ISSN: 2538-5887; Pathobiology Research. 2025; 28 (1): 65-70

The effect of CX training on endothelial microparticles and nitric oxide in women with metabolic syndrome

ARTICLE INFO

Article Type:
Original Paper

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ABSTRACT

Introduction: Endothelial dysfunction is a consequence of obesity and metabolic syndrome. In this study, the effect of CX Works training (CX) on serum endothelial microparticles (EMPs) and nitric oxide (NO) as markers of vascular endothelial function was measured in women with metabolic syndrome.

Methods: For this purpose, 24 sedentary adult obese women were randomly divided into CX (8 weeks, n= 12) and control (no training, n = 12) groups. CX were performed every other day for 8 weeks. Serum NO and EMPs after an overnight fast were measured in both study groups (pre-training) and measurements were repeated 48 hours after the last CX training session (post-training). Independent / paired t-test was used to compare between groups.

Results: CX training resulted in significant increase in serum NO and decrease in EMPs compared to the pre-training ($p<0.05$). No significant change were observed in any variables in control groups ($p>0.05$).

Conclusion: CX training, as a novel exercise modality, is associated with improved vascular endothelial function in women with metabolic syndrome. Measurement of other vascular markers is needed to better understand the mechanisms responsible for these changes.

Keywords:

CX training, Metabolic syndrome, Nitric Oxide, Endothelial microparticles.

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INTRODUCTION

In the past two decades, the incidence of obesity and increased fat mass in industrialized and developing societies has increased significantly, which is the basis for some cardiovascular diseases, respiratory problems, kidney and liver diseases, and type 2 diabetes (1). Each of these diseases alone affects the metabolic function of body tissues, but when several diseases occur simultaneously in obese individuals, it is introduced as metabolic syndrome (1). Metabolic syndrome is known as an obesity-related disorder that includes some metabolic markers such as increased blood glucose, insulin resistance, increased triglycerides and high-density lipoprotein, increased systolic and diastolic blood pressure with decreased low-density lipoprotein and increased waist circumference. At least 4 of these indicators in an individual are indicative of metabolic syndrome (2). These metabolic disorders, in the presence of obesity or metabolic syndrome, are associated with abnormalities such as oxidative stress and vascular endothelial dysfunction (3). Therefore, the diagnosis and strategies for improving markers of vascular endothelial function and

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cardiovascular risk factors in patients with metabolic syndrome are important in the field of clinical sciences.

The endothelium is known as a key factor in regulating blood vessel function, and the role of nitric oxide (NO) as a prominent marker in proper vascular endothelial function is well established, such that reduced vasodilation is one of the consequences of reduced NO levels in the body (4). NO is used as a criterion for assessing cardiovascular health and endothelial function and plays a role as a vasodilator in the balance of vascular tone (5). On the other hand, endothelial microparticles (EMPs) have been introduced as a biomarker of endothelial damage and vascular disorders, which are involved in cardiovascular, inflammatory and metabolic pathogenic mechanisms (6). Increased EMPs lead to reduced nitric oxide synthesis, increased inflammatory reactions, promotion of coagulation processes, and changes in angiogenesis and programmed cell death processes. These particles play an important role in the destruction of blood vessel wall cells in conditions of atherosclerosis (7).

Therefore, it is hypothesized that the development of strategies such as drug therapy or exercise training that reduce EMPs and increase NO, especially in obese individuals or patients with metabolic syndrome, is clinically significant. In this regard, although Ghorashi et al, (2019) reported an improvement in cardiovascular risk factors along with a decrease in EMPs in overweight men (8), the role of CXWORKS training (CX) on EMPs and NO in women with metabolic syndrome has not been studied so far. Among the training methods, CX which focuses on strengthening the upper body muscles, especially the core muscles, has recently received attention (9). This training method is another relatively new exercise introduced by Les Mills. This exercise works mostly on the upper body and aims to strengthen the core muscles (9). Some studies have investigated the effect of this type of training on reducing body fat, improving the function of liver enzymes such as AST, ALT, and ALP, and improving insulin resistance in overweight women (10). So far, most studies have addressed the effects of endurance and resistance training on metabolic, hormonal, and enzymatic components in healthy and diseased populations. However, no study has reported the endothelial effects of CX, which is a combination of both endurance and strength training, especially in women with metabolic syndrome. Based on this limitation, the present study aimed to determine the effect of CX training on serum NO and EMPs as markers of vascular endothelial function in women with metabolic syndrome.

MATERIALS AND METHODS

Subjects: The statistical population of this semi-experimental study consists of obese adult women aged 30 to 45 years of old ($30 \leq BMI \leq 36$) with metabolic syndrome. The statistical sample consists of 24 inactive obese adult women with metabolic syndrome who are purposive sampling selected from the statistical population to participate in the study and are randomly divided into 2 groups: 1) CX group (CXWORKS) "8 weeks of CX training every other day", 2) control group "no intervention".

Inclusion or Exclusion criteria: The main inclusion criteria for the study were obesity ($30 \leq BMI \leq 36$) and metabolic syndrome. In other words, those individuals who had at least 4 of the metabolic syndrome markers (waist circumference >88 cm, fasting glucose >100 mg/dL, systolic blood pressure >120 mm and diastolic blood pressure >90 mm, HDL <50 mg/dL, and TG >150 mg/dL) were included in the study. The study subjects were non-smokers, non-pregnant, and had no history of a controlled diet or regular exercise for at least the past 6 months. Individuals with a history of chronic diseases such as cancer, gastrointestinal and renal diseases, and orthopedic abnormalities were excluded from the study. Irregular participation in exercise training during the study were exclusion criteria.

Anthropometric measurements: Anthropometric indices were recorded both before and after intervention. Height was determined using a rigid tape measure, with participants barefoot, to a precision of 0.1 cm. Measurements of hip and abdominal circumferences were taken at their widest points following a normal exhalation, using a rigid tape measure with a measurement error of less than 0.1 cm. Weight was assessed using a Seca scale accurate to 0.5 kg. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. The percentage of body fat was ascertained using a body composition analyzer (OMRON-BF 508,

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Finland).

Interventions: The duration of the intervention for the study groups was 8 weeks. In CX groups, the training program was conducted for 8 weeks (every other day) and each session lasting 45 minutes under the supervision of a tester. Each exercise session consisted of a 10-minute warm-up, 30-minute CX workout, and 5 minute cool-down. The exercises were divided into three levels: Level 1; 8 exercises, Level 2; 9 exercises, and Level 3; 6 exercises. During the initial week, participants engaged in six Level 1 exercises, six Level 2 exercises, and two Level 3 exercises. Subsequently, each week saw the addition of one exercise per level. By the third week, participants had finished all Level 1 exercises, transitioning this level to a maintenance phase. The completion of Level 2 exercises occurred in the fourth week, after which these exercises also moved to a maintenance phase for the remaining two weeks. By the fifth week, all Level 3 exercises were completed, and participants performed exercises from all three levels (11). The control group maintained their usual lifestyle for eight weeks and did not engage in any physical activity program.

Laboratory and clinical measurements: Fasting blood samples (12-h overnight fast) was collected between the hours of 8 to 9 am (pre-training). Subjects were asked to avoid doing any heavy physical activity for 48 hours before blood sampling. Similar to the pre-training, fasting blood sampling was repeated 48 hours after the last training session (post training). After each blood sampling, serums were immediately separated and stored at -80° until the assays were performed. Nitric oxide was measured by the calorimetric method (Navand Salamat Company, Iran). EMPs was measured by the Cytometer method (BD Biosciences, San Jose, CA, USA).

Statistical Methods: Statistical analyses were performed through statistical software package (SPSS, Version 22.0, SPSS Inc, IL, USA). The Kolmogorov-Smirnov was applied to assess the normal distribution. Independent student t-test was used for comparison of variables between groups at baseline. Paired t-test used to assess the intra-group changes of variables in each group. The statistical significant level was ≤ 0.05.

RESULTS

Changes in some anthropometric indicators in the study groups are summarized in Table 1. In the pre-training, no significant difference was observed in any of the anthropometric markers between the two groups. ($p > 0.05$). However, inter-group changes by paired t-test revealed that CX training significantly reduced body weight, abdominal circumference, and body mass index in the exercise group ($p < 0.05$). On the other hand, body weight and body mass index in the control group increased significantly compared to the pre-test ($p < 0.05$), but abdominal circumference did not change significantly ($p = 0.689$).

As previously mentioned, the main aim of the study was to determine the effect of CX training on insulin levels and insulin resistance as markers of vascular endothelial function. To test this aim, a paired t-test was used (table 2). The findings revealed that CX training led to a significant increase in NO and a significant decrease in EMPs compared to the pre-training ($p > 0.05$), but these variables did not change significantly in the control group ($p < 0.05$).

Table 1: Pre and post-training of anthropometric markers of groups

Group / Variables	CX group			Control group		
	Pre-training	Post-training	Sig	Pre-training	Post-training	Sig
Body weight (kg)	88.7 ± 4.38	85.88 ± 4.11	0.001	90.6 ± 3.59	91.04 ± 3.26	0.025
AC (cm)	106 ± 7	100 ± 8	0.001	107 ± 6	107 ± 5	0.689
BMI (kg/m2)	33.08 ± 1.33	32.05 ± 1.48	0.001	33.03 ± 1.70	33.21 ± 1.72	0.022
AC, abdominal circumference; BMI: body mass index						

Table 2: Pre and post-training of Vascular markers of groups

Group / Variables	CX group			Control group		
	Pre-training	Post-training	Sig	Pre-training	Post-training	Sig
EMPs (ng/mL)	44.1 ± 3.32	36.8 ± 3.03	0.001	43.1 ± 2.85	42.2 ± 1.80	0.321
Nitric oxide (µM)	38.3 ± 1.64	42.4 ± 3.79	0.001	38.7 ± 1.70	37.9 ± 2.30	0.271

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DISCUSSION

The increase in serum NO levels accompanied by a significant decrease in EMPs following CX training are the main findings of the present study. In other words, 8 weeks of CX training with 3 sessions per week resulted in a significant decrease in EMPs and an increase in NO in women with metabolic syndrome compared to those who did not participate in training. Improvement in these vascular function indices was associated with a decrease in weight, body fat percentage, and body mass index in these patients. If we want to examine the change in nitric oxide in response to exercise training, although no change in NO following 6 months of aerobic training in obese women was reported by Zaros et al, (2009) and following 10 weeks of interval training in type 2 diabetic patients by Ghardashli et al, (2016) (12, 13), but consistent with our findings, in the study by Teixeira et al., resistance training led to a significant increase in nitric oxide in elderly women (14). Also, Farahati et al, (2013) have also pointed out the increase in nitric oxide levels as indicators of vascular endothelial function following 8 weeks of aerobic exercise in postmenopausal women (15). On the other hand, in the study by Ghardashi et al, (2016), improvement in vascular endothelial function was reported with emphasis on increased nitric oxide levels along with decreased fasting glucose in response to 3 months of aerobic exercise in obese type 2 diabetic patients (13).

Although direct evidence is not available in this regard, it seems that the possible physiological stimulus that can cause an increase in NO levels due to exercise is shear stress caused by exercise, which can stimulate and activate the nitric oxide synthase enzyme and produce NO by increasing blood flow to active muscles by phosphorylating protein kinase B (16). These findings strengthen the possibility that regular exercise increases pulse pressure and heart rate; it can increase the bioavailability of nitric oxide (17). It also seems that shear stress increases NO through the activation of ion channels, especially potassium channels (18). Another mechanism in increasing NO levels is the stimulation of fibroblast growth factor 2. Exercise increases the production of nitric oxide in the endothelium by stimulating FGF2 and increasing its activity (16). On the other hand, the intensity of exercise is an important determining factor in improving endothelial function. Laboratory studies have also revealed that exercise-induced muscle hypoxia leads to increased nitric oxide synthesis and secretion by increasing the expression and levels of vascular endothelial growth factor through angiogenesis and activation of endothelial nitric oxide synthase phosphorylation (19, 20).

Apart from other markers, increased ENPs are also a major factor in the development of endothelial dysfunction, and obese individuals with hypertension or obesity-related diseases such as metabolic syndrome have higher EMPs than individuals of normal weight. Research has shown that childhood obesity predisposes to the onset of endothelial dysfunction, and increased EMPs in obese children are associated with atherosclerosis (21). In the present study, apart from increasing NO, CX training also resulted in a decrease in EMPs in patients with metabolic syndrome, supporting the role of this training modality in improving vascular endothelial function.

In this context, although in the study of Sadeghifar et al, (2024), aerobic exercise increased NO in women with metabolic syndrome, EMPs levels did not change (22). On the other hand, the results of a study showed that the combination of a healthy diet and regular physical activity leads to improved endothelial function in obese individuals compared to the control group (23). Ghorshi et al, (2019) also reported a decrease in ENPs following circuit training in overweight men (8). It has been noted that EMPs are derived from intercellular adhesion molecules (ICAM-1), vascular cell adhesion molecules, and platelet cell adhesion molecules, in addition to other active peptides such as endoglin derived from endothelial cells (24). Intensification of the transport of specific molecules by EMPs has been observed following hyperglycemia and increased postprandial triglycerides, as well as increased levels of low-density lipoproteins (25). In addition, increased blood glucose levels due to increased NADPH oxidase activity in EMPs lead to increased inflammation and damage to endothelial function, which is mediated by stimulation of endothelial function (26). Also, the association between EMPs derived from endothelial progenitor cells and cardiovascular risk factors leading to aortic stiffening, endothelial dysfunction, and asymptomatic atherosclerosis has been confirmed

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(27). Repeated reports have shown that an increase in circulating small endothelial particles has also been observed in some age-related vascular and metabolic diseases such as dyslipidemia and asymptomatic atherosclerosis (24). In conclusion, exercise training, especially CX training, seems to improve vascular endothelial function in women with metabolic syndrome by affecting serum NO and EMPs levels. According to some laboratory evidence, increased blood flow due to exercise could be a good explanation for the reduction of small endothelial particles along the endothelium, as research has shown that reducing severe stress conditions or adapting to stressful conditions leads to a decrease in the release of small endothelial particles (28,29).

Please revise the first sentence of conclusion, as the data is not enough to support the "effectively improvement of vascular function".

CONCLUSION

CX training is associated with improvements in serum levels of NO and EMPs as markers of vascular endothelial function in women with metabolic syndrome. However, these changes alone do not reflect the effectiveness of this training in improving vascular endothelial function and further studies are needed to better understand the mechanisms responsible for the effects of exercise training on vascular function.

ACKNOWLEDGMENTS

The authors wish to thank the Islamic Azad University of Kish International Branch For their support.

FUNDING

This research was funded by Islamic Azad University, Kish International Branch.

AUTHORS' CONTRIBUTIONS

All authors equally contributed to preparing this article.

CONFLICT OF INTEREST

The authors declared no conflict of interest.

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