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An exercise intervention without weight loss decreases circulating interleukin-6 in lean and obese men with and without type 2 diabetes mellitus

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Abstract

Obesity and type 2 diabetes mellitus (T2DM) have been associated with a state of chronic low-grade inflammation. We examined the effect of exercise without weight loss on circulating inflammatory biomarkers in previously sedentary lean men and obese men with and without T2DM. Middle-aged men (8 lean, 8 obese, and 8 obese with T2DM) performed 60 minutes of aerobic exercise 5 times per week for 12 weeks without a reduction in body weight. Subjects underwent a hyperinsulinemic-euglycemic clamp before and after the 12-week exercise program to assess insulin sensitivity. Circulating interleukin-6 (IL-6), plasminogen activator inhibitor-1 (PAI-1), and C-reactive protein concentrations were measured by sandwich enzyme-linked immunosorbent assay before and after the exercise intervention. Body fat was measured using magnetic resonance imaging, and waist circumference was recorded for each subject pre- and postexercise intervention. Waist circumference and plasma IL-6 concentrations were significantly lower ($P < .05$) after exercise training despite no change in body weight or insulin sensitivity. There were no correlations between insulin sensitivity and IL-6. Fasting plasma PAI-1 concentration was significantly lower in the lean group compared with the obese group both pre- and postexercise intervention ($P < .05$). There were no changes in C-reactive protein or PAI-1 concentrations after exercise training. A 12-week exercise intervention led to reductions in waist circumference and fasting IL-6 concentrations in previously sedentary lean and obese men with or without T2DM, demonstrating significant changes in clinically relevant diabetes-related parameters despite no change in body weight.

1. Introduction

Chronic low-grade inflammation, characterized by abnormal production of adipokines and inflammatory mediators, has been implicated in the pathogenesis of obesity-related chronic diseases including what may be called the obesity–type 2 diabetes mellitus (T2DM)–cardiovascular disease (CVD) triad [1,2]. In particular, novel CVD biomarkers such as interleukin-6 (IL-6) [3,4], the acute-phase reactant C-reactive protein (CRP), [5,6] and the antifibrinolytic plasminogen activator inhibitor-1 (PAI-1) [7,8] are elevated in obesity and have all been associated with insulin resistance, a hallmark of the obesity-diabetes-CVD triad. Increased visceral adipose tissue is also associated with insulin resistance observed in obese men [9,10].

The role of lifestyle intervention in lowering the risk of CVD has been well studied. Lifestyle modifications that include exercise-induced weight loss have been associated with decreases in IL-6, CRP, and PAI-1 concentrations [11-13]. The actual impact of an exercise intervention alone on circulating cytokine concentrations is difficult to evaluate in such studies with an exercise program designed to induce body weight loss. However, other studies have shown that an exercise intervention without weight loss may be an effective strategy to promote favorable metabolic changes in abdominal obesity and waist circumference in obese

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individuals with and without T2DM [14]. It is unclear whether exercise-induced improvements in adiposity and waist circumference in the absence of weight loss may have an impact on circulating inflammatory biomarkers implicated in the obesity-diabetes-CVD triad.

The purpose of this study was to evaluate blood concentrations of 3 CVD biomarkers—IL-6, CRP, and PAI-1—before and after a 12-week exercise intervention without weight loss in previously sedentary lean men and obese men with and without T2DM. Insulin sensitivity and body composition were also assessed before and after the exercise intervention, and the results have been previously reported [15].

2. Methods

2.1. Subjects

Twenty-four men (8 lean, 8 obese, 8 obese with T2DM) were recruited from Kingston, Ontario, through the general media. All subjects were white nonsmokers who consumed, on average, less than 2 alcoholic drinks per day and led a sedentary lifestyle (no participation in any regular physical activity for the past 6 months). Before inclusion in the study, obese men underwent an oral glucose tolerance test to screen for T2DM. Subjects with T2DM were not taking insulin or insulin sensitizers and were free of other complications (CVD, nephropathy, neuropathy, or retinopathy), as confirmed by their physicians. Four subjects with T2DM were treated with glyburide, and their dosage remained constant throughout the exercise intervention. Three subjects (2 obese and 1 T2DM) were on angiotensin-converting enzyme inhibitors for blood pressure, and 3 subjects (1 obese, 2 T2DM) were taking statin medications. All subjects gave their fully informed and written consent before participation in the study, which was conducted in accordance with the ethical guidelines set by the Queen's University (Kingston, Ontario).

2.2. Diet and exercise regimen

Throughout the 4-week baseline period, daily energy requirements for all subjects were determined by estimating resting energy expenditure and multiplying the obtained value by a factor of 1.5 [16]. During this baseline period and throughout the 12-week exercise intervention, subjects followed a diet (55%-60% carbohydrate, 15%-20% protein, and 20%-25% fat) designed to maintain body weight. To achieve weight maintenance, subjects were instructed to consume the energy (kilojoules) needed to compensate for the energy expended during each exercise session. Body weight and energy expenditure were monitored throughout the intervention, and diet was adjusted appropriately to ensure no change in body weight. Subjects maintained daily, detailed food records that were reviewed by the study dietitian on a weekly basis to ensure compliance.

All subjects were required to participate in a 12-week aerobic exercise program, either walking or light jogging on a treadmill for 5 minutes per week at a moderate intensity (~60% $\dot{V}O_2$max). Energy expenditure during each exercise session was determined using the heart rate and oxygen consumption data obtained from the pretreatment graded exercise test and adjusted using subsequent test results performed at weeks 4 and 8. Heart rate during exercise was monitored every 5 minutes using an automated heart rate monitor (Polar Oy, Kempele, Finland). All exercise sessions were by appointment and were supervised.

2.3. Measurement of insulin sensitivity

The methods for measuring insulin sensitivity were previously reported [15]. In brief, to help ensure normal muscle glycogen levels, subjects were asked to consume at least 200 g of carbohydrate and to avoid strenuous activity for a minimum of 4 days before measurements of insulin sensitivity were taken. Insulin sensitivity measurements were made 4 days after the last exercise session to avoid any confounding effects of the last bout of exercise. Individuals with T2DM were asked to refrain from taking their oral hypoglycemic agent for 48 hours before each trial. Glucose uptake was measured using a 3-hour hyperinsulinemic (40 mU $\cdot$ m^{-2} $\cdot$ min^{-1}) euglycemic clamp procedure. All subjects performed one clamp trial before (PRE) and one clamp trial after (POST) the 12-week exercise program. On the day of the clamp procedure, subjects arrived at the hospital at 5:30 AM after a 10- to 12-hour overnight fast and rested in a supine position for 2 hours before initiation of the clamp procedure. A baseline blood sample was taken 30 minutes before the start of the clamp measurement. A catheter was placed into an antecubital vein for the infusion of a normal saline drip (0.9% NaCl), insulin, glucose, and potassium. Insulin was infused at a rate of 40 mU $\cdot$ m^{-2} $\cdot$ min^{-1} for 3 hours. A 20% glucose solution was infused at a rate required to maintain plasma glucose concentration at approximately 5 mmol/L. A second catheter was placed in a heated hand vein and was used to draw blood samples during the clamp (metabolic data previously reported [15]). Plasma glucose was determined by an automated YSI 2300 Glucose Analyzer (YSI, Yellow Springs, OH). The insulin sensitivity data were expressed as the ratio of the amount of glucose metabolized to the prevailing plasma insulin levels [M(mg/kg skeletal muscle/min/μIU/mL) $\times$ 100] during the last 30 minutes of the euglycemic clamp, as previously reported [15].

2.4. Measurement of total adiposity

Whole-body (~46 equidistant images) magnetic resonance imaging data were obtained with a General Electric (Milwaukee, WI) 1.5-T magnet using an established protocol [17]. Once acquired, the magnetic resonance imaging data were transferred to a stand-alone workstation for analysis using specially designed computer software (Tomovision, Montreal, Canada). The procedures for analysis have been previously described [17]. Total adiposity was determined using all 46 images. Visceral adiposity was calculated using the 5 images extending from 5 cm below to 15 cm above L4 through L5. Fat volume units (liters) were converted to mass

Table 1
Subject characteristics

	Lean (n = 8)		Obese (n = 8)		T2DM (n = 8)	
	PRE	POST	PRE	POST	PRE	POST
Age (y)	47.5 ± 2.5	–	47.1 ± 3.1	–	51.0 ± 3.0	–
Body weight (kg)	73.9 ± 2.5	73.5 ± 2.5	97.6 ± 3.4*	97.2 ± 3.4*	93.5 ± 2.9*	93.9 ± 3.2*
BMI (kg/m^2)	24.5 ± 0.5	24.3 ± 0.5	32.4 ± 0.6*	32.2 ± 0.6*	29.9 ± 1.2*	30.1 ± 1.3*
Fasting glucose (mmol/L)	4.6 ± 0.2	4.7 ± 0.2	4.8 ± 0.2	4.6 ± 0.1	7.9 ± 0.8†	7.4 ± 0.8†
Fasting insulin (μU/mL)	7.3 ± 1.4	5.5 ± 0.5	8.4 ± 2.8	7.2 ± 1.2	13.4 ± 3.5	12.3 ± 3.2
Insulin sensitivity (M/I)	26.7 ± 4.0	28.8 ± 3.4	23.2 ± 4.5	23.6 ± 4	15.5 ± 3.2	17.8 ± 3.6
Peak V_{O_2} (mL · kg^{-1} · min^{-1})	42.6 ± 2.2	53.1 ± 1.4‡	32.7 ± 1.3	39.26 ± 1.5‡	33.0 ± 1.7	42.2 ± 2.9‡
Total fat (kg)	20.7 ± 1.5	19.5 ± 1.5‡	35.8 ± 1.6*	33.8 ± 1.7*,‡	30.1 ± 1.7*	28.4 ± 1.8*,‡
Visceral fat (kg)	2.1 ± 0.3	1.8 ± 0.3‡	4.0 ± 0.4*	3.4 ± 0.3*,‡	3.8 ± 0.3*	3.1 ± 0.4*,‡
Waist circumference (cm)	89.2 ± 1.7	86.5 ± 1.8§	108.4 ± 1.6*	105.8 ± 1.4§	106.3 ± 2.4*	103.6 ± 2.2§

Data are expressed as mean ± SEM.
* $P < .05$ vs the lean group.
† $P < .05$ vs the lean and obese groups.
‡ $P < .05$, within-group differences (PRE vs POST).
§ $P < .01$, within-group differences (PRE vs POST).

units (kilograms) by multiplying volumes by the assumed constant density for fat (0.92 kg/L).

2.5. Analytical methods

Blood samples were separated into 2 aliquots: 3 mL was transferred to a nontreated tube for analysis of serum insulin and CRP, and 7 mL was transferred to a sodium heparinized tube for the analysis of plasma IL-6 and total PAI-1 antigen. All samples were analyzed in duplicate. Insulin was determined using a radioimmunoassay method (Coat-a-Count, Diagnostic Products, Los Angeles, CA). Interleukin-6 was determined using a high-sensitivity quantitative sandwich enzyme immunoassay (Quantikine HS, R&D Systems, MN) with an inter- and intra-assay coefficient of variation (CV) of less than 7.8% and a minimum detectable limit of 0.039 pg/mL. For technical reasons, IL-6 for one lean subject was not included in the final analysis. C-reactive protein was determined by quantitative sandwich enzyme immunoassay (ADI, San Antonio, TX) with an inter- and intra-assay CV of less than 7% and a minimum detectable limit of 0.00035 mg/L. Total PAI-1 antigen was determined using a quantitative enzyme immunoassay (DakoCytomation, Glostrup, Denmark) with an inter- and intra-assay CV of less than 3.3% and a minimum detectable limit of 0.1 ng/mL.

2.6. Statistical analyses

A 1-way analysis of variance was used to examine differences in subject characteristics at baseline. A 2-way repeated-measures analysis of variance (group × treatment) was used to evaluate differences between subject groups. Significance was set at $P < .05$. A Tukey post hoc comparison test was used to identify differences and interactions. Statistical procedures were performed using Sigma Stat version 2.03. All data are presented as mean ± SEM.

Table 2
Mean energy expenditure (in kilojoules) at weeks 1, 4, 8, and 12 in lean subjects, obese subjects, and subjects with T2DM during the 12-week exercise

	Week 1*	Week 4†	Week 8†,§	Week 12§
Lean	2381 ± 155	2519 ± 163	2703 ± 238	2920 ± 146
Obese	2146 ± 167	2443 ± 180	2741 ± 159	2795 ± 197
T2DM	2301 ± 84	2761 ± 155	2719 ± 192	3485 ± 314

Data are expressed as mean ± SEM. Weeks that share a symbol (*,†,§) are not statistically different from each other ($P > .05$).

3. Results

3.1. Baseline subject characteristics

Physical and clinical characteristics for the subjects pre- and post-intervention were previously published [15] and have been summarized in Table 1 for completeness of data. As expected, before the exercise intervention (PRE), subjects in the obese and T2DM groups had higher ($P < .05$) body weight, body mass index (BMI), total and visceral adiposity, and waist circumference compared with the lean group (Table 1). Mean energy expenditure was not different among the groups at weeks 1, 4, 8, and 12 (Table 2). Because energy expenditure increased throughout the exercise intervention, subjects were individually counseled to adjust their diet accordingly to maintain body weight.

3.2. Cytokine concentrations at PRE

There were no differences among groups in fasting plasma IL-6 concentration before the start of the exercise program (Table 3). Circulating CRP and PAI-1 concentrations were significantly higher in the obese compared with the lean group at PRE ($P < .05$, Table 2). There were no differences in circulating CRP or PAI-1 concentrations between the lean and T2DM groups and between the obese and T2DM groups.

3.3. Effect of exercise intervention on fasting plasma cytokines

The exercise intervention significantly decreased fasting plasma IL-6 concentration in all subject groups ($P < .05$), with a reduction of 52% observed in the T2DM group,

Table 3
Circulating cytokine concentrations in lean subjects, obese subjects, and subjects with T2DM pre- and postexercise intervention

	Lean (n = 7)			Obese (n = 8)			T2DM (n = 8)		
	PRE	POST	Δ (POST − PRE)	PRE	POST	Δ (POST − PRE)	PRE	POST	Δ (POST − PRE)
Interleukin-6 (pg/mL)	2.8 ± 0.6	1.9 ± 0.4*	−0.9 ± 0.5	5.2 ± 1.5	4.4 ± 0.6*	−0.9 ± 1.9	6.2 ± 1.5	3.0 ± 0.7*	−3.2 ± 1.0
C-reactive protein (mg/L)	1.0 ± 0.3	1.5 ± 0.4	0.5 ± 0.4	3.8 ± 0.8†	4.3 ± 1.0†	0.5 ± 0.5	2.5 ± 0.6	2.8 ± 0.9	0.4 ± 0.5
PAI-1 (ng/mL)	50.8 ± 9.3	44.5 ± 6.8	−6.3 ± 5.7	93.4 ± 8.5†	68.7 ± 10.0†	−24.7 ± 14.2	79.5 ± 12.2	72.1 ± 15.2	−7.4 ± 13.2

Data are expressed as mean ± SEM.
* $P < .05$, significant effect of exercise intervention (PRE vs POST).
† $P < .05$, significantly different from lean.

followed by 32% and 17% in the lean and obese groups, respectively (Table 2). The exercise intervention did not significantly alter CRP levels in lean subjects, obese subjects, or subjects with T2DM (Table 3). Both pre- and postexercise intervention, fasting plasma PAI-1 concentration was significantly lower in the lean group compared with the obese group ($P < .05$, Table 3). Although not statistically significant, fasting PAI-1 concentration in the obese group was 26% lower after the exercise intervention ($P = .09$, Table 3). Overall, there were no differences in fasting concentrations of IL-6, CRP, and PAI-1, either pre- or postexercise intervention, between the obese and T2DM groups and between the lean and T2DM groups.

3.4. Visceral adiposity and circulating cytokines

As previously reported [15], exercise intervention significantly reduced total and visceral adiposity in all 3 groups (Table 1). Furthermore, exercise intervention resulted in a significantly greater decrease in visceral adipose tissue in the obese and T2DM groups compared with that observed in the lean group ($P < .05$). As previously reported [14], there was a significant reduction in waist circumference in all 3 groups after the exercise intervention. Exercise intervention did not have a significant effect on insulin sensitivity in any of the subject groups.

Correlations between plasma IL-6, PAI-1 and CRP; and the percentage of change in visceral adipose tissue; and change in waist circumference were performed within each subject group. No significant correlations between these and circulating cytokine measurements were observed (data not shown). There was no significant correlation between measures of insulin sensitivity and circulating IL-6 concentrations in any of the subject groups (data not shown).

4. Discussion

A 12-week exercise intervention without weight loss resulted in a significant change in the phenotype of obesity. Our study is the first to report a significant decrease in circulating IL-6, alongside a decrease in visceral adipose tissue and waist circumference, in lean subjects, obese subjects, and subjects with T2DM who underwent an exercise program without weight loss. Although no statistically significant correlations were found with our relatively small sample size, it is conceivable that the reduction in IL-6 might be attributed to the observed decreases in visceral adiposity and waist circumference in all groups, further reinforcing waist circumference as an important clinical measurement for evaluating obesity-related health risk and the effectiveness of lifestyle intervention [18,19]. Changes in fasting IL-6 concentrations were not associated with changes in BMI or insulin sensitivity. These findings are novel and suggest that an exercise intervention in previously sedentary men has a positive influence on the CVD biomarker IL-6, even when weight loss is not the goal of the intervention and despite no change in insulin sensitivity.

An elevated fasting IL-6 concentration has been linked to the triad of obesity-T2DM-CVD and is hypothesized to be a significant component of chronic low-grade inflammation now recognized to underlie these conditions [1,3,4]. Interleukin-6 is also known to be released during exercise from both muscle and adipose tissue (for review, see references [20,21]). However, in the present study, cytokine measurements were performed after 4 days of inactivity to attenuate potential effects of the last exercise session. Thus, we did not assess the acute response to exercise, but rather chronic, systemic IL-6 concentrations after an exercise intervention. Significant correlations between a decrease in circulating IL-6 and insulin sensitivity have been reported in subjects who underwent a lifestyle intervention involving exercise to induce weight loss [11,13,22,23] and in individuals who underwent gastric bypass surgery [24,25]. The duration of these lifestyle intervention trials ranges from 6 months to 2 years, whereas the measurements in the gastric bypass surgery studies were made 14 and 17 months postoperatively. Although the structured 12-week exercise protocol used in the current study significantly reduced adiposity and circulating IL-6, a longer intervention may be needed to observe significant correlations between IL-6 and insulin sensitivity as have been previously reported [11,13,22-25]. Evidence also suggests that elevated IL-6 may not be related to insulin sensitivity per se [26], but may, in fact, be strongly related to both the amount and the type of

adipose tissue [27]. More specifically, IL-6 has been significantly correlated with visceral adipose tissue in obese subjects [28]. In the current study, a significant decrease in visceral adipose tissue and waist circumference was observed in all groups, with obese and T2DM groups having a significantly greater loss in visceral adiposity after the exercise intervention [15]. Although not statistically significant, changes in visceral adipose tissue correlated with circulating IL-6 concentrations most strongly within the T2DM group (data not shown). Although we observed similar reductions in visceral adiposity in both the obese and T2DM groups, the magnitude of the decrease in circulating IL-6 observed in the T2DM group (52%) was larger than that seen in the obese group (17%). Although we observed no statistically significant interaction, the relationship between visceral adiposity and IL-6 is complex and may be altered in obesity that is complicated by T2DM. This relationship may have physiologic relevance in this population and requires further study with a larger number of subjects.

Interleukin-6 up-regulates hepatic production of CRP, a well-established marker of systemic inflammation and a novel biomarker associated with increased risk of CVD [29,30]. Studies have observed a correlation between CRP and insulin sensitivity in obese subjects and subjects with T2DM, independently of obesity [6]. In our study, insulin sensitivity did not correlate with fasting CRP in lean subjects, obese subjects, or subjects with T2DM (data not shown). Collectively, these findings suggest that IL-6 may be more responsive to the observed changes in visceral adiposity, whereas CRP concentrations may be more closely related to insulin sensitivity and thus did not change because of the maintenance of insulin sensitivity after the 12-week exercise intervention.

Data on plasma CRP concentrations after exercise or lifestyle intervention have been conflicting with exercise-induced weight loss reported to decrease [31] or has no effect [32] on circulating CRP concentrations in overweight and obese subjects. Similarly, lifestyle interventions involving a combination of exercise and diet modifications may [11,13,33] or may not [23] be associated with decreased CRP concentrations in obese subjects. We found no change in CRP concentrations in lean subjects, obese subjects, and subjects with T2DM despite a 12-week exercise intervention. In agreement with this, Marcell et al [32] recently hypothesized that sufficient weight loss, with or without exercise, may need to occur to facilitate a significant decrease in CRP concentration in sedentary persons. Of physiologic interest is our finding that the exercise intervention resulted in a significant decrease in IL-6 without a concurrent decrease in CRP. In accordance with this, Monzillo et al [23] also reported a decrease in circulating IL-6 without an accompanying decrease in CRP after exercise-induced weight loss in obese subjects with insulin resistance. Conversely, a lifestyle intervention that included both physical activity and dietary counseling reduced fasting CRP without decreasing fasting IL-6 concentration in obese women [34]. In fact, despite a significant reduction in IL-6, we observed a concurrent nonsignificant increase in CRP in all 3 groups, suggesting that other factors, independent of IL-6, must be involved in CRP regulation after exercise intervention. For example, tumor necrosis factor α can alter IL-6–stimulated production of CRP by cultured hepatocytes [35]. Although the physiologic relevance of a nonsignificant increase in CRP after exercise intervention is unknown, these findings provide additional evidence for the complex regulation of these 2 CVD biomarkers.

Increased circulating PAI-1 concentration has emerged as a key risk factor in the clustering of inflammatory biomarkers implicated in obesity, T2DM, and CVD [5,36]. The current study found that PAI-1 is significantly elevated in obese subjects and, to a lesser extent, in those with T2DM compared with lean subjects, a finding that is consistent with the literature [37]. There is evidence to suggest that PAI-1 may decrease with exercise and weight loss [12], but previous studies have not looked at the effect of exercise alone on PAI-1 concentrations. We did observe a sizeable decrease (26%) in fasting PAI-1 concentration within the obese group ($P = .09$, 2-tailed t test). However, because we did not observe a statistically significant change in fasting PAI-1 after exercise intervention, our data may suggest that weight loss must occur to lower plasma PAI-1.

This study examined the impact of exercise without weight loss on 3 CVD biomarkers in previously sedentary lean subjects, obese subjects, and subjects with T2DM. The finding that IL-6 and visceral adiposity decreased significantly, whereas both CRP and insulin sensitivity remained unchanged, is of particular interest. The relatively small number of subjects in each group may have contributed to our inability to observe some statistically significant differences, but provides encouraging data regarding favorable trends in inflammatory status with respect to exercise without weight loss. The length of the exercise intervention may need to be extended beyond 12 weeks to see improvements in the metabolic and clincial end points assessed. Furthermore, although IL-6 was the only significant biomarker to change with exercise, it should not be assumed that IL-6 is uniquely altered in this exercise protocol. There is a plethora of obesity-related cytokines whose responses to exercise intervention require further study. The current findings may provide important insight into further benefits of physical activity in the absence of weight loss, such as changes in body composition and inflammatory markers. Although the overall clinical impact of these findings is unknown, a favorable change in circulating cytokines with moderate exercise without weight loss suggests that increased activity in sedentary individuals may decrease markers of inflammation associated with obesity, T2DM, and CVD. Finally, that these findings occurred with a decrease in waist circumference, a clinically relevant marker of obesity-related health risk [18,19], further reinforces that weight reduction need not be

the sole end point of exercise. These findings provide yet another reason to encourage increasing physical activity as a means to promote health, regardless of metabolic status.

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