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This is a refereed journal and all articles are professionally screened and reviewed **ORIGINAL ARTICLE**

Exercise Training Modulates Insulin Resistance and Inflammatory Cytokines in Obese Non-insulin Dependent Diabetic Patients

[1]Shehab Mahmoud Abd El- Kader, [2]Mamdouh A. Gari and [1]Eman Mohamed Salah El-Den Ashmawy

[1]Department of Physical therapy, Faculty of Applied Medical Sciences, King Abdulaziz University, Saudi Arabia.
[2]Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, King Abdulaziz University, Saudi Arabia.

Shehab Mahmoud Abd El- Kader, Mamdouh A. Gari and Eman Mohamed Salah El-Den Ashmawy; Exercise Training Modulates Insulin Resistance and Inflammatory Cytokines in Obese Non-insulin Dependent Diabetic Patients

ABSTRACT

Background: Some plasma biomarkers of inflammation have been recently recognized as important cardiovascular risk factors. Currently, there is little information about the effects of aerobic exercise training on these biomarkers and the risk of metabolic complications in type 2 diabetes patients. Objective: The aim of this study was compare the impact of moderate versus mild aerobic exercise training on insulin resistance and inflammatory cytokines in obese type 2 diabetic patients. Material and Methods: Fifty obese type 2 diabetic patients of both sexes with body mass index (BMI) ranged from 31 to 36 Kg/m^2, non smokers, free from respiratory, kidney; liver, metabolic and neurological disorders were recorded in this study. Their age ranged from 40 to 55 years. The subjects were included into 2 equal groups; the first group (A) received moderate aerobic exercise training. The second group (B) received mild aerobic exercise training three times a week for 3 months. Results: The mean values of leptin, TNF- α, IL2, IL4, IL6, HOMA-IR and HBA1c were significantly decreased in group (A) and group (B).Also; there was a significant difference between both groups after treatment. Conclusion: Moderate aerobic exercise training is more appropriately modulate insulin resistance, adipocytokines and inflammatory cytokine levels than mild aerobic exercise training in obese type 2 diabetic patients.

Key words: Aerobic Exercise; Insulin Resistance; Inflammatory Cytokine; Obesity and Non- Insulin Dependent Diabetes.

Introduction

Type 2 diabetes is one of the fastest growing public health problems. Cardiovascular disease (CVD), the number one cause of mortality in the USA, is almost twice as common in individuals with diabetes [1]. Morbidity and mortality in type 2 diabetes is mainly associated with atherosclerotic cardiovascular disease and late complications as a result of dysfunction of plasma biomarkers of inflammation including leptin, tumor necrosis factor-α (TNF- α) and interleukin-6 (IL-6). These factors have paracrine/autocrine functions that include regulation of energy expenditure, in part, by modulating whole-body insulin sensitivity [2]. Tumor necrosis factor α (TNF- α) induced insulin resistance by interacting with insulin receptor signaling and through activation of lipolysis and inhibition of lipoprotein lipase. TNF-α was proposed to have preferentially paracrine effects and to be a regulator of insulin resistance at the tissue level [3-5].

Interleukin (IL)-6 and tumor necrosis factor α (TNF-α) are two major pro-inflammatory cytokines, are secreted in significant amounts from 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-α are associated with deterioration of glycemic control, increased IR, and dyslipidemia, contributing to the dysfunctional metabolic status of obese and type 2 diabetic individuals [6]. Adipose tissue is an active endocrine tissue, which secretes hormones, such as adiponectin, resistin, and leptin appear to contribute to inflammation, atherosclerosis, and may be involved in the etiology of type 2

Corresponding Author

Dr. Shehab Mahmoud Abd El- Kader, Faculty of Applied Medical Sciences, Department of Physical Therapy, King Abdulaziz University, P.O.B. 80324, Jeddah, 21589, Saudi Arabia.
E-mail: profshehab@live.com, Ph: +966-569849276.

diabetes, possibly constituting the missing link between obesity and insulin resistance [7]. Leptin alters metabolism by mediating appetite and energy expenditure via feedback mechanism on the hypothalamic satiety-regulating centers and has also been linked to obesity-related IR. Leptin resistance is associated with the development of insulin resistance in individuals with type 2 diabetes, and in animals, administration of leptin reverses insulin resistance [8].

Exercise improves diabetic status and reduces the metabolic risk factors associated with cardiovascular diseases and improves insulin sensitivity [9]. Regular exercise increases maximum oxygen uptake, reduces insulin resistance, reduces obesity and prevents further weight gain, and dampens the inflammatory markers, suggesting that habitual exercise plays an important role in the prevention and treatment of obesity, insulin resistance, and coronary heart disease [10]. Few studies have prospectively examined the effect of exercise on elevated levels of inflammatory biomarkers in diabetic subjects and found contrasting results in terms of efficacy and dependence on weight loss[11,12]. Moreover, the type, dose and intensity of physical activity needed to obtain a significant anti-inflammatory effect in this high-risk population are largely unknown.

Aerobic exercise training prevents the development of chronic inflammation associated with NIDDM by reducing the production of proinflammatory cytokines TNF- α and IL-6. The beneficial effects of regular physical activity in improving insulin resistance, dyslipidemia, and levels of proinflammatory cytokines [13]. The potential mechanisms for the anti-inflammatory effect of exercise, including reduced percentage of body fat and macrophage accumulation in adipose tissue, muscle-released interleukin-6 inhibition of tumor necrosis factor-a, and the cholinergic anti-inflammatory pathway[14].

Circulating inflammatory biomarkers originate from multiple sources, particularly visceral adipose tissue, where excess fat promotes macrophage recruitment and both adipocytes and macrophages secrete numerous cytokines (adipokines), including IL-6, TNF- α and leptin [4]. Skeletal muscle is another source of cytokines, called myokines, among which IL-6 is considered to play a dual role as anti-inflammatory and pro-inflammatory. High-intensity training of long duration may significantly influence myokine production, thus driving the anti-inflammatory effect of exercise [15].

The aim of this study was compare the impact of moderate versus mild aerobic exercise training on insulin resistance and inflammatory cytokines in obese type 2 diabetic patients.

Materials and Methods

Subjects:

Fifty obese type 2 diabetic patients of both sexes with body mass index (BMI) ranged from 31 to 36 Kg/m^2, non smokers, free from respiratory, kidney; liver, metabolic and neurological disorders were recorded in this study. Their age ranged from 40 to 55 years. The subjects were included into 2 equal groups; the first group (A) received moderate aerobic exercise training. The second group (B) received mild aerobic exercise training three times a week for 3 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, with this being announced to the Human Subjects Review Board. However, no adverse effects occurred, and so the data of all the participants were available for analysis.

Methods:

1. Evaluated parameters:

Chemical analysis:

Blood sample after fasting for 12 hours was taken from each patient in clean tubes containing few mg of K2EDTA, centrifuged and plasma was separated and stored frozen at -20° used for estimation of leptin, plasma TNF- α, C- reactive protein (CRP), interleukin-2 (IL-2), interleukin-4(IL-4) , interleukin-6 (IL-6) and glycosylated hemoglobin (HBA_1c) using colorimetric method. Homeostasis Model Assessment-Insulin Resistance (HOMA) index for insulin sensitivity was computed following this equation: [fasting glycemia (mmol/L)· fasting insulin (mIU/L)]/22.5 [16].

2. The Aerobic Exercise Training Program:

The aerobic treadmill-based training program (Track master 400E, gas fitness system, England) was at 65 % to 75 % of the maximum heart rate (HRmax) achieved according to a modified Bruce protocol for group (A) who received moderate intensity aerobic exercise training, where group (B) received mild intensity aerobic exercise training at 55 % to 65% of the maximum heart rate (HRmax) .This rate was defined as the training heart rate (THR). After an initial, 5-minute warm-up phase performed on the treadmill at a low load, each endurance training session lasted 30 minutes and ended with 5-minute recovery and relaxation phase. All patients performed three sessions / week (i.e. a total of 36 sessions per patient over a 3-month period).

Statistical Analysis:

The mean values of leptin, TNF- α, CRP, IL-2, IL-4, IL-6, HOMA-IR and HBA1c obtained before and after three months in both groups were compared using paired "t" test. Independent "t" test was used for the comparison between the two groups ($P<0.05$).

Results:

Fifty obese type 2 diabetic patients of both sexes with body mass index (BMI) ranged from 31 to 36 Kg/m^2. The subjects were included into 2 equal groups; the first group (A) received moderate aerobic exercise training. The second group (B) received mild aerobic exercise training three times a week for 3 months in order to compare the effect of moderate and mild intensity aerobic exercise training on leptin, TNF- α, CRP, IL-6, HOMA-IR and HBA1c in obese type 2 diabetic patients.

The mean values of leptin, TNF- α, CRP, IL-2, IL-4, IL-6, HOMA-IR and HBA1c were significantly decreased in group (A) and group (B) (Table 1and 2 & figure 1 and 2) .Also; there was a significant difference between both groups after treatment (Table 3 and figure 3).So, moderate aerobic exercise training is more appropriate than mild aerobic exercise training.

Table 1: Mean value and significance of Leptin, TNF- α, IL-2, IL-4, IL-6, HOMA-IR and HBA_1c in group (A) before and after treatment.

	Mean ±SD		T-value	P-value
	Before	After		
Leptin (Ng/ml)	6.53 ± 40.87	± 34.655.42	8.41	<0.05
TNF- α (pg/mL)	5.52± 1.98	4.35 ± 1.26	6.72	<0.05
IL-2 (pg/mL)	7.98 ± 2.25	4.43 ± 1.86	5.78	<0.05
IL-4(pg/mL)	5.43± 1.62	3.45± 1.78	5.12	<0.05
IL-6 (pg/mL)	8.89 ± 2.13	5.22 ± 1.69	6.33	<0.05
HBA_1c (%)	7.98 ± 2.56	6.13 ± 1.55	6.11	<0.05
HOMA-IR	4.73 ± 1.28	2.85 ± 1.16	6.42	<0.05

TNF- α = tumor necrosis factor – alpha. IL-2 = Interleukin-2
IL-4 = Interleukin-4 IL-6 = Interleukin-6
HBA1c = glycosylated hemoglobin.
HOMA-IR = Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index.

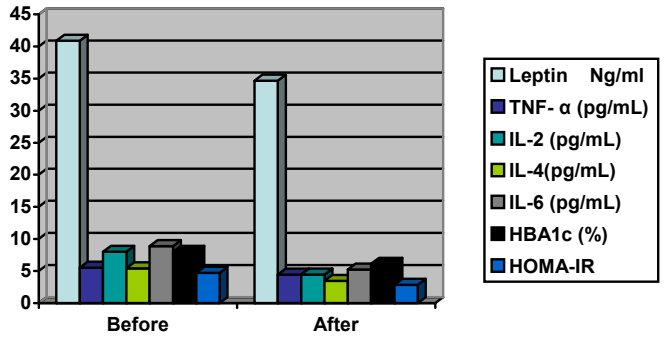

Fig. 1: Mean value and significance of Leptin, TNF- α, IL-2, IL-4, IL-6, HOMA-IR and HBA_1c in group (A) before and after treatment.

Table 2: Mean value and significance of Leptin, TNF- α, IL-2, IL-4, IL-6, HOMA-IR and HBA_1c in group (B) before and after treatment.

	Mean ±SD		T-value	P-value
	Before	After		
Leptin Ng/ml	41.25±6.62	37.34 ± 5.91	4.11	<0.05
TNF- α (pg/mL)	5.71± 1.85	5.01 ± 1.42	3.13	<0.05
IL-2 (pg/mL)	7.88 ± 2.52	6.37 ± 2.16	3.24	<0.05
IL-4(pg/mL)	5.77± 1.84	4.51± 1.42	3.21	<0.05
IL-6 (pg/mL)	8.96 ± 2.53	6.88 ± 2.01	3.19	<0.05
HBA_1c (%)	7.78 ± 2.66	6.93 ± 1.85	3.14	<0.05
HOMA-IR	4.94 ± 1.75	3.92 ± 1.46	3.28	<0.05

TNF- α = tumor necrosis factor – alpha. IL-2 = Interleukin-2
IL-4 = Interleukin-4 IL-6 = Interleukin-6
HBA1c = glycosylated hemoglobin.
HOMA-IR = Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index

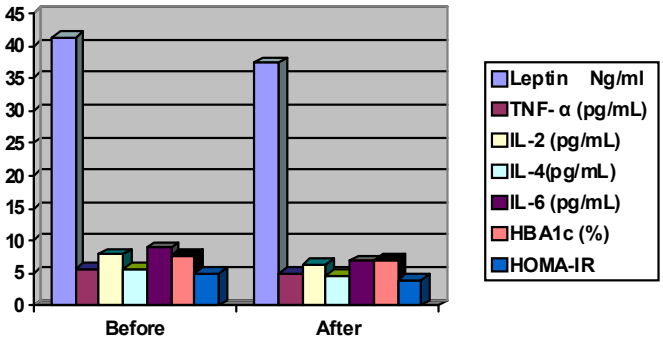

Fig. 2: Mean value and significance of Leptin, TNF- α, IL-2, IL-4, IL-6, HOMA-IR and HBA_1c in group (B) before and after treatment.

Table 3: Mean value and significance of Leptin, TNF- α, IL-2, IL-4, IL-6, HOMA-IR and HBA_1c in group (A) and group (B) after treatment.

	Mean +SD		T-value	P-value
	Group (A)	Group (B)		
Leptin Ng/ml	± 34.655.42	37.34 ± 5.91	4.23	<0.05
TNF- α (pg/mL)	4.35 ± 1.26	5.01 ± 1.42	3.52	<0.05
IL-2 (pg/mL)	4.43 ± 1.86	6.37 ± 2.16	3.14	<0.05
IL-4(pg/mL)	3.45± 1.78	4.51± 1.42	3.12	<0.05
IL-6 (pg/mL)	5.22 ± 1.69	6.88 ± 2.01	3.41	<0.05
HBA_1c (%)	6.13 ± 1.55	6.93 ± 1.85	3.16	<0.05
HOMA-IR	2.85 ± 1.16	3.92 ± 1.46	3.24	<0.05

TNF- α = tumor necrosis factor – alpha. IL-2 = Interleukin-2
IL-4 = Interleukin-4 IL-6 = Interleukin-6
HBA1c = glycosylated hemoglobin.
HOMA-IR = Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) index

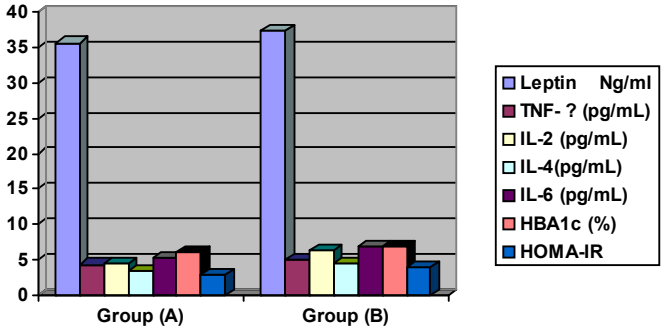

Fig. 3: Mean value and significance of Leptin, TNF- α, IL-2, IL-4, IL-6, HOMA-IR and HBA_1c in group (A) and group (B) after treatment.

Discussion:

As even mild physical exercise that does not affects VO_2max can cause improvement in the in vivo insulin sensitivity if continued for a prolonged period of time, Aerobic exercise training has traditionally been advocated as an essential component in the medical management of type 2 diabetic patients in order to improve the cardiovascular health of these individuals [17]. Regular aerobic exercise decreases cardiovascular risk of people with type 2 diabetes principally by reducing body weight and abdominal visceral fat accumulation with subsequent improvements in insulin sensitivity, blood pressure, lipid profile and glycaemic control [18].

There is a controversy surrounding the beneficial effects of different aerobic exercise intensities on glycemic control and inflammatory cytokines in type 2 diabetes patients, so this study was to compare the impact of moderate versus mild aerobic exercise training on insulin resistance and inflammatory cytokines in obese type 2 diabetic patients. The mean values of leptin, TNF- α, CRP, IL-2, IL-4, IL-6, HOMA-IR and HBA1c were significantly decreased in group (A) received moderate intensity aerobic

exercise training and group (B) received mild intensity aerobic exercise training .Also; there was a significant difference between both groups after treatment, these findings are supported and agreed by several previous studies.

A twice-weekly, 6-month, moderate intensity aerobic-training program, without a concomitant weight loss diet, is associated with significant decreases in circulating P-selectin and ICAM-1 levels and with a less atherogenic lipid profile in overweight, non-smoking, older type 2 diabetic individuals [19].

Eighty-two patients were randomized into 4 groups: sedentary control (A) received low-intensity aerobic exercise, group (B) performed high-intensity aerobic, group (C) performed aerobic and resistance exercises and group (D) performed exercise (with the same caloric expenditure) for 12 months. Physical exercise in type 2 diabetic patients with the metabolic syndrome is associated with a significant reduction of inflammatory and insulin resistance biomarkers, independent of weight loss. Long-term high-intensity (preferably mixed) training, in addition to daytime physical activity, is required to obtain a significant anti-inflammatory effect [20].

It is possible that aerobic exercise decreases subclinical, chronic inflammation and improves endothelial function simply as a result of reducing obesity (particularly visceral obesity) and improving insulin sensitivity [21]. Most published studies showing beneficial effects of moderate aerobic exercise on insulin sensitivity in obese patients have also constantly reported significant reductions in abdominal visceral fat, thus reinforcing the importance of diminished visceral adipose tissue in the treatment of insulin resistance [22, 23].

During regular aerobic exercise, skeletal muscle fibres inhibit the production of the pro-inflammatory cytokine TNF-α and produce several anti-inflammatory cytokines (termed "myokines") that may be involved in mediating the health-beneficial effects of exercise [24]. Additionally, exercise training may reduce mononuclear cell production of pro-inflammatory cytokines by reducing chronic oxidative stress [25]. Exercise has the potential to lower the inflammatory status by the reduction of high-sensitivity C-reactive protein (hs-CRP) and tumor necrosis factor (TNF-α) and the enhancement of adiponectin [26, 27].

Exercise suppresses the production of proinflammatory cytokines and enhances anti-inflammatory cytokines. Because proinflammatory cytokines, IL-6 and TNF-α, have cytotoxic actions, it can be proposed that regular exercise prevents further damage to insulin-producing β-cells by attenuating the production of these [28]. Aerobic exercise decreases subclinical, chronic inflammation and improves endothelial function simply as a result of reducing obesity (particularly visceral obesity) and improving insulin sensitivity [29].

Several studies suggest that training programs which involve a resistive exercise component, that is moderate intensity weight-lifting exercises, may be of particular benefit in type 2 diabetes, due to an effect of increasing insulin action. Increases in muscle mass have been associated with benefits in terms of glycemic control as skeletal muscle represents the largest mass of insulin-sensitive tissue [30-32].

High-intensity exercise training program induced an improvement of biomarkers of inflammation and insulin resistance, with a reduction of IL-6, TNF- α and leptin (associated with decreased insulin, C-peptide, and HOMA-IR) and an increase of IL-4 and IL-10 thus indicating that exercise has a full anti-inflammatory and insulin-sensitizing effect. These results suggest that the beneficial effect of physical activity on CVD morbidity and mortality may depend, at least partly, on the anti-inflammatory effect of exercise, though it is unproven that reducing CRP and other inflammatory biomarkers is effective in decreasing CVD risk. Changes in inflammatory biomarkers in the high-intensity exercise were paralleled by improvements though, to a lesser extent in HbA_{1c} [4].

One study has shown that low- to moderate-intensity exercise training is as effective as moderate- to high-intensity exercise training [33]. Whereas another study reported that high-intensity training was more effective in improving glycemic control [34].

Conclusion:

Moderate aerobic exercise training is more appropriately modulate insulin resistance, adipocytokines and inflammatory cytokine levels than mild aerobic exercise training in obese type 2 diabetic patients.

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