# Low-frequency pulsed electromagnetic fields in orthopedic practice: bone and cartilage repair

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**Abstract**

The use of biophysical stimulation, with low-frequency pulsed electromagnetic fields, to modulate osteogenetic response and favour fracture healing has been the subject of wide-ranging research. Current orthopaedics reviews the different modalities of biophysical treatment in search of solutions most adequate to the pathology, the characteristics of the fracture and those of the patient. It is up to the orthopaedist to assess whether the biomechanical conditions of stability of the fracture site are such as not to jeopardize the osteogenetic process.

Moreover, experimental studies on articular cartilage have demonstrated that low-frequency pulsed electromagnetic fields control inflammation, protect extracellular matrix and favour chondrocytes metabolic activity. The results of two level I clinical study on patients underwent arthroscopic procedures demonstrated that low-frequency pulsed electromagnetic fields favour patients' recovery both in the short (90 days) and in the long term (3 years). The long term benefit results from biophysical chondroprotection of articular cartilage and from prevention of the fibrotic stimuli exerted by pro-inflammatory cytokines on wound tissue.

Biophysical stimulation plays a central role also in regenerative medicine, protecting the repair of tissue from catabolic effects of the inflammatory reaction elicited by the surgical implantation procedure.

**Introduction.**

The physicians' therapeutic means include the use of both chemicals and physical energy. Whereas the use of chemicals (drugs) and ionizing electromagnetic energy for disease treatment has been well defined in medicine and surgery, it has not been the same for non-ionizing electromagnetic energies. Biological systems are able to absorb electromagnetic energy; the use in medicine of physical energy for therapeutic and diagnostic purposes is based on the above observation. In radiotherapy, the property of the biological systems to absorb energy has led to introduce the concept of the dose-effect relationship, that is the dose on which "all" effects should depend, even though the biological targets can show specific susceptibilities.

The capability to modify the activity of a biological target through low-frequency pulsed electromagnetic fields (LF-PEMFs) is a relatively recent acquisition. The dependence of the biological effects on other parameters, for example waveform, frequency, or ratio energy/time, has been addressed and dose response curves for these parameters have been reported by several authors both in *in vitro* and *in vivo* studies. Non-ionizing electromagnetic effects can be ascribed both to thermal effects (present if there is a temperature increase) or to non-thermal effects when the energy transferred to the biological system is extremely low.

Today, several diseases, in different fields of medicine, are treated with non-ionizing electromagnetic energy, so that the clinical applications appear certainly more advanced than the basic research. Unlike drugs, the effect of electromagnetic energy is local and limited to the site of application. No systemic effects are known following the exposure to LF-PEMFs of part of the body.

During the last century, the treatment with electromagnetic energy has been introduced to favor bone and cartilage healing and its clinical use is now based on scientific evidence [1]. Furthermore, non-ionizing electromagnetic fields have been used to treat patients suffering from central nervous system diseases, cancer, pain control, ischemic injury, soft tissue ulcers. Nevertheless, more research is needed in these areas before electromagnetic treatment can be proposed for routine use.

Electromagnetic energy can be applied to the human body by a direct contact or irradiation. In direct contact modality electromagnetic energy is applied through contact electrodes. Otherwise, the biological target can be exposed to the electromagnetic energy through electric or magnetic field generators placed in proximity of the body.

The "clinical biophysics" is that branch of medical science that studies the action process and the effects of non-ionizing LF-PEMFs utilized for therapeutic purposes. The principles on which the clinical biophysics is based are represented by: the recognizability and the specificity of the electromagnetic energy applied. As to recognizability, we mean the capacity of the biological target to recognize the presence of the electromagnetic energy: this aspect becomes more and more important with the lowering of the energy applied. As to specificity, we

978-1-4244-6051-9/11/$26.00 ©2011 IEEE

mean the capacity of the electromagnetic energy applied to the biological target to elicit a response which depends on its physical characteristics: waveform, frequency, duty-cycle, energy, etc. The orthopedic community has played a central role in the development and understanding of the importance of the physical stimuli to control biological activities, having studied the clinical importance of the electric or magnetic stimulation of endogenous bone and cartilage repair.

**Low-frequency pulsed electromagnetic fields in bone repair**

The employment of physical energy to modulate osteogenetic response and, ultimately, to enhance fracture healing is a topic widely researched in Europe. Studies have been conducted to demonstrate that exogenous electrical signals applied to the bone can be of clinical importance, particularly in situations where repair processes have remained incomplete. A number of experimental studies have shown how and to what extent endogenous bone repair can be enhanced in various animal models. In humans, LF-PEMFs are used to finalize bone repair in non-unions as well as fresh fractures. Research performed up to now has enabled evaluation of: a) the different effectiveness of methods of applying electrical stimulation to the bone tissue, and b) modalities, times and doses needed to obtain a positive influence on osteogenesis. Devices have been approved for clinical use by the U.S. Food and Drug Administration and are employed in many countries to accelerate and finalize the healing of fractures and to enhance the spontaneous repair of the bone tissue, i.e. to reactivate it in pathological conditions such as non-unions.

*Stimulation of Reparative Osteogenesis in Osteotomies.*

The study of electromagnetic stimulation on osteotomies represents an original approach in an attempt to quantify the effects of LF-PEMFs in the clinical practice. Three prospective, randomized, double-blind studies have been performed with LF-PEMFs on: a) human femoral intertrochanteric osteotomies [2] b) tibial valgus osteotomies [3] and c) osteotomies in patients undergoing massive bone graft [4]. The studies on osteotomies of femur and tibia showed how the application of electromagnetic stimulation results in enhanced bone healing. In the case of femur osteotomy, 32 patients were investigated. The authors evidenced among LF-PEMFs stimulated patients an increased trabecular bridging on both femur cortexes; furthermore, digital analysis of the bone callus on the medial cortex demonstrated an increase in bone mineral content both at 40 and 90 days in the active group compared to the placebo one ($p<0.05$). In tibial osteotomies study, 40 patients undergoing tibial osteotomies were evaluated. Bone healing at 60 days was scored and it was shown that the number of patients healed in the active group was 2.6 times that in placebo group ($p<0.04$). In the third study the effect of LF-PEMFs stimulation was challenged on patients undergoing massive bone graft following tumor resection. Forty-six patients were included in the study, a total of 83 host graft junctions were investigated. The analysis of variance with the different factors influencing the healing and LF-PEMFs showed that the only significant association was with the use of chemotherapy ($p=0.0005$). Among patients who did not receive adjuvant chemotherapy, healing was achieved in 6.7 months on average in the active group and in 9.4 months in placebo group ($p<0.001$). No difference was observed between control and active groups in the survival number of patients and in the local or distal tumor recurrence.

*Stimulation of Reparative Osteogenesis in Non-Union and Delayed Union.*

In 1982 Bassett reported a success rate of 85% in the treatment with LF-PEMFs of 814 patients suffering from non-unions [5]. Sharrard in 1990 demonstrated the efficacy of LF-PEMFs stimulation in a double-blind study involving 45 tibial shaft fracture in patients suffering from ununited fracture from at least 6 months from trauma [6]. The radiologist's assessment of union was positive in 50% of patients in active group compare to 8% in the placebo group ($p<0.002$). Simonis in 2003 reported the results of the treatment of 34 consecutive patients with tibial non union followed over a period of 5 years; 16 out of 18 (89%) non-unions healed in the active group as compare to 8 out of 16 (50%) in the dummy group ($p=0.02$) [7]. Traina et al. observed that the treatment of non-union with LF-PEMFs is particular indicated when the local bio-mechanical condition (alligment, bone gap, mobility) at the fracture site are adequately controlled; thus he compared 2 groups of contemporany patients suffering from non-union one undergoing surgery and the other been treated with LF-PEMFs [8]. It was found that in the stimulated group the success rate was higher than in the operated group, 84% versus 69% ($p<0.05$), and union was achieved faster in the stimulated group. Furthermore the time to healing was 6.3 months in the group undergoing surgery as compare to 5.3 months in the stimulated group ($p<0.01$).

*Stimulation of Reparative Osteogenesis in the Presence of a Prostheses*

Biophysical stimulation has proven useful to favor experimental bone ingrowth. For the orthopaedic surgeon, the possibility to stimulate osteogenetic activity in the presence of a primitive prosthetic implant—and most

importantly in revision arthroplasty—represents an important therapeutic possibility. Some studies indicate that LF-PEMFs in the short term may resolve pain in subjects with mobilized, painful prostheses [9] and have a positive effect on bone mineral density, on pain and, consequently, functional recovery of subjects in patients undergoing hip revision surgery [10].

**Low frequency pulsed electromagnetic fields in cartilage repair**

Articular cartilage is a complex tissue characterised by chondrocytes that are embedded within an organized dense extracellular matrix of collagen and proteoglycan. Modest damage of the articular cartilage, resulting from trauma or less invasive surgical procedure, produces an inflammatory reaction of the joint cartilage, that can cause irreversible degeneration through the increase of catabolic cytokines synthesis and the decrease of anabolic activity of chondrocytes. Pro-inflammatory cytokines increase the synthesis of matrix degrading enzymes and limit the production of proteoglycans. It is known that physical stimuli modulate cartilage metabolism.

In particular, LF-PEMFs with specific parameters (I-ONE therapy, Igea, Carpi, Italy) allow to treat homogenously the whole cartilage surface and thickness and the underlying subchondral bone. *In vitro*, I-ONE therapy increases the binding between adenosine and $A_{2A}$ adenosine receptor on human neutrophils cell membrane, on bovine chondrocytes and fibroblast-like synoviocytes [11,12]. It has been shown that drugs with $A_{2A}$ adenosine receptor agonist activity prevent articular cartilage degeneration in animals. We hypothesized that the adenosine agonist effect of I-ONE therapy can also prevent cartilage degeneration. *Ex vitro*, in bovine full thickness articular cartilage explants, I-ONE therapy induces the largest increase in proteoglycan synthesis and in IGF-1 synthesis, when cartilage is exposed to specific parameters of pulsed electromagnetic fields [13,14].

These effective parameters were subsequently used in *in vivo* experiments. The effect of I-ONE therapy was investigated on Dunkin Hartley osteoarthritic knee by Mankin score and by histomorphometric and densitometric analysis; I-ONE therapy prevented cartilage degeneration and subchondral bone sclerosis [15]. Osteochondral grafts were performed in the knees of sheep; I-ONE therapy favoured osteochondral grafts integration and prevented cyst-like resorption area formation, that can compromise the stability of graft and the success of the technique [16]. To support the *in vitro* results biochemical analysis of the synovial fluid were also performed in this animal model. The amount of inflammatory catabolic cytokines (IL-1β and TNF-α) in the synovial fluid of I-ONE therapy treated animals was significantly lower than in control animals. On the contrary, TGF-β1 was significantly higher in stimulated animals than it was in controls. These results demonstrate not only the capability of I-ONE therapy to control the inflammatory reaction, but also its capability to favours cartilage anabolic activity.

These results provide the rational to design clinical studies to demonstrate the possibility to transfer the treatment to humans. Two randomized, prospective, double-blind clinical studies (Level I), one conducted to patients treated by arthroscopy with condroabrasion and/or perforations at the knee [17] and the other after anterior cruciate ligament reconstruction [18], demonstrated that biophysical stimulation with I-ONE therapy leads to complete patient's recovery in a significantly shorter time ($p<0.005$). Moreover, a significantly number of subjects stimulated with I-ONE therapy made lower use of anti-inflammatory drugs than the patients in the placebo group. We did not observe negative side effects, patient's compliance was good and treatment was well accepted. I-ONE therapy treatment significantly reduces patients' recovery time, joint swelling and has a chondroprotective effect over articular cartilage. I-ONE treatment is a new therapy for the joint preservation.

**Conclusion**

Today several new areas of medicine are interested in the possibility to utilize non chemical means to treat different pathologies. Some applications are simply at their beginning or still at the preliminary stage of research; however, everything induces to think that these therapeutic possibilities will be more and more utilized. The biophysical therapy with LF-PEMFs has, when compared to the pharmacological treatments, the advantage of being easy to administrate. Being a local therapy it can reach the maximum "concentration" at the treatment site and thus the maximum therapeutic efficacy, without general negative side effects.

The biophysical therapy with LF-PEMFs seems to be suitable for protracted treatments in the presence of chronic degenerative diseases, whereas it does not seem possible to treat systemic disorders. Further development of the clinical application of LF-PEMFs introduces many and complex questions; however, the possibility to recognize and define a therapeutic development area as the clinical biophysics represents a fundamental moment of synthesis necessary to create a common ground of reference for researchers of different fields. While this may favor the development of new technologies, it has also meant the proliferation of systems of treating patients with no scientific basis or study demonstrating their effectiveness. This exposes the patients to the risk of being treated with devices whose efficacy has not been proven or worst that can potentially be harmful. This deficiency will certainly need to be remedied by the responsible authorities in the next future.

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