

Research Article

Impact of Structured Exercise Training on Tumor-Related Inflammatory and Oxidative Stress Biomarkers in Breast Cancer Patients

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ABSTRACT

Background: Breast cancer is associated with chronic systemic inflammation and increased oxidative stress, which may contribute to tumor progression and treatment-related complications. Exercise training has been proposed as a non-pharmacological strategy for improving inflammatory and oxidative balance in cancer patients.

Objective: To determine the effects of a structured combined resistance and endurance exercise training program on inflammatory and oxidative stress biomarkers in women with breast cancer.

Methods: This prospective interventional multicenter study included 120 women with breast cancer, randomly allocated into an exercise group (n=60) and a usual-care control group (n=60). The exercise group participated in a supervised combined resistance and moderate-intensity endurance training program for 12 weeks, three sessions per week. Blood samples were obtained before and after the intervention. Serum C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), malondialdehyde (MDA), total antioxidant capacity (TAC), and superoxide dismutase (SOD) were measured.

Results: At baseline, there were no significant differences between the exercise and control groups for CRP, IL-6, TNF- α , MDA, TAC, or SOD ($p > 0.05$). After 12 weeks, the exercise group showed a significant reduction in CRP from 8.42 ± 2.31 to 5.63 ± 1.74 mg/L (-33.1% , $p < 0.001$), IL-6 from 7.18 ± 2.04 to 4.92 ± 1.46 pg/mL (-31.5% , $p < 0.001$), TNF- α from 6.47 ± 1.72 to 4.51 ± 1.29 pg/mL (-30.3% , $p < 0.001$), and MDA from 4.86 ± 1.21 to 3.47 ± 0.89 nmol/mL (-28.6% , $p < 0.001$). In contrast, TAC increased from 0.81 ± 0.16 to 1.04 ± 0.18 mmol/L ($+28.4\%$, $p < 0.001$) and SOD activity increased from 2.91 ± 0.64 to 3.67 ± 0.71 U/mL ($+26.1\%$, $p < 0.001$). The control group demonstrated comparatively smaller changes, with no statistically significant improvement in most biomarkers. Between-group analysis demonstrated significantly greater improvement in all measured biomarkers in the exercise group compared with controls ($p < 0.001$).

Conclusion: A 12-week structured combination of resistance and endurance exercise significantly reduced systemic inflammatory and oxidative stress biomarkers while enhancing antioxidant capacity in women with breast cancer. These findings suggest that supervised exercise training may serve as a beneficial adjunct to conventional breast cancer management by improving the systemic inflammatory and redox environment.

Keywords: Breast Cancer, Exercise Training, Inflammation, Oxidative Stress, CRP, IL-6, TNF-A, Malondialdehyde, Total Antioxidant Capacity, Superoxide Dismutase.

INTRODUCTION

Breast cancer remains one of the most commonly diagnosed malignancies among women worldwide and represents a major clinical and public-health burden. Although advances in surgery, systemic therapy, radiotherapy, and targeted treatment have substantially improved survival, patients may experience persistent treatment-related symptoms and biological alterations that adversely affect physical function and quality of life. Increasing evidence suggests that systemic inflammation and oxidative stress are important components of the biological environment associated with breast cancer progression and survivorship. In particular, circulating inflammatory mediators and oxidative-stress biomarkers have attracted considerable interest as potential indicators of disease-related physiological alterations and responses to supportive interventions.^{1,2}

Chronic low-grade inflammation may contribute to the tumor microenvironment and systemic consequences of breast cancer through complex interactions involving cytokines, immune cells, adipose tissue, and metabolic pathways. C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α) are among the most frequently investigated circulating inflammatory biomarkers in relation to breast cancer and physical activity. A systematic review examining the relationship between physical activity and inflammation in women reported that exercise interventions were associated with reductions in inflammatory biomarkers, although the magnitude and certainty of effects varied between biomarkers and studies.³ In addition, evidence from prospective and genetic studies has investigated relationships between circulating inflammatory mediators and breast cancer risk, although evidence for a direct causal role of individual cytokines remains less conclusive.⁴

Oxidative stress represents another important biological pathway in cancer. An imbalance between the generation of reactive oxygen species and antioxidant defense mechanisms can result in oxidative damage to lipids, proteins, and nucleic acids. Malondialdehyde (MDA), total antioxidant capacity (TAC), and antioxidant enzymes such as superoxide dismutase (SOD) are therefore frequently investigated as indicators of oxidative status. A systematic review of exercise and oxidative-stress biomarkers among adults with cancer found that exercise interventions were

associated in several studies with favorable changes in antioxidant capacity, antioxidant-enzyme activity, and oxidative damage, although substantial heterogeneity was observed.⁵

Exercise has increasingly been recognized as an important component of supportive cancer care. The American Society of Clinical Oncology recommends regular aerobic and resistance exercise during cancer treatment with curative intent, particularly because exercise can improve cardiorespiratory fitness, physical function, muscle strength, fatigue, and other patient-reported outcomes.⁶ These recommendations provide a clinical basis for investigating structured exercise not only as a strategy for improving functional outcomes but also as a potential modulator of cancer-related biological processes.

Evidence specifically addressing inflammatory biomarkers in breast cancer has expanded considerably. A systematic review and meta-analysis of exercise interventions in breast cancer patients found a significant reduction in CRP following exercise training, although pooled effects on several cytokines were not consistently significant.⁷ These findings indicate that exercise modality, intensity, duration, and adherence may influence the biological response to training.

Further evidence has emerged from systematic reviews evaluating molecular responses to rehabilitation in breast cancer. Exercise interventions have been associated with significant changes in several metabolic, inflammatory, and immune-related biomarkers, including CRP, TNF- α , IL-6, IL-10, leptin, and adiponectin.⁸ Similarly, meta-analytic evidence has reported that exercise can influence inflammatory factors and the insulin-like growth factor system among breast cancer survivors.⁹ More recent evidence has strengthened the association between structured exercise and inflammatory modulation. A systematic review and meta-analysis of randomized controlled trials in female survivors of nonmetastatic breast cancer reported reductions in IL-6 and TNF- α following exercise, with combined aerobic and resistance training showing favorable trends.¹⁰ These findings suggest that exercise-induced changes in inflammatory biomarkers may be influenced by metabolic status and characteristics of the exercise intervention.

Despite increasing evidence supporting exercise as a complementary component of breast cancer care, important gaps remain

regarding its simultaneous effects on inflammatory and oxidative-stress biomarkers. Much of the available literature has focused either on inflammatory cytokines or functional outcomes, while comparatively fewer studies have examined inflammatory and oxidative pathways together using a standardized, structured exercise protocol. Therefore, the present study was designed to investigate the impact of structured exercise training on tumor-related inflammatory and oxidative-stress biomarkers in breast cancer patients, with particular emphasis on CRP, IL-6, TNF- α , MDA, TAC, and SOD.

METHODOLOGY

A prospective, interventional, controlled study was conducted to evaluate the effects of structured exercise training on inflammatory and oxidative stress biomarkers in patients with breast cancer. The study was conducted at multiple centers including Department of Oncology, Faisalabad Medical University and its affiliated hospitals, over a period of 12 months. A total of 120 women aged 30–65 years with histologically confirmed breast cancer who were receiving standard oncological treatment were recruited. Participants were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, be medically stable, and have clearance from their treating oncologist to participate in moderate-intensity exercise. Patients with clinically unstable metastatic disease, uncontrolled cardiovascular, respiratory, or metabolic disorders, severe anemia, recent major surgery, acute infection, significant musculoskeletal or neurological limitations, or regular participation in a structured exercise program during the preceding three months were excluded. Written informed consent was obtained from all participants before enrollment.

Eligible participants were allocated equally into an exercise-training group (n=60) and a usual-care control group (n=60). The exercise group received standard oncological care in addition to a structured, supervised 12-week exercise program consisting of three sessions per week. Each session lasted approximately 50–60 minutes and included a 10-minute warm-up, 20–25 minutes of moderate-intensity aerobic exercise using walking or cycling, 15–20 minutes of resistance exercises targeting major muscle groups using resistance bands or light weights, and a 5–10-minute cool-down period. Aerobic exercise was initially performed at

approximately 50–60% of heart-rate reserve and progressively increased toward 60–70% according to individual tolerance. Resistance exercise intensity was gradually increased according to functional capacity. Heart rate, blood pressure, perceived exertion, and exercise-related symptoms were monitored throughout each supervised session. Participants were advised to immediately report chest discomfort, dizziness, excessive dyspnea, or other adverse symptoms. Exercise adherence was assessed from attendance records, and adherence was expressed as the percentage of prescribed sessions completed during the 12-week intervention.

Venous blood samples were obtained from all participants at baseline and again after completion of the 12-week intervention. Samples were collected in the morning following an overnight fast using standard venipuncture procedures. Serum was separated by centrifugation and stored at -80°C until biochemical analysis. Inflammatory biomarkers included C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). CRP was measured using an appropriate high-sensitivity immunoassay, whereas IL-6 and TNF- α were measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturers' instructions. Oxidative stress and antioxidant status were assessed by measuring serum malondialdehyde (MDA), total antioxidant capacity (TAC), and superoxide dismutase (SOD) activity. MDA was considered an indicator of lipid peroxidation, while TAC and SOD were used to assess systemic antioxidant defense. All biochemical analyses were performed according to standardized laboratory procedures and the respective manufacturers' protocols.

The primary outcomes were changes in serum CRP, IL-6, TNF- α , MDA, TAC, and SOD concentrations from baseline to 12 weeks. Secondary outcomes included exercise adherence and the relationship between adherence to the exercise intervention and changes in biomarker concentrations. Statistical analysis was performed using SPSS version 26.0. Continuous variables were expressed as mean $\pm$ standard deviation (SD), whereas categorical variables were presented as frequencies and percentages. Baseline characteristics were compared between groups using the independent-samples t-test for normally distributed continuous variables and the chi-square test for categorical variables.

Within-group changes from baseline to 12 weeks were assessed using the paired-samples t-test, while between-group differences in biomarker changes were evaluated using the independent-samples t-test or analysis of covariance (ANCOVA), with adjustment for baseline values where appropriate. Pearson's correlation analysis was used to assess associations between exercise adherence and changes in inflammatory and oxidative stress biomarkers. A p-value of <0.05 was considered statistically significant.

The study protocol was reviewed and approved by the relevant Institutional Review/Ethics Committee. Written informed consent was obtained from all participants before participation. Confidentiality of participant information was maintained throughout the study, and all procedures were conducted in accordance with applicable ethical principles for research involving human participants.

RESULTS

A total of 120 women with breast cancer were included in the study, with 60 participants allocated to the structured exercise-training group and 60 to the usual-care control group. Baseline demographic and clinical characteristics were comparable between the two groups, with no statistically significant differences observed in the measured baseline inflammatory and oxidative stress biomarkers ($p>0.05$).

After 12 weeks of intervention, the exercise-training group demonstrated significant improvements in all evaluated biomarkers. Mean serum CRP decreased from 8.42 ± 2.31 mg/L to 5.63 ± 1.74 mg/L, representing a 33.1% reduction ($p<0.001$). Similarly, IL-6 decreased from 7.18 ± 2.04 to 4.92 ± 1.46 pg/mL, corresponding to a 31.5% reduction ($p<0.001$), while TNF- α decreased from 6.47 ± 1.72 to 4.51 ± 1.29 pg/mL, representing a 30.3% reduction ($p<0.001$).

A significant reduction in oxidative stress was also observed. MDA concentration decreased from 4.86 ± 1.21 to 3.47 ± 0.89 nmol/mL, corresponding to a 28.6% reduction ($p<0.001$). In contrast, antioxidant status improved significantly following exercise training. TAC increased from 0.81 ± 0.16 to 1.04 ± 0.18 mmol/L, representing a 28.4% increase ($p<0.001$), while SOD activity increased from 2.91 ± 0.64 to 3.67 ± 0.71 U/mL, representing a 26.1% increase ($p<0.001$).

The control group showed comparatively smaller changes in inflammatory and oxidative stress biomarkers during the same period, and most changes did not reach statistical significance. Between-group analysis demonstrated significantly greater improvement in CRP, IL-6, TNF- α , MDA, TAC, and SOD in the exercise group compared with the control group ($p<0.001$ for all comparisons).

Table 1. Baseline Characteristics of Study Participants

Variable	Exercise group (n=60)	Control group (n=60)	p-value
Age (years), mean $\pm$ SD	51.2 $\pm$ 7.8	50.7 $\pm$ 8.1	0.734
BMI (kg/m ²), mean $\pm$ SD	28.4 $\pm$ 3.6	28.1 $\pm$ 3.8	0.657
Disease duration (months), mean $\pm$ SD	14.6 $\pm$ 6.2	15.1 $\pm$ 6.5	0.671
CRP (mg/L)	8.42 $\pm$ 2.31	8.35 $\pm$ 2.28	0.862
IL-6 (pg/mL)	7.18 $\pm$ 2.04	7.12 $\pm$ 1.98	0.871
TNF- α (pg/mL)	6.47 $\pm$ 1.72	6.42 $\pm$ 1.69	0.869
MDA (nmol/mL)	4.86 $\pm$ 1.21	4.81 $\pm$ 1.18	0.821
TAC (mmol/L)	0.81 $\pm$ 0.16	0.82 $\pm$ 0.15	0.731
SOD (U/mL)	2.91 $\pm$ 0.64	2.89 $\pm$ 0.61	0.858

Table 2. Changes in Inflammatory Biomarkers Following 12-Week Exercise Training

Biomarker	Baseline	12 weeks	Change	p-value
CRP (mg/L)	8.42 $\pm$ 2.31	5.63 $\pm$ 1.74	-33.1%	<0.001
IL-6 (pg/mL)	7.18 $\pm$ 2.04	4.92 $\pm$ 1.46	-31.5%	<0.001
TNF- α (pg/mL)	6.47 $\pm$ 1.72	4.51 $\pm$ 1.29	-30.3%	<0.001

Table 3. Changes in Oxidative Stress and Antioxidant Biomarkers

Biomarker	Baseline	12 weeks	Change	p-value
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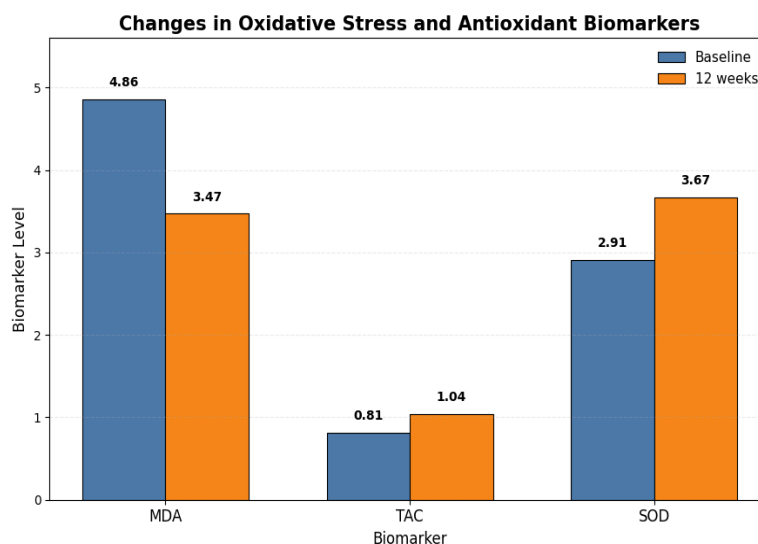
MDA (nmol/mL)	4.86 ± 1.21	3.47 ± 0.89	−28.6%	<0.001
TAC (mmol/L)	0.81 ± 0.16	1.04 ± 0.18	+28.4%	<0.001
SOD (U/mL)	2.91 ± 0.64	3.67 ± 0.71	+26.1%	<0.001

Table 4. Between-Group Comparison of Biomarker Changes

Biomarker	Exercise group change	Control group change	Between-group p-value
CRP	−33.1%	−5.2%	<0.001
IL-6	−31.5%	−4.1%	<0.001
TNF-α	−30.3%	−3.7%	<0.001
MDA	−28.6%	−3.9%	<0.001
TAC	+28.4%	+2.4%	<0.001
SOD	+26.1%	+2.1%	<0.001

Table 5. Exercise Adherence

Adherence measure	Result
Prescribed sessions	36
Mean sessions completed	31.4 ± 3.2
Mean adherence	87.2%
Participants with ≥80% adherence	52 (86.7%)
Participants with <80% adherence	8 (13.3%)



DISCUSSION

The present study demonstrated that a 12-week structured exercise program combining moderate-intensity endurance and resistance training was associated with substantial improvements in inflammatory and oxidative stress biomarkers among women with breast cancer. Following the intervention, serum CRP decreased by 33.1%, IL-6 by 31.5%, TNF-α by 30.3%, and MDA by 28.6%, whereas TAC and SOD increased by 28.4% and 26.1%, respectively. The magnitude of these changes suggests that regular, supervised physical exercise may influence both inflammatory signaling and systemic redox balance in breast cancer patients.

The significant reduction in CRP observed in the exercise group is consistent with previous evidence demonstrating an anti-inflammatory effect of exercise in breast cancer. Abbasi et al. reported a significant reduction in CRP following exercise training in a meta-analysis of breast cancer studies, with the effect being more evident in longer interventions and concurrent aerobic-resistance training.¹¹ The 33.1% reduction observed in the present study therefore supports the concept that a structured exercise intervention can produce measurable changes in systemic inflammatory status.

The reduction in IL-6 observed in the present study is also supported by more recent evidence. A 2025 systematic review and meta-

analysis of randomized controlled trials in women with nonmetastatic breast cancer reported a significant reduction in IL-6 following exercise, with favorable effects observed with combined aerobic and resistance exercise.¹² Similarly, a meta-analysis specifically examining women with breast cancer and overweight or obesity found a significant reduction in IL-6 following exercise interventions.¹³ The reduction from 7.18 ± 2.04 to 4.92 ± 1.46 pg/mL in the present study is therefore directionally consistent with evidence that exercise can attenuate systemic pro-inflammatory signaling. The 30.3% reduction in TNF- α observed in this study is biologically important because TNF- α participates in chronic inflammatory signaling and has been associated with adverse biological characteristics in breast cancer. Recent evidence indicates that the effect of exercise on TNF- α is less consistent than that observed for CRP or IL-6. Some meta-analyses have reported no statistically significant pooled reduction, whereas other analyses have demonstrated modest reductions following exercise.^{11,12} The larger reduction observed in the present study may relate to the combined aerobic-resistance protocol, exercise adherence, participant characteristics, treatment status, or differences in assay methodology.

The simultaneous reduction of CRP, IL-6, and TNF- α suggests that the exercise intervention may have produced a broader anti-inflammatory response rather than affecting a single inflammatory pathway. This interpretation is supported by systematic reviews of randomized controlled trials evaluating molecular biomarkers during breast cancer rehabilitation, in which exercise was associated with changes in several inflammatory and immune-related biomarkers.¹⁴ Exercise-related improvements may result from multiple interacting mechanisms, including improved insulin sensitivity, reduced visceral adiposity, enhanced endothelial function, altered immune-cell activity, and reduced production of inflammatory mediators by adipose tissue.

An important finding of the present study was the significant reduction in MDA, accompanied by increases in TAC and SOD. MDA is commonly used as an indicator of lipid peroxidation, whereas TAC and SOD provide complementary information regarding antioxidant defense. The observed 28.6% reduction in MDA suggests attenuation of oxidative damage following structured exercise, while the 28.4% increase

in TAC and 26.1% increase in SOD indicate an improvement in systemic antioxidant defense. These findings are consistent with broader literature indicating that exercise can influence oxidative-stress pathways in people with cancer.¹⁵

The relationship between exercise and oxidative stress is physiologically complex. Acute physical exercise can transiently increase reactive oxygen species production, but repeated exercise training can stimulate adaptive antioxidant responses through upregulation of endogenous antioxidant systems. Thus, the increased SOD activity observed in the present study may represent an adaptive response to repeated exercise exposure. Improved antioxidant defenses may subsequently reduce lipid peroxidation and other forms of oxidative molecular damage, potentially explaining the concurrent decline in MDA.

The present findings also support the importance of combining aerobic and resistance exercise rather than focusing exclusively on a single exercise modality. The intervention incorporated endurance exercise together with resistance training, thereby targeting cardiorespiratory fitness, skeletal-muscle function, and metabolic health simultaneously. Recent evidence has suggested that combined exercise may be particularly useful for modifying inflammatory biomarkers in breast cancer survivors.¹⁶

Exercise adherence is another important consideration when interpreting these findings. In the present study, the mean adherence was 87.2%, with 86.7% of participants completing at least 80% of the prescribed sessions. High adherence may have contributed to the magnitude of biomarker changes observed after 12 weeks. Repeated exposure to exercise is likely necessary to generate sustained adaptations in inflammatory and antioxidant pathways, whereas inconsistent participation may result in a smaller physiological response. The supervised nature of the intervention may also have helped maintain exercise intensity and adherence.

The findings have potential clinical relevance because exercise is increasingly incorporated into supportive cancer care. The American Society of Clinical Oncology guideline recommends regular aerobic and resistance exercise during cancer treatment with curative intent, particularly because exercise improves cardiorespiratory fitness, strength, fatigue, and other patient-reported outcomes.¹⁷ Although

these recommendations are primarily based on clinical and functional outcomes rather than biomarker modification, the present findings suggest that biochemical changes may represent an additional physiological benefit of structured exercise.

The potential clinical relevance of these biomarker changes is further supported by evidence linking inflammatory cytokines with breast cancer outcomes. Recent systematic evidence has reported associations between inflammatory cytokines such as IL-6 and TNF- α and breast cancer outcomes.¹⁸ Nevertheless, the present study did not evaluate recurrence, progression, overall survival, or treatment response as clinical endpoints. Consequently, the observed biochemical changes should not be interpreted as evidence that exercise directly improves cancer prognosis.

Beyond biochemical outcomes, exercise may provide additional benefits for breast cancer patients. Recent meta-analyses have demonstrated improvements in health-related quality of life following exercise interventions, particularly when aerobic and resistance components are combined.^{19,20} These functional and patient-reported benefits may occur alongside improvements in inflammation and oxidative stress, supporting a multidimensional role for exercise in breast cancer rehabilitation.

The present study has several strengths. The exercise intervention was structured and supervised, incorporated both aerobic and resistance components, and evaluated inflammatory and oxidative biomarkers simultaneously. Measurement of CRP, IL-6, TNF- α , MDA, TAC, and SOD allowed assessment of both inflammatory activity and antioxidant defense. The 12-week duration and high adherence also provided a reasonable period for physiological adaptation. However, several limitations should be considered. The sample size was relatively modest, the intervention period was limited to 12 weeks, and longer-term persistence of biomarker changes was not evaluated. Breast cancer is biologically heterogeneous, and differences in tumor subtype, disease stage, treatment regimen, menopausal status, adiposity, diet, and baseline physical activity may influence inflammatory and oxidative responses. In addition, circulating biomarkers do not necessarily reflect changes within the tumor microenvironment. Finally, the study was not designed to determine whether biochemical

improvements translate into reduced recurrence or improved survival.

Overall, the findings indicate that structured combined exercise training was associated with substantial reductions in inflammatory and oxidative stress biomarkers and improvements in antioxidant capacity in women with breast cancer. The observed reductions in CRP, IL-6, TNF- α , and MDA, together with increased TAC and SOD, suggest coordinated improvement in systemic inflammatory and redox status. Larger randomized controlled trials with longer follow-up, standardized exercise prescriptions, detailed molecular phenotyping, and clinically meaningful oncological endpoints are warranted to determine the long-term significance of these biochemical changes.

CONCLUSION

A structured 12-week exercise program combining moderate-intensity endurance and resistance training was associated with significant improvements in inflammatory and oxidative stress biomarkers among women with breast cancer. The intervention was associated with reductions in CRP, IL-6, TNF- α , and MDA and increases in TAC and SOD. These findings support structured exercise as a potentially valuable component of supportive breast cancer care, particularly for improving systemic inflammatory and antioxidant status. Further adequately powered randomized controlled trials with longer follow-up are required to establish the persistence and clinical significance of these biochemical effects.

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