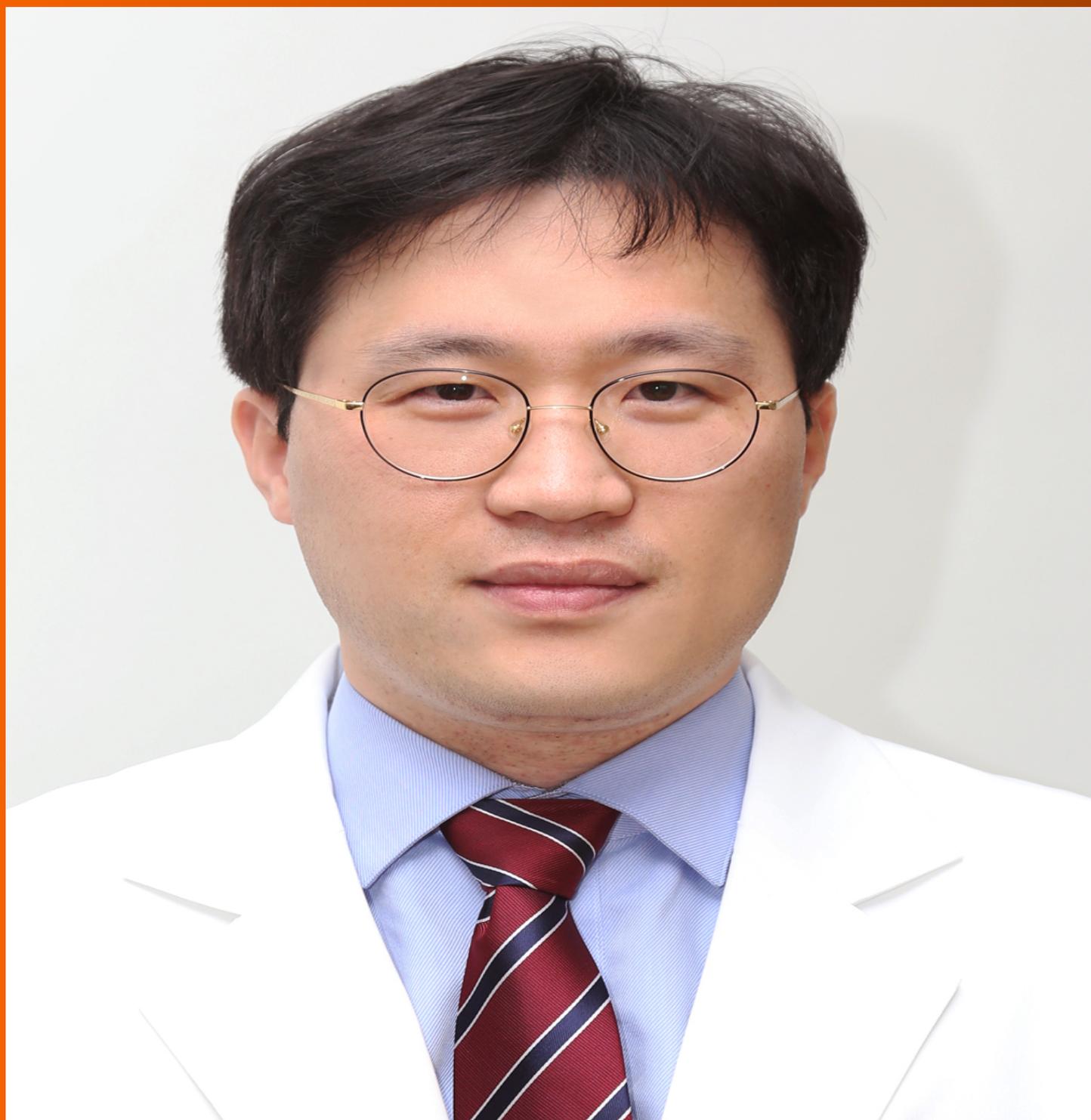


# World Journal of *Orthopedics*

*World J Orthop* 2020 June 18; 11(6): 278-318



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**INDEXING/ABSTRACTING**

The *WJO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Yan-Xia Xing*  
 Proofing Production Department Director: *Xiang Li*  
 Responsible Editorial Office Director: *Ruo-Yu Ma*

**NAME OF JOURNAL**

*World Journal of Orthopedics*

**ISSN**

ISSN 2218-5836 (online)

**LAUNCH DATE**

November 18, 2010

**FREQUENCY**

Monthly

**EDITORS-IN-CHIEF**

Massimiliano Leigheb

**EDITORIAL BOARD MEMBERS**

<http://www.wjgnet.com/2218-5836/editorialboard.htm>

**PUBLICATION DATE**

June 18, 2020

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**PUBLICATION MISCONDUCT**

<https://www.wjgnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjgnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjgnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Role of pulsed electromagnetic fields after joint replacements

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**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.

**Conflict-of-interest statement:** Authors declare no conflict of interests for this article.

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**Manuscript source:** Invited manuscript

**Received:** March 1, 2020

**Peer-review started:** March 2, 2020

**First decision:** April 26, 2020

**Revised:** May 14, 2020

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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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**Accepted:** May 28, 2020  
**Article in press:** May 28, 2020  
**Published online:** June 18, 2020

**P-Reviewer:** Bolshakova BC,  
Rakhsan V

**S-Editor:** Wang J

**L-Editor:** A

**E-Editor:** Xing YX



**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.

**Citation:** Lullini G, Cammisa E, Setti S, Sassoli I, Zaffagnini S, Marcheggiani Muccioli GM. Role of pulsed electromagnetic fields after joint replacements. *World J Orthop* 2020; 11(6): 285-293

**URL:** <https://www.wjgnet.com/2218-5836/full/v11/i6/285.htm>

**DOI:** <https://dx.doi.org/10.5312/wjo.v11.i6.285>

## 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<sup>[1]</sup>. 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*<sup>[2]</sup> 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<sup>[3,4]</sup>. 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<sup>[5,6]</sup>; the positive modulation of components of the Notch signaling pathway involved in bone development, suggesting cooperation between PEMFs and osteogenic microenvironment through Notch pathway<sup>[5]</sup>, 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 Ca<sup>2+</sup><sup>[7]</sup>. 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<sup>[8]</sup>.

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<sup>[9]</sup>. 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.

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## PULSED ELECTROMAGNETIC FIELDS

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PEMFs are employed as an effective method to enhance bone repair because they are safe, non-invasive and have no side effects<sup>[4]</sup>. 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<sup>[7]</sup>. In particular, PEMFs stimulation can transduce signals through conformational changes in transmembrane voltage-dependent channels, resulting in alterations in the ionic equilibrium<sup>[10]</sup> 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<sup>[11]</sup>. 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<sup>[12]</sup>. Many studies suggest both *pre-clinical* and clinical benefits<sup>[13]</sup>.

However, different electromagnetic stimulation parameters can result in different biological effects<sup>[14]</sup>. 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<sup>[15]</sup>. 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<sup>[3]</sup>. At first, the main focus has been on stimulation regimes using 100 Hz PEMF pulses with very low intensities, around 0.2 mT<sup>[13]</sup>. Today, the clinical protocols with most scientific evidence are: (1) 75 Hz and 1.5-2.5 mT (PEMF with square and trapezoidal waves)<sup>[3]</sup>; and (2) 15 Hz and 0.3-1.8 mT (PRF-PEMF with about 4 kHz carrier frequency)<sup>[9]</sup>.

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## INFLAMMATION AND PAIN

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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<sup>[16]</sup>.

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<sup>[1]</sup>, with persistent symptoms even 1 year after surgery<sup>[17]</sup>. 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<sup>[18]</sup>. 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<sup>[19]</sup>.

Hall *et al*<sup>[20]</sup> 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*<sup>[21]</sup> in 2017 showed that PEMF exposure mediates a significant upregulation of A<sub>2A</sub> and A<sub>3</sub>ARs expressed in various human joint cells (synoviocytes, chondrocytes and osteoblasts) or tissues involving a reduction in most of the pro-inflammatory cytokines<sup>[22]</sup> and leading to the reduction of superoxide anion production, PGE<sub>2</sub>, COX-2, IL-6 and IL-8<sup>[23-25]</sup>. In animal models, PEMFs, prevented the degenerative effect of IL-1 $\beta$ , significantly improving cartilage regeneration compared to the non-stimulated lesions, thus explaining the anti-degenerative, reparative and anti-inflammatory effects of PEMFs treatment<sup>[25-27]</sup>. 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<sup>[28]</sup>.

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.

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## OSTEOINTEGRATION

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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- $\alpha$ , IL-6, PGE-2) and a decrease of bone-forming factors (IGF-1, TGF- $\beta$ ). The three principal pro-inflammatory cytokines involved in osteolysis are TNF- $\alpha$ , IL-1 $\beta$  and IL-6: TNF- $\alpha$  acts on osteoclastic cells precursors, while IL-1 $\beta$  and IL-6 increase bone resorption indirectly through the production of RANKL<sup>[29]</sup>.

As above mentioned, the increase of A<sub>2A</sub> and A<sub>3</sub> 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<sup>[21,30]</sup>. As is known, stimulation with square and trapezoidal waves has been proven to double osteoprogenitor and osteoblastic cells<sup>[31]</sup> 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<sup>[31,32]</sup>.

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<sup>[33]</sup> and Nitric Oxide Synthases<sup>[34,35]</sup>.

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)<sup>[36]</sup>. 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<sup>[37]</sup>.

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<sup>[38]</sup>.

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<sup>[39]</sup>.

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

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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<sup>[40,41]</sup>. Moreover inflammatory microenvironment increases osteoclastogenesis with a further increment of bone resorption<sup>[42]</sup>. 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<sup>[43]</sup>. In addition they induced an increase in osteoclastic cells apoptosis<sup>[44]</sup>, OPG and RANKL concentrations<sup>[45]</sup>, 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<sup>[13,15,38,45]</sup>.

## 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*<sup>[46]</sup> 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<sup>[47]</sup> pre- and post-operatively. At 6 mo follow-up, most treated patients were in the 5<sup>th</sup> or 6<sup>th</sup> 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*<sup>[48]</sup> studied PEMFs effects on loosened cemented hip prosthesis. Thirty-seven patients were 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*<sup>[49]</sup> 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 percent 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*<sup>[50]</sup> 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

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 <i>et al</i> <sup>[48]</sup>	THA (cemented)	Stimatic 3000 75 Hz	NS	7,5	6 mo	37	19	18	68	6 (12, 18, 24, 36)	HOS ↑	NS	ROM ↑ HOS ↑	NS
1997	Pado-vani <i>et al</i> <sup>[46]</sup>	THA and revision	NS	NS	8	10 wk	129	89	40	66	6 (20 average)	PMA ↑	NS	PMA ↑	NS
2009	Dallari <i>et al</i> <sup>[50]</sup>	THA revision	Biostim 75 Hz	2 ± 0.2 mT	6	3 mo	30	15	15	68.6 ± 6.5	3	PMA ↑	NS	PMA ↑	NS
2012	Moretti <i>et al</i> <sup>[51]</sup>	TKA	I-ONE 75 Hz	1.5 mT	4	2 mo	30	15	15	60-85	1	VAS ↓	↓	NS	NS
											2	VAS ↓	↓	KSS ↑	SF36 ↑
											6	VAS ↓	NS	KSS ↑	SF36 ↑
											12	VAS ↓	NS	KSS ↑	SF36 ↑
2014	Adra-vanti <i>et al</i> <sup>[52]</sup>	TKA	I-ONE 75 Hz	1.5 ± 0.1 mT	4	2 mo	29	12	17	73.7	1	VAS ↓	↓	KSS ↑	SF36 ↑
											2, 6	VAS ↓	NS	NS	NS
2019	La Verde <i>et al</i> <sup>[53]</sup>	RSA	I-ONE 75 Hz	1.5 mT	4	2 mo	50	25	25	60-75	1	VAS ↓	NS	CMS ↑	NS
											2	VAS ↓	NS	CMS ↑	NS
											3 (6)	VAS ↓	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.

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*<sup>[51]</sup> in 2012 conducted a RCT in 30 patients undergoing TKA. Fifteen patients 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 NSAID utilization at 1, 2 and 6 mo was also recorded.

Adravanti *et al*<sup>[52]</sup> 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*<sup>[51]</sup>. 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



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