Pulsed Electromagnetic Fields May Be Effective for the Management of Primary Osteoporosis: A Systematic Review and Meta-Analysis

Siyi Zhu, Yi Li, Liqiong Wang, Jinming Huang, Kangping Song, Xinling Gan, Xiaona Xiang, Chengqi He, and Lin Yang

***Abstract*— Little is known about the effect of pulsed electromagnetic fields (PEMFs) as an option for preventing osteoporosis. This study sought to investigate the effectiveness of PEMFs for the management of primary osteoporosis in older adults. We searched databases from the inception to date to target trials examining the effects of PEMFs compared to placebo or sham or other agents for the management of primary osteoporosis for a meta-analysis using random effects model. Eight trials including 411 participants were included. PEMFs was non-inferior to conventional pharmacological agents and exercise respectively in preventing the decline of Bone Mineral Density (BMD) at the lumbar (MD 8.76; CI −9.64 to 27.16 and MD 1.33; CI −2.73 to 5.39) and femur neck (MD 0.04; CI −1.09 to 1.16 and MD 1.50; CI −0.26 to 3.26), and significantly improving balance function measured by Berg Balance Scale (BBS) (MD 0.91; CI 0.32 to 1.49) and Timed Up and Go test (MD −3.61; CI −6.37 to −0.85), directly after intervention. The similar trends were observed in BMD and BBS at 12- and 24-weeks follow-up from baseline. PEMFs had positive effects non-inferior to first-line treatment on BMD and better over placebo on balance function in older adults with primary osteoporosis, but with moderate to very low certainty evidence and short-term follow-ups. There is a need for high-quality randomised controlled trials evaluating PEMFs for the management of primary osteoporosis.**

***Index Terms*— Electromagnetic fields, bone density, osteoporotic fractures, physical therapy modalities, disability evaluation.**

I. Introduction

OSTEOPOROSIS is a systemic and multifactorial skeletal disorder characterized by low bone mineral density and skeletal fragility that occur with aging, with a consequent increase of susceptibility to low-trauma fractures [1]. The most prevalent symptoms of osteoporosis are fractures at vertebrae, proximal femur (hip), and wrist affecting patients' physical function and quality of life. It is estimated that over 200 million people worldwide are affected by osteoporosis, accounting for 8.9 million fractures annually [2]. The possibility of osteoporotic fractures exceeds 40% and the probability of hip fracture alone could target 20% in white female population over 50 years old [3]. In China, a higher incidence of hip fractures in men than in women was reported [4]. Each year, osteoporotic fractures account for over 432,000 hospitalizations and 2.5 million medical visits in the USA [5]. The treatment costs for fractures were recorded at nearly $17 billion in the USA in 2005 [6], and €31.7 billion in Europe in 2000 [7]. Therefore, osteoporosis has been identified as a major health burden globally by WHO, due to its high prevalence, disability rate, related mortality and poor quality of life [8].

Distinct from targeting specific clinical disorders and medications that cause low bone mineral density in treating secondary osteoporosis, current interventions and drugs recommended in clinical guidelines are mainly applied to the management of primary osteoporosis [9]. Rehabilitation interventions given its important roles in modifying risk factors related to fractures, restoring function and improving quality of life are frequently recommended as an option in the nonpharmacological management of primary osteoporosis [9], [10]. Pulsed electromagnetic fields (PEMFs) at a specific intensity and frequency have been proved effective in attenuating bone loss and the relief of pain and discomfort after osteoporosis. As we reviewed elsewhere [11], PEMFs were found to be positive at promoting bone formation by stimulating the formation and differentiation of osteoblasts, and negative at inhibiting the function of osteoclasts in bone resorption. Experimental studies suggest that PEMFs may exert effects on Ca^{2+}-related

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This work involved human subjects or animals in its research. The authors confirm that all human/animal subject research procedures and protocols are exempt from review board approval.

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receptors on the bone cell membrane which play a regulatory role in the maintenance of bone remodelling [12]. Further, the exposure of PEMFs could influence the physiopathology of osteoporosis by targeting inflammation and potentially relieving pain via these regulatory processes and improvements in bone remodeling [13].

PEMFs have been widely used as an clinical option for the management of pain and discomfort related to primary osteoporosis since the introduce of its usage for non-union fractures was approved by FDA in 1979 [14]. However, clinical trials evaluating the effectiveness of PEMFs on primary osteoporosis have been conducted with inconsistent results, to which parameters of PEMFs used in studies, follow-up time points and clinical settings differ across studies may lead [11]. In order to expand upon the current knowledge on whether PEMFs is an effective physical agent for primary osteoporosis clinically, a systematic review and meta-analysis of clinical trials was performed to compare PEMFs with placebo or sham or other agents for the management of primary osteoporosis in older adults.

II. Methods

This systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [15]and reported based on Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines (PRISMA) [16]. The protocol of this study is available in PROSPERO (CRD42018099518) [17].

A. Identification and Selection of Studies

We searched the MEDLINE (via Ovid), EMBASE (via Ovid), Web of Science, CENTRAL and CCTR (via The Cochrane Library), Physiotherapy Evidence Database (via PEDro website), CNKI, VIP, Wan Fang, ClinicalTrials.gov (https://www.clinicaltrials.gov/) and Current controlled trials (www.controlled-trials.com) from the inception dates to December 9, 2018, using the keywords *pulsed electromagnetic fields* and *osteoporosis*. The Open Grey (http://www.opengrey.eu/) was searched for the Grey Literature research. The detailed electronic search strategies are provided in Supplemental Material I. An additional search was performed under a mechanism of living systematic review [18] to identify recently published randomized clinical trials (RCTs) from two timepoints-December 10, 2018 to September 30, 2021, and after September 30, 2021-using the databases and keywords described above. The whole procedure was assisted by a librarian from Sichuan University.

Randomised controlled trials or quasi-randomised trials examining the effects of PEMFs compared to placebo or sham or other agents for the management of primary osteoporosis were included if they met the inclusion criteria listed in Box I. Studies were excluded if the study population had a diagnosis of corticosteroid-induced osteoporosis or other secondary osteoporosis (e.g., rheumatoid arthritis), studies where participants had a history of hip replacement or surgery related with osteoporotic fractures, the study type was observational studies, review articles, abstracts, conference reports and book chapters.

A three-stage screening methodology was performed to select relevant RCTs for this review. Primarily, all titles were screened by one reviewer (SYZ) for eligibility and irrelevant papers were excluded accordingly. Secondary, two reviewers (YL and LQW or KPS) independently reviewed each study title and abstract. Thirdly, two independent reviewers (XNX and JMH or XLG) accessed the full text to assess against the eligibility criteria for each potentially eligible study. A third reviewer (CQH or LY) was involved for any disagreement.

B. Assessment of Characteristics of Studies

1) Quality Assessment: The risk of bias was assessed by using the Cochrane Collaboration's 'Risk of bias' tool [15]. Seven key domains were assessed by two reviewers (SYZ and LQW): 1) the randomization sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, 6) selective reporting, and 7) other bias. The included studies were graded as low, unclear, or a high risk of bias. Methodological quality was assessed with the use of Physiotherapy Evidence Database (PEDro) tool [19], which was proved reliable [20] and valid [21]. Each criterion in the PEDro scale with a range of 0-10 was scored 1 ("yes") or 0 ("no, don't know/unclear"). Generally, trials with a PEDro summary score of over five. were considered to have adequate methodological quality [22]. Finally, we used Grading of Recommendations, Assessment, Development and Evaluations (GRADE) [23] to describe the overall quality of the body of evidence.

2) Participants: To be included, studies involved participants were healthy older adults (including those with previous fractures) aged over 50 years with primary osteoporosis [24], recognized by two distinct types [25]: 1) type I occurred in postmenopausal women; 2) type II, known as senile osteoporosis, occurred in both men and women.

3) Interventions: All RCTs applying electromagnetic fields with pulsed signal and extremely low frequencies (between 5 and 300 Hz) for the management of primary osteoporosis were included. The parameters (frequency and intensity) of PEMFs, sessions per week and total duration of the treatment period were recorded to describe the interventions.

4) Outcome Measures: All outcomes were continuous data and recorded as the percent change from baseline to post-intervention and different follow-up timepoints. To be included, trials had to provide original data on at least one of outcomes on bone mass, number of incident fractures, self-reported data on the changes in balance and quality of life, physical activity and function, and adverse events. Primary outcomes were bone mass (e.g., Bone Marrow Density or Bone Mineral Content) immediately post-intervention and at follow-ups, and number of incident fractures. Secondary outcomes were quality of life (e.g., EuroQoL (EQ 5D)) and adverse events (e.g., falls and death). Further, outcomes regarding functional assessments (e.g., Berg Balance Scale, Timed Up and Go test) potentially increasing the risk of falling and fracture were considered eligible as secondary outcomes for the analysis.

C. Data Extraction and Analysis

Two independent reviewers (SYZ and YL) extracted the following information from eligible studies: lead author; year of publication; original country; subject characteristics; study design; treatment information; intervention parameters and the dose per protocol; outcome measures; raw outcome data; follow-up period and other relevant information. Disagreements were resolved by consensus.

All meta-analyses were performed using analysis was performed using Review Manager (RevMan) software (The Cochrane Collaboration, version 5.4). For each included study, the mean difference (MD) of percentage change with 95% confidential intervals (CIs) was calculated when the outcome measures were consistent across studies or else the standard mean difference (SMD) was calculated instead for continuous outcomes (reporting mean and standard deviation (SD) or standard error (SE) of the mean). If the MD was not reported, it was calculated as the change between values of the baseline and post-intervention. In the case that the value of SD (SD_{diff}) was not reported, it was obtained 1) by multiplying SEs of means by the square root of the sample size when standard errors (SEs) of the means were reported, or 2) with SDs at the baseline ($SD_{baseline}$) and post-intervention SD (SD_{post}) in addition to the within-groups bivariate correlation coefficient (r) [26]:

$$SD_{diff} = \sqrt{SD^2_{baseline} + SD^2_{post} - (2 \times r \times SD_{baseline} \times SD_{post}}$$

The I^2statistic was employed for evaluating heterogeneity and a standard Chi^2 test was employed for detecting whether significant heterogeneity existed. Heterogeneity was statistically significant at $P < 0.10$ after due consideration of I^2statistic, of which a value greater than 50% was considered substantial heterogeneity [27]. The random-effects model was applied where the evidence of heterogeneity was found.

The comparison was established between PEMFs and placebo control or exercise in the meta-analysis. The subgroup analysis was conducted to detect the effectiveness relative to different follow-up timepoints (postintervention; follow-up at 12, 24 weeks from baseline). To evaluate the quality and consistency of pooled results, the sensitivity analysis was conducted by deleting each included study. Where the data allowed, assessment of publication bias was performed. All tests were two-tailed, and $P < 0.05$ was considered statistically significant.

III. Results

A. Flow of Studies Through the Review

In total, 806 articles were identified by the initial search and first-round additional search, of which 124 duplicate articles were removed. Further round of the additional search targeted 63 articles conducted after September 30, 2021. Based on title and abstract screening, 632 plus 58 of these articles were excluded. Full texts of 55 articles were read, a further 47 articles were excluded, remaining 8 articles included in the data extraction and analysis of the review (Fig. 1) [28]–[35].

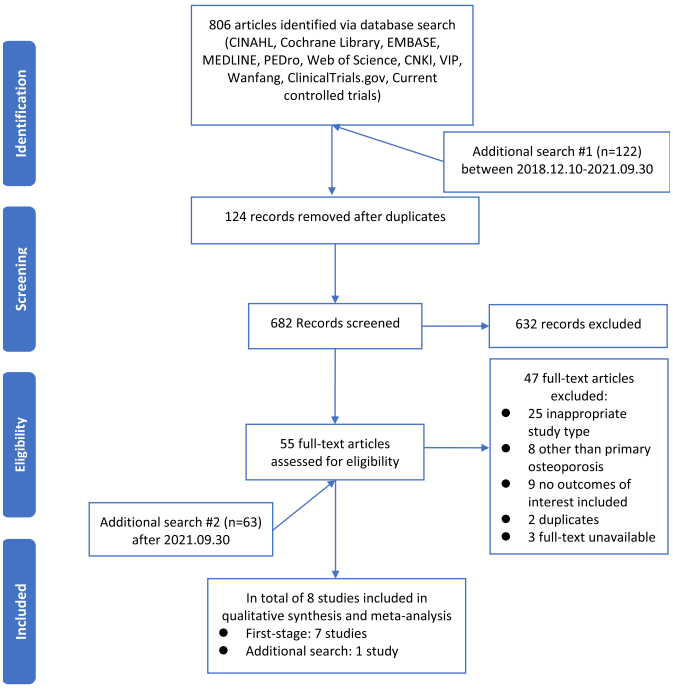

Fig. 1. PRISMA flow of studies through the review.

B. Characteristics of Studies

1) Quality: In PEDro scores, one study was scored under 5 [33], and seven of eight included studies achieved over 5, among which five studies achieved the score over 6 [28], [30]–[32], [35]. Of all included studies, the domain of blinding of participants and personnel was rated as 'high risk of bias' due to the nature of rehabilitation interventions. For other domains, studies were classified as 'unclear risk of bias' for at least 1 aspect or 'high risk of bias' for at least 2 aspects. In results of GRADE, the quality of the evidence for the comparison between PEMFs versus placebo control was low or moderate, and that for the comparison between PEMFs versus exercise was very low. The results of the PEDro scores, risk of bias and GRADE are presented in the supplemental Tables and Figures (Supplemental Material II and III).

2) Participants: In total, data were extracted for 411 participants, comprising 183 participants in PEMFs group and 228 participants in placebo control (alendronate/pharmacological therapy) or exercise group. Mean age ranged from 47.26 to 70 years, with a gender ratio of 49 to 362. Participant characteristics are detailed in Table I.

3) Intervention: The frequency and intensity of PEMFs exposure varied at 8-100 Hz and 1.2-5 mT separately. A range of 30-36 PEMFs sessions, with 30-60 min/session, were prescribed for participants, and 4 to 72 weeks follow-up were conducted across all studies. Control intervention types included first-line pharmacological agents (e.g., Alendronate, intake of Vitamin D and Calcium) and exercise (e.g., whole body vibration and aerobic exercise programme). The intervention characteristics of the included studies are detailed in the Table I.

TABLE I
CHARACTERISTICS OF THE INCLUDED STUDIES

Study	Participant				Intervention: PEMFs		Outcome measures			Follow-up
	Sample size	Study arms	Age (y)	Male/Female	Parameters[a]	Dose per protocol[b]	Primary	Secondary	Efficacy/Effect	
Liu Hf et al, 2013[31]	41	1.PEMFs (n=20) 2.AL (n=21)	61.70 (1.34) 63.14 (4.32)	0/41	N/A; N/A; 0.2 ms	3.82 mT, 8 Hz, 40min/session for a total of 30 sessions.	BMDL	BMDF; 25(OH)D; LE MMT; BBS	Effective as alendronate.	24 weeks
Liu Hf et al, 2014[30]	84	1.PEMFs (n=44) 2.AL (n=40)	62.41 (5.47) 62.63 (4.54)	0/84	N/A; N/A; N/A	3.8 mT, 8-12 Hz, 40min/session for a total of 30 sessions.	BMDL; BMDF	VAS; TUG; BBS	Effective as alendronate.	72 weeks
Shanb, Aa et al, 2017[32]	68	1.PEMFs (n=25) 2.WBV (n=25) 3.AL (n=18)	63.9 (3.9) 64.1 (4.4) 64.5 (4.03)	23/45	N/A; N/A; N/A	5 mT, 33 Hz, 50 min/session, 2 sessions/week for 16 weeks (32 sessions).	BMDL; BMDF	Serum calcium and vitamin D	Effective in conjunction with pharmacological treatment.	N/A
Shanb, A.S.A et al, 2012[33]	30	1.PEMFs (n=15) 2.Ex (n=15)	60-70	0/30	N/A; N/A; N/A	5 mT, 33 Hz, 50 min/session, 3 sessions/week for 12 weeks (36 sessions).	BMDL; BMDF	N/A	Effective as exercise.	N/A
Marwa M. Eid et al, 2021[35]	45	1.PEMFs (n=15) 2.Ex (n=15) 3.PEMFs+Ex (n=15)	47.26 (2.6) 47.33 (2.84) 47.66 (2.22)	0/45	N/A; 230V at 50 or 60Hz (earth contact); N/A	5 mT, 33 Hz, 50 min/session, 3 sessions/week for 12 weeks (36 sessions).	BMDF	N/A	More effective in conjunction with exercise and medications.	N/A
Giordano, N et al, 2001[29]	40	1.PEMFs (n=20) 2.Placebo (n=20)	56.3 (4.0) 55.9 (3.1)	0/40	Sinusoidal waveform; N/A; N/A	1.2 mT, 100 Hz, 60 min/session, 3 sessions/week for 12 weeks (36 sessions).	BMDL; BMDF	Serum and urinary calcium, phosphate; Serum ALP, osteocaltin and PICP; Urinary hydroxyproline	Not effective in increasing BMD, but effective in stimulating osteogenesis.	1 month
Wu, Y.C et al, 2014[34]	43	1.PEMFs (n=24) 2.AL (n=19)	59.08 (4.65) 59.53 (5.40)	0/43	N/A; N/A; N/A	3.8 mT, 8-12 Hz, 40min/session for a total of 30 sessions.	TUG; BBS; Balance function	N/A	Effective as alendronate.	N/A
Abdelaal, AA et al, 2017[28]	60	1.PEMFs (n=20) 2.LLLT (n=20) 3.Med (n=20)	59.85 (2.35) 60.20 (2.17) 60.00 (2.62)	26/34	Rectangular waveform; N/A; N/A	4 mT, 33 Hz, 30 min/session, 3 sessions/week for 12 weeks (36 sessions).	BMDL	N/A	More effective than LLLT and AL group.	N/A

[a]Waveforms; Power supply; Burst width (ms).
[b]Intensity; Frequency; Duration (sessions or weeks).
[c]Abbreviations. PEMFs=Pulsed electromagnetic fields, AL=alendronate, WBV=Whole body vibration, CRT=Circuit weight training, Ex=Exercise, LLLT=low-level laser therapy, mT=millitesla, Hz=Hertz, BMDL=lumbar bone mineral density, BMDF=femur bone mineral density, 25(OH)D=serum 25OH vitamin, LE MMT=total lower-extremity manual muscle test, BBS=Berg Balance Scale, VAS=Visual Analogue Scale, N/A=not applicable, TUG=Timed Up and Go, Med=Medication, ALP=Alkaline Phosphatase, PICP=Procollagen type I carboxy-terminal propeptide.

4) Outcome Measures: The outcome measures in each study with the categories of bone mass and functional assessments are detailed in Table I. No result about number of incident fractures, quality of life, adverse events (e.g., falls and death) was reported across studies included.

C. Effect of Intervention I: PEMFs Versus Control Group

1) Bone Mineral Density (BMD): Four studies (study population, N = 205) [28]–[31] and two studies (study population, N = 81) [29], [31] reported data on percentage change in BMD at the lumbar (Fig. 2A) and femur neck (Fig. 2B) respectively after intervention directly. Low certainty evidence showed that PEMFs has no effect on BMD at the lumbar (MD 8.76; CI -9.64 to 27.16) and femur neck (MD 0.04; CI -1.09 to 1.16) with statistically significant heterogeneity (lumbar: $I^2 = 100\%$, $P < 0.00001$; femur neck: $I^2 = 95\%$, $P < 0.0001$). Two studies (study population, N = 125) [30], [31] performed follow-ups at 12 and 24 weeks from baseline on percentage change in BMD at the lumbar (Fig. 2A). Moderate certainty evidence showed that there is minor but statistically significant effect of placebo agents on BMD at the lumbar at the 12 weeks follow-up (MD -1.32; CI −1.59 to −1.06) with no statistically significant heterogeneity ($I^2 = 0\%$, $P = 0.94$), and the 24 weeks follow-up (MD −2.10; CI −2.71 to −1.49) with

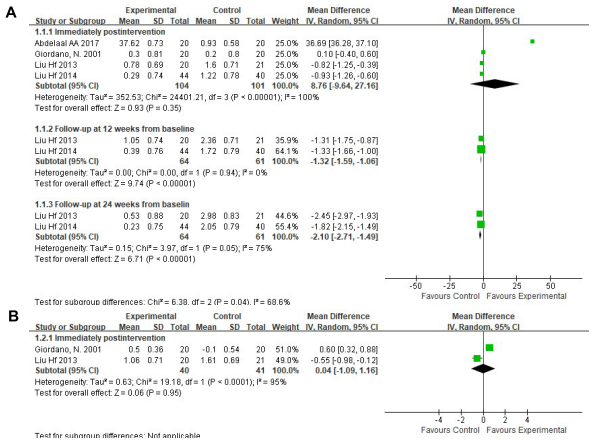

Fig. 2. Forest plot analysis of the effects of PEMFs on BMD at the lumbar (A) and femur neck (B) compared with placebo control. Data are presented as mean difference (MD) between treatment and control groups with a 95% confidence interval (CI). SD = Standard Deviation; BMD = Bone Mineral Density; PEMFs = Pulsed Electromagnetic Fields.

statistically significant heterogeneity ($I^2 = 75\%$, $P = 0.05$). The sensitivity analysis (Supplemental Figure 3) showed that the heterogeneity was decreased ($I^2 = 83\%$, $P = 0.002$) without affecting the effect of PEMFs on BMD at the lumbar after intervention directly (MD −0.57; CI −1.16 to 0.01)

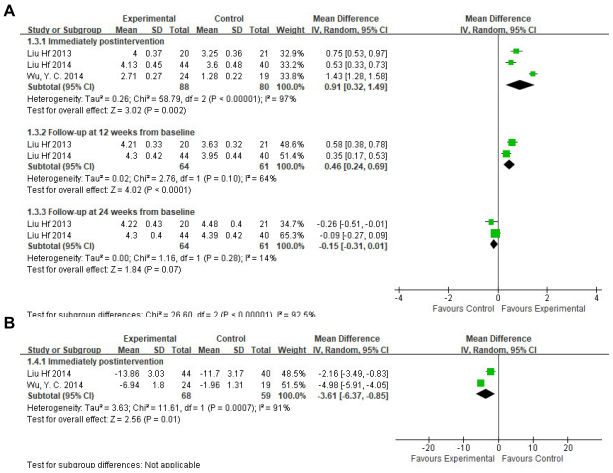

Fig. 3. Forest plot analysis of the effects of PEMFs on balance function measured by BBS (A) and TUG test (B) compared with placebo control. Data are presented as mean difference (MD) between treatment and control groups with a 95% confidence interval (CI). SD = Standard Deviation; BBS = Berg Balance Scale; TUG = Timed Up and Go; PEMFs = Pulsed Electromagnetic Fields.

with the exclusion of one study by Abdelaal [28], and further excluding the study by Giordano [29] led to a change in the effect in favor of placebo (MD -0.89; CI −1.15 to −0.63) and significantly decreased the heterogeneity ($I^2 = 0\%$, $P = 0.69$).

2) Berg Balance Scale (BBS): Three studies (study population, N = 168) [30], [31], [34] conducted the assessment of BBS after intervention directly (Fig. 3A). Low certainty evidence showed that there is statistically significant effect of PEMFs on percentage change in BBS (MD 0.91; CI 0.32 to 1.49) with statistically significant heterogeneity ($I^2 = 97\%$, $P < 0.00001$). Two studies (study population, N = 125) [30], [31] carried out follow-ups at 12 and 24 weeks from baseline on percentage change in BBS (Fig. 3A). Moderate certainty evidence showed that PEMFs has statistically significant effect on BBS at the 12 weeks (MD 0.46; CI 0.24 to 0.69) with statistically significant heterogeneity ($I^2 = 64\%$, $P = 0.10$), then the effect became not significant at 24 weeks (MD −0.15; CI −0.31 to 0.01) with no statistically significant heterogeneity ($I^2 = 14\%$, $P = 0.28$). The sensitivity analysis (Supplemental Figure 4A) showed that excluding the study by Wu, Y. C [34] could decrease the heterogeneity ($I^2 = 52\%$, $P = 0.15$) without changing the effect of PEMFs on BBS after intervention directly.

3) Timed Up and Go (TUG) Test: Two studies (study population, N = 127) [30], [34] assessed the percentage change in TUG test after intervention directly (Fig. 3B). Low certainty evidence showed that there is statistically significant effect of PEMFs on TUG (MD -3.61; CI −6.37 to −0.85) with statistically significant heterogeneity ($I^2 = 91\%$, $P = 0.0007$).

D. Effect of Intervention II: PEMFs Versus Exercise Group

Two studies (study population, N = 80) [32], [33] and three studies (study population, N = 110) [32], [33], [35] investigated the effect of PEMFs on percentage change in BMD at the lumbar (Fig. 4A) and femur neck (Fig. 4B) respectively after intervention directly. Very low certainty evidence showed that PEMFs has no effect on BMD at the lumbar (MD 1.33; CI -2.73 to 5.39) and femur neck (MD 1.50; CI -0.26 to 3.26), both with statistically significant heterogeneity respectively ($I^2 = 100\%$, $P < 0.00001$). The sensitivity analysis (Supplemental Figure 4B) showed that excluding the study by Shanb [32] could lead to a change in the effect on BMD at the femur neck in favor of PEMFs (MD 2.12; CI 0.94 to 3.29), and no statistically significant changes in heterogeneity by excluding any study.

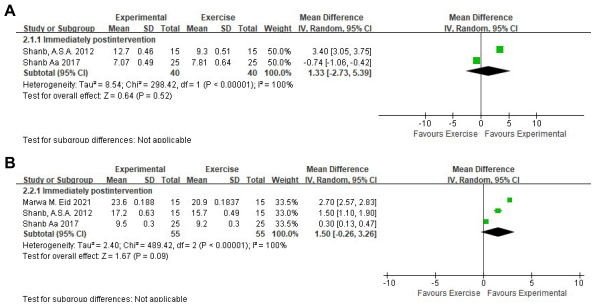

Fig. 4. Forest plot analysis of the effects of PEMFs on BMD at the lumbar (A) and femur neck (B) compared with exercise group. Data are presented as mean difference (MD) between treatment and control groups with a 95% confidence interval (CI). SD = Standard Deviation; BMD = Bone Mineral Density; PEMFs = Pulsed Electromagnetic Fields.

IV. Discussion

This systematic review and meta-analysis of 8 studies involving 411 participants demonstrated PEMFs as a physical therapy was non-inferior to conventional pharmacological agents or exercise in preventing the decline of BMD and balance function for the management of primary osteoporosis in older adults. According to our knowledge, no systematic review and meta-analysis was initiated before, except one network meta-analysis exploring effects of nonpharmacological interventions including PEMFs on balance function only [36], and several narrative reviews including clinical studies were retrieved [11], [37], [38]. Our results are in consistent with findings from previous reviews [11], [36], [37] that PEMFs achieved positive effects on BMD and balance function for older adults with primary osteoporosis, implicating that PEMFs may potentially become a promising treatment option.

Bisphosphonates and exercise were both identified as the first-line interventions for the management of primary osteoporosis in the latest evidence-based guideline [9]. Our study established comparisons between PEMFs and active placebo or exercise based on groups set by included studies, and subgroup analysis was stratified by different intervals between the baseline, post-intervention, and follow-ups. BMD, as a surrogate measure for therapeutic effectiveness, can be assessed by various methods, among which dual x-ray absorptiometry (DXA) was proved to be reliable in the diagnosis of osteoporosis and have relatively good responsiveness in RCT [39], [40]. Our study demonstrated that there was no difference between PEMFs and active placebo or exercise in improving BMD at the lumbar and femur neck in all sub-group

meta-analysis for immediately postintervention, which suggests PEMFs is nearly effective as pharmacological agents or exercise for osteoporosis, but the effect could not last for 12-24 weeks after the intervention of PEMFs was stopped. We further conducted sensitivity analysis to assess stability of above findings with high heterogeneity across comparisons. The results of sensitivity analysis detected changes in levels of heterogeneity and a minor switch in the effect on BMD at the lumbar (in favor of pharmacological agents) and femur neck (in favor of PEMFs) directly after the intervention. The high observed levels of heterogeneity and the minor switch of overall effect may be partially explained by varied PEMFs device and settings across studies. Meanwhile, all studies included were rated as 'high risk of bias' failing to blind of participants and personnel due to the nature of rehabilitation interventions. Further, one study included was considered as inadequate quality of methodology in conducting the study with a PEDro score lower than 5 and being rated 3 aspects of "high risk of bias" in quality appraisal. Therefore, this part of results should be interpreted with caution.

Impaired balance function is an important risk factor increasing the incidence of falling and fracture, which is modifiable by balance-improving interventions [41]. By contrast to results on BMD, statistically significant differences were observed for balance function measured by BBS and TUG after the intervention of PEMFs versus active placebo. In the sub-group analysis, the effect of PEMFs on BBS could last for at least 12 weeks, while no difference was found at 24 weeks follow-up, confirming that PEMFs is as effective as conventional pharmacological agents in improving balance function. In consistent with a previous systematic review [36], it reported that PEMFs exert positive effect on BBS and TUG tests reflecting balance function. However, the network meta-analysis was conducted to further compare the effects of five interventions on balance function with the conclusion that balance and strength training was better than other interventions. Only one study using data on PEMFs was included in the analysis, compared to that we included 3 studies, and no study was ever conducted to directly compare the effect of PEMFs versus other non-pharmacological interventions on balance function, combining these two may explain, in part, the conflicting results. Furthermore, our sensitivity analysis detecting no significant changes in levels of heterogeneity and effect confirmed our results as relatively robust.

To overcome the shortcomings of the "statistically significant difference", the minimum clinically important difference (MCID) defined as "the smallest change that is important to patients" is employed to generate a threshold value for such change [42]. Any patient whose responses help them reach the MCID threshold is considered as responders. Thus, a certain proportion of responders to the total participants involved in a trialed intervention indicates the likelihood of patients under the same condition also responding favorably to the same intervention [43]. However, no definite consensus reached on the MCID of BMD and balance function. Some evidence showed that changes by 2-5% at the lumbar and 8% at the proximal femur [44], a point-drop in BBS associated with a 3-4% increase in risk of falling [45], and an improvement of 2-3 seconds in TUG test were considered as MCID for the older population [46]. In our study, no study included used the MCID and responder rate to evaluate the effect of PEMFs, thus, it is hard to determine the clinical importance of improvements achieved by PEMFs on BMD and balance function compared with placebo and exercise. Furthermore, the successful treatment of osteoporosis is prevention of fractures, while no treatment can completely eliminate fracture risk [9]. Although a certain increase in BMD and the improvement in balance function for osteoporosis may result in a reduction in fracture risk, no risk and number of incident fracture were reported in studies included in our review. Therefore, studies with reporting measures of MCID, fracture risk and incidence in the future are required to further confirm that the effect of PEMFs in treating osteoporosis is of clinical importance to clinicians and patients.

This review has several strengths. To date, we are the first to conduct a systematic review and meta-analysis to explore the effect of PEMFs on BMD and balance function for primary osteoporosis. Secondary, a key finding of this review was that PEMFs as an intervention alone achieved an effect non-inferior to first-line treatment (pharmacological agents and exercise) on improvements in BMD, and even better over placebo in maintaining balance function for older adults with primary osteoporosis. Furthermore, a librarian familiar with the development of searches and a mechanism of living systematic review were involved over a course of 3 years to ensure no study was missed in compliance with the study protocol.

There are several limitations to this review that deserve consideration. The primary limitation of our review was the limited number of included studies with only 8 studies with some concerns of methodological heterogeneity, comprising of 411 participants for the analysis, from which the results of meta-analysis were with relative high heterogeneity and the level of evidence generated were moderate to very low. In some sub-group analyses, only 2-3 studies were included from which some uncertainty in the results interpretation may exist based on data extracted. In addition, as the maximum PEMFs treatment session lasted for 16 weeks and the longest follow-up was 24 weeks for the analysis, while the error among the minimum percentage change in BMD and balance function may stay undetectable and further deepened the uncertainty [44], we use doses of PEMFs exposure (30-36 sessions) prescribed during the study period for included studies to estimate the overall efficacy. Furthermore, the clinical relevance of the findings was limited, combined with no study reported data on MCID, responder rate and incident fracture and only two studies [30], [31] included used intention-to-treat (ITT) analysis. According to accumulated evidence [11], [47], the parameters of non-pharmacological interventions, including intensity, frequency, and duration, were critical to impact changes in outcome measures for osteoporosis, while our study could not conduct the sub-group analysis based on different parameters due to limited information retrieved. Another potential limitation was the systematic search was limited to English and Chinese manuscripts available in full text, and some relevant trials may be missed.

Box 1 Inclusion Criteria

Design

- □ Randomised or quasi-randomised controlled trial
- □ Published in a peer-reviewed journal
- □ Full text available in Chinese and English

Participants

- □ Healthy older adults (including those with previous fractures) aged over 50 years with primary osteoporosis

Intervention

- □ Electromagnetic fields with pulsed signal and extremely low frequencies (between 5 and 300 Hz)

Outcome measures

- □ Primary outcomes: bone mass, number of incident fractures
- □ Secondary outcomes: Functional assessments, quality of life, adverse events

Comparisons

- □ PEMFs versus sham/nothing
- □ PEMFs versus placebo/pharmacological agents
- □ PEMFs versus exercise/other physical agent or intervention
- □ PEMFs plus other intervention versus other intervention

V. Conclusion

In summary, moderate to very low certainty evidence showed that PEMFs as an intervention alone has positive effects: non-inferior to first-line treatment (pharmacological agents and exercise) on BMD and better over placebo on balance function in older adults with primary osteoporosis and should be considered as a promising option in the management of osteoporosis. Although uncertainty about responses to the intervention and changes in outcome measures may be existed but undetectable, our findings may still be fairly stable as we consistently found similar trends in the primary and sensitivity analyses. For further confirming the effect of PEMFs for osteoporosis, adding endpoints like fracture risk and incidence, and outcome measures like MCID and responder rate to the core collection is necessary. In the future, researchers planning a PEMFs study should optimize the study design, with taking factors not limited to undetectable errors under outcomes, parameters of interventions, longer follow-up period, larger sample size and ITT analysis into consideration, to generate high certainty evidence.

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