Effects of Aerobic Exercise Training Program on Resistin, Glycemic Control, and Some Cardiometabolic Risk Factors in Obese Diabetic Men

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ABSTRACT

Background: *Physical activity is a cornerstone of diabetes mellitus treatment and can reduce many risks associated with obesity and diabetes mellitus. Resistin and numerous inflammatory markers (e.g. high sensitivity C - reactive protein) have emerged as a predictor of cardiovascular disease in diabetic obese.* ***Objective:*** *The aim of this study was to evaluate the changes in resistin, glycemic control, lipid profile and C- reactive protein after 14 weeks of aerobic exercise program in obese men with type 2 diabetes mellitus.* ***Design:*** *A 14 week outpatient randomly controlled trial was conducted in obese (BMI > 30 Kg/m^2) type 2 diabetic men (age 40 -50 years). They were randomly assigned to an intervention group (group A) or control group (group B) . The intervention group (n= 18), in addition to regular conventional treatment, received individually prescribed aerobic exercise program for 50 minutes, at 60-75 % of maximum heart rate three times weekly. The control group (n= 16) received regular conventional treatment only. Main outcomes measures including weight, body mass index (BMI), waist circumference (WC), resistin, fasting blood sugar (FBS), glycosylated hemoglobin (Hb A1 c), C-reactive protein (CRP), low-density lipoprotein LDL, and high density lipoprotein HDL.* ***Results:*** *Thirty four obese men with type 2 diabetes and of mean age 44.35 ± 5.74 years participated in the study. Both groups were similar for age, BMI, and duration since onset of diabetes at baseline. Within- group comparison did not show any significant differences (P > 0.05) for all parameters before the study. After 14 weeks of exercise, the intervention group showed reduced body weight, body mass index, resistin, glycemic control (fasting blood sugar and Hb A1C), and C-reactive protein, and increased HDL – c compared with baseline (P < 0.05). The control group did not show any significant differences in resistin, glycemic control and some cardiometabolic risk factors before and after the study (P > 0.05).* ***Conclusions:*** *Obese men with type 2 diabetes mellitus improved in resistin level, glycemic control, and C-reactive protein, and HDL following 12 weeks of aerobic training program.*

Key words: *Obesity, type 2 diabetes mellitus, resistin and aerobic exercises.*

INTRODUCTION

Obesity is characterized by an excess of body fat[25], and in recent years it has been defined as a risk factor for the development of insulin resistance, type 2 diabetes, dyslipoproteinemia, hypertension, and cardiovascular disease. Obesity is accepted as a major health problem because of the threat of morbidity/ mortality from vascular diseases[17]. Obesity is strongly associated with elevated concentrations of circulating markers of inflammation, such as CRP[16]. Elevated plasma levels of CRP have been associated with an increased risk of coronary heart disease and type 2 diabetes[18].

Resistin is a recently discovered protein that is expressed and secreted from adipocytes and is present in the circulation. The first study on resistin revealed that it is an important factor linking obesity, a prominent cause of cardiovascular disease (CVD), and insulin resistance. Several follow up studies have explored the role of resistin in obesity and type 2 diabetes and its underlying mechanism. Recently several studies showed that resistin may also play a pivotal role in inflammation and process of inflammation-related diseases[21].

Inflammatory process has recently been connected with the pathogenesis of atherosclerosis. Recent studies indicate that resistin may promote the initiation or perpetuation of the atherosclerotic state by activating vascular endothelial cells including the promotion of endothelin-1 release and the

up-regulation of adhesion molecules and cytokines[11]. In humans, resistin is expressed in adypocytes, and to an even greater extent in macrophages[8].

Type 2 diabetes is associated with an excessive risk of cardiovascular events[24]. On the other hand, physical activity reduces cardiovascular morbidity in diabetic patients[22]. Resistin and numerous inflammatory markers e.g., high-sensitivity C- reactive protein, interleukin-6 and interleukin-18 have emerged as novel predictors of cardiovascular disease[13]. Regular physical activity confers many physiological and psychological benefits including an improved lipid profile, enhanced insulin sensitivity , lowered blood pressure and an increased energy expenditure which has potential to lower body fat and body weight[9].

Exercise is the major therapeutic modality in the treatment of diabetes mellitus[14]. Regular physical exercise has been reported to be effective in the prevention and delay of onset of type 2 diabetes mellitus, increase insulin sensitivity, and ameliorates glucose metabolism[6]. Exercise training programs can improve the insulin sensitivity, the vascular endothelium function, the glycemic control, and the blood pressure[19].

The purpose of this study was to evaluate the effects on resistin hormone, glycemic control and some cardiometabolic risk factors in diabetic obese men following 14 week of an aerobic exercise program.

SUBJECTS AND METHODS

Subjects

This study was carried out on a sample of 34 volunteer obese men with type 2 diabetes mellitus. Their age ranged from 40-50 years old, randomly selected from outpatient diabetes mellitus clinic of 6th October University. They were divided into two groups:

Group A (the intervention group): included eighteen obese diabetic men, in addition to regular conventional treatment, received prescribed aerobic exercise program.

Group B (the control group): included sixteen obese men with type 2 diabetes mellitus who received their regular conventional treatment only for 14 weeks.

Inclusion Criteria:

1- Obese men (BMI between 30-39.9 kg /m 2) with type 2 diabetes mellitus.
2- Their age ranged from 40-50 years old.
3- The incidence of type 2 DM was less than 5 years.
4- All participants were under oral hypoglycemic drugs.

Exclusion Criteria:

1- Age less than 40 or older than 50 years old.
2- Incidence of type2 DM was more than 5 years.
3- Type 1 diabetes mellitus.
4- Patients with vascular complications.
5- Life-threatening diseases.
6- Thyroid problems.
7- History of cardiovascular disease (angina pectoris, myocardial infarction, chest pain, intermittent claudication, deep venous thrombosis).
8- Musculoskeletal disorders.
9- Liver and renal impairment.
10- Use of medications or supplements relevant to cholesterol-lowering effects.
11- Smokers.

Procedures

All patients signed a written informed consent and were subjected to all of the following evaluation protocol:

1- Detailed medical history and physical examinations including vital signs.
2- Anthropometric measurements: weight, BMI and waist circumference.
3- Laboratory investigations:

Following a 12 h overnight fast, venous blood samples were collected from an antecubital vein (20 ml) in the sitting position after a 20-minute rest between 8:00 and 9:00 A.M. Serum was separated by centrifugation, and samples were stored at – 80 ° c until analyzed in the laboratories of October 6th University hospitals.

Resistin, fasting blood sugar (FBS), glycosylated hemoglobin (Hb A1 C), C-reactive protein (CRP), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were measured. Plasma human resistin was assessed using ELISA method (Bio Vendor, Heidelberg, Germany).

Exercise training:

All subjects were inactive and non reported engaging (more than one time per week) sport activities before the study. Patients in the exercise group underwent a 14-week aerobic exercise training program. Aerobic exercise consisted of walking on a treadmill 50 minutes three times per week with intensity 60-75 % HR max. Exercise modality was based on the recent recommendations of the American Diabetes Associations[3]. We chose walking as the mode of aerobic exercise because it appears to be the most common, most feasible, and safest form for our subjects. The exercise intensity was prescribed based on target heart rates (THRs) calculated from the Karvonen equation[2].

HR maximal-HR rest x (0.6-0.75+ HR rest)

HR maximal was predicted via the 220- age formula.

The workload was individualized according to the initial physical fitness assessment and gradually increased with continuous electrocardiographic measurement. Moreover, subjects in the exercise group were encouraged to increase daily physical activities. Control subjects were instructed to maintain their habitual activities.

Statistical Analysis

Descriptive statistics for all variables were done. Paired t-test was used for before and after treatment program comparison within each group. Independent t-test with $P < 0.05$ performed for comparison between study and control groups.

RESULTS

1- Results of Anthropometric Measurements: before the study, there was no statistically significant difference between the intervention group (A) and the control group (B) regarding mean values of anthropometric measurements (weight, BMI, and waist circumference) with $P > 0.05$. After intervention, a significant improvement was found in the intervention group compared to before the aerobic exercise program in weight and BMI with $P = 0.001$. The results also demonstrated no statistical differences in the mean values of weight, BMI and waist circumference in the control group. (table1).

Table (1): Comparison between mean values of anthropometric measurements before and after treatment within the intervention group (A) and control group (B).

Variable	Intervention group		P	Control group		P
	Before Mean± SD	After Mean± SD		Before Mean± SD	After Mean± SD	
Age (year)	44.5± 5.2			44.8± 4.6		
Weight (Kg)	83.9 ± 4.78	80.5 ± 5.84	0.001*	82.4 ± 5.32	81.93±4.39	0.73
BMI (Kg/m2)	34.75± 3.75	32.12± 3.35	0.001*	34.20±2.86	34.05± 2.43	0.56
W C (cm)	106.21 ± 8.3	103 ±4.35	0.12	104.75±4.4	103 ±2.60	0.075

SD: Standard deviation BMI: Body Mass Index WC: Waist Circumference *Significance at P<0.01

2- Result of Resistin: before the study, there was no statistically difference between the intervention group (A) and the control group (B) regarding mean values of resistin With $P > 0.05$. After the exercise program, a significant improvement was found in the intervention group compared to before the program with $P = 0.001$. The results also demonstrated no statistical differences in the mean values of resistin in the control group before and after the study with P= 0.27 (table2).

Table (2): Comparison between mean values of resistin before and after treatment within the intervention group (A) and control group (B).

Variable	Intervention group		P	Control group		P
	Baseline Mean± SD	After Mean± SD		Baseline Mean± SD	After Mean±SD	
Resistin (ng/ml)	16.6±2.4	10.38±1.6	0.001*	17.4±3.54	16 .89±4.6	0.27

*Significance at P<0.01

3- Results of Fasting Blood Sugar (FBS) and glycosylated hemoglobin (Hb A1C): before the study, there was no statistically difference between the intervention group (A) and the control group (B) regarding mean values of fasting blood sugar and glycosylated hemoglobin (Hb A1C) With P > 0.05. After the exercise program, a highly significant improvement was found in the intervention group compared to before the program with P = 0.001. The results also demonstrated no statistical differences in the mean values of Fasting Blood Sugar (FBS) and glycosylated hemoglobin (Hb A1C) in the control group before and after the study with P > 0.05 (table 3).

Table (3): Comparison between mean values of Fasting blood sugar (FBS) and glycosylated hemoglobin (Hb A1c) before and after treatment within the intervention group (G1) and control group (G2).

Variable	Intervention group		P	Control group		P
	Before Mean± SD	After Mean± SD		Before Mean± SD	After Mean± SD	
FBS	158.54± 18.86	133.28 ± 28.6	0.001*	165.47±12.5	178.11±20.3	0.3
Hb A1c	10.24 ±2.6	7.35 ±1.3	0.001*	10.94 ±3.2	10.38 ±2.9	0.24

FBS: Fasting Blood Sugar Hb A1c: Glycosylated Haemoglobin *Significance at P<0.01

4- Results of CRP, HDL and LDL: before the study, there was no statistically difference between the intervention group (A) and the control group (B) regarding mean values of CRP, HDL and LDL with P> 0.05. After intervention, a significant improvement was found in the intervention group compared to before the exercise program in mean values of CRP and HDLc with P < 0.01 and there was no significant difference in mean value of LDLc with P = 0.08. The results also demonstrated no statistical differences in the mean values of CRP, HDL and LDL in the control group before and after the study with P= 0.17, 0.48 and 0.38 respectively (table 4).

Table (4): Comparison between mean values of CRP, HDL and LDL before and after treatment within the intervention group (A) and control group (B).

Variable	Intervention group		P	Control group		P
	Before Mean± SD	After Mean± SD		Before Mean± SD	After Mean± SD	
CRP	6.57 ± 2.24	4.84±1.34	0.001*	5.78 ± 2.86	5.92 ± 1.54	0.17
HDL	49.28±8.92	54.62±4.37	0.001*	47.83±6.65	48.10±6.50	0.48
LDL	161.42 ±12.30	153.54± 14.76	0.08	165.43± .37	161.27 ± 8.2	0.38

*Significance at P<0.01

DISCUSSION

The most outstanding of this study, which aimed to examine the effects of aerobic exercise training program on resistin, glycemic control (fasting blood sugar, and Hb A1c) and some of cardiometabolic risk factors (CRP, HD Land LDL) in obese men with type 2 diabetes mellitus, is the significant reduction in resistin, glycemic control and CRP and significant increase in HDL (good cholesterol) by means of exercise program.

Body mass index and waist circumference are frequently used to define obesity. Especially central obesity is confirmed to be strongly associated with cardiovascular disease. Favorable effects of aerobic exercise program on lowering body weight and body mass index have been demonstrated[4]. Our result is in agreement with the previous findings since we determined significant reductions in body weight and body mass index of the intervention group subjects.

Our result agrees with Esposito et al.,[7], who reported that exercise increases the uptake of glucose by muscle cells which, consequently, increase the oxidation of glucose which leads to improvement in insulin

resistance and glycemic control (FBS and HbA1c). Our results also agree with Ajediran et al.,[1] who demonstrated that the therapeutic benefits of aerobic exercise include regulation of body weight, reduction of insulin resistance, enhancement of insulin sensitivity, and glycemic control. Exercise training has been shown to be a useful option to treat and prevent type 2 diabetes. Therapeutic effects of exercise training in patients with type 2 diabetes include improvements in glycemic control, cardiorespiratory function, body composition, lipid profiles and skeletal muscle function[20].

In the present study, CRP concentrations were elevated in obese men with type 2 diabetes who were also insulin resistant and fall in parallel with weight loss-associated improvements in glycemic control. CRP levels decreased significantly in the intervention group compared to control group following 12 weeks of aerobic exercise program. Several physiological mechanisms exist to explain the changes in CRP and insulin resistance with exercise. Exercise is known to increase insulin-receptor autophosphorylation, glucose transporter 4 expressions and glucose transport.

Our result agree with Warnberg and et al.,[23] who demonstrated that exercise training reduces CRP both directly by reducing cytokine production in fat , muscle, and mononuclear cells, and indirectly by increased insulin sensitivity, improving endothelial function, and reducing body weight. This finding was in agreement with a previous study which found positive significant correlation between CRP, BMI, and insulin level and insulin resistance. The mechanisms responsible for the association between CRP, BMI and insulin resistance are not yet clearly understood. It is possible that with increasing BMI, adipose tissue is a direct source of proinflammatory cytokines which, in turn, acts as stimuli for CRP synthesis in the liver. This leads to a chronic inflammatory state and contribute to insulin resistance.

In the present study, the HDL concentration was elevated significantly in the intervention group compared to control group following the exercise program. This is in agreement with Couillard et al.,[5] who reported that the most significant effects of exercise on diabesity (diabetic obese) parameters are observed in HDL. The effects of exercise on HDL levels are most clearly seen in obese persons with type 2 diabetes with high TG and low HDL at baseline.

Recently there have been numerous reports on changes in adipocytokines concentration with diet and/or exercise interventions in obese individuals but only a few reports examine these changes in individuals with type 2 diabetes. Monzillo et al.,[15] found no changes in resistin levels in obese and individuals with type 2 diabetes after a weight loss program. Kelly et al.,[12] also found no changes in resistin levels of overweight children who conducted on exercise program of 50-80% of Vo2 max four days per week for eight weeks.

However, despite the similar exercise intensity, Kadoglou et al.,[10] determined significant reductions in serum resistin due to 16-week aerobic exercise training consisting of 45-60 minutes per week in an elderly diabetic population. This agrees with our study, we determined a significant reduction in the resistin level in diabetic obese men following 14-week aerobic exercise program. This may be related to the duration of the exercise period (eight vs. 16 weeks) and 14 week in our study.

These enable us to speculate that the intensity of the physical activity as well as exercise duration and frequency may be important for inducing positive adaptations in this cytokine since we determined significant reductions in the resistin levels as a result of high intensity walking exercises. Therefore, considering these results, we may express that walking with moderate or high- intensity for 12 weeks 3 days per week appears to be more effective in causing reductions in resistin levels in the diabetic obese men.

Conclusions

- Diabetic obese exhibits several risk factors for the development of cardiovascular disease. Exercise intervention reduces resistin hormone which, in turn, may prevent type 2 diabetes.
- Exercise intervention also reduces CRP, which is effective in preventing the

occurrence of cardiovascular events.

- Regular physical activity is one of the most important non-pharmacologic tools in reducing the overall cardiometabolic risk via regulating the body weight, blood pressure and the lipid profile.
- Further studies will be required to assess the responses related to the degree of obesity, as well as the intensity and the duration of intervention on resistin in diabetic obese.

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الملخص العربي

تأثيرات برنامج التمرينات الهوائية علي الريسيستين والتحكم في مستوي سكر الدم وبعض عوامل الخطر علي القلب في مرضي السمنة والمصابين بمرض البوال السكر ي

المقدمة : تعتبر التمارين العلاجية حجر الزاوية في علاج مرضي البوال السكري ومن الممكن أن يقلل من الأخطار المرتبطة بمرض السمنة والبوال السكري . يعتبر الريسيستين ؛ وبعض أنواع دلالات الالتهابات من الأسباب المتوقعة لمرض القلب والأوعية الدموية في الرجال من مرضي السمنة والمصابين بمرض البوال السكري . **الهدف من الدراسة :** الهدف من هذه الدراسة هو تقيم التغيرات في مستوي الريسيستين ومستوي السكر في الدم والهيموجلوبين المجلكز وصورة دهون الدم والبروتين النشط ج قبل وبعد 14 أسبوع من برنامج التمرينات الهوائية في الرجال من مرضي السمنة والبوال السكري . **تصميم البحث :** هذه التجربة أجريت لمدة 14 أسبوع على مرضي السمنة والبوال السكري . وقسم المرضي عشوائيا إلي مجموعتين : المجموعة الأولي : (مجموعة الدراسة) العدد 18 مريض .. تأخذ برنامج علاجي عبارة عن تمارين هوائية لمدة 50 دقيقة من 60 إلي 75% من أعلي معدل نبض القلب بالإضافة إلي علاجهم الدوائي. المجموعة الثانية : (المجموعة الضابطة) العدد 16 مريض .. تأخذ علاجها الدوائي فقط . وكانت القياسات كالأتي وزن الجسم – مؤشر كتلة الجسم – محيط الوسط – مستوي الريسيستين في الدم ومستوي السكر في الدم والهيموجلوبين المجلكز وصورة دهون الدم والبروتين النشط ج والكولسترول المنخفض الكثافة والكولسترول العالي الكثافة . **النتائج :** أظهرت الدراسة والتي أجريت علي عدد 34 من الرجال من مرضي السمنة والنوع الثاني من البوال السكري نتائج ذات دلاله إحصائية في التقليل من الوزن ومؤشر كتلة الجسم– مستوي الريسيستين في الدم ومستوي السكر في الدم والهيموجلوبين المجلكز والبروتين النشط ج وزيادة الكولسترول العالي الكثافة بالمقارنة بقبل الدراسة . بينما لم تظهر المجموعة الضابطة أي تغيير بعد الدراسة مقارنة بقبلها . **الخلاصة :** انخفض– مستوي الريسيستين في الدم ومستوي السكر في الدم والهيموجلوبين المجلكز والبروتين النشط ج وتحسن الكولسترول العالي الكثافة بعد برنامج من التمرينات الهوائية لمدة 14 أسبوع .

الكلمات الدالة : السمنة - البول السكري – الريسيستين – التمرينات العلاجية .