Original Article

The effect of combined Pilates and yoga training on insulin and leptin level in breast cancer survivors: A randomized clinical trial

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Abstract

Context: Elevated levels of insulin and leptin can be associated with poor prognosis in breast cancer patients. A safe and effective exercise protocol seems necessary as an adjuvant therapy in breast cancer patients.

Aims: This study aimed to assess the effect of concurrent yoga and Pilates training on insulin and leptin in breast cancer survivors.

Setting and Design: This study was a randomized clinical trial research with control group in a selected oncology and radiotherapy center in Rasht, Iran, in 2019.

Materials and Methods: This clinical trial was performed on thirty breast cancer survivors. The participants were allocated in exercise group ($n = 15$) and control group ($n = 15$) by simple randomly. Exercise group underwent 12 weeks of concurrent yoga and Pilates training, 3 sessions/week and 75 min of workout in each session. Every participant completed the demographic questionnaire. Weight, insulin, leptin, carcinoembryonic antigen (CEA), and cancer antigen 15-3 (CA 15-3) levels were measured before and after 12 weeks of exercise in both groups.

Statistical Analysis Used: Data were analyzed using descriptive statistics, one-way ANCOVA, and paired *t*-test and Wilcoxon.

Results: Mean score of weight in the exercise group decreased from 73.03 ± 16.75 to 69.92 ± 15.46 ($P = 0.01$), but in control group, there was no significant improvement (from 85.54 ± 11.7 to 85.27 ± 9.71). There was a significant decrease in leptin levels (from 33.70 ± 15.93 to 21.21 ± 15.37) in exercise group ($P = 0.02$). However, there was no significant effect on insulin (from 7.66 ± 2.96 to 10.67 ± 4.51), CEA, and CA 15-3 ($P > 0.05$).

Conclusion: Twelve weeks of concurrent yoga and Pilates training have positive effects on leptin levels in breast cancer survivors.

Keywords: Breast cancer, Insulin, Leptin, Pilates training, Yoga

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INTRODUCTION

Brest cancer is the second most common cancer among women (25% of all cancer cases).[1,2] Epidemiological researches have shown that Iranian women diagnosed with breast cancer a decade earlier than women from other ethnicities and younger age at presentation is related with poor prognosis.[3] Breast cancer treatment has various emotional and physical adverse effects such as fatigue, decreased aerobic capacity, weight gain, and hypertension. Obesity is an independent risk factor for breast cancer and its recurrence and can be an adverse effect of chemotherapy and surgery.[4] One of the adipose tissue products is leptin.[5] Leptin is a multifunctional polypeptide molecule which regulates food intake, inflammation, cell differentiation, and proliferation.[6] Leptin is mainly synthesized not only by distant or local adipocytes but also by cancer-associated fibroblasts and plays an important role in breast tumorogenesis and control breast cancer manner as an endocrine, paracrine, and autocrine hormone.[7-11] Leptin effects on breast cancer proliferation independently way and also through insulin signaling pathway.[12] Obesity can lead to insulin resistance and hyperinsulinemia which is related to breast cancer recurrence and mortality.[13-15] In addition to blood glucose control, insulin and insulin-like growth factor (IGF) regulate cell growth and proliferation.[16,17] Even though obesity leads to insulin resistance, but breast cancer cells express higher levels of insulin receptors and they are more sensitive to insulin than normal breast cells.[1]

Despite advances in early detection and treatment of breast cancer, 20%–30% of patients experience relapse or metastasis.[18] Hence, monitoring the progression or recurrence of the disease seems necessary in any intervention. A noninvasive tool for assessing progression or relapse of malignancies is tumor markers. In breast cancer, carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA 15-3) are the most widely used serum tumor markers.[19,20] CEA is from immunoglobulin family and involve in cell adhesion. Normally, it presents as very low levels in blood but can increase in specific malignancies.[21,22] CA 15-3 is a mucinous glycoprotein (also known as MUC-1) and exist in all epithelial cell membranes but CA 15-3 serum levels increase in breast cancer.[23,24] Previous researches estimate the sensitivity and specificity of CEA 56.7% and 92%, respectively, and for CA 15-3 44.5% and 84.5%, respectively, for diagnosis of breast cancer recurrence and progression.[25]

Exercise is an adjuvant therapy for breast cancer,[26] and different researches have shown that it has no side effects or cancer survivors at any dose, type, or timing.[27] Exercise increases energy consumption and reduces adipose tissue, therefore reduces leptin synthesis.[28] Possible mechanisms of exercise for hyperinsulinemia improvement are increasing postsynaptic insulin receptors, increasing glucose transporter proteins, reducing secretion and clearance of free fatty acids, increasing glucose delivery to muscles, and promoting muscle tendency to glucose.[4]

Breast cancer survivors have poor compliance for continuous exercise training but gentler training such as Yoga and Tai Chi have shown to be improve regular attendance.[29] Pilates exercise is focus on breathing, endurance, and body control.[30,31] Yoga is a mind–body exercise which can promote muscular strength, energy, and relaxation.[32] These exercises can reduce adipose tissue and improve insulin sensitivity through better oxygenation and intermittent muscular contraction.[33] However, the most effective duration and intensity of exercise training is still controversial. The chronic process of breast cancer, frequent hospitalization, poor general condition, and inactivity decrease the aerobic and anaerobic capacity in patients so an easy, safe, cheap, and effective exercise program can lead to changes in lifestyle and promote patients' prognosis and general health. It is also important to choose a safe intervention so control the relapse and metastasis during intervention through measuring breast cancer tumor markers seems reasonable. This research was conducted with the aim of investigating the effect of combined Pilates and yoga training on insulin and leptin level in breast cancer survivors.

MATERIALS AND METHODS

This study was a randomized clinical trial conducted in a selected oncology and radiotherapy center in Rasht, Iran, in 2019. The present study has been registered with code "IRCT20150531022498N34" in the Iranian Registry of Clinical Trials and approved by Ethical Committee of Azad University, Lahijan Branch with code "IR.IAU.LIAU.REC.1399.008."

The participants were breast cancer survivors referring to a selected oncology and radiotherapy center in Rasht, Iran. The inclusion criteria were age between 35 and 50 years old, breast cancer survivors undergoing partial mastectomy, termination of chemotherapy and radiotherapy for at least 6 months, ability to perform exercise trainings, and the approval of their oncologist for safety of this kind of intervention on their patients. The exclusion criteria were consist of more than 3 consecutive sessions or four intermittent sessions absence from the training, injury during training, and lack of interest in continuing the training.

Sample size was estimated with G*Power software 1.3.9.2 (*t*-test; $\alpha = 0.05$; $\beta = 0.80$; Cohen's D = 0.95; df = 28).[34,35] Thirty breast cancer survivors were selected through availability sampling and were allocated by simple randomly using sequentially numbered containers to control and exercise groups. Patients were matched based on their disease stage and their treatment protocol. Each group had 15 people.

Exercise group performed 12 weeks of combined yoga and Pilates training, three sessions per week, 75 min each session.[36-38] Exercise program was taught both individually and in groups by an exercise physiologist professor. The exercise training consists of 10 min warming up, 30 min Pilates training, 30 min yoga training, and 5 min cooling down. Pilates training consists of spine stretch, the saw, mermaid, oblique roll up, hundreds, one leg stretch, two leg stretch, scissors, shoulder bridge, hip twist, clam, arm opening, sidekick, and swan dive. Yoga training consists of six rounds of Tadasana, Upward salute pose, Uttanasana, Hadrasana, Dandasana, Knees, chest, and chin pose, Cobra pose, Urdhva Mukha Svansana, and repetition of Tadasana, Upward salute pose, Uttanasana and Hadrasana. Control group was advised to do their routine daily activities.

Ethical considerations

All participants attend to the program with complete awareness and satisfaction and all of them signed a written consent. Every participant in both groups was free to leave the program if they willing to do so.

Research tools

Before the program, every participant completed a demographic form consisted of age, marital status, number of children, occupational and educational status, history of surgery, chemotherapy and radiotherapy, and disease duration. Before and after 12 weeks of training, weight (by using Soehnle scales made in China) and levels of insulin and leptin hormones and CEA and CA 15-3 tumor markers were measured. For blood analysis, 5 ml blood was obtained from bracial vein between 7 and 9 am. All blood samples from exercise group obtained a day before first training session and 24 h after last training session and after at least 8 h fasting (blood samples from control group were obtained in the same day as exercise group). Samples were obtained with venoject, mixed with heparin to prevent blood clotting, and centrifuged immediately. All samples were stored at −28°C until further analysis. Leptin levels were measured using medignost kit (Germany). Insulin levels were determined using Dia plusinc kit (Canada). CEA levels were measured using CanAg CEA EIA kit (Sweden). CA 15-3 levels were measured using CanAg CA 15-3 EIA kit (Sweden). All samples were measured with ELISA auto-analyzer (Stat Fax 303 pluse, ELISA Awarness, USA). All samples were measured in a same laboratory before and after the intervention.

Data analysis

Primary outcomes were changes in insulin and leptin levels and secondary outcomes were changes in tumor marker levels following intervention. For the exact analysis, mean, standard deviation, and median were reported for quantitative data, and frequency was reported for qualitative data. Shapiro–Wilk test was used to assess the normal distribution. Parametric data were evaluated by one-way ANCOVA and paired *t*-test, and nonparametric data were evaluated by Wilcoxon applied by SPSS software 25 (Chicago, Illinois, USA). $P < 0.05$ was considered statistically significant.

RESULTS

The samples entered in this study included breast cancer survivors. From control group, four participants did not attend for the final evaluation, and from exercise group, two participants were absent in four intermittent sessions. Therefore, they were excluded from the study. Finally, the exercise group was consisting of 13 participants and control group was consisting of 11 participants [Chart 1]. The results of Shapiro–Wilk test showed that insulin, CEA, and CA 15-3 were followed the normal distribution, while weight and leptin did not follow the normal distribution.

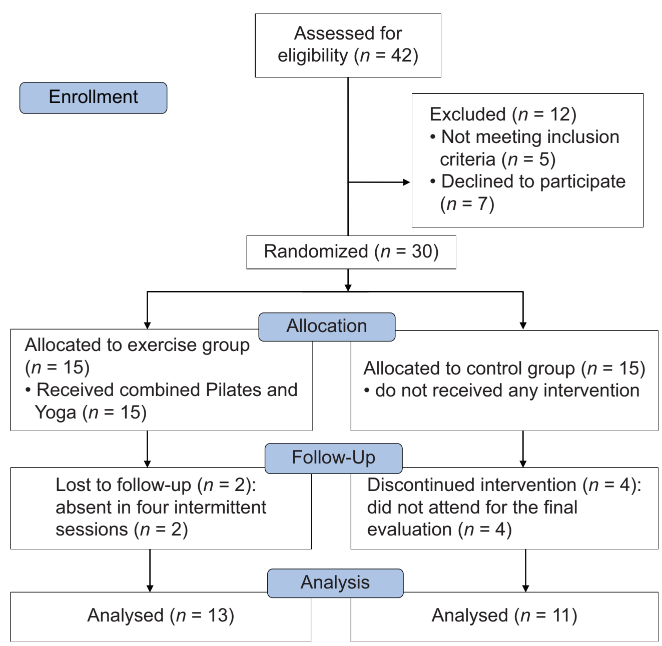

Chart 1: Enrollment of breast cancer survivors in the study groups

The demographic hormones and tumor markers' data of participants are described in Table 1.

At the beginning of study, the insulin, CA 15-3, and CEA levels were significantly different in exercise and control group. Levene's test was demonstrated that the variance of insulin ($P = 0.881$; $F = 0.02$), CA 15-3 ($P = 0.27$; $F = 0.63$), and CEA ($P = 0.460$; $F = 0.56$) in two groups was equal. Therefore, we used the ANCOVA test and consider the pretest data as covariates to eliminate the effect of pretest data on the results of our analysis. The research finding indicated that weight and leptin levels were significantly decreased in exercise group after 12 weeks of combined yoga and Pilates training ($P = 0.01$ and $P = 0.02$, respectively), but there was not any significant changes in insulin levels ($P = 0.16$). Furthermore, no significant changes were seen in CA 15-3 and CEA levels ($P = 0.60$ and $P = 0.21$, respectively) [Tables 2-4].

Table 1: The comparison of the mean and standard deviation of the demographic, hormones, and tumor markers data before the intervention with exercise and control groups

Exercise groups (follow up)	Mean±SD		*P*
	Exercise group	Control group	
Age (pretest)	46.30±4.76	45.00±4.64	0.30
Weight (pretest)	73.03±16.75	85.54±11.17	0.01
Insulin (pretest)	7.66±2.96	8.98±4.85	0.01
Leptin (pretest)	33.70±15.93	51.09±45.39	0.38
CA 15-3 (pretest)	19.77±8.70	17.50±7.43	0.01
CEA (pretest)	1.60±0.77	1.79±0.55	0.01

SD: Standard deviation, CEA: Carcinoembryonic antigen, CA 15-3: Cancer antigen 15-3

DISCUSSION

The findings of this study showed that, after 12 weeks of combined Pilates and yoga exercises, weight and leptin levels have significantly decreased.

Obesity is associated with metabolic syndrome and can cause elevation in insulin and IGF levels. Chronic release of free fatty acid from adipose tissue is also lead to increased insulin, leptin, interleukin-6, and tumor necrosis factor-α secretion.[39] Leptin activates several intracellular signaling pathways such as Janus kinase 2-signal transducer and activator of transcription 3 (JAK2-STAT3), mitogen-activated protein kinase, and phosphatidyl inositol 3-kinase-protein kinase B (PI3K-AKT) pathways,[40,41] which are involved in cell proliferation and apoptosis. Different studies have shown that over secretion of leptin can be associated with breast cancer occurrence and overexpression of its receptor in tumoral cells can be associated with metastasis.[42,43]

Table 2: The comparison of the mean and standard deviation of insulin, cancer antigen 15-3, and carcinoembryonic antigen before and after the intervention with exercise and control groups

Variable	Source	Type III sum of squares	df	Mean square	*F*	Significance	ηp²
Insulin	Corrected model	446.382	2	223.191	47.184	0.001	0.818
	Intercept	6.415	1	6.415	1.356	0.257	0.061
	Insulin before	446.174	1	446.174	94.324	0.001	0.818
	Group	10.053	1	10.053	2.125	0.160	0.092
CA 15-3	Corrected model	979.934	2	489.967	11.682	0.001	0.527
	Intercept	81.572	1	81.572	1.945	0.178	0.085
	CA 15-3 before	918.306	1	918.306	21.895	0.001	0.510
	Group	11.744	1	11.744	0.280	0.602	0.013
CEA	Corrected model	9.665	2	4.832	45.699	0.001	0.813
	Intercept	0.113	1	0.113	1.065	0.314	0.048
	CEA before	9.664	1	9.664	91.393	0.001	0.813
	Group	0.174	1	0.174	1.650	0.213	0.073

CEA: Carcinoembryonic antigen, CA 15-3: Cancer antigen 15-3

Table 3: The comparison of the mean and standard deviation of insulin, cancer antigen 15-3, and carcinoembryonic antigen before and after the intervention with exercise and control groups

Groups	Mean±SD		*P* (*t*)
	Preintervention	Postintervention	
Insulin (μIU/ml)			
Exercise	7.66±2.96	10.67±4.51	0.001*
Control	8.98±4.85	10.86±5.48	0.007*
CA 15-3 (μIU/ml)			
Exercise	19.77±8.70	21.16±9.91	0.575
Control	17.50±7.43	17.94±7.86	0.497
CEA (ng/ml)			
Exercise	1.60±0.77	1.83±0.74	0.019*
Control	1.79±0.55	1.84±0.72	0.637

*Paired *t*-test. SD: Standard deviation, CEA: Carcinoembryonic antigen, CA 15-3: Cancer antigen 15-3

Table 4: The comparison of the mean and standard deviation of weight and leptin before and after the intervention with exercise and control groups

Exercise groups Follow up	Median (1st quartile-3rd quartile) Preintervention	Median (1st quartile-3rd quartile) Postintervention	*Z*	*P*
Weight (kg)				
Exercise	71.00 (61.50-80.10)	68.00 (60.00-76.00)	−3.062	0.002*
Control	84.00 (75.00-95.00)	83.00 (78.99-95.00)	−0.358	0.720
Leptin (ng/ml)				
Exercise	43.80 (17.25-47.45)	17.60 (7.80-35.95)	−2.201	0.028*
Control	43.50 (24.30-50.10)	44.20 (26.30-48.60)	0.001	1.000

*Wilcoxon

Some researches result in decreasing of leptin levels following 12-week walking in women with breast cancer.[44] However, in contrast with the present study, some showed that there were no significant changes in leptin levels after 12 weeks of Pilates training or combination of diet and aerobic exercise.[45,46] The different intensity of exercise protocol performed in this study could be the reason of its different results from the present study. Chronic exercise can decrease the fat storage and adipose tissue is known to be the main source of leptin. Exercise can also establish a new set point and promote the sensitivity of leptin receptors.[28]

A clinical trial showed that moderate intensity aerobic exercise had no significant effect on serum insulin levels.[47] However, in contrast with the present study, some studies showed that 2 weeks of Pilates exercises can reduce serum insulin in women.[48] Another study has demonstrated that 4 months of moderate-intensity combined training had a significant effect on serum insulin in breast cancer survivors.[49] Furthermore, another study showed that 3 months of aerobic exercise significantly reduced insulin levels in women surviving breast cancer.[50] A randomized clinical trial on diabetic patients showed a significant reduction of insulin following 8 weeks aerobic training.[51] This discrepancy could be due to different types, intensity, and duration of exercise training protocols. Intermittent muscle contraction during exercise lead to glucose consumption followed by reduction in insulin production.[52] Exercise also promotes glucose sensitivity through increasing tissue perfusion and oxygenation.[33] Tumor markers were measured to confirm that this kind of intervention is safe in breast cancer survivors and is not associated with relapse or metastasis of the disease.

One of the limitations of this project was the small number of samples, limited period of intervention, and short-term follow-up. Furthermore, due to variation of insulin and tumor marker levels in different menstrual cycle and their interaction with sexual hormones, we suggest considering menstrual phase and sexual hormone levels in future studies and following up participants for long-term effects of exercise training.

CONCLUSION

Based on the findings obtained in this study, we conclude that weight and leptin might be involved in breast cancer proliferation modulated by regular concurrent Pilates and yoga exercise. However, there was no significant effect on insulin. As Yoga and Pilates training are safe, cheap, and available even at home and according to their potential effects on regulating body metabolism, it seems reasonable to concentrate more on these kinds of exercises in breast cancer survivors.

Conflicts of interest

There are no conflicts of interest.

Authors' contribution

R. Shabani was involved in conducting the research and collecting the parts together, drafting the article, H. Saeidi doing the visits and, following up process with the patients, S. Ebrahimpour collecting data, S. Dehghanzade doing data analysis and revising the article critically.

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