

Low Versus Moderate Intensity Aerobic Exercises on Bone Mineral Density in Breast Cancer Patients Undergoing Radiotherapy: A Randomized Controlled Trial

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ABSTRACT

Background: Breast cancer is one of the most common malignancies affecting women, and improved survival has increased attention to treatment-related complications that may influence long-term health. Anticancer treatment can adversely affect the skeleton through ovarian dysfunction, estrogen deprivation, endocrine changes, reduced physical activity, and alterations in body composition and bone remodeling. Declining bone mineral density (BMD) is clinically important because it may contribute to osteopenia, osteoporosis, and future skeletal morbidity. Exercise is recommended as part of breast-cancer rehabilitation, and weight-bearing aerobic activity provides repeated mechanical loading and muscle-generated forces that may support bone formation and preservation. However, skeletal adaptation may differ according to exercise intensity and anatomical site, and direct evidence comparing low- and moderate-intensity aerobic exercise during radiotherapy remains limited. **Purpose:** To compare the effects of low- and moderate-intensity supervised aerobic treadmill exercise with a control condition on BMD in women with breast cancer undergoing radiotherapy. **Subjects and Methods:** Sixty-six women with stage I-III breast cancer were randomized equally to Low-intensity, Moderate-intensity, and Control groups (22/group). The Low-intensity group exercised at 35-60% of age-predicted HRmax and the Moderate-intensity group at 65-75% HRmax, four times weekly for 12 weeks. All groups received the same approximately 15-minute standardized physical therapy program (range-of-motion exercises, stretching, and strengthening exercises), while the Control group received this program without additional treadmill exercise. Areal BMD was measured by DXA at L1-L4, femoral neck, total hip, and 33% radius before and after the 12-week intervention; lumbar-spine BMD was the primary outcome. A mixed-design MANOVA evaluated time, treatment, and treatment-by-time effects, followed by Bonferroni-corrected comparisons. **Results:** A significant treatment-by-time interaction was observed (Wilks' $\Lambda=0.18$, $F(8,120)=20.24$, $p<0.001$, partial $\eta^2=0.57$). BMD increased significantly at all measured sites in both exercise groups, while no significant changes occurred in the Control group. The Moderate-intensity group had significantly higher post-treatment BMD than both the Low-intensity and Control groups at L1-L4, femoral neck, and total hip; no significant between-group difference was observed at the 33% radius. Lumbar-spine BMD increased by 3.57%, 10.08%, and 1.70% in the Low-intensity, Moderate-intensity, and Control groups, respectively. **Conclusion:** Moderate-intensity treadmill exercise produced a greater BMD response than low-intensity exercise at the lumbar spine, femoral neck, and total hip, supporting a site-specific skeletal response.

Keywords: breast cancer; radiotherapy; aerobic exercise; bone mineral density; rehabilitation; DXA; exercise intensity.

INTRODUCTION

Breast cancer remains a major global health burden, while advances in screening, diagnosis, and treatment have increased the number of women living during and beyond therapy.^{1,2} As survival improves, attention has increasingly shifted toward treatment-related complications that may influence long-term function and quality of life. Skeletal health is an important part of this concern because breast cancer and its treatments can disturb bone remodeling and contribute to progressive loss of bone mineral density (BMD).^{3,4}

Bone loss in women with breast cancer is multifactorial. Ovarian dysfunction, estrogen deprivation, premature menopause, endocrine therapy, previous chemotherapy exposure, reduced physical activity, and changes in body composition may each influence skeletal metabolism.³⁻⁵ These factors are particularly relevant when BMD is assessed during active cancer treatment because changes observed over time may reflect the combined effects of disease, systemic treatment, hormonal status, and physical activity rather than a single treatment component.³⁻⁵

Radiotherapy is a central component of curative breast-cancer treatment.⁶ The lumbar spine, proximal femur, and 33% radius are not typical direct targets of standard breast radiotherapy; nevertheless, the radiotherapy period represents an active-treatment window during which systemic and behavioral factors affecting bone health may coexist.^{3,6} Exercise and rehabilitation interventions that can be delivered safely during this period may help preserve physical function and support musculoskeletal health during active treatment.⁷

Exercise is widely recommended as part of breast-cancer rehabilitation because it can improve physical function, cardiorespiratory fitness, body composition, and quality of life.⁸ Weight-bearing aerobic exercise also provides repeated mechanical loading and muscle-generated forces that may influence bone remodeling.^{9,10} However, the skeletal response to exercise is not uniform and may vary according to exercise mode, intensity, duration, supervision, menopausal status, baseline bone health, and the anatomical site being assessed.^{9,10}

Previous trials have reported preservation or improvement of BMD at selected skeletal sites in women treated for breast cancer.¹¹⁻¹⁴ In contrast, systematic reviews have demonstrated variability in pooled lumbar-spine, femoral-neck, and total-hip outcomes.^{15,16} Many earlier exercise programs combined aerobic, resistance, or impact-loading components, making it difficult to isolate the specific contribution of aerobic exercise intensity.^{8,13,14} Direct

comparisons of low- and moderate-intensity aerobic exercise performed with a similar mode, frequency, and duration therefore remain limited, particularly during radiotherapy.^{11,12}

Accordingly, the present study investigated whether aerobic exercise intensity influences skeletal response when the major components of the exercise prescription are held relatively constant. The primary objective was to compare lumbar-spine (L1-L4) BMD responses to low- and moderate-intensity supervised treadmill exercise delivered during radiotherapy within the same standardized physical therapy program. Femoral-neck, total-hip, and 33% radius BMD were evaluated as additional skeletal outcomes.

SUBJECTS AND METHODS

This three-group, pre/post-treatment randomized controlled trial was conducted at Nasser Institute Hospital, Cairo, Egypt. Baseline and post-intervention DXA assessments were performed at the same center. The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of the Faculty of Physical Therapy, Cairo University, Egypt (Approval No: P.T.REC/012/003015; approved on 10 November 2020).

Participants

Sixty-six women with breast cancer undergoing radiotherapy participated in the study and were allocated equally to the Low-intensity, Moderate-intensity, and Control groups (22 participants per group). Eligible participants were women aged 40-55 years with a confirmed diagnosis of stage I-III breast cancer who were undergoing radiotherapy and had a body mass index between 18.5 and 40 kg/m². They were required to understand the study instructions, have no evidence of distant metastasis or stage IV disease, and have no uncontrolled endocrine, rheumatologic, cardiac, or vascular disorder that could interfere with exercise participation or bone metabolism. Eligibility also required sufficient functional capacity and exercise tolerance to perform treadmill walking safely, as confirmed by a pre-exercise treadmill-based six-minute walk test used for functional and safety screening, together with adequate cognitive ability to provide informed consent and follow the study instructions. Women were not eligible if they received concurrent chemotherapy during the 12-week intervention period, regularly participated in a structured exercise program outside the study, or had a musculoskeletal or neurological condition that could prevent safe treadmill walking or interfere with completion of the exercise program.

Sample Size Determination

The required sample size was calculated a priori using G*Power version 3.1.9.2. The calculation was based on a fixed-effects one-way ANOVA with three independent groups and the primary lumbar-spine BMD outcome. Assuming Cohen's $f=0.40$, $\alpha=0.05$, and statistical power of 80%, the required total sample was 66 participants, with 22 participants in each group.

Recruitment and Randomization

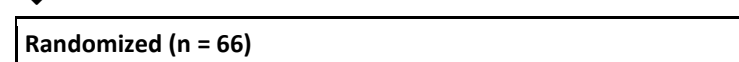
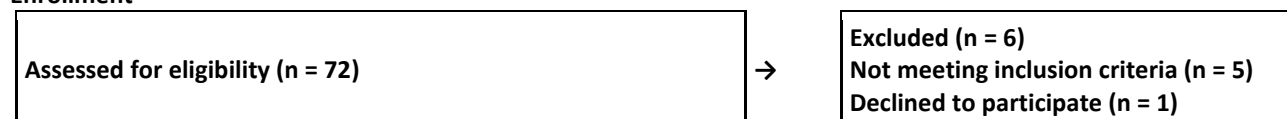
Participants were recruited from Nasser Institute Hospital and underwent baseline clinical and DXA assessment before group allocation. Randomization was stratified by menopausal status to balance premenopausal and postmenopausal participants across groups. Within each stratum, participants were randomly allocated in a 1:1:1 ratio using permuted blocks of six to the Low-intensity, Moderate-intensity, or Control group. Each group included 12 premenopausal and 10 postmenopausal women.

Participant Flow Diagram

Participant enrollment, allocation, follow-up, and analysis are summarized in Figure 1. All 66 randomized participants were included in the final analysis.

Figure 1. Participant flow Diagram.

Enrollment



Allocation

Group A - Low-intensity Allocated to intervention (n = 22)	Group B - Moderate-intensity Allocated to intervention (n = 22)	Group C - Control Allocated to control condition (n = 22)
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Follow-up

Group A Low-intensity exercise Post-intervention data available for final analysis (n = 22)	Group B Moderate-intensity exercise Post-intervention data available for final analysis (n = 22)	Group C Control Post-intervention data available for final analysis (n = 22)
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Analysis

Group A Low-intensity exercise Analyzed (n = 22)	Group B Moderate-intensity exercise Analyzed (n = 22)	Group C Control Analyzed (n = 22)
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Outcome Measures

Baseline descriptive variables included age, weight, height, body mass index, menopausal status, cancer stage, and surgery type. The primary outcome was areal BMD (g/cm²) of the lumbar spine (L1-L4); secondary skeletal outcomes were femoral-neck BMD, total-hip BMD, and 33% radius BMD. All BMD outcomes were assessed at baseline and after the 12-week intervention using the same Lunar Prodigy Primo DXA system (GE Healthcare, Madison, WI, USA; system identifier PR+351832). The same scan mode, participant positioning, acquisition protocol, analysis procedures, and region-of-interest assessment were used at both time points. Scans were reviewed for positioning, artifacts, and region-of-interest consistency before analysis.

Intervention

The intervention period lasted 12 weeks, with four supervised treatment sessions per week. All participants continued their prescribed medical treatment and received the same standardized physical therapy program (range-of-motion exercises, stretching, and strengthening exercises). The Low- and Moderate-intensity groups additionally performed supervised treadmill walking.

Group A - Low-intensity aerobic exercise: Treadmill exercise was prescribed at 35-60% of age-predicted maximum heart rate (HR_{max}=220-age).

Group B - Moderate-intensity aerobic exercise: Treadmill exercise was prescribed at 65-75% of age-predicted HR_{max}. For both exercise groups, each treadmill session consisted of a 10-minute warm-up, 30 minutes of active treadmill walking, and a 5-minute cool-down. Treadmill speed was individually adjusted to maintain the assigned heart-rate range. Progression was achieved by gradually increasing treadmill speed within the prescribed heart-rate zone while keeping the active walking duration unchanged.

Group C - Control: Participants received the standardized physical therapy program without additional aerobic treadmill exercise.

Standardized physical therapy program. The program lasted approximately 15 minutes and was applied to all three groups in the same sequence and general dosage. It consisted of approximately 5 minutes of active upper- and lower-limb range-of-motion exercises, 5 minutes of low-load sustained stretching, and 5 minutes of isometric and dynamic strengthening. Range-of-motion exercises were generally performed for approximately 5-10 repetitions. Stretching exercises were maintained for approximately 15-60 seconds per stretch. During strengthening, isometric contractions were maintained for approximately 6-10 seconds, while dynamic strengthening exercises were performed using the same standardized sequence and session duration across groups.

Physiological monitoring and safety. Heart rate was monitored continuously throughout treadmill exercise using a Polar H10 chest-strap heart-rate sensor. Peripheral oxygen saturation and pulse rate were monitored using a Granzia Pulsox 304 fingertip pulse oximeter. Participants were monitored during and after treatment sessions for adverse events, abnormal symptoms, or exercise-related intolerance. When clinically concerning symptoms occurred, the session was modified, interrupted, or discontinued as appropriate.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows, version 25.0. Continuous baseline characteristics were compared among groups using one-way ANOVA, while menopausal status, cancer stage, and surgery type were compared using the chi-square test. Assumptions for mixed-design MANOVA were evaluated using the Shapiro-Wilk test for normality, Levene's test for homogeneity of variances, Box's M test for homogeneity of covariance matrices, and examination of multivariate outliers, linearity, and multicollinearity. A mixed-design MANOVA was used to evaluate the effects of time, treatment group, and the treatment-by-time interaction across L1-L4, femoral-neck, total-hip, and 33% radius BMD. Bonferroni-corrected post-hoc comparisons were used for subsequent multiple comparisons. Percentage improvement was calculated as [(post-treatment BMD - pre-treatment BMD) / pre-treatment BMD] × 100 and was used descriptively. Statistical significance was set at p<0.05.

Informed Consent

The study procedures were explained to all participants before enrollment, and written informed consent was obtained from each participant before any study-specific assessment or intervention was performed.

RESULTS

Subject Characteristics

All 66 randomized participants were included in the final analysis, with 22 participants in each group. There were no statistically significant baseline differences among groups in age, weight, height, BMI, menopausal status, cancer stage, or surgery type (all $p>0.05$).

Table 1. Baseline characteristics of participants.

Characteristic	Low intensity (n=22)	Moderate intensity (n=22)	Control (n=22)	p value
Age (years), mean $\pm$ SD	48.95 $\pm$ 3.29	48.86 $\pm$ 2.96	49.64 $\pm$ 2.63	0.64
Weight (kg), mean $\pm$ SD	73.40 $\pm$ 12.87	74.55 $\pm$ 9.97	74.18 $\pm$ 9.16	0.94
Height (cm), mean $\pm$ SD	164.18 $\pm$ 4.75	163.77 $\pm$ 3.89	165.36 $\pm$ 4.05	0.44
BMI (kg/m ²), mean $\pm$ SD	27.36 $\pm$ 5.37	27.88 $\pm$ 4.33	27.18 $\pm$ 3.62	0.87
Premenopausal, n (%)	12 (54.5%)	12 (54.5%)	12 (54.5%)	1.00
Postmenopausal, n (%)	10 (45.5%)	10 (45.5%)	10 (45.5%)	
Cancer stage I, n (%)	6 (27.3%)	8 (36.4%)	8 (36.4%)	0.89
Cancer stage II, n (%)	9 (40.9%)	6 (27.3%)	7 (31.8%)	
Cancer stage III, n (%)	7 (31.8%)	8 (36.4%)	7 (31.8%)	
Breast-conserving surgery, n (%)	11 (50.0%)	9 (40.9%)	12 (54.5%)	0.65
Modified radical mastectomy, n (%)	11 (50.0%)	13 (59.1%)	10 (45.5%)	

SD, standard deviation; BMI, body mass index.

Effect of Treatment on BMD

Mixed-design MANOVA showed a significant treatment-by-time interaction (Wilks' $\Lambda=0.18$, $F(8,120)=20.24$, $p<0.001$, partial $\eta^2=0.57$). Significant main effects were also observed for time (Wilks' $\Lambda=0.11$, $F(4,60)=123.57$, $p<0.001$, partial $\eta^2=0.89$) and treatment (Wilks' $\Lambda=0.70$, $F(8,120)=2.91$, $p=0.005$, partial $\eta^2=0.16$).

Table 2. Multivariate effects from mixed-design MANOVA.

Effect	Wilks' Λ	F	df	p value	Partial η^2
Treatment $\times$ time	0.18	20.24	8, 120	<0.001	0.57
Time	0.11	123.57	4, 60	<0.001	0.89
Treatment	0.70	2.91	8, 120	0.005	0.16

i. Within-group Comparison

BMD increased significantly at all four measured skeletal sites in both exercise groups ($p<0.01$), whereas no significant pre-to-post change was observed in the Control group ($p>0.05$). The largest relative improvement occurred at L1-L4 in the Moderate-intensity group (10.08%).

Table 3. Pre- and post-treatment BMD within each group.

Site	Group	Pre BMD mean $\pm$ SD	Post BMD mean $\pm$ SD	MD	Change (%)	p value
L1-L4	Low	0.841 $\pm$ 0.045	0.871 $\pm$ 0.050	-0.030	3.57%	0.001
	Moderate	0.833 $\pm$ 0.039	0.917 $\pm$ 0.056	-0.084	10.08%	0.001
	Control	0.825 $\pm$ 0.056	0.839 $\pm$ 0.053	-0.014	1.70%	0.06
Femoral neck	Low	1.019 $\pm$ 0.057	1.048 $\pm$ 0.049	-0.029	2.85%	0.001
	Moderate	1.044 $\pm$ 0.061	1.112 $\pm$ 0.073	-0.068	6.51%	0.001
	Control	1.034 $\pm$ 0.053	1.043 $\pm$ 0.076	-0.009	0.87%	0.21
Total hip	Low	0.899 $\pm$ 0.045	0.928 $\pm$ 0.049	-0.029	3.23%	0.001

Site	Group	Pre BMD mean $\pm$ SD	Post BMD mean $\pm$ SD	MD	Change (%)	p value
	Moderate	0.923 $\pm$ 0.055	0.968 $\pm$ 0.051	-0.045	4.88%	0.001
	Control	0.915 $\pm$ 0.052	0.916 $\pm$ 0.056	-0.001	0.11%	0.54
33% radius	Low	0.834 $\pm$ 0.081	0.846 $\pm$ 0.085	-0.012	1.44%	0.006
	Moderate	0.841 $\pm$ 0.095	0.856 $\pm$ 0.095	-0.015	1.78%	0.001
	Control	0.834 $\pm$ 0.105	0.836 $\pm$ 0.102	-0.002	0.24%	0.64

BMD, bone mineral density (g/cm²); MD, mean difference calculated as pre-treatment minus post-treatment BMD; therefore, a negative MD indicates an increase after treatment.

ii. Between-group Comparison

Post-treatment BMD at L1-L4 was significantly higher in the Moderate-intensity group than in the Low-intensity group ($p=0.01$) and the Control group ($p=0.001$), whereas the Low-intensity and Control groups did not differ significantly ($p=0.11$). The Moderate-intensity group also had significantly higher post-treatment BMD than both other groups at the femoral neck and total hip. No significant pairwise differences were observed at the 33% radius.

Table 4. Bonferroni-corrected post-treatment pairwise comparisons.

Site	Low vs Moderate MD (95% CI)	p	Low vs Control MD (95% CI)	p	Moderate vs Control MD (95% CI)	p	Partial η^2
L1-L4	-0.046 (-0.084, -0.007)	0.01	0.032 (-0.006, 0.071)	0.11	0.078 (0.039, 0.117)	0.001	0.274
Femoral neck	-0.064 (-0.113, -0.016)	0.006	0.005 (-0.044, 0.053)	0.98	0.069 (0.020, 0.117)	0.003	0.186
Total hip	-0.040 (-0.077, -0.002)	0.03	0.012 (-0.026, 0.049)	0.74	0.052 (0.014, 0.089)	0.005	0.157
33% radius	-0.010 (-0.079, 0.058)	0.93	0.010 (-0.058, 0.078)	0.93	0.020 (-0.048, 0.089)	0.75	0.008

MD, mean difference; CI, confidence interval; η^2 , partial eta squared.

DISCUSSION

The principal finding of this randomized controlled trial was a strong treatment-by-time interaction across the four measured BMD sites, with the greatest post-treatment skeletal response in the Moderate-intensity group. Both exercise groups demonstrated significant within-group BMD increases at the lumbar spine, femoral neck, total hip, and 33% radius, whereas the Control group showed no significant change. Between groups, moderate-intensity exercise produced significantly higher post-treatment BMD than both low-intensity exercise and control at L1-L4, the femoral neck, and the total hip. In contrast, the 33% radius showed no significant between-group difference, indicating a site-specific rather than uniform skeletal response.

The lumbar-spine response is clinically relevant because the vertebral bodies contain a high proportion of metabolically active trabecular (spongy) bone, which may respond more rapidly to changes in mechanical loading and bone turnover than predominantly cortical skeletal sites.¹⁷ Weight-bearing aerobic exercise can provide repeated mechanical loading and muscle-generated forces that may influence bone remodeling. This may partly explain why the greatest relative improvement in the present study was observed at L1-L4, particularly in the Moderate-intensity group. Previous work in women receiving breast-cancer treatment has suggested that aerobic exercise can help preserve lumbar-spine BMD relative to usual care, although earlier studies did not directly compare two prescribed aerobic intensities under otherwise similar training conditions.¹¹ Moderate-intensity exercise during endocrine therapy has also shown positive effects on skeletal outcomes, supporting the possibility that a sufficiently challenging aerobic stimulus may be more effective than a lower-intensity prescription for selected skeletal outcomes.¹²

The significant findings at the femoral neck and total hip are consistent with the concept that exercise effects on bone depend on anatomical site and loading characteristics. Previous supervised, resistance, and impact exercise trials have reported preservation at selected skeletal sites, while systematic reviews have shown variation in pooled BMD effects across the lumbar spine, hip, and femoral neck.¹³⁻¹⁶ Differences in exercise mode, intensity, intervention duration, menopausal status, cancer treatment, and baseline skeletal health may contribute to this variability. The absence of a between-group effect at the 33% radius may reflect the lower direct mechanical loading of the forearm during

treadmill walking. This is consistent with the concept that skeletal adaptation is site-specific and depends on the magnitude, distribution, and direction of mechanical strain. An exercise prescription that effectively loads the axial skeleton and lower extremities may therefore not provide a comparable osteogenic stimulus at a peripheral upper-limb cortical site.^{9,10} Given that the present study included both premenopausal and postmenopausal women, clinical interpretation of DXA findings should also consider the appropriate DXA-derived index. The present study evaluated absolute areal BMD values (g/cm²) rather than T-scores or Z-scores. In postmenopausal women, a T-score of -1.0 or higher is considered normal, values between -1.0 and -2.5 indicate low bone mass (osteopenia), and values of -2.5 or lower indicate osteoporosis. In premenopausal women, Z-scores are generally preferred, with values above -2.0 considered within the expected range for age and values of -2.0 or lower considered below the expected range for age.

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From a rehabilitation perspective, the findings support the use of supervised moderate-intensity treadmill exercise at 65-75% of age-predicted HRmax within a structured physical therapy program for clinically stable women undergoing radiotherapy when supporting bone health is a rehabilitation objective. Exercise prescription should remain individualized according to clinical status, symptoms, tolerance, and safety considerations.

LIMITATIONS

The 12-week intervention period limits conclusions regarding the long-term persistence of the observed BMD changes. The study was powered for the primary lumbar-spine outcome, whereas the femoral neck, total hip, and 33% radius were secondary skeletal outcomes and were not separately powered. Participants were recruited from a limited clinical setting and were restricted to 40–55 years of age. Bone-turnover markers were not measured, and potentially influential factors such as dietary calcium and vitamin D intake, habitual physical activity, endocrine therapy, and bone-active medications were not fully controlled. Future larger multicenter studies with extended follow-up are needed to determine whether the observed BMD improvements are maintained over time and whether the response to aerobic exercise intensity differs between premenopausal and postmenopausal women.

CONCLUSION

A 12-week supervised aerobic treadmill program produced significant BMD improvements in women with breast cancer undergoing radiotherapy, with the Moderate-intensity group demonstrating the greatest post-treatment response at the lumbar spine, femoral neck, and total hip. No significant between-group effect was observed at the 33% radius. These findings support a site-specific skeletal response and suggest that moderate-intensity aerobic exercise may be a useful component of individualized rehabilitation programs aimed at supporting bone health during radiotherapy.

ACKNOWLEDGMENT

The authors would like to thank all participants who took part in this study.

DISCLOSURE STATEMENT

The authors declare no conflict of interest.

FUNDING

This study received no external funding.

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