Biophysical therapy using the pulsating electromagnetic field as adjunctive therapy for implant osseointegration – A review

ABSTRACT

Development of procedures which accelerate osseointegration of dental implants, reduce the period of healing, and lead to an early rehabilitation of the patient are required for successful oral rehabilitation. Pulsed electromagnetic field (PEMF) is a noninvasive, therapeutic form of low field magnetic stimulation that has been used for healing bone non unions and various fractures. It acts on osteoblasts and bone, affecting their metabolism, therefore, increasing the tissue integration of the implanted devices and their clinical success. A broad range of settings that includes magnetic field intensity, frequency and duration of application, etc. used for PEMFs stimulation is a hurdle to properly define treatment protocols and extensive research is needed to overcome this issue. The present review includes studies that investigated the effects of PEMFs on the response of bone cells to different classes of biomaterials and the reports that focused on in vivo and in vitro investigations of biomaterials implanted in bone. This study is expected to serve as a guide for researchers and clinicians to bring into their clinical use these strategies to improve implant osseointegration in deficient and osteoporotic bone.

Keywords: Implants, osseointegration, pulsed electromagnetic field

BACKGROUND

Dental implants post insertion into the jawbones require a time for osseointegration with the adjacent bone which normally varies between 3 and 6 months or more. The months of waiting, and the limited function during this time, involve discomfort and hardship for the patient. So it has become necessary for dental clinicians and research workers to seek easier and more effective ways of improving and accelerating the osseointegration of dental implants. Development of procedures which accelerate osseointegration of dental implants, reduce the period of healing, and lead to an early rehabilitation of the patient are required for successful oral rehabilitation. The survival rate of dental implants over a 10-year observation has been reported to be higher than 90%. Their success depends on the quality and quantity of available bone in which they are inserted. Implants with deficient primary stability frequently may require additional time for osseointegration or may sometimes fail. The primary stability of an implant depends mainly on its design characteristics and the available quantity and quality of recipient’s bone. Both macro geometry and micro characteristics of implant surfaces play an important role in initial implant stability and also surface properties of dental implants made of titanium and its alloys have been enhanced considerably through the improvement of design and various surface treatments.

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These modifications along with various improvised surgical principles and prosthetic rules enhance the primary implant stability of dental implants. Still, situations are present that require a greater and faster implant osseointegration. The intrinsic potential of the body for bone regeneration can be stimulated through noninvasive adjunctive treatments such as the application of pulsating electromagnetic field therapy, low-intensity pulsed ultrasound (LIPUS), and low-level laser therapy (LLLT). These methods of biophysical stimulation of bone union were developed initially to enhance the healing of fractures, healing of bone nonunions and have been hypothesized to improve implant osseointegration. A broad range of settings that includes magnetic field intensity, frequency, signals and duration of application, etc. used for pulsed electromagnetic fields (PEMFs) stimulation still represents a hurdle to better define treatment protocols and extensive research is needed to overcome this issue. The present review includes studies that investigated the effects of PEMFs on the response of bone cells to different classes of biomaterials and the reports that focused on in vivo and in vitro investigations of biomaterials implanted in bone. This study sought to examine bone-implant union and its latest trend as well as the biophysical stimulation to enhance the union. This study is expected to serve as a guide for researchers and clinicians to bring into their clinical use these strategies to improve implant osseointegration in deficient and osteoporotic bone.

**PULSED ELECTROMAGNETIC FIELD**

The use of PEMF was approved by the Food and Drug Administration (FDA) in 1979 and has been used clinically for over 40 years following convincing evidence that electric currents can accelerate bone formation. It was discovered that everyday bone movements during physical activity produce endogenous electrical currents in the bone that could modulate bone cell activity (Wolff’s law). PEMF is a noninvasive, therapeutic form of low field magnetic stimulation that has been used for healing bone nonunions and various fractures. It is known to generate pulsating magnetic frequencies within the body that accelerate the process of healing and reduce postoperative pain and promote faster tissue swelling. The early devices were based on animal studies and used implanted and semi-invasive electrodes delivering direct current to the fracture site. Bassett et al. 1964 reported on significantly increased endosteal bone formation around the cathode of insulated battery implants whose electrodes were implanted in the femurs of 12 dogs. Jansen et al. 2010 showed that PEMF exposure of human bone marrow-derived stromal cells induced differentiation and enhanced the mineralization of bone, which supports the theory that PEMF induces an osteogenic response in vivo and may therefore stimulate fracture healing. Tabrah et al. 1990 noted a positive effect in the improvement of the bone mineral density of osteoporotic women which increased significantly in the immediate area of the field during the exposure period and decreased during the following 36 weeks.

**PULSED ELECTROMAGNETIC FIELD APPLICATION AROUND METALLIC IMPLANTS**

**In vitro studies**

Fassina et al. 2008 had worked on a model of Saos-2 osteoblastic cells on titanium fiber-mesh scaffolds and continuously stimulated with 1.3 ms trapezoidal pulses at 75 Hz, 2 mT in bioreactors for 22 days. They observed that PEMFs increased the expression of transforming growth factor (TGF) and upregulated the deposition of bone matrix on the scaffolds, by increasing the expression of Decorin, Osteopontin, and Type I collagen. Atalay et al. 2013 evaluated the effects of PEMF on neonatal rat calvarial osteoblast-like cells cultured on commercially pure titanium (cpTi) and titanium-zirconium alloy (TiZr) discs with hydrophilic surface properties. Cell proliferation rates, cell numbers, cell viability rates, alkaline phosphatase, and midkine levels were measured at 24 and 72 h. Cell proliferation in the machine surface group was lower than SLActive + PEMF and machine surface + PEMF. They concluded that although TiZr surfaces are similar to cpTi surfaces in terms of biocompatibility, PEMF application has a higher stimulative effect on cells cultured on cpTi surfaces when compared to TiZr surfaces.

Wang et al. 2014 cultured rat osteoblasts on three types of titanium surfaces (Flat, Micro, and Nano) under PEMF stimulation or control conditions. It was found that protein adsorption was significantly increased by the PEMF. The number of osteoblasts attached to the surfaces in the PEMF group was substantially greater than that in the control group after 1.5 h incubation. The cell proliferation on the implant surfaces was significantly promoted by the PEMF. The expression of osteogenesis-related genes, including bone morphogenetic proteins (BMP-2), osteocalcin, collagen type I (COL-1), alkaline phosphatase (ALP), Runx2, and OSX, were up-regulated on all the surfaces by PEMF stimulation. The use of PEMFs might be a potential adjuvant treatment for improving the osseointegration process.

Jing et al. 2016 used 15 Hz, 5 ms long PEMF bursts with 2 mT intensity to stimulate MC3T3-E1 cells on porous titanium scaffolds (70% porosity, 750 μm pore size) for 2 h/day for 3 days. Besides observing an increase in cell
proliferation and expression of differentiation markers Runx2 and Osterix, two important transcription factors activated in osteoblasts, the group reported that PEMF treatment increased -catenin, Lrp6, and Wnt1 expression, important components of the canonical Wnt1 pathway, at the mRNA and protein levels. Remarkably, these findings were confirmed in vivo after implanting porous titanium scaffolds in cylindrical defects in the femur of rabbits, which were then treated for up to 12 weeks with PEMFs. MicroCT analysis of the defects showed that PEMF treatment significantly improved bone architectural parameters, such as bone volume, trabecular volume, trabecular number and spacing, and dynamic histomorphometry demonstrated that, Mineralizing Surface and BFR were significantly higher in rabbits treated with PEMFs than control animals. Bloise et al. 2018[13] in their study evaluated the effect of a daily PEMF-exposure on osteogenic differentiation of hBM-MSCs seeded onto nanostructured TiO2 (with clusters under 100 nm of dimension). TiO2-seeded cells were exposed to PEMF (magnetic field intensity: 2 mT; the intensity of induced electric field: 5 mV; frequency: 75 Hz) and examined in terms of cell physiology modifications and osteogenic differentiation. Results showed that PEMF exposure affected TiO2-seeded cells osteogenesis by interfering with selective calcium-related osteogenic pathways, and greatly enhanced hBM-MSCs osteogenic features such as the expression of early/late osteogenic genes and protein production (e.g., ALP, COL-I, osteocalcin, and osteopontin) and ALP activity. Finally, PEMF-treated cells resulted to secrete into conditioned media higher amounts of BMP-2, DCN, and COL-I than untreated cell cultures. Their findings reconfirm the osteoinductive potential of PEMF, suggesting that its combination with TiO2 nanostructured surface might be a great option in bone tissue engineering applications.

In vivo studies on animal models
Numerous in vivo studies on the use of PEMF for bone regeneration have been reported since the early 1990’s. Table 1 is a list of various studies involving use of PEMF around metallic implants between 1990 to 2021. Spadaro et al. 1990[12] studied movable and stationary intramedullary wire implants made of stainless steel in rabbits treated with a pulsing electromagnetic field (PEMF) for of 15 hz for 4 h/day for 3 weeks and compared them with identical control animals without PEMF. Their results showed that PEMF-treated movable implants in the femur induced 44% more bone than untreated movable implants.

Iijiri et al. 1994[13] found that electromagnetic stimulation was useful for achieving further bone ingrowth into a porous-coated implant inserted into the humerus cavity of a Japanese albino rabbit. Implants coated with beads of 250–300 µ in diameter around a stem of 1.7 mm in diameter were stimulated by PEMF s at 0.2 mT, 10 Hz, 25 µs for 5 or 10 h for 14 days.

Matsumoto et al. 2000[14] in their study demonstrated PEMF application at different intensities, duration of application, and length of treatment in weeks. Their study concluded that the bone contact ratio and bone area ratio of the 0.2 mT and 0.3 mT-treated femurs were significantly larger than the respective value of the 0.8 mT-treated femurs of Japanese rabbits (P < 0.001). A PEMF with a pulse width of 25 µs and a pulse frequency of 100 Hz was applied. PEMF stimulation was applied for 4 h or 8 h/day, at a magnetic intensity of 0.2 mT, 0.3 mT, or 0.8 mT. The bone contact ratios of the PEMF-treated femurs were significantly larger than those of the control groups. No significant difference in bone contact ratio or bone area ratio was observed whether PEMF was applied for 4 h/day or 8 h/day. Although a significantly greater amount of bone had formed around the implant of the 2-week treated femurs than the 1-week treated femurs, no significant difference was observed between the 2-week and 4-week treated femurs. This study highlighted the importance to select the proper magnetic intensity, duration per day, and length of treatment.

Buzza et al. 2003[15] evaluated the histologic and mechanical healing process in dental implants under the action of PEMF. In their study Forty-eight commercially pure implant fixtures were implanted in tibiae metaphysis of 12 New Zealand white rabbits divided into experimental (PEMF) and control groups. A PEMF with the pulse width of 85 µs and a pulse frequency of 20 Mc was applied for 30 min per day. The animals were killed 21 and 42 days after implantation. Mechanical tests did not show significant differences between the groups (P > 0.05); however, statistically significant differences were observed over time (P < 0.0001). Similar histologic features were achieved for both groups. Their results suggested that PEMF stimulation does not improve the bone-healing process around commercially pure dental implants. Ozen et al. 2004[16] in their study used Ti-6Al-4V dental implants which were inserted into the mandible of 28 New Zealand rabbits (6 weeks old). Fourteen were stimulated with PEMFs for 2 consecutive weeks, 4 h/day, at a magnetic intensity of 0.2 milli Tesla (mT), frequency 100 Hz, and pulse 25 µs while the other 14 animals were not treated (control group). The rabbits were sacrificed at 2 and 8 weeks for histopathologic analysis around the implants. Significant differences in bone osteoblastic activity and new trabecular bone formation were observed between the control group and the PEMF treated group at week 8 (P < 0.001). Results demonstrated that the highest amount of new bone formation was observed 8 weeks after stimulation in the PEMF treated group.
Akca et al. 2007\textsuperscript{[17]} investigated the effects of PEMFs on the integration of cylindrical titanium implants in osteoporosis-induced tibias of ovariectomized rats. Ten animals were stimulated for 0.2 mT, 4 h/day for 14 days and PEMF stimulation increased bone volume and trabecular number in the peri-implant bone, as determined by a microCT analysis. Grana et al.\textsuperscript{[18]} investigated the effects of 60 ms, 1.9 Hz PEMF bursts of 50 Hz sinusoidal trains at an intensity of 72 mT administered for 30 min/twice a day on bone healing around titanium mini implants in rat tibias and found a significant increase in the amount of newly formed bone around implants at 10 and 20 days after surgeries. They concluded that short daily electromagnetic stimulation appears to be a promising treatment for acceleration of both bone-healing and peri-implant bone formation.

Nascimento et al. 2012\textsuperscript{[19]} in an in vivo study evaluated the effect of a constant electromagnetic field (CEF) on bone

| Study | Experimental model | Biomaterial implants | PEMF | Field intensity (Mt) | PEMF waveform | Exposure | Finding |
|-------|-------------------|---------------------|------|---------------------|--------------|----------|---------|
| Spadaro et al., 1990 | Placement in the medullary canal of femur and tibia in rabbits | Stainless steel wire | 5 ms, 15 Hz PEMF bursts of 4 kHz pulses | N/A | Quasi-square (trapezoidal pulses) | 4 h/day for 2 weeks | 44% more bone formation around movable implants |
| Iiiri et al., 1994 | Rabbit femurs | Beaded titanium implants | 25 μs PEMF Pulses at 10 Hz | 0.2 | N/A | 5-10 h/day for 2 weeks | Significant bone ingrowth |
| Matsumoto et al., 2000 | Rabbit femurs | Ti-6Al-4V dental implants | 100 Hz, 25 μs | 0.2, 0.3, 0.8 | N/A | 4 or 8 h/day for up 2-4 weeks | Significant bone formation in 0.2, 0.3 in 2 weeks compared to 0.8 group at 2 weeks |
| Buza et al., 2003 | Rabbit tibia | Commercially available titanium dental implants | 85 μs long pulses at 20 MHz | 1 W | N/A | 30 min/day for 21 or 42 days | No improve the in bone-healing process |
| Özcan et al., 2004 | Rabbit mandibles, 14 implants as test and 14 as control | Ti-6Al-4V dental implants | 100 Hz, 25 μs PEMFs | 0.2 | N/A | 4 h/day for 14 days | Highest amount of new bone formation was observed 8 weeks in pemf group-histological analysis |
| Akca et al., 2007 | Tibias of ovariectomized rats | Cylindrical titanium implants | 100 Hz, 25 μs PEMFs | 0.2 | N/A | 4 hours/day for 14 days | Increased bone volume and trabecular number micro CT analysis |
| Grana et al., 2008 | Rat tibias | Cylindrical threaded titanium implants | 60 ms, 1.9 Hz PEMF Bursts of 50 Hz | 72 | Quasi-square (with sinusoidal pulses) | 30 min/ twice a day | Increased bone formation |
| Nascimento et al., 2012 | Dog mandibles, immediate postextraction | Commercially available titanium dental implants | 1 MHz, 25 μs-long pulses | 0.8 | N/A | 20 min/day for 2 weeks | Constant electromagnetic field stimulation did not improve the bone-healing |
| Barak et al., 2016 | Rabbit tibias | Commercially available titanium dental implants | 10 Hz | 0.2 and 0.4 | N/A | 24 h/day for 2 or 4 weeks | 48% higher BIC in the test implants on micro CT analysis |
| Cai et al., 2018 | Rabbit femurs | Cylindrical sintered Ti2448 implants | 5 Hz, 5 m PEMF Bursts of 4.5 kHz pulses | 2 | Quasi-square (with square pulses) | 2 h/day for 8 weeks | Improved bone architecture, mechanical properties, and porous titanium osseointegration combination of HF-PESW stimulation with HAPc coating on Ti implants promotes an accelerated healing |
| Oltean-Dan et al., 2019 | Albino Wister rats | Coated titanium implants | 400 pulses/s, 25.35 W, with a peak power of 975 W | N/A | 10 min/day for 2 weeks | Improved bone architecture, mechanical properties, and porous titanium osseointegration combination of HF-PESW stimulation with HAPc coating on Ti implants promotes an accelerated healing |
| Nunes et al., 2021 | Sixty male rats (Wistar) | Titanium implants | 15 Hz | 1 mT | N/A | 5 days/week for 3, 7, 21, and 45 days | 1 h PEMF exposed had greater removal torque tests than 3 h exposed in bone volume and bone mineral density, cell viability, total protein content, and mineralization nodules |
| Gujjalapudi et al., 2016 | Human trial | Twenty tidal spiral implants | Continuous magnetic field | 0.5 T | N/A | 12-15 h daily for 12 weeks | Static magnetic field may provide favorable environment for early bone healing and increased primary stability |
| Nayak et al., 2020 | Human trial | Commercially available titanium dental implants | 10-50 kHz for 30 days | 0.05-0.5 mT | N/A | 30 days | Increased in primary stability of 6.8%, compared to a decrease of 7.6% in the control group |
healing around dental implants in dogs. A CEF at the magnetic intensity of 0.8 mT with a pulse width of 25 μs and frequency of 1.5 MHz was applied on the implants for 20 min per day for 2 weeks. They concluded that CEF stimulation in this animal experimental model did not improve the bone-healing process around dental implants when compared to the control group, serving as an important consideration for studies involving the optimal stimulation time per day and the optimal duration of treatment with CEF on promoting osseointegration in patients with dental implants.

Barak et al. 2016\cite{20} results suggested an acceleration of the osseointegration process by more than three times upon insertion of a total of 22 implants in the proximal tibial metaphysis of 22 rabbits. The animals were euthanized after 2 and 4 weeks, and the samples were processed for micro-computed tomography and histology. The peri-implant volume was divided into coronal (where the PEMF was the strongest) and apical regions. Most of the effects of the tested device were confined to the coronal region. Two weeks postimplantation, test implants showed a significant 56% higher trabecular bone fraction (BV/TV), associated with enhanced trabecular number (Tb. N, +37%) and connectivity density (Conn. D, +73%) as compared to the control group; at 4 weeks, the PEMF induced a 69% increase in BV/TV and 34% increase of Tb. N. There was no difference in the trabecular thickness (Tb. Th) at either time point. They observed a 48% higher bone-to-implant contact (BIC) in the test implants versus controls after 2 weeks; this increase tended to remain stable until the 4th week. Mature trabecular and woven bone were observed in direct contact with the implant surface with no gaps or connective tissue at the bone-implant interface.

Cai et al. 2018\cite{21} studied the effects of exogenous PEMF stimulation on type 1 diabetes mellitus associated osteopathy in alloxan-treated rabbits. They found that PEMF improved bone architecture, mechanical properties, and improved osseointegration around porous titanium implants by promoting bone anabolism through a canonical Wnt/-catenin signaling-associated mechanism.

Oltean-Dan et al. 2019\cite{22} recently in an in vivo study on albino Wistar rats showed that the combination of Ti implants, coated with porous biomimetic HAPc (hydroxyapatite) composite and pulse electromagnetic short wave stimulation positively influenced the bone consolidation process in its early phase. Their findings indicated an innovative approach to enhance bone consolidation and improve fracture healing around Ti implants. Porous hydroxyapatite coating has the ability to bond with the bone tissue and improve the implant stability and reduce the healing time after surgery.

Nunes et al. 2021\cite{23} evaluated two protocols of PEMF on osseointegration and establish one that addresses ideal parameters for its use in dentistry, especially in the optimization of the implants osseointegration process. Sixty male rats (Wistar) were allocated into three experimental groups: control (GC), test A (GTA, 3 h exposed), and test B (GTB, 1 h exposed). All animals received titanium implants in both tibias, and PEMF application (15 Hz, ± 1 mT, 5 days/week) occurred only in the test groups. They were euthanized at 03, 07, 21, and 45 days after PEMF therapy. 1 h pemf exposed showed better results compared with 3 h exposed group in removal torque tests, in bone volume and bone mineral density, cell viability, total protein content, and mineralization nodules (P < 0.05). Three hours exposed group showed better performance in trabecular bone thickness and cell proliferation compared with 1 h exposed group (P < 0.05). In the histomorphometric analysis and number of trabeculae, there were no differences in the test groups. They concluded that PEMF was effective in optimizing the events in bone tissue that lead to osseointegration, especially when applied for a shorter time and in the initial periods of bone healing.

HUMAN TRIALS

Gujjalapudi et al. 2016\cite{24} et al. placed twenty tidal spiral implants and used a safer magnet (Neodymium Boron Iron) on 10 patients between 50 and 75 years of age at two sites on edentulous mandible with D1 and D2 bone type with one site as a control. Both the implants were compared for stability using resonance frequency analyzer (RFA) at Days 0, 30, 60, and 90. Results: The average ISQ value for implants at 0 day in the B and D regions was 68.6 and 68.7, respectively. The average ISQ value at the 30th day, 60th day, and 90th day was 73.25, 76.05, and 78.95, respectively, on the magnetic side. Whereas on the non-magnetic side at 30th day, 60th day, and 90th day was 68.45, 72.05, and 74.45, respectively. The implant stability quotient values obtained on the magnetic side were significantly greater than on the nonmagnetic side.

Nayak et al. 2020\cite{25} studied 19 subjects (40 implants in total) and randomly allocated them to the PEMF group or control group. Subjects in the PEMF group received an activated miniaturized electromagnetic device (MED) while the control group received a sham healing cap. Implants stability was assessed by resonance frequency analyses (RFA) via implant stability quotient (ISQ) calculations. RFA were recorded at immediately after procedure, and then 2, 4, 6, 8 and 12 weeks later. Radiographic analysis was performed at baseline, 6 and 12 weeks after implant placement and proinflammatory cytokines were evaluated in peri-implant crevicular fluid. They reported that the PEMF group presented higher ISQ mean values when compared to the control group. In the primary
stability period (the first 2 weeks) MED group depicted an increase in stability of 6.8%, compared to a decrease of 7.6% in the control group related to the baseline. They reported an overall stability increase of 13% in the MED treated group ($P = 0.02$), in contrast, the overall stability in the control group decreased by 2% ($P = 0.008$). Tumor necrosis factor- concentration during the first 4 weeks was lower in the MED treated group. A continuous PEMF generated by a miniature device attached to an implant may stimulate the stability of the implants at the early healing period.

**DISCUSSION**

Novel biophysical approaches that promote oral tissue healing offer various advantages due to their nonconsumable nature, ease of access to oral wounds, and efficacy of promoting the endogenous healing process that would reduce frequent patient visits and reduce the cost of overall therapy. Numerous studies over the past decades have hypothesized that biophysical methods such as pulsating electromagnetic fields and bio modulation have the potential to affect osteoblastic behavior both in vivo and in vitro and hence can be a potential tool to improve the clinical outcome of several regenerative and prosthetic therapies in orthopedics and dentistry. The bio modulation of physiological processes by PEMF depends upon (i) the physiological state of the injured tissue (ii) effective dosimetry of the applied PEMF at the target site. Studies (both in vitro and in vivo) have shown that biophysical stimulation induces (i) an increase in osteoblast differentiation, promoting the production of collagen and of the main matrix glycoproteins osteocalcin and osteopontin (ii) stimulates the mineralisation process and (iii) plays an inhibitory role in the process of osteoclast differentiation and exerts a protective action against osteolysis. Bone matrix induction by PEMF is similar to those induced by growth factors such as TGF- 1, BMPs and growth factor insulin-like growth factor-4, indicating that the effects induced by a biophysical stimulus are of significant medical importance. Numerous studies have analyzed the effects of biophysical stimulation on osteoblast proliferation and have highlighted a dose-response effect for the following parameters (i) signal waveforms, (ii) PEMF intensity, frequencies, and (iii) exposure times.

**Signal waveforms**

The existing PEMF has different types of waveforms including asymmetrical, biphasic, sinusoidal, quasi-square/rectangular, and trapezoidal. Among them, quasi-rectangular and quasi-triangular PEMF were approved by FDA as the safe and effective treatment for fractures. In their review of the use pemf on titanium implants, Galli et al. highlighted that most animal studies have used the quasi square/rectangular and trapezoidal signal waveforms.

**Magnetic field intensity and frequency**

It has been shown that at least 3 amplitude windows exist: at 50-100T (5-10 Gauss), 15-20 mT (150-200 Gauss), and 45-50 mT (450-500 Gauss) the maximum response that was observed within the range of 10-100 mT. The frequency of electromagnetic fields used in clinical treatment is usually < 100 Hz and the magnetic flux density is between 0.1 m T and 30 m T. The response of cells and tissues to PEMF in the presence of titanium devices, for orthopedic or dental use, has been investigated using a vast range of PEMF approaches and settings but besides a few attempts in the early 2000s with 100 Hz PEMF pulses with very light intensities, around 0.2 mT. Matsumoto et al. in their study demonstrated PEMF application at different intensities, duration of application and length of treatment in weeks. Their study concluded that the bone contact ratio and bone area ratio of the 0.2 mT and 0.3 mT-treated femurs were significantly larger than the respective value of the 0.8 mT-treated femurs of Japanese rabbits ($P < 0.001$). No significant difference in bone contact ratio or bone area ratio was observed whether PEMF was applied for 4 h/day or 8 h/day. Although a significantly greater amount of bone had formed around the implant of the 2-week treated femurs than the 1-week treated femurs, no significant difference was observed between the 2-week and 4-week treated femurs. This study highlighted the importance to select the proper magnetic intensity, duration per day, and length of treatment. Most recent studies have used 15 Hz-75 Hz trapezoidal stimuli, with higher intensity, around 1-2 mT. Apart from one in vitro animal study of Grana et al. had used a higher intensity of 72 m T most animal studies have used intensities in the range of 0.2-2 mT. Broader screening studies testing across a spectrum of amplitudes and frequencies are still missing with the purpose of establishing better and more reliable clinical protocols. Gujjalapudi et al. reported in a human trial reported an increase in primary stability of commercially available dental implants by using 0.5 m T continuous electromagnetic field application for 12–15 h. Nayak et al. 2020 that continuous PEMF generated by a miniature device generation 0.5 mT attached to an implant stimulated the stability of the implants at the early healing period.

**Duration**

Most studies involving fracture unions have supported a finding that an increase in the average daily “dose” of PEMF stimulation was associated with acceleration in the rate of fracture healing. A recent study followed 1382 patients treated with PEMF stimulation and demonstrated that the average healing time was reduced by 6 days for each
additional hour of daily PEMF treatment. Matsumoto et al.[14] in their study demonstrated PEMF application at different intensities, duration of application, and length of treatment in weeks. No significant difference in bone contact ratio or bone area ratio was observed whether PEMF was applied for 4 h/day or 8 h/day. Although a significantly greater amount of bone had formed around the implant of the 2-week treated femurs than the 1-week treated femurs, no significant difference was observed between the 2-week and 4-week treated femurs. The two human studies of Gujjalapudi et al.[24] and Nayak et al.[25] also reported improved early healing and primary stability of dental implants when applied for a continuous or a 12–14 h in a 2 week period after implant placement.

CONCLUSION

The use of PEMF treatment though has favorable outcomes as reported in various in vivo and invitro researches there is still the need for more defined and better controlled/monitored treatment modalities. The varied observations and effects can be attributed to various factors like the use of different animal species in the different studies, various implantation sites (trabecular or cortical bone, intramedullary), different biomaterials (ceramic or metallic), and with different intensity, frequency, signal waveform, and duration of the stimulation. A multicentric trial with the involvement of engineers, biophysicists, biologists, and medical practitioners to further study and develop the PEMF use because of the necessity of a broad range of settings that includes magnetic field intensity, frequency, and duration of application. PEMFs stimulation for various treatments and defining proper treatment protocols and warrants extensive research. It is, therefore, essential to design well-controlled randomized clinical studies to assess and confirm the efficacy.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Frost HM. Wolff’s Law and bone’s structural adaptations to mechanical usage: An overview for clinicians. Angle Orthod 1994;64:175-88.
2. Gupta AK, Srivastava KP, Avasthi S. Pulsed electromagnetic stimulation in nonunion of tibial diaphyseal fractures. Indian J Orthop 2009;43:156-60.
3. Goldstein C, Sprague S, Petrisor BA. Electrical stimulation for fracture healing: Current evidence. J Orthop Trauma 2010;24 Suppl 1:S62-5.
4. Bassett CA, Pawluk RJ, Becker RO. Effects of electric currents on bone in vivo. Nature 1964;204:652-4.
5. Jansen JH, van der Jagt OP, Punt BJ, Verhaar JA, van Leeuwen JP, Weinars H, et al. Stimulation of osteogenesis from osteoprogenitor cells by pulsed electromagnetic fields: An in vitro study. BMC Musculoskelet Disord 2010;11:188.
6. Tabrah F, Hoffmeier M, Gilbert F Jr, Bathin S, Bassett CA. Bone density changes in osteoporosis-prone women exposed to pulsed electromagnetic fields (PEMFs). J Bone Miner Res 1990;5:437-42.
7. Fassina L, Saino E, Visai L, Silvani G, Cusella De Angelis MG, Mazzini G, et al. Electromagnetic enhancement of a culture of human SAOS-2 osteoblasts seeded onto titanium fiber-mesh scaffolds. J Biomed Mater Res A 2008;87:750-9.
8. Atalay B, Aybar B, Ergüven M, Emes Y, Bartun O, Akça K, et al. The effects of pulsed electromagnetic field (PEMF) on osteoblast-like cells cultured on titanium and titanium-zirconium surfaces. J Craniofac Surg 2013;24:2127-34.
9. Wang J, An Y, Li F, Li D, Jing D, Guo T, et al. The effects of pulsed electromagnetic field on the functions of osteoblasts on implant surfaces with different topographies. Acta Biomater 2014;10:975-85.
10. Jing D, Zhao M, Tong S, Xu F, Cai J, Shen G, et al. Pulsed electromagnetic fields promote osteogenesis and osseointegration of porous titanium implants in bone defect repair through a Wnt/ -catenin signaling-associated mechanism. Sci Rep 2016;6:32045.
11. Bloise N, Petecchia L, Cecarelli G, Fassina L, Usai C, Bertoglio F, et al. The effect of pulsed electromagnetic field exposure on osteoinduction of human mesenchymal stem cells cultured on nano-TiO2 surfaces. PLoS One 2018;13:e0199046.
12. Spadaro JA, Albanese SA, Chase SE. Electromagnetic effects on bone formation at implants in the medullary canal in rabbits. J Orthop Res 1990;8:685-93.
13. Ijiri K, Matsunaga S, Fukuyama K. The effect of pulsing electromagnetic field on bone ingrowth into a porous coated implant. Anticancer Res 1996;16:2853-6.
14. Matsumoto H, Ochi M, Abiko Y, Hirose Y, Kaku T, Sakaguchi K. Pulsed electromagnetic fields promote bone formation around dental implants inserted into the femur of rabbits. Clin Oral Implants Res 2000;11:354-60.
15. Buzzá EP, Shibli JA, Barbeiro RH, de Albergaria Barbosa JR. Effects of electromagnetic field on bone healing around commercially pure titanium surface: Histologic and mechanical study in Rabbits. Implant Dentistry vol. 12. 182–187 (2003).
16. 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 J Med Sci 2004;34:91-5.
17. Akca K, Sarac E, Baysal U, Fanuscu M, Chang TL, Cehreli M. Micro-morphologic changes around biophysically-stimulated titanium implants in ovariecтомized rats. Head Face Med 2007;3:28.
18. Grana DR, Marcos HJ, Kokubu GA. Pulsed electromagnetic fields as adjuvant therapy in bone healing and peri-implant bone formation: An experimental study in rats. Acta Odontol Latinoam 2008;21:77-83.
19. do Nascimento C, Issa JP, Mello AS, de Albuquerque RF Jr. Effect of electromagnetic field on bone ingrowth around dental implants after immediate placement in the dog mandible: A pilot study. Gerodontology 2012;29:e1249-51.
20. Barak S, Neuman M, Iezzi G, Piattelli A, Perrotti V, Gabet Y. A new device for improving dental implants anchorage: A histological and micro-computed tomography study in the rabbit. Clin Oral Implants Res 2016;27:935-42.
21. Cai J, Li W, Sun T, Li X, Luo E, Jing D. Pulsed electromagnetic fields preserve bone architecture and mechanical properties and stimulate porous implant osseointegration by promoting bone anabolism in type 1 diabetic rabbits. Osteoporos Int 2018;29:1177-91.
22. Oltean-Dan D, Dogaru GB. Enhancement of bone consolidation using high-frequency pulsed electromagnetic short-waves and titanium implants coated with biomimetic composite. Aquat Microb Ecol 2013;59:147-56.
23. Nunes CM, Ferreira CL, Bernardo DV. Evaluation of pulsed electromagnetic field protocols in implant osseointegration: *In vivo* and *in vitro* study. Clin Oral 2021.

24. Gujjalapudi M, Anam C, Mamidi P, Chiluka R, Kumar AG, Bibinagar R. Effect of magnetic field on bone healing around endosseous implants – *An in vivo* study. J Clin Diagn Res 2016;10:F01-4.

25. Nayak BP, Dolkart O, Satwalekar P, Kumar YP, Chandrasekar A, Fromovich O, *et al.* Effect of the pulsed electromagnetic field (PEMF) on dental implants stability: A randomized controlled clinical trial. Materials 2020;13:1667.

26. Li J, Zeng Z, Zhao Y, Jing D, Tang C, Ding Y, *et al.* Effects of low-intensity pulsed electromagnetic fields on bone microarchitecture, mechanical strength and bone turnover in type 2 diabetic db/db mice. Sci Rep 2017;7:10834.

27. Chang WH, Chen LT, Sun JS, Lin FH. Effect of pulse-burst electromagnetic field stimulation on osteoblast cell activities. Bioelectromagnetics 2004;25:457-65.

28. 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.

29. Markov MS. Pulsed electromagnetic field therapy history, state of the art and future. Environmentalist 2007;27:465-75.