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Research Article

Effect of Six Months of Aerobic Exercise on Plasma Interleukin-6 and Tumor Necrosis Factor-Alpha as Breast Cancer Risk Factors in Postmenopausal Women: A Randomized Controlled Trial

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Abstract

Background: Increased physical activity is associated with a reduction in the risk of breast cancer; however, the exact mechanism of the reduction is not yet completely known.
Objectives: This study aimed to investigate the effect of six months of aerobic exercise on the plasma interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α) levels as breast cancer risk factors in postmenopausal women.
Patients and Methods: This study was a randomized controlled trial. We randomly assigned 41 postmenopausal, sedentary women aged 50 to 74 to either an exercise or a control group. The intervention involved facility-based aerobic exercise (three days/week, at 70 - 80% of the maximum heart rate, for six months).
Results: Twenty-seven women completed the study. The plasma IL-6 level decreased by 21.3% in the exercisers and by 6.9% in the controls, and the intervention effect was significant (P = 0.001). The plasma TNF-α level decreased by 17.1% and 10.8% in the exercisers and controls, respectively, although the effect of exercise was not statistically significant (P = 0.28). Overall, long-term aerobic exercise may result in a decreased IL-6 concentration.
Conclusions: We suggest that regular aerobic exercise can favorably alter the inflammatory profile, which is a known risk factor in breast cancer development, in postmenopausal women.

Keywords: Aerobic Exercise, Breast Cancer, Inflammation, Postmenopausal Women

1. Background

Breast cancer is the second most common cancer worldwide and it is by far the most frequent malignancy among women in both more and less developed regions, with an estimated 1.67 million new breast cancer cases (25% of all cancers) being diagnosed in 2012 (1). In its recent guidelines, the world health organization (WHO) emphasized the significant role of physical activity in reducing the incidence of some types of cancer, including breast cancer (2). Physical inactivity is one of the few behavioral risk factors amenable to change and as such it represents an opportunity to reduce the burden of disease stemming from breast cancer (3). Additionally, epidemiologic evidence suggests that increased physical activity is associated with a reduction in the risk of breast cancer (3-7). However, the available evidence is more robust for postmenopausal women than for premenopausal women (3, 8). A multitude of mechanisms have been proposed for the breast cancer-reducing effects of physical activity, although none have yet been completely understood. The presumed mechanisms include: body weight or composition, circulating hormones, oxidative stress, insulin resistance pathway, inflammation, and immune function (9-11).

Adipokines are biologically active polypeptides produced by adipocytes, of which tumor necrosis factor-alpha (TNF-α) and plasma interleukin (IL)-6 are considered to be markers of inflammation (12, 13). Chronic inflammation has been proposed to be involved in the development of some kinds of cancer, including breast cancer, and it may predispose an individual to cancer (14). Increased levels of pro-inflammatory factors such as TNF-α and IL-6 have hence been associated with an increased risk of breast cancer (15, 16). One way in which these cytokines could potentially promote breast cancer is their involvement in the increased production of aromatase, which in turn leads to the increased synthesis of estrogen (17).

Physical activity might reduce systemic inflammation, either alone or in combination with body weight, through the decreased production of macrophage or adipocyte pro-inflammatory cytokines (10). Indeed, cross-sectional studies support the link between long-term physical activity and reduced levels of inflammatory markers (18, 19). However, interventional studies have reported decreases in these markers in some (20, 21), but not all (22), of the implemented interventions. In general, the mechanisms through which physical activity is linked to breast cancer are quite complicated (10). While the mechanisms for how physical activity affects the risk of breast cancer in postmenopausal women are not yet well understood, a few randomized controlled trials (RCTs) have investigated the effect of physical activity on the presumed biomarkers of breast cancer. The necessity of conducting long-term RCTs to study the effects of physical activity on the potential biomarkers of breast cancer has been asserted frequently (8, 23, 24).

2. Objectives

The present study aimed to investigate the effect of a six-month supervised aerobic training program on the plasma IL-6 and TNF-α concentrations in postmenopausal women.

3. Patients and Methods

This study was a randomized controlled trial intended to investigate the effect of six months of aerobic exercise training on the blood TNF-α and IL-6 concentrations in postmenopausal women at baseline and after six months. We conducted the study in Qazvin, Iran, from 2012 to 2014. Prior to the initiation of the study, written informed consent was obtained from all participants. All of the study procedures were approved by the research ethics committee of the breast cancer research center, ACER. The estimation of sample size was based on a presumed effect size of ~ 0.8 for TNF-α and ~ 0.9 for IL-6 (25, 26), a statistical power of 80%, and a type I error of 5%, which yielded 19 subjects per group.

3.1. Participants

The subjects were recruited from the families of Qazvin Islamic Azad University's staff and students. All of the participants were interviewed and their height, weight, and BMI were measured. Only those participants who met the following criteria were included in the study: A, aged 50 to 74, B, sedentary (i.e., taking exercise for no more than 90 minutes per week), C, postmenopausal (i.e., having had no menses over the past year), D, a BMI between 22 and 40 kg.m^{-2}, E, no hormone therapy during the past six months, F, no co-morbidities such as diabetes or cardiovascular diseases, G, no cancer history, and H, an acceptable level of physical fitness as determined via the modified Balke treadmill test. After preliminary screening, we had identified 41 eligible subjects who were then randomly assigned to either the control or exercise groups. The participants visited Qazvin championship headquarters at baseline and after six months.

3.2. Exercise Intervention

The participants in the intervention group engaged in aerobic exercise three days/week for six months. Each session consisted of at least 50 minutes exercise at 70 - 80% of the maximum heart rate (HRmax). The exercise intervention was fully supervised by certified exercise trainers. The participants wore a heart rate monitor (Polar FT2) to ensure that the exercise sessions were conducted in the target heart rate zone. The exercise sessions started with 15 to 20 minutes at 45 - 50% HRmax, before gradually increasing in intensity and duration until the 8th week, and then maintaining this level. Exercise adherence was monitored through exercise logs verified by the exercise trainers. The logs were reviewed weekly by the study staff. The control participants were asked to not change their physical activity levels for the duration of the trial. All of the participants were asked to maintain their usual diet.

3.3. Outcomes and Measurements

The plasma concentrations of IL-6 and TNF-α, participants' aerobic fitness, and the anthropometric measures were assessed at baseline and after six months. Participants' socio-demographic information, level of physical activity, reproductive factors, and medical history were assessed by an interview at baseline only. Participants' blood pressure and fasting blood glucose were also measured at baseline only.

Blood samples were taken between 07:00 and 10:00 after a 12 hours fast. The participants were in a seated position. The participants were instructed to refrain from exercise for at least 48 hours prior to blood collection. The plasma concentrations of IL-6 and TNF-α were assessed using ELISA kits (Bioassay Technology Laboratory, China). The blood samples were processed within one hour of collection and then stored at -70°C. Participants' aerobic fitness (i.e., maximal oxygen uptake) was measured via the modified Balke treadmill test (27). We measured the participants' body weight to the nearest 0.1 kg and their height to the nearest 0.1 cm in order to compute their body mass index (BMI). We estimated the participants' body fat percentage through skinfold thickness as measured by a skinfold caliper.

3.4. Statistical Analysis

The Kolmogorov-Smirnov test was used to determine whether the data sets were normally distributed. As our data were normally distributed, in the primary analysis we used the independent-samples t-test to compare the mean percentage changes between the exercisers and the controls in spite of the relatively small sample size. We used an intention-to-treat analysis in which the investigation into the intervention effect is based on the allocation at the time of randomization regardless of adherence or compliance status. In the secondary analyses, we divided the exercisers into two subgroups according to their exercise adherence, changes in BMI, body fat, and aerobic fitness. Then, we compared these subgroups with the controls using the Mann-Whitney and Kruskal-Wallis tests. All of the analyses were conducted using IBM SPSS Statistics, version 22, and the significance level was set at 5%.

4. Results

The study included 41 women (19 controls and 22 in the exercise group) at baseline and 27 women at six months (14 controls and 13 in the exercise group). There were no significant differences between the intervention and control groups in terms of the baseline characteristics (Table 1). The average age and BMI of the participants were 54.5 $\pm$ 5.8 and 27.9 $\pm$ 3.2, respectively. The average body fat percentage of the participants was 41.9 $\pm$ 4.8, indicating that they were obese. Their average aerobic fitness was 23.1 $\pm$ 8.1, which was below average.

The average adherence to exercise was 99 min/week (the goal was 150 min/week). Aerobic fitness increased by 17.1% in the intervention group, while it decreased by 4.6% in the control group from baseline to the 6th month ($P = 0.001$). The percentage of body fat decreased by 2.1% and 0.4% in the intervention and control group, respectively ($P = 0.08$). The BMI decreased by 1.2% in the exercise group, while it increased by 1.4% in the control group ($P = 0.004$). The plasma IL-6 level decreased by 21.3% in the exercisers and by 6.9% in the controls, and the intervention effect was statistically significant ($P = 0.001$). The plasma TNF-α level also decreased by 17.1% and 10.8% in the exercisers and controls, respectively, although the exercise effect was not statistically significant ($P = 0.28$) (Table 2).

In the secondary analyses, we divided the exercisers into two subgroups according to changes in several factors, including their body fat percentage, BMI, adherence to exercise, and aerobic fitness, in order to further investigate the modification effects of these factors. In the IL-6 analyses, we found a statistically significant difference between both of the subgroups and the controls (Table 3). The secondary analyses of the TNF-α changes failed to reveal a significant difference between the exercise subgroups and the controls (Table 4). However, the exercisers who had lost more body fat exhibited greater decreases in BMI and they gained more aerobic fitness when compared with the other subgroups. They also displayed greater decreases in the TNF-α concentration.

5. Discussion

We administered a fully supervised exercise intervention to investigate the effect of aerobic exercise on the plasma concentration of IL-6 and TNF-α. After the six-month exercise intervention, the IL-6 level decreased more in the exercise group when compared with the control group. Additionally, BMI decreased and aerobic fitness increased in the exercisers. In the subgroup analyses, we observed that the IL-6 percentage changes exhibited significant differences in all the exercise subgroups when compared with the controls over six months. On the other hand, the subgroup analyses of the TNF-α level failed to show any significant differences between the exercise subgroups and the controls. Therefore, it could be suggested that these factors do not have any modifying effect on the IL-6 and TNF-α levels.

Recent evidence has suggested that regular physical exercise may induce an anti-inflammatory state in the human body. In the present study, we found that women who engaged in regular aerobic exercise exhibited improvements in the inflammatory profile. However, it is unclear why the exercise-induced changes in the TNF-α levels were not significant. Similarly, Kohut et al. (28) found that ten months of aerobic training was associated with a significant reduction in IL-6 levels, but not in TNF-α levels, in older adults. One possible explanation for this might be related to the amount of fat loss required to elicit significant changes in the TNF-α concentration. In line with our findings, Kern et al. (29) observed that both IL-6 and TNF-α were overexpressed in adipose tissue; however, in contrast to the circulating levels of TNF-α, the plasma IL-6 had a strong relationship with obesity. Thus, they suggested that the local expression of TNF-α and the plasma concentrations of IL-6 are higher in obese persons. Based on Kern et al.'s study (29), we can speculate that the exercise intervention favorably altered TNF-α expression, although significant changes required greater body fat loss than we observed in our study. It should be noted that in some similar RCTs, non-significant changes in the IL-6 level were reported (25, 30, 31), Thus, further studies are required to investigate local changes in TNF-α and IL-6 in postmenopausal women.

Our exercise intervention was fully supervised so as to accurately monitor the exercise intervention parameters. We considered strict inclusion criteria, such as being postmenopausal and sedentary, in order to homogenize the study population; hence, the results may not be generalized to other subgroups. Our study does have some limita-

Table 1. Baseline Characteristics of the Participants[a]

Characteristics	Exercise Group	Control Group	P Value
N	22	19	
Age, y	58.8 ± 6.4	55.3 ± 5.2	0.29
Weight, kg	71.2 ± 9.8	65.7 ± 6.1	0.08
Percentage of body fat	42.5 ± 2.4	40.1 ± 4.3	0.84
BMI, kg.m^{-2}	28.2 ± 3.4	29.9 ± 2.3	0.09
FBS, mg.dL^{-1}	101.2 ± 12.1	101.52 ± 10.1	0.72
Systolic blood pressure, mmHg	119.3 ± 17.6	110.52 ± 16.4	0.56
Diastolic blood pressure, mmHg	77.72 ± 8.6	73.15 ± 10.5	0.55
Maximal oxygen consumption, ml.kg^{-1}.min^{-1}	25.2 ± 8.7	21.5 ± 7.4	0.77
TNF-α, ng.L^{-1}	23.1 ± 5.3	23.3 ± 3.7	0.09
IL-6, ng.L^{-1}	48.6 ± 7.7	53.1 ± 9.3	0.48
Education, No. (%)			
Illiterate	2 (10)	8 (42)	0.09
High school	14 (63)	8 (42)	
Collegiate	6 (27)	3 (16)	
Employment, No. (%)			
Housewife	21 (95)	19 (100)	0.38
Employed	1 (5)	0 (0)	
Marital status, No. (%)			
Married	22 (100)	18 (95)	0.40
Never married	0 (0)	1 (5)	
Marriage age, No. (%)			
< 15 y	5 (22)	5 (27)	0.47
15 - 20 y	9 (40)	12 (64)	
> 20 y	8 (37)	1 (10)	

Abbreviations: BMI, Body Mass Index; FBS, Fasting Blood Sugar; IL-6, Interleukin-6; TNF-α Tumor Necrosis Factor-Alpha.
[a]Values are expressed as mean ± SD unless otherwise indicated.

tions. First, the sample size was relatively small and therefore the results should be interpreted with caution. Second, it was difficult to monitor the participants' diet over the trial period. We only investigated some inflammatory factors in the blood, although there are other candidate inflammatory factors related to exercise and breast cancer. Thus, future studies should consider other inflammatory factors as well as the gene expression of these biomarkers.

In conclusion, our findings suggest that long-term aerobic exercise may result in a decreased IL-6 concentration. Overall, we suggest that regular aerobic exercise can favorably alter the inflammatory profile, which is a risk factor in breast cancer development, in postmenopausal women.

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Footnotes

Authors' Contribution: Study concept and design: Azam Abdollahpour and Nasim Khosravi, acquisition of data: Azam Abdollahpour, Nasim Khosravi, and Zohreh Eskandari, analysis and interpretation of data: Nasim Khosravi and Shahpar Haghighat, drafting of the manuscript: Azam Abdollahpour, Nasim Khosravi, and Shahpar Haghighat, critical revision of the manuscript for important intellectual content: Azam Abdollahpour, Nasim Khosravi, Shahpar Haghight, and Zohreh Eskandari, statistical analysis: Nasim Khosravi and Shahpar Haghighat, administrative, technical, and material support: Azam Abdollahpour, Nasim Khosravi, Shahpar Haghighat, and Zohreh Eskandari, study supervision: Azam Abdollahpour.

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Table 2. Difference Between the Exercise and Control Groups in Terms of the Plasma Concentration of IL-6 and TNF-α at Baseline and After Six Months

Variable	Baseline (Mean ± SD)	Six Months (Mean ± SD)	Percentage Changes (%)	P Value
IL-6, ng.L^{-1}				
Exercisers	48.6 ± 7.7	38.1 ± 6.1	-21.3	
Controls	53.1 ± 9.3	49.3 ± 11.1	-6.9	0.001[a]
TNF-α, ng.L^{-1}				
Exercisers	23.1 ± 5.3	18.4 ± 2.1	-17.1	
Controls	23.3 ± 3.7	20.6 ± 3.1	-10.8	0.28
BMI				
Exercisers	28.9 ± 3.3	28.5 ± 3.2	-1.2	
Controls	27.2 ± 2.4	27.3 ± 2.4	+1.4	0.004[a]
Percentage of body fat				
Exercisers	42.5 ± 2.4	41.7 ± 3.1	-2.1	
Controls	40.1 ± 4.3	39.8 ± 2.4	-0.4	0.08
Fitness				
Exercisers	24.7 ± 6.1	28.6 ± 6.7	+17.1	
Controls	21.4 ± 4.5	20.3 ± 5.3	-4.6	0.001[a]

Abbreviations: BMI, Body Mass Index; IL-6, Interleukin-6; TNF-α Tumor Necrosis Factor-Alpha.
[a] Statistically significant difference.

Table 3. Difference Between the Exercise Subgroups and the Control Group in Terms of the Plasma Concentration of IL-6 (ng.L^{-1})[a]

	N	Baseline (Mean ± SD)	Six Month (Mean ± SD)	Percentage Change (%)	P Value	
					Mann-Whitney Test	Kruskal-Wallis
Controls	14	53.1 ± 9.3	49.3 ± 11.1	-6.9	Ref.	
Exercisers subgroups						
Change in aerobic fitness						
Gained ≤ 15% aerobic fitness	7	52.7 ± 7.2	40.6 ± 5.9	-22.9	0.002[a]	0.001[a]
Gained > 15% aerobic fitness	6	43.7 ± 5.2	35.2 ± 5.2	-19.5	0.004[a]	
Change in BMI						
BMI decreased < 1%	5	47.2 ± 6.05	38.6 ± 5.9	-18.5	0.01[a]	0.001[a]
BMI decreased ≥ 1%	8	49.7 ± 9.2	37.7 ± 6.6	-23.5	0.00[a]	
Change in body fat percentage						
Body fat decreased < 2%	5	49.4 ± 7.6	37.8 ± 6.4	-23.3	0.004[a]	0.001[a]
Body fat decreased ≥ 2%	8	48.1 ± 8.2	38.3 ± 6.2	-20.1	0.002[a]	
Exercise adherence						
Adherence < 100 min/week	7	45.1 ± 6.6	35.8 ± 4.8	-20.2	0.003[a]	0.001[a]
Adherence > 100 min/week	6	52.8 ± 7.1	40.8 ± 6.6	-22.7	0.003[a]	

Abbreviations: BMI, Body Mass Index; IL-6, Interleukin-6.
[a] Statistically significant difference.

Table 4. Difference Between the Exercise Subgroups and the Control Group in Terms of the Plasma Concentration of TNF-α (ng.L^{-1})[a]

	N	Baseline (Mean $\pm$ SD)	Six Month (Mean $\pm$ SD)	Percentage Change (%)	P Value	
					Mann-Whitney test	Kruskal-Wallis
Controls	14	23.3 $\pm$ 3.7	20.6 $\pm$ 3.1	-10.8	Ref.	
Exercisers subgroups						
Change in aerobic fitness						
Gained $\leq$ 15% aerobic fitness	7	21.6 $\pm$ 3.3	19.05 $\pm$ 1.3	-9.9	1.0	0.27
Gained > 15% aerobic fitness	6	24.8 $\pm$ 6.9	17.6 $\pm$ 2.7	-25.6	0.07	
Change in BMI						
BMI decreased < 1%	5	21.01 $\pm$ 1.1	19.1 $\pm$ 1.3	-8.7	0.93	0.27
BMI decreased $\geq$ 1%	8	24.9 $\pm$ 6.9	17.8 $\pm$ 2.6	-24	0.86	
Change in body fat percentage						
Body fat decreased < 2%	5	20.1 $\pm$ 1.4	19.2 $\pm$ 1.5	-4.1	0.35	0.27
Body fat decreased $\geq$ 2%	8	25.1 $\pm$ 6.1	17.9 $\pm$ 2.4	-25.3	0.29	
Exercise adherence						
Adherence < 100 min/week	7	25.1 $\pm$ 6.6	18.2 $\pm$ 2.8	-23.5	0.13	0.27
Adherence > 100 min/week	6	20.7 $\pm$ 2.03	18.5 $\pm$ 1.2	-9.7	0.86	

Abbreviations: BMI, Body Mass Index; TNF-α, Tumor Necrosis Factor-Alpha.
[a] Statistically significant difference.

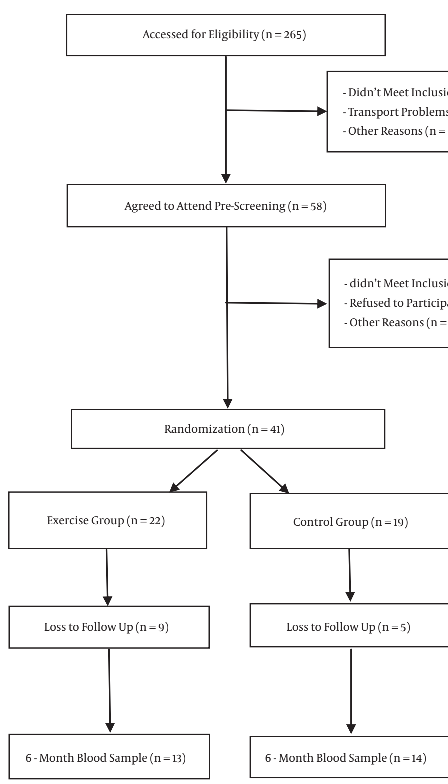

Figure 1. Study Procedure.

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