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Plasma leptin and adiponectin concentrations in postmenopausal women with breast cancer following aerobic exercise

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Abstract

Introduction: Breast cancer is the most common cancer in postmenopausal women. Exercise affects breast cancer risk and outcomes, but little is known about the mechanisms through which this effect may be mediated. The purpose of this study was to investigate the effect of 12 weeks aerobic exercise on plasma leptin and adiponectin in postmenopausal women with breast cancer.

Material & Methods: Nineteen postmenopausal women with breast cancer (aged: 55±2.7 years;±SD) volunteered to participate in this study. The subjects were randomly

assigned to training group (n=11) or control group (n=8). Subjects in the experimental group performed 12 weeks of an exercise program which consisted of 25 to 45 minutes of walking with an intensity of 45-65% of target heart rate, three times a week.

Results: Body mass and BMI decreased ($P<0.05$) after 12 weeks exercise training compared to the control group, while no significant change in body fat percent and WHR were found. Plasma leptin decreased ($P<0.05$) and plasma adiponectin increased ($P<0.05$) in response to 12 weeks aerobic exercise training compared to the control group, while insulin resistance determined by HOMA-IR did not change in the training group.

Conclusions: In summary, 12 weeks aerobic exercise increase plasma adiponectin and decrease plasma leptin in postmenopausal women with breast cancer.

Key words: Breast cancer, Adiponectin, Leptin, Postmenopausal women, Walking

1. Introduction

In 2004 in the United States, invasive breast cancer was the most commonly diagnosed cancer in women (age-adjusted incidence rate at 118 per 100,000 women) (1). Obesity is related to many metabolic disorders like type 2 diabetes mellitus, coronary heart disease, and hypertension, and is notably associated with an increased risk for breast cancer in postmenopausal women (2). Recent researches indicate adipose tissue as an endocrine organ, which secretes adiponectin, leptin and other cytokines (3). Adiponectin is a 30 kDa protein hormone that has independently characterized (4,5). Increased plasma adiponectin concentration is associated with improvement in glucose tolerance, insulin sensitivity and cardiovascular disease (6,7). Serum adiponectin level has been reported to be reduced among Taiwanese breast cancer patients as compared to controls (8).

Leptin is a 16 kDa polypeptide hormone encoded by the obese gene that is involved in the regulation of energy balance, reproduction, and immunity, and acts as a proinflammatory factor (9). In stark contrast with adiponectin, plasma leptin concentration increases with body mass index (10). Current hypotheses suggest that adiponectin and leptin could play a role in breast cancer development (11). Several studies have demonstrated that low serum adiponectin levels and high serum leptin levels are associated with increased risk for breast cancer (8,12). Furthermore, Chen et al. (2006) reported that the ratio between serum leptin and serum adiponectin correlated positively with tumor size (8).

Although several risk factors are proposed for breast cancer, low levels of physical activity may be one of the most modifiable. Excess body weight and low physical activity together may account for one quarter to one third of all breast cancer cases (13). Exercise training is a useful therapy for improving obesity and it is demonstrated that exercise – induced change in adipose tissue, increases adiponectin mRNA expression and plasma concentrations and decreases plasma leptin (14,15). Thus, exercise may decrease risk of breast cancer through several possible mechanisms including change in hormone level, immune function and reduction in weight gain (16). However, Ligibel et al. (2009) reported that adiponectin and leptin values did not change after 16 weeks exercise in breast cancer survivors (17). Few studies have been carried out to comprehensively analyze the effect of exercise training on adiponectin and leptin levels in women with breast cancer. Therefore, we evaluated the effect of 12 weeks aerobic exercise on plasma adiponectin and leptin concentrations in postmenopausal women with breast cancer.

2. Material & Methods

Subjects and inclusion criteria

Subjects selected from the Center of Oncology and Radiotherapy of Shahid Beheshti Hospital in Shiraz. A list of the names and medical records of 1954 women with breast cancer who came to this center for treatment from 2009 to 2011 were given a survey. After primary survey, 342 women of 50 to 65 years old were selected. These women received surgery, chemotherapy and radiotherapy and they had current hormone therapy. They were in stage I to IIIB. They should not have specific

illness and in the past 6 month should not have any experience of a menstrual cycle. Also, they should not have participated in any exercise training or physical activity in past 6 month and their body mass should not have changed in this period (last 6 month) as much as 10% of their whole body mass. All the patients invited to participate in this study by telephone. Among all, 32 women indicated their readiness to participate in this study and 22 women were present in meeting day. The physical activity readiness questionnaire (PAR-Q) and written informed consent was obtained from all of the subjects. By surveying the questionnaire, it was specified that 22 of them had conditions for taking part in this study. These 22 women divided into two groups randomly; intervention group and control group. At the end of exercise training program 19 women (8 women in control group and 11 women in intervention group) completed the relevant measurements of the post tests. This study was approved by the Shiraz branch, Islamic Azad University Ethics Committee.

Exercise Training Protocol

The intervention group took part in supervised walking program, three times per week for 12 weeks. The walking program started at 45% of heart rate reserve (HRR) for 25 minutes in weeks 1 to 4. Duration of walking from 5^{th} to 8^{th} weeks was 35 minutes and intensity was 55% of HRR. From 9^{th} to 12^{th} weeks, duration of walking was 45 minutes with intensity of 65% of HRR. Each participant was equipped with a heart rate monitor (Polar, FS3c, Finland) to ensure accuracy of the exercise level. The control group participated in measurements only and they were asked not to participate in any physical activity or exercise training.

Measurements

Anthropometric and body composition measurements

Height and body mass were measured, and body mass index (BMI) was calculated by dividing body mass (kg) by height (m^2). Waist circumference was determined by obtaining the minimum circumference (narrowest part of the torso, above the umbilicus) and the maximum hip circumference while standing with their heels together. The waist to hip

ratio (WHR) was calculated by dividing waist by hip circumference (cm) (18). Fat mass and lean body mass were assessed by bioelectrical impedance analysis using a Body Composition Analyzer (Tina, Inbody 3.0, Japan).

Measurement of VO_{2max}

VO_{2max} was determined by Rockport One-Mile Fitness Walking Test. In this test, an individual walked 1 mile (1.6 km) as fast as possible on a track surface. Total time was recorded and HR was obtained in the final minute (18). VO_{2max} was calculated by following formula:

$$VO_{2max} = [139.68 - (0.388 \times \text{age (year)})] - [0.077 \times \text{body mass (Pb)}] - [3.265 \times \text{time (min)}] - [0.156 \times \text{HR}]$$

Biochemical analyses

Fasting blood samples were collected at rest (before intervention) and after intervention. All the subjects fasted at least for 12 hours and a fasting blood sample was obtained by venipuncture. Plasma leptin levels were determined in duplicate via an enzyme-linked immunosorbent assay (ELISA) kits (Diagnostics Biochem Canada, Inc). The intra and inter-assay coefficients of variation for leptin were $<5\%$ and a sensitivity of 0.5 ng/ml. The plasma adiponectin level was measured in duplicate using an enzyme-linked immunosorbent assay (ELISA) kits (Adiponectin Inc, Seoul, Korea). The intra and inter-assay coefficients of variation for adiponectin were $<4.9\%$ and a sensitivity of 1 ng/ml. Plasma glucose was determined by the enzymatic (GOD-PAP, Giucose Oxidase-Amino Antipyrine) colorimetric method (Pars Azmoun, Tehran, Iran). The intra and inter-assay coefficients of variation for glucose were $<1.3\%$ and a sensitivity of 1 mg/dl. The serum insulin level was measured by a radioimmunoassay (RIA) and the insulin resistance index was calculated according to the homeostasis model assessment (HOMA-IR) which correlates well with the euglycemic hyperinsulinemic clamp in people with diabetes (19). All the measurements were obtained twice and recorded by one staff that was blinded to subjects in pre and post tests.

Statistical Analysis

Data were analyzed using SPSS software for windows (version 13, SPSS, Inc., Chicago, IL). Results were expressed as the mean±SD and distributions of all variables were assessed for normality using kolmogorov-smirnov test. Mean values of two groups in pre and post tests were compared by paired-samples t-test and independent-samples t-test for all variables and Mann- Whitney U test for fasting glucose. Pearson and spearman's correlation were performed to calculate a correlation. The significance level of this study was set at $P<0.05$.

3. Results

Changes in anthropometric variables and aerobic fitness

Anthropometric and body composition characteristics and maximal oxygen consumption of the subjects at baseline and after training are presented in Table 1. Before the intervention, there were no significant differences in any of variables among the two groups. Body mass and BMI decreased ($P<0.05$) after 12 weeks exercise training compared to the control group, while no significant change in body fat percent and WHR were found. After 12 weeks intervention, maximal oxygen consumption increased ($P<0.05$) in the training group, while no significant change in the control group was found.

Changes in fasting glucose, fasting insulin and HOMA-IR

Our results showed that fasting glucose and insulin and insulin resistance determined by HOMA-IR did not change in the training group (Table 1).

Changes in plasma leptin and adiponectin levels

Plasma leptin decreased ($P<0.05$, 23.4%) and plasma adiponectin increased ($P<0.05$, 20%) in response to 12 weeks aerobic exercise training compared to the control group. Plasma leptin concentration at baseline was positively correlated with BMI ($r=0.57$, $P=0.01$) and body fat percent ($r=0.61$, $P=0.005$). The plasma leptin decrease after training was associated with the decrease of body mass ($r=0.47$, $P=0.04$) and BMI ($r=0.63$, $P=0.004$). Plasma adiponectin concentration at baseline was negatively correlated with body fat percent ($r=-0.54$, $P=0.01$) and

HOMA-IR (r=-0.49, P=0.03). The plasma adiponectin increase after training was associated with the decrease of body fat percent (r=-0.58, P=0.008) and WHR (r = -0.51, P=0.02).

Table 1. Anthropometric, body composition, physiological and biochemical characteristics (mean±SD) of the subjects before and after training

	Baseline (mean±SD)	After intervention (mean±SD)	Paired t-test (Sig)	ANCOVA	Changes (%)
Body mass (kg)					
Exercise (n=11)	67.8±8.7	65.5±8.9	0.001*	0.001*	- 3.3
Control (n=9)	71.3±14.5	71.5±13.5	0.7		0.02
BMI (Kg/m^2)					
Exercise (n=11)	28.8±3.1	27.5±3.3	0.001*	0.001*	- 4.5
Control (n=9)	29.1±5.3	29.2±4.8	0.6		0.3
Body fat (%)					
Exercise (n=11)	37.7±5.7	37±6.3	0.2	0.3	- 1.8
Control (n=9)	33.9±6.6	34±6.1	0.7		0.2
WHR					
Exercise (n=11)	0.92±0.06	0.91±0.06	0.8	0.9	- 1.08
Control (n=9)	0.92±0.03	0.92±0.03	0.3		0
VO_{2max} (ml.Kg^{-1}.min^{-1})					
Exercise (n=11)	28.8±5.9	34.8±5.8	0.001*	0.001*	20.8
Control (n=9)	20.7±9.6	19.6±8.8	0.08		- 5.3
Fasting glucose (mg/dl)					
Exercise (n=11)	103.4±53.8	102.8±38.03	0.9	0.09	- 0.5
Control (n=9)	84.3±11.3	91.2±8.7	0.1		8.1
Fasting insulin (μU/ml)					
Exercise (n=11)	10.5±4.7	8.6±3.9	0.2	0.7	- 18
Control (n=9)	15.8±10.4	14.8±8.5	0.5		- 6.3
HOMA-IR					
Exercise (n=11)	2.9±2.6	2.2±1.2	0.2	0.4	- 24.1
Control (n=9)	3.3±2.3	3.3±1.9	0.9		0
Leptin (ng/ml)					
Exercise (n=11)	32.9±17.8	25.2±14.5	0.01*	0.01*	- 23.4
Control (n=9)	25.8±9.04	27.05±8.9	0.1		4.8
Adiponectin (μg/ml)					
Exercise (n=11)	0.8±0.4	0.96±0.5	0.007*	0.007*	20
Control (n=9)	1.06±0.5	1.03±0.5	0.3		- 2.8

Data are the mean±SE of baseline and final values of the anthropometric, body composition, physiological and biochemical changes on each variable in each group. Comparison different significance between groups after 12 weeks exercise was determined by using the ANCOVA test. *P<0.01.

4. Discussion

Obesity is an established risk factor for breast cancer in postmenopausal women (20). Several studies have demonstrated that adiponectin and leptin, which are both adipocyte secreted hormones that are deregulated in obesity, associated with increased risk for breast cancer (8,12). Exercise training may reduce the adipose tissue, although it is not well known whether exercise – induced change in adipose tissue, increases plasma adiponectin and decreases plasma leptin concentrations in postmenopausal women with breast cancer or not. Thus we studied the effect of 12 weeks aerobic exercise on plasma adiponectin and leptin concentrations in postmenopausal women with breast cancer.

Plasma adiponectin increased by 20% in response to 12 weeks aerobic exercise training. Previous studies demonstrated that training greater than 2 months that employs enough exercise volume (frequency, intensity, and duration) to reduce body weight will increase adiponectin levels (15,21). A majority of studies suggest that weight loss produced by exercise, and not exercise *per se*, may be the driving mechanism for increases in adiponectin (22,23). There are negative relationships between plasma adiponectin levels and weight, body mass index and body fat mass (24). Adiponectin is secreted initially by fat but levels are reduced as fat depots increase (25). Previous reports showed that adiponectin levels are inversely correlated with subcutaneous and visceral fat mass (24,26). Circulating adiponectin levels are reduced, when adipocyte size increased by means that, decreased fat cell size, increased expression and plasma concentrations of adiponectin (22). There were significant association between plasma adiponectin with body fat percent and WHR after 12 weeks training, thus it seems that exercise-induced changes in body composition may play an important role in increasing plasma adiponectin in postmenopausal women with breast cancer. Several studies have shown that exercise induced improvement in insulin sensitivity are associated with the increase in

adiponectin concentration (27,28). Insulin suppresses expression and/or secretion of adiponectin from adipocytes, whereas adiponectin increases insulin sensitivity by increasing fat oxidation and reducing circulating fatty acid levels and intracellular triglycerides in liver and muscle (29). Fasting glucose and insulin and insulin resistance determined by HOMA-IR did not change in the training group and there were no significant relationship between plasma adiponectin and insulin resistance. Thus an increase in adiponectin may not attribute to an enhancement of insulin sensitivity in women with breast cancer.

The results, on the other hand, showed that plasma leptin decreased (23.4%) after 12 weeks aerobic exercise training. A number of studies have investigated the effects of training on leptin concentrations. These studies have tended to report either no effect of training on leptin concentrations with short-term training ($<$ 12 weeks), (30,31) or a reduction in leptin levels in long-term training ($\geq$ 12 weeks) studies (14,28). There are several reasons that can explain the modification of the response of leptin to muscular exercise. Exercise can reduce fat mass, play a significant role in energy expenditure and affect hormonal concentrations including insulin, cortisol, catecholamines, estrogen, testosterone, and growth hormone that may alter leptin concentrations (31,32). Exercise is known to effectively reduce obesity (fat mass), thus, if leptin levels are affected, this may provide some explanation of how exercise affects obesity. The plasma leptin decrease after training was associated with the decrease of body mass and BMI, thus it seems that exercise-induced changes in body fat may play an important role in decreasing plasma leptin in postmenopausal women with breast cancer. The other hand, several factors, such as, the intensity and the duration of the exercise, the nutritional status of the subject, the circadian rhythm of leptin, the hour of blood sampling and the caloric imbalance imposed by the exercise are effective on changes of plasma leptin concentration (14).

5. Conclusion

In conclusion, the present study suggests that aerobic exercise may indirectly increase plasma adiponectin and decrease plasma leptin in postmenopausal women with breast cancer when an intervention is accompanied by improve in body composition.

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Conflict of interests: No conflict of interests amongst authors.

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