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# Role of pulsed electromagnetic fields after joint replacements

Lullini G *et al*. Pemfs in joint replacements

Giada Lullini, Eugenio Cammisa, Stefania Setti, Iacopo Sassoli, Stefano Zaffagnini, Giulio Maria Marcheggiani Muccioli

**Eugenio Cammisa, Iacopo Sassoli, Stefano Zaffagnini,Giulio Maria Marcheggiani Muccioli,** II Orthopaedic and Traumatology Clinic, IRCCS Istituto Ortopedico Rizzoli - DIBINEM - University of Bologna, Bologna 40100, Italy

**Giada Lullini,** Laboratorio di Analisi del Movimento e di valutazione funzionale protesi

IRCCS Istituto Ortopedico Rizzoli - DIBINEM - University of Bologna, Bologna 40100, Italy

**Stefania Setti,** Laboratory of Clinical Biophysics,IGEA Clinical Biophysics, 41012 Carpi, Italy

**Author contributions:** Lullini G conceived the study idea, and designed the research with Marcheggiani Muccioli GM; Cammisa E and Sassoli I wrote the manuscript, collected and analyzed the data, Lullini G, Setti S and Zaffagnini S edited and revised the manuscript.

**Corresponding author: Giulio Maria Marcheggiani Muccioli, MD, PhD, Academic Research, Adjunct Professor, Doctor,** II Orthopaedic and Traumatology Clinic, IRCCS Istituto Ortopedico Rizzoli - DIBINEM - University of Bologna, via Pupilli 1, Bologna 40100, Italy. marcheggianimuccioli@me.com

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**Abstract**

Although the rate of patients reporting satisfaction is generally high after joint replacement surgery, up to 23% after total hip replacement and 34% after total knee arthroplasty of treated subjects report discomfort or pain 1 year after surgery. Moreover, chronic or subacute inflammation is reported in some cases even a long time after surgery. Another open and debated issue in prosthetic surgery is implant survivorship, especially when related to good prosthesis bone ingrowth. Pulsed Electro Magnetic Fields (PEMFs) treatment, although initially recommended after total joint replacement to promote bone ingrowth and to reduce inflammation and pain, is not currently part of usual clinical practice. The purpose of this review was to analyze existing literature on PEMFs effects in joint replacement surgery and to report results of clinical studies and current indications. We selected all currently available prospective studies or RCT on the use of PEMFs in total joint replacement with the purpose of investigating effects of PEMFs on recovery, pain relief and patients’ satisfaction following hip, knee or shoulder arthroplasty. All the studies analyzed reported no adverse effects, and good patient compliance to the treatment. The available literature shows that early control of joint inflammation process in the first days after surgery through the use of PEMFs should be considered an effective completion of the surgical procedure to improve the patient’s functional recovery

**Key words:** Pulsed Electromagnetic Fields; Joint replacement; Osteointegration; Prosthesis outcome; Pain; Inflammation

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**Core tip:** Pulsed Electro Magnetic Fields are a safe treatment, generally well tolerated by the patients.They have been shown to aid the recovery after joint substitution surgery, acting as an inflammation modulator and reducing pain in the first months after surgery.Further studies should be conducted on the long-term effects of PEMFs on implants integration and survival.

# INTRODUCTION

Joint prosthesis is a common surgical procedure for the treatment of joints degeneration.

In recent years, the number of patients undergoing joint replacement is increasing worldwide with a prevision of further increase in the next decade. At the same time treated patients are younger and more active, therefore with higher expectations and requiring high final functional outcome. Although the rate of patients reporting satisfaction is generally high, up to 23% after total hip replacement and 34% after total knee arthroplasty of treated subjects report discomfort or pain 1 year after surgery[1]. Moreover, chronic or subacute inflammation is described in some cases even a long time after surgery. Since a valid rehabilitation process correlates to patients’ compliance, a painful joint can interfere with recovery and good functional outcome. Another open and debated issue in prosthetic surgery is the survival of implants, especially when associated to good prosthesis bone ingrowth. Aseptic prosthesis loosening is not uncommon and always requires revision surgery, with an increase in morbidity and mortality, especially in elderly patients. Bozic *et al*[2] reported that revision total knee arthroplasty (TKA) and total hip arthroplasty (THA) rate increased by 39% (revision burden, 9.1%-9.6%) and 23% (revision burden, 15.4%-14.6%) respectively. Revision THAs were performed more often in older patients compared with revision TKAs.

Whilst the ongoing improvements in biomaterials, surgical indications and techniques, another approach may entail the stimulation of bone intrinsic potential of regeneration with adjuvant therapies, in order to accelerate and maximize bone ingrowth, reduce pain and enhance clinical recovery, improving the final outcome. Therefore, effective treatment strategy for promoting bone growth and remodeling is needed.

In recent years Pulsed Electro Magnetic Fields (PEMFs) have been gaining popularity due to the finding that the cell membrane plays an important role in the bone stimulation. The physical agents trigger, by means of cell membrane components, intracellular events that result in a biological response. Preclinical studies have shown how PEMFs activate membrane receptors and transmembrane channels which can have a promoting effect on bone cell function, bone mineralization, bone repair and reduction of the inflammatory process[3,4]. In recent years, exposure to PEMFs was tested on human mesenchymal stem cells (hMSCs) demonstrating an osteogenic differentiation with a significant increase in the production of osteogenesis-related markers including alkaline phosphatase activity, osteocalcin levels and matrix mineralization[5,6]; the positive modulation of components of the Notch signaling pathway involved in bone development, suggesting cooperation between PEMFs and osteogenic microenvironment through Notch pathway[5], a favorable effect in the early stage of osteoblast differentiation by stimulating the expression of voltage-gated Ca Channels and the modulation of the concentration of cytosolic free Ca2+[7]. Additional in vivo animal studies demonstrated that PEMFs stimulate osteoblast activity during the healing process, showing that the amount of newly deposited bone and mineral apposition rate inside the transcortical holes are significantly greater in the treated limbs compared to controls in horses[8].

In the last century, PEMF treatment was proposed in humans to prevent bone loss in osteoporosis, hyperparathyroidism, glucocorticoids or ovariectomy, diabetes, to treat delayed unions, non-unions, fractures or osteotomies[9]. The first attempts to use PEMFs after joint replacement had the purpose to facilitate implant osteointegration thanks to improved osteogenesis and bone ingrowth. Although PEMFs treatment was recommended after total joint replacement (in the 90s) to promote bone ingrowth since these first studies, they are not currently part of usual clinical practice. The purpose of this review was to analyze existing literature on PEMFs effects in joint replacement surgery and to report results of clinical studies and current indications.

# PULSED ELECTROMAGNETIC FIELDS

PEMFs are employed as an effective method to enhance bone repair because they are safe, non-invasive and have no side effects[4]. The PEMFs signal is delivered as pulses over time, with square or trapezoidal waveforms, focalized to the site of treatment. PEMFs exert their biological effect on cell membranes and on the system of gap junctions between cells, inducing an electric field in the tissue able to regulate many cellular functions[7]. In particular, PEMFs stimulation can transduce signals through conformational changes in transmembrane voltage-dependent channels, resulting in alterations in the ionic equilibrium[10] increasing calcium uptake and cytosolic concentration and activating calmodulin , which is the trigger for many signaling pathways leading to a proliferative response of bone cells[11]. Exposure with PEMFs of human osteoblast-like cells appear to act on bone formation by inducing upregulation of several genes related to osteoblast differentiation and proliferation (HOXA10, AKT1), cytoskeleton formation involved in the intercellular junctions and the synthesis of collagenous and non-collagenous matrix components thus exerting an anabolic effect on cells[12]. Many studies suggest both *pre-clinical* and clinical benefits[13].

However, different electromagnetic stimulation parameters can result in different biological effects[14]. The influence of PEMFs on human osteoblast proliferation and calcified matrix production over biomaterial scaffolds, was also investigated showing that under electromagnetic stimulation polyurethane scaffolds can be suitable to calcified matrix coating and that the coating is greatly enhanced, making the biomaterial useful for bio-integration[15]. In clinical practice, the limited number of randomized controlled trials and the heterogeneity of the available studies make it difficult to quantitatively evaluate the right protocol of treatment with precision.

The effects of PEMFs are focalized to the site of application and no systemic effects have been observed following exposure to pulsed low-energy magnetic fields. Recently, the principles of pharmacological research have been adopted to identify, characterize and optimize the biophysical stimuli parameters (amplitude, frequency, waveform and exposure time), and to assess how specific stimuli and combination of parameters modulate a particular cell function. The gathered evidence has been forming the basis of the clinical biophysics application based on the following key principles of biophysical stimulation: (1) The ability of the physical stimulus to act selectively on cell targets; (2) Signal specificity, *i.e.*, the effect depends on waveform, frequency, duration and energy; (3) Identification of the dose-response effects; and (4) The signal should maintain the characteristics identified as being effective at the disease site[3]. At first, the main focus has been on stimulation regimes using 100 Hz PEMF pulses with very low intensities, around 0.2 mT[13]. Today, the clinical protocols with most scientific evidence are: (1) 75 Hz and 1.5-2.5 mT (PEMF with square and trapezoidal waves)[3]; and (2) 15 Hz and 0.3-1.8 mT (PRF-PEMF with about 4 kHz carrier frequency)[9].

# INFLAMMATION AND PAIN

Pain relief and restoration of function are considered the main goals of arthroplasty surgery and they are strongly correlated with patient satisfaction and expectations fulfillment. Persistent pain in the first months after surgery is a strong predictor of long term patient dissatisfaction[16].

About 7% to 23% of patients after total hip arthroplasty and 10% to 34% after total knee arthroplasty report long-term pain and poor functional outcome[1], with persistent symptoms even 1 year after surgery[17]. A high score on the Visual Analogic Scale (VAS) for pain 3 mo after joint replacement was shown to be a predictor for chronic pain after 1 year[18]. The key role of local inflammation in functional recovery and pain resolution is well established. A positive correlation between Knee Society Score (KSS) and serum CRP levels sixth months after surgery was found even though no relation between systemic inflammatory markers and late functional recovery could be assessed[19].

Hall *et al*[20] showed that in patients with high IL-6 and CRP serum concentrations after total hip arthroplasty, longer walking distances are achieved later on. To the best of authors’ knowledge, no pharmacologic treatment is currently available to provide a persistent decrease in local inflammatory response. A transient suppression of IL-6 production was achieved only by high doses of opioids with concomitant side effects. The lack of a valid treatment free of contraindication highlights the need of better strategies to control local inflammation in the early stages after surgery.

Several *in-vitro* studies were conducted on PEMFs effects on inflammatory cells modulation. Varani *et al*[21] in 2017 showed that PEMF exposure mediates a significant upregulation of A2A and A3ARs expressed in various human joint cells (synoviocytes, chondrocytes and osteoblasts) or tissues involving a reduction in most of the pro-inflammatory cytokines[22] and leading to the reduction of superoxide anion production, PGE2, COX-2, IL-6 and IL-8[23-25]. In animal models, PEMFs, prevented the degenerative effect of IL-1β, significantly improving cartilage regeneration compared to the non-stimulated lesions, thus explaining the anti-degenerative, reparative and anti-inflammatory effects of PEMFs treatment[25-27]. Recently using in vitro and in vivo models, it has shown that when PEMF stimulation is applied to engineered constructs, it has a robust effect on glycosaminoglycans deposition and can enhance engineered cartilage repair through modulation of cartilage growth and healing[28].

The regulation of inflammatory response due to PEMFs can be effective in reducing pain thus limiting the use of non-steroidal anti-inflammatory drugs and improving the functional outcome in humans. Moreover, this treatment is free from side effects and is well accepted by patients.

# OSTEOINTEGRATION

Events leading to the integration of an implant into the bone tissue take place at the interface between bone and implant. The first response after surgery is the formation of a hematoma and a characteristic local inflammatory environment, consisting in the increase of pro-inflammatory cytokines (TNF-α, IL-6, PGE-2) and a decrease of bone-forming factors (IGF-1, TGF-β). The three principal pro-inflammatory cytokines involved in osteolysis are TNF-α, IL-1β and IL-6: TNF-α acts on osteoclastic cells precursors, while IL-1β and IL-6 increase bone resorption indirectly through the production of RANKL[29].

As above mentioned, the increase of A2A and A3 adenosine receptors induced by PEMFs reduces pro-inflammatory cytokines. In addition, PEMFs through the increase of adenosine receptors, act as positive modulators of the endogenous agonist adenosine producing a more physiological effect which may not be accompanied by the side effects, desensitization, and receptor downregulation often associated to the use of exogenous agonists[21,30]. As is known, stimulation with square and trapezoidal waves has been proven to double osteoprogenitor and osteoblastic cells[31] differentiation and proliferation rate, as well as extracellular matrix production. Moreover these waves can affect cell morphology and act on primary cilia, inducing pseudopodia and cytoskeletal reorganization, aligning cells along main axis[31,32].

The positive effects on bone growth may be the result of both a primary effect of PEMFs on the bone and an induced one, due to the increased vascular growth, secondary to the release of angiogenetic factors such as IL-8, bFGF ,VEGF[33] and Nitric Oxide Synthases[34,35].

PEMFs resulted effective in increasing the amount of new bone around hydroxyapatite porous implants in the proximal tibia of rabbits, while not so significant effects were detected in tricalcium phosphate ones, probably due to different pore size (the greater the diameter, the greater the effectiveness of the stimulation)[36]. PEMFs were also investigated as a tool to promote the integration of porous titanium implants in the diaphysis of rabbit humerus bones and shown to increase bone ingrowth by a 14-day stimulation[37].

In PEMF-treated patients, an improvement in bone-to-implant contact, bone area ratio of rough-surfaced implants, mineral apposition rate and bone formation rate were observed. Also, an improvement in mechanical properties in terms of hardness to micro-indentation was detected[38].

In some studies, no differences were observed between 2 and a 6 wk PEMF stimulation period in osteoblastic cells counts ; this could further indicate that PEMF promote a long-acting bone formation[39].

# PEMFS IN ASEPTIC LOOSENING DUE TO BONE REABSORPTION AND PERIPROSTHETIC OSTEOLYSIS

As known, osteolysis negatively affects long-term duration of prosthetic implants: debris (Ultra High Molecular Weight Poly-Ethylene, UHMWPE), but also metal ion or ceramic particles) accumulate at peri-prosthetic interface and trigger a chain of events, such as macrophage activation, with production of catabolic enzymes and pro-inflammatory cytokines[40,41]. Moreover inflammatory microenvironment increases osteoclastogenesis with a further increment of bone resorption[42]. Currently, aseptic loosening due to osteolysis can be successfully treated only by revision surgery, thus increasing morbidity and mortality, especially in elderly patients.

In *in-vitro* studies, PEMFs were able to counteract UHMWPE-mediated osteoclastogenesis in rat peripheral blood mononuclear cells and to increase cell viability maintaining pro-inflammatory cytokines at low levels, thus decreasing bone resorption [43]. In addition they induced an increase in osteoclastic cells apoptosis[44], OPG and RANKL concentrations[45], resulting in a drastic reduction of the fibrous capsule between bone and implant formation. Many preclinical *in-vivo* studies demonstrated how PEMFs can increase trabecular bone volume around implants heads and ameliorate bone contact around prosthesis[13,15,38,45].

# PEMFS IN CLINICAL PRACTICE

We selected all currently available prospective studies or randomized controlled study (RCT) on the use of PEMFs in total joint replacement with the purpose of investigating effects of PEMFs on recovery, pain relief and patients’ satisfaction following hip, knee or shoulder arthroplasty.

In 1989 Padovani *et al*[46] investigated 300 patients who underwent primary or revision total hip arthroplasty with 20 mo of medium follow-up. Eighty-nine patients were treated with PEMFs at 75 Hz for 8 h a day, starting the second and third day after surgery, for about 70 d. The two cohorts of patients were functionally and clinically evaluated with the Merle D’Aubigne score[47] pre- and post-operatively. At 6 mo follow-up, most treated patients were in the 5th or 6th grade of pain and authors ascribe these poor results to the existing pre-operative conditions, such as previous arthrodesis or chronic hip luxation. A slight acceleration in osteointegration was radiographically detected in the first six months in both control and treated cohorts. A faster clinical recovery was also observed in the treated group, especially in terms of pain reduction and subsequent articular function and walking. In particular, a total pain remission was achieved after 5 mo to 6 mo in the treated group and after 7 mo to 8 mo in the control group. Even though results were encouraging, the lack of a longer follow-up time does not allow to evaluate late bone modifications and implants survival. Moreover this study lacks a proper randomization of patients and a quantitative analysis of described parameters (Table 1).

In 1991 Kennedy *et al*[48] studied PEMFs effects on loosened cemented hip prosthesis. Thirty-seven patients where included in this study and 19 were treated with PEMFs at 15Hz. Patients were evaluated before therapy and at 12, 18, 24 and 36 mo with the Harris hip score. At month 6, after the end of the treatment, 57% of PEMF treated patients showed a Harris score greater than 80, while only 11% of the control did. No radiological differences were found between groups. However, three years after surgery all patient but 2 (1 in the control group and 1 in the treated group) had a clinical relapse and were treated with revision surgery; these results suggest the use of PEMF for delay revision surgery.

Rispoli *et al*[49] studied 42 patients reporting pain 6 mo after hip primary or revision surgery. Patients were treated for 60 d with Calcitonin, vitamin D and NSADs together with 75 Hz PEMFs stimulation. Clinical and radiographic evaluation were performed 4 mo after the end of treatment and at 1 year follow up. A correlation between stimulation time and positive outcomes was observed. Ninety-two% of stimulated patients (treated for at least 6 h a day for more than 360 h totally) had improved functional and clinical scores. Results were limited by previous diseases and biomechanical conditions. Moreover, data suggest a dose-related effect.

In 2009 Dallari *et al*[50] performed a prospective randomized, double-blind study investigating the effects of PEMFs in 30 subjects undergoing hip revision surgery after femoral stem mobilization. Surgery was performed with a trans-femoral approach through an “open-book” osteotomy. The stem used was a Wagner SL revision stem of titanium-aluminum-niobium alloy. Treated patients were stimulated from day 7 to day 90 post-operatively. The device was used 6 h per day. The peak amplitude of the magnetic field produced by the device was 2 mT at 75 Hz. At 90 d, a better integration of the medial and distal cortex of femur was observed, by bone densitometry measurements, in PEMFs treated subjects compared to the control group. Patients were functionally and clinically evaluated with the Merle D’Aubigne score at baseline and 90 d post-operatively. Results showed that, after 90 d, treated group had an increase in the Merle D’Aubigne score of 77% compared to the preoperatively score. The increase recorded in the control group was 44%. This study, even with a small sample size, shows how PEMFs can have an important role in prosthesis loosening treatment with a significant decrease of pain and improvement in functional outcome in the short term. Effects on bone mineralization and prosthesis integration are encouraging, even though a longer follow-up would be necessary.

Moretti *et al*[51] in 2012 conducted a RCT in 30 patients undergoing TKA. Fifteen patient**s** were treated with PEMFs, for 4 h daily, for 60 d starting 7 d after surgery. The device used generated a peak magnetic field of 1.5 mT at a frequency of 75 Hz. Objective and subjective measurement were evaluated at baseline and at 1, 2, 6 and 12 mo after surgery. The results showed a higher increase in KSS functional score at 2, 6 and 12 mo. It has to be noted the baseline functional scores were also different between groups. SF36 health survey score in the treated group was significantly higher than in the control group, while VAS values were significantly lower, and the difference between groups was maintained at all follow-up visits. A reduction in swelling at 1 and 2 mo after surgery, and a statistically significant difference in NSAID utilization at 1, 2 and 6 mo was also recorded.

Adravanti *et al*[52] in 2014 conducted a similar RCT in 26 patients undergoing TKA. The device used and the stimulation protocol of treatment were the same used by Moretti *et al*[51]. KSS function and knee score at one month showed a difference between groups that was statistically significant, with higher scores in the treated group. Two and six months after surgery the functional score of both groups significantly improved with respect to baseline, with no significant difference between groups. One month after TKA, pain was significantly better in the treated compared with the control group. Pain was still significantly lower in the treated group at six months follow-up. Swelling evaluation showed significantly better results in the treated group at 1 and 2 mo follow-up compared with the baseline and control group. One month after surgery, the SF-36 pain evaluation showed a significant improvement for the treated group only, with non-significant differences at 2 and 6 mo.

Patients were re-evaluated at long term follow-up (3 years). Patients with persistent pain represented 7 % of the treated group and 33% of the control group. All the patients in the treated group reported walking without limitation or walking aids, whereas 27 % of patients in the control group occasionally used walking aids. The results of this study further suggest that the pain reduction obtained in the early postoperative period can be a predictor of long-term outcome. The authors suggest that PEMF therapy should be considered an effective completion of the TKA procedure.

In 2019, La Verde *et al*[53] conducted a randomized prospective study on PEMFs effects in reverse total shoulder arthroplasty. 50 patients were enrolled and equally divided into a control group and a treated group. The medical device and the treatment of protocol was the same use in the previous studies[51,52]. Clinical evaluation was performed with the Constant score, VAS score and percentage of shoulder functionality compared to the contralateral one. Better function and lower pain were reported at 1, 2 and 3 mo postoperative evaluations in the PEMFs treated group. At six months follow-up no significant differences were found between groups.

# CONCLUSION

The analysis of the literature included in this review confirms how a specific combination of physical parameters of PEMFs can represent a powerful tool after joint replacement surgery[3]. All the studies analyzed reported no adverse effects, and good patient compliance to the treatment.

Effects on pain management, swelling and local inflammation can have a positive impact on patient satisfaction and can facilitate a faster recovery, allowing a more intense rehabilitation protocol even though it is still unclear if PEMFs effects can be detected also in the long term. Some studies suggest long lasting effects with remarkable improvements between treated group and controls even 3 years after surgery, while other studies do not find benefits in treated patients in the long term.

Several reports suggest positive effects on the implant integration even though better results are detected when PEMFs is performed as adjuvant therapy after surgery. Regarding the management of periprosthetic osteolysis and implant mobilization, the study conducted by Dallari *et al*[50] reports promising results with a remarkable improvement in bone mineralization around the implant and satisfying clinical and functional scores. Overall PEMFs stimulation is considered a valid therapy when associated to a standard rehabilitation clinical protocol. In conclusion, the use of PEMFs in the early control of joint inflammation process during the first days after surgery should be considered an effective completion of the surgical procedure to improve the patient’s functional recovery.

**REFERENCES**

1 **Beswick AD**, Wylde V, Gooberman-Hill R, Blom A, Dieppe P. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. *BMJ Open* 2012; **2**: e000435 [PMID: 22357571 DOI: 10.1136/bmjopen-2011-000435]

2 **Bozic KJ**, Kamath AF, Ong K, Lau E, Kurtz S, Chan V, Vail TP, Rubash H, Berry DJ. Comparative Epidemiology of Revision Arthroplasty: Failed THA Poses Greater Clinical and Economic Burdens Than Failed TKA. *Clin Orthop Relat Res* 2015; **473**: 2131-2138 [PMID: 25467789 DOI: 10.1007/s11999-014-4078-8]

3 **Massari L**, Benazzo F, Falez F, Perugia D, Pietrogrande L, Setti S, Osti R, Vaienti E, Ruosi C, Cadossi R. Biophysical stimulation of bone and cartilage: state of the art and future perspectives. *Int Orthop* 2019; **43**: 539-551 [PMID: 30645684 DOI: 10.1007/s00264-018-4274-3]

4 **Yuan J**, Xin F, Jiang W. Underlying Signaling Pathways and Therapeutic Applications of Pulsed Electromagnetic Fields in Bone Repair. *Cell Physiol Biochem* 2018; **46**: 1581-1594 [PMID: 29694967 DOI: 10.1159/000489206]

5 **Bagheri L**, Pellati A, Rizzo P, Aquila G, Massari L, De Mattei M, Ongaro A. Notch pathway is active during osteogenic differentiation of human bone marrow mesenchymal stem cells induced by pulsed electromagnetic fields. *J Tissue Eng Regen Med* 2018; **12**: 304-315 [PMID: 28482141 DOI: 10.1002/term.2455]

6 **Ongaro A**, Pellati A, Bagheri L, Fortini C, Setti S, De Mattei M. Pulsed electromagnetic fields stimulate osteogenic differentiation in human bone marrow and adipose tissue derived mesenchymal stem cells. *Bioelectromagnetics* 2014; **35**: 426-436 [PMID: 25099126 DOI: 10.1002/bem.21862]

7 **Petecchia L**, Sbrana F, Utzeri R, Vercellino M, Usai C, Visai L, Vassalli M, Gavazzo P. Electro-magnetic field promotes osteogenic differentiation of BM-hMSCs through a selective action on Ca(2+)-related mechanisms. *Sci Rep* 2015; **5**: 13856 [PMID: 26364969 DOI: 10.1038/srep13856]

8 **Canè V**, Botti P, Soana S. Pulsed magnetic fields improve osteoblast activity during the repair of an experimental osseous defect. *J Orthop Res* 1993; **11**: 664-670 [PMID: 8410466 DOI: 10.1002/jor.1100110508]

9 **Galli C**, Pedrazzi G, Mattioli-Belmonte M, Guizzardi S. The Use of Pulsed Electromagnetic Fields to Promote Bone Responses to Biomaterials *In Vitro* and *In Vivo*. *Int J Biomater* 2018; **2018**: 8935750 [PMID: 30254677 DOI: 10.1155/2018/8935750]

10 **Wu S**, Yu Q, Lai A, Tian J. Pulsed electromagnetic field induces Ca2+-dependent osteoblastogenesis in C3H10T1/2 mesenchymal cells through the Wnt-Ca2+/Wnt-β-catenin signaling pathway. *Biochem Biophys Res Commun* 2018; **503**: 715-721 [PMID: 29909008 DOI: 10.1016/j.bbrc.2018.06.066]

11 **Brighton CT**, Wang W, Seldes R, Zhang G, Pollack SR. Signal transduction in electrically stimulated bone cells. *J Bone Joint Surg Am* 2001; **83**: 1514-1523 [PMID: 11679602 DOI: 10.2106/00004623-200110000-00009]

12 **Sollazzo V**, Palmieri A, Pezzetti F, Massari L, Carinci F. Effects of pulsed electromagnetic fields on human osteoblastlike cells (MG-63): a pilot study. *Clin Orthop Relat Res* 2010; **468**: 2260-2277 [PMID: 20387020 DOI: 10.1007/s11999-010-1341-5]

13 **Fini M**, Giavaresi G, Setti S, Martini L, Torricelli P, Giardino R. Current trends in the enhancement of biomaterial osteointegration: biophysical stimulation. *Int J Artif Organs* 2004; **27**: 681-690 [PMID: 15478539 DOI: 10.1177/039139880402700806]

14 **Sakai Y**, Patterson TE, Ibiwoye MO, Midura RJ, Zborowski M, Grabiner MD, Wolfman A. Exposure of mouse preosteoblasts to pulsed electromagnetic fields reduces the amount of mature, type I collagen in the extracellular matrix. *J Orthop Res* 2006; **24**: 242-253 [PMID: 16435357 DOI: 10.1002/jor.20012]

15 **Fassina L**, Visai L, Benazzo F, Benedetti L, Calligaro A, De Angelis MG, Farina A, Maliardi V, Magenes G. Effects of electromagnetic stimulation on calcified matrix production by SAOS-2 cells over a polyurethane porous scaffold. *Tissue Eng* 2006; **12**: 1985-1999 [PMID: 16889527 DOI: 10.1089/ten.2006.12.1985]

16 **Vissers MM**, de Groot IB, Reijman M, Bussmann JB, Stam HJ, Verhaar JA. Functional capacity and actual daily activity do not contribute to patient satisfaction after total knee arthroplasty. *BMC Musculoskelet Disord* 2010; **11**: 121 [PMID: 20553584 DOI: 10.1186/1471-2474-11-121]

17 **Baker PN**, van der Meulen JH, Lewsey J, Gregg PJ; National Joint Registry for England and Wales. The role of pain and function in determining patient satisfaction after total knee replacement. Data from the National Joint Registry for England and Wales. *J Bone Joint Surg Br* 2007; **89**: 893-900 [PMID: 17673581 DOI: 10.1302/0301-620X.89B7.19091]

18 **Williams DP**, O'Brien S, Doran E, Price AJ, Beard DJ, Murray DW, Beverland DE. Early postoperative predictors of satisfaction following total knee arthroplasty. *Knee* 2013; **20**: 442-446 [PMID: 23777807 DOI: 10.1016/j.knee.2013.05.011]

19 **Ugraş AA**, Kural C, Kural A, Demirez F, Koldaş M, Cetinus E. Which is more important after total knee arthroplasty: Local inflammatory response or systemic inflammatory response? *Knee* 2011; **18**: 113-116 [PMID: 20466551 DOI: 10.1016/j.knee.2010.03.004]

20 **Hall GM**, Peerbhoy D, Shenkin A, Parker CJ, Salmon P. Relationship of the functional recovery after hip arthroplasty to the neuroendocrine and inflammatory responses. *Br J Anaesth* 2001; **87**: 537-542 [PMID: 11878721 DOI: 10.1093/bja/87.4.537]

21 **Varani K**, Vincenzi F, Ravani A, Pasquini S, Merighi S, Gessi S, Setti S, Cadossi M, Borea PA, Cadossi R. Adenosine Receptors as a Biological Pathway for the Anti-Inflammatory and Beneficial Effects of Low Frequency Low Energy Pulsed Electromagnetic Fields. *Mediators Inflamm* 2017; **2017**: 2740963 [PMID: 28255202 DOI: 10.1155/2017/2740963]

22 **Sorkin A**, von Zastrow M. Endocytosis and signalling: intertwining molecular networks. *Nat Rev Mol Cell Biol* 2009; **10**: 609-622 [PMID: 19696798 DOI: 10.1038/nrm2748]

23 **Della Bella E**, Tschon M, Stagni C, Dallari D, Fini M. BIOPHYSICAL STIMULATION FOR NONUNIONS. *J Biol Regul Homeost Agents* 2015; **29**: 25-38 [PMID: 26652488]

24 **Streit A**, Watson BC, Granata JD, Philbin TM, Lin HN, O'Connor JP, Lin S. Effect on Clinical Outcome and Growth Factor Synthesis With Adjunctive Use of Pulsed Electromagnetic Fields for Fifth Metatarsal Nonunion Fracture: A Double-Blind Randomized Study. *Foot Ankle Int* 2016; **37**: 919-923 [PMID: 27287343 DOI: 10.1177/1071100716652621]

25 **Veronesi F**, Cadossi M, Giavaresi G, Martini L, Setti S, Buda R, Giannini S, Fini M. Pulsed electromagnetic fields combined with a collagenous scaffold and bone marrow concentrate enhance osteochondral regeneration: an in vivo study. *BMC Musculoskelet Disord* 2015; **16**: 233 [PMID: 26328626 DOI: 10.1186/s12891-015-0683-2]

26 **Benazzo F**, Cadossi M, Cavani F, Fini M, Giavaresi G, Setti S, Cadossi R, Giardino R. Cartilage repair with osteochondral autografts in sheep: effect of biophysical stimulation with pulsed electromagnetic fields. *J Orthop Res* 2008; **26**: 631-642 [PMID: 18176941 DOI: 10.1002/jor.20530]

27 **Fini M**, Torricelli P, Giavaresi G, Aldini NN, Cavani F, Setti S, Nicolini A, Carpi A, Giardino R. Effect of pulsed electromagnetic field stimulation on knee cartilage, subchondral and epyphiseal trabecular bone of aged Dunkin Hartley guinea pigs. *Biomed Pharmacother* 2008; **62**: 709-715 [PMID: 17459652 DOI: 10.1016/j.biopha.2007.03.001]

28 **Stefani RM**, Barbosa S, Tan AR, Setti S, Stoker AM, Ateshian GA, Cadossi R, Vunjak-Novakovic G, Aaron RK, Cook JL, Bulinski JC, Hung CT. Pulsed electromagnetic fields promote repair of focal articular cartilage defects with engineered osteochondral constructs. *Biotechnol Bioeng* 2020; **117**: 1584-1596 [PMID: 31985051 DOI: 10.1002/bit.27287]

29 **Obando-Pereda GA**, Fischer L, Stach-Machado DR. Titanium and zirconia particle-induced pro-inflammatory gene expression in cultured macrophages and osteolysis, inflammatory hyperalgesia and edema in vivo. *Life Sci* 2014; **97**: 96-106 [PMID: 24252315 DOI: 10.1016/j.lfs.2013.11.008]

30 **Kenakin T**. Principles: receptor theory in pharmacology. *Trends Pharmacol Sci* 2004; **25**: 186-192 [PMID: 15063082 DOI: 10.1016/j.tips.2004.02.012]

31 **Galli C**, Pedrazzi G, Guizzardi S. The cellular effects of Pulsed Electromagnetic Fields on osteoblasts: A review. *Bioelectromagnetics* 2019; **40**: 211-233 [PMID: 30908726 DOI: 10.1002/bem.22187]

32 **Wang J**, An Y, Li F, Li D, Jing D, Guo T, Luo E, Ma C. The effects of pulsed electromagnetic field on the functions of osteoblasts on implant surfaces with different topographies. *Acta Biomater* 2014; **10**: 975-985 [PMID: 24140610 DOI: 10.1016/j.actbio.2013.10.008]

33 **Reher P**, Doan N, Bradnock B, Meghji S, Harris M. Effect of ultrasound on the production of IL-8, basic FGF and VEGF. *Cytokine* 1999; **11**: 416-423 [PMID: 10346981 DOI: 10.1006/cyto.1998.0444]

34 **Patruno A**, Amerio P, Pesce M, Vianale G, Di Luzio S, Tulli A, Franceschelli S, Grilli A, Muraro R, Reale M. Extremely low frequency electromagnetic fields modulate expression of inducible nitric oxide synthase, endothelial nitric oxide synthase and cyclooxygenase-2 in the human keratinocyte cell line HaCat: potential therapeutic effects in wound healing. *Br J Dermatol* 2010; **162**: 258-266 [PMID: 19799606 DOI: 10.1111/j.1365-2133.2009.09527.x]

35 **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**: 933-940 [PMID: 17427956 DOI: 10.1002/jor.20373]

36 **Shimizu T**, Zerwekh JE, Videman T, Gill K, Mooney V, Holmes RE, Hagler HK. Bone ingrowth into porous calcium phosphate ceramics: influence of pulsing electromagnetic field. *J Orthop Res* 1988; **6**: 248-258 [PMID: 2830390 DOI: 10.1002/jor.1100060212]

37 **Ijiri K**, Matsunaga S, Fukuyama K, Maeda S, Sakou T, Kitano M, Senba I. The effect of pulsing electromagnetic field on bone ingrowth into a porous coated implant. *Anticancer Res* 1996; **16**: 2853-2856 [PMID: 8917397]

38 **Fini M**, Giavaresi G, Giardino R, Cavani F, Cadossi R. Histomorphometric and mechanical analysis of the hydroxyapatite-bone interface after electromagnetic stimulation: an experimental study in rabbits. *J Bone Joint Surg Br* 2006; **88**: 123-128 [PMID: 16365135 DOI: 10.1302/0301-620X.88B1.16496]

39 **Özen J,** Atay A, Oruç S, Dalkiz M, Beydemir B, Develi S. Evaluation of Pulsed Electromagnetic Fields on Bone Healing After Implant Placement in the Rabbit Mandibular Model. *Turkish Journal of Medical Sciences* 2004; **34**: 91-95

40 **Sartori M**, Vincenzi F, Ravani A, Cepollaro S, Martini L, Varani K, Fini M, Tschon M. RAW 264.7 co-cultured with ultra-high molecular weight polyethylene particles spontaneously differentiate into osteoclasts: an in vitro model of periprosthetic osteolysis. *J Biomed Mater Res A* 2017; **105**: 510-520 [PMID: 27667508 DOI: 10.1002/jbm.a.35912]

41 **Vallés G**, García-Cimbrelo E, Vilaboa N. Involvement of extracellular Hsp72 in wear particle-mediated osteolysis. *Acta Biomater* 2012; **8**: 1146-1155 [PMID: 22198139 DOI: 10.1016/j.actbio.2011.12.001]

42 **Nam D**, Bostrom MP, Fahlgren A. Emerging ideas: Instability-induced periprosthetic osteolysis is not dependent on the fibrous tissue interface. *Clin Orthop Relat Res* 2013; **471**: 1758-1762 [PMID: 23463289 DOI: 10.1007/s11999-013-2896-8]

43 **Tschon M**, Veronesi F, Contartese D, Sartori M, Martini L, Vincenzi F, Ravani A, Varani K, Fini M. Effects of pulsed electromagnetic fields and platelet rich plasma in preventing osteoclastogenesis in an in vitro model of osteolysis. *J Cell Physiol* 2018; **233**: 2645-2656 [PMID: 28786478 DOI: 10.1002/jcp.26143]

44 **Wang P**, Liu J, Yang Y, Zhai M, Shao X, Yan Z, Zhang X, Wu Y, Cao L, Sui B, Luo E, Jing D. Differential intensity-dependent effects of pulsed electromagnetic fields on RANKL-induced osteoclast formation, apoptosis, and bone resorbing ability in RAW264.7 cells. *Bioelectromagnetics* 2017; **38**: 602-612 [PMID: 28741320 DOI: 10.1002/bem.22070]

45 **Veronesi F**, Fini M, Sartori M, Parrilli A, Martini L, Tschon M. Pulsed electromagnetic fields and platelet rich plasma alone and combined for the treatment of wear-mediated periprosthetic osteolysis: An in vivo study. *Acta Biomater* 2018; **77**: 106-115 [PMID: 29981946 DOI: 10.1016/j.actbio.2018.07.012]

46 **Padovani G,** Masetti C, Andreoli I, Ferretti M. L’utilizzo dei CEMP nell’artrodesi d’anca non cementata (impianti primari e revisioni): presupposti biologici e nostra casistica. In: Modulazione biofisica dell’osteogenesi mediante campi elettromagnetici pulsati. Traina GC, Pipino F, Massari L, Molfetta L, Cadossi R; 1999: 115-124

47 **D'aubigne RM**, POSTEL M. Functional results of hip arthroplasty with acrylic prosthesis. *J Bone Joint Surg Am* 1954; **36-A**: 451-475 [PMID: 13163078]

48 **Kennedy WF**, Roberts CG, Zuege RC, Dicus WT. Use of pulsed electromagnetic fields in treatment of loosened cemented hip prostheses. A double-blind trial. *Clin Orthop Relat Res* 1993; **286**: 198-205 [PMID: 8425345]

49 **Rispoli FP,** Corolla FM, Mussner R. The Use of Low Frequency Pulsing Electromagnetic Fields in Patients with Painful Hip Prostheses. *J Bioelectricity* 1988; **7**: 181-187 [DOI: 10.3109/15368378809027748]

50 **Dallari D,** Fini M, Giavaresi G, Del Piccolo N, Stagni C, Amendola L, Rani N, Gnudi S, Giardino R. Effects of pulsed electromagnetic stimulation on patients undergoing hip revision prostheses: A randomized prospective double-blind study. *Bioelectromagnetics* 2009; **30**: 423-430 [PMID: 19384914 DOI: 10.1002/bem.20492]

51 **Moretti B**, Notarnicola A, Moretti L, Setti S, De Terlizzi F, Pesce V, Patella V. I-ONE therapy in patients undergoing total knee arthroplasty: a prospective, randomized and controlled study. *BMC Musculoskelet Disord* 2012; **13**: 88 [PMID: 22672794 DOI: 10.1186/1471-2474-13-88]

52 **Adravanti P**, Nicoletti S, Setti S, Ampollini A, de Girolamo L. Effect of pulsed electromagnetic field therapy in patients undergoing total knee arthroplasty: a randomised controlled trial. *Int Orthop* 2014; **38**: 397-403 [PMID: 24352823 DOI: 10.1007/s00264-013-2216-7]

53 **La Verde L,** Franceschetti E, Palumbo A, Giovannetti E, Ranieri R, Sorini G, Rosa MA, Franceschi F. Applicazione dei campi magnetici pulsati nei pazienti sottoposti a protesi inversa di spalla: valutazione clinica e funzionale. *Giornale Italiano di Ortopedia e Traumatologia* 2019; **45**: 37-46

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**Table 1 Compared to Placebo**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Year** | **Ref.** | **Surgical procedure** | **Device and frequency** | **Peak amplitude Intensity** | **Daily PEMF Exposure (h/die)** | **Treatment Period** | **All** | **+** | **-** | **Mean Age (yr)** | **Follow up (mo)** | **Pain** | **Swelling** | **Mobility** | **Quality of life** |
| 1993 | Kennedy *et al*[48] | THA (cemented) | Stimatic 300075 Hz | NS | 7,5 | 6 mo | 37 | 19 | 18 | 68 | 6(12, 18, 24, 36) | HOS ➚ | NS | ROM ➚HOS ➚ | NS |
| 1997 | Padovani *et al*[46] | THA and revision | NS | NS | 8 | 10 wk | 129 | 89 | 40 | 66 | 6(20 average) | PMA ➚ | NS | PMA ➚ | NS |
| 2009 | Dallari *et al*[50] | THA revision | Biostim75 Hz | 2 ± 0,2 mT | 6 | 3 mo | 30 | 15 | 15 | 68.6 ± 6.5 | 3 | PMA ➚ | NS | PMA ➚ | NS |
| 2012 | Moretti *et al*[51] | TKA | I-ONE75 Hz | 1,5 mT | 4 | 2 mo | 30 | 15 | 15 | 60-85 | 1 | VAS ➘ | ➘ | NS | NS |
| 2 | VAS ➘KSS ➚ | ➘ | KSS ➚ | SF36 ➚ |
| 6 | VAS ➘KSS ➚ | NS | KSS ➚ | SF36 ➚ |
| 12 | VAS ➘ | NS | KSS ➚ | SF36 ➚ |
| 2014 | Adravanti *et al*[52] | TKA | I-ONE75 Hz | 1,5 ± 0,1 mT | 4 | 2 mo | 29 | 12 | 17 | 73.7 | 1 | VAS ➘KSS ➚ | ➘ | KSS ➚ | SF36 ➚ |
| 2, 6 | VAS ➘ | NS | NS | NS |
| 2019 | La Verde *et al*[53] | RSA | I-ONE75 Hz | 1,5 mT | 4 | 2 mo | 50 | 25 | 25 | 60-75 | 1 | VAS ➘CMS ➚ | NS | CMS ➚ | NS |
| 2 | VAS ➘CMS ➚ | NS | CMS ➚ | NS |
| 3 (6) | VAS ➘CMS ➚ | NS | CMS ➚ | NS |

THA: Total hip arthroplasty; TKA: Total knee arthroplasty; RSA: Reverse shoulder arthroplasty; HOS: Harris hip score; ROM: Range of motion; PMA: Merle D’Aubigné-Postel hip score; VAS: Visual analog scale; KSS: Knee score society; SF36: Short form (36) health survey; CMS: Constant-Murley shoulder outcome score; NS: Not significant.