WORKSHOP ON BIOMATERIALS
BMAT 2005 – (PP.69–94) – WARSAW, 2005.

Physical Regulation of Bone Growth with PEMF-Biostim

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Bone tissue is known to be sensitive to physical stimuli, electromagnetic, electric and mechanic. Different technologies for bone growth stimulation have been developed over the last 25 years. Pulsed Electromagnetic Field (PEMF) stimulation has been used to enhance fracture healing especially in case of non-unions. The mechanism through which PEMF favour osteogenesis is by exogenously stimulating the endogenous production of growth factors, like TGF-β1. Besides reparative osteogenesis for fracture healing, studies have been performed in an attempt to optimise osteogenetic response around implant, so that implant fixation can be achieved in shorter time and the contact between guest bone and implant is maximized. In this chapter we review the fundamental basis of bone growth stimulation and the results of most recent experiments conducted in animals to investigate the usefulness of PEMF to enhance implant fixation. Finally, we report the results of the limited clinical experience present in the literature relating to PEMF stimulation of hip prosthesis.

Key words: *pulsed electromagnetic fields, osteogenesis, hydroxyapatite*

1. Introduction

The bone growth stimulation (BGS) of osteogenesis belongs in the area of research of bioengineering and biophysics. It is employed in many countries in the orthopedic field to promote and reactivate the formation of bone tissue. The scientific origins of the BGS techniques are acknowledged to lie in the by

now classic studies performed first by Fukada and Yasuda [1], then by Bassett and Becker [2]. The aforementioned studies performed in the 1950s and 1960s highlighted the relation between bone tissue mechanical deformation and electric potentials.

Bone generates two types of electric signal: one in response to mechanical deformation, the other in the absence of deformation.

The signal induced in bone by structural deformation following the application of a load (not necessarily vital), has a dual origin: (a) direct piezoelectric effect, and (b) electrokinetic phenomenon of the flow potential, [3–9].

Independently of the mechanism, piezoelectric or electrokinetic, by which it is generated, the electric signal induced by the mechanical deformation, characterized by the site, direction and amplitude necessary to modulate the bone remodelling, has been considered to be the transducer of a physical force in a cell response. It is, indeed, intelligible from the cells, as is proved by the cellular effects that can be activated by exogenous electric signals similar to the endogenous ones [8]. The aforesaid electric signal has thus been taken to be the indication of the mechanism that determines the continuous adaptation of the mechanical competence of bone to variations in load, according to the well-known law of Wolff.

In the absence of mechanical stress, the living bone generates an electrical signal detectable in vivo as surface stationary bioelectric potential and ex vivo as stationary electric (ionic) current that can be measured.

Despite the different experimental conditions of detection, both the electrical signals induced by mechanical deformation and those generated by vital bone in its absence have been interpreted as local control factors of bone remodelling/modelling and reparative osteogenesis. Ever since the first detection of these signals it has therefore been held that inducing them in bone by means of external generators could be of clinical importance particularly in situations where repair processes have remained incomplete [8,10–15].

In the research sector involved in the histophysiology of bone tissue, the above observations regarding the relation between bone tissue and electric potentials have aroused great interest in the possibility of active intervention, with physical stimuli on the cell-metabolic activity of bone, especially on the osteoblasts.

A number of experimental studies have shown how and to what extent, in various animal models, it is possible to enhance endogenous bone repair with the aim of promoting osteogenesis by applying physical stimuli. In humans,

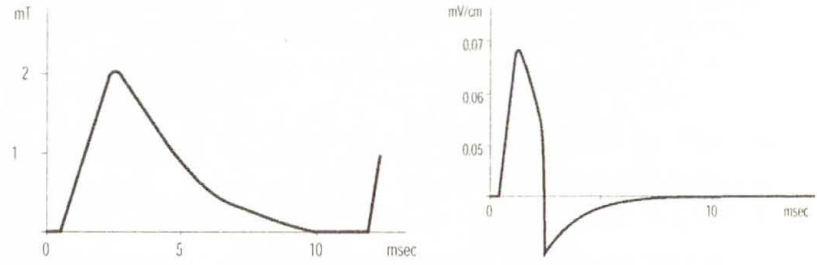
BGS has been studied with the goal of enhancing the spontaneous repair capacity of bone tissue, i.e. to reactivate it in pathological conditions such as non-unions, [16–20].

To understand the principles of BGS it is important to recall from physics that to every electric field in conductive media, as are biological tissues, there corresponds a current density and vice versa. Moreover, a magnetic field variable in time induces an electric field. Lastly, every ion, when subjected to an electric or magnetic field, is subject to a Lorentz force. The electrical component of this force is given by the product of the ionic charge multiplied by the intensity of the electric field, while the magnetic component is proportional to the product of the ionic charge multiplied by the velocity of the ion and the intensity of the magnetic field. On the basis of these premisses, biophysical enhancement of osteogenesis with electromagnetic fields has been developed: alternating electric currents externally induced by pulsed electromagnetic fields (PEMF) in the bone tissue are capable of modulating local cell activity; PEMF do not necessitate physical contact between application device and tissue.

2. Mechanism of Action of PEMF

The biological activity in the bone exposed to PEMF may be modulated both by means of the magnetic component varying in time and by means of the electrical component, i.e. the induced electric field. PEMF signals used for BGS, like Biostim, are characterized by a complex wave form, whose predominant spectral content ranges between a few tenths to a ten thousandths of hertz [13] (Fig. 1).

Various mathematical models have been developed to explain the biological effects of the inductive systems: cyclotronic resonance, ligand-receptor interaction, and stochastic resonance. The first two have certainly received attention and are in any case compatible with experimental evidence [21,22]. By now there is broad consensus on the fact that the main sites of action of PEMFs are at the level of cell membrane, and the most favoured candidates are the membrane receptors and Ca^{2+} channels [23–25]. Pathways of signal transduction (Ca^{2+} transport) through the cell membrane have been identified in bone cells exposed to electromagnetic fields, when Ca^{2+} influx is increased by PEMF exposure, it may lead to an increase in cell proliferation. Experiments *in vitro* have shown that exposure to PEMF favours the prolife-



(a) (b)

FIGURE 1. (a) Waveform of the magnetic field, (b) Waveform of the electric tension induced in a standard coil probe by the electromagnetic field.

ration of elements of the immune system and is able to favour neoangiogenesis in cultures of endothelial cells. Electromagnetic stimulation of human bone cells recovered from a non-union site succeeded in increasing the expression and release of TGF-β1 [25–32]. In vivo, authors have observed an increase in the formation of bone tissue [33] and a shorter healing time of experimental fractures and/or bone lesions [34–36]. Studies of newly formed bone tissue performed with tetracycline labeling have demonstrated that the ability of the osteoblastic activity to lay down bone tissue (mineral apposition rate), i.e. to form trabeculae in vivo is doubled, following exposure to PEMF [37].

Threshold values for the magnetic field intensity, the values of frequency of the field and the waveform of the magnetic field have been described. Dose response curves have been observed for the exposure length.

In clinical practice BGS is employed to heal fractures that have not consolidated at least 6 months after trauma, . BGS is maintained until consolidation occurs; common experience suggests, however, that if the X-ray images show no trend towards healing of the fracture at 90 days from start of BGS treatment, it is advisable to abort the treatment and consider alternative solutions. BGS should be initiated only if the mechanical stability, the alignment of the fracture are guaranteed and if a gap is present its extension should not exceed half of the diameter of the fractured bone.

BGS has been approved for clinical use by the U.S.A. Food and Drug Administration 30 years ago. Since then every year tens of thousands of patients undergo treatment throughout the world [38]. Nevertheless only products whose clinical effectiveness is well documented in the literature should be used.

3. Demonstration of Effectiveness in Humans

Over the last twenty years in which electromagnetic stimulation of osteogenesis has been in clinical use, a great number of clinical studies have been performed: using the appropriate double-blind or control group protocols these have shown the ability of the aforesaid stimulation to promote osteogenetic activity in humans and hence to favour bone consolidation. These research protocols were dictated by the need to discriminate effectively between the effects of electromagnetic stimulation and other possible associated orthopedic manoeuvres, and to quantify the efficacy of the treatments in human subjects [39, 44]. Table 1 reports a list of the studies with double blind or control group, taken from the literature.

TABLE 1. Clinical studies regarding demonstration of the osteogenetic effect of BGS with PEMF

Author	Pathology	Protocol
Fontanesi 1986 [36]	Recent Tibia Fractures	Control
Borsalino 1988 [45]	Femur Osteotomies	Double-blind
Aaron 1989 [46]	Avascular Necrosis	Control
Lee 1989 [47]	Vertebral Arthrodesis	Double-blind
Traina 1991 [44]	Pseudoarthrosis	Control
Sharrard 1990 [48]	Tibia Delayed Union	Double-blind
Mooney 1990 [49]	Vertebral Arthrodesis	Double-blind
Simonis 2003 [50]	Pseudoarthrosis	Double-blind
Mammi 1993 [51]	Tibia Osteotomies	Double-blind
Capanna 1994 [52]	Osteotomies + Bone Grafts	Double-blind
Hinsenkamp 1984 [53]	Recent Fracture with External Fixators	Control
Betti 1997 [54]	Recent Femur Fractures	Double-blind

4. Rationale for Employment of BGS in Clinical Practice

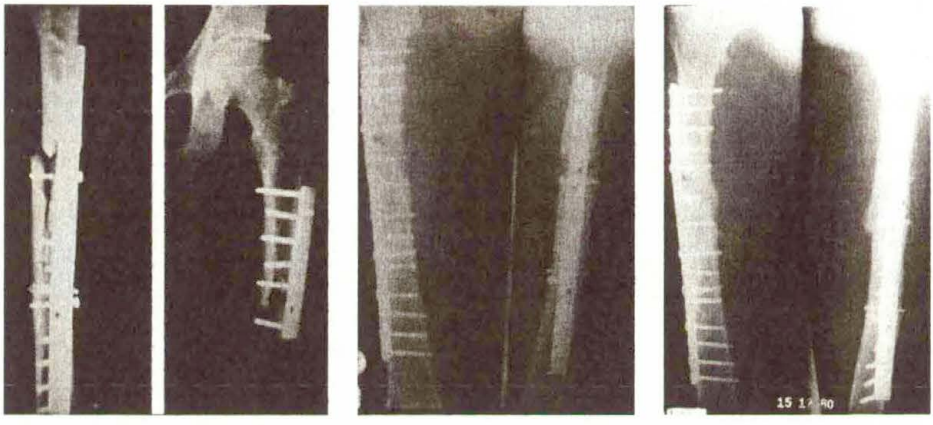
In orthopedic-traumatologic practice, osteogenetic activity aimed at consolidation of a fracture continually comes up against problems of mechanical and biological kind [14].

The repair process in bone tissue is especially complex owing to the structural characteristics of the tissue itself, the loads and forces in question, and the times necessary for healing.

Among the factors that may jeopardize a repair process at bone tissue level, primary consideration is usually accorded to the mechanical aspects,

on which orthopedic research has successfully been focused for upwards of 50 years. More recently it has been observed that failed consolidation can be ascribed to an insufficient osteogenetic response at the level of the fracture site, rather than to inadequate immobilization.

Assessment of the mechanical and biological factors that have hindered bone consolidation is the particular responsibility of the orthopedic surgeon, who, on the basis of knowledge and experience, can apply the solution best able to heal the patient (Fig. 2).



(a) (b) (c)

FIGURE 2. Infected non union 10 months from trauma, (a) At the beginning of the Biostim-PEMF stimulation; (b) after two months of Biostim treatment; (c) end of treatment after 4 months.

Just as stimulation of a fracture with evident problems of mobility or diastasis between the stumps is contraindicated, so it appears useless to operate on a patient with a satisfactory mechanical stability of the lesion when the problem can be attributed to an impaired osteogenetic response [41–44].

Failed fracture healing can originate either from technical mistakes (the orthopedic procedure has damaged the normal healing potential) or from an inadequate spontaneous biological bone activity (thus the impaired endogenous biological response prevents healing even in the presence of a proper orthopedic treatment); in some instances both events are present. Frost has assessed that only 40–50% of failed consolidations can be ascribed to problems of a strictly mechanical kind [14]. In all other failed consolidations,

therapy focused on the biological response suggests itself. A variety of options are available to the orthopedic surgeon to reactivate the repair process: intervention on the stumps, bone grafts [55], biophysical stimulation.

These observations represent the rationale for indication of treatment by biophysical stimulation: bearing in mind these principles, the rate of sucess, that is, of consolidations obtained with biophysical stimulation exceeds 90 per cent.

4.1. Biophysical Stimulation in Presence of Implants

PEMF stimulation in presence of steel or alloys is not in itself contraindicated; the therapeutic effect of the inductive systems is not hindered by the presence of the implanted metals. Nevertheless, the presence of metal may, at least partly, screen the electric field and thus interfere with its spatial configuration. According to the literature, this fact does not appear to affect importantly the osteogenetic response at the site of the lesion for example in presence of non-unions. In any case, there are no indications of interference such as to lead to phenomena of electrolysis of metals with production of toxic substances [36, 38, 42, 56].

Based on above safety considerations PEMF use to favour biomaterial osteointegration has been considered to limit complications associated to implant failure.

Aseptic loosening of implants is still a serious complication in orthopaedic, dental and maxillofacial reconstructive surgery and this is particularly the case when bone stock and healing potential are compromised [57]. Some biological predictive risks for implantation surgery success have been identified, they are related to genetic factors [58], the patient's health status [59], and the complexity of the bone healing processes around an implanted biomaterial [60].

Bone is a heterogeneous tissue, which is subjected to mechanical forces, it remodels throughout life, and it is influenced by age, diseases, drugs, commonly used by patients, that may interfere with bone metabolism, finally by systemic and local factors [60, 61]. To limit the risk of aseptic loosening, much research has been done to promote bone formation at the bone-biomaterial interface by combining proper biomaterials and surgical techniques with different biological stimulating factors such as growth factors (GF) and bone morphogenetic proteins (BMPs), alone or in combination with bone grafts

[62–67]. However, many questions remain unanswered about their effectiveness, safety, optimal dosages or concentrations, and regardless of evidence to date, the long-term effects of some of these biological stimulators cannot be authoritatively predicted and may have covert influences not immediately expressed. Other methods that have been attempted to enhance endogenous bone healing around biomaterials are different forms of biophysical stimulations such as pulsed electromagnetic field [68–77].

The activation of the osteogenetic activity immediately after the insertion of an implant favours its integration and, most importantly, guarantees the implant stability in the long term. It is accepted that there is a time window to form bone around an implant after which fibrous tissue will be formed. To enhance bone implant osteointegration, many strategies have been developed as regards both the implant characteristics and the biological activity of the guest tissue.

Improvement of biomaterial properties has been investigated: optimization of implant material, implant design, surface morphology and osteogenetic coatings [78–83]. An accelerated stable fixation between bone and implant would allow early or immediate loading of the device, with important implications in terms of decreased patient morbidity and health care costs [78]. In this connection, it should be remembered that, even in healthy conditions, progression of bone ingrowth in biomaterials is a very slow process [84].

PEMF stimulation has been investigated both experimentally and clinically as orthopaedic treatments for several decades. This knowledge has at least two important consequences: 1) the strong potentiality of PEMF stimulation to enhance orthopaedic implant fixation on the basis of the assumption that the process of bone healing around implants involves the activation of osteogenetic processes similar to those of the bone healing of fractures and defects, at least in terms of initial host response [85]; 2) biophysical stimulation techniques proposed to enhance biomaterial osteointegration are already well-known as far as safety, dosage and exposure time are concerned, because their use has been established since many years to enhance fracture healing. Consequently, this knowledge may greatly facilitate and accelerate the transfer of the methodology to clinical application to favour implant osteointegration. One should bear in mind that the control of the local environment by exogenous physical stimuli is achieved by exposing only the specific region/area of interest, and this means that they can trigger a therapeutic effect by delivering locally the optimal effective dose. Thus, the treatment

can be performed in the absence of systemic effects and complies with the principle of limiting iatrogenic side effects.

Here we review experimental and clinical studies published in the literature over the last 20 years on the combined use of biomaterials and PEMF, the possible mechanism of action and effectiveness of PEMF stimulation for the enhancement of bone healing processes around implanted biomaterials.

5. Pulsed Electromagnetic Fields

Table 2 summarises the animal studies on the effect of PEMF on bone implant osteointegration, [68–74].

Shimizu et al. [68] studied the effect of PEMF on bone ingrowth into porous ceramics together with the associated implant degradation. They implanted porous hydroxyapatite (HA) and tricalcium phosphate (TCP) nails in the proximal tibia diaphysis of 34 rabbits that were euthanized at 1, 2, 3, 4 and 6 weeks. The experimental animals were treated with PEMF for 8 hrs/day (intensity: 1.8 G, frequency: 1.5 Hz; burst width: 26 ms). HA and TCP behaved differently. For HA, the amount of new bone was significantly greater in the PEMF group at 3 and 4 weeks after surgery as compared with that of the control group. Also significant increases in volume fraction of bone, mean width of newly formed bone trabeculae and boundary fraction of bone to the HA surface in the PEMF group were observed in the cortical bone.

Spadaro et al. [69] studied whether a PEMF stimulus would modify bone formation around movable or stationary implants in the medullar canal of the rabbit long bones in the relative absence of bone trauma. They implanted a Kirschner wire (316 stainless steel) in the medullary canal of the femurs and tibias of 18 rabbits. The animals were treated daily with PEMFs for 4 hrs/day (frequency: 15 Hz) or left untreated and were euthanized at 3 weeks for histology and measurement of new trabecular bone and of cortical geometry. Bone measurements showed that in stationary implants both the PEMF and control groups had little bone formation, while in movable implants the PEMF appeared to increase motion-stimulated bone formation. This increase was statistically significant only for the femoral implants. Also the average cross-sectional area of the medullary canal in femurs containing movable implants was significantly higher in the PEMF-treated animals compared with unexposed movable controls. The authors concluded that PEMF enhanced

TABLE 2. In vivo experimental studies on biomaterial osteointegration after pulsed electromagnetic field stimulation (1985–2004), experimental animal studies.

Implant Site	Biomaterials	Main Results	Ref.
Proximal tibial diaphysis of rabbits	HA TCP	Significantly greater amount of new bone, volume fraction of bone, mean width of newly formed bone trabeculae, boundary fraction of bone to the HA surface in PEMF-treated animals. No similar effect on bone ingrowth into TCP pores.	68
Movable and stationary implants in the tibial and femoral canal of rabbits	316 stainless steel	Significant improvement of bone formation in movable implants in PEMF-treated animals at 3 weeks vs. controls	69
Humerus medullar cavity of rabbits	Ti6Al4V	Significant improvement of new bone area around Ti6Al4V in PEMF-treated animals vs controls	70
Distal femur of rabbits	Ti6Al4V	Significant improvement of Ti6Al4V osteointegration in PEMF-treated animals also depending on dosage and exposure time	71
Distal femur of rabbits	HA	Significant improvement of bone-HA contact ratio and bone mineralization in PEMF-treated animals vs controls	72
Medial tibial cortex in the proximal tibia of rabbits	Natural and synthetic HA	PEMF-treated animals showed more advanced bone formation in both forms of apatite vs controls	73
Tibial metaphysis of rabbits	Titanium	No significant differences in Ti osteointegration between PEMF-treated and control animals	74

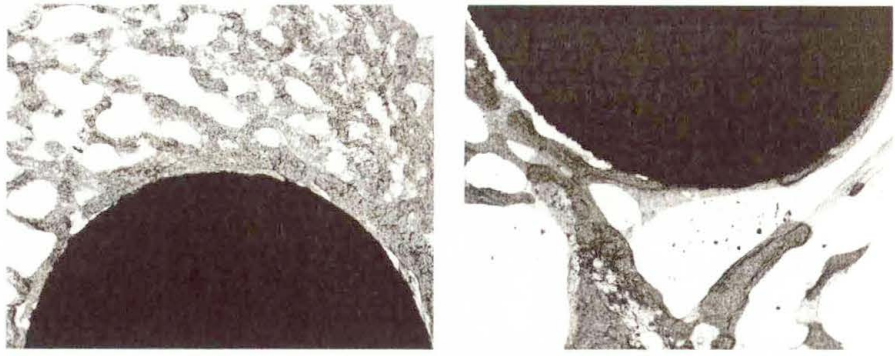
osteogenesis in the presence of another stimulus (i.e. traumatic or mechanical) and that this effect depended also on the implant site (more evident in the femur than in the tibia).

Ijiri et al. [70] implanted a coated porous Ti6Al4V stem in the diaphyseal marrow cavity of the humerus of 20 rabbits. The experimental animals underwent PEMF stimulation (intensity: 2 G; frequency: 10 Hz; pulse width: 25 μsec) for 5 and 10 hrs/day from the 1st to the 14th consecutive days after surgery. During both stimulations a significant increase in the area of

newly re-grown bone around implants in experimental animals was observed. These authors also observed that the beneficial effect of stimulation was time-dependent with a significantly larger effect for longer stimulation time (10 hrs. versus 5 hrs). The authors concluded that PEMF stimulation should be clinically applied to promote bone ingrowth after total joint replacement.

Matsumoto et al. [71] studied bone formation around rough-surfaced dental implants as a function of: a) magnetic field intensity (0.2 mT, 0.3 mT, 0.8 mT for 8 hrs/day for 2 weeks), b) length of daily stimulation (4 and 8 hrs. at a magnetic field intensity of 0.2 mT for 2 weeks) and c) duration of treatment (1, 2 and 4 weeks at a magnetic field intensity of 0.2 mT for 8 hrs/day). Dental implants made of Ti6Al4V were implanted in the distal femur of 45 rabbits. Histological and histomorphometric observations were performed on 5 rabbits per group at the selected experimental times. Quantitative data showed that the bone contact and bone area ratio of each experimental group stimulated with PEMF at 0.2, 0.3 and 0.8 mT were significantly higher than that of unstimulated controls. The low amplitude PEMF (0.2 and 0.3 mT) promoted a greater degree of bone formation than 0.8 mT. The daily length of stimulation was not an important factor; bone contact ratio and bone area ratio of the femurs treated with PEMF for 4 hrs./day and those treated 8 hrs./day did not differ significantly. Finally, the bone contact ratio and bone area ratio of the femurs treated with PEMF for 1, 2 and 4 weeks were significantly higher than those of the control groups without significant differences between femurs treated for 2 and 4 weeks respectively. The authors concluded that PEMF stimulation might be useful for promoting bone formation around rough-surfaced dental implants.

Fini et al. [72] investigated the effect of PEMF (frequency: 75 Hz, intensity: 1.6 mT, impulse width 1.35 ms) in 12 rabbits after placing HA cylindrical nails in the trabecular bone of the distal femurs. Experimental animals were stimulated for 6 hrs./day for 3 consecutive weeks while control animals were sham-treated. A group of animals were sacrificed at the end of the period of stimulation (at 3 weeks) and another group after a 3-week non-stimulation period (6 weeks after surgery) for histomorphometry and microhardness testing (these analyses were performed at different distances from the bone-biomaterial interface). Figure 3 shows the amount of bone in contact with HA in stimulated animals at 3 weeks was higher than in control ones.



(a) (b)

FIGURE 3. Microradiographs at the interface between the trabecular bone and the Hydroxyapatite in the stimulated animals (a) and in the control ones (b).

Affinity Index results (Fig. 4) showed a significant increase in bone contact in PEMF-treated animals versus controls at both experimental times. Also a significant increase in bone microhardness (mineralization) in PEMF versus control groups was observed at the bone-HA interface. The authors concluded that their results would recommend an early PEMF stimulation after implantation in bone in patients when bone tissue response could be expected to be negatively affected by local or general factors.

Ottani et al. [73] investigated the effect of PEMF in bone ingrowth in porous ceramics (natural and synthesis HA) and associated implant degradation in the proximal tibia in 12 rabbits. One group of animal was exposed immediately after surgery and every 12 hrs. thereafter to 30 min. treatment with PEMF (frequency: 50 Hz, intensity: 8 mT peak). At 2 and 4 weeks the animals were sacrificed for histology, transmission and scanning electron microscopy (TEM, SEM) evaluation. At 2 weeks, PEMF-treated animals, in which natural HA was implanted, showed a stronger osteogenic response. At 4 weeks, PEMF-treated animals showed more advanced bone formation than controls in both forms of HA used.

Finally, Buzzà et al. [74] investigated the performance of the bone-healing process around commercially-pure titanium implants subjected to extraction forces after insertion in the metaphyses of 12 rabbit tibiae. The experimental animals were stimulated with PEMF for 21 and 42 days. At the end of the study, extraction torque and histology were assessed. No statistically significant differences were observed between untreated and PEMF-treated animals

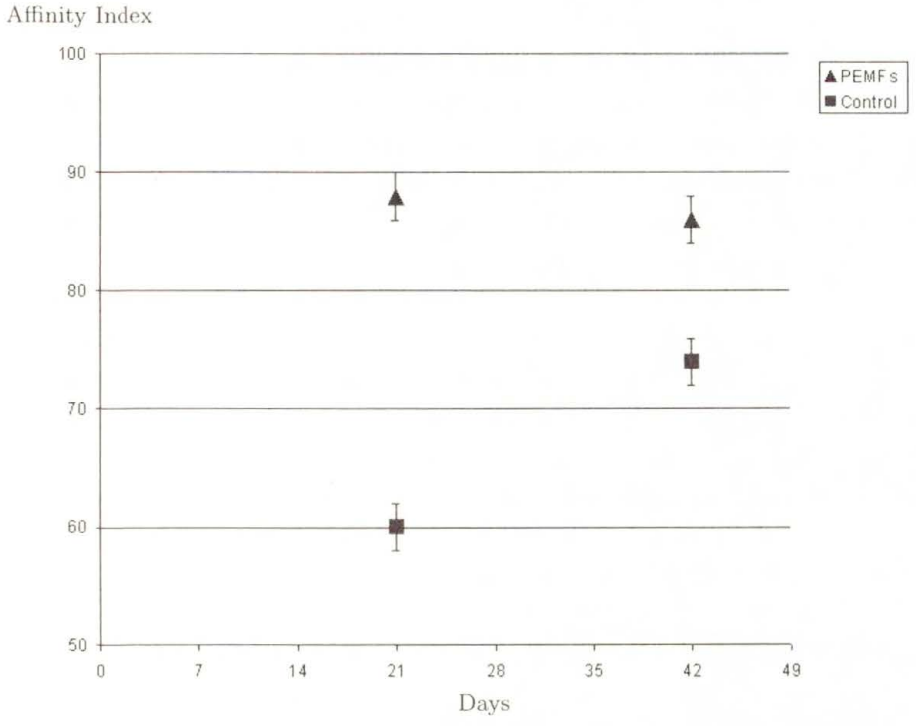


FIGURE 4. Affinity index results of Control Group and PEMFs Group at 3 and 6 weeks.

as far as extraction torque was concerned. Similar histological features were found for both groups. Results suggested that PEMF stimulation did not improve the bone-healing process around commercially-pure titanium dental implants either in cortical or medullar regions. The authors explained the difference in the results of their study and those of other authors by the duration of stimulation and intensity of electromagnetic power, and the different biomaterials implanted.

Different experimental studies have investigated how and to what extent exogenous applied biophysical stimuli can positively modify the biological events occurring at the interface of the host tissue with the implanted biomaterials [68–77]. Almost all the studies demonstrated that different forms of biophysical stimulation can significantly enhance osteointegration of biomaterials implanted in the skeletal system. No side effects have been reported. Positive results were obtained in different animal species (small and large-sized, rodents and non-rodents), different implant sites (trabecular, cortical

and intramedullary), using different kinds of biomaterials (metallic and ceramic), different PEMF, different physical parameters, and stimulation exposure times. However, differences in the rate of beneficial effects of the stimulation were observed, and researchers agree that it is important to determine the minimal essential intensity of stimulation per day, the period of time over which this should be continued, and that other factors, such as the biomaterial properties and the implant site may be considered.

Many authors state that biomaterial composition and surface properties (i.e. porosity and roughness) might influence the results of applied stimuli [68, 74]. The capacity of vascular invasion of implanted materials seems to contribute to some of the observed differences in the level of effectiveness of PEMF stimulation. Shimizu et al. suggest that HA-coated surfaces present a better degree of vascularization than commercial pure titanium surfaces and this could explain a reduced response to stimulation of titanium-made materials with respect to ceramic-made ones [68]. The same authors observed differences between materials of the same class (HA and TCP) because of differences in pore sizes: the greater the diameter of the pore the greater the effectiveness of PEMF stimulation. It was also reported that materials that already trigger a strong osteogenetic response minimize the susceptibility to the beneficial effect of biophysical stimulation [73].

As far as implant site is concerned, differences in bone vascularity, cellularity, and mechanical stimuli at each skeletal site could influence the amount of increased osteointegration, as observed by Spadaro et al. [69]. The same authors, after having studied bone response around intramedullary nails following PEMF exposure in the absence of bone trauma, emphasized the importance also of mechanical or traumatic stimuli at the implant site to enhance the PEMF osteogenetic effect. After observing a particular response to PEMF stimulation in movable implants, the authors suggest that their results may be transferred to clinical application in loosened orthopaedic implants, while a stable fixation may reduce the beneficial effects of PEMF and, as recently suggested, also for ultrasound for recent fractures [69, 86].

Obviously, the success and integration of a biomaterial depends on the intrinsic properties of the biomaterial itself but, as reported by Linder after a series of experimental studies on different biomaterials implanted in bone, osteointegration should be regarded not as an exclusive reaction to a specific implant material, but as the expression of the inherent basic healing potential of bone [87, 88]. Therefore, as far as the possible mechanism of action

of biophysical stimulation is concerned, the pathophysiology of the process of bone ingrowth around an implanted biomaterial may be briefly recalled. The insertion of the implant is the beginning of a series of complex processes in both time and space. Following the surgical procedure, the time course of events may be described in terms of two main phases: a) an early phase characterised by the hematoma, the local inflammatory reaction, the release of a cascade of mediators that stimulate vessel formation, activate osteoblasts and the migration, proliferation and differentiation of mesenchymal stem cells. The hematoma is then replaced; b) a late phase when the primary regenerated bone is remodelled to mature, lamellar bone [88–90]. The remodelling process consists of resorption of the already formed bone and apposition of new matrix in a lamellar pattern. The structural organization of the lamellar bone is conditioned by the quantity and distribution of the primary bone around the implant and by mechanical forces applied.

Each of the tested stimulations is claimed to modify some of these responses in a manner potentially beneficial to the ultimate fate of the implant. Regarding the inflammatory reaction that always follows implantation surgery, it changes over time and could in many instances have the characteristics of a chronic inflammatory reaction. Its modulation plays a fundamental role in limiting the fibrous tissue formation and improve the integration processes [89].

PEMF saturation binding experiments revealed a significant increase of A2a adenosine receptor density in human neutrophils treated with PEMF accompanied by a significant increase in adenylcyclase activity and reduction of superoxide anion production as a result of upregulation of A2a receptors [91]. Adenosine limits inflammatory response through receptor-mediated regulation. Modulation of adenosine receptor activity represents a natural mechanism of controlling inflammation. Nevertheless further studies are required to clarify the role of this mechanism on bone ingrowth and aseptic loosening.

The local concentration of cell-signalling molecules, including cytokines, interleukins and GFs such as platelet derived growth factor (PDGF), transforming growth factor beta 1 (TGF-β1), insulin like growth factor (IGF), fibroblast growth factor (FGF), vascular endothelial growth factor (VEGF), and BMPs, is now well recognised as playing the main role in starting, maintaining and promoting bone repair because of their effect on cell chemotaxis/mitogenesis, collagen synthesis, angiogenesis, and bone matrix formation. On the contrary proinflammatrory cytokines, such as interleukins (IL)

1, 6, Tumor Necrosis Factor alfa (TNF-α) play an important role in the pathophisiology of osteolysis and implant failure [92].

To explain why PEMF can be active biologically, data from in vitro studies show that osteoprogenitor cells and osteoblasts respond to PEMF stimulation by increasing proliferation, TGF-β1, IGF-2 production, BMP-2 and 4 mRNA transcription and extracellular matrix production [93–98].

There is a close relationship between vascularization and bone ingrowth following implantation. It has been suggested that some of the observed effects of PEMF on bone ingrowth may be ascribed to a primary effect on vascular growth also mediated by endothelial release of FGF [99–101].

6. Clinical Experience

Actually, as far as biomaterial osteointegration is concerned, only PEMF stimulation was applied in humans to enhance outcomes of hip prostheses [102–106]. In 1985, Ascherl et al. [102] performed a multicentered trial on the effect of PEMF in more than 1000 patients having loosened hip prostheses. They reported successful treatment in 69.5% of patients. Also radiographic evidence of refixation of some implants was reported. Rispoli et al. [103] reported successful treatment with PEMF in 76% of patients with painful uncemented hip prostheses. More recently, Kennedy et al. [104] performed a double blind study on 37 patients with femoral component loosening randomly assigned to receive an active PEMF stimulator (frequency: 15 Hz; pulse burst: 5 ms) for at least 8 hrs./day for 6 months or a control stimulator. Patients were checked with a clinical score (Harris hip score) and radiographic investigation. 53% of patients were treated successfully with PEMF versus 11% of control patients. However, a relapse rate among the successfully treated patients was seen at 14 months post-stimulation, and the relapse rate increased to 90% at 3 years. The authors suggest that for loosened cemented hip prostheses, use of PEMF is a treatment option only to delay revision hip surgery. In 1995, Steinberg et al. [105] reported a case of a 44-year-old patient in whom osteolytic changes that developed around the distal end of the femoral prosthesis appeared to reverse with the combined use of anti-inflammatory drug and PEMF. A study on the effect of PEMF treatment in 24 patients with aseptic loosening of hip prostheses was performed also by Konrad et al. [106]. After 6 months of treatment and 1 year later, pain and hip function improved significantly and there was also a significant improve-

ment in both isotope scans and ultrasonography. The authors concluded that PEMF were effective but no improvement could be expected in patients with severe pain due to osteolysis.

In conclusion, results of experimental studies suggest that adjuvant PEMF stimulation could represent a useful tool for orthopaedic surgeons in order to enhance endogenous bone healing around implants. However, few clinical studies have been carried out in this field and are mainly focused on pain relief in patients with hip prostheses. Most of the evidence on the clinical potential of PEMF comes from case series and case reports. While it has been recognized that these types of studies represent the starting point, they are not definitive and there is a need for well-controlled randomized clinical studies to assess scientific evidence to support the current use of PEMF in combination with biomaterial implantation and to determine whether biophysical stimulation provides a beneficial effects.

Recently a prospective randomised double-blind study was conducted involving patients undergoing hip revision surgery. The surgical technique used foresaw the use of bone grafts and femur osteotomy. Patients were evaluated with clinical scores and by DEXA analysis. Active stimulated patients showed an earlier recovery and increased bone mineral density 90 days after surgery.

The above clinical experiences are certainly indicative for the use of PEMF to favour implant fixation and patient recovery, nevertheless larger double-blind studies are necessary to definitely validate this indication for use.

6.1. Contraindications and Side Effects of PEMF Stimulation

In Europe, unlike in the USA, the employment of stimulation is not regulated. Hence it comes about that, at times, patients are treated with signals that are not supported by any studies regarding either their biological safety or their therapeutic efficacy. The risk for the patient is that of undergoing treatment that may be useless or may even worsen the pathological situation. Complications following clinical employment of uncontrolled signals have been documented, including inhibition of osteogenesis, bone reabsorption and hence increase of diastases between the fracture stumps. This confirms the experimental observations on the ability of certain signals to inhibit osteogenetic activity [20, 107, 108].

Literature contains no evidence of negative side effects in patients undergoing treatment with the methods and dosages described above, whose therapeutic effectiveness had been proved.

Some patients mention a disagreeable burning sensation combined with pain while undergoing treatment. However, the symptoms always resolved spontaneously on interrupting the treatment. This effect has been attributed to intolerance and hypersensitivity.

Even though it does not constitute a real contraindication, it should be noted how electrical stimulation with faradic systems is to be preferred to the other methods in cases where there is insufficient guarantee of correct use of the stimulators (patients with mental disorders, Alzheimer's disease, alcohol or substance abuse).

7. Conclusions

The study and identification of the mechanisms of action through which PEMF stimulation enhances endogenous bone repair has built a sound scientific basis for these treatment modalities. The effect of physical stimuli depends on the site of interaction at membrane level and identifies different pathways of transduction depending on whether electrical, magnetic or mechanical energy are used. Furthermore, the biological effects depend on the characteristics of the signal employed: frequency, intensity, waveform and length of treatment. PEMF stimulation represents an important and reliable treatment specifically in the hands of the orthopedic surgeon: PEMF stimulation is able to restore and augment osteogenetic activity in bone tissue, and is indicated in all situations where there is clear evidence of impaired osteogenetic response.

PEMF stimulation needs to be carried out under medical supervision. It constitutes a specific therapy in the armoury of the orthopedic surgeon, who is able to discriminate among mechanical and biological problems; its use is not recommended in inadequate mechanical conditions. It must be performed only with equipment of proven efficacy and biological safety, following the methods and dosages described in the literature.

PEMF stimulation is an important area of biophysics applied to human pathology. It requires care and precision in use if it is to ensure the success expected by physicians and patients.

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