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. 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. 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\(^37\), capacitive coupling (CC), inductive coupling (IC) or pulsed EMFs, static magnetic field (SMF) and combined magnetic field (CMF)\(^38\). 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\(^39\). 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\(^39\). 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\(^39\). Since the stimulator is implanted, the therapeutic treatment is continuous and is removed upon the healing occurrence\(^39\). DC stimulators provide constant uniform current at the target site during the
entire battery life, increasing the patient compliance to the therapy. 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.

**Capacitive Current**

CC is a non-invasive method and has been popularized during the 1980s. 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. 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. The induced electric fields are sufficient enough for bone stimulation and initiating physiological processes in tissues.

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. 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.

**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. 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. The magnetic field produces an electric field, whose magnitude depends on the tissue type at the stimulating site and characteristics of magnetic field. 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. Furthermore, they can be easily and conveniently used by patients at home and in most cases patients are allowed to bear weight. 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. 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. In PEMFs, low-level electromagnetic fields are created which in turn are converted to electric fields at fracture or target sites.

Previous studies showed that the PEMF imitates the body’s normal physiologic processes. 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.

**Magnetic field**

Magnetic fields have various biological effects some of them can be used as therapeutic effects for different disorders. 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. 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, anti-inflammatory, 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. 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.\(^\text{22, 36, 48, 50}\)

Combined Magnetic Field

CMF that became popular in the 1990s combines a static DC electric field and a sinusoidal waveform 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.\(^\text{51}\) CMFs have been shown to stimulate bone formation and fracture healing in animal model systems.\(^\text{54, 55}\) Previous studies have shown that theses therapeutic methods may act by stimulating endogenous production of growth factors that regulate the healing process.\(^\text{56}\) The first clinical application of combined magnetic fields was on long bone nonunion healing and received FDA approval in 1994.\(^\text{57}\)

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 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 \((\text{O}_2 + 2\text{H}_2\text{O} + 4\text{e}^- \rightarrow 4\text{OH})\) creating end products referred to as faradic products.\(^\text{59, 60}\) The hydroxyl ions \((\text{OH}^-)\) formation at the cathode decreases the oxygen concentration and increases the pH.\(^\text{59}\) The resulting environment prevents bone resorption and increase bone formation by increasing osteoblast and decreasing osteoclast activities.\(^\text{59}\) A second faradic product is hydrogen peroxide \((\text{H}_2\text{O}_2)\) formed at the cathode site and improves osteoclast differentiation.\(^\text{59}\) The resorption by the osteoclasts in turn activates bone formation by the osteoblasts. The second effect of \(\text{H}_2\text{O}_2\) 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.\(^\text{61}\) Another mechanism of action by DC is reportedly increasing growth factor synthesis by osteoblasts, such as bone morphogenetic proteins (BMPs).\(^\text{62}\)

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.\(^\text{44, 58}\) 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.\(^\text{58}\) 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-\(\beta1\)) by activated osteoblasts.\(^\text{63}\)

Mechanism of action of IC

Previous studies indicated two main mechanisms for IC techniques.\(^\text{56, 64, 65}\) First, increasing the calcium uptake of bone through inactivating its signal to parathyroid hormone. Second, activation of intracellular calcium stores.\(^\text{56}\) 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. 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 ankle arthroscopy and also in osteonecrosis of the femoral head has been shown by different studies. However, findings of previous studies have not shown effective outcomes from the use of DC in nonunion and delayed union fractures.

### 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

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<tr>
<th>Technique</th>
<th>Musculoskeletal disorders</th>
<th>Mechanisms of action</th>
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<tr>
<td>DC</td>
<td>Spinal fusion Osteonecrosis of the femoral head</td>
<td>Electrochemical reaction at the cathode, Increasing pH; decreasing oxygen; increasing osteoblast; decreasing osteoclast; increasing vascular endothelial growth factor</td>
</tr>
<tr>
<td>CC</td>
<td>Spinal fusion; delayed union fractures; Nonunion fractures</td>
<td>Activation of intracellular calcium stores; Increasing osteoblast; altering BMPs; calcium translocation via voltage-gated calcium channels; enhancing activated calmodulin</td>
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<tr>
<td>IC (PEMF)</td>
<td>Bone healing; Spinal fusion; Osteotomy; Fresh fracture; Osteoporosis; Osteoarthritis Delayed union fractures; nonunion fractures</td>
<td>Increasing the calcium uptake of bone; activation of intracellular calcium stores; enhancing activated calmodulin; altering BMPs, TGF-β1, and gene expression</td>
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<tr>
<td>SMG</td>
<td>Rheumatoid Arthritis; Osteoarthritis; chronic pain; Osteonecrosis; Back pain</td>
<td>cytoprotection of cells; stimulation of growth factor synthesis; anti-inflammatory; analgesic effects</td>
</tr>
<tr>
<td>CMF</td>
<td>Spine fusion; Osteoarthritis; Osteoporosis; Nonunion fractures</td>
<td>Increasing osteoblast; decreasing osteoclast; altering BMPs and gene expression;</td>
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</table>
CCs have been used to enhance bone healing in nonunions, delayed unions, and spinal fusion (Table 1)\(^{41, 57, 68, 69}\). In the nonunion fractures especially long bone nonunions and spinal fusion, CC showed the best therapeutic outcome\(^{57, 69}\).

ICs (PEMFs) have been widely used for bone healing in unions and nonunions, osteoporosis, osteotomies, osteoarthritis, and rheumatoid arthritis and osteoarthritis related pains management\(^{15, 16, 18, 70-77}\) (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\(^{22, 31, 33-36, 47, 48, 50, 78, 79}\). 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.

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