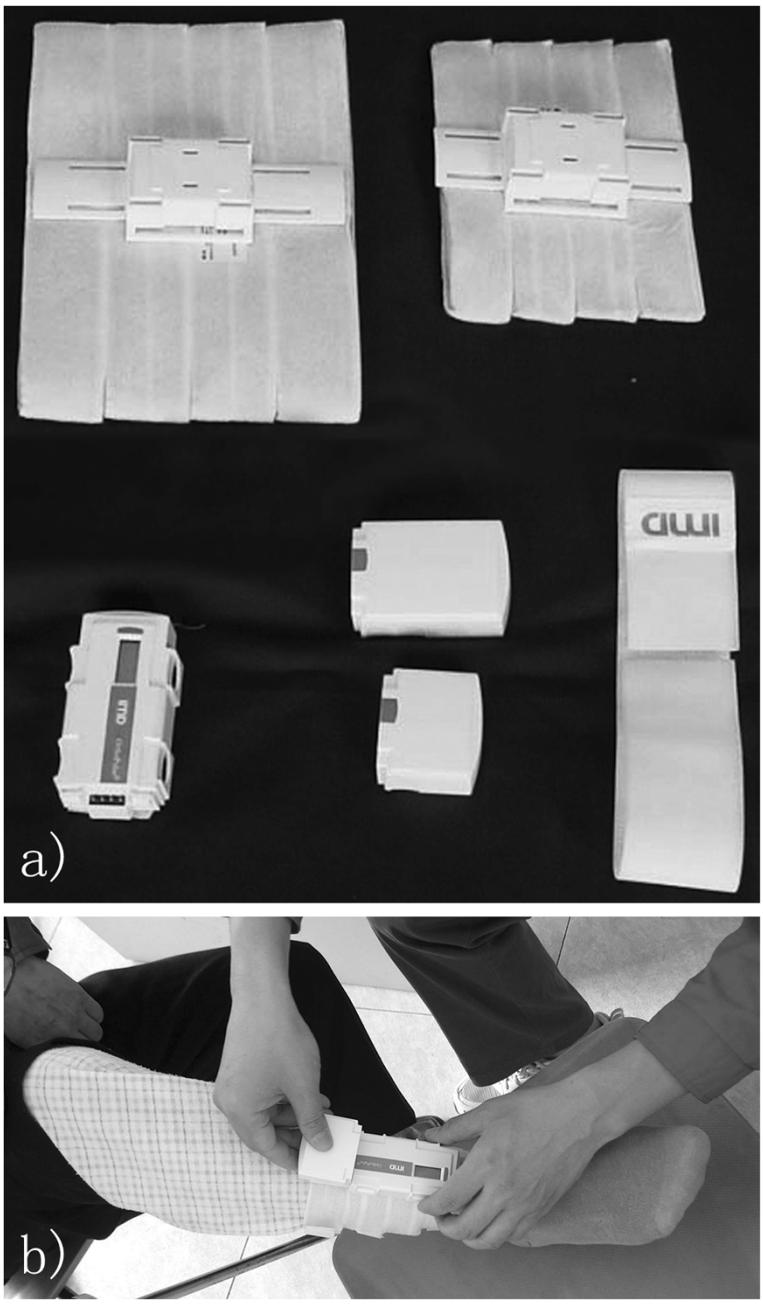



**Figure 2 The portable treatment equipments used in the study.** (**a**) A set of Orthopulse® II stimulator consisted of different sizes of coils, signal generator, batteries, and removable fixation band; (**b**) Patient in Group 1 received pulsed electromagnetic field treatment with the coil centered over the fracture site.

bearing was encouraged unless it compromised the stability of the fractured area. All patients were requested to record their potential discomfort and the duration of the treatment. They were also asked to refrain from smoking, alcohol abuse, or additional forms of therapy during the study period. Biweekly contact through phone calls was performed by two research assistants to exclude patients with poor compliance.

### Outcomes

Clinical and radiological assessments were performed monthly following commencement of the treatment. Clinical evaluations of pain when stressed and motion at the fracture site were carried out by two senior surgeons (JFW and XSQ) independently, who were blinded to the grouping information. The consensus was derived from further discussion if necessary. Another two blinded

surgeons (JX and YXC) reviewed the anteroposterior and lateral radiographs of the fracture to assess cortical bridging. Union was considered positive when there was no pain during joint stressing or during motion at the fracture site, and callus bridging was present for three out of four cortices on orthogonal radiographs [21]. Treatment was ceased in all patients when union was achieved or no radiographic progress to union was observed for a continuous three-month period (Figure 1).

### Statistical methods

Group demographics were compared using independent *t*-test or Fisher's exact test. The successful rate of fracture union was calculated after three months of treatment and at the end of the study in each group, with the difference between groups compared with Fisher's exact test. SPSS version 15.0 software (SPSS Inc, Chicago, IL) was used and the level of significance was set as 0.05.

## Results

During the study period, 92 patients with delayed union were recruited, with 64 patients meeting our inclusion criteria for early PEMF or sham treatment initiated 16 weeks and not more than 6 months postoperatively (Figure 1). Four patients dropped out after a short period of treatment, and another two patients, who received herbal supplements during the study, were excluded. The remaining 58 patients were included for statistical analysis. Patient demographics (Table 1) were comparable between the two groups, with no significant differences determined for patient age ($P = 0.450$), fracture site ($P = 0.439$), or method of fixation ($P = 0.430$). The original fracture sites included the humerus (5 cases), the ulna and/or radius (4 cases), the femur (24 cases), and the tibia (25 cases).

A total of 31 patients received PEMF treatment, whilst the remaining 27 cases were assigned to the control group (Table 1). Before treatment, the average elapsed time since fracture operation were 4.8 months and 5.1 months in the two groups, respectively ($P = 0.238$). Following three months of treatment, 12 cases achieved union with a success rate of 38.7% (95% confidence interval (CI), 0.21 to 0.57) in Group 1 (Figure 3). Meanwhile, the fracture union success rate was 22.2% (6 out of 27, 95% CI, 0.08 to 0.42) for Group 2, which was slightly lower than that for Group 1 ($P = 0.256$), but not statistically significant. The relative risk of fracture union was 1.74 (95% CI, 0.76 to 4.01). Radiographic progress to union was observed in 17 patients in each of the groups, who subsequently received extended PEMF or sham treatment. At the end of the study, the average lengths of treatment were 4.8 months and 4.4 months in the two groups ($P = 0.489$), with a union rate of 77.4% (24 out of 31, 95% CI, 0.58 to 0.90) in Group 1 (Figure 4) compared with a union rate of 48.1% (13 out of 27, 95% CI, 0.28 to 0.68) in Group 2 ($P = 0.029$, Table 1). The relative risk of fracture union was 1.61 (95% CI, 1.04 to 2.48). The total times from operation to the end of the study were averaged at 9.6 months and 9.5 months in Group 1 and Group 2 respectively ($P = 0.849$). No discomfort was reported by the patients in either group during treatment.

**Table 1 Patient demographics and results**

| | Treatment group | Control group | P Value |
|---|---|---|---|
| No. of patients | 31 | 27 | |
| Age (*Yr.*)* | 41.1 ± 14.5 (range 19 to 68) | 38.4 ± 11.6 (range 20 to 62) | 0.450 |
| Fracture Site (No. of patients) | | | 0..439 |
| Femur | 10 | 14 | |
| Tibia | 16 | 9 | |
| Humerus | 3 | 2 | |
| Radius and/or Ulna | 2 | 2 | |
| Methods of Fixation | | | 0.430 |
| Plate | 18 | 12 | |
| Intramedullary Nail | 13 | 15 | |
| Elapsed Time before Treatment (*Mo.*)* | 4.8 ± 0.9 (range 4 to 6) | 5.1 ± 0.8 (range 4 to 6) | 0.238 |
| Duration of Treatment (*Mo.*)* | 4.8 ± 2.3 (range 2 to 12) | 4.4 ± 1.6 (range 2 to 7) | 0.489 |
| Rate of fracture union (3 *Mo.*) | 38.7% | 22.2% | 0.256 |
| Rate of fracture union (Endpoint) | 77.4% | 48.1% | 0.029 |
| Total Time from Operation to Endpoint (*Mo.*)* | 9.6 ± 2.3 (range 7 to 17) | 9.5 ± 1.5 (range 7 to 12) | 0.849 |

* presented as mean ± SD.

## Discussion

In this randomized controlled study, we investigated, for the first time, the clinical efficacy of the early application of PEMF treatment in postoperative delayed union of long-bone fractures. Following three months of PEMF treatment, patients showed a higher rate of union (38.7%) than the sham-treated patients (22.2%), but this difference failed to achieve statistical significance. At the end of the study, PEMF treatment, conducted for an average duration of 4.8 months, led to a success rate of 77.4%, which is significantly higher than that in the control group (48.1%).

Clinically, the concepts and techniques surrounding the surgical management of long-bone fractures have evolved rapidly in recent decades. By comparison, the ensuing individual progress of fracture healing, in terms

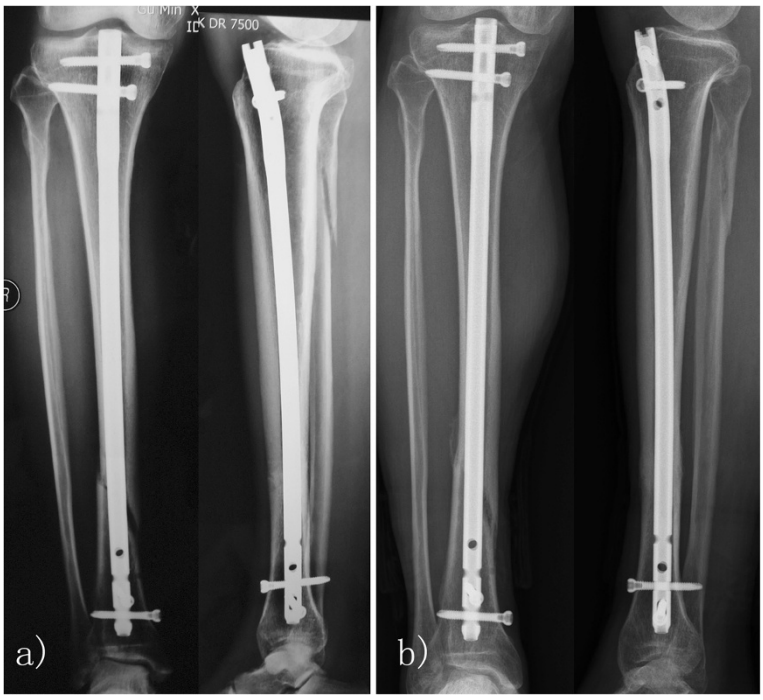



**Figure 3 Delayed union of tibia fracture treated with PEMF.** (**a**) A delayed union of tibia fracture was observed in a 65-year-old male patient following close reduction and intramedullary fixation 16 weeks ago. PEMF treatment was initiated; (**b**) Fracture union was observed after 3 months of treatment.

of biological and mechanical changes after surgery, has been poorly examined, despite the impaired healing rate of 5-10% in long-bone fracture patients. Among the multidisciplinary approaches explored to treat delayed union and nonunion fractures, the majority of studies employ the use of invasive procedures, such as surgical debridement, bone grafting and harvesting, or local injections [22,23], and hence, these procedures have been primarily examined in established nonunions. For delayed unions, noninvasive interventions, such as PEMF, are preferred before further invasive procedures are considered [4,24].

The original aim for this study was to instigate PEMF treatment immediately after the diagnosis of a post-operative delayed union (at 16 weeks after fracture). In our opinion, an earlier intervention is likely to be more effective because of the potentially deteriorated state of the biological environment after 16 weeks of delayed union or nonunion [25,26]. However in most published trials, PEMF stimulation was deferred until 6 months or

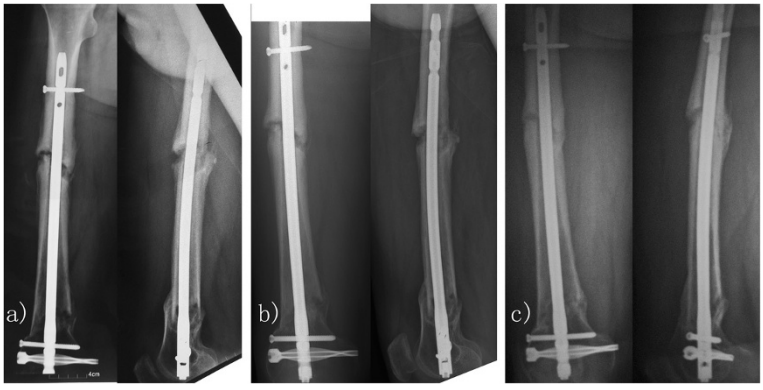



**Figure 4 Delayed union of femoral fracture treated with PEMF.** (**a**) PEMF treatment was started in a 59-year-old male patient who received reduction and intramedullary fixation 5 months ago; (**b**) Radiographies showed progress to union following 3 months of treatment; (**c**) Fracture united after 8 months of treatment.

later after fracture, with very few studies addressing the early application of PEMF in patients with delayed union. Sharrard conducted a randomized controlled trial with PEMF treatment initiated on patients with tibial delayed unions at 16 to 32 weeks after fracture [18]. Although the results revealed a significantly higher rate of union than the control, the authors did not specify the information and outcomes pertaining to the patients who received earlier intervention. A case series by Bassett addressed the effect of PEMF on 125 cases of delayed union and nonunion [27], with the earliest intervention started at four months after fracture. However, here again, the author only presented the overall success rate of the patients treated with PEMF within the nine month study period, without clarifying the impact of an early application of PEMF treatment. Similarly, in a report by Colson, there was a lack of consideration of the early effects of PEMF amongst 33 cases of long-bone delayed union or nonunion with treatment commenced from 2 to 120 months after fracture [28]. As such, our study provides pertinent evidence for the early application of PEMF on the delayed union of long-bone fractures.

The success rate following PEMF treatment in delayed union or nonunion varies dramatically (15.4–93.9%) across published studies due to different parametric settings and treatment strategies [28,29]. Considering studies with more than 30 subjects enrolled for PEMF treatment (a total of 12 studies, as summarized by Griffin), the average success rate was 80.1% (ranging from 67.6% to 93.9%) [10]. Using the same instrument as that used in our study, Punt examined a case series on established nonunions and achieved a success rate of 76–79% [14]. These results are comparable with the final success rate in our study (77.4%), demonstrating the similar stimulative effect of PEMF on delayed union, despite its earlier application in the present study. Therefore, our "sooner rather than later" hypothesis did not necessarily prevail for the clinical efficacy of PEMF. A recent report by Adie on the negative effect of PEMF on acute tibial shaft fractures further supports this [30].

Considering the treatment duration, no significant difference was observed between the groups in our study. However, the total time from fracture surgery to the end of PEMF treatment was obviously shortened in our study (9.6 months on average) compared with that in other studies who initiated PEMF stimulation after a postoperative window of 6 months, or longer in some cases (over 17.1 months in Heckman's study, and 11.6 months in de Haas's study) [15,16], not to mention the studies wherein PEMF treatment was applied in established nonunions. The early application of PEMF treatment, therefore, benefitted the patients by reducing the fracture suffering time. In clinical practice, PEMF treatment for delayed unions should be considered and initiated as early as possible, making patients fully aware of the success rate but also the increased cost.

At present, a definitive reason for the occurrence of a delayed union remains far from conclusive [31]. Both systemic and local factors are believed to be involved [23,32]. In our study, strict inclusion and exclusion criteria were set with reference to previously published clinical trials to rule out the interference of confounding variables such as metabolic disease, medication, smoking, alcohol abuse, infection, and unfavorable reduction or fixation from previous operations [11,18,20]. However, there were several factors constrained by practicality that may have influenced the outcome. For instance, the degree and extent of local damage caused by the accident or previous operation was difficult to trace. Further, patient activity levels, as a subject-related factor, could not be standardized during the study period, despite our recommendations for protected weight bearing. Another limitation of the present study was the relatively small numbers of patient for each fracture site or fixation method. We therefore could only draw an overall conclusion. Besides, serum biochemical markers were not measured in this study, which may potentially shed light on the biological mechanism of the early application of PEMF treatment.

## Conclusions

In conclusion, within the limitations discussed above, the early application of PEMF treatment promotes fracture healing and leads to a significantly increased rate of union compared with the sham treatment. Even though the final success rate in this study was not superior to that measured in other PEMF trials, we show that our patients benefitted from a reduced overall suffering time between fracture and repair.

#### Competing interests

There's no competing interests. No benefits in any form have been received or will be received related directly or indirectly to the subject of this article.

#### Authors' contributions

All authors read and agreed with the contents of the manuscript. JX and YXC participated in the study design and the radiographic outcome assessment. JFW and XSQ carried out the clinical outcome analysis. HFS was in charge of interpreting the data analysis and drafting the manuscript. YHW and YQ assisted in revising the manuscript. All authors read and approved the final manuscript.

#### Acknowledgements

This study was supported by the Starting Grant for Young Scientific and Technological Talents (Nanjing Health Bureau, QYK10147), the Key Program of Nanjing Medical Science and Technique Development Foundation (ZKX10007), and the Fundamental Research Funds for the Central Universities (0214-1434-0029). The authors would like to thank Mr. Zhao-feng JIANG and Ms. Xiao-xia ZHONG for their help in patient follow-up and data collection.

Received: 10 April 2012 Accepted: 17 January 2013
Published: 19 January 2013

## References

1. Tseng SS, Lee MA, Reddi AH: **Nonunions and the potential of stem cells in fracture-healing.** *J Bone Joint Surg Am* 2008, **90**(Suppl 1):92–98.
2. Einhorn TA, Laurencin CT, Lyons K: **An AAOS-NIH symposium. Fracture repair: challenges, opportunities, and directions for future research.** *J Bone Joint Surg Am* 2008, **90**(2):438–442.
3. Calori GM, Mazza E, Colombo M, Ripamonti C, Tagliabue L: **Treatment of long bone non-unions with polytherapy: Indications and clinical results.** *Injury* 2011, **42**(6):587–590.
4. Chao EY, Inoue N: **Biophysical stimulation of bone fracture repair, regeneration and remodelling.** *Eur Cell Mater* 2003, **6**:72–84. discussion 84–75.
5. Shi HF, Cheung WH, Qin L, Leung AH, Leung KS: **Low-magnitude high-frequency vibration treatment augments fracture healing in ovariectomy-induced osteoporotic bone.** *Bone* 2010, **46**(5):1299–1305.
6. Bassett CA, Pilla AA, Pawluk RJ: **A non-operative salvage of surgically-resistant pseudarthroses and non-unions by pulsing electromagnetic fields, A preliminary report.** *Clin Orthop Relat Res* 1977, **124**:128–143.
7. Mollon B, da Silva V, Busse JW, Einhorn TA, Bhandari M: **Electrical stimulation for long-bone fracture-healing: a meta-analysis of randomized controlled trials.** *J Bone Joint Surg Am* 2008, **90**(11):2322–2330.
8. Griffin XL, Costa ML, Parsons N, Smith N: **Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults.** *Cochrane Database Syst Rev* 2011, **4**:CD008471.
9. Novicoff WM, Manaswi A, Hogan MV, Brubaker SM, Mihalko WM, Saleh KJ: **Critical analysis of the evidence for current technologies in bone-healing and repair.** *J Bone Joint Surg Am* 2008, **90**(Suppl 1):85–91.
10. Griffin XL, Warner F, Costa M: **The role of electromagnetic stimulation in the management of established non-union of long bone fractures: what is the evidence?** *Injury* 2008, **39**(4):419–429.
11. Barker AT, Dixon RA, Sharrard WJ, Sutcliffe ML: **Pulsed magnetic field therapy for tibial non-union, Interim results of a double-blind trial.** *Lancet* 1984, **1**(8384):994–996.
12. Scott G, King JB: **A prospective, double-blind trial of electrical capacitive coupling in the treatment of non-union of long bones.** *J Bone Joint Surg Am* 1994, **76**(6):820–826.
13. Simonis RB, Parnell EJ, Ray PS, Peacock JL: **Electrical treatment of tibial non-union: a prospective, randomised, double-blind trial.** *Injury* 2003, **34**(5):357–362.
14. Punt BJ, den Hoed PT, Fontijne WPJ: **Pulsed electromagnetic fields in the treatment of nonunion.** *Eur J Orthop Surg Traumatol* 2008, **18**(2):127–133.
15. Heckman JD, Ingram AJ, Loyd RD, Luck JV Jr, Mayer PW: **Nonunion treatment with pulsed electromagnetic fields.** *Clin Orthop Relat Res* 1981, **161**:58–66.
16. de Haas WG, Beaupre A, Cameron H, English E: **The Canadian experience with pulsed magnetic fields in the treatment of ununited tibial fractures.** *Clin Orthop Relat Res* 1986, **208**:55–58.
17. Meskens MW, Stuyck JA, Mulier JC: **Treatment of delayed union and nonunion of the tibia by pulsed electromagnetic fields, A retrospective follow-up.** *Bull Hosp Jt Dis Orthop Inst* 1988, **48**(2):170–175.
18. Sharrard WJ: **A double-blind trial of pulsed electromagnetic fields for delayed union of tibial fractures.** *J Bone Joint Surg Br* 1990, **72**(3):347–355.
19. Marsell R, Einhorn TA: **The biology of fracture healing.** *Injury* 2011, **42**(6):551–555.
20. Campbell WC, Canale ST, Beaty JH: *Campbell's operative orthopaedics*. 11th edition. Philadelphia, PA: Mosby/Elsevier; 2008.
21. Dijkman BG, Sprague S, Schemitsch EH, Bhandari M: **When is a fracture healed? Radiographic and clinical criteria revisited.** *J Orthop Trauma* 2010, **24**(Suppl 1):S76–S80.
22. Zimmermann G, Moghaddam A: **Trauma: Non-union: New trends.** In *European Instructional Lectures. Volume 10*. 1st edition. Edited by Bentley G: Dordrecht Heidelberg London New York: Springer; 2010:15–19.
23. Rodriguez-Merchan EC, Forriol F: **Nonunion: general principles and experimental data.** *Clin Orthop Relat Res* 2004, **419**:4–12.
24. Khan Y, Laurencin CT: **Fracture repair with ultrasound: clinical and cell-based evaluation.** *J Bone Joint Surg Am* 2008, **90**(Suppl 1):138–144.
25. Seebach C, Henrich D, Tewksbury R, Wilhelm K, Marzi I: **Number and proliferative capacity of human mesenchymal stem cells are modulated positively in multiple trauma patients and negatively in atrophic nonunions.** *Calcif Tissue Int* 2007, **80**(4):294–300.
26. Hofmann A, Ritz U, Hessmann MH, Schmid C, Tresch A, Rompe JD, Meurer A, Rommens PM: **Cell viability, osteoblast differentiation, and gene expression are altered in human osteoblasts from hypertrophic fracture non-unions.** *Bone* 2008, **42**(5):894–906.
27. Bassett CA, Mitchell SN, Gaston SR: **Treatment of ununited tibial diaphyseal fractures with pulsing electromagnetic fields.** *J Bone Joint Surg Am* 1981, **63**(4):511–523.
28. Colson DJ, Browett JP, Fiddian NJ, Watson B: **Treatment of delayed- and non-union of fractures using pulsed electromagnetic fields.** *J Biomed Eng* 1988, **10**(4):301–304.
29. Freedman LS: **Pulsating electromagnetic fields in the treatment of delayed and non-union of fractures: results from a district general hospital.** *Injury* 1985, **16**(5):315–317.
30. Adie S, Harris IA, Naylor JM, Rae H, Dao A, Yong S, Ying V: **Pulsed electromagnetic field stimulation for acute tibial shaft fractures: a multicenter, double-blind, randomized trial.** *J Bone Joint Surg Am* 2011, **93**(17):1569–1576.
31. Hayda RA, Brighton CT, Esterhai JL Jr: **Pathophysiology of delayed healing.** *Clin Orthop Relat Res* 1998, **355 Suppl**:S31–S40.
32. Marsh D: **Concepts of fracture union, delayed union, and nonunion.** *Clin Orthop Relat Res* 1998, **355 Suppl**:S22–S30.

doi:10.1186/1471-2474-14-35
**Cite this article as:** Shi *et al.*: Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study. *BMC Musculoskeletal Disorders* 2013 **14**:35.

# AMERICAN SOCIETY FOR LASER MEDICINE AND SURGERY

# LATE-BREAKING ABSTRACTS

# ABSTRACTS

## CUTANEOUS LASER SURGERY

### #LB1

#### HIGH POWERED BLUE LIGHT PROPERTIES IN SKIN, BONE, MUSCLE, CARTILAGE AND FAT

**Christopher Zachary, Kathryn Serowka, Morgan Gustavsson, Paul Rudy, Paul Binun**

*University of California, Lumany, Irvine, CA*

**Background:** A high-power blue semiconductor laser system was developed and utilized in order to ascertain potential clinical indications using a variety of animal tissues. This highly efficient, handheld device was constructed using new laser technology, and may be of significant interest in both the medical and industrial worlds.

**Study:** This study utilized a high intensity 446 nm semiconductor laser system in two modes to ascertain the laser tissue interaction in skin, muscle, fat, cartilage and bone. Using multi beam and single beam configurations, continuous wave (CW) power was delivered with intensities between 10 and 1000 W/mm2. Tissues were exposed with pulse durations from 100 msec to multiple seconds. Direct visual observation of laser tissue interaction was observed and analyzed histologically.

**Results:** Both modalities induced striking vaporization of skin, the multibeam module being more efficient at debulking tissue, and the single module providing efficient drilling and tissue incision. Muscle similarly could be drilled or vaporized, but fat simply melted. Cartilage had a unique response in that, at low powers, this device could be used for cartilage shaping, and at high powers, creating clean and discrete holes of up to one centimeter. Histologically, full thickness skin vaporization was confirmed with a high degree of coagulation and few or no red blood cells in tissue specimens.

**Conclusion:** Blue wavelengths have not previously been described in this capacity. We have demonstrated that high power CW blue laser light can efficiently vaporize skin, muscle and cartilage with little or no bleeding. This could hold significant implications for the future in cutaneous laser surgery, and also robotic endoscopic surgeries, in particular for otolaryngology, orthopedic, urological, pulmonary, and potentially neurological surgery.



### #LB2

#### EFFECTS OF POWER DENSITY AND PULSE MODULATION ON ABLATIVE FRACTIONAL LESION GEOMETRY

**Garuna Kositratna, David Welford, Martin Jaspan, Matthew Louis Hibert, Dieter Manstein**

*Massachusetts General Hospital, Harvard Medical School, Boston, MA, Endeavour Laser Technologies Inc., Hathorne, MA*

**Background:** Ablative fractional laser treatments have become widely used. They are typically characterized by wavelength, pulse energy and spot size. While effects of power density have been investigated for large-spot, standard ablative techniques, there is very limited data available related to the effects of power density for ablative fractional lesions. It is also a challenge to vary in a controlled manner the power density of ablative $CO_2$ laser pulses, as they have typically a very irregular pulse profile. We used a custom-built, high-frequency pulse-width-modulated $CO_2$ laser to investigate the effects of variation in power density on fractional lesion geometry.

**Study:** Full thickness human skin samples, procured as discarded tissue from abdominal surgery, were used for the tissue exposures. An UltraPulse $CO_2$ laser (Lumenis, Yokneam, Israel) was modified to allow for a high-frequency pulse-width-modulation of the laser. This allowed the generation of quasi-CW mode pulses over a wide range (1–0 W) of output power in a controlled manner. The energy per pulse was kept at a constant level of 100 mJ per pulse with a constant spot size of 120 μm. The resulting fractional lesion geometry was assessed and quantified by histology.

**Results:** Reduction of power density resulted in a reduction of ablation depth in particular for power densities of 20 W and lower. Ablation and coagulation zone diameters were relatively independent over a wide power range. For power levels of less than 5 W, the ablation zone diameter was decreased and the coagulation zone increased.

**Conclusion:** Power level has a significant effect on the ablation depth and coagulation zone. This should be taken into consideration when characterizing ablative fractional lesions.

### #LB3

#### FRACTIONAL $CO_2$ LASER IN THE TREATMENT OF PRIMARY CUTANEOUS AMYLOIDOSIS: THE POSSIBLE MECHANISMS OF ACTION

**Marwa Fawzi, Samia Esamt, Safinaz Sayed, Heba Gawdat, Wael Mostafa Mohammed, Heba Saad**

*Cairo University, Maadi Militaty Hospital, Cairo, Egypt*

Published online in Wiley Online Library (wileyonlinelibrary.com).
DOI 10.1002/lsm.22252

**Background:** Current available treatments for primary cutaneous amyloidosis are quite disappointing. This study aims at assessing the efficacy of different modes of fractional $CO_2$ laser in the treatment primary cutaneous amyloidosis.
**Study:** Twenty five patients, 16 with macular amyloidosis and 6 with lichen amyloidosis were treated by 3–4 sessions of fractional $CO_2$ laser using two modes, superficial ablative mode [short pulse duration, 500 msec and lower fluences, 10–15 J] and a rejuvination mode [longer pulse durations, 800 msec and higher fluences, 25 J]. Skin biopsies were obtained prior to treatment, and one month after the end of the last sessions. Results were evaluated clinically, histologically [hematoxylin and eosin and Congo red staining] and by image analysis. In order to study the mechanism of action, 3 patients were subjected to additional biopsies on the second, fourth, and sixth day after the first treatment session.
**Results:** At the end of the treatment sessions, there was a significant improvement in color, texture as well as pruritus in both macular and lichen amyloidosis. Histologically, a significant reduction in the amount of amyloid was demonstrated in hematoxylin and eosin as well as Congo red stained sections. Image analysis showed a decrease in the amount of melanin deposits that did not reach statistical significance. A significant decrease in epidermal thickness was also obtained. Biopsies, taken during the first week, failed to demonstrate any amyloid material in the created microthermal treatment zones. Clinical and histopathological results of the two treatment parameters showed no significant differences. Transient post-inflammatory hyperpigmentation was observed only in two patients in the areas treated by the rejuvenating mode.
**Conclusion:** Fractional $CO_2$ is a safe and effective method for treatment of primary cutaneous amyloidosis. The superficial ablative mode is recommended for both clinical subtypes. Although induction of transepidermal elimination is suggested, the exact mechanism of action cannot be determined.

## #LB4

### COMPARING THE EFFECTIVENESS OF LOW FLUENCE QUALITY SWITCHED Nd:YAG LASER AND LOW FLUENCE QUALITY SWITCHED ALEXANDRITE LASER FOR MANAGEMENT OF MELASMA IN ASIANS: PRELIMINARY STUDY OF A DOUBLE-BLINDED, SIDE-BY-SIDE COMPARISON

**Kei Negishi, Shiho Tanaka, Saori Tobita, Shingo Wakamatsu**

*Aoyama Institute of Women's Medicine, Tokyo Women's Medical University, Tokyo, Japan*

**Background:** Low fluence quality switched Nd:YAG laser (QSYL) has been used to treat melasma in recent years. Many published articles showed its efficacy and safety while using appropriate parameters. However, there is no report using other wavelengths for the same purpose. This study's objective is to compare the efficacy and safety for melasma using QSYL and quality switched alexandrite laser (QSAL) by side-by-side comparison.
**Study:** In a prospective double-blinded study, twenty-two Japanese females with melasma on their cheeks, age $49.5 \pm 6.2$, skin photo type III or IV were enrolled. All cases received QSYL at 1064 nm, $2.13 \pm 0.19$ J/cm2 on one cheek and QSAL at 755 nm, $0.77 \pm 0.12$ J/cm2 on the other cheek; both treated 3 passes with 6 mm spot size by randomized manner at 2-weeks apart without any anesthesia or combination therapy. Efficacy was evaluated by two blinded assessors using modified Melasma Area and Severity Index (mMASI), measured data by spectrophotometer and multi-LED reflectance device at 2 to 8 weeks after the last treatment. Patients' preference also recorded.
**Results:** Number of treatments was $5.2 \pm 2.0$. mMASI and melanin index on QSYL and QSAL treated side were decreased from $24.6 \pm 8.0$ to $8.9 \pm 5.6$ (63.8% improvement), $25.2 \pm 7.3$ to $8.9 \pm 6.8$ (64.8%) and $202.8 \pm 49.2$ to $160.0 \pm 35.0$ (23.1%), $204.3 \pm 50.8$ to $157.0 \pm 36.5$ (23.2%), respectively. Data from multi-LED reflectance device showed similar improvement. All data, including patient preferences showed no statistical differences. All cases responded to treatment and no case showed severe adverse effect including worsening of melasma.
**Conclusion:** To our knowledge, this is the first study to use a direct side-by-side comparison of QSYL and QSAL to treat melasma using low fluence, multiple passes and treatments. Our data showed both lasers successfully managed melasma in Asians at early weeks of evaluation.

## #LB5

### RADIOFREQUENCY AND MAGNETIC PULSE FOR BODY CONTOURING: BRAZILIAN MULTI-CENTER EXPERIENCE

**Rafael Nunes, Ana Paula Martins, Guilherme Nunes, Mario Nascimento, Kleber Kumaira, Elisa Frade, Danielle Costa, Fernanda Silva, Ana Claudia Galvan**

*Dr Laser Advanced Laser Center, Belo Horizonte, Brazil, Dr Laser Advanced Laser Center, Rio De Janeiro, Brazil, Dr Laser Advanced Laser Center, Campo Grande, Brazil*

**Background:** Body Sculpting has been the objective of several procedures. In Brazil, the desire for body contouring improvements is more frequent than ever in everyday practice. In Brazil the combination of Multipolar Radiofrequency and Magnetic Pulse technology has become a common modality in the aesthetic market for non-invasive body contouring.
**Study:** A multicenter study in Brasil: Belo Horizonte, Campo Grande and Sete Lagoas with 260 subjects, 234 females, 26 males, 20–65 years old (avg 43), body mass index 23–29 (avg 26,4). Treated areas: Abdomen, Flanks, Arms and lipodystrophy areas in legs. 1 or 2 areas of 20 cm × 20 cm during the same session. Subjects were submitted to 6 sessions, spaced 1 week apart. Treatment protocol use Magnetic Pulse and MultiPolar Radiofrequency applied for 60 second over the area treated so that the surface temperature reached 40–42 Celsius. After reaching this temperature kept applying for another 15 minutes, always with the temperature maintained between 40–42 Celsius.
**Results:** Photographs and circumference measurements were made at fixed reference points (Example: Abdomen Area - Upper, Middle and Lower Abdomen) before treatment and 2 weeks after the final session. Improvement in body contouring was noticed on all subjects. No adverse side effects were recorded during or after the treatment.
**Conclusion:** In the Brazilian experience the combination of MultiPolar Radiofrequency and Magnetic Pulse has proven to be safe and effective for the purpose of body contouring and with a high subject satisfaction.

## #LB6

### RESOLUTION OF POST SURGICAL AND FILLER BRUISING USING OPTIMIZED PULSED LIGHT

**Vic Narurkar**

*San Francisco, CA*

# RF AND PULSED MAGNETIC FIELD COMBINATION: AN INNOVATIVE APPROACH TO EFFECTIVELY ADDRESS SKIN LAXITY, BODY RESHAPING AND CELLULITE.

Leonardo Marini, MD, Trieste, Italy

Many different RF devices have claimed clinical efficacy in rejuvenating the skin through controlled dermal and subcutaneous fat bulk heating. Multipolar RF has shown to be superior to monopolar and bi-polar RF in effectively inducing a sequential electro-thermal tissue stratification effect improving patient comfort and decreasing side effects. Pulsed Magnetic Fields (PMF) have proven to accelerate angiogenesis, cutaneous wound healing, bone and nerve repair. PMF also decrease post-surgical pain and edema as well as negatively influence bacterial and tumoral cell growth.

The association of these two technologies seems to produce a synergistically effective dermal-hypodermal tissue functional improvement inducing long term collagen remodelling, adipose tissue reshaping and cellulite regression. Venus Freeze is the first technical example where these two innovative bio-medical strategies are intimately associated.

Temperature-induced intracellular synthesis of stress proteins could theoretically stand as the very base of the tissue bio-stimulation leading to optimization of cellular function. PMF-induced cellular and around-cell positive micro-environmental changes ideally contribute to speed up and consolidate tissue functional improvements. Long term results are very promising and can be progressively visible 2-4 months after one series of 6-10 treatments.

Patient satisfaction is very high (85% of treated patients); fair-to-acceptable (10%); minimal (5%). Minimal transient side effects were reported and were considered absolutely acceptable by both patients and physicians. More studies are nevertheless required to further understand the full potential of this extremely innovative technique.