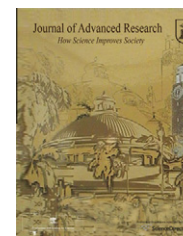




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## SHORT COMMUNICATION

# Aerobic versus resistance exercise training in modulation of insulin resistance, adipocytokines and inflammatory cytokine levels in obese type 2 diabetic patients

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### KEYWORDS

Aerobic exercise;  
Resistance exercise;  
Insulin resistance;  
Adipocytokines;  
Inflammatory cytokine;  
Obesity

**Abstract** It is suggested that adipocytokines secreted by adipose tissue play a role in the development of obesity-related complications and diabetes. Regular aerobic exercise has been shown to reduce the risk of metabolic complications in obese type 2 diabetic subjects. The aim of this study was to compare the impact of aerobic versus resistance training on insulin resistance, adipocytokines and inflammatory cytokine in obese type 2 diabetic patients. Forty obese type 2 diabetic patients of both sexes with body mass index (BMI) ranging from 31 to 35 kg/m<sup>2</sup>, non smokers, and free from respiratory, kidney, liver, metabolic and neurological disorders, were selected for this study. Their ages ranged from 34 to 56 years. The subjects were divided into two equal groups: the first group received aerobic exercise training. The second group (B) received resisted exercise training three times a week for three months. The mean values of tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL-6), Assessment-Insulin Resistance (HOMA) index for insulin sensitivity and glycosylated hemoglobin (HBA<sub>1c</sub>), were significantly decreased in both groups. Also, there was a significant difference between the groups after treatment on all measured variables. It is suggested that in obese type 2 diabetic patients aerobic exercise is more appropriate for modulating insulin resistance, adipocytokines and inflammatory cytokine levels than is resisted exercise training.

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## Introduction

Adipose tissue is an active endocrine tissue, which secretes hormones, such as adiponectin, resistin and leptin, referred to as adipocytokines. Adipocytokines appear to contribute to inflammation and atherosclerosis and may be involved in the etiology of type 2 diabetes, possibly constituting the missing link between obesity and insulin resistance (IR) [1].

Interleukin (IL)-6 and tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ) are two major pro-inflammatory cytokines, secreted in significant amounts by adipose tissue and, consequently, obese women (healthy and diabetic) have higher cytokine levels than healthy, lean women. Furthermore, increased levels of IL-6 and TNF- $\alpha$  are associated with deterioration of glycemic control, increased IR, and dyslipidemia, contributing to the dysfunctional metabolic status of obese and type 2 diabetic individuals [2].

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 [3].

Exercise suppresses the production of proinflammatory cytokines and enhances anti-inflammatory cytokines. Because proinflammatory cytokines IL-6 and TNF- $\alpha$  have cytotoxic actions, it can be proposed that regular exercise prevents further damage to insulin-producing  $\beta$ -cells by attenuating the production of these proinflammatory cytokines [4].

Aerobic exercise decreases subclinical, chronic inflammation and improves endothelial function simply as a result of reducing obesity (particularly visceral obesity) and improving insulin sensitivity [5,6].

Several studies suggest that training programmes that involve a resistive exercise component (i.e., moderate intensity weight-lifting exercises) may be of particular benefit in type 2 diabetes due to an effect of increasing insulin action. An increase in muscle mass has been associated with benefits in terms of glycemic control as skeletal muscle represents the largest mass of insulin-sensitive tissue [7–9].

Aerobic exercise intervention, but not flexibility/resistance exercise, reduces serum inflammatory cytokines including IL-18, CRP and IL-6 among older adults [10].

Apart from the controversy surrounding the beneficial effects of exercise on glycemic control in type 1 diabetes patients, the question remains as to which type of activity is better: aerobic exercise or resistance training? This study was aimed at comparing the impact of aerobic versus resistance training on insulin resistance, adipocytokines and inflammatory cytokine in obese type 2 diabetic patients.

## Patients and methods

### Subjects

Forty obese type 2 diabetic patients of both sexes with body mass index (BMI) ranging from 31 to 35 kg/m<sup>2</sup>, non smokers, and free from respiratory, kidney, liver, metabolic and neurological disorders, were selected randomly from the Cairo University Hospital. Their ages ranged from 34 to 56 years. The subjects were divided into two equal groups: the first group (A) received aerobic exercise training; the second group (B) received resisted exercise training three times a week for three

months. Informed consent was obtained from all participants. All participants were free to withdraw from the study at any time. If any adverse effects had occurred, the experiment would have been stopped and the Human Subjects Review Board would have been informed. However, no adverse effects occurred, and so the data of all the participants were available for analysis.

### Evaluated parameters

#### Chemical analysis

A blood sample after fasting for 12 h was taken from each patient in clean tubes containing 10 mg of K<sub>2</sub>EDTA and centrifuged; plasma was separated and stored frozen at –20 °C; and plasma TNF- $\alpha$ , interleukin-6 (IL-6) and glycosylated hemoglobin (HBA<sub>1c</sub>) were estimated using a colorimetric method. Homeostasis Model Assessment-Insulin Resistance (HOMA) index for insulin sensitivity was computed using the following equation: [fasting glycemia (mmol/L)  $\times$  fasting insulin (mIU/L)]/22.5 [11].

#### Aerobic exercise training

Patients in group A were submitted to a 40 min aerobic session on a treadmill. The initial 5-min warm-up phase was performed on the treadmill at a low load. Each training session lasted 30 min and ended with a 5-min recovery and relaxation phase either walking or running, based on heart rate, until the target heart rate according to the American College of Sport Medicine guidelines was reached. The programme began with 10 min of stretching exercises for the major muscles of the upper and lower limbs and was conducted using the maximal heart rate index (HR<sub>max</sub>) estimated by: 220-age. First 2 weeks = 60–70% of HR<sub>max</sub>, 3rd to 12th weeks = 70–80% of HR<sub>max</sub> [12].

#### Resistance exercise training

Patients in group B were submitted to a 40 min session of resistance training. The programme began with 10 min of stretching for the major muscles of the upper and lower limbs and was conducted with exercises on eight resistance machines. The manual resistance machines used were chest press, bicep curl, triceps extension, lower back, abdominals, leg press, leg curl and leg extension. Subjects performed three sets of 8–12 repetitions, with 60 s of rest between each set. Resistance was increased by five pounds after the subject was able to complete three sets of eight repetitions on three consecutive days. Subjects were trained using between 60% and 80% of their one maximal repetition weight (1-RM) [13].

#### Statistical analysis

The mean values of TNF- $\alpha$ , IL-6, HOMA-IR and HBA<sub>1c</sub> obtained before and after three months in both groups were compared using the paired “*t*” test. An independent “*t*” test was used for the comparison between the two groups ( $P < 0.05$ ).

## Results

The study involved forty obese type 2 diabetic patients of both sexes with a BMI ranging from 31 to 35 kg/m<sup>2</sup>, and aged from 34 to 56 years. The subjects were divided into two equal

groups: the first group (A) received aerobic exercise training. The second group (B) received resisted exercise training three times a week for three months in order to compare the effect of aerobic and resisted exercise intensity on TNF- $\alpha$ , IL-6, HOMA-IR and HBA<sub>1c</sub> in obese type 2 diabetic patients.

The mean values of TNF- $\alpha$ , IL-6, HOMA-IR and HBA<sub>1c</sub> were significantly decreased from 6.23  $\pm$  1.81, 3.42  $\pm$  1.24, 7.96  $\pm$  1.24 and 4.78  $\pm$  2.17 to 4.40  $\pm$  1.23, 1.54  $\pm$  1.6, 6.05  $\pm$  0.87 and 2.82  $\pm$  1.31, respectively, in group A and from 6.45  $\pm$  1.87, 3.52  $\pm$  1.56, 7.88  $\pm$  1.45 and 4.94  $\pm$  2.43 to 5.23  $\pm$  1.36, 2.98  $\pm$  1.5, 7.64  $\pm$  0.97 and 3.91  $\pm$  1.25, respectively, in group B (Tables 1 and 2). Also, there was a significant difference between the groups after treatment (Table 3). So, it can be concluded that aerobic exercise training was more appropriate than resisted exercise training.

**Discussion**

There has been only limited research on the effects of exercise as the sole intervention on these adipocytokines in individuals with type 2 diabetes. The aim of this study was to compare changes in insulin resistance, adipocytokines and inflammatory cytokine including TNF- $\alpha$  and interleukin-6 (IL-6), HOMA-IR and HbA<sub>1c</sub>, after aerobic and resistance exercise training in obese type 2 diabetic patients. The mean values of TNF- $\alpha$ , IL-6, HOMA-IR and HBA<sub>1c</sub> were significantly decreased in both group A and group B. Also, there was a significant difference between the groups after treatment. This

**Table 1** Mean value and significance of TNF- $\alpha$ , IL-6, HOMA-IR and HBA<sub>1c</sub> in group A before and after treatment.

P-value	t value	Mean $\pm$ SD		Value
		After	Before	
0.009	5.94	4.40 $\pm$ 1.23	6.23 $\pm$ 1.81	TNF- $\alpha$ (pg/mL)
0.007	6.82	1.54 $\pm$ 1.6	3.42 $\pm$ 1.24	IL-6 (pg/mL)
0.008	5.32	6.05 $\pm$ 0.87	7.96 $\pm$ 1.24	HBA <sub>1c</sub> (%)
0.005	6.80	2.82 $\pm$ 1.31	4.78 $\pm$ 2.17	HOMA-IR

TNF- $\alpha$  = tumour necrosis factor- $\alpha$ .  
 IL-6 = interleukin-6.  
 HBA<sub>1c</sub> = glycosylated hemoglobin.  
 HOMA-IR = Homeostasis Model Assessment-Insulin Resistance index.

**Table 2** Mean value and significance of TNF- $\alpha$ , IL-6, HOMA-IR and HBA<sub>1c</sub> in group B before and after treatment.

P-value	t value	Mean $\pm$ SD		Value
		After	Before	
0.016	3.43	5.23 $\pm$ 1.36	6.45 $\pm$ 1.87	TNF- $\alpha$ (pg/mL)
0.023	3.72	2.98 $\pm$ 1.5	3.52 $\pm$ 1.56	IL-6 (pg/mL)
0.045	3.27	7.64 $\pm$ 0.97	7.88 $\pm$ 1.45	HBA <sub>1c</sub> (%)
0.037	3.45	3.91 $\pm$ 1.25	4.94 $\pm$ 2.43	HOMA-IR

TNF- $\alpha$  = tumour necrosis factor- $\alpha$ .  
 IL-6 = interleukin-6.  
 HBA<sub>1c</sub> = glycosylated hemoglobin.  
 HOMA-IR = Homeostasis Model Assessment-Insulin Resistance index.

**Table 3** Mean value and significance of TNF- $\alpha$ , IL-6, HOMA-IR and HBA<sub>1c</sub> in group A and group B after treatment.

P-value	t value	Mean $\pm$ SD		Value
		Group B	Group A	
0.076	3.45	5.23 $\pm$ 1.36	4.40 $\pm$ 1.23	TNF- $\alpha$ (pg/mL)
0.011	3.88	2.98 $\pm$ 1.5	1.54 $\pm$ 1.6	IL-6 (pg/mL)
0.023	3.62	7.64 $\pm$ 0.97	6.05 $\pm$ 0.87	HBA <sub>1c</sub> (%)
0.084	3.46	3.91 $\pm$ 1.25	2.82 $\pm$ 1.31	HOMA-IR

TNF- $\alpha$  = tumour necrosis factor- $\alpha$ .  
 IL-6 = interleukin-6.  
 HBA<sub>1c</sub> = glycosylated hemoglobin.  
 HOMA-IR = Homeostasis Model Assessment-Insulin Resistance index.

means that in obese type 2 diabetic patients aerobic exercise is more appropriate for modulating insulin resistance, adipocytokines and inflammatory cytokine levels than is resisted exercise training. The results of this study confirmed those of many previous studies.

Obesity and T2DM are associated with insulin resistance. Adipocytes not only secrete free fatty acids but also release a variety of adipokines including tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), plasminogen activator inhibitor 1 (PAI-1), angiotensin II, acylation stimulating protein, interleukin-6 (IL-6), adiposin, resistin and adiponectin. These factors have paracrine/autocrine functions that include regulation of energy expenditure, in part by modulating whole-body insulin sensitivity. Perturbations in the balance between beneficial and harmful adipokines may result in several metabolic abnormalities of which insulin resistance is of paramount significance, being common in obesity and T2DM [13].

Cytokines IL-6 and TNF- $\alpha$  each play a significant role in the pathogenesis of T2D. Proinflammatory cytokines TNF- $\alpha$  and IL-6 can cause atrophy of the islets of Langerhans. However, exercise training increased insulin production and/or secretion as a result of hypertrophy and replication of the pancreatic  $\beta$ -cells, and glucose transporter-2 and protein kinase B were significantly elevated after exercise training [14].

Aerobic exercise training is an accepted therapeutic strategy in the management of type 2 diabetes mellitus (T2DM) because of its beneficial effects. Exercise improves diabetic status and reduces the metabolic risk factors associated with cardiovascular diseases and improves insulin sensitivity [15].

Long-term aerobic exercise training produces beneficial improvements in glucose tolerance and insulin response to glucose and may even normalize glucose levels in impaired individuals and diabetics [16]. However, short-term training protocols have also been shown to produce similar changes in glucose tolerance and/or insulin sensitivity in obese individuals when performed at moderate intensities (i.e., 67–70% VO<sub>2</sub> max) [17,18].

A 12-week thrice-weekly swimming training was associated with improved measurements of chronic inflammation markers as noted by an increase in the levels of adiponectin and a reduction in C-reactive protein. The improvements in insulin sensitivity resulting from swimming exercise appeared to be related to changes in these inflammatory mediators [19].

A 12-week exercise intervention resulted in 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 programme without weight loss [3].

Aerobic exercise intervention, but not flexibility/resistance exercise, reduces serum inflammatory cytokines including IL-18, CRP and IL-6 among older adults; this reduction would be mediated, in part, by improvements in psychosocial factors and/or by  $\beta$ -adrenergic receptor mechanisms [10].

The potential mechanisms for the anti-inflammatory effect of exercise include reduced percentage of body fat and macrophage accumulation in adipose tissue, muscle-released interleukin-6 inhibition of tumour necrosis factor- $\alpha$ , and the cholinergic anti-inflammatory pathway [20].

Mechanisms underlying improved glucose tolerance in type 2 DM in conjunction with physical training include an increase in the glucose clearance rate associated with an increased muscular blood flow and an increased ability to extract glucose. This demonstrated that physical activity can play a role in the improvement of glucose tolerance and insulin sensitivity [21,22].

The beneficial effects of exercise could be related to a decrease in the circulating levels of UA, IL-6 and TNF- $\alpha$ , a consequence of which may be improved insulin resistance and endothelial dysfunction [23–25]. The significant reduction in the expression of IL-6 and TNF- $\alpha$  in the pancreatic islets of diabetic ZDF rats that performed regular exercise as observed in the present study suggests that exercise reduces inflammation [26]. This anti-inflammatory effect of regular exercise may prolong the life of islet cells and empower them to produce insulin for a much longer period [27,28].

Aerobic exercise intervention, but not flexibility/resistance exercise, reduces serum inflammatory cytokines including IL-18, CRP and IL-6 among older adults; this reduction would be mediated, in part, by improvements in psychosocial factors and/or by  $\beta$ -adrenergic receptor mechanisms [10].

Mosher et al. (1998) showed beneficial effects on glycated hemoglobin in eleven type 1 diabetes patients after a 12-week period of both aerobic exercise and resistance training [27]. Similar beneficial results were also demonstrated by Campaigne et al. in adolescents with type 1 diabetes after 12 weeks of vigorous games and recreational activities [28].

Resistance exercise modalities that increase muscle mass may improve glycemic control and insulin resistance. In addition, combined aerobic and resistance exercises improve endothelial vasodilator function and may therefore increase blood flow and glucose uptake in active muscle beds. It has therefore been proposed that both aerobic and resistance exercise have beneficial effects in subjects with type 2 diabetes, possibly through different mechanisms [29,30].

## Conclusions

In obese type 2 diabetic patients aerobic exercise is more appropriate for modulating insulin resistance, adipocytokines and inflammatory cytokine levels than is resisted exercise training.

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