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Long-term effects of resistance exercise with and without vascular occlusion on TNF-α, IL-6 and IL-15 secretion in non-athletic women

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RESEARCH ARTICLE

Abstract

Resistance training is associated with reduced risk of low-grade inflammation related diseases. This study aimed to consider the effect of two methods of resistance training with and without vascular occlusion on changes in some serum cytokines in young non-athlete women. Thirty non-athlete women (20 to 30 years of age) were randomly divided into three groups (n=10 in each): resistance training without vascular occlusion (traditional), resistance training with vascular occlusion, and a control group. Resistance training was conducted three sessions for 8 weeks. In the vascular occlusion group, prior to the main exercise, the proximal part of both thighs was closed with a rubber tourniquet and the resistance exercise was performed with an intensity of 20-30% 1-repetition maximum (1RM) until fatigue. In the group without vascular occlusion, the same exercise were performed with similar intensity (with 70-80% 1RM until fatigue). Serum interleukin (IL)-15, IL-6, and tumour necrosis factor-alpha (TNF-α) were measured by ELISA method. One-way ANOVA was employed to compare the changes in the studied variables. The results show that serum levels of IL-6 and TNF-α and IL-15 do not have a significant change in groups with and without obstruction ($P>0.05$). Numerous studies have evaluated the positive effects of vascular occlusion on muscle hypertrophy and strength during rehabilitation. According to the results of the present study, it seems that the use of vascular occlusion exercise has less effect on inflammatory or IL-15.

Keywords: interleukin-15, inflammatory cytokine, resistance exercise, vascular occlusion, young women

1. Introduction

Muscle strength is one of the most important bio motor abilities, which is a key factor in health and performance (Fransson *et al.*, 2018). It is stated that the decrease in muscle strength and volume is associated with many disorders and diseases such as muscle atrophy, insulin resistance, and inflammation (Laurent *et al.*, 2019). Performing regular resistance training increases muscle strength and improves well-being (Nunes *et al.*, 2021). Studies show that intense strength training (more than 70 to 80% of maximum repetition) increases strength and muscle hypertrophy. Therefore, resistance training with less intensity will not cause muscle hypertrophy (Manini and Clark, 2009). However, based on the previous studies, high-intensity strength training is not suitable for certain groups, such as the elderly and non-athlete women.

Researchers believe that exercise training, especially strenuous exercise training induces more damage particularly in muscle tissue, and plays an important role in releasing various substances such as intracellular proteins and inflammatory cytokines (Andring, 2006), so that physical activity (strenuous exercise training) may cause the production of free radicals, coagulation, as well as inflammation. The increase in inflammation is caused by proinflammatory cytokines such as interleukin (IL)-6 and tumour necrosis factor-alpha (TNF-α) (Xie *et al.*, 2011).

Phillips *et al.* (2012) showed that resistance training reduced subclinical inflammation in obese, postmenopausal women. Tolouei Azar *et al.* (2021) indicated that eight weeks of resistance training led to an increase in serum levels of IL-15 and a decrease in serum levels of insulin, glucose, and insulin resistance; however, it had no significant effect on serum levels of IL-6 and TNF-α. Based on the results of this study, it seems that resistance training may lead to improved insulin resistance in elderly men with type 2 diabetes mellitus (T2DM) by enhancing the circulating levels of IL-15 (Tolouei Azar *et al.*, 2021). IL-6 primarily has pre-inflammatory effects, releasing acute-phase proteins from liver cells such as C-reactive protein (CRP). In the pro-inflammatory state, IL-6 acts as a mechanism for the pathogen to destroy the cells, and in the anti-inflammatory state, it can improve muscle cell haemostasis. Studies show that IL-6 plays a direct role in the expression of TNF-α mRNA (Apple *et al.*, 1988). It has been shown that in humans, rhIL-6 injection increases TNF-α receptors (Starkie *et al.*, 2003); however, muscle secretion of IL-6 can decrease TNF-α. The effects of physical activity on IL-6 and TNF-α are also paradoxical. Starkey *et al.* (2005) found that 180 min of leg exercise significantly increased IL-6 during exercise, but this does not change the levels of TNF-α. Greiwe *et al.* (2001) indicated that three months of strength training reduced TNF-α mRNA. However, other researchers observed a significant increase in TNF-α after strength and endurance training (Libardi *et al.*, 2012). The increase in interleukin-15 has also been reported during contractile activity. An increase in this cytokine (IL-15) has been reported following resistance training (Pérez-López *et al.*, 2018). Interleukin-15 can be used as an anabolic factor causing muscle hypertrophy in muscle cells (Quinn *et al.*, 2002). Meanwhile, it has been suggested that interleukin-15 may reduce programmed cell death of muscle fibres by affecting TNF-α signalling (Figueras *et al.*, 2004). Therefore, the correct exercise training program and the use of appropriate training modality can have different effects (Holm *et al.*, 2008). Resistance training with vascular occlusion (RTVO) is a type of exercise training that can improve the speed of muscle hypertrophy (Kawada, 2005).

In the RTVO, the blood flow is restricted or stopped around the proximal arm or thigh by closing a flexible rubber band or tourniquet (Sato, 2005). The intensity of these exercises is usually considered between 20 and 30% of a maximum repetition (approximately equivalent to the intensity of daily activity of individuals) (Loenneke and Pujol, 2009). Resistance training with vascular occlusion compared to traditional resistance training (TRT), even for a short period of time (for example, one week) can have positive effects on strength and muscle mass (Karabulut *et al.*, 2007). Resistance exercise is a healthy, safe, and promising training method for physicians and coaches of sports teams that in addition to increasing strength. Resistance exercise improves the quality of life of elderly, cardiovascular patients, orthopaedic, obese, neuromuscular, as well as diabetic patients and in rehabilitation (Fujita *et al.*, 2008). It seems that monitoring serum levels of IL-6, TNF-α, and IL-15 following various resistance training programs can be important. Furthermore, useful information has been provided on how non-athlete women adapt in terms of inflammatory status after resistance exercise. Numerous studies have indicated that eight weeks of resistance training can reduce pre-inflammatory cytokine and increase anti-inflammatory cytokine in health and disease conditions (Chen *et al.*, 2018; Macêdo Santiago *et al.*, 2018; Strasser *et al.*, 2012; White *et al.*, 2006). Limited studies have examined the effects of blockage of RTVO in inactive women by examining the role of inflammatory factors. In this study, we, therefore, used eight weeks of resistance training with RTVO to consider cytokine change in non-athletic women.

2. Materials and methods

Subjects

Thirty non-athlete women (20 to 30 years of age) participated in the present study. The subjects were randomly divided into three groups: control, traditional resistance training, and resistance training with vascular occlusion (n=10 in each group) (Figure 1). All participants provided written informed consent. The study was approved by the Baqiyatallah University of medical science ethics committee (code no: IR.BMSU.BAQ.REC.1399.034).

Inclusion criteria included: (1) non-athlete women with ages of 20-30; (2) sedentary lifestyle over the last six months; (3) not experiencing any orthopaedic injuries. Exclusion criteria comprised of: (1) smoking during the exercise-training period; (2) occurrence of myocardial infarction, cardiac arrest, symptomatic or sustained ventricular tachycardia, or current angina over the previous six months; (3) musculoskeletal or respiratory problems or other comorbidities that contraindicate exercise.

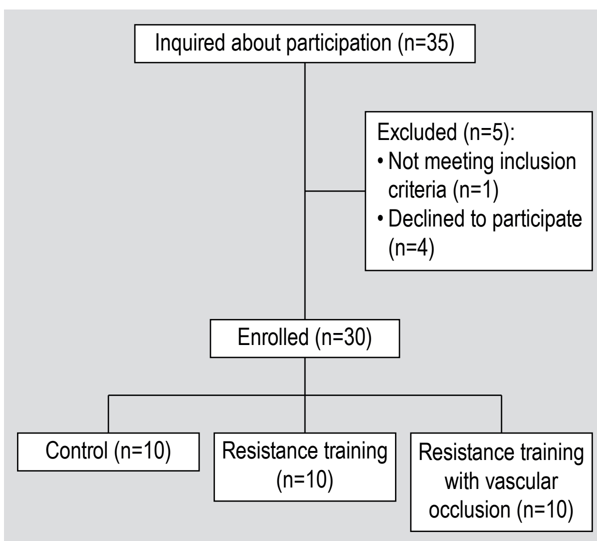

Figure 1. Consort chart showing distribution of participants in the study.

Exercise training protocol

The exercise program consisted of eight weeks, three sessions per week. Each session included 10 min warm-up, and 10 min cool-down. The main exercise program consisted of three movements for the lower limbs, including knee opening, leg press, and hack squat in four sets. In the group with vascular occlusion, before the main exercise, the proximal part of both thighs was closed with a rubber tourniquet and the exercise was performed with an intensity of 20-30% 1RM until fatigue. In the group without vascular occlusion (traditional resistance training), the same movements were performed with 80-70% 1RM until fatigue. The rest between sets was 1-1.5 min. In the vascular occlusion group, the tourniquet was opened between the movements to restore blood flow and was closed before the next movement. Exercises were performed for eight weeks (three sessions per week and 60 min per session for a total of 24 sessions). All exercise training was performed at 10:00 a.m. The control group did not receive any strength-training program during this period (Table 1).

Biochemical analysis

For the first study and 48 h following the last training session (at 08:00 a.m.), the blood sample was taken from the arm in the operated side to measure serum IL-15, IL-6 and TNF-α. Serum IL-15 and IL-6 was measured with a ELISA kit (ZellBio, Lonsee, Germany). TNF-α was measured using an immunometric laboratory method (Human TNF-α, TNFSF1A, DY210, R&D Systems, Minneapolis, MA, USA).

Statistical analysis

The Kolmogorov-Smirnov test was used to check that all data were normally distributed. Descriptive data included means and standard deviation (SD). A one-way analysis of variance was used to compare the changes of the studied variables in all three groups. Dependent t-test was also used for intragroup changes. The collected data were analysed using SPSS version 24.0 (IBM Corporation, Armonk, NY, USA).

3. Results

Physiological measurement

The age, height, weight, and BMI of the subjects are presented in Table 2.

Serum IL-6, IL-15 and TNF-α

Serum changes of IL-6, IL-15 and TNF-α are shown in Figures 2A-C, respectively. A dependent t-test was employed to evaluate the differences between pre-training and post-training IL-6, IL-15 and TNF-α in resistance training groups with and without vascular occlusion. The results showed that there is not any significant change in pre-training and post-training values of serum IL-6 (P>0.05), IL-15 (P>0.05) and TNF-α (P>0.05) in different groups. Based on the results of the ANOVA test, there were no significant changes in IL-6 (P=0.446), IL-15 (P=0.621), and TNF-α (P=0.621) in different groups of the study (post-training).

Table 1. Exercise training for different groups of the study.

Groups	Warm-up (min)	Resistance exercise	Sets	Vascular occlusion	1RM (%)	Session	Cool-down (min)
Resistance training	10	knee opening, leg press, hack squat	4	no	70-80	24 (3/weeks)	10
Resistance training with vascular occlusion	10	knee opening, leg press, hack squat	4	yes	20-30	24 (3/weeks)	10

Table 2. Physiological characteristics of the subjects participating in the study.[1]

	Age (year)	Height (cm)	Weight Pre (kg)	Weight post (kg)	BMI Pre	BMI Post
Without VO	22.8±2.8	164.1±3.6	65.5±3.5	65.0±3.6	24.3±0.4	24.1±0.5
With VO	24±3.9	165.4±3.7	67.1±3.7	66.8±2.7	24.5±0.4	24.3±0.4
Control	23.5±2.5	165.1±3.6	66.4±3.3	66.5±2.9	24.3±0.3	24.3±0.4

[1] VO = vascular occlusion; Pre = pre-training; Post = post-training; BMI = body mass index.

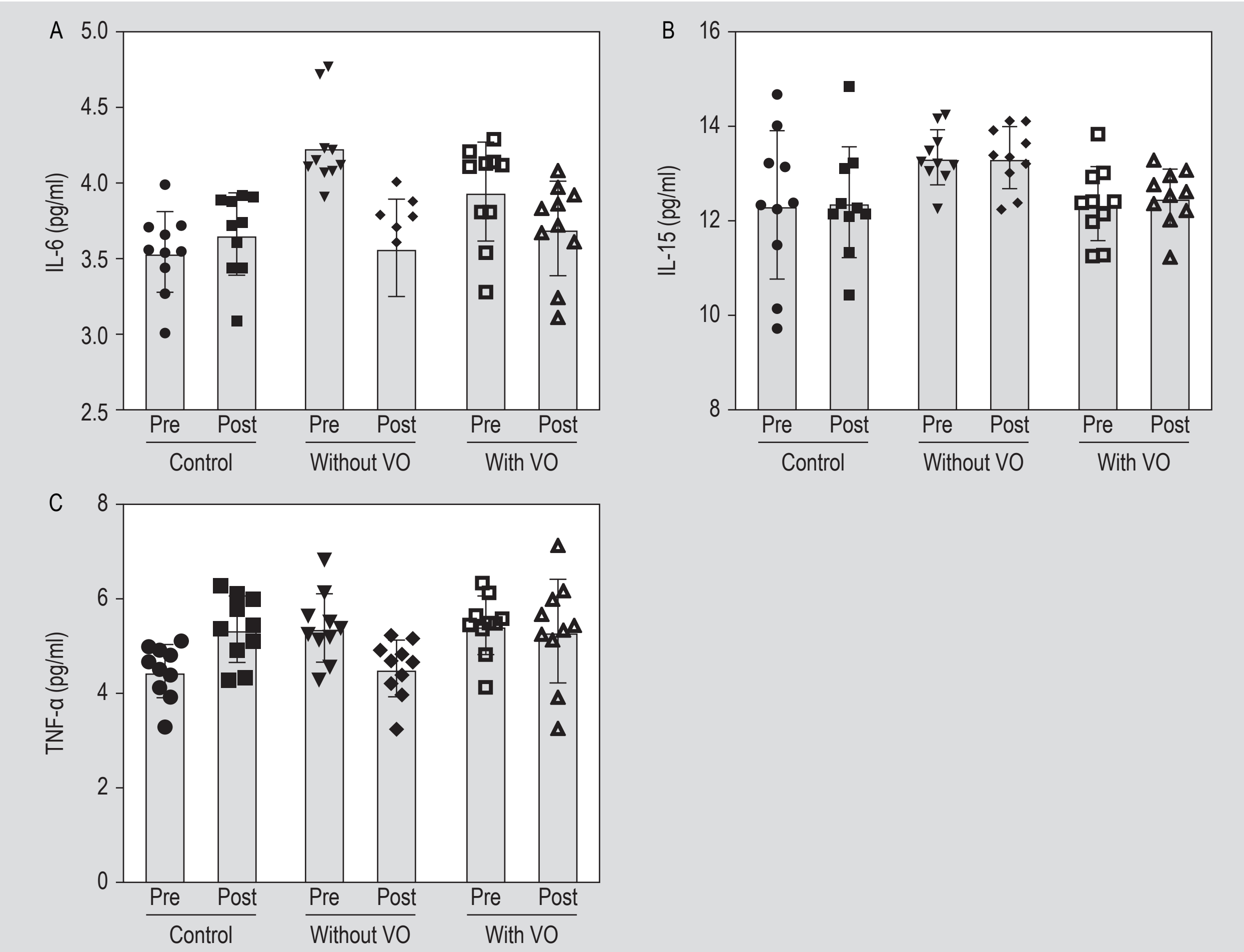

Figure 2. Serum levels of (A) interleukin (IL)-6, (B) IL-15 and (C) tumour necrosis factor (TNF)-α in different groups of the study. Data were shown as mean ± standard deviation. VO = vascular occlusion; Pre = pre-training; Post = post-training.

4. Discussion

This study aimed to investigate the effect of resistance training with and without vascular occlusion on IL-6, IL-15 and TNF-α in non-athlete women. As per the results of the present study, eight weeks of resistance training had no significant effect on IL-6 and TNF-α in non-athlete women (pre- and post-test), and in this regard, there was no significant difference between the two types of resistance training with and without vascular occlusion. Previous studies have shown that aerobic exercise reduces plasma levels of TNF-α (Pitsavos *et al.*, 2005), and IL-6 (Colbert *et al.*, 2004). In contrast, other studies have shown that physical activity changes the serum levels of TNF-α (Bruunsgaard *et al.*, 2004) and IL-6 (Bruunsgaard *et al.*, 2004). It seems the lack of change of these cytokines with exercise training in our study could be attributed to using different measurement methods (Bruunsgaard *et al.*, 2004), short duration of exercise program and weight loss program (Nicklas *et al.*, 2004), as well as low serum levels of inflammatory markers in healthy subjects (Gielen *et al.*, 2003). TNF-α and IL-6 are associated with insulin resistance in T2 DM subjects (Bugera *et al.*, 2018). While moderate-intensity exercise may be capable of promoting weight loss and thus improving insulin resistance, studies have demonstrated that the impact of vigorous-intensity exercise training may be more effective in mitigating insulin resistance (Nassis *et al.*, 2005). It is, therefore, possible that improving insulin resistance through physical activity is a mechanism that justifies a reduction in inflammation and inflammatory cytokine. This hypothesis has been proven in previous studies (Haghighi *et al.*, 2005), but this is not observed in the present study, which may be due to the health of the present subjects. It seems that obesity (due to the production and gene expression of cytokines associated with inflammation of TNF-α and IL-6) is a risk factor that is strongly associated with high levels of inflammation (Colbert *et al.*, 2004), thus reducing body fat and increased lipolysis due to physical activity is a mechanism that reduces inflammation. As mentioned, in the present study the subjects were healthy non-athlete girls of normal weight. Therefore, it seems reasonable not to see inflammatory cytokine change in this study. However, a number of epidemiological studies have suggested that the relationship between more physical activity and higher physical fitness with less inflammation is independent of total obesity and abdominal obesity (Colbert *et al.*, 2004).

Evidence from human and animal research shows that aerobic exercise significantly reduces oxidative stress and inflammation by increasing the body's antioxidant capacity (Souissi *et al.*, 2020). Physical activity also reduces the production of inflammatory cytokines from mononuclear cells by reducing the gene expression of inflammatory cytokines in muscle tissue or by reducing the daily episodes of hypoxia by strengthening the cardiorespiratory system. The response of TNF-α to resistance training is unclear (De Salles *et al.*, 2010). High-intensity resistance training seems to reduce its circulating concentration, even when there is no change in body fat mass (Flack *et al.*, 2011). Balducci *et al.* (2010) demonstrated that in subjects who performed 12 months of high-intensity combined aerobic and resistance training, a greater reduction in CRP, IL-6, IL-1β, and TNF-α was observed compared to aerobic exercise. Meanwhile, the concentration of anti-inflammatory cytokines (IL-4 and IL-10) was also increased more in the combined exercise group (Balducci *et al.*, 2010). Levinger *et al.* (2009) did not observe a change in inflammatory cytokine due to resistance training and suggested that a long training period is necessary to regulate inflammatory cytokine after exercise training. It seems that one reason for not changing the serum levels of TNF-α and IL-6 in the present study is the type and duration of the exercise training. Linke *et al.* (2005) displayed a significant decrease in TNF-α after six months of endurance training in patients with heart failure. It seems that inflammatory cytokines usually decrease when the length of the training period is long, or the subjects are in the period of illness. Tsukui *et al.* (2000) also observed a significant decrease in TNF-α in the serum of subjects after five months of moderate-intensity aerobic exercise. Studies reported a significant decrease in TNF-α following exercise training in long-term periods. However, eight weeks of resistance training in the present study (regardless of vascular occlusion or without vascular occlusion) could not change the level of TNF-α and IL-6.

Meanwhile, based on the results of this study, eight weeks of resistance training had no significant effect on IL-15 in non-athlete women, and in this regard, there was no significant difference between the two types of resistance training with and without vascular occlusion. Studies in consideration of IL-15 with vascular occlusion are limited; this appears to be the first study to examine the effect of resistance training with and without vascular occlusion on IL-15. It has been shown that IL-15 mRNA levels in human skeletal muscle are highly regulated following strength training (Nielsen and Pedersen, 2007). Ajuwon and Spurlock (2004) suggested that IL-15 may be produced by organs in response to immune stress. Therefore, the action of IL-15 on muscle mass and fat can be important for exercise and physical activities. However, conflicting evidence exists concerning whether circulating IL-15 is released from skeletal muscle tissue in response to exercise or other physiological stimuli. The clinical implications of this study were that the intensity of VO training should be increased in female subjects with resistance training (Das and Paton, 2022). Also, more training volume should be used to get better results with VO training.

This study also had several limitations, including a lack of measurement of inflammatory factors at the gene level, not considering cellular signalling pathway of these inflammatory factors, lack of different training modalities, and not using male subjects. It is suggested that researchers consider these limitations in future studies.

The results of the present study showed that serum levels of IL-6, TNF-α and IL-15 did not change significantly following eight weeks of resistance training with and without vascular occlusion. As per the results of the present study, it seems that the use of vascular occlusion resistance exercise (20-30% 1RM) does not have any effect on inflammatory or anti-inflammatory factors. However, more studies are needed in this area, especially in subjects with muscle atrophy.

Conflict of interest

The authors declare that they have no competing interests.

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