Research Article

The effect of nonlinear resistance training on serum myostatin and insulin resistance in women with breast cancer

Shiva Shahrokhian*, Abdul Hamid Habibi, Saeed Shakerian

Abstract

Background: Obesity, insulin resistance and myostatin levels are known to be risk factors for breast cancer. The aim of this study was to evaluate the effect of nonlinear resistance training on serum myostatin levels and insulin resistance in women with breast cancer.

Methods: In the present quasi experimental study, 20 women with breast cancer were selected by random sampling from patients referred to Imam Hassan Chemotherapy Center Dezful, Iran and randomly selected in the group of resistance training with non-linear training and control groups. Exercise intervention included 12 weeks of resistance training, 3 sessions per week and each training session including training of different muscle groups with 40%-90% maximum repetition was performed. Fasting blood sampling was performed 48 hours before and after the intervention period. Dependent t-test and analysis of covariance were used for statistical analysis ($P \leq 0.05$).

Results: After training period, there was a significant decrease was founded in body fat percentage (P=0.038), serum myostatin level (P=0.023), fasting insulin (P<0.001) and insulin resistance (P<0.001) in the training group compared to the control group, but there was no significant difference was observed in the variables of weight (P=0.603), body mass index (P=0.965) and fasting glucose (P=0.410).

Conclusion: According to the results of resistance training with improving body composition and insulin resistance has a positive role in reducing the complications associated with breast cancer and these changes are probably related to the metabolic effects of myostatin, a myocene associated with skeletal muscle growth is created.

Department of Exercise Physiology, Ahvaz Shahid Chamran University, Iran

Corresponding author: *Shiva Shahrokhian*

E-mail: *shahrokhian2021@gmail.com*

Received: *29 December 2021, Manuscript No. ajdm-21-49763;* ***Editor assigned:*** *31 December 2021, PreQC No. ajdm-21-49763(PQ);* ***Reviewed:*** *14 January 2022, QC No ajdm-21-49763;* ***Revised:*** *19 January 2022, Manuscript No. ajdm-21-49763 (R);* ***Published:*** *26 January 2022,* ***DOI:*** *10.54931/ajdm- 30.1.4.*

Introduction

Breast cancer is the most common cancer in women, usually due to the abnormal growth and division of different breast cells.[1] Breast cancer is a malignant tumor that starts in the breast cells and is able to spread (metastasize) and can actually attack the surrounding tissues.[2] The first complication in a person with breast cancer is inflammation in the area of the tumor and cancerous tissues. Inflammation both plays a key role in tumor development in breast cancer and affects tumor proliferation, angiogenesis, metastasis, and resistance to treatment. The main features of cancer related inflammation include leukocyte infiltration, cytokine production, tissue remodeling, and angiogenesis.[2]

Obesity and insulin resistance are both known risk factors for breast cancer and are associated with late stage disease and poor prognosis.[3] Obesity and overweight appear to play a role in insulin resistance by increasing inflammatory markers as well as the production of cytokines secreted by various tissues, including adipokines.[4] The International Agency for Research on Cancer estimates that 25% of the causes of cancer are obesity or overweight and sedentary lifestyle.[5,6] Weight gain of 1.5 times the normal range increases the risk of breast cancer. In particular, weight gain after the age of eighteen significantly increases the risk of developing this cancer and there is a significant relationship between high body mass index and breast cancer, especially in the postmenopausal period[7,8] Inactivity is also an effective factor in insulin resistance.[9]

Myostatin, a myokin known to inhibit skeletal muscle growth, has been linked to the development of insulin resistance. However, little is known about the regulation of myostatin in human obesity and insulin resistance.[10] Research on cancer patients has shown that myostatin is a new tumor causing agent that causes cachexia in these patients.[11] In this regard, Lokireddy et al.; [11] Costelli et al.[12] and Aversa et al.[13] reported the role of myostatin signaling in reducing muscle mass in cancer.

One of the factors affecting body composition is lifestyle. Therefore, researchers study physical activity as an effective factor on physiological and anthropometric function in women with breast cancer.[6] Previous research has shown that one of the most important non-pharmacological interventions that can help improve the quality of life of cancer patients is exercise.[14,15] The benefits of exercise have been confirmed for patients with breast cancer, and physical inactivity can increase the risk of breast cancer by 2 to 5 times.[16] Exercise may also reduce many of the side effects of cancer treatment, including chemotherapy and radiation therapy.[17] In fact, one of the reasons for recommending exercise activities for cancer survivors is that the numerous biotoxicities that occur in the body during cancer treatment are favorably neutralized by exercise ac-

tivities.[18] In this regard, Irwin et al. showed that the risk of death from breast cancer is reduced by 45% in women who were physically active before the diagnosis but then exercised.[19]

Resistance training is a strong stimulus for increasing the size of muscle fibers and hypertrophy, in which myostatin changes play a role in regulating muscle growth.[20] Considering that resistance training is a non-pharmacological solution to maintain body muscle mass in cancer patients[21], this style of exercise can be used to treat and reduce the side effects of cancer treatment such as chemotherapy. Efforts to achieve enhancement of muscle strength and muscle hypertrophy throughout the training path are related to the period of the training program in which the muscles adapt to the training. Exercise trainers use training schedules and changes in training intensity and volume during training sessions to find the solution to find the fastest path to hypertrophy in the training program.[22] In fact, training periodization is one of these variables that can affect training results and adaptations. Training periodization is the manipulation and regular changes in the training process to develop training adaptation and avoid the phase of incompatibility and uniformity of training responses. Although there are different models of workout periodization, two types of traditional or linear periodization and nonlinear or wave periodization are more commonly used. In linear periodization the volume of training decreases as the intensity of training increases linearly throughout the training program. But in nonlinear or wave periodization, Intensity and volume of training alternate daily or weekly[23,24] Linear periodization is a classic type of periodization in which the intensity of the exercise is gradually increased, resulting in a reduction in the volume of exercise within and between the exercise cycles. Nonlinear periodization is characterized by frequent changes in training intensity and volume during the training period. In this timing style, instead of changing the intensity of the exercise during a training period, they make these changes on a weekly or even daily basis. Given that the purpose of scheduling is to create metabolic fatigue, mechanical overload, or a combination of both, which allows for optimal flexibility over a long period of training by manipulating training stimuli?[22]

Given that insulin resistance is associated with body composition and obesity and myostatin is a myokine associated with muscle mass;[3,13] It is important to examine the changes in these variables in intervention programs in the treatment of breast cancer. The need for this study justifies the need for the present study, which has not specifically studied the effect of nonlinear resistance training on insulin resistance and myostatin levels in women with breast cancer.

According to the above, the aim of this study was to compare the effect of nonlinear resistance training on insulin resistance and serum myosatin level in women with breast cancer.

Methodology

In the present quasi experimental study, 20 women with breast cancer referred to Imam Hassan Chemotherapy and Radiotherapy Center in Dezful, Iran were selected by random sampling method. Criteria for inclusion in this study include definitive diagnosis of breast cancer by an oncologist, disease level 1-2, chemotherapy intervention, no pain and fatigue and declaration of readiness to cooperate, no severe vision and hearing problems, age range 50-40 years and light Life was inactive (maximum oxygen consumption was less than 40 ml/kg/min). Exclusion criteria included dissatisfaction with participation in the research project, failure to follow the exercise intervention program, having periods of pain and fatigue during the training and patient death.

After selecting the research samples in an educational session that was conducted jointly with the presence of the nurse and tips about educational services, issues such as how to use the drug, side effects of taking the drug, scheduling the use of drugs by introducing centers that provide medical services to patients were educated. In addition to the training tips provided by the nurse, tips on the research design and how to participate in it were presented to patients by the researcher, and after signing the informed consent, a schedule for physiological tests and blood sampling was coordinated. Then, the subjects were randomly divided into 3 groups: Linear resistance training, nonlinear resistance training and control group.

In this study, exercise intervention included a resistance training program with non-linear periodization for patients with breast cancer, which included 12 weeks of training with 3 training sessions per week. Exercise workout included seated leg extension, leg curl, dumbbell chest press, incline dumbbell chest press, sitting rowing, dead lift, and abdominal crunch, lat pull down, back thigh, dumbbell shoulder press, biceps barbell and triceps barbell. Based on nonlinear resistance training, it has been suggested by Kramer and Fleck.[25] The implementation of the training program in the nonlinear schedule is such that the intensity of training in training sessions is different (Tables 1-4). The intensity of the exercise in the present study will be calculated based on a maximum repetition (1RM) for different movements using Brzezinski formula.[26]

Table 1: *Period, repetition, training load and rest time according to training intensity*

Intensity	Very light	light	Moderate	Heavy
Exercise load (1RM)	40	60	75	90
set	1	2	3	3
Repetition	20	15	10	4
Rest between movements	1	01-Feb	02-Mar	03-May

1RM=Weight ÷ (1.0278-0.0278 × Number of repetitions)

The control group was trained to maintain normal physical activity and leisure and not to participate in any new exercise programs during the research period. After the research intervention period, the control group participants who participated in the baseline measurements and 12 week post-test had the opportunity to participate in a program similar to the training group.

Table 2: *Intensity of nonlinear resistance training in training sessions*

Week Season	1	2	3	4	5	6	7	8	9	10	11	12
1	L	L	M	VL	M	L	VL	H	L	M	L	VL
2	M	VL	H	H	M	M	M	VL	L	M	M	H
3	L	H	L	L	L	H	L	M	H	VL	VL	L

L: Light; VL: Very light; M: Moderate; H: Heavy

Table 3: *Demographic and anthropometric characteristics of the subjects*

Variables	Training group	control group
Age (yrs)	45.20 ± 3.05	43.60 ± 2.76
Height (cm)	156.10 ± 4.43	156.92 ± 3.37
Weight (kg)	72.68 ± 3.29	73.14 ± 3.10
BMI (kg/m2)	29.83 ± 0.83	29.71 ± 1.14
BF%	39.12 ± 1.96	37.57 ± 2.11

Before the intervention, training was performed to evaluate blood variables in patients. Blood sampling was performed at a specific time of 7-8 in the morning and fasting (8-10 hours of night fasting). Due to the fact that physical activity may affect the level of blood variables, the subjects were told not to do strenuous exercise on the day before blood sampling and if so, the researcher must be informed. Blood samples were taken 48 hours after the last training session to assess the research variables for the post test.

Fasting serum glucose were measured by kits (Pars Azmoon®, Tehran, Iran) and using the photometric methods and an autoanalyzer (Biotecnica instrument®, Rome, Italy). The serum fasting insulin levels were assessed by the Enzyme Linked Immunosorbent Assay (ELISA) method and using the human insulin kit (ZellBio®, Ulm, Germany). HOMA-IR was calculated using the following formula: HOMA-IR=[fasting glucose (mmol/l) × fasting insulin (mU/l)/22.5].

Data were used using descriptive statistical tests (frequency, mean and standard deviation) and Shapirovilk statistical tests to check the normality of information and Leven test to check the homogeneity of variances. Analysis of

Table. 4: *Results of paired sample t-test for in-group comparison of research variables*

Variables	group	Pre test	Post test	t	P	F	P
Weight	Training	72.68 ± 3.29	71.64 ± 3.43	1.647	0.134	0.28	0.603
(Kg)	control	73.14 ± 3.10	72.44 ± 3.34	1.008	0.34		
BMI	Training	29.83 ± 0.83	29.41± 1.20	1.67	0.129	0.002	0.965
(kg/m2)	control	29.71 ± 1.14	29.44 ± 1.60	0.992	0.347		
PBF%	Training	39.12 ± 1.96	36.16 ± 1.19	8.348	0.001*	5.005	0.038*
	control	37.57 ± 2.11	37.99 ± 2.30	-0.976	0.354		
Myostatin	Training	26.31 ± 5.67	21.82 ± 4.68	4.346	0.002*	6.174	0.023*
(ng/ml)	control	26.43± 6.04	26.59± 5.44	-0.12	0.907		
Glucose	Training	5.76 ± 0.45	5.58 ± 0.25	1.571	0.151	0.71	0.41
(mmol/l)	control	5.64 ± 0.45	5.71 ± 0.39	-0.797	0.446		
Insulin	Training	10.50 ± 1.27	7.98 ± 0.66	6.097	0.001*	0.28	0.001*
(mU/l)	control	10.20± 1.03	9.85 ± 0.74	1.909	0.089		
HOMA-IR	Training	2.69 ± 0.38	1.98 ± 0.21	6.299	0.001*	0.28	0.001*
	control	2.57 ± 0.41	2.50 ± 0.27	1.227	0.251		

BMI: Body mass indexes; PBF: Percent Body Fat;*: P< 0.05.

covariance was used to analyse the differences between groups and statistical analysis was performed using SPSS software version 26 and a significance level of $P \leq 0.05$.

Results and Discussion

The results of paired sample t-test showed a significant decrease in body fat percentage (P<0.001), serum myostatin level (P=0.002), fasting insulin (P<0.001), and insulin resistance index (P<0.001) in the ratio exercise group. Baseline values were observed but no significant differences were observed in weight, body mass index and fasting glucose (P>0.05); In the control group, no significant differences were observed compared to the baseline values in any of the research variables (P>0.05). Also, in the study of intergroup changes, the results of analysis of covariance showed that changes in body fat percentage (P=0.038), serum myostatin level (P=0.023), fasting insulin (P<0.001), and insulin resistance index (P<0.001) It was significant in the exercise group compared to the control group.

The results of the present study showed that after the training period, a significant reduction in insulin resistance and body fat percentage was observed. Bruno et al. Also reported that aerobic exercise plays a positive role in reducing insulin resistance in women with breast cancer by improving body composition.[27] Chang et al. Also reported in their study that after a period of combined aerobic and resistance training, in addition to increasing physical fitness, a significant improvement in insulin sensitivity was observed in women with breast cancer.[28] The results of this study were consistent with the improvement in insulin resistance in our study. Regarding the effect of exercise on glucose uptake, it can be said that one session of physical activity stimulates glucose uptake through the up regulation of exercise on GLUT4 levels in skeletal muscle membranes. This effect is independent of insulin and glucose uptake continues for several hours after the end of physical activity. Physical activity also increases insulin sensitivity in skeletal muscle. This effect lasts for several hours after the end of physical activity and is clearly dependent on insulin and insulin function.[29] Regarding the chronic effect of regular exercise on insulin resistance, it can be said that exercise training by increasing cell sensitivity with insulin dependent molecular pathways that improve insulin signaling (ACC and MAPKs PI3-kinase) as well as insulin independent pathways (Akt and mTOR AMP-kinase), are involved in improving insulin signaling as well as better glucose uptake.[9,29]

Also, in our study, a significant decrease in serum myostatin level was observed after the period of nonlinear resistance training; which was in line with the reduction in body fat percentage as well as insulin resistance. Previous research has shown that resistance exercise has an effective role in improving body composition and reducing insulin resistance is associated with weight loss and a decrease in body fat percentage;[30,31] Myostatin is a myokine associated with muscle mass[13] and insulin resistance[10] that is more concentrated in women with breast cancer than in healthy women.[32] It seems that the decrease in serum myostatin in the present study is due to the effects of resistance training on reducing body fat percentage as well as insulin resistance in women with breast cancer. The effects of myostatin on glucose metabolism may be due to the effects on muscle tissue itself, as only inhibition of myostatin signaling in skeletal muscle, not fat, indicates an improvement in insulin sensitivity.[33] According to myostatin, myostatin is an inhibitor of muscle growth[10] and on the other hand, resistance training is a muscle stress for hypertrophy that is adapted by inhibiting myostatin,[34] it can be said that part of the effects Insulin resistance training is associated with changes in glucose metabolism in muscle, which may be associated with decreased serum myostatin.[33]

Conclusion

Our study was the first randomized controlled trial to investigate the effects of resistance training with nonlinear timing of insulin resistance and serum myostatin levels as a biomarker associated with breast cancer associated with insulin resistance and obesity as two associated complications. Overall, the results of the present study showed that a 12 week period of regular resistance training with nonlinear timing reduced body fat percentage and insulin resistance in women with breast cancer. The results of our research also indicate the beneficial role of resistance training in reducing serum myostatin as a biomarker associated with cachexia due to cancer, which is also associated with obesity as well as insulin resistance. Given that the complications of breast cancer are associated with obesity as well as insulin resistance, the clinical effects of resistance training on women with breast cancer can be considered useful; therefore, it is recommended that women with breast cancer use a resistance training program to reduce the complications of cancer and the treatments associated with this disease.

Appreciation

The authors thank the Imam Hassan (AS) Chemotherapy and Radiotherapy Centre in Dezful, the participating patients and all those who contributed to the present study.

References

1. Fathollahi Shoorabeh F, Tarverdyzadeh B, Aminbaksahayesh S, et al. Effect of 8 weeks resistance training on some antioxidant/oxidative indexes in postmenopausal women with breast cancer. HMS; 2020:23:4:279-83.
2. Vanaky B, Shakeri N, Nikbakht H, et al. The effect of 6 weeks swimming and consumption of zingiber officinale roscoe extract on some inflammatory and anti-inflammatory factors in heart tissue of mice induced by breast cancer. J. Med. Plan; 2018:4:68:32-40.
3. Rose D, Komninou D, Stephenson G, et al. Obesity, Adipocytokines, and insulin resistance in breast can-

cer. Obes Rev; 2004:5:3:153-65.

4. Hosseinpour Delavar S, Boyerahmadi A, Soleymani A, et al. Effect of eight weeks of aerobic interval training and urtica dioica supplement on some inflammatory indicators and glycemic control in men with type 2 diabetes. Jundishapur J. Med. Sci; 2020:19:2:123-35.
5. Bianchini F, Kaaks R, Vainio H, et al. Weight control and physical activity in cancer prevention. Obes Rev; 2002:3:1:5-8.
6. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, et al. Effects of aerobic and resistance exercise on metabolic syndrome, Sarcopenic obesity, And circulating biomarkers in overweight or obese survivors of breast cancer: A randomized controlled trial. J Clin Oncol; 2018:36:9:875-83.
7. Herrero F, San Juan AF, Fleck SJ, et al. Combined aerobic and resistance training in breast cancer survivors: A randomized, Controlled pilot trial. Int. J. Sports Med.; 2006:27:07:573-80.
8. Nikander R, Sievänen H, Ojala K, et al. Effect of a vigorous aerobic regimen on physical performance in breast cancer patients: A randomized controlled pilot trial. Acta Oncol.; 2007:46:2:181-6.
9. Ghalavand A, Delaramnasab M, Ghanaati S, et al. Comparison of the effect of telenursing and aerobic training on cardiometabolic and anthropometric indices in patients with type 2 diabetes. RJMS; 2021:28:4:34-45.
10. Amor M, Itariu BK, Moreno-Viedma V, et al. Serum myostatin is upregulated in obesity and correlates with insulin resistance in humans. Exp. Clin; 2019:127:08:550-6.
11. Lokireddy S, Wijesoma IW, Bonala S, et al. Myostatin is a novel tumoral factor that induces cancer cachexia. Biochem; 2012:446:1:23-36.
12. Costelli PM, Muscaritoli A, Bonetto F, et al. Muscle myostatin signalling is enhanced in experimental cancer cachexia. Eur. J. Clin. Invest.. 2008:38:531-9.
13. Aversa Z, Bonetto A, Penna F, et al. Changes in myostatin signaling in non-weight-losing cancer patients. Ann. Surg. Oncol.; 2012:19:4:1350-6.
14. Hersch J, Juraskova I, Price M, et al. Psychosocial interventions and quality of life in gynaecological cancer patients: A systematic review. Psycho-Oncol.; 2009:18:8:795-810.
15. Galvão DA, Newton RU. Review of exercise intervention studies in cancer patients. J. Clin. Oncol.; 2005:23:4:899-909.
16. Shahar S, Salleh RM, Ghazali AR, et al. Roles of adiposity, lifetime physical activity and serum adiponectin in occurrence of breast cancer among Malaysian women in Klang Valley. Asian Pac J Cancer Prev;2010:11:1:61-6.
17. Repka CP, Hayward R. Oxidative stress and fitness changes in cancer patients after exercise training. MSSE; 2016:48:4:607-14.
18. Mijwel S, Jervaeus A, Bolam KA, et al. High-intensity exercise during chemotherapy induces beneficial effects 12 months into breast cancer survivorship. J. Cancer Surviv.; 2019:13:2:244-56.
19. Irwin ML, Smith AW, McTiernan A, et al. Influence of pre-and postdiagnosis physical activity on mortality in breast cancer survivors: The health, Eating, Activity, and lifestyle study. J. Clin. Oncol.; 2008:26:24:3958.
20. Latres E, Pangilinan J, Miloscio L, et al. Myostatin blockade with a fully human monoclonal antibody induces muscle hypertrophy and reverses muscle atrophy in young and aged mice. Skeletal muscle; 2015:5:1:1.
21. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: A multicenter randomized controlled trial. J. Clin. Oncol.; 2007:25:28:4396-404.
22. Majeedkutty N, Jabbar M, Min M, et al. Effect of linear and non-linear periodized resistance training on dynamic postural control and functional movement screen. MOJ Yoga Phy Ther; 2018:3:1:18-22.
23. Khodaei K, Hamedinia MR, Hosseini Kakhak SA, et al. The effect of sixweeks plyometric training with nonlinear periodization on hormonal changes, Muscle hypertrophy and leg muscles elastic property in male athletes (nonlinear periodization of plyometric training and hormonal changes). Sport Physiology; 2015:8:31:45-62.
24. Bradley-Popovich GE, Haff GG. Nonlinear versus linear periodization models. Strength Cond J STRENGTH COND J; 2001:23:1:42.
25. Kraemer WJ, Fleck SJ. Optimizing strength training: Designing nonlinear periodization workouts: Human Kinetics; 2007.
26. Brzycki M. Strength testing predicting a one-rep max from reps-to-fatigue. JOPERD; 1993:64:1:88-90.
27. Bruno E, Roveda E, Vitale J, et al. Effect of aerobic exercise intervention on markers of insulin resistance in breast cancer women. J. Cancer Care; 2018:27:2:e12617.
28. Chang JS, Kim TH, Kong ID, et al. Exercise intervention lowers aberrant serum WISP-1 levels with insulin resistance in breast cancer survivors: A randomized controlled trial. Scientific reports; 2020:10:1:1-9.
29. Tahan P, Ghalavand A, Heydarzadi S, et al. Effects of aerobic interval training on iron stores and gly-

cemic control in men with type 2 diabetes. RJMS; 2020:27:8:105-14.

30. Ghalavand A, Shakerian S, Zakerkish M, et al. The effect of resistance training on anthropometric characteristics and lipid profile in men with type 2 diabetes referred to golestan hospital. Jundishapur J. Med. Sci.; 2017:13:6:709-20.
31. Tresierras MA, Balady GJ. Resistance training in the treatment of diabetes and obesity: Mechanisms and outcomes. J. Cardiopulm; 2009:29:2:67-75.
32. Hasani F, Gholami M, Ghazalian F, et al. Effect of six weeks of endurance training on tumor volume and muscle myostatin levels in female mice with breast cancer: implications for cachexia. Iranian Quar. J. of Breast Dis.; 2018:11:3:44-5.
33. Guo T, Jou W, Chanturiya T, et al. Myostatin inhibition in muscle, but not adipose tissue, decreases fat mass and improves insulin sensitivity. PloS one; 2009:4:3:e4937.
34. Walker KS, Kambadur R, Sharma M, et al. Resistance training alters plasma myostatin but not IGF-1 in healthy men. Med Sci Sports Exerc; 2004:36:5:787-93.