The Effects of Eight Weeks Moderate- and High-Intensity Circuit Resistance Training on the Levels of Serum Amyloid A and Insulin Resistance in Sedentary Men

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Abstract
Introduction: Obesity-related inflammation has an important role in increasing the risk of various pathological conditions, including insulin resistance. In this study, the effects of 8 weeks of moderate and high-intensity circuit resistance training on the levels of serum amyloid A (SAA) and insulin resistance were investigated in sedentary men.
Methods: In this study, 36 sedentary men (average BMI: 30.64 ± 3.14 kg/m^2, age of 20 to 35 years old) were randomly assigned to the control (C), moderate-intensity circuit resistance training (MRT), and high-intensity circuit resistance training (HRT) groups. The training protocol was performed during eight weeks (three sessions per week). Blood samples were collected before and after eight weeks of training, and serum levels of SAA, insulin, and glucose were measured. The data were analyzed by SPSS-24 software using the analysis of covariance (ANCOVA) test with the Bonferroni post hoc test.
Results: The present study's findings indicated that SAA levels and insulin resistance significantly reduced in the HRT and MRT groups compared to the control group ($P < 0.001$). However, our results showed that the changes observed in SAA and insulin resistance were not significantly different between the HRT and MRT groups ($P > 0.05$).
Conclusion: It seems that HRT has no extra effects on inflammation and insulin resistance compared to MRT; however, changes in the levels of other inflammatory mediators should be determined.
Keywords: Exercise training, Obesity, Insulin resistance, Inflammation

Introduction

Obesity is recognized as a pathological condition caused by enhancing energy intake and decreasing energy consumption, and its prevalence is rapidly rising worldwide.[1] Sedentary lifestyle and physical inactivity are the main risk factors for overweight and obesity, leading to a remarkable increase in the risk of related metabolic diseases including type 2 diabetes and cardiovascular disease.[2] Obesity-related metabolic disorders' pathogenesis is associated with a systemic low-grade inflammatory state.[3] Its suggested that pathological effects of obesity are largely related to dysfunction in adipokines' (adipose tissue secretory factors) secretion.[4] Most known adipokines are proinflammatory mediators, including interleukin 6 (IL-6), leptin, tumor necrosis factor α (TNF-α), resistin, lipocalin 2, and others, which are elevated in obesity, increasing the incidence of metabolic and cardiovascular diseases.[5]

Serum amyloid A (SAA) is another lipolytic and proinflammatory adipokine, which its upregulation in obese individuals' adipose tissue indicates that SAA plays an important role in systemic and local inflammation and production of free fatty acids (FFAs). Serum amyloid A is known as a direct link between obesity and its related conditions, including atherosclerosis and insulin resistance[6] and an important acute phase plasma protein that is mainly synthesized by the liver.[7] With a 9-11 kDa molecular weight, SAA is transported in combination

with HDL and has a high binding affinity for HDL.[8] In humans, SAA is a major modulator of inflammation and has a critical function in the metabolism and transport of cholesterol, which its circulating levels can increase up to 1000-fold following the body's response to various injuries, inflammation, trauma and neoplasia.[9] In addition to the liver tissue, it has been reported that SAA is synthesized and secreted by other tissues, especially the adipose tissue.[10]

Despite the low levels of SAA in normal conditions, SAA levels remarkably increase in inflammatory conditions, and therefore, targeting and modulating SAA levels can play an important role in counteracting its pathological effects.[8] In addition, SAA levels significantly increase in obese individuals, and there is a direct correlation between SAA levels and body mass index (BMI), and a significant decrease in circulatory SAA levels was observed after weight loss.[11] Some researchers have attributed the observed decrease in the levels of SAA following weight loss to the down-regulation of SAA production in the adipose tissue.[6] Due to the role of exercise in weight loss, and its proven effects against obesity, it seems that exercise training can affect SAA levels. In this regard, a study showed that 12 weeks of aerobic training significantly decreased IL-6 and SAA levels in postmenopausal women with metabolic syndrome.[12] However, there is inadequate information regarding the effect of exercises with different types and intensities on SAA levels. Therefore, in the present study, the researchers investigated the effects of circuit resistance training (moderate and high-intensity) for eight weeks on the serum levels of SAA and insulin resistance in inactive men.

Materials and Methods
Participants
Sedentary healthy young men with the age ranging from 20 to 35 years old in Tehran, Iran, were recruited after making announcements in some public places (parks, streets, gyms, etc.) of District six of Tehran. Because of the use the high-intensity resistance training and the important role of SAA in obesity, the healthy overweight and obese men were chosen as participants. Finally, 36 men were selected for participation in the present study. The subjects were randomly chosen for conducting the intervention. All subjects participated in the present study voluntarily.

Sample Size Calculation
In order to calculate the sample size, a previously reported formula was used,[13] and 12 subjects were chosen for each group. In addition, similar previous studies have suggested that 8-12 subjects for each group is appropriate and acceptable for conducting research in the exercise

physiology field.[14,15]

$$n_A = kn_B \ and \ n_B = \left(1 + \frac{1}{k}\right)\left(\sigma \frac{z_{1-a/2} + z_{1-\beta}}{\mu_A - \mu_B}\right)^2$$

$$1 - \beta = \Phi\left(z - z_{1-a/2}\right) + \Phi\left(-z - z_{1-a/2}\right), z = \frac{\mu_A - \mu_B}{\sigma\sqrt{\frac{1}{n_A} + \frac{1}{n_B}}}$$

Inclusion and Exclusion Criteria
The health benefits of circuit resistance training program and its possible disadvantages and injuries compared to traditional resistance and aerobic training were explained to the participants in the first session. In addition, the subjects were informed about how to perform the circuit resistance training program session. If the subjects agreed, they were included in our study and signed the informed consent. Inclusion criteria were the lack of cardiovascular diseases & hypertension, no history of stroke, heart failure, malignancy, and lack of type 2 diabetes, following a sedentary lifestyle at least in the last year, not taking part in regular exercise training, not using processed supplements for two months before and during the study, and no medical prohibition or physical restrictions for conducting the exercise training program. Moreover, regular absenteeism in circuit resistance training sessions, injury during exercise, the subject's inability for completion the exercise, refusing to cooperate in pre-test and post-test blood sampling, the subject's unwillingness to continue the training program, and taking medications or supplements during the research were regarded as exclusion criteria.

Study Design
The present study's subjects were randomly assigned to three different groups (each group consisted of 12 participants), including control, high-intensity circuit resistance training (HRT), and moderate-intensity circuit resistance training (MRT). The training program was conducted for eight weeks (three sessions per week) on non-consecutive days, which included exercises for the upper and lower body parts, including biceps and triceps curls, leg extension and flexion, Lat pull down, chest press, squats, and sit-ups. The MRT group conducted each exercise for three sets and 10–12 repetitions with 65%–70% of 1RM with 1–2 min rest between sets. Moreover, training intensity for the HRT group was 85%–90% of 1RM with three sets of 3–6 repetitions and 3–4 minutes rest between sets.[16] The subjects in the control group continued the daily routine lifestyle and did not take part in any exercise training program during eight weeks of the intervention.

Blood Sampling and Analysis
Blood sampling was conducted before and after eight

weeks of the intervention, and subjects presented in the laboratory after 12 hours of overnight fasting. In the post-test stage, blood samples were collected 48 hours after the last exercise training session. Subjects were prohibited from any strenuous physical activity or exercise at least 24 hours before blood sample collection. The blood samples were collected from the subject's right-hand vein in both blood sampling stages. The blood samples collected were poured into a tube containing EDTA and subsequently centrifuged for 10 minutes at 3000 rpm. The obtained plasma samples were kept in a freezer until further testing. The plasma levels of SAA (Cusabio, catalog number: CSB-E08589h, sensitivity: 39 ng/mL) and insulin (Demeditec, Cat Num: DE2935, sensitivity: 1.76 µIU/mL) were measured by ELISA. The glucose level was determined by Pars Azmoun kit (Iran), and insulin resistance was calculated using a previously reported formula: [glucose (mg/dL) × insulin (µIU/mL)] ÷ 405.[17]

Statistical Analysis

For data analysis, the researchers used the SPSS software version 24. The Shapiro–Wilk test represented that data distribution was normal ($P > 0.05$). Between-group changes were compared by the analysis of covariance (ANCOVA) test and the Bonferroni post hoc test. Changes in the variables after eight weeks of the intervention compared to the baseline levels were determined by the paired t test. The significance level was considered at $P < 0.05$ for all statistical tests.

Results

After eight weeks of the intervention, all subjects completed the considered protocol (control, MRT, HRT), and none of them were excluded from the study. In Table 1, the participants' characteristics, including age, height, weight, and BMI in different groups were indicated. There was no significant difference between the groups in terms of age, height, weight, and BMI ($P > 0.05$) (Table 1).

The ANCOVA test indicated a significant difference between the groups (control, MRT, HRT) for glucose, insulin, insulin resistance, percent body fat, BMI, and body weight ($P < 0.001$). According to Bonferroni post hoc test, glucose levels decreased significantly in the MRT ($P = 0.002$) and HRT ($P < 0.001$) groups compared to the control group. Moreover, a significant decrease in insulin

Table 1. Subjects' Characteristics (Mean ± SD)

Variables	Control	MRT	HRT	P
Age (y)	27.2 ± 3.54	26.9 ± 3.32	27.8 ± 3.21	0.803
Height (cm)	173.5 ± 3.44	174.3 ± 4.62	173.8 ± 4.49	0.896
Weight (kg)	87.3 ± 7.84	88.9 ± 4.73	87.1 ± 6.37	0.746
BMI (kg/m²)	28.9 ± 1.92	29.2 ± 1.40	28.7 ± 1.20	0.748

MRT: moderate-intensity circuit resistance training, HRT: high-intensity circuit resistance training.

levels and insulin resistance was observed in the MRT and HRT groups compared to the control group ($P < 0.001$). On the other hand, significant reductions in percent body fat, BMI, and body weight were observed in the MRT and HRT groups compared to the control group ($P < 0.001$). However, there was no significant difference between the MRT and HRT groups for glucose levels ($P > 0.99$), insulin levels ($P > 0.99$), insulin resistance ($P > 0.99$), percent body fat ($P > 0.99$), BMI ($P = 0.763$), and body weight ($P > 0.99$) (Table 2). In addition, the paired t-test indicated a significant reduction in glucose levels, insulin levels, HOMA-IR, percent body fat, BMI and also body weight after eight weeks of the intervention (MRT and HRT) compared to baseline levels ($P < 0.05$) (Table 2).

According to ANCOVA, changes in SAA levels were significant comparing different groups ($P < 0.001$). The Bonferroni post-hoc test showed that SAA levels in the MRT and HRT groups significantly decreased compared to the control group ($P < 0.001$). However, no statistically significant difference was noticed between the MRT and HRT groups ($P > 099$). In addition, paired t test findings represented a significant reduction in SAA level after eight weeks in the MRT and HRT groups compared to the baseline ($P < 0.001$, Figure 1). However, observed changes in the control group were insignificant ($P = 0.293$).

The Pearson correlation between different variables (BMI, PBF, glucose, insulin, HOMA-IR, and SAA) have been reported in Table 3. A significant positive correlation was observed between SAA levels and BMI ($P < 0.001$), PBF ($P < 0.001$), glucose ($P = 0.003$), insulin ($P = 0.001$), and HOMA-IR ($P = 0.001$). In addition, the correlation between other variables was significant statistically (Table 3).

Discussion

The present study's main finding was that eight weeks circuit resistance training with moderate- and high-intensity resulted in a significant downregulation of plasma SAA levels, percent body fat, and insulin resistance and there was no significant difference between circuit resistance training with moderate- and high-intensity for the changes observed in SAA, percent body fat, and insulin resistance. Moreover, SAA had a positive significant correlation with BMI, PBF, glucose, insulin, and insulin resistance.

Its suggested that adipokine secretion impairment in obesity provides a link between insulin resistance and weight gain, and changes in circulating levels of adipokines are considered as a major risk factor for type 2 diabetes.[18] SAA is a proinflammatory adipokine that is increased significantly in obese subjects.[7] It has been reported that the upregulation of SAA levels in obese individuals due to its secretion from the adipose tissue has led to an increase in inflammation, which finally enhances the risk of insulin resistance and atherosclerosis.[19] Changes in SAA levels are significantly correlated with changes in

Table 2. The Studied Variables Before and After Eight Weeks of Moderate- and High-circuit Resistance Training

Variables	Stage	Control	MRT	HRT	Between Groups P Value (Post-test Comparison)
Glucose (mg/dL)	Pre-test	93.5±7.52	92.4±7.26	95.6±9.13	<0.001
	Post-test	92.8±6.84	89.3±5.56	91.4±8.02	
Paired *t* test		0.275	0.001	<0.001	-
Insulin (mU/mL)	Pre-test	9.4±1.79	8.9±1.64	8.6±1.63	<0.001
	Post-test	9.2±1.81	7.4±1.11	7.1±0.93	
Paired *t* test		0.099	<0.001	<0.001	-
Insulin resistance (HOMA-IR)	Pre-test	2.18±0.53	2.05±0.45	2.06±0.76	<0.001
	Post-test	2.12±0.50	1.63±0.31	1.61±0.53	
Paired *t* test		0.301	<0.001	<0.001	-
Percent body fat (PBF) (%)	Pre-test	30.5±3.51	31.6±3.06	29.7±2.79	<0.001
	Post-test	31.0±3.67	29.5±3.18	27.9±2.81	
Paired *t* test		0.023	<0.001	<0.001	-
BMI (kg/m²)	Pre-test	28.9±1.92	29.2±1.40	28.8±1.20	<0.001
	Post-test	29.0±1.91	28.8±1.35	28.2±1.29	
Paired *t* test		0.217	0.003	<0.001	-
Body weight (kg)	Pre-test	87.3±7.84	88.9±4.73	87.1±6.37	<0.001
	Post-test	87.5±7.78	87.4±4.54	85.4±6.54	
Paired *t* test		0.230	<0.001	<0.001	-

Abbreviations: HRT: High-intensity circuit resistance training, MRT: Moderate-intensity circuit resistance training, HOMA-IR: homeostatic model assessment for insulin resistance.
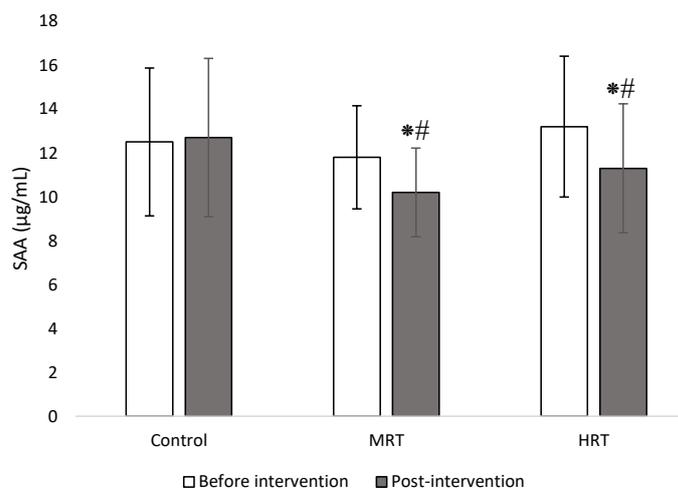
Figure 1. SAA levels before and after the intervention (Mean±SD). ∗ Significant reduction compared to the control group. # Significant reduction compared to baseline

the other inflammatory cytokines, including C-reactive protein (CRP), and simultaneous increase of CRP and SAA levels has been observed in obese individuals, those with insulin resistance, and diabetic patients.[20] Animal studies have also shown that SAA levels can be considered as an insulin resistance marker in mice, which its levels increase progressively following high-fat diet-induced obesity, resulting in insulin resistance.[21]

The upregulation of SAA in adipocytes (which has attracted a lot of attention as a major site of SAA secretion) in insulin resistance has been observed, the protective role of SAA in insulin sensitivity has been attributed partly to increased activation of the JNK signaling pathway in adipocytes.[22] However, due to limited information, the exact effects of SAA on insulin resistance requires further investigation. The present study's findings indicated a decrease in SAA levels following eight weeks circuit resistance training with moderate- and high-intensity that was associated with a significant decrease in insulin resistance, which emphasizes the role of SAA in increasing insulin resistance. In contrast, exercise training can decrease insulin resistance and improve glucose

Table 3. Pearson Correlation Between Variables

Variables	Correlation Indices	BMI	PBF	Glucose	Insulin	HOMA-IR	SAA
BMI	Pearson correlation	1	0.707	0.376	0.387	0.372	0.639
	P value	-	<0.001	0.024	0.020	0.025	<0.001
PBF	Pearson correlation	0.707	1	0.561	0.590	0.569	0.696
	P value	<0.001	-	<0.001	<0.001	<0.001	<0.001
Glucose	Pearson correlation	0.376	0.561	1	0.632	0.752	0.478
	P value	0.024	<0.001	-	<0.001	<0.001	0.003
Insulin	Pearson correlation	0.387	0.590	0.632	1	0.977	0.537
	P value	0.020	<0.001	<0.001	-	<0.001	<0.001
HOMA-IR	Pearson correlation	0.372	0.569	0.752	0.977	1	0.534
	P value	0.025	<0.001	<0.001	<0.001	-	0.001
SAA	Pearson correlation	0.639	0.696	0.478	0.537	0.534	1
	P value	<0.001	<0.001	0.003	0.001	0.001	-

Abbreviations: BMI: Body Mass Index, PBF: Percent Body Fat HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, SAA: Serum Amyloid A.

metabolism by lowering SAA levels. Although the results are contradictory about exercise training effects on the levels of SAA, most studies have reported that exercise training results in a decrease in SAA levels.[12,23] However, no change in circulating SAA levels has been shown after exercise training.[24]

Consistent with the present findings, Saghebjoo et al suggested that eight weeks of aerobic training in postmenopausal women with metabolic syndrome led to a statistically significant reduction of SAA levels, followed by a significant decrease in other inflammatory mediators such as IL-6 and Vaspin, as well as body fat percentage and fat mass as one of the major sites for the production of inflammatory mediators.[12] In this regard, Zhao et al indicated that SAA levels had a positive correlation with BMI, and weight loss could lead to a decrease in SAA levels.[11] In our study, a simultaneous decrease in SAA levels, percent body fat, body weight, and BMI was observed in both trained (MRT, HRT) groups. Given that the adipose tissue is recognized as a major site for SAA secretion,[19] reduced fat mass can largely explain the observed decrease in SAA levels after eight weeks of MRT and HRT in the present study. Despite the importance of weight loss and lowering body fat percentage in the downregulation of SAA levels, it seems that weight loss alone cannot exert a significant effect on circulating levels of SAA. For example, Ryan et al suggested that after six months of aerobic training and weight loss in obese or overweight postmenopausal women, a decrease in SAA level was significant only in the training + weight loss group, but changes of SAA levels were insignificant in the weight loss group (calories restricted to 300 to 500 calories per day) despite a significant decrease in body fat percentage and body weight.[25]

These contradictory findings can be attributed to the secretion of SAA from other tissues other than the adipose tissue. In this regard, Mehrabani et al showed that SAA levels immediately after acute endurance exercise (cycling with 65% of maximum oxygen consumption) in obese and normal weight young men significantly increased compared to baseline SAA levels, and the increase of SAA level in the obese group after endurance exercise was higher compared to the normal-weight group.[26] The upregulation of SAA levels immediately after exercise represents the possible secretion of SAA from other tissues, especially the skeletal muscle. However, confirming this hypothesis that SAA can act as a myokine (in addition to its role as an inflammatory adipokine) should be investigated in future studies.

In another study, Kolahdouzi et al confirmed our findings and suggested a significant reduction in the plasma levels of SAA in obese men following eight weeks resistance training with 65%-85% one repetition maximum (1RM), which was consistent with the present results, showing a decrease in SAA levels along with a significant reduction in insulin resistance and BMI.[23] Numerous studies have confirmed the role of SAA in the pathogenesis of insulin resistance, and it has been reported that SAA can disturb glucose metabolism in adipocytes, leading to insulin resistance.[27] Although the present study showed a significant effect of circuit resistance training with moderate- and high-intensity in decreasing SAA levels, some researchers indicated that even 12 weeks low-intensity resistance training resulted in the significant downregulation of SAA and CRP levels, insulin resistance, systolic blood pressure, as well as significant improvements in lipid profile (reduction of triglyceride and total cholesterol) in older women.[28] These findings suggested that modulating systemic inflammation (decrease in SAA, CRP, etc) could be considered as an important part of exercise training positive effect. Unfortunately, the changes in CRP levels, lipid profile, as well as other inflammatory mediators such as IL-6 and anti-inflammatory mediators like IL-10, have not been

investigated in the present study. In another study and in contrast to the present findings, Campbell et al reported that 12 months of moderate-intensity aerobic training in postmenopausal women had no significant effect on SAA levels and other inflammatory mediators including IL-6 and CRP.[29] These contradictory findings compared to ours may be related to different types of exerted exercise training. In addition, Campbell et al indicated that there was a positive correlation between the observed decrease in body fat percentage and circulating levels of CRP and SAA,[29] which represented the importance of changes in fat mass as a major site of SAA secretion.

Given that SAA have a high affinity for HDL binding, and it is mainly transported in the circulation as an HDL apolipoprotein,[30] increased HDL levels following exercise training can lead to increased SAA binding to HDL, thereby resulting in no significant change in SAA levels after exercise training.[12,31] Moreover, Safarzade et al showed that four weeks of resistance training in diabetic rats increased the serum concentration of apo-A1 and decreased glucose levels, without a significant change in SAA levels.[24] Moreover, regardless of different subjects' characteristics and their pathological conditions, this difference can be attributed to the short period (4 weeks against 8 weeks in present study) of exercise training program compared to the present study.

According to above-mentioned studies, it seems that different intensities of exercise training (even low intensities) can lead to a decrease in SAA levels, which this effect of exercise training can be mediated through various mechanisms. Due to the present study's limitations, including the small sample size, not considering low-intensity circuit resistance training, and no measurement of the changes in other inflammatory and anti-inflammatory factors, we could not discuss SAA interaction with other inflammatory and anti-inflammatory mediators. Therefore, identifying the mechanism of SAA reduction after exercise training needs further investigation. In addition, at the same time with moderate- and high-intensity circuit resistance training, we recommend to determine the effect of low-intensity circuit resistance training.

Conclusion
The present study's findings indicated that despite the significant effects of circuit resistance training with moderate- and high-intensity on decreasing SAA levels and insulin resistance, there was no significant difference between moderate- and high-intensity circuit resistance training regarding the changes observed in SAA levels and insulin resistance.

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