Effect of Aerobic Exercise Training on Serum Leptin and Inflammatory Cytokine in Obese Diabetic Post Menopausal Women

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ABSTRACT

Purpose: *This study was conducted to examine the effect of exercise on leptin and inflammatory cytokines [C-reactive protein (CRP) and Interleukin-6 (IL-6)] in obese post menopausal women with type 2 diabetes.* ***Study design:*** *Twenty four obese post menopausal women with type 2 diabetes for at least 3 years, their age ranged from 51-60 years (55.65±3.45years) and body mass index (BMI) > 32kg/m^2 (33.03±1.32 kg/m^2) were submitted to aerobic exercise training on treadmill (30minutes, 3 times per week) for 3 months. Evaluation was done before and after 3 months of exercise.* ***Results:*** *Collected data revealed small changes in body weight, BMI and percentage of body fat after 3 months of exercise training without significant differences. Also, training resulted in small non significant reduction in all cytokines (CRP and IL-6) but leptin was decrease significantly (P<0.05).* ***Conclusion:*** *The findings provide evidence that exercise could reduce the inflammation process in obese diabetic post menopausal women. Thus, exercise may play a vital role in controlling inflammatory markers during aging process. Additional studies are needed to assess the effects of different modes and intensities of exercise on inflammation.*
Key words: *Exercise, Leptin, Cytokines, Obesity, Diabetes, Menopause.*

INTRODUCTION

Menopause is associated with an increased risk for cardiovascular and metabolic diseases[25]. The etiology of the effect of the menopause on cardiovascular and metabolic diseases may be linked with changes in body fat distribution which is more similar to men (android adiposity) due to diminished estrogen secretion. Thus, this increase in the abdominal visceral adipose tissue is associated with the metabolic syndrome, including type 2 diabetes, hypertension and dyslipidemia[23].

Researches have demonstrated that 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, atherosclerosis and may be involved in the etiology of type 2 diabetes[9, 10,13].

Leptin alters metabolism by mediating appetite and energy expenditure via feedback mechanism on the hypothalamic satiety-regulating centers and has been linked to obesity related insulin resistance (IR)[28] as serum leptin levels were found to be highly correlated with percentage of body fat. Also, leptin resistance is associated with the development of IR in individuals with type 2 diabetes [11, 28].

Interleukin-6 (IL-6) is one of the major pro-inflammatory cytokines that is secreted in significant amounts from adipose tissue and consequently obese women (healthy and

diabetic) have higher IL-6 than healthy lean women[7]. IL-6 is also known to regulate C-reactive protein (CRP) release from liver. Furthermore, increased level of IL-6 is associated with deterioration of glycemic control, increased IR and dyslipidemia, contributing to the dysfunctional metabolic status of obese and type 2 diabetic individuals[22].

Numerous studies have demonstrated that exercise reduces the morbidity and mortality of vascular diseases, also, it reduces the risk of illness; improve health and ultimately quality of life[4, 20]. Exercise reduces leptin levels in obese individuals and decrease visceral fat[21, 24] but most of the previous research has focused on obese individuals. The few studies conducted on individuals with type 2 diabetes[1, 3, 11] have provided conflicting results from those found on obese individuals, indicating that this population does not respond in the same manner to exercise. Furthermore, limited research exists on the effects of exercise alone as the sole intervention on those individuals with type 2 diabetes.

Also, the change in inflammatory cytokines concentration with exercise in obese individuals was reported by many studies[5,19], but no reports were found to examine these changes in individuals with type 2 diabetes.

So, the purpose of the present study was to investigate the effect of exercise on leptin and the inflammatory cytokines (IL-6 and CRP) in obese post menopausal women with type 2 diabetes.

SUBJECTS, MATERIALS AND METHODS

Subjects

Twenty four obese post menopausal women with type 2 diabetes (51-60years old) were participated in this study from Outpatient Clinic of Gynecology, Kasr El-Aini University Hospital. All women were post menopausal for a minimum of 5 years (7.8±1.5 years), obese (body mass index BMI > 30 Kg/m^2) and diagnosed with type 2 diabetes for at least 3 years (4.7±1.2 years) as well as receiving a stable dose of the same oral hypoglycemic drugs (combination of sulfonylureas and metaformin) for a minimum of 1 year.

Women on insulin, hormonal replacement therapy and ß blockers were excluded. Also, none of the women participated in any type of regular exercise or diet treatment for the prior year as well as during the study and all had stable weight as well as in good health with no major complications related to diabetes such as cardiovascular disease and neuropathies. All participated women were asked to continue their typical eating patterns. Before participation in the study, each woman signed an informed consent.

Instruments

1-Electronic bicycle ergometer connected with metabolic cart (Morgan) was used to determine the Vo_{2max} for all women.

2-Body fat analyzer (Biodynamics SN330) was used to determine the percentage of the body fat.

3- Weight and height scale was used to measure the weight and height of each woman.

4- Elisa reader (Laboratory System Multiscan) was used for estimation of the serum glucose, leptin and the inflammatory cytokines (IL-6 and CRP).

PROCEDURES

I- Evaluative Procedures

Evaluations had been performed for all women at the time of admission to the study and after 3 months of participation in the exercise program as follows:

1- Body mass index (BMI), each woman was weighted into the nearest kilograms and her height was measured without shoes to the nearest meters. Then BMI was calculated by dividing weight (Kg) per height^2 (m^2).

2- Body fat percentage, was assessed by using body fat analyzer in which electrodes were placed at midpoint on the dorsum of the hand (just above meta carpo phalangeal joint and at wrist joint) and at mid point on the dorsum of the same side of the foot (just above meta tarso phalangeal joint and at ankle joint). After calibration of the machine, a painless, localized electric signal was started to pass through the body tissue and impedance to current flow was determined. The impedance was converted to represent the percentage of the body fat.

3- Blood sampling, a venous blood samples were drawn from each woman after a 12-hour overnight fast for measurement of fasting blood glucose, leptin, IL-6 and CRP concentrations.

4- Exercise stress test, only before starting the suggesting program, exercise stress test was performed to determine maximum oxygen uptake (Vo_{2max}) using open circuit spiriometry during an incremental protocol on electronic bicycle ergometer[13].

II- Exercise Procedures

The exercise training program was performed on an electronic treadmill three times per week for three month. The exercise session consisted of five minutes of warm up which involved walking without either resistance or inclination at the pathway of the treadmill, followed by active stage of the exercise for twenty minutes of walking with 15° inclination at the walkway of the treadmill at 65-70% of Vo_{2max} and ended by five minutes of cool down as the same as warm up. On the other day, each woman was asked to brisk walk for 30 minutes daily.

III-Statistical analysis

Changes in the measured variables (fasting blood glucose, leptin, IL-6 and CRP) between before and after 3 months of exercise training were evaluated by paired t test. Also, the relation between percentage of body fat and serum fasting blood glucose, leptin, CRP and IL-6 was evaluated by Pearson's correlation test.

RESULTS

All women participated in this study were obese as their mean body weight, BMI and percentage of body fat was 91.17±4.92 kg, 33.03±1.32 kg/m^2 and 39.87±3.31% respectively. As an effect of the aerobic exercise training, the women mean body weight, BMI and percentage of body fat were reduced by 2.95 kg, 1.06 kg/m^2 and 1.61% respectively, but these reductions were statistically non significant (P> 0.05) after 3 months of aerobic exercise training, (table 1).

Table (1): Physical characteristics of women before and after 3 months of aerobic exercise training.

Variables	Before training	After 3 months of exercise training	% of change	Level of significance
Weight (kg)	91.17±4.92	88.22±5.21	↓3.24	P<0.92
BMI (kg/m^2)	33.03±1.32	31.97±1.40	↓3.21	P<0.76
% of body fat	39.87±3.31%	38.26±3.22%	↓4.04	P<0.09

As mentioned in table (2) and figure (1), before starting the study the mean values of fasting blood glucose was 148.71 ± 24.4mg/dl and reduced to 116.92 ± 16.87mg/dl after 3 months of aerobic exercise training which was statistically significant decreased (P<0.05).

The mean values of serum leptin, CRP and IL-6 were 49.25 ± 7.30 ng/ml, 7.51 ± 4.20 mg/L and 2.50 ± 1.50 pg/ml respectively while after 3months of exercise training they were 38.41 ± 5.66ng/ml, 6.24 ± 3.50 mg/L and 2.05 ± 1.57 pg/ml respectively and the mean reductions with respect to the pre training values were 22%, 17% and 18% respectively and these reductions were statistically non significant (P>0.05) except leptin which showed a significant reduction (P<0.05).

Table (2): Mean values of serum fasting blood glucose, leptin, CRP and IL-6 before and after 3 months of aerobic exercise training.

Variables	Before training	After 3 months of exercise training	% of change	Level of significance
Fasting blood glucose (mg/dl)	148.71±24.4	116.92±16.87	↓21	P<0.05
Leptin (ng/ml)	49.25±7.30	38.41±5.66	↓22	P<0.05
CRP (mg/L)	7.51±4.20	6.24±3.50	↓17	P<0.08
IL-6 (pg/ml)	2.50±1.50	2,05±1.57	↓18	P<0.09

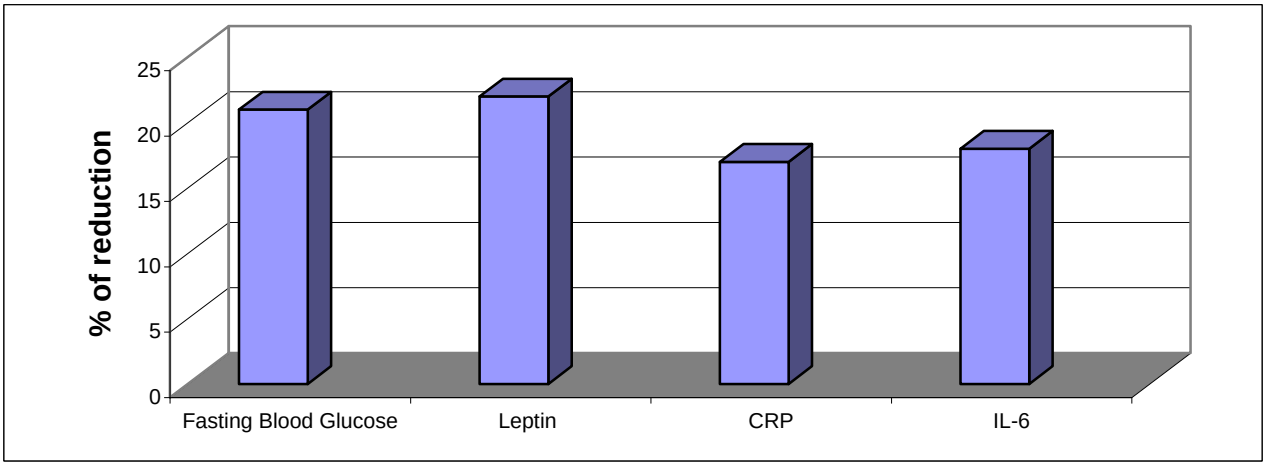

Fig. (1): Percentage of reduction of serum fasting blood glucose, leptin, CRP and IL-6 after 3 months of exercise training with respect to the pre training values.

There was a positive correlation between percentage of body fat and serum fasting blood glucose (r =0.36, P<0.04 & r =0.42, P<0.02), Leptin (r=0.49. P<0.01 & r= 0.37, P<0.04), CRP (r=0.39, P<0.03 & r=0.38, P<0.03) and IL-6 (r=0.38, P<0.03 & r=0.36, P<0.05) before

and after 3 months of exercise training program.

DISCUSSION

Exercise has become a vital part of women's life as it reduces the risk of occurrence of many diseases when it is performed on a regular basis[14]. The lack of evidence for harmful effects of exercise in diabetic post menopausal women indicates that exercise during this period is safe and prevent many diseases[8].

The results of the present study demonstrate that 12 weeks of moderate intensity aerobic exercise training significantly decrease serum leptin level in type 2 diabetic post menopausal women which supported by the study of Ishii et al., (2001)[11] who reported that serum leptin level decreased significantly in type 2 diabetic subjects after 6 weeks of aerobic exercise training without alterations in body fat mass. In contrast, neither 9 months of exercise (70% of maximum heart rate for 30 minutes to 80% of maximum heart rate for 50 minutes, minimum 3 times per week) in older post menopausal women[15] nor 20 weeks of endurance training (55% of Vo_{2max} for 30 minutes to 75% of Vo_{2max} for 50minutes, 3 times per week) in 97 sedentary adults[21] had no effects on leptin level, independent of its effects on adiposity.

In the present study, absence of significant fat loss after 3 months of exercise training could be explained by no modification of their diet intake as energy intake was not assessed.

A number of studies have shown that exercise training is associated with improvement in glucose tolerance and insulin sensitivity [2,3]. Results of the present study on fasting blood glucose suggested that it altered by exercise, which could perhaps explain the positive effects of regular exercise on leptin level.

A few factors have to be considered in the interpretation of the present results, exercise training might produce alterations in the production and/ or clearance of leptin that could be reflected by plasma measurement of leptin; furthermore, there is evidence that leptin circulates in either a free form (bioactive form) or in bounded to leptin binding proteins and that the ratio of these two forms varies in obese individuals and most of the circulating (60-98%) is in the bound form and that fasting had no effect on bound leptin[26]. Moreover, leptin levels also exhibit diurnal variation with a rise during overnight fast[27] and fall in the morning if fasting is prolonged[16]. In the present study blood samples were taken at the same time of the day before and after training and diurnal variation could not responsible for the positive differences observed in the leptin in response to exercise training.

In the present study, the reduction in CRP concentrations after exercise come in agreement with earlier work conducted in obese individuals [5,18,19]. Exercise alone also resulted in similar reductions which induced by diet and diet + exercise that come inconsistent with findings of previous study[18]. The present findings, however, contrast those of Youn et al.,[29] who noted that diet alone did not decrease chronic inflammation in obese post menopausal women and that diet and exercise was required. Nevertheless, present findings indicate that individuals with type 2 diabetes with very high CRP level respond favorably to the typically prescribed exercise, however in 3 months of exercise training period, this change are small and the high CRP level still leave these women at high risk of cardiovascular disease.

Slight but not significant reduction in IL-6 level was observed with exercise, similar to

findings from other studies [5,12]. The reduction in IL-6 appeared to be related to the initial IL-6 level of these women, as those women with the highest baseline IL-6 had the most change. Other researchers have speculated that reductions in total body fat mass, particularly subcutaneous fat tissue may play role in decreases in IL-6 level [7,19].

Exercise alone in weight loss produced marginal reduction in IL-6 level in diabetic women. To date, no study has reported the chronic effects of exercise alone, without dietary control on IL-6 level in healthy or diseased individuals. However, previous studies in healthy, athletic individuals have reported increased local inflammation with intense exercise, possibly attributed to microdamage of the active muscle tissue[17]. In contrast, Febbraio and Pedersen[6] have shown a marked increase in IL-6 with exercise that originates primarily from the contracting muscles.

This study demonstrated the difficulty in alternating the cytokines in obese post menopausal women with type 2 diabetes which may be attributed to the different metabolic status of these populations. As part of type 2 diabetes, there are metabolic disturbances at the level of the adipose tissue, the skeletal muscle as well as the pancreatic beta cell. Potentially, the more disturbed hormonal and metabolic milieu of the type 2 diabetic individuals may result in more resistance of the adipose tissue to weight loss and hence alter the response in cytokine levels. So, larger weight loss, a longer experimental period or greater improvement in IR needs to occur before changes in the cytokines.

Furthermore, our women with type 2 diabetes may have microvascular damage that can not alter in a short period of exercise training alone (3months).

Conclusion

In conclusion, aerobic exercise training resulted in a significant decrease in fasting blood glucose and leptin as well as a small decrease in weight, % of body fat, CRP and IL-6 in post menopausal obese diabetic women which may help to improve the metabolic status of these individuals. These findings imply the need for further studies to assess the effects of different modes and intensities as well as diet programs in such cases.

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الملخص العربي

تأثير التمرينات الهوائية على مستوى اللبتين ودلالات الالتهابات (سيتوكيناز) لدى السيدات البدينات المصابات بالبوال السكرى بعد انقطاع الدورة الشهرية

هدف الدراسة: تهدف هذه الدراسة الى تقييم ت أثير برنامج التمرينات الهوائية على مستوى اللبتين و دلالات الالتهابات [(سيتوكيناز)(انترليوكين-6 وتفاعل البروتين-سى)] لدى السيدات البدينات المصابات بالبوال السكرى بعد انقطاع الدورة الشهرية . **خطوات الدراسة:** واشتركت فى هذه الدراسة 24 سيدة ممن تتراوح اعمارهن بين 51-60 سنة و معدل الوزن الى الطول اكثر من 32 كجم/م2 فى برنامج التمرينات الهوائية على جهاز الجرى لمدة 30 دقيقة 3مرات اسبوعيا لمدة 3 اشهر . **النتائج :** و قد اظهرت النتائج نقص غير فعال فى الوزن و معدل الوزن الى الطو ل والنسبة المئوية للدهون بالجسم و أيضا فى دلالات الالتهابات [(سيتوكيناز)(انترليوكين- 6 وتفاعل البروتين-سى)] ولكن مستوى اللبتين فقد أظهر نقصا فعالا بعد 3 أشهر من التمرينات . **الخلاصة :** وعليه يمكن استنتاج أن 3 اشهر من التمرينات تساعد بصورة فعالة فى تقليل الالتهابات لدى السيدات البدينات المصابات بالبوال السكرى بعد انقطاع الدورة الشهرية ولكن يجب إجراء دراسات اخرى لتقييم تاثير الانواع والشدات المختلفة من التمرينات على دلالات الالتهابات لدى هؤلاء السيدات .

الكلمات الدالة: التمرينات الهوائية- اللبتين- سيتوكيناز- السمنة- البوال السكرى- انقطاع الدورة الشهرية.