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Therapeutic Applications of Electromagnetic Fields in Musculoskeletal Disorders: A Review of Current Techniques and Mechanisms of Action

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ABSTRACT

Electromagnetic fields (EMFs) have been increasingly used as an alternative or adjunctive treatment option for musculoskeletal disorders (MSDs) like fractures, arthritis and osteoporosis. The electromagnetic based treatments can be divided into four main groups based on their physical characteristics and consequent biological effects: Direct current, capacitive coupling, inductive coupling (pulsed EMF), and combined magnetic fields. Despite the wide range of treatment modalities and various applications of EMFs in MSDs, the mechanism of actions of each modality are not yet completely understood. In addition, there was no comprehensive comparative study on different modalities to determine the appropriate technique for each MSD. The present study aims to review the most common EMF based therapeutic methods for MSDs and compare their therapeutic efficiency for each disorder. Furthermore, the mechanisms of action of each method are discussed.

Key words: Musculoskeletal Disorders, Electromagnetic field, treatment, Bone fracture, osteoporosis, Arthritis, Mechanism of Action.

INTRODUCTION

Medical and health related applications of electromagnetic fields (EMFs) are dated back over thousands years ago. The first written document on a bioelectric event dated back 4000 BC that describes catfish as a fish that releases the troops[1]. The first written document on the medical application of electricity is from the year A.D. 46, when Scribonius Largus recommended the use of torpedo fish for curing headaches and gouty arthritis[2] The first medical application of EMFs as a field of study has its roots in the 18th and 19th centuries when scientists in Europe and the United States first began to investigate the medical application of electromagnetism.

In the early 1800s scientists in physics and biology have found a relation between physical forces including mechanical, electrical, magnetic forces and ultrasonic waves and bone biology. Mechanical, electrical, and magnetic forces as well as ultrasonic waves have all been reported to influence bone growth and healing. EMF stimulations have then been developed for exerting therapeutic and also diagnostic outcomes. The study of electricity and medicine continued into the 20th century, with Becker and Selden[3] exploring new pathways in the understanding of evolution, acupuncture, psychic phenomenon, and healing. In 1954, Fukada and Yasuda published a study on the piezoelectric properties of dry bone and stress-generated electrical potentials directly relating to callus formation[4]. In 1962, Becker *et al.*[5] and Bassett *et al.*[6] described the electrical properties of hydrated bone. Their findings were confirmed by Friedenberg and Brighton[7] in 1966. In line with these findings, Shamos and Lavine (1967) evaluated the piezoelectric properties of biological tissues[8]. These findings have drawn research interests of scientists to seek the potential therapeutic applications of EMFs in different Musculoskeletal Disorders (MSDs). Therefore, different technologies have been tested for the biophysical stimulation of bone formation, including extracorporeal shock-waves electrical and electromagnetic, laser, mechanical, and ultrasound[9].

Selective control of cell function by spatially configured, weak, time varying magnetic fields has resulted in a new line of research in biology and medicine. Field parameters for therapeutic, pulsed EMFs (PEMFs) were designed to induce voltages similar to the bio-potential within the body and during dynamic mechanical deformation of connective tissues. As a result, various serious MSDs have been treated successfully over the past two decades.

Musculoskeletal Disorders and electromagnetic fields

Delay or failure of fracture healing is a common, significant clinical problem confronting orthopedic surgeons. The treatment options for these fractures can be divided into two main groups of invasive surgical techniques and noninvasive techniques. Invasive surgical techniques include internal and external fixation, bone grafting, and even amputation. Noninvasive options include bone growth stimulation which can be achieved through EMFs and ultrasound wave.

Any injury to bones like fracture and damage initiates a unique self-regeneration process to form new bone to heal the damaged site[10-12]. Fracture healing is a complicated metabolic process its speed and amplitude depend on the interaction of various factors such as activating and using of reparative cells and genes[10,12]. If these factors are inadequate or interrupted, fracture healing is delayed or impaired, resulting in a nonunion of the bone. Approximately 10% of the annual fracture patients in the world experience nonunion and/or delayed unions that impose significant economic burden and also decrease the quality of life of patients[13]. Therefore, different research groups have started to develop new modalities to enhance bone healing process. The results were development of different techniques for improving the treatment process of MSDs[14-36].

The underpinning idea of EMFs applications in MSDs has its root in the piezoelectric effect explaining converting electromagnetic oscillations to mechanical vibrations and vice versa. In the early 1950s, Fukada and Yasuda demonstrated that imposing stress to a bone to cause deformity will generate electrical potentials: In the compression areas the bone is electronegative and causes bone resorption, whereas areas under tension are electropositive and produce bone[4]. Therefore, subsequent developments were based on the idea that stimulating these endogenous electric fields using an electrical stimulation device would enhance bone healing. The common non-drug treatment techniques of MSDs can be divided into electric field, electromagnetic field, magnetic field, and low intensity pulsed ultrasound (LIPUS). There are five clinical methods of administering electrical current to bone or damaged site including direct current (DC), capacitive coupling (CC), inductive coupling (IC) or pulsed EMFs, static magnetic field (SMF) and combined magnetic field (CMF) [Ryaby, 1998 #235]. In the following sections we introduce each technique, its physical principles and applications in treatment of MSDs.

Direct Current

DC had been substantially developed during the 1960s through 1970s as the predecessor to modern day bone growth stimulator technology. DC is an invasive method where implanted electrodes, wire leads of various lengths, are surgically placed directly at the fracture or fusion site [Lieberman, 2002 #336]. DC techniques are commonly used during initial spinal fusion procedures, these stimulators also are implanted during fixation and bone grafting of nonunions. A cathode is placed at the site of the bone defect with an anode in the soft adjacent tissue [Lieberman, 2002 #336]. Osteogenesis is reportedly to be stimulated at the cathodal electrode site using currents ranging 5 to 100 μA and varying the number of electrodes between 2 and 4[Lieberman, 2002 #338]. Since the stimulator is implanted, the therapeutic treatment is continuous and is removed upon the healing occurrence [Lieberman, 2002 #338]. DC stimulators provide constant uniform current at the target site during the entire battery life, increasing the patient compliance to the therapy[21]. The disadvantages of DC stimulators are battery life of approximately 6-8 months, difficulty placing hardware, short circuits from leads touching other lead wires (or any metal), tissue reaction, soft tissue discomfort, risk of infection, and a second procedure for hardware removal [Evans, 2001 #337].

Capacitive Current

CC is a non-invasive method and has been popularized during the 1980s [Brighton, 1985 #343]. an external power source is connected to two wires which are attached to two cutaneous electrodes applied on the opposite sides of the bone or target region to be stimulated[37] [Cain, 2001 #345]. The external power source, using potentials of 1 to 10 V, produces electromagnetic fields at frequency range of 20–200 kHz that induce electric fields with the magnitude ranging 1 to 100 mV/cm [Cain, 2001 #345]. The induced electric fields are sufficient enough for bone stimulation and initiating physiological processes in tissues [Brighton, 1985 #344].

The disadvantages of CC include short lifespan of battery for instance when using the unit for 24 hours, patients must change batteries daily. In addition, despite the small and lightweight of electrodes, they may cause irritation of the skin in the contact sites [Nelson, 2003 #346]. One of the proposed mechanisms of action in CC is that the electro-stimulation regulates gated ion channels to increase the flux of calcium within the cells [Lorich, 1998 #347].

Inductive Current

IC, otherwise known as pulsed electromagnetic fields (PEMFs), has been popularized in the 1970s. It is noninvasive and enhances bone and joint healing by PEMF stimulation. IC is performed by placing 1 or 2 current-carrying coils on the skin over the fracture or damaged site[38]. Based on the Faraday's law of induction, flowing current through the coils, produces a magnetic field at right angles to the coil base that can be directed within the fractures site[38]. The magnetic field produces an electric field, whose magnitude depends on the tissue type at the stimulating site and characteristics of magnetic field [Aaron, 2004 #254;Aaron, 2006 #18]. Electromagnetic fields varying from 0.1 to 20 G are usually used to create an electrical field of 1 to 100 mV/cm at the target site. IC techniques are beneficial treatment options as they are noninvasive, painless, and surgery free[38]. Furthermore, they can be easily and conveniently used by patients at home and in most cases patients are allowed to bear weight[38]. The first PEMF device was introduced in 1979 for fracture healing, and used an externally applied coil adjustable in size for fracture location. The power unit for IC techniques can be used through or placed under casting material, with the patient wearing an external battery for up to 10 hours of daily application [Cain, 2001 #345]. By creating an electrical signal in bone after energizing the coil, the device enhances the treatment of nonunions, using the bioelectrical principles of bone healing [Nelson, 2003 #346]. In PEMFs, low-level electromagnetic fields are created which in turn are converted to electric fields at fracture or target sites [Aaron, 2004 #254;Aaron, 2006 #18].

Previous studies showed that the PEMF imitates the body's normal physiologic processes [Nelson, 2003 #346]. The PEMF signal is a complex waveform often in biphasic and quasi-rectangular, varying in amplitude and frequency. The disadvantage of IC technique is heavy weight of the power source and unit of system which can result in the patient noncompliance [Bassett, 1989 #260].

Magnetic field

Magnetic fields have various biological effects some of them can be used as therapeutic effects for different disorders[31, 33, 35, 36, 39-41]. The important therapeutic point in the application of magnetic fields in MSDs is that South and North pole has different physiological and biological effects on living organizations[35,36,40,41]. In this regard, different and even opposite effects are expected from North pole, South pole and concurrent application of both poles. Despite the belief that the energies of a magnet are homogeneous (the same), the magnetism does indeed consist of two separate and distinct energies with opposite effects on all matter, especially in medicine. Some of biological effects of North pole include pain relieving, antiinflammation, alkaline effect, inhibiting infection. However, the reported South pole effects include increasing inflammation, excitatory effects on bio-systems, decreasing tissue oxygen, acidic effects and promoting microorganisms.(22, 39) The magnetic fields based treatments can be divided into two groups: SMF and CMF.

Static Magnetic Field

SMFs have shown different therapeutic effects in humans and animal models including anti-inflammatory, pain relieving, antibacterial and inhibition/excitation effects. The SMFs have therapeutic in different organisms and systems including cardiovascular, skeleton, endocrine and reproductive systems[22, 36, 40, 42].

Combined Magnetic field

CMF that became popular in the 1990s combines a static DC electric field and a sinusoidal waveform[43] produced by external coils placed on the targeted site or worn by patient. The average use of CMF treatment is about 30 min daily for few to several days. The use of CMF is based on theoretic calculations that predicted coupling to calcium-dependent cellular signaling processes in tissues[44, 45]. CMFs have been shown to stimulate bone formation and fracture healing in animal model systems[46, 47]. Previous studies have shown that theses therapeutic methods may act by stimulating endogenous production of growth factors that regulate the healing process[48]. The first clinical application of combined magnetic fields was on long bone nonunion healing and received FDA approval in 1994[49].

The ease of use and short daily application are some advantages of CMFs that can improve patient compliance to the technique. One of the possible mechanisms of action of CMFs in influencing cell signaling is presumably through intracellular stores of calcium to increase[50, 51] levels and result in bone cell proliferation.

Mechanisms of Action

Despite the various studies conducted on the therapeutic effects of EMFs fields on the MSDs, the mechanisms of actions of the techniques are not completely understood. There have been several in vitro and in vivo studies conducted to shed light on the mechanisms of actions of each EMF based treatment modality. After the reviewing some of these studies with outstanding outcomes, we have divided the mechanism of action proposed for each technique (Table 1). In the following sections the most frequent reported mechanism of action for DC, CC, IC, and magnetic field are discussed.

Mechanism of action of DC

Previous in vitro studies on the effects and mechanisms of action of DC indicated that this technique stimulates osteogenesis through electrochemical reactions at the cathode site ($O2 + 2H_2O + 4e \rightarrow 4OH$) creating end products referred to as faradic products[52-53]. The hydroxyl ions (OH) formation at the cathode decreases the oxygen concentration and increases the pH[52]. The resulting environment prevents bone resorption and increase bone formation by increasing osteoblast and decreasing osteoclast activities (52). A second faradic product is hydrogen peroxide (H_2O_2)[53] formed at the cathode site and improves osteoclast differentiation[52]. The resorption by the osteoclasts in turn activates bone formation by the osteoblasts. The second effect of H2O2 is probably because of its stimulating effect on the releasing of vascular endothelial growth factor by macrophages, which is important for angiogenesis in fracture healing[54]. Another mechanism of action by DC is reportedly increasing growth factor synthesis by osteoblasts, such as bone morphogenetic proteins (BMPs)[55].

Mechanism of action of CC

Some in vitro studies conducted on the mechanism of action of CC techniques demonstrated the main mechanism of bone formation stimulation is through calcium translocation via voltage-gated calcium channels[50,51]. Based on this mechanism, CC technique enhances the activated calmodulin levels through a chain of reactions. Activated calmodulin has been shown to promote cellular proliferation in bone by up-regulating nucleotide synthesis and various enzymatic proteins, which increases callus formation and maturation[51]. Other mechanism by which CC improves bone healing process is the activation of growth factors like mRNA expression of BMPs and transforming growth factor-beta 1 (TGF-β1) by activated osteoblasts[56].

Mechanism of action of IC

Previous studies indicated two main mechanisms for IC techniques[51, 57, 58]. First, increasing the calcium uptake of bone through inactivating its signal to parathyroid hormone. Second, activation of intracellular calcium stores[51]. These stores then increase activated calmodulin levels, which enhance osteoblast cell proliferation. This is the key difference to CC, where the activation of intracellular calcium is from an extracellular pathway[51]. In addition, previous studies have reported that IC stimulates bone healing by up-regulation of growth factor production including some of BMPs, TGF-β1, and insulin growth factor-2 by osteoblasts.

Modification of intracellular calcium is one of the important mechanisms by which IC and CC influence on the bone healing process. These techniques up-regulate calcium, which is important in bone healing, as it has a role in the mineralization of bone and conducts the communication between cell surface receptors, antibodies, and hormones for DNA synthesis needed for bone healing.

Appropriate Technique for an MSD

Reviewing the previous studies conducted on the therapeutic efficacy of different EMF techniques on different MSDs showed that some methods have higher efficiency for specific disorders. This might be due to the mechanisms of actions of the method in one hand and the different nature of different MSDs. Table 1 shows the MSDs for which each therapeutic technique shows the effective outcomes.

DCs have been used to enhance bone healing in spinal fusion, nonunions, delayed unions, and as an adjunct for promotion of bone healing in ankle surgery (Table 1). The therapeutic efficacy of DC as an adjunct in hind-foot fusion and revision

Table 1: Therapeutic applications of each EMF for different MSDs along with the proposed mechanisms of action. DC: direct current, CC: capacitive coupling, IC: Inductive coupling, PEMF: pulsed electromagnetic field, SMF: static magnetic field, CMF: Combined magnetic field. BMPs: bone morphogenetic proteins, TGF-β1: transforming growth factor-beta 1

Technique	Musculoskeletal disorders	Mechanisms of action
DC	Spinal fusion Osteonecrosis of the femoral head	Electrochemical reaction at the cathode, Increasing pH; decreasing oxygen; increasing osteoblast; decreasing osteoclast; increasing vascular endothelial growth factor
CC	Spinal fusion; delayed union fractures; Nonunion fractures	Activation of intracellular calcium stores; Increasing osteoblast; altering BMPs; calcium translocation via voltage-gated calcium channels; enhancing activated calmodulin
IC (PEMF)	Bone healing ; Spinal fusion; Osteotomy; Fresh fracture; Osteoporosis; Osteoarthritis Delayed union fractures; nonunion fractures	Increasing the calcium uptake of bone; activation of intracellular calcium stores; enhancing activated calmodulin; altering BMPs, TGF-β1, and gene expression
SMG	Rheumatoid Arthritis; Osteoarthritis; chronic pain; Osteonecrosis; Back pain	cytoprotection of cells; stimulation of growth factor synthesis; anti-inflammatory; analgesic effects
CMF	Spine fusion; Osteoarthritis; Osteoporosis; Nonunion fractures	Increasing osteoblast; decreasing osteoclast; altering BMPs and gene expression;

ankle arthrosis and also in osteonecrosis of the femoral head has been shown by different study[59-61]. However, findings of previous studies have not shown effective outcomes from the use of DC in nonunion and delayed union fractures.

CCs have been used to enhance bone healing in nonunions, delayed unions, and spinal fusion (Table 1)[49, 62-64]. In the nonunion fractures especially long bone nonunions and spinal fusion, CC showed the best therapeutic outcome[49, 64].

ICs (PEMFs) have been widely used for bone healing in unions and nonunions, osteoporosis, osteotomies, osteoarthritis, and rheumatoid arthritis and osteoarthritis related pains management[15, 16, 18, 65-72] (Table 1). The use of PEMFs for bone healing, spinal fusion, femoral and tibial osteotomies, fresh fracture, congenital pseudoarthrosis, osteoporosis, osteoarthritis, and delayed union and nonunion fractures showed significant therapeutic outcomes.

SMFs have been used for various MSDs especially for osteoarthritis, osteonecrosis, rheumatoid arthritis, pain management in low back pain and osteoarthritis and also for anti-inflammatory and infection purposes[22,31,33-36,39,40,42,73, 74]. SMFs showed high performance in rheumatoid arthritis, osteoarthritis, chronic pain, osteonecrosis and back pain. The main point in the SMF applications is that North pole and South pole has different and sometimes opposite effects on biological tissue which should be considered in therapeutic applications.

CMFs have been utilized for different MSDs and showed the higher efficiency for spine fusion, osteoarthritis, osteoporosis and nonunion fractures. Among the different therapeutic EMF methods for MSDs, PEMF and CMF have shown greater potential and can be developed to more extent to obtain higher therapeutic outcomes for different disorders. Table 1 shows the therapeutic applications of each EMF based treatment for different MSDs along with the proposed mechanisms of action.

CONCLUSION

EMF stimulations have therapeutic benefits for different MSDs such as bone aiding internal and external fixation, enhancing delayed restoration and osteotomies, increasing bone mineral density, reducing chronic pain, treating fresh fractures, and aiding femoral osteonecrosis, preventing and treating osteoporosis, rheumatoid arthritis and osteoarthritis.

Among the current therapeutic methods of EMFs, PEMF and CMF have higher therapeutic potential and flexibility to be developed for different MSDs.

DC works by an electrochemical reaction at the cathode. CC modulates molecular pathways and growth factors to enhance proliferation and differentiation of the osteoblast. IC enhances osteoblast differentiation and proliferation through alteration of growth factors, gene expression, and trans-membrane signaling. Furthermore, modification of intracellular calcium is one of the important mechanisms by which IC and CC influence on the bone healing process. The exact mechanism by which EMF stimulation improves bone repair is not clear and further studies are needed to fulfill the gap.

REFERENCES

1. Malmivuo J, Plonsey R. Bioelectromagnetism: principles and applications of bioelectric and biomagnetic fields: Oxford University Press (1995).
2. Kellaway P. The part played by electric fish in the early history of bioelectricity and electrotherapy. *Bulletin of the History of Medicine.* **20**(2):112-37 (1946).
3. Becker RO, Selden G, Bichell D. The body electric: electromagnetism and the foundation of life: Quill New York (1985).
4. Fukada E, Yasuda I. On the piezoelectric effect of bone. *Journal of the Physical Society of Japan*. **12**(10):1158-62 (1957).
5. Becker R, Bassett C, Bachman C, Frost H. Bone biodynamics. *Bioelectrical factors*

controlling bone structure. 213-31 (1964).

6. Bassett CAL, Pawluk RJ. Effects of electric currents on bone in vivo. *Nature*. **204**:652-4 (1964).
7. Friedenberg Z, Brighton CT. Bioelectric potentials in bone. *The Journal of bone and joint surgery American volume.* **48**(5):915-23 (1966).
8. Shamos MH. Piezoelectricity as a fundamental property of biological tissues. *Nature.* **213**: 267-9 (1967).
9. Behrens SB, Deren ME, Monchik KO. A review of bone growth stimulation for fracture treatment. *Current Orthopaedic Practice.* **24**(1):84-91 (2013).
10. Chen JC, Castillo AB, Jacobs CR. Chapter 20 - Cellular and Molecular Mechano transduction in Bone. In: Marcus R, Feldman D, Dempster DW, Luckey M, Cauley JA, editors. Osteoporosis (Fourth Edition). San Diego: Academic Press; p. 453-75 (2013).
11. Praemer A, Furner S, Rice DP, Surgeons AAoO. Musculoskeletal conditions in the United States (1992).
12. Wraighte PJ, Scammell BE. Principles of fracture healing. Surgery (Oxford). **24**(6): 198-207 (2006).
13. Woolf AD, Pfleger B. Burden of major musculoskeletal conditions. *Bulletin of the World Health Organization.* **81**(9): 646-56 (2003).
14. Aaron RK, Ciombor DM, Wang S, Simon B. Clinical biophysics: the promotion of skeletal repair by physical forces. Annals of the New York Academy of Sciences. **1068**: 513-31 (2006).
15. 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).
16. Bassett CA. Fundamental and practical aspects of therapeutic uses of pulsed electromagnetic fields (PEMFs). *Critical reviews in biomedical engineering*. **17**(5): 451-529 (1989).
17. Biering-Sorensen F, Hansen B, Lee BS. Non-pharmacological treatment and prevention of bone loss after spinal cord injury: a systematic review. *Spinal cord.* **47**(7): 508-18 (2009).
18. Bilotta TW, Zati A, Gnudi S, Figus E, Giardino R, Fini M, et al. Electromagnetic fields in the treatment of postmenopausal osteoporosis: an experimental study conducted by densitometric, dry ash weight and metabolic analysis of bone tissue. *La Chirurgia degli organi di movimento.* **79**(3): 309-13 (1994).
19. Gupta A, Meswania J, Pollock R, Cannon SR, Briggs TW, Taylor S, et al. Non-invasive distal femoral expandable endoprosthesis for limb-salvage surgery in paediatric tumours. *The Journal of bone and joint surgery British volume.* **88**(5): 649-54 (2006).
20. Jayanand, Behari J, Lochan R. Effects of low level pulsed radio frequency fields on induced osteoporosis in rat bone. *Indian journal of experimental biology*. **41**(6):581-6 (2003).
21. Tamma R, dell'Endice S, Notarnicola A, Moretti L, Patella S, Patella V, et al. Extracorporeal shock waves stimulate osteoblast activities. Ultrasound in medicine & biology. **35**(12): 2093-100 (2009).
22. Trock DH. Electromagnetic fields and magnets. Investigational treatment for musculoskeletal disorders. *Rheumatic diseases clinics of North America*. **26**(1):51-62, viii (2000).
23. Zhou J, He H, Yang L, Chen S, Guo H, Xia L, et al. Effects of pulsed electromagnetic fields on bone mass and Wnt/beta-catenin signaling pathway in ovariectomized rats. *Archives of medical research.* **43**(4): 274-82 (2012).
24. Busse JW, Bhandari M, Kulkarni AV, Tunks E. The effect of low-intensity pulsed ultrasound therapy on time to fracture healing: a meta-analysis. *Canadian Medical Association Journal.* **166**(4): 437-41 (2002).
25. Cheung WH, Chin WC, Qin L, Leung KS. Low intensity pulsed ultrasound enhances fracture healing in both ovariectomy-induced osteoporotic and age-matched normal bones. *Journal of orthopaedic research : official publication of the Orthopaedic Research Society.* **30**(1):129-36 (2012).
26. Gebauer D, Mayr E, Orthner E, Ryaby JP. Low-intensity pulsed ultrasound: effects on nonunions. *Ultrasound in medicine & biology.* **31**(10): 1391-402 (2005).
27. Huang T, He C. [The update progress of physical treatment for osteoporosis]. Sheng wu yi xue gong cheng xue za zhi = Journal

of biomedical engineering = Shengwu yixue gongchengxue zazhi. **28**(5): 1057-60 (2011).

28. Pilla A, Mont M, Nasser P, Khan S, Figueiredo M, Kaufman J, et al. Non-invasive low-intensity pulsed ultrasound accelerates bone healing in the rabbit. *Journal of orthopaedic trauma.* **4**(3): 246-53 (1990).
29. Rutten S, Nolte PA, Korstjens CM, van Duin MA, Klein-Nulend J. Low-intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula. Bone. **43**(2): 348-54 (2008).
30. Schofer MD, Block JE, Aigner J, Schmelz A. Improved healing response in delayed unions of the tibia with low-intensity pulsed ultrasound: results of a randomized sham-controlled trial. BMC musculoskeletal disorders. **11**(1): 229 (2010).
31. Bruce G, Howlett C, Huckstep R. Effect of a static magnetic field on fracture healing in a rabbit radius: preliminary results. *Clinical orthopaedics and related research.* **222**: 300-6 (1987).
32. Eccles NK. A critical review of randomized controlled trials of static magnets for pain relief. *Journal of alternative and complementary medicine.* **11**(3): 495-509 (2005).
33. Hinman MR, Ford J, Heyl H. Effects of static magnets on chronic knee pain and physical function: a double-blind study. *Alternative therapies in health and medicine.* **8**(4): 50-5 (2002).
34. Segal NA, Toda Y, Huston J, Saeki Y, Shimizu M, Fuchs H, et al. Two configurations of static magnetic fields for treating rheumatoid arthritis of the knee: a double-blind clinical trial. *Archives of physical medicine and rehabilitation.* **82**(10): 1453-60 (2001).
35. Xu S, Okano H, Ohkubo C. Acute effects of whole-body exposure to static magnetic fields and 50-Hz electromagnetic fields on muscle microcirculation in anesthetized mice. *Bioelectrochemistry.* **53**(1): 127-35 (2001).
36. Yu S, Shang P. A review of bioeffects of static magnetic field on rodent models. *Progress in biophysics and molecular biology* (2013).
37. Lieberman JR, Daluiski A, Einhorn TA. The role of growth factors in the repair of bone biology and clinical applications. *The Journal of Bone & Joint Surgery*. **84**(6): 1032-44 (2002).
38. Evans R, Foltz D, Foltz K. Electrical stimulation with bone and wound healing. *Clinics in podiatric medicine and surgery.* **18**(1): 79-95 (2001).
39. Vallbona C, Hazlewood CF, Jurida G. Response of pain to static magnetic fields in postpolio patients: a double-blind pilot study. *Archives of physical medicine and rehabilitation.* **78**(11): 1200-3 (1997).
40. McDonald F. Effect of static magnetic fields on osteoblasts and fibroblasts in vitro. *Bioelectromagnetics*. **14**(3): 187-96 (1993).
41. Miyakoshi J. The review of cellular effects of a static magnetic field. Science and *Technology of Advanced Materials.* **7**(4): 305-7 (2006).
42. Yan Q, Tomita N, Ikada Y. Effects of static magnetic field on bone formation of rat femurs. *Medical engineering & physics.* **20**(6): 397-402 (1998).
43. Ryaby JT. Clinical effects of electromagnetic and electric fields on fracture healing. *Clinical orthopaedics and related research*. **355**: S205-S15 (1998).
44. McLeod BR, Liboff AR. Cyclotron resonance in cell membranes: The theory of the mechanism. Mechanistic Approaches to Interactions of Electric and Electromagnetic Fields with Living Systems: Springer; 97-108 (1987).
45. Fitzsimmons R, Ryaby J, Magee F, Baylink D. Combined magnetic fields increased net calcium flux in bone cells. *Calcified tissue international.* **55**(5): 376-80 (1994).
46. Deibert MC, Mcleod BR, Smith SD, Liboff AR. Ion resonance electromagnetic field stimulation of fracture healing in rabbits with a fibular ostectomy. *Journal of orthopaedic research.* **12**(6): 878-85 (1994).
47. Fitzsimmons RJ, Ryaby JT, Mohan S, Magee FP, Baylink DJ. Combined magnetic fields increase insulin-like growth factor-II in TE-85 human osteosarcoma bone cell cultures. *Endocrinology*. **136**(7): 3100-6 (1995).
48. Linovitz RJ, Pathria M, Bernhardt M, Green D, Law MD, McGuire RA, et al. Combined magnetic fields accelerate and increase spine fusion: a double-blind, randomized, placebo

controlled study. *Spine.* 27(13): 1383-9; discussion 9 (2002).

49. Scott G, King J. A prospective, double-blind trial of electrical capacitive coupling in the treatment of non-union of long bones. *Journal of Bone and Joint Surgery-A-American* **76**(6): 820-6 (1994).
50. Lorich DG, Brighton CT, Gupta R, Corsetti JR, Levine SE, Gelb ID, et al. Biochemical pathway mediating the response of bone cells to capacitive coupling. *Clinical orthopaedics and related research.* **350**: 246-56 (1998).
51. Brighton CT, Wang W, Seldes R, Zhang G, Pollack SR. Signal transduction in electrically stimulated bone cells. *The Journal of Bone & Joint Surgery.* **83**(10): 1514-23 (2001).
52. Bodamyali T, Kanczler J, Simon B, Blake D, Stevens C. Effect of faradic products on direct current-stimulated calvarial organ culture calcium levels. *Biochemical and biophysical research communications.* **264**(3): 657-61 (1999).
53. Kim IS, Song JK, Zhang YL, Lee TH, Cho TH, Song YM, *et al.* Biphasic electric current stimulates proliferation and induces VEGF production in osteoblasts. Biochimica et Biophysica Acta (BBA*)-Molecular Cell Research.* **1763**(9): 907-16 (2006).
54. Cho M, Hunt TK, Hussain MZ. Hydrogen peroxide stimulates macrophage vascular endothelial growth factor release. American *Journal of physiology-heart and circulatory physiology.* **280**(5): H2357-H63 (2001).
55. Gan JC, Glazer PA. Electrical stimulation therapies for spinal fusions: current concepts*. European Spine Journal.* **15**(9):1301-11 (2006).
56. Zhuang H, Wang W, Seldes RM, Tahernia AD, Fan H, Brighton CT. Electrical stimulation induces the level of TGF-beta1 mRNA in osteoblastic cells by a mechanism involving calcium/calmodulin pathway. *Biochem Biophys Res Commun.* **237**(2): 225-9 (1997).
57. Yen Patton G, Patton WF, Beer DM, Jacobson BS. Endothelial cell response to pulsed electromagnetic fields: stimulation of growth rate and angiogenesis in vitro. *Journal of cellular physiology*. **134**(1): 37-46 (1988).
58. Nagai M, Ota M. Pulsating electromagnetic field stimulates mRNA expression of bone morphogenetic protein-2 and-4. *Journal of dental research.* **73**(10): 1601-5 (1994).
59. Ciombor DM, Aaron RK. The role of electrical stimulation in bone repair. *Foot and ankle clinics*. **10**(4): 579-93 (2005).
60. Paterson D, Lewis G, Cass C. Treatment of congenital pseudarthrosis of the tibia with direct current stimulation. *Clinical orthopaedics and related research.* **148**: 129-35 (1980).
61. Steinberg Me, Brighton Ct, Corces A, Hayken Gd, Steinberg Dr, Strafford B, et al. Osteonecrosis of the femoral head: results of core decompression and grafting with and without electrical stimulation. *Clinical orthopaedics and related research.* **249**: 199-208 (1989).
62. Brighton CT, Hozack WJ, Brager MD, Windsor RE, Pollack SR, Vreslovic EJ, et al. Fracture healing in the rabbit fibula when subjected to various capacitively coupled electrical fields. *Journal of orthopaedic research.* **3**(3): 331-40 (1985).
63. Brighton CT, Pollack SR. Treatment of Recalcitrant Non-Union with. *Bone*. **10**: 2 (1985).
64. Goodwin CB, Brighton CT, Guyer RD, Johnson JR, Light KI, Yuan HA. A double-blind study of capacitively coupled electrical stimulation as an adjunct to lumbar spinal fusions. Spine. **24**(13):1349-56; discussion 57 (1999).
65. Chang K, Chang WH-S, Huang S, Huang S, Shih C. Pulsed electromagnetic fields stimulation affects osteoclast formation by modulation of osteoprotegerin, RANK ligand and macrophage colony-stimulating factor. *Journal of Orthopaedic Research.* **23**(6): 1308-14 (2005).
66. Ciombor DM, Aaron RK, Wang S, Simon B. Modification of osteoarthritis by pulsed electromagnetic field-a morphological study. Osteoarthritis and cartilage / OARS, *Osteoarthritis Research Society*. **11**(6):455-62 (2003).
67. 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. *Biomedicine & pharmacotherapy =*

Biomedecine & pharmacotherapie. **59**(7): 388-94 (2005).

68. Ganguly KS, Sarkar AK, Datta AK, Rakshit A. A study of the effects of pulsed electromagnetic field therapy with respect to serological grouping in rheumatoid arthritis. *Journal of the Indian Medical Association.* **96**(9): 272-5 (1998).
69. Inoue N, Ohnishi I, Chen D, Deitz LW, Schwardt JD, Chao EYS. Effect of pulsed electromagnetic fields (PEMF) on late-phase osteotomy gap healing in a canine tibial model. *Journal of Orthopaedic Research.* **20**(5): 1106-14 (2002).
70. Jing D, Cai J, Wu Y, Shen G, Li F, Xu Q, *et al*. Pulsed Electromagnetic Fields Partially Preserve Bone Mass, Microarchitecture, and Strength by Promoting Bone Formation in Hindlimb-Suspended Rats. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research (2014).
71. Saltzman C, Lightfoot A, Amendola A. PEMF as treatment for delayed healing of foot and ankle arthrodesis. Foot & ankle international / American Orthopaedic Foot and Ankle Society [and] Swiss Foot and Ankle Society. **25**(11): 771-3 (2004).
72. Shen WW, Zhao JH. Pulsed electromagnetic fields stimulation affects BMD and local factor production of rats with disuse osteoporosis. *Bioelectromagnetics*. **31**(2): 113-9 (2010).
73. Kroeling P, Gross A, Graham N, Burnie SJ, Szeto G, Goldsmith CH, et al. Electrotherapy for neck pain. *The Cochrane database of systematic reviews*. **8**: CD004251 (2013).
74. Taniguchi N, Kanai S. Efficacy of static magnetic field for locomotor activity of experimental osteopenia. *Evidence-Based Complementary and Alternative Medicine.* **4**(1): 99-105 (2007).