Different intensity circuit resistance training effect on the plasma level of the inflammatory cytokines, IL-6 and TNF-α in postmenopausal women

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Abstract

Introduction: Obesity related inflammation plays an important role in the pathogenesis of insulin resistance and type 2 diabetes. In contrast, exercise training can decrease insulin resistance by modulating inflammation. The aim of present study was to investigate the effect of 12 weeks different intensity circuit resistance training on the levels of the inflammatory mediators, IL-6 and TNF-α in obese postmenopausal women.

Materials and Methods: In the study, 44 postmenopausal women with average age of 56.07 ± 3.18 years old were selected and randomly assigned in four group including the control, low (L-RT), moderate (M-RT) and high intensity circuit resistance training (H-RT) groups. Circuit resistance training for L-RT, M-RT and H-RT groups, respectively, was conducted with 40, 60 and 80 percent of one repetition maximum. Blood sampling prepared in the pre and post-test stages and the plasma levels of TNF-α and IL-6 were measured by an immunoassay method.

Results: There was no significant difference between the groups under study for TNF-α levels (P = 0.097), but inter group difference indicated that a significant decrease in the level of TNF-α in H-RT group (P = 0.004). The IL-6 levels showed a significant between-groups difference (P = 0.013) and also a significant decrease in the levels of IL-6 in H-RT group compared to L-RT group were observed (P = 0.049). Moreover, inter group analysis indicated significant decrease in the level of IL-6 only in H-RT group (P = 0.002).

Conclusion: It seems that, the highest intensity circuit resistance training is more effective in downregulation of inflammatory mediators, and, in turn, the modulation of inflammation is associated with the decreased insulin resistance.

Keywords: Inflammation, Menopause, Obesity, Insulin resistance

Introduction

Menopause is an inevitable component of ageing in women, which are associated with significant increases of metabolic diseases such as obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease (1). Obesity is an inflammatory condition (2), which considered as a main risk factor for insulin resistance and play an important role in diabetes pathogenesis (3). Adipose tissue macrophages are the main sources of proinflammatory cytokines production such as TNF-α and IL-6, which in turn can inhibit insulin action in adipose tissue, on the other hand, anti-inflammatory macrophages are essential for maintaining the normal insulin sensitivity (4). Regular exercise training is recognized as an effective strategy for modulating the cardiovascular risk factors (5). According to previous studies, resistance and aerobic training result in improves the glucose metabolism (6). Resistance training is

associated with decrease the low-grade chronic inflammation, and decrease cardiovascular disease and type 2 diabetes prevalence (7). In addition, the anti-inflammatory effects of resistance training have been reported in overweight subjects (8). Although the exact mechanism for these changes is unknown, it seems that resistance training improves insulin resistance by altering the production of inflammatory and anti-inflammatory cytokines which is affected by exercise intensity, and physiological stress induced by intensive resistance training acts as a potent stimulant for muscle hypertrophy and control of inflammatory responses (9).
It is reported that circuit endurance and resistance training is more effective compared to traditional training (10), but the optimal training intensity is still controversial and mainly moderate intensity training has been suggested (11). However, higher intensity exercise training led to a greater increase in physical fitness (12). In support of this hypothesis, researchers have reported that circuit aerobic and resistance training improves cardiovascular risk factors more than traditional exercise training (13). Circuit resistance training is a new and perfect training method to stimulate both muscular strength and cardiorespiratory capacity (14). Circuit resistance training is an effective strategy for increasing the maximal oxygen consumption, ventilation capacity and muscle strength, body composition improvement and decreasing the inflammatory factors (15, 16). Despite the relative improvement of muscular strength following the common circuit resistance training (40-60% RM) (14), high-intensity circuit resistance training has been shown to increase muscle strength, muscle mass, and bone density in the elderly, which was similar to the traditional high-intensity resistance training (17).
Increase in insulin sensitivity following exercise training is due to activation of macrophage-stimulated glucose transporter-4 (GLUT4) translocation to membrane (18) and also, insulin sensitivity improvement after regular exercise training is associated with macrophage polarization to anti-inflammatory properties in adipose tissue and skeletal muscle (18, 19). However, the effect of different intensities circuit resistance training specially in postmenopausal women on the levels of inflammatory and anti-inflammatory mediators is not yet fully understood. On the other hand, circuit resistance training has been proposed as an effective training method for increasing both muscular strength and cardiorespiratory capacity, which can exert metabolic benefits similar both resistance and aerobic training in a shorter period of time (14). Therefore, identifying the ideal intensity for circuit resistance training in order to improve insulin resistance, and determined the main mechanisms involved in inflammation-induced insulin resistance can provide new insights into therapeutic goals for obese people. Accordingly, the aim of the present study was to investigate the effect of different intensity circuit resistance training on the levels of on the levels of inflammatory cytokines and insulin resistance in obese postmenopausal women.

Materials and Methods

Subjects and Study Design

This study was semi-experimental research, which performed based on pre-test and post-test design. The participants were consisted of obese postmenopausal women [average age of 56.07 ± 3.18 years old, average body mass index (BMI) 33.43 ± 1.29 $kg.m^2$] who were selected among the recruited subjects. All subjects voluntarily participated in this research and finally 44 postmenopausal women with age ranging from 48 to 65 years old were chosen to participate in the present research. Inclusion criteria were 1) at least 12 months have passed after the last menstrual period, 2) non-addiction to drugs or alcohol, 3) didn't take part in regular exercise training

in last year, 4) no kidney, liver, cardiovascular disease and diabetes, 5) BMI equal or greater than 30 kg.m^2, and the absence of any injuries or physical problems. Exclusion criteria were included the absence of regular participation in exercise training sessions, injuries during the exercise training, unwillingness to continue research protocol, medical prohibition to participate in exercise training, and forced to take certain drugs or supplements.

Ethical approval for the study was obtained from Islamic Azad University, Central Tehran Branch ethics committee. After checkup by a gynecologist and confirming the menopause, subjects were qualified to take part in the considered intervention. Menopause was confirmed by menopausal levels of estradiol (<120 pmol/l) and follicle-stimulating hormone (FSH > 30 IU/L). Firstly, all steps and research methods were explained to subjects and after full knowledge and completion of the medical questionnaire, all of them signed written consent. In the first session, the participants height and weight were measured and in the second session, subjects one-repetition maximum (1RM) determined. The subjects were then matched based on weight, height and BMI and divided into four equal groups (11 person in each group). The study groups including: 1) control (C), 2) low intensity circuit resistance training (L-RT), 3) moderate intensity circuit resistance training (M-RT) and 4) High-intensity circuit resistance training (H-RT). Three training groups completed their research protocol, but the control group was asked to continue daily routine lives and don't take part in regular training.

The circular resistance training protocol consisted of eight movements (squat, biceps curl, chest press, knee extension, knee curl, shoulder press with barbell, leg press, underhand cable pulldowns) for upper and lower limb, which conducted as a circuit at different intensities (14, 20). The training group consist of 1) H-RT: Three sets with 10 repetitions at 80% 1RM, 2) M-RT: Three sets with 13 repetitions at 60% 1RM, 3) L-RT) Three sets with 20 repetitions at 40% 1RM. Training volume was calculated based on the Baechle et al (1994) formula (training volume= Weight × number of repetitions × number of sets) (21). The between sets rest considered two minutes and was inactive (22). The subjects 1RM was calculated using Brzycki equation (23) which reported in following:
1-RM = weight (kg) /1.0278 – (number of repetitions to fatigue × 0.0278)

Blood Samples and Biochemical Analysis

The first fasting blood sample was taken 72 hours before and the second blood sample was taken 72 hours after a 12-week intervention from the subject's forearm vein. Blood samples were transferred to special test tubes for serum and plasma (tubes containing sodium citrate) preparation, and then centrifuged at 3000 rpm for 10 minutes. The obtained serum and plasma samples were stored at -70 °C. Then, the circulating variables were measured using kits and special laboratory methods.

Plasma levels of TNF-α (Biovendor, catalog number: RD194015200R, sensitivity: 0.65 pg.ml), IL-6 (Elabscience, catalog number: E-EL-H0109, sensitivity: 0.69 pg/ml) and insulin (Demeditec, catalog number: DE2935, sensitivity: 1.76 µIU/ml) were measured by ELISA method. In addition, glucose levels were measured by an enzymatic kit (Pars Azmoun, Iran). Moreover, insulin resistance calculates with following formula (24):
(Fasting plasma insulin [µU/mL] × 360 / [fasting plasma glucose {mg/dL} – 63])

Statistical Analysis

In order to data analysis, graph pad prism statistical software was used and Excel software was used to draw the graphs. Between group differences were analyzed by repeated measures analysis of variance and Bonferroni post hoc test. Intragroup

changes were also analyzed by means of dependent t-test. Significance level for all stages of data analysis was considered at P < 0.05.

Results

The subjects characteristics including age, height, body weight and BMI in different research groups were reported as mean ± standard deviation (Table 1). TNF-α levels analysis by means of repeated measures analysis of variance test showed that the effect of time (P = 0.08, F1, 40 = 3.23) and time-group interaction (P = 0.097, F2,40 = 3.25) was not significant. Therefore, there is no significant difference between the effect of 12 weeks circuit resistance training with different intensities on the plasma level's TNF-α in obese postmenopausal women. In fact, different intensities circuit resistance training doesn't have a significant effect on TNF-α levels compared to control group.

Table 1. Physical characteristics of the subjects participating in the current study.

Variables	Control	L-RT	M-RT	H-RT
Age (years)	56.71 ± 3.92	54.92 ± 2.68	57.45 ± 2.88	55.31 ± 3.24
Height (cm)	163.92 ± 3.20	164.20 ± 2.71	162.33 ± 2.62	163.22 ± 1.75
Body weight (kg)	89.80 ± 2.11	88.93 ± 2.85	88.42 ± 1.98	89.23 ± 2.22
BMI ($kg.m^2$)	33.43 ± 1.51	33.01 ± 1.44	33.56 ± 1.34	33.71 ± 0.71

L-RT: low intensity circuit resistance training, M-RT: moderate intensity circuit resistance training, HRT: high intensity circuit resistance training, and BMI: body mass index.

Intragroup analysis of TNF-α levels using dependent t-test, showed that TNF-α levels changes after 12 weeks in control (P = 0.53), L-RT (P = 0.60) and M-RT (P = 0.32) groups was not statistically significant. However, significant decrease of TNF-α in H-RT group (P = 0.004) were observed (Figure 1).

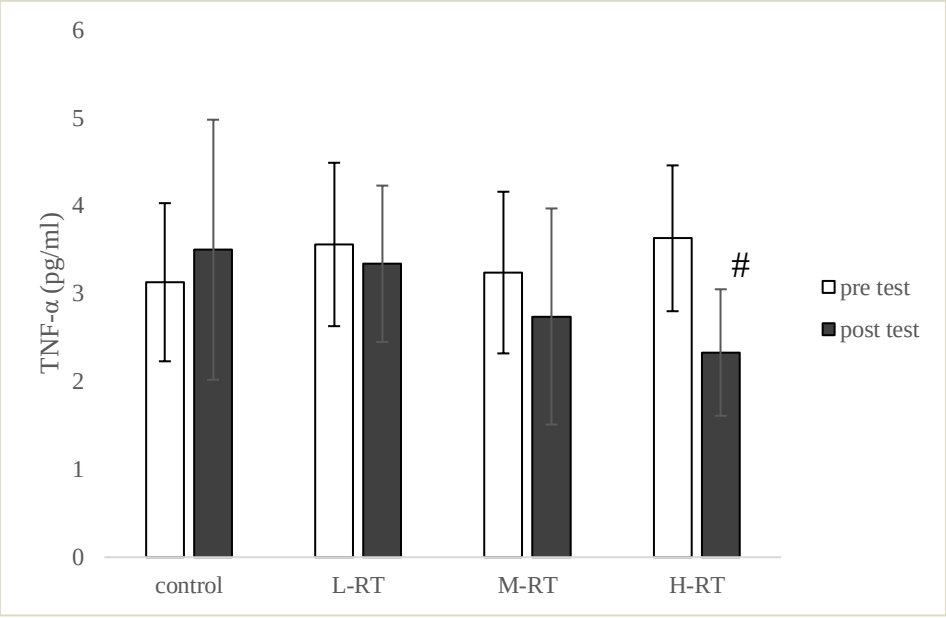

Figure 1. TNF-α levels in the post test step exhibited a significant decrease compared to the pre-test. L-RT: low intensity circuit resistance training, M-RT: moderate intensity circuit resistance training, and HRT: high intensity circuit resistance training.

Analysis of IL-6 findings indicated that the effect of time (P = 0.059, $F_{1, 40}$ = 3.76) was not significant. While, time-group interaction (P = 0.013, $F_{1, 40}$ = 4.07) was statistically significant. The results of Bonferroni post hoc test for IL-6 showed no significant difference between control group with L-RT (P < 0.99), M-RT (P =

0.25) and H-RT (P = 0.61) groups. In addition, there is no significant difference between L-RT and M-RT group (P = 0.21). The only significant difference was observed between L-RT and H-RT groups (P = 0.049). Analysis of intragroup changes in IL-6 levels using dependent t-test showed that IL-6 changes in control (P = 0.79), L-RT (P = 0.17) and M-RT (P = 0.18) groups was not statistically significant. but, a significant decrease in IL-6 levels was observed in the H-RT group after 12 weeks circuit resistance training (Figure 2).

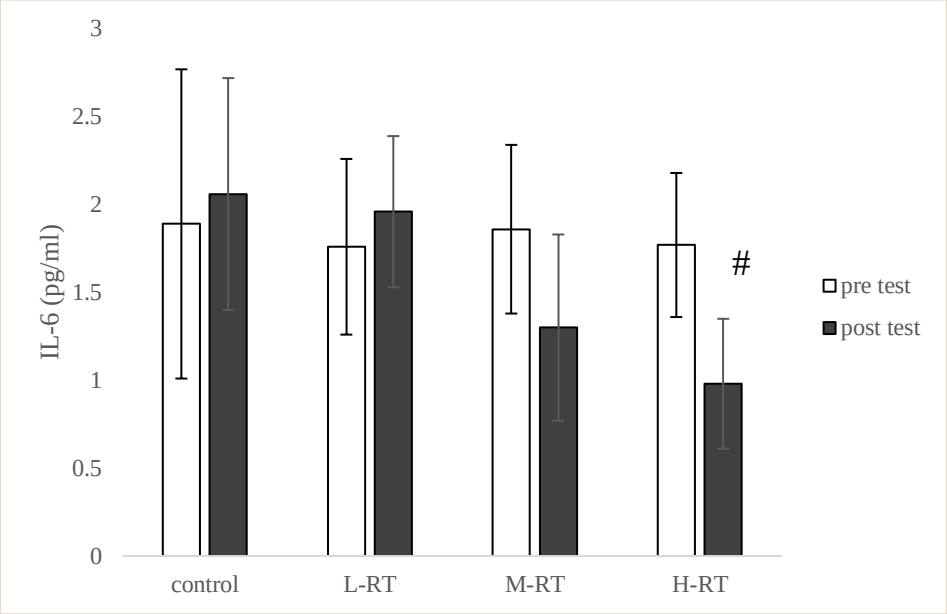

Figure 2. IL-6 levels in the post test step exhibited a significant decrease compared to the pre-test. L-RT: low intensity circuit resistance training, M-RT: moderate intensity circuit resistance training, and HRT: high intensity circuit resistance training.

Discussion

This study main findings were that 12 weeks circuit resistance training with 80% of 1RM intensity in postmenopausal women leads to a significant decrease in IL-6 and TNF-α levels. However, circuit resistance training with 40 and 60% of 1RM had no significant effect on the levels of IL-6 and TNF-α. It should be noted that, there is no significant difference between groups for TNF-α levels, but IL-6 levels significantly decreased in H-RT compared to the L-RT group. Our results indicated that high-intensity circuit resistance training play an important role in decreasing inflammatory mediators. In the present study, despite the decrease in the levels of IL-6 and TNF-α in the L-RT and M-RT groups, the observed changes were not statistically significant. IL-6 is a proinflammatory cytokine produced by immune cells such as monocytes, macrophages, T cells, and also by non-immune cells including fibroblasts, endothelial cells, and adipocytes. In addition, IL-6 secretion by subcutaneous and visceral adipose tissue has been reported (25). Therefore, obesity have been recognized as a major risk factor for increased levels of inflammatory mediators such as TNF-α and IL-6 (26). In contrast, exercise training plays an important role in reducing fat mass and thus modulating the chronic inflammation, especially in overweight and obese individuals (27), and anti-inflammatory effects of different exercise training including circuit resistance training have been confirmed (28).

Consistent with present findings, its reported that progressive circuit resistance training (65-85% 1RM) for 12 weeks in obese men led to decrease in the levels of

some inflammatory markers including CRP and chemerin and accordingly, researchers have identified high-intensity circuit resistance training as an effective method to improve inflammation and cardiovascular risk factors (19). Peake et al (2011) suggested that long-term (18 months) progressive resistance training in older men is associated with significant decrease in IL-6 levels (29). Some researchers have also shown the role of circuit resistance training (40 to 80% of RM) in reducing other inflammatory mediators such as IL-17 (30). We observed that despite inflammatory factors (IL-6 and TNF-α) reduction in the intense circuit resistance training (80% 1RM) group, no significant change was observed in trained groups with 40 and 60% of 1RM. Consistent with the present findings, Tayebi et al (2019) indicated that despite TNF-α levels decrease after 12 weeks circuit resistance training with 35 and 55% of 1RM in postmenopausal women, the observed changes were not significant (31). It seems that even long term (one year) low and moderate intensity resistance training, don't have a significant effect on the levels of inflammatory mediators such as IL-6, but decrease in the levels of other inflammatory factors including CRP were observed (8).

In general, its suggested that anti-inflammatory effects of exercise training exert through a different mechanism, including the reduction of visceral adipose tissue, the secretion of anti-inflammatory cytokines from contracting muscle (called myokines), and decrease in expression of toll-like receptors (TLRs) on the monocytes and macrophages. According to animal studies findings, exercise training can also exert its anti-inflammatory effects through other mechanisms such as inhibiting the infiltration of monocytes and macrophages into adipose tissue and changing the phenotype of macrophages within adipose tissue (32). Some studies have also attributed the anti-inflammatory effect of exercise training to its role in improvement the mitochondrial function (33). However, some researchers have reported that moderate intensity (65-70% 1RM) and even high intensity (85-90% 1RM) resistance training don't have a significant effect on the levels of IL-6 and TNF-α in sedentary men (34). Contradiction with our findings can be attributed to the difference in implementation of resistance training program (traditional versus circuit) and especially different in subjects' characteristics. In particular, the present study subjects were obese postmenopausal women who showed weight loss and BMI reduction after exercise training program, while the above study subjects had normal weight and don't change in IL-6 and TNF-α levels was associated with no change in body weight (34). Considering that adipose tissue, especially visceral adipose tissue is known as the major site for inflammatory mediators' secretion (35), these findings seem reasonable.

In addition, we suggested that different intensities of circuit resistance training (40, 60 and 80% of RM) result in significant decrease of insulin resistance, which its decrease in H-RT (80% of RM) group was further, which emphasizes the relationship between exercise training intensity and improving insulin resistance. Previous studies have suggested the positive effect of high-intensity circuit resistance training for improving insulin resistance (19). Some researchers have also reported that high-intensity circuit resistance training even in short-term is associated with insulin resistance decrease in obese subjects, and therefore high-intensity circuit resistance training has attracted a lot of attention as a cost-effective way to improve glycemic status and reduce cardiovascular risk factors. (36). The greater effect of high-intensity circuit resistance training on insulin resistance improvement probably is due to local changes in the muscle as well as the greater number of muscles that are stimulated during exercise (36).

In addition, decrease in inflammatory mediators is one of the effective

mechanisms in improving insulin resistance and the role of inflammation in the pathogenesis of insulin resistance, especially in obesity, has been proven (37), as further reduction of inflammation in the H-RT group was associated with a further decrease in insulin resistance. Modulation of lipolysis process, alteration of glucose uptake by adipose tissue, and indirectly by increasing levels of FFAs that inhibit the insulin signaling pathway, have been suggested as a possible mechanism for inflammation role in insulin resistance pathogenesis (38). Moreover, another major mechanism by which inflammation leads to increased insulin resistance is the inhibition of insulin receptors (39). Despite the present findings, considering that in the present study, the levels of other inflammatory mediators (such as IL-1β, MCP-1, CRP) and especially anti-inflammatory mediators (IL-10, IL-4) has not been studied, it is difficult to conclude about the effect of different intensities circuit resistance training on inflammation and further researches are needed.

Conclusion

According to present study findings, it seems that high-intensity circuit resistance training is more effective in decreasing inflammatory mediators and insulin resistance compared with low and moderate intensities, which the greater effect of intensive circuit resistance training probably is related to further skeletal muscles involving during exercise sessions. Therefore, in order to maximize the resistance training adaptations, participate in the high-intensity circuit resistance training is recommended.

Conflict of Interest

The authors declare that no conflict of interest exists.

Acknowledgments

The present study written based on exercise physiology Ph. D thesis and was approved by Islamic Azad University, Central Tehran Branch ethics committee.

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