PROTOCOL

Comparing the Effect of Bone-loading Exercises and Pulsed Electromagnetic Fields on Bone Turnover Markers in Women with Osteoporosis: A Randomized Clinical Trial Study Protocol

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Abstract

Objective: Given the bone sensitivity to mechanical stimulus, bone-loading exercises and applying the Pulsed Electromagnetic Fields (PEMF(s)) are recommended for promoting bone strength. In this context, these two interventions 's effect on bone turnover markers (BTMs) in osteoporosis patients is yet to be clarified; consequently, an attempt is made in this study to compare the effect of these two interventions on bone turnover markers in women with Postmenopausal Osteoporosis (PMOP).

Methods: This study is design as a randomized, single-center, three-arms, controlled trial. A total of 51 women with PMOP will be randomly assigned to three groups of 17, using opaque, sealed envelopes containing labels for A, B, and C groups. Group A) will receive bone-loading exercises, B) will follow the PEMF(s) and C) will be exposed to the combination of A and B. These three groups will require intervention for 24 sessions (2 sessions/week) next to their routine medical treatment (Alendronate+ Calcium+ Vitamin D). The primary outcome of this study is the serum biomarker of bone formation (bone-specific alkaline phosphatase, BSALP) and resorption (N-terminal telopeptide, NTX). The secondary outcomes consist of thoracic kyphosis angle, fear of falling, and quality of life. The outcomes are measured three times: at baseline, after 24 sessions of intervention, and at 12 weeks follow-up. A primary outcome will be measured and reported by a laboratory expert who is blinded to the participant grouping.

Result: The trial has the code of ethics for research (IR.TUMS.FNM.REC.1401.126) and the code of Iranian Registry of Clinical Trials (IRCT) (IRCT20221202056687N1). Study results are expected to be available by mid-2024.

Conclusion: This trial will provide new practical knowledge on the bone-loading exercises and PEMFS(s)'s effect on PMOP women. This knowledge is of the essence for physiotherapists, clinicians, other healthcare professionals, and policymakers in the healthcare system.

Level of evidence: Not applicable.

Keywords: Bone turnover markers, Exercises, Postmenopausal osteoporosis, Pulsed electromagnetic fields

Introduction

Osteoporosis is a chronic progressive bone disease diagnosed by a decrease in bone mass and density. This decrease increases susceptibility to fracture.[1, 2] In addition to disabilities and high therapeutic costs, such fractures may even lead to mortality.[3, 4] About 50% of individuals aged 60 and older have osteoporosis, 80% of which are women with postmenopausal osteoporosis (PMOP).[5, 6]

The objective of any intervention regarding osteoporosis is to reduce the risk of bone fracture, which is one of the best

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predictors in determining bone strength.[7] Consuming bisphosphonates (BPs), such as Alendronate or Risedronate, is effective in improving bone strength by inhibiting bone resorption in osteoporosis patients. However, there are some concerns regarding their long-term consumption.[1, 8]

In addition to BPs, numerous physiotherapy interventions are recommended due to the piezoelectric properties of bone tissue.[9] Researchers have reported that bone-loading exercises (resistance and impact training) are effective on bone mineral density.[10] These exercises are associated with various positive effects on the health of women with PMOP.[11] Despite the positive effect of exercise, PMOP women usually face some musculoskeletal problems. Nevertheless, some of the associated limitations include regular participation and adherence to exercise programs; consequently, some clinicians are reluctant to prescribe bone-loading exercises for patients' musculoskeletal problems.[12, 13]

Applying an effective physical modality on bone metabolism, including the pulsed electromagnetic fields (PEMFs), is assumed to be a choice in such cases. The utilization of PEMF to stimulate osteogenesis relies on the concept of stimulating the natural endogenous streaming potential in bone. This intervention promotes calcium deposition in bone and contributes to mineral metabolism,[13, 14] though its effect on bone strength in women with PMOP has yet to be determined.

Bone strength is a complex issue and cannot be determined merely by Bone Mineral Density (BMD). Bone turnover markers (BTMs) are the other indicators of bone strength and show changes in bone metabolism. BTMs are sensitive either to short or long-term therapeutic intervention periods.[13, 15]

To date, the effects of bone-loading exercises and PEMFs on bone strength in PMOP women concerning BTMs have not been compared.

Other related consequences of osteoporosis, such as the kyphotic-postural changes and increased fear of falling (FOF), can potentially increase the risk of falling and have a negative effect on the quality of life (QOL) in PMOP women.[16, 17]

Increased thoracic kyphosis could play a considerable role in gait disorder, spine biomechanical alternations, height shrinkage, back pain, and most importantly, increased risk of compression vertebral fractures.[18, 19]

In this study, a randomized controlled trial (RCT) is designed to compare the effect of bone-loading exercises, PEMFs, and bone-loading exercises with PEMFs on BTMs and other important problems related to the health of PMOP women. It also aims to compare the durability of the effects after a 3-month post-intervention follow-up.

Our central hypothesis is that participants randomized to the bone-loading exercise + PEMFs would have a greater improvement in BTMs than participants in either the PEMF or bone-loading exercise group.

Materials and Methods

Ethnic approval

This study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences (code: IR.TUMS.FNM.REC.1401.126). All participants will sign a written informed consent before the study begins. Patients will be assured of the possibility of study withdrawal at any research stage without explanation. Careful and complete explanations are given when obtaining consent at screening and enrollment to ensure participant understanding. This trial was registered (IRCT20221202056687N1) on 15 December 2022 in the Iranian Registry of Clinical Trials (IRCT).

This study protocol follows the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) guidelines for the quality of the clinical trials. The SPIRIT 2013 checklist is applied in this study protocol [Figure 1].

	Enrolment	**Allocation**	**Post-allocation**		
TIME POINT	***-T1***	**T0**	***T1***	***T2***	***T3***
ENROLMENT:					
Eligibility screen	X				
Informed consent		X			
Demographic Questionnaire		X			
Allocation		X			
INTERVENTIONS:					
PEMFs			X		
Exercise			X		
PEMFS +Exercise			X		
ASSESSMENTS:					
BTMs		X		X	X
Thoracic kyphosis		X		X	X
Fear of Falling		X		X	X
Quality of life		X		X	X

-T1: Pre-study, Screening/Consent; T0: Pre-study/baseline Randomization;
T1: study/intervention; T2: study, after 24-session interventions; T3:12-week follow up.

Figure 1. The SPIRIT schematic diagram of the study schedule

Objectives

To compare the effect of bone-loading exercises, PEMFs, and bone-loading exercises + PEMFs on BTMs changes (formation: BSALP, resorption: Serum NTX), Thoracic kyphosis angle, FOF, QOL at baseline, a 3-month intervention, and a 3-month follow-up.

Research Design

This protocol is a single-center RCT with three parallel arms (1:1:1), which will be measured repeatedly during three major data collection points (at baseline, 3-month intervention, and 3-month follow-up). Subjects are randomized into three groups: A) Bone-loading exercises, B) PEMFs, and C) Bone-loading exercises + PEMFs. The intervention is conducted in 24 sessions (2 sessions/week) for 3 months, depending on the group program. Regardless of this grouping, all participants will receive the same routine medical treatment (Alendronate 70 mg/week + calcium + vitamin D) during the intervention. The individuals in the 3-month follow-up are subjected to the rheumatologist's supervision as well.

BTMs are the primary outcome of this study, and the secondary outcomes are thoracic kyphosis angle, FOF, and QOL. The flow diagram of the study protocol is presented in [Figure 2].

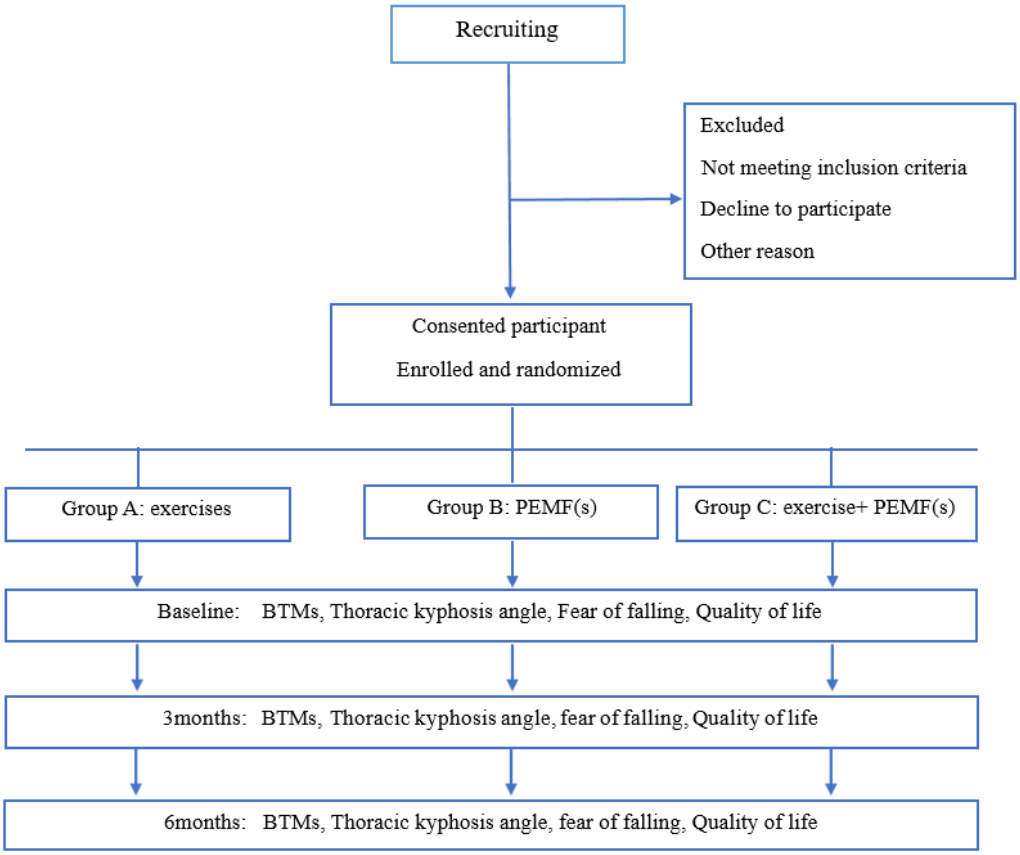

Figure 2. Flow diagram of study protocol.. PEMF(s): Pulsed Electromagnetic Fields

Sample Size

We utilized the formula for comparison of means and employed Stata software to estimate the sample size, adhering to parameters derived from a previous study.[20] The mean values and standard deviations of Serum OC (ng/ml) in the two intervention and control groups, utilized for sample size estimation, were 17.4±2.6 and 13.6±2.4, taking into account a significance level of 0.01 and a power of 90%. Based on the output of this calculation, 13 participants were required in each group.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \times (\delta_1^2 + \delta_2^2)}{(\mu_1 - \mu_2)^2} = 13 \; per \; group$$

To account for potential loss to follow-up during the study, a 30% attrition rate was taken into account, resulting in the examination of 17 participants in each group. In case of drop-outs, noncompliance, or missing outcomes, an intention-to-treat analysis will be run.

Eligibility, randomization, and blinding

The patients will be referred by rheumatologist from the outpatients of the Rheumatology clinic. The inclusion and exclusion criteria for participant eligibility are provided in [Table1].

After the confirmation of eligibility, 51 participants will be randomly assigned into bone-loading exercises (A), PEMFs (B), or bone-loading exercise + PEMFs (C) groups using sealed envelopes containing A, B, or C tags. An employee from the Rehabilitation Center, who is not involved in the study, will randomly draw out an envelope from a box and show it to the physiotherapist for treatment. The use of opaque envelopes ensures the concealment and randomization.

The nature of the intervention makes it impossible to blind participants; however, they will not be aware that there are three research groups. All treatment procedures and measurement of secondary outcomes will be done by the same physiotherapist. BTMs as a primary outcome will be measured and reported by the laboratory expert, who is blinded to grouping. A professional academic biostatistician blinded to study groups will conduct all analyses.

Table1. Inclusion and exclusion criteria in the study

Inclusion Criteria	Exclusion Criteria
• Women's age between 55-68 year	• Participants subject to regular exercises
• Body mass index between 22 and 30 Kg/m^2	• Bisphosphonate in the last 6 months
• Reached menopause at least 5 years before the study	• Hormone therapy in the last 6 months
• BMD T-score for the hip or lumbar spine of -2.5 SD or less	• History of surgery in the spine or the pelvic region
• No history of osteoporotic fracture	• Received physiotherapy modalities in the last 6 months
• No history of ovariectomy surgery	• Any condition that prohibits optimal calcium, vitamin D, exercise, PEMFs, or Alendronate

Group A: bone-loading exercises

This exercise session will begin with a 5-minute warm-up, followed by squats, step-ups and step-downs, lower limb exercises, and back extension. The physiotherapist, the supervisor, will be responsible for customizing the proper turns of exercises and the progress therein. The exercise session will end with a 5-minute cool-down.

Before the first exercise session, 1-repetition maximum (RM) will be calculated via an equation[21] based on 10RM of lower limb exercise (hip abduction/extension and knee extension). For the squat, step-ups/step-downs, and back extensor exercises, the 1-RM will not be considered due to physical conditions; therefore, for the progression of the exercise, the external force will be applied with the weighted vest.

Adding external weights in the pockets, preferably the back pockets, would prevent flexor torque. To do the lower limb exercise (hip abduction/extension and knee extension), weight cuffs will be put on the right and left ankles with Velcro. Details of the bone-loading exercises protocol and progression are expressed in [Tables 2 and 3].

Group B: PEMFs

In this group, the participants will be exposed to 45-minute PEMFs subjected to the following parameters: 30 Hz, 40 Gauss, and rectangular waveform.The exposure system (Magno 915 G, Novin, Iran) consists of one 70-cm solenoid positioned on the participant's lumbar and hip regions in a lying supine position. The considered parameters for PEMFs are the ones that are effective on bone metabolism in PMOP women.[22-24]

Group C: bone-loading exercises + PEMFs

The participants in this group will receive a combination of A and B interventions. In this group, the same bone-loading exercises will be applied as in group A in addition to PEMFs with the same intensity and frequency as in group B.

Study Outcomes

Primary Outcome Measures

Bone Turnover Markers

The blood samples will be taken at the baseline and 3 and 6 months later at a fixed time in the morning (8.30-9.30 am) to eliminate the circadian effect on the fluctuation of bone biomarkers in serum. To mitigate any effect from the previous intervention session, all samples will be taken 2 days after the last session following a 12-hour fasting period. The blood serum will be separated and assayed for the resorption biomarker using blood serum NTX (nmol/BCE/L) and the formation biomarker using blood serum (BSALP) (U/C) through an enzyme-linked immunosorbent assay following the manufacturer's protocol.[25]

Secondary Outcome Measures

Thoracic kyphosis angle

The thoracic kyphosis angle will be assessed using the photogrammetry method. This involves locating the seventh cervical (C7) and twelfth thoracic (T12) spinous processes through palpation and then attaching light-weighted markers to these points on the skin using double-sided tape. Participants will be asked to stand with their feet bare and shoulder-width apart, with arms flexed and positioned on the clavicles.

The camera (Nikon D3300, Thailand) will be fixed 120 cm from the patient at 130 cm height perpendicular to the subject's position. To prevent camera movement, its pod's points will be marked and reviewed before each photo-shooting session. The photos will be taken from the sagittal plane. A digital image in a flash will be imported to the Digimizer Image software 5.3.4 (BVBA, Ostend, Belgium). Reliability and validity of this method would be measured, and acceptable results would be reported.[26-28]

Table 2. Bone-loading exercises in detail

Exercise	Weeks	Detail	Set/repetition	Progression
Squat	Week 1	Hands in front, doing squat (45 knee flexion) without external load	3 sets of 10 repetitions. The tenth repetition of each set is with a slow jump	Without external load
	Week 2-Week 12	Doing squat (45 knee flexion) by using a weighted vest		The external load will be increased by 2% of body weight every week based on the tolerance level of the patient
Step-up and step-down	Week 1	Step-up and step-down	3 sets of 10 repetitions. The tenth repetition in each set is accompanied by a slow jump-down	Without external load
	Week 2-Week 12			The external load will be increased by 2% of body weight every week based on the tolerance level of each patient
Back extension	Week 1-Week 12	Do back extension from a prone lying position	30 repetitions in each phase	Reaching 30 repetitions without load and then 1 kg load will be added progressively

Table 3. Exercise progression of training at the knee extension and hip abduction and extension exercises

First and second weeks	3 sets with 50% 1RM
Third and fourth weeks	2 sets with 50% 1RM, 1 set with 60% 1RM
Fifth and sixth weeks	3 sets with 60% 1RM
Seventh and eighth weeks	2 sets with 60% 1RM, 1 set with 70% 1RM
Ninth and tenth weeks	3 sets with 70% 1RM
Eleventh and twelfth weeks	2 sets with 70% 1RM, 1 set with 90% 1RM

Fear of falling

The FOF will be quantified through the Persian version of the Falls Efficacy Scale-International (FES-I), which is a reliable and valid tool. The level of concern about falling is assessed through FES-1 on a 4-point Likert scale across 16 daily activities. The scores range from 16 to 64, with higher scores indicating greater concern about falling.[29]

Quality of life

The Persian version of the European Foundation for Osteoporosis (QUALEFFO-41) is applied to assess QoL. This 41-item questionnaire consists of 5 separate subscales: pain (5 items), physical health (17 items), social activity (7 items), mental health (9 items), and general health (3 items). The validity and reliability of the Persian version of this questionnaire have been proven.[30, 31]

Time plan of the study

Recruitment began in March 2023 and is to be completed in winter 2023. The intervention will continue 12 weeks after the last inclusion with at least a 3-month follow-up. Data collection will last 6 months after recruitment and be provided for publication for peer review.

Adherence

Adherence will be calculated as the percentage of completed sessions out of the total prescribed intervention sessions (24 sessions=100%).

Adverse effects

Bone-loading exercises are a safe intervention; however,

potential risks include falls, pain, fractures, joint pain, and muscle soreness. Gastrointestinal problems may appear by consuming BPs in some patients.[32] Any adverse effects or discomforts during the intervention session or at any other time will be assessed and recorded by the physiotherapist.

Statistical Analysis

Before analyzing the data, the normal data distribution will be checked using the Shapiro-Wilk test. For the normally distributed data, the means and SDs will be calculated; otherwise, the median (interquartile range) will be reported. The differences in the demographic data of the groups will be analyzed through the one-way ANOVA test. As to normal data distribution, the repeated measures ANOVA will be applied to examine differences between groups (3 groups) and within groups (three measurements at the baseline, 3-month intervention, and 3-month follow-up) on outcomes. The interaction will be reported as the "group vs. time" using the Bonferroni post-hoc test with adjusted P values.

If the assumption of normality is violated, the generalized estimating equation will be adopted. The SPSS software (version 26, Chicago, IL) will be used, and the significance level will be considered at an alpha of ≤ 0.05.

Data access

The data will be secured on a computer and will be available upon request from the corresponding author.

Results

The bone-loading exercises program and its progression are completely planned. The study protocol has received the code of the Iranian Registry of Clinical Trials (IRCT20221202056687N1). Study results are expected to be available by mid-2024.

Discussion

Given the high prevalence of osteoporosis and the increase in the elderly population, non-invasive physiotherapy interventions, such as bone-loading exercises and PEMFs, are considered practical. Relying only on medical treatment has not improved different aspects of PMOP women's health.[33,34]

Bone strength is determined by BMD and bone quality factors consisting of bone microarchitecture, geometry, and BTMs.[35, 36] only a few studies have examined changes in BTMs after implementing interventions. Therefore, more comprehensive research is required to measure the BTMs as they detect the dynamics of bone turnover.

The results of this study will show not only the changes in BTMs after a 24-session intervention but also the sustainability of the induced effects through the 3-month post-intervention follow-up. The results would provide further evidence of the bone-loading exercises and PEMFs on BTMs in PMOP women.

BPs are considered in all groups because short-term application of BPs is relatively safe and standard in caring for PMOP women's health. The findings here will determine the better physiotherapy intervention in addition to standard pharmacology care for PMOP women.

In this protocol, two mechanical stimulations (bone-loading exercises and PEMFs) are combined in group C, and their effect will be compared with each intervention in groups A and B. However, many physiotherapy protocols suggest the combined intervention to reach better results.[35] In contrast, some studies have shown possible desensitization of mechanoreceptors that may prevent further osteogenic effects after applying two mechanical stimulation.[35]

In addition to BTMs changes, increased thoracic kyphosis angle and FOF are other important challenges for PMOP women, which could be associated with enhanced risk of fractures. Moreover, FOF can negatively impact the patient's self-confidence, self-image, and QOL.[37,38]

Therefore, this protocol intends to conduct a comprehensive assessment and will compare the effect of bone-loading exercises, PEMFs, and the combination of these two interventions on BTMs, thoracic kyphosis angle, FOF, and QOL. The obtained results could potentially enrich better decision-making procedures for prescribing proper rehabilitation protocols to improve PMOP women's health.

Conclusion

The advantage of this study protocol lies in the methodology adopted in RCT with a primary outcome assessor-blinding. A 2-day interval between the last session of the intervention and outcome measurement is a matter of high concern in this study.

The potential challenge regarding this proposed study is maintaining the continuity of 24 treatment sessions. Therefore, the subjects are asked to attend two intervention sessions per week. The patients' non-punctual attendance is a drawback that can be resolved by making regular phone calls and reminding them to be punctual, as well as by providing free-of-charge treatment and compensating for their travel expenses traveling to and from the rehabilitation center. These strategies aim to increase patient recruitment and reduce the drop-out rate. It is hoped that these considerations will prevent drop-outs in the subjects.

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Authors Contribution:

ASH, AS and FS presented the study conception and idea. ASH, SF and FS designed bone-loading exercise program and study protocol. FS drafted the first version of this manuscript that was reviewed and revised critically for intellectual content by ASH and SF. Revisions were performed by AS, SF and FS. All authors read, commented and approval final manuscript for submission.

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Declaration of Ethical Approval for Study: This study is reviewed and approved by the Ethics Committee of Tehran University of medical sciences (code: IR.TUMS.FNM.REC.1401.126). In this endeavor, the researcher will introduce herself to the participants. After expressing the project objectives, and assuring the participants about the data confidentiality and the possibility of withdrawing from the study, a written consent form will be signed by the participants.

Declaration of Informed Consent: there is no information (names, initials, hospital identification numbers, or photographs) in the submitted manuscript that can be used to identify patient.

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