CURRENT THERAPEUTIC RESEARCH
VOL. 62, NO. 3, MARCH 2001

Effect of Electromagnetic Fields on Bone Mineral Density and Biochemical Markers of Bone Turnover in Osteoporosis: A Single-Blind, Randomized Pilot Study

Nicola Giordano, MD,[1] Emilio Battisti, MD,[2] Simone Geraci, MD,[1] Marco Fortunato, PhD,[2] Clorinda Santacroce, MD,[1] Mario Rigato, PhD,[2] Luigi Gennari, MD,[1] and Carlo Gennari, MD[1]

[1]Institute of Internal Medicine and [2]Section of Medical Physics, Department of Physics, University of Siena, Siena, Italy

ABSTRACT

Background: The effect of pulsed electromagnetic fields (PEMFs) on bone formation and remodeling has been evaluated in several studies in the last 30 years, but the results of these studies have been equivocal. Objective: The aim of this study was to investigate the effects of PEMFs on bone mineral density (BMD) and the biochemical markers of bone turnover in patients with postmenopausal osteoporosis.

Methods: In this single-blind, randomized study, 40 outpatients were exposed to 100-Hz PEMFs (n = 20) or to a placebo electromagnetic field (n = 20) for 60 minutes per day, 3 times a week for 3 months. BMD was measured at baseline and at the end of treatment, and biochemical markers of bone metabolism were measured at baseline, after 3 months' treatment, and 1 month after treatment cessation.

Results: Treatment with PEMFs did not cause a significant increase in BMD in either group. However, in the group treated with 100-Hz PEMFs, a significant increase in serum osteocalcin and serum procollagen type I C-terminal propeptide was observed during treatment ($P < 0.001$ vs baseline); these parameters returned to baseline values 1 month after the end of treatment.

Conclusions: These findings suggest that PEMFs may stimulate osteogenesis, possibly by increasing osteoblastic activity, in postmenopausal women with osteoporosis.

Key words: pulsed electromagnetic fields, low frequency, osteoporosis, bone mineral density, osteocalcin, procollagen type I C-terminal propeptide.
(*Curr Ther Res Clin Exp.* 2001;62:187–193)

Accepted for publication January 17, 2001.

0011-393X/01/$19.00

INTRODUCTION

In the last 30 years, the effect of pulsed electromagnetic fields (PEMFs) on bone formation and remodeling has been investigated in several studies.[1–4] A number of studies have reported that PEMFs are capable of eliciting in vitro and in vivo bioeffects. The interaction between PEMFs and the cytoplasmic membrane,[5,6] as well as the effect of PEMFs on osteogenesis,[1,2,4,7,8] has been demonstrated. The assumed therapeutic effect of PEMFs is based on the well-known piezoelectric properties of bone and evidence that mechanical stress is the first signal that induces osteogenesis.[9,10] Several researchers[11–15] have investigated the therapeutic efficacy of PEMFs in osteoporosis, but have not obtained positive results. To clarify these conflicting results, we compared the effect of PEMFs versus placebo electromagnetic fields on bone mineral density (BMD) and biochemical markers of bone metabolism in women with postmenopausal osteoporosis.

PATIENTS AND METHODS

Forty outpatients with postmenopausal osteoporosis diagnosed according to the Criteria of the Fifth Consensus Development Conference[16] were enrolled in the study. Patients were informed about the procedure and the aim of the study, in accordance with the Declaration of Helsinki (1964) and the Hong Kong revision (1989), and gave informed consent. For 4 months (3-month treatment period and 1 month after the end of treatment), patients were required to discontinue use of any drug that might interfere with bone metabolism. Patients with concomitant or past degenerative or inflammatory osteoarticular disease that might interfere with the biochemical markers of bone turnover were excluded from the study.

The 40 patients were divided in a 1:1 ratio into 2 groups using a randomization list. Group A (n = 20) was exposed to 100-Hz PEMFs for 60 minutes per day, 3 times a week for 3 months. We used pulsing, extremely low frequency electromagnetic fields generated by an electromagnetic device specifically designed for this study. The field consisted of a static and a sinusoidal component. The relative magnetic induction B at a point in the field varies with time, according to the equation $B = B^* + B^\circ \sin t$, where B^* is the static component, B° is the amplitude of oscillation of the variable component (the pulsation), and t is the time. The field was generated by a pair of 80 mm × 50 mm electromagnets, with the divergence of the magnetic flux lines sufficient to expose the entire spine and pelvis to the field. The power was regulated to maintain the value of B^* at ~10 G at 10 cm from each polar expansion when the interpolar distance was 30 cm, the typical mean distance in clinical practice. The ripple factor B°/B^* was ~15%, so that the value of B° was 1 to 2 G. The sinusoidal waveform and the frequency of 100 Hz are the most suitable in our experience[17] and have been tested in previous investigations.[13,14] In group B, we used the same appliance, without activating the electromagnetic field, at the same times and for the same period as for group A.

BMD measurements were performed before and after treatment by dual x-ray absorptiometry (DXA) using a Hologic QDR 1000 (Hologic Inc, Waltham, Massachusetts) at the level of the lumbar spine and femoral neck, the skeletal segments most commonly investigated by DXA in osteoporosis. Before and after treatment and 1 month after treatment cessation, at the same time of day in the morning, the following biochemical markers of bone metabolism were measured in all patients while they were in the fasting state: serum calcium (atomic absorption method), serum phosphate (colorimetric method, Phosphofix, Menarini Diagnostic, Florence, Italy), total serum alkaline phosphatase (ALP) (colorimetric method, Phosphofix, Menarini Diagnostic), serum osteocalcin (125I RIA kit, Incstar Corporation, Stillwater, Minnesota), serum procollagen type I C-terminal propeptide (PICP) (125I RIA kit, Orion Diagnostica, Espoo, Finland), and urinary calcium (atomic absorption method), phosphate (colorimetric method, Phosphofix, Menarini Diagnostic), and hydroxyproline (OHP) (high-performance liquid chromatography, Bio-Rad, Munich, Germany). The serum and urine samples were obtained at the same time of day from all patients, because serum osteocalcin and PICP can have a circadian as well as a diurnal variation.[18–20] Moreover, all the pretreatment and posttreatment marker assays were performed in 2 batches to avoid the possibility of intraindividual and interindividual variability.[20] Statistical analysis of the data was performed using the Student paired *t* test.

RESULTS

The baseline characteristics of the patients are shown in Table I. No significant differences were found between groups at baseline.

The 20 patients exposed to the placebo electromagnetic field (group B) did not show any significant changes from baseline in BMD or any of the biochemical markers measured (Table II). As shown in Table III, the 20 patients exposed to PEMFs (group A) did not show any significant increases in BMD, changes in serum and urinary calcium levels, serum and urinary phosphate, urinary OHP, or serum ALP; however, these patients showed a significant increase in serum osteocalcin and PICP ($P < 0.001$).

Table I. Baseline characteristics (mean ± SD) of the 40 enrolled women, by treatment group.

	Placebo (n = 20)	PEMFs (n = 20)
Age, y	55.9 ± 3.1	56.3 ± 4.0
Age at menarche, y	12.4 ± 1.2	12.9 ± 2.2
Age at menopause, y	48.7 ± 3.2	49.2 ± 3.4
Years since menopause	6.1 ± 3.2	6.4 ± 3.3

PEMFs = pulsed electromagnetic fields.

Table II. Evaluation of bone mineral density (BMD) and biochemical markers of bone metabolism in 20 postmenopausal women at baseline, after 3 months of placebo treatment, and 1 month posttreatment.*

	Normal Value	Baseline	3 Months	1 Month Posttreatment
BMD, g/cm^2				
Lumbar spine (L2–L4)		0.849 ± 0.09	0.847 ± 0.04	
Femoral neck		0.739 ± 0.03	0.740 ± 0.06	
Serum				
Calcium, mg/mL	8.6–10.4	9.1 ± 0.8	9.2 ± 1.2	9.0 ± 0.6
Phosphate, mg/mL	2.5–4.8	3.3 ± 1.2	3.2 ± 1.4	3.4 ± 1.1
ALP, UKA	5–14	10.8 ± 1.1	9.9 ± 0.8	10.2 ± 1.3
Osteocalcin, mg/mL	3.4–7.1	5.5 ± 0.2	5.4 ± 0.6	5.3 ± 0.3
PICP, ng/mL	50–170	102.9 ± 29.2	104.0 ± 33.3	103.6 ± 28.6
Urine (24-h samples)†				
Calcium, mg/d	50–250	191.0 ± 38.8	190.0 ± 36.6	189.0 ± 35.3
Phosphate, mg/d	300–800	604.0 ± 38.5	599.0 ± 40.6	603.0 ± 41.3
OHP, mg/d	10–30	19.6 ± 5.9	18.3 ± 3.6	18.4 ± 4.4

ALP = alkaline phosphatase; PICP = procollagen type I C-terminal propeptide; OHP = hydroxyproline.
*Data are presented as mean ± SD.
†Urine measurements were normalized to creatinine.

In the patients exposed to placebo, there was no significant change between the values for biochemical markers of bone turnover obtained at baseline and those obtained 1 month after the end of treatment (Table II). In contrast, in the 20 patients exposed to 100-Hz PEMFs, serum osteocalcin and PICP levels increased after 3 months of PEMF treatment, but returned to baseline values 1 month after the end of treatment (Table III).

DISCUSSION

The lack of changes in biochemical markers of bone turnover in the placebo group, the increase in osteocalcin and PICP at the end of the 3-month treatment period with PEMFs, and the normalization of these values 1 month after discontinuing PEMF treatment suggest that PEMFs affect bone metabolism, possibly by stimulating osteogenesis, particularly osteoblastic activity.[2,4,6–9] In our study, the increase in osteocalcin and PICP at the third month of therapy is a significant finding, because the patients discontinued any medication that could interfere with the biochemical markers of bone turnover. The predictable lack of increase in BMD in the patients exposed to PEMFs is probably due to the comparatively short duration of PEMF treatment; the efficacy of treatments for osteoporosis is usually not evaluated until 6 to 12 months after the start of therapy. Nevertheless, 3 months' exposure to PEMFs seems to be sufficient to stimulate osteogenesis, as demonstrated by the increase in osteocalcin and

Table III. Evaluation of bone mineral density (BMD) and biochemical markers of bone metabolism in 20 postmenopausal women at baseline, after 3 months of treatment with pulsed electromagnetic fields, and 1 month posttreatment.*

	Normal Value	Baseline	3 Months	1 Month Posttreatment
BMD, g/cm^2				
Lumbar spine (L2–L4)		0.851 ± 0.03	0.854 ± 0.09	
Femoral neck		0.740 ± 0.02	0.736 ± 0.04	
Serum				
Calcium, mg/mL	8.6–10.4	9.3 ± 1.6	9.0 ± 1.4	9.1 ± 0.5
Phosphate, mg/mL	2.5–4.8	3.2 ± 1.1	3.4 ± 1.3	3.3 ± 1.2
ALP, UKA	5–14	10.2 ± 2.1	9.3 ± 2.8	9.9 ± 1.8
Osteocalcin, mg/mL	3.4–7.1	5.6 ± 0.8	7.0 ± 0.7†	5.7 ± 1.1
PICP, ng/mL	50–170	100.2 ± 30.1	134.0 ± 20.7†	105.0 ± 26.8
Urine (24-h samples)‡				
Calcium, mg/d	50–250	185.0 ± 36.9	191.0 ± 40.6	187.0 ± 40.8
Phosphate, mg/d	300–800	614.0 ± 40.2	587.0 ± 40.6	603.0 ± 46.2
OHP, mg/d	10–30	19.0 ± 6.3	18.7 ± 4.9	17.9 ± 4.2

ALP = alkaline phosphatase; PICP = procollagen type I C-terminal propeptide; OHP = hydroxyproline.
*Data are presented as mean ± SD.
†$P < 0.001$ (Student paired t test).
‡Urine measurements were normalized to creatinine.

PICP, which are the earliest markers of bone growth. The absence of changes in serum levels of ALP is probably due to the fact that ALP is synthesized by both bone and liver, and thus serum ALP is not a specific measure of osteogenesis.

Further longer-term studies (6–12 months) that include a larger number of patients and the specific measurement of skeletal ALP are warranted. The conflicting data on the therapeutic efficacy of PEMFs in osteoporosis may also be the result of the different types and frequencies of PEMFs (30–150 Hz) used in previous studies.[11–15] Therefore, researchers should agree on a standard type and frequency of PEMFs, as well as the optimal length of exposure, to be used in future studies of PEMFs in osteoporosis.

CONCLUSION

The results of this study suggest that PEMFs may stimulate osteogenesis, possibly by increasing osteoblastic activity, in postmenopausal women with osteoporosis.

REFERENCES

1. Bassett CAL, Pawluk RJ, Becker RO. Effects of electric currents on bone in vivo. *Nature.* 1964;204:652–654.

2. Bassett CA, Valdes MG, Hernandez E. Modification of fracture repair with selected pulsing electromagnetic fields. *J Bone Joint Surg Am.* 1982;64:888–895.

3. Trock DH. Electromagnetic fields and magnets. Investigational treatment for musculoskeletal disorders. *Rheum Dis Clin North Am.* 2000;26:51–62.

4. McLeod KJ, Rubin CT. The effect of low-frequency electrical fields on osteogenesis. *J Bone Joint Surg Am.* 1992;74:920–929.

5. Schimmelpfeng J, Stein JC, Dertinger H. Action of 50 Hz magnetic fields on cyclic AMP and intercellular communication in monolayers and spheroids of mammalian cells. *Bioelectromagnetics.* 1995;16:381–386.

6. Valberg PA, Kavet R, Rafferty CN. Can low-level 50/60 Hz electric and magnetic fields cause biological effects? *Radiat Res.* 1997;148:2–21.

7. Eyres KS, Saleh M, Kanis JA. Effect of pulsed electromagnetic fields on bone formation and bone loss during limb lengthening. *Bone.* 1996;18:505–509.

8. Kaspar D, Seidl W, Neidlinger-Wilke C, et al. Dynamic cell stretching increases human osteoblast proliferation and CICP synthesis but decreases osteocalcin synthesis and alkaline phosphatase activity. *J Biomech.* 2000;33:45–51.

9. Fukada E, Yasuda I. On the piezo-electric effect of bone. *J Phys Soc Jpn.* 1957;12: 1158–1162.

10. Becker RO. Electrical osteogenesis—pro and con. *Calcif Tissue Res.* 1978;26:93–97.

11. Martin RB, Gutman W. The effect of electric fields on osteoporosis of disuse. *Calcif Tissue Res.* 1978;25:23–27.

12. Tabrah F, Hoffmeier M, Gilbert F Jr, et al. Bone density changes in osteoporosis-prone women exposed to pulsed electromagnetic fields (PEMFs). *J Bone Miner Res.* 1990;5:437–442.

13. Takano-Yamamoto T, Kawakami M, Sakuda M. Effect of a pulsing electromagnetic field on demineralized bone matrix–induced bone formation in a bony defect in the premaxilla of rats. *J Dent Res.* 1992;71:1920–1925.

14. Bilotta TW, Zati A, Gnudi S, et al. Electromagnetic fields in the treatment of postmenopausal osteoporosis: An experimental study conducted by densitometric, dry ash weight and metabolic analysis of bone tissue. *Chir Organi Mov.* 1994;79:309–313.

15. Tabrah FL, Ross P, Hoffmeier M, Gilbert F Jr. Clinical report on long-term bone density after short-term EMF application. *Bioelectromagnetics.* 1998;19:75–78.

16. Consensus development conference: Diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med.* 1993;94:646–650.

17. Giordano N, Battisti E, Geraci S, et al. Analgesic-antiinflammatory effect of a 100 Hz variable magnetic field in RA. *Clin Exp Rheumatol.* 2000;18:263. Letter.

18. Hassager C, Risteli J, Risteli L, et al. Diurnal variation in serum markers of type I collagen synthesis and degradation in healthy premenopausal women. *J Bone Miner Res.* 1992;7:1307–1311.

19. Gertz BJ, Clemens JD, Holland SD, et al. Application of a new serum assay for type I collagen cross-linked N-telopeptides: Assessment of diurnal changes in bone turnover with and without alendronate treatment. *Calcif Tissue Int.* 1998;63:102–106.

20. Lian JB, Stein GS, Canalis E, et al. Bone formation: Osteoblast lineage cells, growth factors, matrix proteins, and mineralization process. In: Favus MJ, ed. *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism.* Philadelphia: Lippincott Williams & Wilkins; 1999:14–30.

Address correspondence to:
Nicola Giordano, MD
Institute of Internal Medicine
University of Siena
Policlinico Le Scotte
Viale Bracci 1
53100 Siena, Italy
E-mail: Giordanon@unisi.it