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"The effect of aerobic exercise on bone formation and resorption markers and the quality of life tests in postmenopausal osteopenic patients"

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Abstract

Mini-abstract The aim of the current study was to examine the effects of light- to moderate intensity aerobic exercise on bone mineral density (BMD) in postmenopausal osteopenic women by using bone formation and resorption markers. In the current study, P1NP and CTX levels increased in both the exercise and the control group.

Summary The aim of the current study was to examine the effects of light- to moderate-intensity aerobic exercise on bone mineral density (BMD) in postmenopausal osteopenic women by using rapidly responsive bone formation and resorption markers.

Purpose In this prospective, randomized, controlled, single-blind clinical study, women aged 45–65 years with BMD T scores between − 1 and − 2.5 measured by double X-ray absorptiometry (DXA) were included after evaluation of exclusion criteria and the women were divided into 2 groups: aerobic exercise group and control group (exercise, $n = 25$; control, $n = 25$). At baseline and at the 12-week follow-up, the serum levels of bone formation and resorption biomarkers, including procollagen type 1 N-terminal propeptide (P1NP), cross-linked C-telopeptide of type I collagen (CTX), osteocalcin, oxidative markers such as malondialdehyde, nonbone-specific total alkaline phosphatase, 25(OH) D3, and parathyroid hormone (PTH), were examined in all patients.

Results A statistically significant increase in P1NP and CTX levels was noted in both the exercise and control groups at the 12-week evaluation compared to baseline ($p > 0.05$). Although there was no significant change in osteocalcin levels in the control group ($p > 0.05$), a statistically significant increase was observed in the exercise group ($p < 0.05$). In the exercise group, no significant changes were observed in bone formation or resorption markers, including P1NP, CTX, osteocalcin, and total ALP, or in oxidative stress markers, such as malondialdehyde, compared to those in the control group ($p > 0.05$).

Conclusion In conclusion, the current study revealed that regular walking exercise of light to moderate intensity significantly contributes to improvements in pain, walking speed, balance, lower extremity dynamic balance, and activities of daily living in postmenopausal women with osteopenia compared to inactive individuals.

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Keywords Postmenopausal osteoporosis, P1NP, CTX, Exercise, Osteocalsin, Malondialdehyde

Introduction

Osteoporosis is a systemic skeletal disease characterized by decreased bone mass and microarchitectural deterioration of bone tissue, leading to fragility and increased risk of fractures [1]. In the treatment and prevention of osteoporosis, pharmacological methods such as antiresorptive and anabolic agents are utilized, in addition to nonpharmacological treatments such as adequate calcium and vitamin D intake, resistance exercises, quitting smoking, which limits alcohol/caffeine consumption, and fall prevention [2, 3]. Therapeutic exercises for osteoporosis can be classified into two groups: weight-bearing aerobic exercises such as walking, running, dancing, and resistance exercises using one's body weight or external resistance [4]. Studies indicate a positive relationship between bone mineral density (BMD) and exercise, with high-intensity exercise being particularly effective at increasing BMD [5]. The results of the randomized controlled trial that examined the effects of exercise in the prevention and treatment of PMO; the most effective type of exercise for femoral neck BMD was non-weight-bearing high-impact exercise, such as graded resistance strength training for the lower extremities. And the most effective intervention for spine BMD was combination exercise programs compared with control groups. DWBHF (Dynamic weight-bearing exercise high force exercises (e.g., jogging, jumping) improved BMD at the hip and trochanter, DWBLF(Dynamic weight-bearing exercise low force) exercises (e.g., walking, Tai Chi) improved BMD at the spine and wrist, and NWBHF(Non-weight-bearing exercise high force) exercises (e.g., resistance training) improved BMD at the femoral neck and spine compared to controls [6].

In the current study, the investigators chose a combination of walking exercise as an aerobic exercise and balance, posture and resistance exercises with body weight and weights that can be easily applied to people of all age groups and those with comorbidities, because high-intensity exercises can increase the risk of falls and fractures in individuals with osteoporosis.

Bone turnover markers allow for the independent assessment of bone resorption and formation by measuring their concentrations in blood and urine [7]. These markers do not play a role in diagnosing osteoporosis but provide early response evaluation posttreatment compared to measuring bone mineral density (BMD) [8, 9]. Bone resorption and formation markers can complement BMD measurements by DXA in monitoring osteoporosis treatment. They offer quicker responses than DXA scans and provide insights into skeletal physiology, enabling earlier assessment of treatment responses in patients receiving medical therapy [10].

Intensive exercise can increase bone formation markers while potentially decreasing bone resorption markers. It is important to avoid intense exercise the day before measurements is taken. The impact of exercise on bone turnover markers (BTMs) depends on the type, duration, and intensity of the exercise [11]. The International Osteoporosis Foundation (IOF) and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) recommend evaluating P1NP for bone formation activity and evaluating CTX-1 concentrations for bone resorption activity. Both markers should be assessed in all studies concerning bone health [7, 12].

Oxidative stress is considered an important pathogenic factor of osteoporosis at the cellular and molecular level. It induces osteocyte apoptosis and altered levels of specific factors such as receptor activator κB ligand (RANKL), sclerostin and fibroblast growth factor 23, leading to impaired bone remodeling and increased bone resorption [13]. Increased osteoclastic activity occurring in osteoporosis results in increased production of ROS in the form of superoxide. Lipid peroxidation is one of the most deleterious effects of ROS, and the end product of lipid peroxidation, malondialdehyde (MDA), also serves as a measure of osteoclastic activity. For this reason, increased levels of MDA as a marker of oxidative stress can be detected in individuals with osteoporosis [14, 15].

The aim of the current study was to examine the effects of light- to moderate-intensity aerobic exercise on bone mineral density in postmenopausal osteopenic women by using rapidly responsive bone formation and resorption markers.

Materials and methods

This prospective, randomized, controlled, single-blind clinical study was planned at the Physical Medicine and Rehabilitation (PMR) Clinic of Bursa Yüksek Ihtisas Training and Research Hospital. Ethical approval for the study was obtained from the local ethics committee (number 2011-KAEK-252022/10 – 02). The study included volunteer participants who were postmenopausal women from Türkiye aged 45–65 years, who presented to the PMR clinic as outpatients between 15 November 2022 and 15 November 2023. Participants were selected based on bone mineral density (BMD) T-scores between −1 and −2.5, measured by dual-energy X-ray absorptiometry (DXA), and were evaluated according to the exclusion criteria to ensure eligibility for inclusion in the study. Patients with conditions other

than osteoporosis that could affect the concentrations of bone formation and resorption markers, such as vertebral compression fracture, a history of traumatic or nontraumatic fractures in the past year, thyroid hormone disorders, parathyroid hormone disorders, liver function disorders, kidney function disorders, chronic heart failure, a history of malignancy, a history of rheumatological diseases, corticosteroid use, immunosuppressive drug use, anticonvulsant and heparin use, and those who could not complete sessions due to mechanical pain exacerbated during aerobic exercise on a treadmill (such as knee and hip osteoarthritis, back pain, etc.) were excluded from the study. Participants were determined to be in menopause by their gynecology and obstetrics doctors. FSH and estrogen levels, which can be used in the diagnosis of menopause, were not evaluated. Participants were not taking antiresorptive or anabolic agent treatments used in the pharmacological treatment of osteoporosis or HRT, which can be used during menopause.

Fifty patients who met these criteria were included in the study. Each patient was informed about the purpose of the study, the application method, duration, potential problems, and side effects, and they signed a consent form. The patients included in the study were numbered and divided into two groups by simple randomization using the closed envelope method: aerobic exercise group ($n = 25$) and control group ($n = 25$). Three patients in the exercise group and two patients in the control group did not participate in the follow-up examination conducted in the 12th week, so the study included 45 patients (exercise, $n = 22$; control, $n = 23$) (Fig. 1).

Treatment protocol

All patients were prescribed 2000 IU of vitamin D (cholecalciferol) and 1200 mg of calcium carbonate daily for 12 weeks. The aerobic exercise program and assessments were conducted at the Exercise Room of Hospital. The exercise group participated in a supervised aerobic

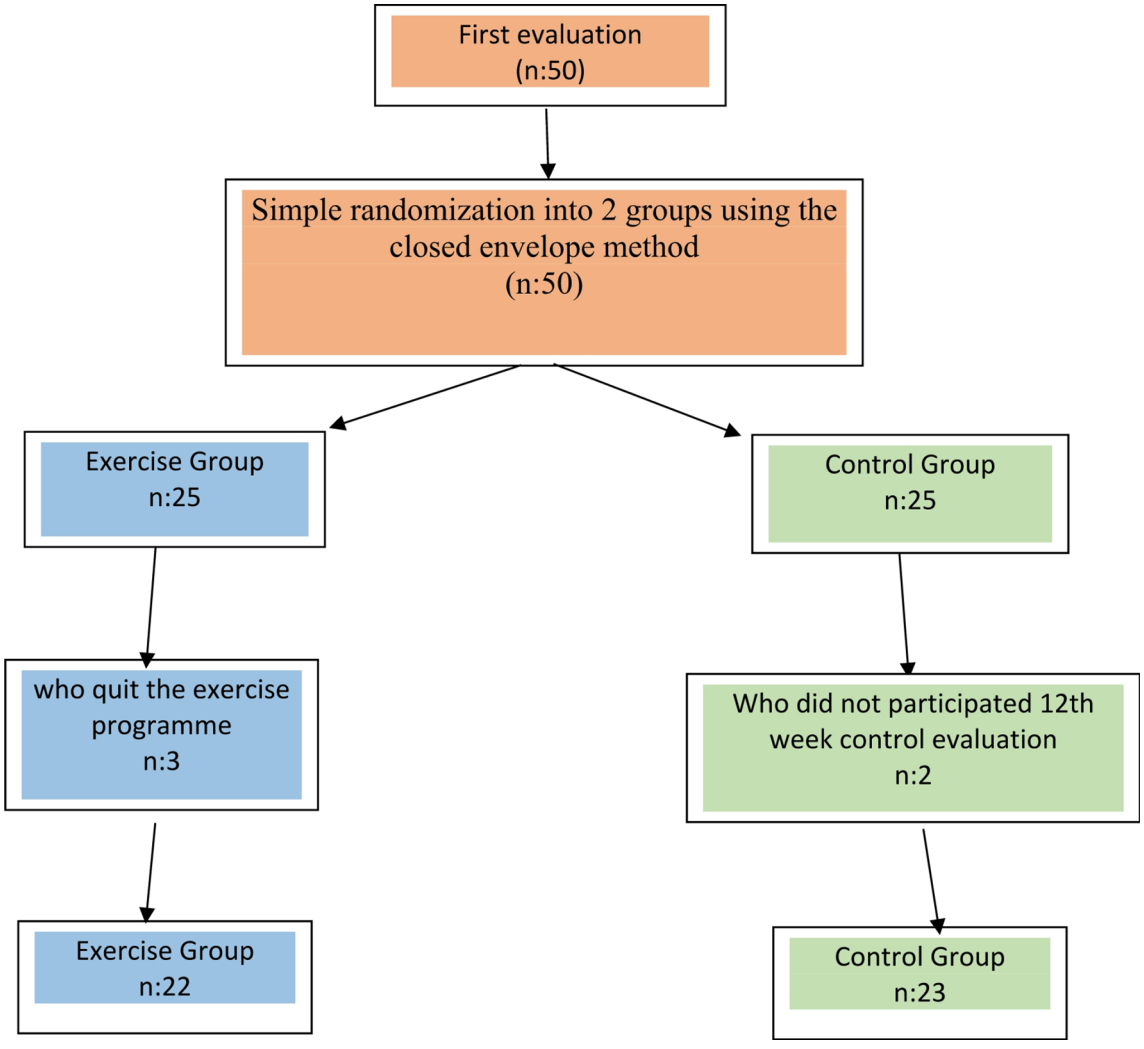

Fig. 1 Flow chart showing the process of study

exercise program involving treadmill walking (model: Grand Power: 2.5 HP, DP2011017654) for 4 weeks, 3 days a week, for 30 min a day, at an intensity of 40–60% of the maximal heart rate. Additionally, they were shown an exercise program at the initial assessment that included balance, posture, and endurance exercises using body weight and weights to be performed 3 days a week, with 3 sets of 10 repetitions. The exercise program consisted of a 10-minute warm-up, 30 min of aerobic exercise, and a 10-minute cool-down. All participants completed the exercise program under supervision. Blood pressure, pulse, and oxygen saturation were measured with a pulse oximeter before and after each exercise session. The control group was not included in any exercise program. Patients in the exercise group continued outdoor walking, balance, posture, and resistance exercises for up to 12 weeks of follow-up between November 2022 and May 2023 and were followed up by phone once a week.

Evaluation parameters

Nottingham Health Profile questionnaire (NHP) is a questionnaire consisting of 38 detailed health-related questions to measure the quality of life of patients [16, 17]. Visual analog scale (VAS) was used to evaluate and monitor the level of pain felt by the patients [18, 19]. 6-minute walk test (6MWT) was used to assess the functional capacity of patients and is a valid and reliable test as an indicator of physical endurance in elderly individuals [20]. International Physical Activity Questionnaire (short form)(IPAQs) is a widely used scoring system to assess daily physical activity levels, and its reliability increases with repeated measurement studies [21, 22]. Berg Balance Scale (BBS) is a 14-question test used to evaluate the balance and fall risk of elderly individuals [23, 24]. 30-second sit-to-stand test questionnaires(30s-CST) evaluates the patient's lower extremity strength and dynamic balance during activity [25]. Validity and reliability studies of all these tests have been conducted.

The serum levels of bone formation and resorption biomarkers, including procollagen type 1 N-terminal propeptide (P1NP), cross-linked C-telopeptide of type I collagen (CTX), osteocalcin, oxidative markers such as malondialdehyde, nonbone-specific total alkaline phosphatase, 25(OH)D3, and parathyroid hormone (PTH), were evaluated. Blood samples were collected from peripheral venous blood from participants after a 12-h fast and at least 24 h of exercise avoidance between 8:00 and 10:00 in the morning using yellow-capped biochemistry tubes. The collected blood samples were allowed to clot at room temperature for 10–20 min and then centrifuged at 2000–3000 ×g for 20 min using a centrifuge device (model: 800D, SN: 221015850, MFG DATE: 2022.10) in the clinic. The serum portion was separated into Eppendorf tubes. The samples were stored at -80 °C in the biochemistry laboratory of the hospital. Collected serum samples were analyzed using the Heales Multimode Reader MB-580 device in the biochemistry laboratory of Atlas Biotechnology Laboratory Equipment Industry and Trade Inc. For automatic measurements, Human Total Procollagen Type I N-Terminal Propeptide (Total-P1NP) (ng/ml) (Catalog No: E2119Hu), Human Cross-Linked Type I Collagen C-Telopeptide (CTX-I) (ng/ml) (Catalog No: E3700Hu), Human Osteocalcin N-terminal (OC-N) (ng/ml) (Catalog No: E7186Hu), and Human Malondialdehyde (MDA) (nmol/ml) (Catalog No: E1371Hu) ELISA kits were used, with intra-assay precision less than 8% and inter-assay coefficient of variation (CV) less than 10%.

At baseline and at the 12-week follow-up measurements of current weight and waist circumference and all evaluation parameters were recorded.

Statistical analysis

SPSS version 25 statistical software was used for data analysis. Descriptive findings for categorical variables are expressed as percentages, and continuous variables are presented as the mean ± standard error and median, minimum, and maximum values. For binary analyses, the chi-square test was used for categorical variables, while the Mann–Whitney U test and the Wilcoxon signed-rank test were employed for continuous variables since they did not meet the normal distribution prerequisites.

Results

The study group consisted of 45 individuals with an average age of 56.2 ± 0.7 years (range 47–64); the average age at menopause was 46.2 ± 0.7 years (range 35–55), the average lumbar T score was − 1.7 ± 0.1 (range − 2.7 to 0), and the average femoral neck T score was − 0.9 ± 0.1 (range − 2.4 to -0.6). The control group was significantly older than the exercise group ($p < 0.05$).

Plasma volume status (PV) was calculated using the Kaplan-Hakim formula based on hematocrit and weight measurements taken at baseline and at week 12. To calculate PV for females using this formula, plasma volume = (1-hematocrit) x (a + (b x weight (kg)); a = 864 and b = 47.9 were used [26]. PV was initially calculated as 2.63 + 0.45(L) in the exercise group and 2.95 + 0.53(L) in the control group; and at week 12, it was calculated as 2.61 + 0.44(L) in the exercise group and 2.93 + 0.53(L) in the control group. No statistically significant difference was found within the group and between the groups.

In the evaluation of the NHP questionnaire, VAS, BBS score, sit-to-stand test (30 s-CST) score, IPAQ test, 25(OH)D3 vitamin level, PTH, ALP blood levels, bone formation markers P1NP, CTX, and osteocalcin or the oxidative stress marker malondialdehyde no statistically

significant differences were found between the groups at the beginning ($p > 0.05$).

At week 12, the scores of NHP for all sub-parameters in the exercise group were significantly lower than those in the control group ($p < 0.05$). Examining the differences in scores at week 12, it was observed that all parameters except for NHP 2 significantly greater in exercise group ($p < 0.05$) (Table 1).

The 30 s-CST and BBS scores were significantly greater at week 12 in exercise group than in the control group ($p < 0.05$), and the VAS score was significantly lower ($p < 0.05$). In the 6MWT, there was a significant difference between the groups at the start, with the exercise group walking a greater distance in 6 min ($p < 0.05$). During weeks 12, there was a statistically significant increase in walking speed in the exercise group compared to the control group ($p < 0.05$) (Table 2).

A comparison of the clinical examinations and questionnaires conducted at the start and at week 12 among the exercise group participants (Table 3) revealed a statistically significant decrease in the VAS score ($p < 0.05$), a statistically significant increase in the IPAQ score, BBS score and 6-MWT ($p < 0.05$) and a statistically significant decrease in all sub-parameters of the NHP ($p < 0.05$).

In the comparison of the baseline and 12th week data between the groups (Table 4), there was no statistically significant difference in P1NP, CTX, Osteocalcin, ALP, PTH, Malondialdehyde levels ($p > 0.05$). At the 12th week, the 25(OH)D3 vitamin level was significantly greater in the exercise group than in the control group ($p < 0.05$).

When the serum markers of the exercise group participants at the beginning and at the 12th week were compared (Table 5), a statistically significant increase ($p < 0.05$) in the levels of P1NP, CTX, osteocalcin, and 25(OH)D3 was detected, and a statistically significant decrease ($p < 0.05$) in the levels of ALP was detected. There was no statistically significant change in the levels of malondialdehyde or PTH ($p > 0.05$).When comparing the intragroup data of the control group participants at the beginning and 12th weeks (Table 5), a statistically significant increase was observed in the levels of P1NP and CTX ($p < 0.05$) There was no statistically significant change in osteocalcin, ALP, PTH and malondialdehyde levels ($p > 0.05$). A statistically significant increase was observed in 25(OH)D3 levels ($p < 0.05$).

No side effects were observed in the participants due to the exercise programs.

Discussion

The current study revealed that regular, moderate-intensity walking exercise in postmenopausal women with osteopenia led to significant improvements in pain, walking speed, balance, lower extremity muscle strength, and daily living activities. In the exercise group, no significant changes were observed in bone formation or resorption markers, including P1NP, CTX, osteocalcin, and total ALP, or in oxidative stress markers, such as malondialdehyde, compared to those in the control group. However, a statistically significant increase in P1NP and CTX levels was noted in both the exercise and control groups at the 12-week evaluation compared to baseline. While there was no significant change in osteocalcin levels in the control group, a statistically significant increase was observed in the exercise group.

While the treatment of osteoporotic patients is more clearly defined by guidelines, the treatment of osteopenic

Table 1 Nottingham health profile data comparison at week 0 and 12

	Week 0			Week 12			Difference value		
Parameter	**Group 1 (*n* = 22)**	**Group 2 (*n* = 23)**	***P* Value**	**Group 1 (*n* = 22)**	**Group 2 (*n* = 23)**	***P* Value**	**Group 1 (*n* = 22)**	**Group 2 (*n* = 23)**	***P* Value**
NHP Pain	37.4±6.0 (35.9, 0-100)	47.7±6.8 (43.1, 0-100)	0.323	12.3±2.3 (14.4, 0-30.2)	34.7±5.1 (29.2, 0-89.5)	**0.001**	-25.1±5.9 (-24.9, -100-23.4)	-12.9±4.9 (-8.9, -85.2-21.2)	**0.046**
NHP Emotional	48.4±6.9 (47.2, 0-100)	41.8±6.6 (33.7, 0-100)	0.440	15.7±3.8 (10.1, 0-57.5)	35.3±6.1 (24.4, 0-90.2)	**0.018**	-32.7±7.2 (-34.6, -100-25.9)	-6.5±3.8 (-9.3, -40.3-37.3)	**0.005**
NHP Sleep	41.9±6.2 (46.2, 0-77.6)	49.4±5.5 (55.9, 0-77.6)	0.348	15.2±5.1 (0, 0-77.6)	47.5±5.9 (44.1, 0-100.0)	**< 0.001**	-26.7±6.2 (-21.7, -77.6-34.3)	-1.9±7.2 (3.5, -77.6-55.9)	**0.013**
NHP Social	37.8±7.4 (22.0, 0-100)	25.6±5.6 (20.1, 0–84.0)	0.263	5.4±2.3 (0, 0-35.3)	20.9±5.8 (0, 0-100)	**0.024**	-32.5±6.7 (-22.0, -100-0)	-4.6±5.2 (0, -46.1-57.9)	**0.003**
NHP Physical	22.3±3.6 (21, 0-54.8)	31.1±4.0 (32.6, 0-67.2)	0.088	6.8±1.8 (0, 0-21.9)	29.3±4.0 (30.7, 0-67.2)	**< 0.001**	-15.5±3.7 (-15.2, -54.8-12.6)	-1.8±3.1 (0.2, -41.9-20.1)	**0.002**
NHP Energy	64.7±8.9 (100, 0-100)	65.3±9.2 (100, 0-100)	0.970	3.9±2.3 (0, 0-39.2)	52.2±8.8 (60.8, 0-100)	**< 0.001**	-60.8±8.9 (-76, -100-0)	-13.1±9.4 (0, -100-76)	**0.001**
NHP2	1.4±0.4 (1, 0–7)	1.6±0.5 (0, 0–6)	0.923	0.2±0.1 (0, 0–2)	1.1±0.4 (0, 0–7)	**0.014**	-1.2±0.4 (-0.5, -7-0)	-0.5±0.4 (0, -5-3)	**0.067**
NHP Total	248.8±26.9 (266.2, 43.4-466.8)	258.4±28.3 (253.5, 0-488.0)	0.874	58.7±8.7 (58.7, 0-136.5)	220.0±25.4 (213.3 9.9-458.4)	**< 0.001**	-190.1±28.7 (-181.9, -466.8-18.3)	-38.4±23.1 (-25.2 -286.5-145.7)	**0.001**

Note NHP: Nottingham Health Profile, NHP2: Nottingham Health Profile Sect. 2

Table 2 Comparison of physical activity index, Berg balance scale (BBS), sit-to-stand test (30s-CST), 6-minute walk test, VAS, week 0 and week 12 data between groups

	Parameter	Exercise Group (*n* = 22)	Control Group (*n* = 23)	*P* Value
Physical Activity Index (IPAQs)	IPAQs Week 0	475.8 ±100.9 (321.7, 0–1866)	390.5±84.6 (297, 0–1611)	0.532
	IPAQs Week 12	1013.8±105.7 (945, 297–2097)	541.7±92.1 (396, 0–1510)	0.001
	IPAOs difference	538.1±95.7 (417.3, 15-1866)	151.2±63.9 (33, -248-819)	< 0.001
Berg Balance Scale (BBS)	BDS Week 0	54.9 ±0.3 (55.5, 51–56)	54.6±0.4 (55, 48–56)	0.923
	BDS Week 12	56±0 (56, 56–56)	54.2±0.3 (54, 51–56)	< 0.001
	BDS difference	1.1±0.3 (0.5, 0–5)	-0.4±0.4 (0, -4-4)	0.003
Sit-to-Stand Test (30s-CST)	30s-CST Week 0	10.8±0.3 (11, 8–14)	10.6±0.3 (11, 7–14)	0.091
	30s-CST Week 12	15.1±0.4 (14.7, 11.5–20)	11.2±0.4 (11, 7–14)	< 0.001
	30s-CST Difference	4.3±0.3 (4, 1–8)	0,7±0,3 (1, -1.5-4)	< 0.001
6-minute walk test (6MWT)	6MWT Week 0	470±12.8 (482.5, 370–560)	422.6±17.8 (420, 270–610)	0.037
	6MWT Week 12	595±17.5 (610, 430–720)	439.1±15.2 (420, 300–590)	< 0.001
	6MWT Difference	125±15.2 (130, 20–250)	16.6±10.8 (0, -60-160)	< 0.001
Visual Analog Scale	VAS Week 0	4.5±0.3 (4.5, 2–8)	4.9±0.4 (5, 2–9)	0.426
	VAS Week 12	2.5±0.2 (2, 0–5)	4.8±0.3 (5, 2–8)	< 0.001
	VAS Difference	-2.0±0.3 (-2, (-5)-0)	-0.1±0.5 (0, (-6)-3)	0.02

Note IPAQs: International Physical Activity Questionnaire-Short Form, BBS: Berg Balance Scale, 30s-CST: 30-Second Sit-to-Stand Test, VAS: Visual Analog Scale

patients is more controversial [27]. Therefore, early treatment and follow-up of patients diagnosed with osteopenia are important [28]. Exercise plays a significant role in both the treatment and prophylaxis of osteoporosis, and the specific type and frequency of exercise to be recommended is still a subject of research. This understanding has led to the recognition of osteosarcopenia syndrome, where osteoporosis and sarcopenia coexist [29].

A literature review by Zhang et al. on the potential mechanisms and pathways through which exercise may impact osteoporosis pathology highlighted that mechanical stress caused by exercise influences the release of phytohormones and cytokines, affecting apoptosis, autophagy, and inflammatory reactions in the pathophysiology of osteoporosis [30]. This has led to need for searching for bone formation and resorption markers to exercise response.

As a result of 43 randomized controlled trials examined by Howe et al. to investigate the effects of exercise in the prevent and treatment of PMO; the most effective exercise type for femoral neck BMD is non-weight bearing high force exercise such as progressive resistance strength training for the lower limbs. And the most effective intervention for BMD at the spine was combination exercise programmes compared with control groups [6]. Aerobic exercise has been shown to increase osteoblast enzymatic activity, and better improvements in BMD have been seen in sedentary individuals who are included in a long-term exercise program, especially for 6–12 months, compared to those who do active exercise. Although walking alone cannot prevent BMD loss, it is recommended because it improves the quality of daily life. However, aerobic exercise can limit BMD loss when done at high speed and intensity [4]. In the current study, postmenopausal osteopenic patients were divided into two groups: an exercise group and a control group. The exercise group underwent a 12-week program consisting of 30 min of aerobic exercise on a treadmill at a speed of 3–5 km/h combined with dorsal extensor strengthening, balance, posture exercises and endurance exercises using body weight and weights to three times a week. The control group did not participate in any exercise program.

In a randomized controlled trial by Hettchen et al. comparing high-intensity and low-intensity exercise in early postmenopausal women with osteopenia or osteoporosis, significant effects on lumbar BMD were observed in the high-intensity group, while no significant effect was found on total femur BMD [31]. In this study, patients performed low to moderate-intensity exercise program.

In a study by Filipović et al. investigating the effects of a 12-week exercise program on functional status in postmenopausal osteoporotic women, a significant improvement in lower extremity muscle strength and dynamic balance was observed in the exercise group compared to the control group, which did not receive any exercise program. At the 12th week of follow-up, significant improvements were noted in both groups, with the improvement in the control group likely attributed to the use of oral bisphosphonates and vitamin D supplements [32]. In the current study, the physical activity levels of the patients were assessed using the IPAQ, a significant increase was observed in the average score of the exercise group from 475.8 to 1013.8 at the 12-week follow-up, with no significant change in the control group. In the BBS and 30 s-CST tests, which evaluate balance, fall risk, and dynamic lower extremity balance, while the 12th week evaluation showed significant improvements in the exercise group's BBS score from 54.9 to 56 and 30 s-CST score from 10.8 to 15.1 compared to the control group. In the control group, there was a significant increase in the 30 s-CST score from 10.6 to 11.2, with no significant change in the BBS score. In the 6-minute walk test (6MWT), which is a crucial indicator of functional capacity, the exercise group's walking distance

Table 3 IPAQs, BBS, 30s-CST, 6-minute walk test, Nottingham health profile week 0 and week 12 data comparison within exercise and control group participants

	Exercise Group			Control Group		
Parameters	**Week 0**	**Week 12**	***P* value (0-12w)**	**Week 0**	**Week 12**	***P* value (0-12w)**
VAS	4.5±0.3 (4.5, 2–8)	2.5±0.2 (2, 0–5)	**<0.001**	4.9±0.4 (5, 2–9)	4.8±0.3 (5, 2–8)	0.984
IPAQs	475.8±100.9 (321.7, 0–1866)	1013.8±105.7 (945, 297–2097)	**<0.001**	390.5±84.6 (297, 0–1611)	541.7±92.1 (396, 0–1510)	0.064
BBS	54.9 ±0.3 (55.5, 51–56)	56±0 (56, 56–56)	**0.003**	54.6±0.4 (55, 48–56)	54.2±0.3 (54, 51–56)	0.280
30s-CST	10.8±0.3 (11, 8–14)	15.1±0.4 (14.7, 11.5–20)	**<0.001**	10.6±0.3 (11, 7–14)	11.2±0.4 (11, 7–14)	**0.030**
6MWT	470±12.8 (482.5, 370–560)	595±17.5 (610, 430–720)	**<0.001**	422.6±17.8 (420, 270–610)	439.1±15.2 (420, 300–590)	0.384
NSP Pain	37.4±6.0 (35.9, 0-100)	12.3±2.3 (14.4, 0-30.2)	**0.001**	47.7±6.8 (43.1, 0-100)	34.7±5.1 (29.2, 0-89.5)	**0.010**
NSP Emotional	48.4±6.9 (47.2, 0-100)	15.7±3.8 (10.1, 0-57.5)	**0.001**	41.8±6.6 (33.7, 0-100)	35.3±6.1 (24.4, 0-90.2)	0.110
NSP Sleep	41.9±6.2 (46.2, 0-77.6)	15.2±5.1 (0, 0-77.6)	**0.001**	49.4±5.5 (55.9, 0-77.6)	47.5±5.9 (44.1, 0-100.0)	0.948
NSP Social	37.8±7.4 (22.0, 0-100)	5.4±2.3 (0, 0-35.3)	**<0.001**	25.6±5.6 (20.1, 0–84.0)	20.9±5.8 (0, 0-100)	0.365
NSP Physical	22.3±3.6 (21, 0-54.8)	6.8±1.8 (0, 0-21.9)	**0.001**	31.1±4.0 (32.6, 0-67.2)	29.3±4.0 (30.7, 0-67.2)	0.970
NSP Energy	64.7±8.9 (100, 0-100)	3.9±2.3 (0, 0-39.2)	**<0.001**	65.3 ±9.2 (100, 0–100)	52.2±8.8 (60.8, 0-100)	0.197
NSP2	1.4±0.4 (1, 0–7)	0.2±0.1 (0, 0–2)	**0.003**	1.6±0.5 (0, 0–6)	1.1±0.4 (0, 0–7)	0.179
NSP Total	248.8±26.9 (266.2, 43.4-466.8)	58.7±8.7 (58.7, 0-136.5)	**<0.001**	258.4±28.3 (253.5, 0-488.0)	220.0±25.4 (213.3 9.9-458.4)	0.171

Note IPAQs: International Physical Activity Questionnaire-Short Form, BBS: Berg Balance Scale, 30s-CST: 30-Second Sit-to-Stand Test, VAS: Visual Analog Scale NHP: Nottingham Health Profile, NHP2: Nottingham Health Profile Sect. 2

significantly increased from 470 m/6 min to 595 m/6 min at the 12th week of evaluation, while no significant change was observed in the control group. The NHP questionnaire was used to assess the impact of osteoporosis on daily living activities in all patients. Significant improvements were observed in all sub-parameters of NHP in the exercise group. The current study shows that regular aerobic exercise improves walking speed, balance, lower extremity muscle strength and daily life quality, as shown in other studies.

In a study by Siwapituk et al. evaluating the effects of supervised treadmill exercise for 30 min three times a week for 3 months at a 55–70% maximum heart rate on bone formation and resorption markers P1NP and CTX in 18 postmenopausal women with osteoporosis, significant increases in P1NP and CTX levels were observed at the 3rd month follow-up. Despite expectations of a decrease in CTX levels, an increase was observed [33]. In the current study, patients were divided into exercise and control groups, with the exercise group receiving supervised treadmill exercise for the first 4 weeks and continuing with a home exercise program up to the 12th week. The control group did not participate in any exercise program. Significant increases in P1NP and CTX levels were observed in both groups at the 12-week follow-up compared to baseline, with no significant differences between the groups. The investigators' literature review did not identify any studies comparing changes in serum P1NP and CTX levels between exercise and non-exercise control groups. In the current study is the first to evaluate this phenomenon, but since the 12-week cholecalciferol and calcium carbonate supplement recommended to all patients may also have an effect on BTMs, the effect of aerobic exercise alone could not be observed.

In the study conducted by Mohr et al. on the effects of soccer and swimming on bone formation in middle-aged sedentary women, an increase was found in the P1NP, CTX and Osteocalcin levels in the soccer group, while no change was found in the swimming groups. The P1NP (formation)/CTX-1 (resorption) ratio did not change during the intervention in any of the groups [11]. In the current study, the investigator measured serum osteocalcin levels at the beginning and at the 12th week of follow-up. In the exercise group, the osteocalcin level significantly increased, whereas in the control group, there was no statistically significant change. The increase in P1NP, CTX and osteocalcin levels in the exercise group indicates that regular walking exercise provides a strong osteogenic stimulus. However, when compared with calcium carbonate and cholecalciferol intervention, no significant difference was found in P1NP and CTX levels in the exercise group except for osteocalcin levels.

In the study by Eastwell et al. comparing the relationship between vitamin D levels and bone turnover markers (BTMs) in healthy premenopausal women, no significant difference was found in BTM among women with vitamin D insufficiency, deficiency, or adequate vitamin D. There was a positive correlation between PTH and bone ALP levels, while a negative correlation was found between 25(OH)D3 levels and bone ALP levels [34]. In the current study, a significant decrease in total nonspecific bone ALP levels was observed in the exercise

Table 4 Comparison of laboratory values (P1NP, CTX, osteocalcin, Malondialdehyde) between groups

		Exercise Group (*n* = 22)	Control Group (*n* = 23)	*P* Value
Type 1 Procollagen N-terminal Propeptide (ng/ml)	**P1NP(ng/ml) Week 0**	316.6±40.1 (263.7, 179.8–1065)	320.8±51.7 (268.4, 182.3–1417.1)	0.919
	P1NP(ng/ml) Week 12	484.9±58.1 (424.1, 238.5–1342.9)	477.1±70.3 (389.6, 253.1–1927.5)	0.803
	P1NP Difference	168.2±31.7 (157, −127.4 −498.9)	156.2±24.1 (137.8, 9.3–510.4)	0.650
Free Collagen Cross-Linked C-Telopeptide (ng/ml)	**CTX(ng/ml) Week 0**	7.3±1.2 (5.6, 3.1–28.1)	7±1.4 (4.6, 2.6–37.1)	0.271
	CTX(ng/ml) Week 12	9.8±1.8 (6.8, 5.6–39.9)	11.2±2 (7.3, 2.2–40.2)	0.555
	CTX Difference	2.4±0.8 (1.6, −3.4–14.5)	4.2±1.5 (2.3, −2.4–35.1	0.482
Osteocalcin (ng/ml)	**OCN (ng/ml) Week 0**	8.3±2 (6, 1.7–46.9)	10.1±3.2 (5.4, 1.6–78.9)	0.982
	OCN (ng/ml) Week 12	10.9±2.3 (7.5, 2.9–52.6))	12.8±3.2 (10.6, 2.4–63.8)	0.874
	OCN (ng/ml) Difference	2.5±1 (1.2, −8.3–13)	2.6±2.9 (1.1, −23.4–59.1)	0.376
Malondialdehyde (nmol/ml)	**MDA (nmol/ml) Week 0**	8±1.9 (5.3, 2.9–46.4)	8.7±2.6 (4.9, 3.7–66.5)	0.666
	MDA (nmol/ml) Week 12	9.4±1.8 (6.2, 3.5–36.9)	11.5±3.2 (6.3, 3.7–66.9)	0.919
	MDA (nmol/ml) Difference	1.3±1.4 (0.9, −15.4–19	2.8±2.1 (0.7, −8.7–46.7	0.874

Note: P1NP: Type 1 Procollagen N-terminal Propeptide **CTX**: Free Collagen Cross-Linked C-Telopeptide **OCN**: Osteocalcin

MDA: Malondialdehyde

group at baseline and at the 12-week follow-up, whereas no changes were noted in the control group. No significant change was detected in PTH levels in either group. No correlation was found between changes in the serum 25(OH)D3 concentration and changes in the serum P1NP, CTX, or osteocalcin concentration in either the exercise or control group. A statistically significant correlation was found between P1NP and osteocalcin in the exercise group and between osteocalcin and CTX in the control group.

In a meta-analysis by Voulgaridou et al., which investigated the effects of vitamin D and calcium supplementation, both individually and in combination, on BMD, PTH, serum calcium, 25(OH)D3, bone turnover markers (BTMs), and osteoporotic fractures, it was found that while cholecalciferol alone did not increase BMD, the combined use of cholecalciferol and calcium supplementation did. Most studies included in the review found no significant effect of interventions with vitamin D on BTMs. Interventions with vitamin D and calcium supplements showed increases, decreases, or no significant changes [35]. In the current study, the investigators measured serum 25(OH)D3 and PTH levels at baseline and 12-week follow-up for all patients. An increase in mean serum 25(OH)D3 levels was observed in both groups due to cholecalciferol intervention. The patients in the exercise group also did outdoor walking in addition to walking on a treadmill during the follow-up period between November 2022 and June 2023. Although the serum 25(0 H)D3 level increased in both groups due to the vitamin D supplement given by the investigators, a statistically significant increase was observed in the exercise group. The investigators think that the significant difference may be due to the exercise group spending more time outdoors. When the investigators evaluated the

Table 5 Intragroup comparison of P1NP, CTX, osteocalcin, malondialdehyde, 25(OH)D3, ALP, PTH values at baseline and 12th week for exercise and control groups

	Exercise Group			Control Group		
	Week 0	**Week 12**	***P* value (0–12 w)**	**Week 0**	**Week 12**	***P* value (0–12 w)**
P1NP (ng/ml)	316.6±40.1 (263.7, 179.8–1065)	484.9±58.1 (424.1, 238.5–1342.9)	**< 0.001**	320.8±51.7 (268.4, 182.3–1417.1)	477.1±70.3 (389.6, 253.1–1927.5)	**< 0.001**
CTX (ng/ml)	7.3±1.2 (5.6, 3.1–28.1)	9.8±1.8 (6.8, 5.6–39.9)	**0.002**	7±1.4 (4.6, 2.6–37.1)	11.2±2 (7.3, 2.2–40.2)	**0.001**
Osteocalcin (ng/ml)	8.3±2 (6, 1.7–46.9)	10.9±2.3 (7.5, 2.9–52.6))	**0.013**	10.1±3.2 (5.4, 1.6–78.9)	12.8±3.2 (10.6, 2.4–63.8)	0.362
MDA (nmol/ml)	8±1.9 (5.3, 2.9–46.4)	9.4±1.8 (6.2, 3.5–36.9)	0.095	8.7±2.6 (4.9, 3.7–66.5)	11.5±3.2 (6.3, 3.7–66.9)	0.083
25(OH)D3 (ng/ml)	16.5±1.8 (15.8, 4.4–30.7)	35.3±2 (32.9, 21.8–60.2)	**< 0.001**	18.6±2.9 (12.1, 5.9–53.7)	28.1±2.2 (27.4, 7.5–46.4)	**0.023**
ALP (U/L)	81±3.8 (85, 47–124)	74.7±4.2 (76.5, 44–128)	**0.013**	83.1±4.9 (82, 50–164)	81.4±5 (86, 42– 152)	0.553
PTH (pg/ml)	72.1±7.4 (62.5, 28.6–152)	65.9±6.2 (57.9, 30.9–150)	0.537	72.2±5.1 (62.5, 40–127.9)	72.8±4.5 (66, 46–120)	0.533

Note: P1NP: Type 1 Procollagen N-terminal Propeptide **CTX**: Free Collagen Cross-Linked C-Telopeptide **OCN**: Osteocalcin

MDA: Malondialdehyde **ALP**: Alkaline phosphotase **PTH**: Parathormone

data in the control group that received only cholecalciferol and calcium intervention, a statistically significant increase in P1NP and CTX levels was observed at week 12, while no statistically significant change was observed in osteocalcin and malondialdehyde levels. Further studies, with appropriate doses controlled, are needed to determine the role of bone metabolism markers in the treatment of osteoporosis.

In the systematic review and meta-analysis by Zhou et al., which investigated the relationship between oxidative stress-related markers and postmenopausal osteoporosis, no significant differences in malondialdehyde or vitamin B12 levels in either plasma or serum were found between the control group and the postmenopausal osteoporosis group [36]. In a systematic review and meta-analysis by Zhao et al. examining the effects of oxidative stress biomarkers on postmenopausal osteoporosis, malondialdehyde and vitamin B12 levels were found to be increased in patients with postmenopausal osteoporosis compared to the control group, while uric acid levels were decreased [14]. In the current study, the serum malondialdehyde levels increased from 8 ng/ml to 9.4 ng/ml in the exercise group and from 8.7 ng/ml to 11.5 ng/ml in the control group at baseline and at the 12-week follow-up; however, these changes were not statistically significant. No significant changes were found in the serum vitamin B12 or uric acid levels between the exercise group and the control group at baseline or at the 12-week follow-up.

While no significant difference was found in the serum P1NP and CTX levels between the groups at baseline and at the 12-week follow-up, an increase in the P1NP and CTX levels was observed at the 12th week in both groups. The statistically significant increase in P1NP and CTX levels in both groups is thought to be due to the increase in bone turnover caused by the cholecalciferol and calcium carbonate supplementation recommended to all patients for 12 weeks. It may be possible to observe the effects of exercise and supplements more clearly with an additional control group without cholecalciferol and calcium intervention. Since the duration of the exercise was short and the intensity was light-moderate, significant improvements in P1NP and CTX levels may not have been seen in the exercise group compared to the control group. The significant increase in osteocalcin levels, an indicator of osteoblast activity, in the exercise group may suggest that bone formation increased positively compared to the control group.

The limitations of the current study include its relatively small sample size and short follow-up period of 12 weeks, which may not capture long-term effects. Due to the short follow-up period and high radiation exposure, the investigators did not evaluate BMD with DXA at the 12-week follow-up. Additionally, patients in the control group were not restricted in their daily activities, and their self-reported physical activity levels were not objectively measured. Future studies with larger sample sizes and longer follow-up periods, as well as objective measures of physical activity, are needed to confirm the investigators' findings and provide more comprehensive insights into the long-term benefits of regular exercise in postmenopausal women with osteopenia. The investigators did not evaluate FSH levels to control for menopausal status.

Conclusion

In conclusion, P1NP and CTX serum levels increased in both exercise and control groups at 12 weeks follow-up. Osteocalcin levels increased significantly in the exercise group, while total nonspecific bone ALP levels decreased. No significant change was observed in these values in the control group.

The current study indicated that regular walking exercise of light to moderate intensity significantly contributes to improvements in pain, walking speed, balance, lower extremity dynamic balance, and activities of daily living in postmenopausal women with osteopenia compared to inactive individuals.

There is a need for more research to determine the ideal exercise program and frequency that can be recommended to patients for the prevention and treatment of osteoporosis, which is a major public health issue affecting a large portion of the population.

Supplementary Information

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Supplementary Material 1

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Author contributions

K.N.D. and M.K.A. wrote the introduction, materials-methods, results and discussion sections of the main manuscript. MKA wrote the abstract and KND prepared figure 1; Tables 1, 2, 3, 4 and 5. All authors reviewed the manuscript.

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Data availability

The datasets used and/or analyzed during the current study are provided within the manuscript and supplementary information file.

Declarations

Ethics approval and consent to participate

Ethical approval for the study was obtained from University of Health Sciences Bursa Yüksek Ihtisas Training and Research Hospital the local ethics committee (number 2011-KAEK-252022/10 – 02) at 19 Oct 2022, and with the Helsinki declaration and comparable ethical standarts. Each patient included in the study was informed about the purpose of the study, the method

of application, duration, possible problems and side effects, and signed a consent form.

Consent of publication
Not applicable.

Conflicting interests
Kübra Nur Deniz and Meliha Kasapoğlu Aksoy declared no conflicts of interest with respect to the authorship and/or publication of this article.

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References

1. Peck W. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. Am J Med. 1993;94(6):646–50.
2. Tu KN, et al. Osteoporosis: a review of treatment options. Pharm Ther. 2018;43(2):92.
3. Klibanski A, et al. Osteoporosis prevention, diagnosis, and therapy. JAMA. 2001;285(6):785–95.
4. Benedetti MG et al. The effectiveness of physical exercise on bone density in osteoporotic patients. BioMed research international, 2018. 2018.
5. Todd J, Robinson R. Osteoporosis and exercise. Postgrad Med J. 2003;79(932):320–3.
6. Howe TE et al. Exercise for preventing and treating osteoporosis in postmenopausal women. Cochrane Database Syst Reviews, 2011(7).
7. Eastell R, Szulc P. Use of bone turnover markers in postmenopausal osteoporosis. Lancet Diabetes Endocrinol. 2017;5(11):908–23.
8. Greenblatt MB, Tsai JN, Wein MN. Bone turnover markers in the diagnosis and monitoring of metabolic bone disease. Clin Chem. 2017;63(2):464–74.
9. Lorentzon M, et al. Algorithm for the use of biochemical markers of bone turnover in the diagnosis, assessment and follow-up of treatment for osteoporosis. Adv Therapy. 2019;36:2811–24.
10. Jain S, Camacho P. Use of bone turnover markers in the management of osteoporosis. Curr Opin Endocrinol Diabetes Obes. 2018;25(6):366–72.
11. Mohr M, et al. Effects of soccer vs swim training on bone formation in sedentary middle-aged women. Eur J Appl Physiol. 2015;115:2671–9.
12. Vasikaran S, et al. International osteoporosis foundation and international federation of clinical chemistry and laboratory medicine position on bone marker standards in osteoporosis. Clin Chem Lab Med (CCLM). 2011;49(8):1271–4.
13. Marcucci G, et al. Oxidative stress and natural antioxidants in osteoporosis: novel preventive and therapeutic approaches. Antioxidants. 2023;12(2):373.
14. Zhao F, et al. Correlation of oxidative stress-related biomarkers with postmenopausal osteoporosis: a systematic review and meta-analysis. Archives Osteoporos. 2021;16:1–10.
15. Yang S, et al. Association between global biomarkers of oxidative stress and hip fracture in postmenopausal women: a prospective study. J Bone Miner Res. 2014;29(12):2577–83.
16. Hunt SM, McEwen J, McKenna SP. Measuring health status: a new tool for clinicians and epidemiologists. J Royal Coll Gen Practitioners. 1985;35(273):185–8.
17. Kücükdeveci A, et al. The development and psychometric assessment of the Turkish version of the Nottingham health profile. Int J Rehabil Res. 2000;23(1):31–8.
18. Price DD, et al. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. Pain. 1983;17(1):45–56.
19. VASSS ODIO. Validation of the Turkish version of the visual analog scale spine score in patients with spinal fractures. Acta Orthop Traumatol Turc. 2011;45(5):353–8.
20. Rikli RE, Jones CJ. The reliability and validity of a 6-minute walk test as a measure of physical endurance in older adults. J Aging Phys Act. 1998;6(4):363–75.
21. Lee PH, et al. Validity of the international physical activity questionnaire short form (IPAQ-SF): A systematic review. Int J Behav Nutr Phys Activity. 2011;8(1):1–11.
22. Saglam M, et al. International physical activity questionnaire: reliability and validity of the Turkish version. Percept Mot Skills. 2010;111(1):278–84.
23. Sahin F, et al. Reliability and validity of the Turkish version of the Berg balance scale. J Geriatr Phys Ther. 2008;31(1):32–7.
24. Bogle Thorbahn LD, Newton RA. Use of the Berg balance test to predict falls in elderly persons. Phys Ther. 1996;76(6):576–83.
25. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. 1999;70(2):113–9.
26. KAPIAN AA. A simple and accurate method for prescribing plasma exchange. ASAIO J. 1990;36(3):M597–599.
27. Eriksen EF. Treatment of osteopenia. Reviews Endocr Metabolic Disorders. 2012;13:209–23.
28. Shoback D, et al. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. J Clin Endocrinol Metabolism. 2020;105(3):587–94.
29. Cariati I, et al. Role of physical activity in bone–muscle crosstalk: biological aspects and clinical implications. J Funct Morphology Kinesiol. 2021;6(2):55.
30. Zhang L, et al. Exercise for osteoporosis: A literature review of pathology and mechanism. Front Immunol. 2022;13:1005665.
31. Hettchen M et al. Changes in menopausal risk factors in early postmenopausal osteopenic women after 13 months of high-intensity exercise: the randomized controlled ACTLIFE-RCT. Clin Interv Aging, 2021: pp. 83–96.
32. FilipoviĆ TN, et al. A 12-week exercise program improves functional status in postmenopausal osteoporotic women: randomized controlled study. Eur J Phys Rehabil Med. 2020;57(1):120–30.
33. Siwapituk W, Kitisomprayoonkul W. Bone turnover increases during supervised treadmill walking in Thai postmenopausal women. Osteoporos Sarcopenia. 2016;2(1):41–4.
34. Eastell R, et al. Reference intervals of bone turnover markers in healthy premenopausal women: results from a cross-sectional European study. Bone. 2012;50(5):1141–7.
35. Voulgaridou G, et al. Vitamin D and calcium in osteoporosis, and the role of bone turnover markers: A narrative review of recent data from RCTs. Diseases. 2023;11(1):29.
36. Zhou Q et al. Oxidative stress-related biomarkers in postmenopausal osteoporosis: a systematic review and meta-analyses. Disease markers, 2016. 2016.

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