CLINICAL STUDY

Effect of exercise training on plasma visfatin and eotaxin levels

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Abstract

Objective: Visfatin, a novel adipokine, was revealed to be associated with obesity and to have insulin-mimetic effect. Eotaxin, which is an important chemokine in asthma, was recently reported to be associated with obesity in mice and humans. We evaluated the effect of exercise training on plasma visfatin and eotaxin levels in association with cardiovascular risk factors.

Design: Forty-eight non-diabetic Korean women were evaluated before and after a 12 week exercise program including aerobic exercise (45 min/session, 300 Kcal/day) and muscle strength training (20 min/session, 100 Kcal/day) five times per week.

Results: Plasma visfatin concentrations were elevated in obese subjects (body mass index, BMI ≥ 25 kg/m²) when compared with non-obese subjects (16.4 ± 13.4 ng/ml vs 7.7 ± 5.2 ng/ml, $P=0.006$), and eotaxin concentrations were elevated in subjects with central obesity (waist circumference, WC ≥ 80 cm) when compared with those without central obesity (73.6 ± 17.8 pg/ml vs 64.2 ± 4.2 pg/ml, $P=0.005$). In multiple regression analyses, visfatin levels were associated with BMI ($R^2=0.255$) and eotaxin levels were associated with WC and body weight ($R^2=0.307$). After the exercise program, body weight, blood pressure, fasting glucose, and insulin resistance of participants were decreased. Furthermore, plasma visfatin levels were significantly decreased from 13.6 ± 12.0 to 7.7 ± 7.9 ng/ml ($P=0.026$) and eotaxin levels were reduced from 72.0 ± 16.7 to 66.9 ± 14.2 pg/ml ($P=0.018$).

Conclusions: Exercise training with weight loss induced a significant reduction of plasma visfatin and eotaxin levels in non-diabetic Korean women.

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Introduction

Visfatin is a recently discovered adipokine, which is highly expressed in visceral fat. Adipocyte visfatin expression and plasma concentrations increase with obesity in animals (1) and humans (2). Furthermore, mice on a high-fat diet had higher plasma visfatin levels when compared with mice fed normal chow (1). Interestingly, visfatin treatment did not promote insulin resistance (IR), but exhibited an insulin mimetic effect. Visfatin treatment in diabetic mice improved insulin sensitivity *in vivo* and resulted in decreased glucose and insulin levels. This insulin-mimetic action of visfatin is mediated by binding to the insulin receptor itself but via a distinct binding site (1). A recent study demonstrated elevated plasma visfatin level in patients with type 2 diabetes (3). Furthermore, Haider *et al.* reported that increased plasma visfatin levels in morbidly obese Caucasians were reduced after gastric banding operation (4).

The incidence and prevalence of both obesity and asthma are increasing in the US and worldwide (5, 6).

Previous studies have reported that levels of obesity are associated with asthma symptoms (7), and that the body mass index (BMI) is a significant predictor of bronchial hyperresponsiveness (8). Furthermore, both obesity and asthma are known to be chronic inflammatory conditions. Recent studies have found that obesity was associated with infiltration of macrophages into adipose tissue, and that genes related to immunity including chemokines are up-regulated in adipose tissue from obese mice (9, 10). Recently, Vasudevan *et al.* reported that eotaxin is a secretory product of adipose tissue and that its plasma levels are increased in obesity (11). However, studies on the association between eotaxin and obesity are limited. Furthermore, exercise-induced changes in eotaxin concentrations have not been described. Exercise training has proved to be useful in the management of insulin-resistant states including obesity (12). Therefore, we examined the effect of exercise training on plasma visfatin and eotaxin levels in non-diabetic Korean women in the present study.

Subjects and methods

Forty-eight women aged between 30 and 55 years were recruited for this study via advertisements in local newspapers. All subjects were healthy, overweight, or obese (BMI between 23.0 and 25.0 kg/m² or BMI $\geq$ 25.0 kg/m²), and they had a stable body weight (<2 kg/6 months weight change) and a sedentary lifestyle (<20 min exercise twice per week). Obesity was defined with BMI according to the Asia-Pacific criteria (APC-BMI: $\geq$ 25 kg/m²) (13). To define central obesity, we used the APC for central obesity based on waist circumference (APC-WC) as defined by the World Health Organization (WHO) (WC $\geq$ 80 cm) (13). Subjects were screened by medical history questionnaire, physical examination, fasting blood profile, and a graded exercise treadmill test in an attempt to exclude those with cardiovascular disease. We excluded candidates who smoked, had diabetes, had cardiovascular disease or any other major illness, or were taking medications that could have affected laboratory test results. Informed consent was obtained from all participants before the start of the study, and the ethical committee of our institution, in accordance with the Declaration of Helsinki of the World Medical Association, approved the study.

Exercise protocol

All exercise training sessions were supervised by an exercise physiologist. Participants were encouraged to train five times per week, consisting of a brief warm-up, followed by $\sim$ 45 min per session of aerobic exercise at an intensity of 60–75% of age-predicted maximum heart rate ($\sim$ 300 Kcal/day) and 20 min of muscle strength training ($\sim$ 100 Kcal/day), followed by a brief cool down. The training program started at 40% of observed maximal heart rate and gradually increased to 60–75% of maximal heart rate by week 12. Aerobic exercise training included treadmill walking/running (M901T, Motus Co., Seoul, Korea) and cycling (CY8866R, Sunny Co., Seoul, Korea).

Laboratory measurements

Blood samples were drawn after a 12-h overnight fast and were kept at -80°C for subsequent assay. We collected blood samples within 24–48 h after the last exercise bout. The glucose oxidase method was employed to measure plasma glucose, and a human insulin-specific RIA kit (Linco Research Inc., St Charles, MO, USA) was used to measure insulin levels. This kit has a reactivity of <0.2% with human proinsulin, and its intra-assay coefficient of variation (CV) is 4.4%. IR was calculated as (fasting glucose (mmol/l) $\times$ fasting insulin ($\mu\text{u/ml}$)/22.5) by the homeostasis model assessment (HOMA) (14). Plasma visfatin levels were

measured using a visfatin EIA kit (Phoenix Pharmaceuticals, Belmont, CA, USA), with an intra-assay CV of 6.1%. Plasma eotaxin levels were measured using a Quantikine kit (R&D Systems, Belmont, CA, USA), with an intra-assay CV of 2.7%.

Statistical analyses

Data are expressed as means $\pm$ s.d. Differences between obese and non-obese groups were tested using the Mann–Whitney *U* test or Student's *t*-test. The Wilcoxon matched-pairs test or paired *t*-test was used for comparison of variables before and after exercise. The repeated measures ANOVA approach was used for comparison of visfatin and eotaxin before and after exercise and for comparison of variables between the obese and non-obese groups. Non-normally distributed variables were analyzed using log-transformed values. Simple and multiple regression analyses were used to examine the association between visfatin or eotaxin concentrations and the values of other biomarkers. Age, body weight, BMI, WC, systolic blood pressure, diastolic blood pressure, percent body fat, fasting glucose, and HOMA-IR were employed as independent variables in multiple regression analyses. Significant independent variables were chosen using the stepwise variable selection method. A *P* value of <0.05 was accepted to indicate statistical significance. Data were analyzed using SPSS for Windows (version 10.0; SPSS Inc., Chicago, IL, USA).

Results

Clinical and biochemical characteristics of the study subjects before and after exercise training are presented in Table 1. The mean age of study subjects was 47.1 ± 6.4 years, and most of them were premenopausal women except two. Their average BMI was 27.0 ± 2.9 and 36 women (75%) were obese using the APC obesity based on BMI (APC-BMI: $\geq$ 25 kg/m²). Obese women showed elevated plasma visfatin levels when compared with non-obese ones (16.4 ± 13.4 ng/ml vs 7.7 ± 5.2 ng/ml, *P*=0.006), although eotaxin levels were not different between them (79.0 ± 21.6 pg/ml vs 69.4 ± 13.9 pg/ml, *P*=0.075). However, women with central obesity (WC $\geq$ 80 cm, 73.6 ± 17.8 pg/ml) showed higher plasma eotaxin levels when compared with those without central obesity (WC < 80 cm, 64.2 ± 4.2 pg/ml, *P*=0.005).

In Table 2, plasma visfatin levels were associated with body weight, BMI, and WC in simple regression analysis. However, we could not observe any relationship among blood pressure, percent body fat, fasting glucose levels, IR index, and plasma visfatin levels. In a multiple regression analysis, visfatin levels were independently associated with BMI ($R^2=0.255$).

Table 1 Anthropometric and biological parameters of study subjects before and after the exercise program.

	Non-obese		Obese	
	Before	After	Before	After
Age (years)	48.4 ± 5.6		46.5 ± 6.8	
Height (cm)	156.4 ± 5.7		158.1 ± 5.2	
Weight (kg)	58.1 ± 5.0	54.0 ± 4.9 [†]	70.9 ± 6.0	65.8 ± 6.8 [†]
Body mass index (kg/m ²)	23.7 ± 1.1	22.2 ± 1.3 [†]	28.4 ± 2.1	26.3 ± 2.1 [†]
Waist circumference (cm)	80.8 ± 5.8	75.3 ± 6.5 [†]	88.8 ± 5.1	84.2 ± 6.5 [†]
Waist-to-hip ratio	0.85 ± 0.06	0.84 ± 0.05	0.89 ± 0.05	0.87 ± 0.04 [*]
SBP (mmHg)	122.5 ± 12.8	116.4 ± 9.3 [*]	131.0 ± 18.7	122.5 ± 16.9 [†]
DBP (mmHg)	76.4 ± 10.6	74.3 ± 6.5	85.1 ± 10.9	80.7 ± 11.2 [*]
Percent body fat	33.4 ± 1.9	30.4 ± 3.1 [†]	37.6 ± 4.6	32.2 ± 3.7 [†]
Glucose (mmol/l)	5.0 ± 0.5	4.5 ± 0.4 [*]	4.6 ± 0.5	4.3 ± 0.5 [*]
Insulin (IU/l)	13.0 ± 4.6	10.0 ± 6.9	13.8 ± 7.8	10.9 ± 8.7
HOMA-IR	2.6 ± 0.9	1.7 ± 0.8 [*]	2.7 ± 1.6	2.0 ± 1.0 [*]

SBP, systolic blood pressure; DBP, diastolic blood pressure; and HOMA-IR, homeostasis model assessment insulin resistance. Data are presented as means ± s.d. * $P < 0.05$; [†] $P < 0.01$.

On the other hand, plasma eotaxin levels were significantly associated with body weight and WC both in simple and multiple regression analyses ($R^2 = 0.307$) (Table 3).

After 12 weeks of the exercise training program, all but one subject had lost weight, which was accompanied with a significantly decreased BMI, WC, blood pressure, percent body fat mass, glucose, and HOMA-IR (Table 1). Furthermore, plasma visfatin levels were also significantly decreased from 13.6 ± 12.0 to 7.7 ± 7.9 ng/ml ($P = 0.026$). In addition, plasma eotaxin concentrations were significantly reduced from 72.0 ± 16.7 to 66.9 ± 14.2 pg/ml ($P = 0.018$) (Fig. 1).

Discussion

The present study demonstrated that exercise training with weight loss can reduce visfatin and eotaxin levels in non-diabetic Korean women. Central obesity is a well-known risk factor for IR and the metabolic syndrome.

Recently, Fukuhara *et al.* identified visfatin as a new adipokine that is preferentially produced in the visceral adipose tissue of obese mice and humans (1). Although the function of visfatin is not currently understood, visfatin may have a dual role: an autocrine/paracrine function that facilitates differentiation and fat deposition on visceral adipose tissue, and an endocrine role that modulate insulin sensitivity in peripheral organs (15). Therefore, visfatin may facilitate glucose control; on the other hand, it may promote the development of obesity (16). There is some debate whether visfatin synthesis is up-regulated in obesity. Although some studies suggest that visfatin is related to the development of the metabolic syndrome (1), others reported that visfatin gene expression was not associated with the metabolic syndrome in diseased rats when compared with lean controls (17). Pagano *et al.* reported that plasma visfatin levels are reduced in human obesity (18). In the present study including obese and non-obese Korean subjects, visfatin concentrations were

Table 2 Linear regression analysis of variables associated with baseline visfatin levels in subjects studied.

	Simple		Multiple	
	Estimate	P	Estimate	P
Age	-0.017	0.421		
Weight	0.042	0.013		
Body mass index	0.120	0.012	0.190	0.005
Waist circumference	0.059	0.007		
SBP	0.005	0.549		
DBP	0.014	0.279		
Percent body fat	0.058	0.076		
Glucose	0.390	0.252		
Insulin	-0.017	0.459		
HOMA-IR	-0.049	0.664		

SBP, systolic blood pressure; DBP, diastolic blood pressure; and HOMA-IR, homeostasis model assessment insulin resistance. $R^2 = 0.255$.

Table 3 Linear regression analysis of variables associated with baseline eotaxin levels in subjects studied.

	Simple		Multiple	
	Estimate	P	Estimate	P
Age	-0.002	0.741		
Weight	-0.007	0.047	-0.019	0.001
BMI	-0.009	0.425		
WC	0.005	0.332	0.021	0.011
SBP	-0.001	0.783		
DBP	-0.002	0.463		
% body fat	-0.004	0.607		
Glucose	0.062	0.424		
Insulin	0.007	0.214		
HOMA-IR	0.037	0.155		

BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; and HOMA-IR, homeostasis model assessment insulin resistance. $R^2 = 0.307$.

Figure 1 Changes in visfatin (A) and eotaxin (B) before and after a 12 week exercise program. The box plot displays the 25th (median) and 75th percentiles and the minimum and maximum levels as horizontal lines outside the box.

significantly increased in obese individuals when compared with non-obese ones.

Recently, there have been reports about elevated plasma visfatin levels in patients with type 2 diabetes (3) and gestational diabetes mellitus (19). In a former study, Chen *et al.* reported that plasma visfatin was associated with age, waist-to-hip ratio (WHR), fasting insulin, adiponectin levels, and HOMA-IR in simple regression analysis, whereas in multiple regression analysis, only

WHR remained positively associated with plasma visfatin level (3). In another study of Berndt *et al.*, no significant correlation was found between visfatin plasma concentrations and various parameters of insulin sensitivity, including fasting insulin and glucose infusion rate during the steady state of an euglycemic-hyperinsulinemic clamp (2). In the present study, including non-diabetic participants, plasma visfatin levels were associated with body weight, BMI, and WC in simple regression analysis, whereas only BMI was independently associated with visfatin levels in multiple regression analysis. While R^2 values explain only 26% of the variance for visfatin, this level of explained variance might be meaningful, because there are a number of important, known contributors to BMI. However, we could not find any relationship between visfatin concentrations and IR in the present study.

Eotaxin is known to play a crucial role in the pathogenesis of extrinsic asthma. Plasma eotaxin levels were significantly higher in patients with acute asthma symptoms and airflow obstruction in a case-control study (20). Another study demonstrated a direct relationship between eotaxin levels and asthma diagnosis, and an inverse relationship to lung function (21). Obesity and asthma are two chronic inflammatory conditions whose incidence and prevalence are increasing worldwide (5, 6). Vasudevan *et al.* recently found that circulating levels of eotaxin in serum/plasma are increased in diet-induced obesity in both mice and humans (11). They proposed the 'ectopic eotaxin model', i.e., the ectopic expression of eotaxin in adipose tissue induces Th2 cell-dependent inflammation in the lung. In addition, eotaxin and cytokines produced by adipose tissue may possibly directly influence airway hyperresponsiveness, thereby leading to an increased prevalence and severity of asthma symptoms in obese individuals. However, no other study regarding the association between eotaxin and obesity has been reported thereafter. In the present study including non-Caucasian subjects, we found that participants with central obesity had higher circulating levels of eotaxin when compared to those without central obesity. Eotaxin mRNA levels have been reported to be 4.7-fold higher in visceral adipose tissue than in s.c. adipose tissue (11).

Low levels of physical activity are related to most components of the metabolic syndrome (22). Regular exercise has long been associated with a reduced risk of obesity, type 2 diabetes, and cardiovascular disease (23, 24). Furthermore, there is a growing body of literature that implicates lifestyle change, specifically decreased physical activity, as a contributor to the increase in asthma prevalence and severity (25). Rasmussen *et al.* in their 10.5-year prospective of 757 children concluded that decreased physical fitness was significantly correlated with the development of asthma (26). Another study of 262 twin pairs showed that the twin who participated in conditioning exercise had a

decreased risk of asthma when compared with the more sedentary co-twin (relative risk 0.55, 95% confidence interval 0.34–0.88) (27). Several recent reports have supported the benefits and safety of exercise in asthmatic subjects (28, 29). Therefore, Lucas *et al.* suggested that frequent moderately intense activity conferred protective effects against asthma (25).

Changes in adipokine levels might be an important clue to understanding the beneficial effects of exercise. Pasman *et al.* reported that endurance exercise training decreased plasma leptin levels independently of changes in plasma insulin levels and body fat percentage (30). However, adiponectin was not altered with exercise training despite enhanced insulin action (31). In another study, weight loss by lifestyle modification including hypocaloric diet and moderate physical activity was associated with a significant decrease in leptin and interleukin-6 and a tendency toward a decrease in tumour necrosis factor- α level in obese subjects (32).

In the present study, we found that plasma visfatin and eotaxin levels were reduced after exercise training with weight loss. These results suggest that changes in visfatin and eotaxin levels may be associated with the beneficial effect of exercise. Further studies are needed to elucidate the mechanisms responsible for the effects of exercise on visfatin and eotaxin.

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