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Vascular Senescence and Resistance Exercise Training: Focus on Circulating Endothelial Cell-Derived MicroRNA-92a and Endothelin-1

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ABSTRACT

Background and objectives: Vascular senescence refers to specific aging-associated changes in the endothelial cells. The purpose of this study was to investigate effects of 12 weeks of resistance training with elastic bands on circulating endothelial cell-derived microRNA-92a and endothelin-1 (ET-1) in elderly women with osteosarcopenic obesity (OSO).

Methods: In the present randomized clinical trial, 48 elderly women with OSO were randomly divided into a control group (n=22) and an experimental group (n=26). The subjects in the intervention group performed 12 weeks of resistance training with elastic bands three times a week. The participants became familiar with targeted number of repetitions and OMNI-resistance exercise scale to control exercise intensity.

Results: The mean age, body fat percentage, body mass index (BMI), and bone mineral density T-score for the hip and L1-L4 lumbar spine of the subjects were 64.13±3.68 years, 45.4%±6.56, 33.1±3.71 kg/m², and -1.86±1.42, respectively. After the 12-week resistance training, we observed a significant decrease in serum level of mir-92a in the experimental group compared to the control group ($p=0.03$). However, there was no significant difference between the study groups in terms of body weight, BMI, body fat percentage, total cholesterol, and ET-1 ($p \geq 0.05$).

Conclusion: The 12-week resistance training program seems to modulate and decrease serum mir-92a expression in elderly women with OSO. The lack of a significant change in BMI, body fat percentage, and ET-1 levels following the exercise training might be due to the type and intensity of the exercises.

Keywords: Resistance Training, Obesity, Sarcopenia, Osteoporosis, Aged, Vascular Stiffness.

INTRODUCTION

Osteosarcopenic obesity (OSO) is a syndrome characterized by hormonal changes, decreased physical activity, decreased dietary protein or vitamin D deficiency as well as increased body fat percentage (1, 2). It is associated with some catabolismic conditions caused by chronic inflammation and osteoporosis (3, 4).

Vascular aging is associated with age-related changes in the vessels, including formation of atherosclerotic plaques, arterial stiffness, fibrosis, and increased thickness of the tunica media of the vessels. It can affect the threshold, process, and severity of various cardiovascular diseases, thus making it one of the most important risk indicators of mortality in patients with cardiovascular disease (5-8). It has been shown that endothelial cell-derived miR-92a is increased in vascular senescence, and inhibiting miR-92a expression could suppress oxidative stress or inflammatory factors (9). As the proinflammatory regulator in endothelial cells, miR-92a is reduced both in arteries of older adults and mouse model of vascular aging, and activates inflammatory cytokines and increases monocyte adhesion molecules (10).

Exercise training, even at low and moderate intensities, is essential for maintaining and improving muscle strength and quality, balance, and range of motion in the elderly (8). Today, elastic bands are widely used for rehabilitation purposes because of their cost-effectiveness, easy accessibility, impact on body composition, physical function, physiological adaptation, and applicability in a range of upper and lower body exercises (8).

Both aerobic exercise and resistance training improve endothelial function. Aerobic exercise is associated with lower levels of stiffness in the central arteries, indicating that regular exercise can reduce or prevent aging and arterial stiffness (8, 11, 12). In contrast, the effects of resistance training are not as well-known as aerobic exercise, although current data suggest a role in ameliorating endothelial dysfunction. However, chronic resistance training has been shown to improve vascular function and reduce the risk of hypertension (13). In addition, there is an inverse correlation between muscular strength and aortic stiffness, suggesting that improving muscle strength may also be beneficial for vascular health. Williams et al. (2013) showed that resistance training can improve vascular function in older women (14).

Various studies have been recently conducted on the effects of acute and chronic exercises on circulating miRNAs. For example, Barber et al. reported up-regulation of miR-92a in response to 20 weeks of regular endurance training (15). In another study, three weeks of acute resistance training decreased miR-92a levels in cerebral cortex of mice after traumatic brain injury, indicating the important role of mir-92a in exercise training-induced adaptation following traumatic brain injury (16).

In the present study, we hypothesized that resistance training using elastic bands may improve the age-related decline in endothelial function. For this purpose, we examined levels of vascular aging-related serum mir-92a and endothelin-1 (ET-1) in elderly women with OSO following 12 weeks of resistance training with elastic bands.

MATERIALS AND METHODS

This randomized clinical trial was performed based on the CONSORT statement for randomized trials of non-pharmacologic treatments (17, 18). This trial was approved by the Iranian Ethics Committee of Sport Sciences Research Center (ethical code: IR.SSRC.REC.1398.040). In this study, out of 102 referred patients to an orthopaedic specialist, 32 cases due to absence of inclusion criteria and seven cases due to unwillingness to participate were excluded from the study. The remaining 63 subjects were randomly divided into an experimental group (n=32) and a control group (n=31). The final sample size was estimated to be 63 by considering 20% dropout. In this study, eligible patients were selected using dual-energy X-ray absorptiometry (DEXA), age range of 60-80 years, body fat percentage of >32%, body mass index (BMI) of >30 kg/m^2, -2.5≤T-score≤-1 from L1-L4 or whole femur or femoral head, and 10-m walking speed (10 MWT) of ≤ 1 meter per second squared (19, 20). exercise for more than 30 minutes during the past six months, and taking no dietary supplements for the past three months. Exclusion criteria were parallel exercise, following a weight loss diet of more than 5 kg in the last three months, hormone therapy, or taking any medication that affects bone density, adipose tissue, or the hormonal system.

Informed written consent was obtained from all patients after initial evaluation and randomization. The patients in the control group did not participate in any diet or exercise programs and were instructed no to change their usual diet and physical activity during the study period.

The subjects were trained about the exercise method during two sessions prior to the start of the exercise protocol. In addition, the patients were trained to control exercise intensity using the targeted number of repetitions and the OMNI-resistance exercise scale (OMNI-RES) in the first two sessions (21, 22). During resistance exercise with elastic bands, the patients could easily adjust the resistance intensity by increasing or decreasing the arm distance. They were asked to choose a suitable elastic band that allowed them to perform 20-repetition maximum (12). In general, resistance training with elastic bands (Thera Band®, Hygienic Co., Akron, OH, USA) was designed and accomplished to train all major muscle groups. The exercise volume and intensity were constantly increased three times a week under the supervision and control of the researchers. The patients were divided into four groups of 6-8 people to facilitate control, monitoring, and increasing the accuracy of the movements. Each group participated in a training session at a specified time under the direct and full supervision of the researcher. The exercises were performed according to the guidelines of the American College of Sports Medicine for resistance training in elderly. Each training session began with a 10-minute warm up, then resistance training with elastic band (35-40 minutes) was performed in a controlled and slow manner for each of the six muscle groups (legs, back, abdomen, chest, shoulders, and arms). The training session ended with 5-minute cool down. In order to adhere to the principle of overload, the intensity of exercise was increased every two weeks by changing the elastic bands. In addition, training volume increased by increasing the number of sets from one to two sets and progression based on individual recovery.

This was defined by the ability of the patient to perform two more repetitions in the second set, and reporting resistance of less than 7 (0: very easy to 10: very difficult) for active muscle based on the OMNI scale (21). It should be noted that all training programs were performed daily, between 8:00 and 12:00 AM (23).

Blood sampling (5 ml blood) and the DEXA method were performed after measuring the initial functional tests. Forty eight hours after the last training session, blood sampling, DEXA method, and anthropometric, functional and laboratory measurements were performed. Serum ET-1 concentrations were measured with an enzyme-linked immunosorbent assay (ELISA) kit (Eastbiopharm, Zhejiang, China) using an ELISA plate reader [STATFAX2100, Multi-detection Multi Plate Reader, USA (inter-assay: CV< %12, intra-assay: CV< %10)]. The mir-92a expression levels were measured in blood serum samples by real time RT-PCR, and the U6 gene was used as the control gene.

Two-way analysis of variance (group×time design) was applied for intergroup comparisons. Effect size (ES) was calculated using partial eta squared test. All tests were carried out in SPSS 22 software at the significance level of 0.05.

RESULTS

At baseline, no difference was observed between the study groups (Table 1).

Table 1- Comparison of baseline characteristics of participants in the resistance training and control groups

Variable	Group	Baseline	t	P-value
Age (years)	Con (n=31)	64.05±3.35	-0.067	0.947
	Ex (n=32)	64.11±3.81		
BMI (kg/m^2)	Con (n=31)	32.53±2.01	-0.761	0.451
	Ex (n=32)	33.72±3.15		
Daily calorie	Con (n=31)	1778.05±91.44	-0.276	0.797
	Ex (n=32)	1802.19±88.54		
Carbohydrate (%)	Con (n=31)	55.13±6.73	-0.752	0.398
	Ex (n=32)	56.38±4.95		
Fat (%)	Con (n=31)	28.23±4.82	0.644	0.522
	Ex (n=32)	27.66±3.44		
Protein (%)	Con (n=31)	16.96±2.09	0.981	0.334
	Ex (n=32)	15.92±1.86		
Vitamin D (IU/day)	Con (n=31)	91.11±6.53	-1.034	0.273
	Ex (n=32)	93.35±8.11		
Calcium (mg/day)	Con (n=31)	733.08±400.30	0.485	0.618
	Ex (n=32)	729.29±288.24		
Phosphate (mg/day)	Con (n=31)	1411±524.81	0.398	0.689
	Ex (n=32)	1368.7±363.93		

In addition, inter-group comparisons showed a significant decrease in serum mir-92a expression in the experimental group compared to the control group (p=0.03). There was no significant difference in body weight, BMI, body fat percentage, and ET-1 (Figure 1 and 2).

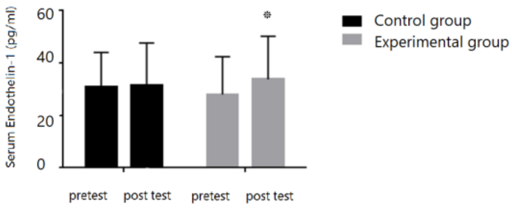

Figure 1-Serum ET-1 levels following the 12-week resistance training

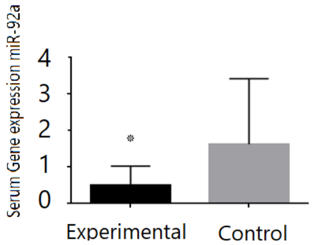

Figure 2- Serum miR-92a changes following the 12-week resistance training

DISCUSSION

In the present study, we found that resistance training with elastic bands affected serum mir-92a levels in women with OSO syndrome. However, we found no significant difference in body weight, BMI, body fat percentage, and serum ET-1 between the study groups.

Although miRNAs have emerged as potential key mediators of exercise adaptation in muscles, such as the smooth and skeletal muscles, specific threshold intensities required for up-regulation of specific miRNAs and of muscle-specific markers have not been rigorously assessed until now. In our study, it was observed that miR-92a expression and endothelial ET-1 levels were significantly affected by the 12-week resistance training. Some studies have pointed out the role of miR-92a in the cellular processes of obesity and its increased expression in adipocytes of obese and cardiovascular patients (24, 25). In addition, other studies reported an increase in serum mir-92a expression along with an increase in inflammatory markers in elderly patients with acute myocardial infarction, and a significant reverse correlation between serum mir-92a expression and inflammatory markers, such as tumor necrosis factor-α and C-reactive protein (26-28). Barber et al. reported that circulating miR-92a-3p levels decreased after 20 weeks of chronic endurance training in previously sedentary adults (29). Furthermore, Párrizas et al. (2015) observed a decrease in the level of miR-92 following 12 weeks of aerobic exercise training in older subjects (30). Taurino et al. illustrated that a 10-weeks endurance exercise training program increased both circulating miR-92a and miR-92b in patients with cardiovascular disease (31). Furthermore, Nielsen showed regulation of circulating miR-92a levels following 12 weeks endurance training in healthy trained men (32).

Endothelium secretes some vasodilation factors such as ET-1, and increased levels of ET-1 in the elderly have been associated with elevated blood pressure and cardiovascular disease (33, 34). Our findings are consistent with the results of some studies (35-38) but inconsistent with the results of another study (38).

The present study showed that the 12-week resistance training in OSO women did not change serum ET-1 levels. Indeed, there is a difference between serum and endothelial ET-1 concentration. It has been shown that endothelial ET-1 but not serum ET-1 concentrations are changed in some conditions, such as following exercise training (39). In our study, the elastic band resistance training did not change serum levels of ET-1 in OSO women, indicating that serum ET-1 is not involved in vascular adaptations to resistance training. Another explanation could be that the signal transduction pathways of endothelin receptors may be changed after the 12-week resistance training in OSO women. Therefore, it seems that the 12-week resistance training may alter ET receptors of the endothelial cells in OSO women without changing serum ET-1 levels. However, we cannot confirm that the 12-week resistance training changed endothelial ET receptors.

CONCLUSION

Based on the results, it can be concluded that the resistance training with elastic bands can significantly affect miR-92a expression in elderly women with OSO. The training also caused non-significant improvements in total serum levels of vascular aging biomarkers and ET-1. Our results could be beneficial for determining an optimal protocol for elderly women with OSO. More research is required to compare the effectiveness of machine- and elastic band- resistance training protocols at different intensities and volumes.

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DECLARATIONS

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Ethics approvals and consent to participate

This study was approved by the Iranian Ethics Committee of Sport Sciences Research Center (ethical code: IR.SSRC.REC.1398.040). Informed consent was obtained from all subjects prior to participation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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