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Research Article

The Effect of Exercise Type on Inflammatory Markers in Obese Survivors With Breast Cancer: Randomized Control Trial

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Abstract

Background: Breast cancer is the most common cancer diagnosed in women throughout the world and the leading cause of cancer-related deaths in women

Objectives: The current study aimed to investigate the effect of eight weeks of training on IL-6, TNF-α and hCRP in postmenopausal breast cancer survivors.

Patients and Methods: Twenty-seven postmenopausal breast cancer survivors with mean age of 44.1 ± 4.6, mean height of 158 ± 5.9 cm and mean Body Mass Index (BMI) of 30.2 ± 3.2 kg/m^2, were randomly divided to three groups; continuous, interval and the control groups. Inflammatory markers, anthropometric variables and VO_2 peak were measured before and after the eight weeks. Statistical analysis of the data was carried out using the Kruskal-Wallis and Wilcoxon test at a significance level of $P < 0.05$.

Results: The anthropometric variables, body fat percentage and adipose tissue reduced significantly in both exercise groups ($P < 0.05$), and the difference between the two groups was not significant in terms of this reduction. No significant changes were observed in the control group ($P > 0.05$). The human C-Reactive Protein (hCRP) levels showed a significant reduction in the continuous group ($P = 0.015$), and the reductions in Tumor Necrosis Factor alpha (TNF-α) and Interleukin6 (IL-6) were also greater in this group than in the other two groups. No significant differences were observed between the two exercise groups in their inflammatory markers.

Conclusions: Exercise can improve anthropometric variables, body composition and VO_2 peak and reduce some inflammatory markers in breast cancer survivors.

Keywords: Training, Inflammatory Markers, Breast Cancer

1. Background

Breast cancer is the most common cancer diagnosed in women throughout the world and the leading cause of cancer-related deaths in women. In 2012, the American cancer society reported 1.7 million cases of breast cancer and 521 900 cases of breast cancer-related death across the world (1). A number of inflammatory markers including Interleukin6 (IL-6), tumor necrosis factor alpha (TNF-α) and C-reactive protein (CRP) increase in breast cancer as well as in several other types of cancers (2-4). Increased CRP is associated with a risk of death and heart disease in patients with breast cancer (5-7). Tumor Necrosis Factor alpha is one of the main cytokines secreted from the adipose tissue that increases the concentration of pro-inflammatory cytokines (CRP and IL-6); as a growth factor, it can induce tumor growth and cancer metastasis (8, 9). The IL-6 expression in breast tissue is associated with the grade of the tumor (10, 11). Previous studies have shown that, compared to healthy women, breast cancer survivors have higher amounts of circulating cytokines, a disorder that may persist for up to five years after the diagnosis of cancer (12). Obesity, being overweight and inactivity are among factors that cause mild chronic inflammation and can increase the risk of cardiovascular diseases, breast cancer recurrence and death in breast cancer survivors. This risk factor is further highlighted by the fact that the majority of breast cancer survivors are overweight or obese. The combination of being overweight and inactive has been attributed to a quarter of all the cases of cancer (12-14).

2. Objectives

Despite all the studies conducted to date, the question that remains is which type of exercise can affect inflammatory markers in postmenopausal breast cancer survivors, and requires further investigations. The present study was therefore conducted to assess the effect of eight weeks of continuous and interval treadmill exercise on IL-6, TNF-α and hCRP in breast cancer survivors.

3. Patients and Methods

A total of 31 women aged 30 to 50 years, with stage I-III breast cancer and a body mass index of above 25 kg/m^2, who had undergone surgery, radiotherapy and or chemotherapy, from whose course of treatment, a minimum of six months had passed, and who were not postmenopausal at the time of diagnosis but had become postmenopausal with the treatments and were thus undergoing hormone therapy with Tamoxifen and/or Letrozole, participated in the study, voluntarily. These women had not performed regular physical activity before entering the study. Women with a history of metastasis, cardiovascular diseases and diabetes were excluded from the study. According to the inclusion criteria and accessibility to different patients, we could not determine the right sample size. Thus, based on accessibility and previous studies, 27 patients voluntarily participated in the research. The study type, objectives, and methods were then verbally explained to the participants (aged 44.1 $\pm$ 4.6, with a height of 158 $\pm$ 5.9 cm and a BMI of 30.2 $\pm$ 3.2 kg/m^2). Next, anthropometric variables, treatment history, inflammatory markers and VO_2 peak were measured as the pretest and all of them filled out the physical activity readiness questionnaire (PAR-Q) and consent forms. After this step, the patients that voluntarily participated in the study, and were included in the study according to the inclusion criteria, were divided to three groups using a simple random method, including continuous exercise (n = 9), interval exercise (n = 9) and control (n = 9). The three groups were matched according to their anthropometric variables and treatment history. The exercise course included eight weeks of continuous and interval exercises for three sessions per week. At the end of the 24 sessions of the intervention, one participant from the interval exercise group and three from the control group were withdrawn from the study, and the post-test inflammatory markers, anthropometric variables and VO_2 peak were measured for 23 participants.

3.1. The Measurement of the Variables

Height without shoes was measured using a stadiometer (Danesh Salar Iranian Co, made in Iran). Body weight, body mass index, adipose tissue, body fat percentage and Waist to Hip Ratio (WHR) were measured using a body composition analyzer (Inbody-220, made in Korea). The participants were divided to two groups for having their Vo_2 peak measured in two consecutive days using the Balke test for women on a treadmill (Technogym, made in Italy) at the site of the national olympic academy of Iran

3.2. Blood Measurements

Five-milliliter samples of 12-hour fasting blood were collected from the brachial vein from each participant 48 hours before beginning and 48 hours after finishing the eight weeks of exercise. Participants were asked not to exercise during these 48 hours. To measure the inflammatory markers, the 5-mL blood samples were transferred to the Endocrinology and metabolism research institute in Tehran in test tubes containing anti-protease and then kept frozen at -80°C until the analysis. For the separation of serum and plasma, samples were kept at room temperature for 30 minutes and then centrifuged (using a Hettich centrifuge made in Germany) at 3000 rpm and 4°C for a period of 10 minutes. All the pre and post-intervention measurements were performed by the same technician. The TNF-α was measured using a France Diaclone kit with a sensitivity of 8 pg/mL and through the enzyme linked immunosorbent assay (ELISA) method, IL-6 was measured using a France Diaclone kit with a sensitivity of 2 pg/mL and through the ELISA method, and hCRP was measured using a kit made by Diagnostics Biochem Canada Inc. with a sensitivity of 10 ng/mL and through the ELISA method.

3.3. Continuous and Interval Exercise Protocol

The exercise program was designed for breast cancer survivors according to the ACSM's guidelines (15) and included eight weeks of exercise (three times per week) for both exercise groups. Before proceeding with the planned treadmill exercises, the participants performed 15 minutes of stretch movements to warm up; after the main exercises, they spent five minutes to cool down.

3.4. Statistical Analyses

Data were analyzed using the SPSS-21 (made in USA) software at a significance level of 0.05. Mean and standard deviation were used to describe the variables. The Kolmogorov-Smirnov was applied to examine the normality of data in pre-test and post-test in three group and the results indicated that most data were not distributed normally. Hence, the Kruskal-Wallis test was used to compare the study variables between the three groups. Also, the Wilcoxon test was used to compare the pre and post-intervention changes in the variables in each group, separately.

Table 1. The Training Schedule

Training Group	Week 1		Week 2		Week 3		Week 4	
	Training Time	Intensity	Training Time	Intensity	Training Time	Intensity	Training Time	Intensity
Continuous group	15 minutes	30 THR%	15 minutes	35 THR%	20 minutes	40 THR%	20 minutes	40 THR%
Interval group	5 ×3 minutes; 2 minutes rest between sets	40 THR%	5 ×3 minutes; 2 minutes rest between sets	45 THR%	5 × 4 minutes, 2 minutes rest between sets	50 THR%	5 × 4 minutes, 1 minute rest between sets	50 THR%
Training group	Week 5		Week 6		Week 7		Week 8	
	Training Time	Intensity	Training Time	Intensity	Training Time	Intensity	Training Time	Intensity
Continuous group	25 minutes	40 THR%	30 minutes	45 THR%	35 minutes	50THR%	40 minutes	50 THR%
Interval group	5 × 5 minutes; 1 minute rest between sets	55 THR%	6 × 5 minutes; 1 minute rest between sets	55 THR%	7 ×5 minutes; 1 minute rest between sets	60 THR%	8 × 5 minutes; 1 minute rest between sets	60 THR%

4. Results

The highest reduction in weight (P = 0.012), BMI (P = 0.012), body fat percentage (P = 0.012) and adipose tissue (P = 0.012) and the highest increase in VO_2 peak (P = 0.012) occurred in the interval exercise group. The waist-hip ratio reduced equally in both exercise groups (P = 0.01). A significant difference was observed between the exercise groups and the control group regarding the improvements made in these markers. The anthropometric variables, body fat percentage and adipose tissue decreased significantly in both exercise groups ($P < 0.05$); however, the difference between the two exercise groups was not significant ($P > 0.05$).

In the continuous exercise group, a significant reduction was observed in hCRP (P = 0.015), and the reduction in TNF-α and IL-6 was also higher in this group compared to the two other groups

5. Discussion

Eight weeks of continuous and interval exercise yielded a significant difference between the exercise groups and the control group in improvements made in their anthropometric variables, body composition, and VO_2 peak; however, no statistically significant differences were observed between the two exercise groups .Nevertheless, except for the waist to hip ratio, which reduced equally in both exercise groups, the other variables showed a greater reduction in the interval exercise group compared to the continuous exercise group. No statistically significant differences were observed between the three groups in their TNF-α, hCRP and IL-6 after the eight-week period. However, only the continuous exercise group showed a significant reduction in hCRP after the intervention. Moreover, TNF-α and IL-6 showed the highest reduction in the continuous exercise group compared to the two other groups, which was consistent with the results obtained by Pakiz et al. (16), who examined the effect of 16 weeks of moderate-intensity physical activity on 68 overweight breast cancer survivors (44 women in the exercise group and 24 in the control group) and showed favorable changes in the subjects' IL-6 and TNF-α. Some studies have already documented inflammatory markers' relationship with body fat percentage and WHR. Koda et al. (17) and Ross et al. (18) both reported a reduction in waist circumference due to regular exercise, and showed that exercise can lead to a significant reduction in abdominal and visceral fat in both males and females even without any weight loss and regardless of age. They also showed that exercise is followed by an increase in circulating adiponectin and a reduction in pro-inflammatory adipokines, including IL-6, TNF-α and leptin, and has positive consequences, including increased insulin sensitivity, reduced resting IL-6 and TNF-α and eventually CRP. Stelzer et al. (19) and Giannopoulou et al. (20) found a direct relationship between body fat percentage and IL-6 values. Hong et al. (21), Bays et al. (22) and Cinti et al. (23) proposed the reduction in WHR and visceral fat to have contributed to the reduction in IL-6 and TNF-α, since a reduction in visceral fat prevents macrophages' infiltration into adipose tissue, and a reduction in leptin can contribute to the reduction in resting IL-6 and TNF-α, followed by a reduction in CRP. Rommel et al. (24) and Tomaszewski et al. (25) showed that physical activity is inversely related to BMI and WHR, which are themselves directly related to CRP.

Since, in the continuous exercise group, significant reductions were observed in weight (3.1 kg on average), BMI

Table 2. Participants' Pre and Post-intervention Variables

Variable	Control Group, N = 6	Continuous Group, N = 9	Interval Group, N = 8	P Value Between Groups
Weight, kg				0.225
Pre test	81.7 ± 12.3	75.4 ± 10.9	75.4 ± 6.6	
Post test	80.9 ± 12.0	72.3 ± 10.8	71.9 ± 6.8	
P value	0.207	0.008[a]	0.012[a]	
BMI, kg/m^2				0.638
Pre test	30.9 ±4.07	30.0 ± 3.4	29.9 ± 2.8	
Post test	30.6 ± 4.05	28.8 ± 3.4	28.5 ± 2.8	
P value	0.345	0.008[a]	0.012[a]	
Adipose tissue, kg				0.335
Pre test	35.2 ± 7.8	32.9 ± 7.5	31.9 ± 4.9	
Post test	34.9 ± 7.6	30.9 ± 8.1	28.8 ± 5.7	
P value	0.892	0.008[a]	0.012[a]	
Body fat, %				0.795
Pre test	43.1 ± 4.8	43.3 ± 4.5	42.4 ± 5.3	
Post test	42.9 ±4.04	41.9 ± 5.2	39.9 ±7.1	
P value	0.684	0.008[a]	0.012[a]	
Waist to hip ratio				0.892
Pre test	0.9 ± 0.04	1.0 ± 0.07	1.0 ± 0.04	
Post test	0.9 ± 0.06	0.9 ± 0.07	0.9 ± 0.03	
P value	0.223	0.016[a]	0.010[a]	
Vo_2 peak, mL. kg^{-1}. min^{-1}				0.183
Pre test	28.1 ± 3.4	27.3 ± 5.4	24.06 ± 4.5	
Post test	33.2 ± 3.08	38.6 ± 6.8	37.1 ± 6.8	
P value	0.028[a]	0.008[a]	0.012[a]	

[a] P Value is significant for variable changes.

and WHR, which have been shown in previous studies to be associated with the reduction in CRP, these reductions may have contributed to hCRP reduction. Furthermore, the significant reductions in adipose tissue (by 2 kg) and WHR, possibly through the reduction in visceral fat and the subsequent reduction in leptin and then in the inflammatory marker hCRP, appear to be of particular importance, because despite the lower weight loss and adipose tissue reduction in this group compared to in the interval exercise group, and given that WHR reduced equally in both exercise groups, and also in line with studies conducted by Gleeson et al. (26) and Mathur et al. (27), it can be inferred that a reduction in abdominal and visceral fat and WHR has a greater role in reducing inflammatory markers compared to simple weight loss and, essentially, is independent of it.

The eight-week interval and continuous treadmill exercises almost ineffectiveness in changing inflammatory markers may be attributed to the low intensity of the exercises. Given the significant effect of exercise in the present study on body fat percentage, adipose tissue and WHR, the lack of significant changes in the subjects' inflammatory markers may have been due to the small sample size and the short duration of the intervention program. Nevertheless, the present study used a low to moderate intensity for the exercises, and moderate intensity exercise thus appears to be effective in reducing inflammatory markers if practiced over a longer period; since in this study significant reduction was observed in hCRP and a reducing tendency was also noticed in other inflammatory markers, which is consistent with the study conducted by Rogers et al. (28), who reported a low to medium reduction in IL-6 and TNF-α as a result of, 150-minute moderate-intensity aerobic exercise and twice-weekly endurance exercise. The

Table 3. Participants' Pre and Post-Intervention Inflammatory Markers

Inflammatory Marker	Control Group	Continuous Group	Interval Group	P Value Between Groups
IL6, pg/mL				0.696
Pretest	3.6 ± 0.8	3.9 ± 1.4	3.7 ± 1.3	
Post test	3.4 ± 1.1	3.2 ± 0.5	3.3 ± 1.02	
P value	0.463	0.137	0.263	
TNFα, pg/mL				0.648
Pretest	16.6 ± 4.9	22.9 ± 16.07	38.5 ± 45.8	
Post test	16.01 ± 4.7	17.9 ± 7.3	33.8 ± 34.3	
P value	0.753	0.286	0.575	
hCRP, ng/mL				0.558
Pretest	4209.6 ± 2799.3	4405.6 ± 26.3	3089.7 ± 2763.3	
Post test	3174.1 ± 2552.8	3077 ± 2149.7	2339.2 ± 2533.1	
P value	0.068	0.015[a]	0.123	

[a] P value is significant for variable changes.

weekly frequency of exercise may also be another factor contributing to the lack of significant reductions in inflammatory markers. Kiecolt-Glaser et al. (29) studied the effect of 12 weeks of yoga (two 90-minute sessions per week) on 200 breast cancer survivors, and found in their second analysis that an increase in the weekly frequency of exercise leads to a significant reduction in IL-6 but not in TNF-α.

5.1. Conclusion

Exercise can improve anthropometric variables, body composition and VO_2 peak and reduce some inflammatory markers in breast cancer survivors. Continuous exercise with an intensity of 35% to 50% of the target heart rate had a significant effect on hCRP. It can therefore be concluded that an appropriate exercise program at a low to moderate intensity is probably more effective in reducing hCRP compared to high-intensity exercises. The reduction in abdominal and visceral fat and WHR also appear to be more effective in reducing inflammatory markers compared to simple weight loss and, essentially, independent of it.

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Footnotes

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