Effect of Exercise Training on Inflammation Status Among People with Metabolic Syndrome

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Abstract

Background: Metabolic syndrome is associated with chronic low-grade inflammation, a condition thought to play a key role in the pathogenesis of the syndrome. Among a number of proinflammatory cytokines, interleukin-18 (IL-18) seems to be the best marker for inflammation among people with metabolic syndrome. The aim of this study was to examine the effect of aerobic training versus strength training on circulating IL-18 and other proinflammatory markers in people with metabolic syndrome.

Methods: Thirty-one inactive men and women with metabolic syndrome were randomized to either high-intensity aerobic interval training (AIT, $n=11$), strength training (ST, $n=10$), or a control group ($n=10$). Exercise training was carried out three times per week for 12 weeks. Serum insulin, high-sensitivity C-reactive protein (hsCRP), IL-18, IL-6, and tumor necrosis factor- α (TNF- α) were measured before and after the intervention.

Results: Serum IL-18 was reduced by 43% after AIT ($P<0.001$). Although there was no change in TNF- α from baseline after AIT, the levels were lower compared to the ST ($P=0.032$) and control groups ($P=0.039$) after the intervention. Total body fat was reduced after AIT (from $33.9\pm7.3\%$ to $32.2\pm7.9\%$, $P<0.001$) and ST (from $31.2\pm3.9\%$ to $29.7\pm3.4\%$, $P=0.025$). There were no changes in serum IL-6, insulin, or hsCRP within or between the groups.

Conclusion: Both ST and AIT reduced fat mass. However, only the latter intervention was associated with a more favorable inflammatory status among people with metabolic syndrome. Clinical Trial Registration Information: <http://clinicaltrials.gov/show/NCT00986024/>.

Introduction

METABOLIC SYNDROME IS A condition in which a clustering of metabolic risk factors occurs together, increasing the risk of premature death.^{1,2} Today there is a general agreement that the definition of metabolic syndrome should include central obesity, dyslipidemia, hypertension, and elevated fasting glucose.³ In addition, metabolic syndrome is associated with chronic low-grade inflammation,^{4–8} a condition in which inflammatory markers in the circulation are slightly elevated. Acute inflammation is a natural defense against injury and infection, whereas chronic inflammation may contribute to a number of diseases.^{9,10} The unfavorable influence of the circulating proinflammatory markers differs between tissues and involves dysregulation of metabolism in skeletal muscle,¹¹ plaque formation in the endothelium,¹² and dysfunction of immune cells.¹³

It has been proposed that some proinflammatory markers should be included in the definition of metabolic syndrome,^{4,8,14,15} and traditionally C-reactive protein (CRP) has been the main marker for inflammation status. However, it has been shown that serum interleukin-18 (IL-18) is a strong and independent risk predictor for metabolic syndrome,¹⁶ and a number of studies have suggested that the cytokine plays a pivotal role in the pathogenesis of the syndrome.^{4,16,17} Interestingly, serum levels of IL-18 remain an independent predictor of metabolic syndrome, even after adjustment for other risk factors comprising metabolic syndrome.¹⁶ The current guidelines for managing metabolic syndrome highlight lifestyle changes as the first-line therapy.⁶ It is, however, not well documented how different types of exercise affect low-grade inflammation among people with metabolic syndrome. Therefore, the aim of this study was to evaluate the effect of aerobic training versus strength

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training on the circulation of IL-18 and other proinflammatory markers in people with metabolic syndrome.

Material and Methods

Participants and study design

Thirty-three inactive men and 10 women (49.8 ± 9.1 years), with metabolic syndrome were included in this study. The participants were selected from the area around Trondheim, Norway, between 2006 and 2007; they were recruited voluntarily after they responded to an advertisement in the local newspaper. People with unstable angina pectoris, uncompensated heart failure, myocardial infarction during the past 4 weeks, complex ventricular arrhythmias, and kidney failure were excluded from the study. The participants received oral and written information about the experimental protocol and procedures, and signed a written consent to participate. Two persons, 1 in the control group and 1 in the strength-training group, failed to complete the training (Fig. 1). The Regional Committee for Medical Research Ethics approved the study, and the study was conducted in accordance with the Declaration of Helsinki.

Intervention

In this study, the participants were randomized to aerobic interval training (AIT), strength training (ST), or control groups. In addition, as previously described,¹⁸ there was also one group performing a combined exercise program ($n = 11$); however, this group was not included in the analysis of this study, because Trøseid et al.¹⁹ had already reported that combined exercise can reduce inflammation in people with metabolic syndrome. The unit of Applied Clinical Research at the Norwegian University of Science and Technology carried out all randomization procedures to secure complete blinded randomization. The exercise program consisted of three sessions per week for 12 weeks. All training sessions were carefully supervised by an exercise physiologist. The AIT group performed 4×4 min of intervals at 90% of maximal heart rate, with a 3-min active recovery period at approximately 70% of peak heart rate (HR_{peak}) between each

interval. Each session started with 10 min of warm-up and ended with a 5-min cool-down period, amounting to 43 min of total exercise time. ST group performed two sets of 15–20 repetitions at approximately 40%–50% of 1 repetition maximum (1 RM) as a warm-up. The following exercises were performed twice weekly (program 1): Low row, bench press, and hack lift. An alternative program was performed once each week (program 2): Deltoid exercise (lateral raise exercise), triceps pull down, biceps curl, low-row, and core exercises (plank exercise). The intensity of the exercise was 80% of 1 RM, and one exercise session lasted for approximately 40 min. The training procedures have been described in detail previously.¹⁸

Laboratory procedures

Participants arrived at the laboratory after an overnight fast, and blood samples were obtained from an arm vein. Water intake was allowed as was the intake of everyday medication. The participants were asked to refrain from any vigorous exercise the last 48 hr prior to blood sampling. High sensitivity (hs) CRP was measured immediately using standard procedures at St.Olav's University Hospital, Trondheim. Serum samples were prepared by drawing whole blood directly into tubes that contained no anticoagulant and letting them clot at room temperature for 30 min. The serum was transferred into separate tubes after centrifugal treatment at 3,000 rpm for 10 min at 4°C. Aliquots of serum were stored at -80°C for later analysis. Serum IL-6, IL-18, tumor necrosis factor- α (TNF- α), and insulin were measured using enzyme-linked immunosorbent assay (ELISA) (IL-6 #Q6000B R&D Systems, Minneapolis, MN; IL-18 #7620 Q6000B R&D Systems; TNF- α #QTA00B Q6000B R&D Systems; insulin #EZ-HIASF-14K Millipore, Billerica, MA). The minimum detection limit for each kit was: 0.16 pg/mL for IL-6, 12.5 pg/mL for IL-18, 0.39 pg/mL for TNF- α , and 0.73 $\mu\text{U/mL}$ for insulin. The ELISA was performed by a fully automated Dynex Magellan (DS2™) machine, which allowed elimination of the variations that occur with manual processes (*i.e.*, pipetting). Standards and controls were measured as duplicates, whereas most of the samples were single measurements. The intraassay variation was below 6%.

Fat mass

Body composition was measured by using dual-energy X-ray absorptiometry (DXA) scanning (HologicDiscovery-A, Bedford, MA).²⁰

Food questionnaire

Total calorie intake and food composition were registered with an 11-page food questionnaire at the first and last week of the intervention. The questionnaire included 180 food items that are adapted to the Norwegian meal patterns.²¹

Statistical analysis

Descriptive data were reported as mean values $\pm$ standard deviation (SD). When data followed normal distribution, a paired-sample *t*-test was used to compare within-group differences before and after the intervention. The nonparametric Wilcoxon test was used if the assumptions of normality and homogeneity of variance were in doubt. The

FIG. 1. Flowchart of the participants throughout the study. AIT, aerobic interval training; ST, strength training.

TABLE 1. DESCRIPTIVE DATA OF THE PARTICIPANTS

	Control	AIT	ST
Number of participants	10	11	10
Age, mean in years (SD)	47.3 (10.2)	49.9 (10.1)	50.9 (7.6)
Weight (kg), mean (SD)	100.9 (9.4)	99.7 (18.7)	103.4 (17.1)
BMI (kg/m ²), mean (SD)	31.9 (4.1)	31.3 (4.3)	32.3 (4.2)
Waist (cm), mean (SD)	108.7 (9.3)	109.6 (10.0)	106.2 (8.6)
SBP (mmHg), mean (SD)	141.5 (12.3)	140 (14.6)	142.7 (14.2)
DBP (mmHg), mean (SD)	90.1 (7.1)	89.0 (8.1)	90.7 (10.9)
TG (mmol/L), mean (SD)	1.7 (0.8)	2.3 (1.0)	1.8 (0.9)
Glucose (mmol/L), mean (SD)	6.2 (2.1)	6.0 (1.1)	6.6 (2.0)
HDL (mmol/L), mean (SD)	1.29 (0.35)	1.17 (0.35)	1.15 (0.18)
Medication (number of participants)			
Thyroxin	0	1	0
Metformin	0	0	1
Angiotensin II blockers	2	1	2
ACE antagonist	1	0	1
Ca ²⁺ antagonists	0	0	1

AIT, aerobic interval training; ST, strength training; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglycerides; HDL, high-density lipoprotein; ACE, angiotensin-converting enzyme.

effect of the intervention is presented as median, 25–75 quartiles, and total range. Analysis of covariance (ANCOVA), making a regression model (general linear model, GLM), was used to test between-group differences, with the difference/delta value as a dependent factor, group variable as fixed factor, and baseline values as covariate (Vickers and Altman, 2007). A *P* value < 0.05 was considered significant. All statistics were analyzed by SPSS (version 17.0)

Results

Descriptive data

Descriptive data of the participants with metabolic syndrome are presented in Table 1 (some data were previously reported in Stensvold et al.¹⁸). There were no significant differences between the groups in the any of the five components defining the metabolic syndrome or in age or weight at baseline (Table 1). No change in body weight was observed; however, fat mass was significantly reduced after ST (*P* = 0.03) and AIT (*P* < 0.01). We have previously shown that AIT increased $\dot{V}O_{2\max}$ by 11%, whereas ST increased maximal leg strength by 45%, and that both AIT and ST reduced waist circumference and improved endothelial function.¹⁸ No unintended effects were observed during the study. One subject from the control group increased the prescribed dosage of statins 3 weeks before the posttest.

Proinflammatory markers

Figure 2, A–E, shows the changes in serum levels of IL-18, TNF- α , IL-6, hsCRP, and insulin in the AIT, ST, and control groups. There were no significant differences at baseline between the groups in any of the markers. Serum IL-18 was reduced by 43% after AIT (*P* < 0.001) (from 161.4 ± 105.4 to 92.3 ± 92.7 pg/mL), and the change was significant compared to ST (*P* = 0.009) and control (*P* = 0.024). There was a 10% increase in serum TNF- α from pre to post after ST (from 3.9 ± 0.8 to 4.3 ± 0.9 pg/mL, *P* = 0.014). Although TNF- α did not change significantly from baseline after AIT, the levels of TNF- α at follow-up were 14% (*P* = 0.032) and 12% (*P* = 0.039)

lower compared to ST and control groups, respectively. There were no changes in serum IL-6, insulin, or hsCRP within or between the groups.

Correlation

There was a correlation between change in fat mass and change in plasma TNF- α (Pearson correlation = 0.48, *P* = 0.009). There was no significant correlation between change in fat mass and change in plasma IL-18 (Pearson correlation = 0.253, *P* = 0.177).

Food questionnaire

There were no significant changes in total energy intake (kcal) or macronutrient composition before compared to after the intervention (Table 2).

Discussion

The main finding in the present study was that high-intensity AIT and not ST was associated with a more favorable inflammatory status among people with metabolic syndrome. Because low-grade inflammation seems to be involved in the pathogenesis of metabolic syndrome,^{4,8,22} effective and inexpensive antiinflammatory strategies may lead to improved prevention and treatment of the syndrome.

Growing evidence suggests that IL-18 plays an important role in the development of metabolic syndrome.^{4,17,23} Through a cascade of reactions, IL-18 stimulates inflammation and immune responses in the human body.^{17,24,25} In rats, overexpression of IL-18 protein aggravated insulin resistance and led to enhanced vascular inflammation and remodeling.²⁶ In addition, data from animal models indicate that IL-18 is directly involved in cardiomyopathy, because it has been shown that overexpression of the IL-18 protein exaggerated left ventricular remodeling and diastolic dysfunction.²⁷ Previously, it had been shown that aerobic exercise can reduce IL-18 levels in patients with type 2 diabetes,²⁸ in elderly adults,²⁹ and in obese women.³⁰

FIG. 2. Change in serum interleukin-18 (IL-18) (**A**), tumor necrosis factor- α (TNF- α) (**B**), IL-6 (**C**), high-sensitivity C-reactive protein (hsCRP) (**D**), and insulin (**E**) after the intervention. Median, 25–75 quartiles, and total range are presented. AIT, aerobic interval training; ST, strength training; o, outlier excluded from the analysis. (†) Significant ($P < 0.05$) change after the intervention; (*) significantly ($P < 0.05$) different from control; significantly ($P < 0.05$) different from ST and control [DS2].

However, Christiansen et al. reported no change in circulation inflammatory markers after 12 weeks of endurance training.³¹ In addition, Trøseid et al.¹⁹ have reported that exercise training can reduce serum IL-18 in people with metabolic syndrome. This intervention, however, was an

amalgamation of both AIT and ST, and thus the observed effect could not be attributed to a particular type of exercise.

Our data clearly demonstrate that AIT reduces serum IL-18, whereas ST has no such effect. Twelve weeks of high-intensity exercise training did not have an effect on the other

TABLE 2. BODY COMPOSITION AND ENERGY INTAKE BEFORE (PRE) AND AFTER (POST) THE INTERVENTION

	Control		AIT		ST	
	Pre	Post	Pre	Post	Pre	Post
Weight, kg	100.9 ± 9.4	101.6 ± 10.2	99.7 ± 18.7	98.3 ± 13.3	103.4 ± 17.1	102.5 ± 17.2
Fat mass, kg	34.6 ± 8.8	34.2 ± 8.4	33.5 ± 8.6	31.3 ± 9.0 ^{†,*}	32.3 ± 7.0	30.5 ± 5.7*
Energy intake, kcal	2,044 ± 490	1,998 ± 385	2,584 ± 758	2,269 ± 548	2,633 ± 647	2,377 ± 422
Protein, %	18	18	16	17	16	17
Fat, %	35	35	32	34	33	33
Carbohydrate, %	44	45	48	46	46	46

AIT, aerobic interval training; ST, strength training; kcal, kilocalorie.

[†]Significant ($P < 0.05$) change after the intervention.

*Significantly ($P < 0.05$) different from ST and control; significantly ($P < 0.05$) different from control [DS3].

measured inflammatory markers. Most likely the exercise period was too short to induce a change, as was previously shown in a study conducted by Balducci et al.,³² in which 1 year of high-intensity aerobic exercise significantly reduced CRP and IL-6 in people with type 2 diabetes and metabolic syndrome. The majority of the clinical studies examining the effect of exercise on inflammatory markers are endurance studies,³³ whereas the data from ST studies are few and conflicting.³⁴ In our study, serum TNF- α was increased after ST. A review on the effect of ST on cytokines from 2010 concluded that ST had no effect on serum TNF- α .³⁴ Interestingly, only one of the studies included in the analysis was a randomized controlled trial.³⁵ The increase in TNF- α seen in our study might be due to delayed-onset muscle soreness (DOMS), as blood samples were obtained 48 hr after last exercise session, and DOMS usually peaks 24–72 hr following cessation of exercise.³⁶

Because adipose tissue has been characterized as an endocrine organ, it is reasonable to assume that a reduction in fat mass can influence circulation proinflammatory markers. There was a decrease in fat mass after both ST and AIT in our study, yet only the latter intervention resulted in a more favorable inflammatory status. Surprisingly, a reduction in fat mass was not associated with better inflammatory status after ST. However, there was a correlation between the change in fat mass and the change in TNF- α overall. There could be several explanations for the observed differences after ST and AIT seen in our study: (1) There was an insignificantly larger reduction in fat mass seen after AIT; (2) ST and AIT might induce different adaptations in adipose tissue; and (3) tissues other than adipose could have contributed to the systemic level of proinflammatory markers.

Diet can have an impact on circulatory levels of inflammatory markers,³⁷ and it has previously been shown that exercise training without weight loss has no effect on inflammation.³⁸ On the contrary, Bruun et al.³⁹ showed that the reduction in plasma IL-18 after 15 weeks of lifestyle intervention was not related to the change in body mass index (BMI). In our study total energy intake (kJ) and food composition did not change during the interventions for any of the groups. However, there was a nonsignificant reduction of ≈ 300 kcal in AIT and ST. Together with the increased energy expenditure, the overall energy balance probably changed in these groups. Because there was no correlation between the change in either weight or fat mass and IL-18, the change is very likely to be attributed to the exercise itself. It has been suggested that the antiinflammatory response to exercise training is, to a great extent, mediated through antiinflammatory cytokines (myokines) released from the skeletal muscle acutely after exercise.^{10,40} The antiinflammatory effect of myokines involves both stimulation of lipolysis and an enhanced fat oxidation.⁴¹ In addition, myokines can inhibit the production of proinflammatory cytokines.¹⁰ Blood samples were not collected after an acute exercise bout in our study. Thus, we cannot say if the change in inflammatory status was caused by the acute release of myokines.

Limitations

The limited number of participants, variation in age, and the inclusion of both genders can probably explain a relatively large individual difference seen in this study. Thus,

larger studies are required to confirm our findings. The role of cytokines in a specific physiological situation can be very complex,³³ and further research is needed to examine how circulation, cytokines, and the downstream mechanism are involved in the metabolic dysfunction seen with metabolic syndrome. It was not possible in this study to assess whether inflammation is an association or a causation of metabolic syndrome. However, regardless of the mechanism, the negative implications of chronic low-grade inflammation emphasizes the importance of modifying this condition.

Conclusion

Our study is the first to indicate that AIT could be effective in reducing low-grade inflammation in people with metabolic syndrome. Our study adds information to the growing literature on the effect of exercise training as a treatment for metabolic syndrome.

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Author Disclosure Statement

No competing financial interests exist.

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