

Original Article

Effects of Supervised Aerobic Exercise Training on Serum Adiponectin and Parameters of Lipid and Glucose Metabolism in Subjects with Moderate Dyslipidemia

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Aim: To examine the effects of supervised aerobic exercise training on serum adiponectin and lipids, including triglyceride (TG)-rich lipoproteins, in moderate dyslipidemic subjects.

Methods: Twenty-five dyslipidemic patients [mean body mass index (BMI) = 24.6 kg/m²; mean age = 39 years; mean total cholesterol = 226 mg/dL; mean TG = 149 mg/dL] without metabolic syndrome, diabetes, and hypertension underwent supervised aerobic exercise training (60 min/day, 2 to 3 times/week) at an intensity of 60–80% of age-predicted maximal heart rate for 16 weeks. Lipoprotein cholesterol levels were measured by our established anion-exchange HPLC method.

Results: Aerobic exercise training significantly decreased BMI, cholesterol levels of LDL- and IDL-, and markedly reduced VLDL-cholesterol at week 8 (–45%) and week 16 (–50%), but changes in TG and HDL-cholesterol were not significant. Adiponectin significantly increased by 51% and HOMA-R was significantly decreased at week 16, although changes in these parameters were not significant at week 8. There was no significant relationship between changes in adiponectin and in VLDL- or IDL- cholesterol, but changes in adiponectin were inversely but insignificantly associated with changes in BMI ($r = -0.343$, $p = 0.095$).

Conclusions: These results suggest that supervised aerobic exercise training two to three times/week in the presence of body weight loss increases serum adiponectin with an improved lipid profile and insulin sensitivity at week 16 in non-obese moderate dyslipidemic patients, and that VLDL-cholesterol is markedly decreased by supervised aerobic exercise training.

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Key words; Adiponectin, HOMA-R, Aerobic exercise training, VLDL-cholesterol

Introduction

Metabolic syndrome is a cluster of cardiovascular risk factors, including dyslipidemia, impaired glycemic

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control, elevated blood pressures, and abdominal obesity, and individuals with metabolic syndrome are associated with increased cardiovascular morbidity and mortality¹⁻⁴). Adiponectin is an adipocyte-secreted protein that has been proposed to play a significant role in lipid and glucose metabolism, and is decreased if individuals are obese, and a decreased serum adiponectin predicts cardiovascular diseases and the future development of type 2 diabetes¹⁻⁶). In addition, adiponectin levels are markedly low in patients with type 2b

dyslipidemia among type 2 diabetes patients⁵).

Excess visceral fat, found in metabolic syndrome, is associated with insulin resistance and cardiovascular risk factors, and the visceral fat area is inversely correlated with adiponectin^{3, 6}. Because visceral fat accumulation and obesity are induced by physical inactivity, and regular exercise reduces not only body weight but also visceral fat, exercise training could be effective at reducing metabolic disorders^{3, 7}. Therefore, it is of clinical significance to investigate whether exercise training can increase serum adiponectin levels because lifestyle modifications, including exercise training, are emphasized for the prevention of metabolic syndrome and its consequences.

Although insulin-sensitizing actions by exercise training are possibly linked with increased serum adiponectin levels, changes in serum adiponectin are still controversial and should be carefully interpreted in the context of human subjects and animal models, the intensity and duration of the exercise program, the presence or absence of obesity or insulin resistance, and the various forms of adiponectin measured [high-molecular-weight (HMW) or total adiponectin]⁸).

A large number of studies have shown favorable effects of exercise training on serum lipid levels, and aerobic or endurance exercise training usually decreases triglyceride (TG) and increases high-density lipoprotein (HDL)-cholesterol, but resistance exercise training consistently does not^{9, 10}. Serum TG concentrations are usually decreased, and greater reductions in TG after exercise training are often reported for persons previously inactive with higher concentrations of baseline TG; however, changes in serum concentrations of TG-rich lipoprotein levels [(chylomicron, very low density lipoprotein (VLDL), intermediate density lipoprotein (IDL)] after aerobic exercise training are not well defined.

From the viewpoint of preventive medicine, the present study investigated whether supervised aerobic exercise training for 16 weeks could increase serum adiponectin and ameliorate glucose and lipid metabolism, including TG-rich lipoproteins, in individuals with mild dyslipidemia and without severe obesity, metabolic syndrome diagnosed by Japanese guidelines⁴, diabetes, and hypertension.

Methods

The present study was aimed at participants in a supervised exercise training course of a ubiquitous health project to improve employees' health at the Wellness center of a certain electric company in Tokyo, Japan. Twenty-five subjects (22 men and 3 women),

aged 39 ± 7 years; with low density lipoprotein (LDL) cholesterol levels ≥ 140 mg/dL and/ or TG levels ≥ 150 mg/dL were enrolled. Excluded were subjects with body mass index (BMI) > 30 kg/m², diabetes, hypertension, cardiovascular diseases, use of agents affecting lipid and glucose metabolism, liver dysfunction, renal dysfunction, and endocrine diseases. BMI > 25 kg/m² in place of waist circumference was used for the diagnosis of metabolic syndrome using Japanese criteria⁴. The study was approved and programmed as an annual plan for health promotion by the Wellness center of the electric company. The participants received guidance and a lecture on nutrition and diet therapy from dietitians and doctors at the Wellness center.

Blood samples were obtained after a 12-h overnight fast and 48-h alcohol abstinence prior to the intervention (week 0), and at mid-intervention (week 8) and the end of the study (week 16). Body composition and blood samples were examined at baseline and at weeks 8 and 16. The exercise training program lasted for 16 weeks and consisted of sessions of aerobic exercise 2 to 3 times a week performed at the fitness facility and supervised by an exercise instructor. After a 10-min warm-up, the study subjects performed aerobic exercise on a treadmill or ergometer for 60 min at the intensity corresponding to the individually recommended target heart rates at an intensity of 60–80% of age-predicted maximal heart rate, which would be around $138 - \text{age (years)}/2$ according to Japan Atherosclerosis Society guidelines¹¹, and then moved on to a 10-min cool-down. Exercise was supervised by an exercise specialist to maintain the quality of the workout and optimize the exercise prescription. The attendance rate for the supervised exercise training was approximately 80%; however, self-motivated exercise training at home was not limited and not monitored.

Fasting blood samples were collected, and cholesterol levels of HDL, LDL, IDL, VLDL, and chylomicron were measured by HPLC^{5, 12}. Briefly, serum lipoproteins were separated on a column containing diethylaminoethyl-ligand nonporous polymer-based gel by elution with a step gradient of sodium perchlorate concentration, and detected by a post-column reaction with a reagent containing cholesterol esterase and cholesterol oxidase. Serum total adiponectin was measured by ELISA obtained commercially from Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan)⁵, and HMW adiponectin was also measured by ELISA using a monoclonal antibody against human HMW adiponectin (Fujirebio, Tokyo, Japan)¹³. Serum insulin, total cholesterol (TC), TG, fasting plasma glucose (FPG), and hemoglobin (Hb)A1c were measured conventionally. The homeostasis model assessment of insu-

lin resistance (HOMA-R), a surrogate marker for insulin resistance¹⁴), was calculated as fasting insulin (mU/L) \times plasma glucose (mg/dL)/405.

Values are given as the mean \pm standard deviation (SD). The significance of differences in parameters among values at baseline, week 8, and week 16 was assessed by repeated-measures ANOVA and followed by Fisher's PLSD comparison method. Correlations between variables were evaluated by Pearson's simple linear regression analysis. $p < 0.05$ was considered significant.

Results

At baseline, BMI, LDL-cholesterol, HDL-cholesterol, TG, HOMA-R, and adiponectin were 24.6 ± 3.4 kg/m², 145 ± 27 mg/dL, 52 ± 17 mg/dL, 149 ± 59 mg/dL, 2.2 ± 1.1 , and 4.9 ± 2.4 (μ g/mL), respectively (**Table 1**). Subjects who had severe obesity and insulin resistance were not included in the current study. Even though BMI > 25 kg/m² in place of waist circumference was used for the diagnosis of metabolic syndrome using Japanese criteria⁴), subjects with metabolic syndrome also were not included.

As compared with baseline values, BMI modestly but significantly decreased to 24.0 at week 8 and to 23.9 at week 16, and TC and LDL-cholesterol decreased significantly at week 8 and week 16 (**Table 2**); however, HDL-cholesterol did not change significantly throughout the study, and TG showed a trend towards a decrease at week 8 and week 16, but not significantly. Apolipoprotein A1 levels were not changed during the study, but apolipoprotein B levels signifi-

Table 1. Characteristics of Study Subjects

Age (years)	39 \pm 6
Gender (male/female)	22/3
Body mass index (kg/m ²)	24.6 \pm 3.4
Total cholesterol (mg/dL)	226 \pm 28
Triglyceride (mg/dL)	149 \pm 59
LDL-cholesterol (mg/dL)	145 \pm 27
HDL-cholesterol (mg/dL)	52 \pm 17
Fasting plasma glucose (mg/dL)	91 \pm 9
Insulin (mU/mL)	10.0 \pm 4.9
HOMA-R (Homeostasis model assessment)	2.2 \pm 1.1
HbA1c (%)	4.9 \pm 0.4
Adiponectin (μ g/mL)	4.9 \pm 2.4

cantly decreased at week 16 as compared with the baseline (**Table 2**). In the TG-rich lipoproteins, IDL-cholesterol significantly decreased at both week 8 and week 16, and VLDL-cholesterol markedly decreased at week 8 and week 16 as compared with the baseline (**Table 2**).

Serum adiponectin and HOMA-R did not change significantly after 8 weeks of exercise training, but HOMA-R decreased from 2.2 ± 1.1 at baseline to 1.8 ± 1.1 at week 16 ($p < 0.05$), while adiponectin significantly increased from 4.9 ± 2.4 at baseline to 7.5 ± 3.9 at week 16 ($p < 0.001$) (**Fig. 1**). Adiponectin values at week 16 were also greater than those at week 8. In addition to no significant changes in total adiponectin at week 8, HMW adiponectin levels and the percentage of HMW adiponectin did not change after 8-week exercise training, similar to total adiponectin (**Table 2**).

Table 2. Changes in metabolic parameters by 16-week supervised aerobic exercise

	Baseline	Week 8	Week 16
BMI (kg/m ²)	24.6 \pm 3.4	24.0 \pm 3.4**	23.9 \pm 3.4***
TC (mg/dL)	226 \pm 28	213 \pm 32*	214 \pm 24*
TG (mg/dL)	149 \pm 59	129 \pm 63	127 \pm 59
HDL-C (mg/dL)	52 \pm 17	51 \pm 15	55 \pm 14
LDL-C (mg/dL)	145 \pm 27	131 \pm 21*	129 \pm 21**
IDL-C (mg/dL)	6.7 \pm 4.0	4.0 \pm 2.2***	3.7 \pm 2.0***
VLDL-C (mg/dL)	20.1 \pm 10.7	9.7 \pm 6.2***	8.8 \pm 5.9***
Chylomicron-C (mg/dL)	4.2 \pm 4.0	3.4 \pm 2.8	3.1 \pm 2.5
Apolipoprotein A1 (mg/dL)	143 \pm 29	143 \pm 25	143 \pm 21
Apolipoprotein B (mg/dL)	111 \pm 20	104 \pm 23	101 \pm 21*
HMW adiponectin (μ g/mL)	3.3 \pm 2.4	2.8 \pm 1.5	NA
Percentage of HMW Adiponectin (%)	59.7 \pm 13.6	53.6 \pm 11.9	NA

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$

NA, not assessed; HMW, high molecular weight

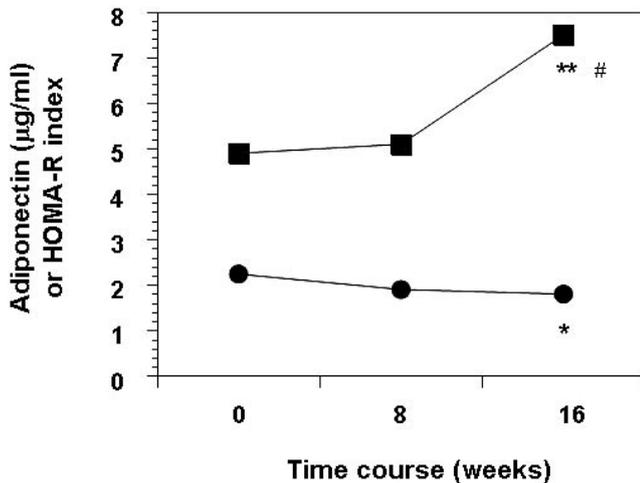


Fig. 1. Changes in adiponectin and HOMA-R by 16-week supervised aerobic exercise. Closed square and circle show adiponectin and HOMA-R, respectively.

* $p < 0.05$; ** $p < 0.001$ as compared with the baseline levels
$p < 0.001$ as compared with the levels at week 8.

The relationships between changes in adiponectin and changes in IDL- and VLDL-cholesterol were tested, but the adiponectin changes did not correlate with the changes in IDL-cholesterol ($r = -0.127$, $p = 0.57$) and VLDL-cholesterol ($r = -0.032$, $p = 0.88$). Increased adiponectin was inversely but insignificantly correlated with decreased BMI ($r = -0.343$, $p = 0.095$).

Discussion

In the present study we found that supervised aerobic exercise training 2 to 3 times a week for 16 weeks in the presence of body weight loss increased serum adiponectin levels and ameliorated insulin resistance and serum lipoproteins (VLDL-, IDL-, and LDL-cholesterol) in subjects with moderate dyslipidemia and without metabolic syndrome, diabetes, and hypertension; however, inconsistent results have emerged from previous studies investigating the effects of aerobic exercise training on serum adiponectin levels⁸. Such a controversy might partly be explained by the influence of differences in the studied subjects, the intensity and duration of the exercise program, the baseline presence or absence of obesity or insulin resistance, and the various forms of adiponectin measured.

Previous reports from various protocol studies indicate that adiponectin levels do not change in healthy non-obese humans regardless of their improved insulin sensitivity, and suggest that a direct effect of exercise training on adiponectin levels is unlikely to represent the mechanisms of improved

insulin resistance^{8, 15-17}); however, in insulin-resistant subjects, exercise training is recommended as a therapy to improve insulin resistance^{18, 19}), but previous studies in overweight and/or diabetic subjects have reported conflicting results^{8, 19, 20}. The presence or absence of body weight loss after exercise training may not necessarily determine whether exercise training can increase serum adiponectin levels, but exercise training can exert a presumable effect on serum adiponectin levels in insulin-resistant and obese individuals through the reduction of fat mass with body weight loss^{8, 20-22}. Recently, Ando, *et al.* have shown that twice-weekly aerobic exercise training in the absence of weight loss does not change HMW adiponectin or adiponectin oligomeric distribution²³. In the present study, body weight was reduced slightly but significantly by 16-week exercise training, and serum adiponectin levels were significantly increased, but adiponectin levels were not changed, contrary to significant body weight reductions, after 8-week exercise training. However, the relationship between changes in adiponectin and in BMI was on the verge of statistical significance, although it should be carefully interpreted because of the small study. Therefore, the present study might also demonstrate the relevance of not only body weight reductions but also other undefined factors to increased adiponectin by aerobic exercise training.

Although the exercise frequency and training duration might also affect the effect of exercise training on serum adiponectin levels, the baseline profiles of studied subjects (obese or non-obese, insulin-resistant or non-insulin-resistant) could affect serum adiponectin changes after exercise training rather than the exercise frequency and duration^{8, 20}. Previous papers showed an inverse relationship between HOMA-R and serum adiponectin, implicating the role of adiponectin in the mechanism of improved insulin resistance^{1, 2, 24, 25}. In line with these reports, 16-week exercise training could decrease HOMA-R in concert with increased adiponectin, whereas 8-week exercise training did not decrease HOMA-R or increase adiponectin. This might be attributed to that markedly insulin-resistant subjects were not included in the present study because subjects with metabolic syndrome and diabetes were excluded. Moreover, it could be interpreted that 8 weeks might be too short for an intervention period to increase serum adiponectin levels, and 16 weeks at least might be an appropriate exercise intervention period; however, this remains to be clarified because the exercise effects are susceptible to the diverse conditions set by the study design. Furthermore, the influence of self-motivated exercise training

at home on changes in adiponectin and insulin resistance remains possible but unclear.

Adiponectin has been shown to circulate in blood in several multimeric forms, and these different forms have been postulated to have different biological activity²⁶. HMW adiponectin recently has been proposed to be the biological active form of adiponectin, and it has been supposed that HMW adiponectin predicts metabolic parameters better than total adiponectin²⁷. Several studies have reported an association between HMW adiponectin and insulin sensitivity^{2, 26, 27}, but whether this relationship is greater than the well-documented associations of total adiponectin with insulin sensitivity and metabolic parameters is unconcluded. The superiority of HMW over total adiponectin in evaluating metabolic variables was not supposed at baseline and after exercise training²⁸. Similarly, the present study showed no significant changes in HMW adiponectin and the percentage of HMW adiponectin in a similar trend with the change in total adiponectin after 8-week exercise. A recent report demonstrated that changes in HMW adiponectin reflect changes in total adiponectin, and that total and HMW adiponectin were equally useful in assessing metabolic risk in patients with coronary artery disease²⁹.

Previous reports have indicated that exercise training reduces TG and increases HDL-cholesterol^{9, 10, 30}. In particular, greater TG reductions and greater HDL-cholesterol elevations after exercise training are often found in previously inactive persons with higher baseline TG levels/lower HDL-cholesterol levels or in patients with impaired glucose tolerance/diabetes. In the present study, TG decreased modestly with no statistical significance, and HDL-cholesterol did not change after exercise training for 16 weeks. The baseline TG levels were not so high, only 5 subjects had a lower HDL-cholesterol level than 40 mg/dL before the exercise training, and the present study did not include patients with metabolic syndrome and diabetes, which is why exercise training failed to significantly change TG and HDL-cholesterol in the present study; however, it is of interest that exercise training significantly decreased VLDL-cholesterol at week 8 and week 16. Tsekouras *et al.* reported that 2-month supervised aerobic exercise did not change TG levels but decreased VLDL-TG levels significantly in healthy non-obese men³¹. Similarly, another report showed that 6-month supervised aerobic exercise decreased VLDL-TG and VLDL-cholesterol with serum TG in moderately obese patients with type 2 diabetes³². These two papers also presented VLDL kinetics data, indicating the significantly decreased secretion of VLDL-TG or VLDL-apolipoprotein B. Therefore, the

marked reductions in VLDL-cholesterol in the present study might be attributed to a decrease in hepatic VLDL secretion to blood circulation. Qiao *et al.* reported that adiponectin reduced plasma triglyceride by increasing VLDL triglyceride catabolism³³, and thereby the increased adiponectin may reduce VLDL levels after exercise training. However, changes in adiponectin did not significantly correlate with changes in IDL- and VLDL-cholesterol in the present study. The reductions in IDL- and LDL-cholesterol found in the present study might have been due to marked VLDL-cholesterol reductions in relation to the lipoprotein metabolism pathway, but its detailed mechanisms remain to be clarified.

In conclusion, the present study provides evidence that supervised aerobic exercise 2 to 3 times a week in the presence of body weight loss increases serum adiponectin with an improved lipid profile and insulin sensitivity at week 16 in non-obese, moderate hyperlipidemic subjects without metabolic syndrome and diabetes, and that VLDL-cholesterol is markedly decreased by supervised aerobic exercise.

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Conflict of Interests

None declared.

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