The effect of long-term aerobic exercise on serum adiponectin and insulin sensitivity in type 2 diabetic patients

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Abstract:
Introduction: Obesity and overweight is known to play a key role in spread of type II diabetes mellitus. This study aimed to compare baseline values of insulin sensitivity and serum adiponectin between healthy men and patients with type 2 diabetes and to determine the effect of weight loss due to long-term aerobic exercise on these variables in patients with type 2 diabetes.

Materials and Methods: In this study, 30 adult men with type II diabetes were randomly divided into experimental and control groups and anthropometric indices, fasting glucose, adiponectin, serum insulin and insulin sensitivity were measured before and after a three month period. Statistical t-test in SPSS software was used to compare the baseline values and also determine the effect of aerobic exercise on variables.

Results: In the baseline conditions, fasting glucose and serum insulin were lower and serum adiponectin and insulin sensitivity were higher in healthy subjects than diabetic patients. Serum adiponectin levels and insulin sensitivity increased significantly after aerobic exercise in the experimental group. Insulin levels remained unchanged and fasting glucose concentration and all anthropometrical indices decreased significantly in the experimental group. All variables remained unchanged in the control group.

Conclusion: Based on the findings, it can be concluded that aerobic exercise program will lead to increase in insulin sensitivity and serum adiponectin level in patients with type 2 diabetes.

Keywords: Diabetes Mellitus, Aerobic Exercise, Adiponectin, Weight Loss

Introduction
Cardiovascular diseases are a major cause of mortality throughout the world (1). Lipid disorders in metabolic syndrome and diabetes are predisposing factors to cardiovascular diseases. Inflammation is one of the main factors for the metabolic syndrome and type II diabetes because of impaired concentration of pre-inflammatory and anti-inflammatory cytokines of the blood circulation (2). Recently, the role of hormones secreted by adipose tissue as skeletal muscle metabolism regulators and development of insulin resistance and ultimately type II diabetes have attracted many researchers’
attention. Adiponectin is an anti-inflammatory cytokine with a molecular weight 30 kDa that is secreted mainly by adipose tissue and unlike other adipokines its concentration is decreased in obesity (4-3). At the present, adiponectin is known as one of the most important adipokines to better understand the relationship between obesity and metabolic diseases such as diabetes type II (6-5). Research studies have revealed that this peptide hormone has anti-diabetic (7), anti-inflammatory and anti-atherogenic properties (8). The findings of epidemiological studies show that plasma adiponectin decreases in cardiac patients (9), obese people (4) and people with diabetes type II (10). Adiponectin concentration is negatively correlated with insulin resistance and blood glucose concentration (11).

However, some conflicting findings have been observed regarding adiponectin properties and its relationship with other metabolic and hormonal factors. Some studies have shown that adiponectin is secreted mainly by adipose tissue and the size of abdominal obesity and body mass index are inversely correlated with plasma adiponectin levels (12). Furthermore, a recent study showed no correlation between adiponectin baseline values and amounts of visceral adipose tissue and other fat factors in obese women (13). Increases in adiponectin levels and insulin sensitivity usually have been observed after body fat reduction through an appropriate diet (13). Systemic adiponectin levels are increased by inflammation reduction mediators related to obesity (14). Adiponectin increases in response to diet-induced weight loss; however, some studies suggested that an appropriate weight loss to change adiponectin levels should be more than 10% of initial weight (15-16).

The effect of exercise on adiponectin levels has not yet been fully addressed because different studies in this regard have not obtained compatible results (17). Moderate intensity exercise improves blood adiponectin concentration (17). In people with diabetes and insulin resistance, exercise has been suggested as a non-pharmacological treatment to increase serum adiponectin and improve of insulin sensitivity (18). Also, after eight weeks of swimming in diabetic rats, a significant increase was observed in serum adiponectin levels and its mRNA gene expression in visceral adipose tissue. However, in another study, the improved sensitivity and resistance to insulin due to weight loss was not attributed to adiponectin, but to other cytokines secreted by adipose tissue (19-20). Also, some studies suggested that insulin sensitivity improved through exercise and independent of adiponectin changes (17). Also in a recent study, no change was observed in adiponectin levels despite the increase in insulin function following a long-term endurance exercise program (21). Despite the report of increase in blood adiponectin levels after exercise, especially long-term activities in some studies, some findings indicate no change in peptide hormone levels even due to weight loss or improved body composition. Yet a final point of view in this regard has not been provided. The current study in addition to comparing the baseline values of this peptide hormone and other determining factors for type II diabetes such as blood glucose level between diabetic patients and healthy subjects, also aimed to assess the effect of a long-term aerobic exercise program on serum levels of this hormone and other variables.

**Materials and Methods**

The present quasi-experimental study was performed on a group of obese adult men with type 2 diabetes in Islamshahr aged 38 to 50 years. Participants were randomly assigned to two experimental and control groups each with 15 people. The control group consisted of non-diabetic obese men with similar age and physical conditions of...
diabetic patients. The diabetic patients were non-smokers and non-athletes and in a 6-month period prior to the study had not participated in any regular exercise program. Those who had a history of cardiovascular, renal, and gastrointestinal diseases, cancer, different types of respiratory diseases, as well as having mobility problems or orthopedic abnormalities were excluded from the study. To measure patients’ aerobic fitness level, the standard ergometry test YMCA was used on a laboratory bicycle ergometer (22). The initial level of aerobic fitness in patients was estimated 27±7.13 ml per minute per kilogram of body weight. Also, a group of 15 healthy non-diabetic obese people with physical and anthropometric characteristics (weight, body fat percentage, body mass index) and with the same age range of diabetic patients participated in the study just in order to compare baseline values of their biochemical indices with those of diabetic patients. In fact, non-diabetic obese group participated in this study just because baseline values of their mentioned variables are compared with those of diabetic patients. All patients completed the written consent form of participation in the study. Obesity criterion for participation in the study was considered having a body mass index greater than 29 (23). Data related to patients’ height, age and anthropometric indices were measured and recorded at university physiology laboratory. Participant’s weight was measured in light clothing by a digital scale (Taiwan, precision 100 g) and their standing height without shoes was measured by a stadiometer. Body mass index (BMI) was calculated using body weight (kg) divided by height squared (in meters). By using a non-elastic fabric tape measure, the size of the largest part of waist and hip circumferences were measured. The body fat percentage was calculated by body composition measuring device (Omron, Finland). After measuring anthropometric indices and other primary specifications, all patients and healthy subjects attended the laboratory for blood sampling after 10 to 12 hours of fasting between 8 am to 9 am and after recording the resting heart rate in the sitting position 8 ml of blood was taken from their brachial vein to measure biochemical indices of serum adiponectin, insulin and fasting glucose. All patients and healthy subjects were advised to avoid using drugs that affect the metabolism of carbohydrates and fats for at least 24 hours before blood sampling and also to refrain from participating in any physical activity for 48 hours before blood sampling. In addition, those patients who according to doctor’s recommendation could not stop taking blood-glucose lowering medication 12 hours before blood sampling were excluded.

Blood sampling was studied in healthy group only in order to compare their baseline values of serum adiponectin and insulin sensitivity with those of diabetic patients. After sampling, diabetic patients in the experimental group participated in a three-month aerobic exercise program three times per week with exercise intensity from 50 to 70 heart rate reserve. The exercise intensity was low in the first sessions and the intensity and volume of the exercise gradually increased during the next sessions. Each session began with a warm-up, and continued with aerobic activities in the form of running on a flat surface and group aerobic exercises and finally ended in cooling down. The control group did not participate in any special exercise program over the course of three-month period. Finally, 48 hours after the last exercise session, anthropometric indices and blood sampling were measured in diabetic patients of experimental and control groups to evaluate the effect of exercise program on the mentioned biochemical indices.

Insulin sensitivity was measured by the levels of insulin and fasting glucose. In fact, insulin sensitivity is an estimation of insulin's ability to lower blood glucose,
which is related to the inhibition of glucose release from the liver and stimulated blood glucose uptake by body cells. It is calculated by entering the amount of insulin and fasting glucose in the related formula (24).

Insulin sensitivity = 1/ \log(fasting insulin) + \log(fasting glucose)

Fasting glucose was measured by glucose oxidase method (Pars Azmoon, Iran) with glucose intra- and inter-group coefficients 1.74% and 1.19%, respectively, and measurement sensitivity of 5 milligrams per deciliter. In order to separate the serum, blood samples were centrifuged for 10 minutes at a speed 2000 rpm. Then obtained serum was kept at – 80°C until the adiponectin and insulin variables were measured by ELISA method. Serum adiponectin level was measured by a kit made by Biovendor Company in Czech through ELISA method with intra- and inter-group coefficients 5.9% and 6.3%, respectively, and sensitivity 0.47µg/ml. Serum insulin was measured by laboratory kit Demeditec (Germany) through ELISA method with intra- and inter-group coefficients of 2.6% and 2.88% and sensitivity of 76.1 µIU/ml.

Statistical analysis: Student t-test was used in SPSS software version 15 to compare the variables in both groups at baseline and also to determine the effects of exercise program on each variable. Also, Pearson correlation test was used to determine the relationship between changes in adiponectin and changes in other variables through the exercise program. The \( P \)-value<0.05 was considered significant.

Results
In the present study, the levels of serum adiponectin, insulin, fasting glucose, and also insulin sensitivity in patients with type 2 diabetes were compared to healthy subjects and the effect of three-month aerobic exercise on these variables and anthropometric indices of diabetic patients were examined. The levels related to anthropometric, physiological and biochemical indices in healthy subjects and diabetic patients before and after exercise are shown in Table 1. Based on data analysis, the results of independent t-test showed that adiponectin levels were significantly lower in diabetic patients than in healthy subjects. Also, diabetic patients had higher fasting glucose concentration \((p = 0.002)\) and lower insulin sensitivity than healthy subjects \((P = 0.011)\). The levels of biochemical variables and anthropometric indices were similar in both diabetic control and experimental groups \((P<0.05)\). However, the statistical results of paired t-test showed a significant increase in serum adiponectin levels in diabetic patients of the experimental group through a three-month exercise program \((P=0.034)\). Serum insulin concentration was not changed by aerobic exercise \((P=0.340)\). All anthropometric indices such as body mass index \((P=0.006)\), body fat percentage \((P=0.003)\) and abdominal circumference \((P=0.013)\) decreased significantly following a three-month exercise program. Fasting glucose concentration also decreased in the experimental group \((P=0.000)\). Insulin sensitivity in diabetic patients significantly increased following the aerobic exercise \((P=0.023)\). No significant change was observed in biochemical variables and anthropometric indices in control group \((P<0.05)\).

Discussion
Lifestyle changes such as weight loss and regular exercise are known as non-pharmacological interventions with beneficial effects on metabolic and cardiovascular risk factors (25). Adipose tissue secretes biologically active cytokines called adipokines in addition to its role as fat reserves and thermal insulation. Impairment in their levels is associated with obesity and its related diseases such as metabolic syndrome, cardiovascular diseases and type II
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diabetes (26). Statistical findings of the current study showed that adiponectin levels in patients with type II diabetes were much lower than those in healthy subjects. Also these patients had lower insulin sensitivity and higher fasting glucose levels than healthy group. Reduced adiponectin levels and insulin sensitivity as well as hypoglycemia in diabetic patients have also been reported in most other studies (27-28). In this regard, research has revealed that adiponectin directly or indirectly promotes insulin sensitivity (28) and inhibits inflammatory mediators such as C-reactive protein (CRP), interleukin-6 and tumor necrosis factor-alpha (29).

### Table 1 Mean and standard deviation of anthropometric, physiological, and biochemical indices in healthy subjects and also diabetic patients before and after exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>P value</th>
<th>Diabetic control group pre-test</th>
<th>Post-test</th>
<th>P value</th>
<th>Diabetic experimental group pre-test</th>
<th>Post-test</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (kg)</td>
<td>Healthy Group</td>
<td>0.123</td>
<td>90.44±6.23</td>
<td>91.24±6.12</td>
<td>0.345</td>
<td>91.58±7.26</td>
<td>86.12±8.23</td>
<td>0.009</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Healthy Group</td>
<td>0.651</td>
<td>172±7</td>
<td>173±6</td>
<td>---</td>
<td>173±6</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Healthy Group</td>
<td>0.711</td>
<td>43±8</td>
<td>45±7</td>
<td>---</td>
<td>44±7</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>Healthy Group</td>
<td>0.214</td>
<td>103±6.23</td>
<td>104±7.43</td>
<td>0.652</td>
<td>99±7.16</td>
<td>0.013</td>
<td>---------</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>Healthy Group</td>
<td>0.232</td>
<td>31±1.21</td>
<td>31±1.2</td>
<td>0.432</td>
<td>28±3.1</td>
<td>0.006</td>
<td>---------</td>
</tr>
<tr>
<td>Body fat percentage (%)</td>
<td>Healthy Group</td>
<td>0.323</td>
<td>27.34±5.51</td>
<td>27.65±5.32</td>
<td>0.266</td>
<td>24.13±4.32</td>
<td>0.003</td>
<td>---------</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>Healthy Group</td>
<td>0.002</td>
<td>219±42</td>
<td>221±56</td>
<td>0.512</td>
<td>188±45</td>
<td>0.000</td>
<td>---------</td>
</tr>
<tr>
<td>Insulin sensitivity</td>
<td>Healthy Group</td>
<td>0.011</td>
<td>0.49±0.009</td>
<td>0.50±0.10</td>
<td>0.652</td>
<td>0.56±0.09</td>
<td>0.023</td>
<td>---------</td>
</tr>
<tr>
<td>Insulin (µIU/ml)</td>
<td>Healthy Group</td>
<td>0.033</td>
<td>7.73±1.12</td>
<td>8.06±1.43</td>
<td>0.459</td>
<td>8.43±1.76</td>
<td>0.340</td>
<td>---------</td>
</tr>
<tr>
<td>Adiponectin (ng/ml)</td>
<td>Healthy Group</td>
<td>0.029</td>
<td>6.23±1.11</td>
<td>6.35±1.23</td>
<td>0.865</td>
<td>6.98±1.98</td>
<td>0.034</td>
<td>---------</td>
</tr>
</tbody>
</table>

†Statistical difference compared to pre-test values of dependent variables in experimental group of diabetic patients (P<0.05).

Increased systemic adiponectin levels enhance glucose uptake into skeletal muscle and fat oxidation (30). The similarity of adiponectin to insulin has shown that this peptide hormone is effective in hyperglycemia improvement and metabolic abnormalities related to obesity and type II diabetes (30). Similar to insulin, the effect of exercise on adiponectin also leads to acceleration of or increase in blood glucose uptake and increased fat oxidation (31).

It has been revealed that increased visceral fat tissue is a more appropriate predictor than other anthropometric indices for identifying insulin resistance, type II diabetes and cardiovascular diseases (27). The findings of the current study showed that adiponectin levels inversely correlated with visceral fat levels in diabetic patients. In other words, increased visceral fat was associated with reduced systemic adiponectin. The major finding of the current study was increase in serum adiponectin levels through a three-month exercise in diabetic patients in the experimental group. Aerobic exercise program led to 34% increase in serum adiponectin levels in diabetic patients, while the sedentary diabetic group did not experience any change in adiponectin. In confirming these findings, a significant increase has been reported in a study in insulin sensitivity and plasma adiponectin levels in 62 people with type II diabetes after 16 weeks of exercise (32). Also in
another study 4 weeks of exercise led to a significant increase in plasma adiponectin in diabetic people (33). An increase in adiponectin level and insulin sensitivity through aerobic exercise has been also reported in other studies (34).

In the present study, the increase in adiponectin levels was associated with significantly reduced fasting glucose. However, in some studies, a significant reduction in fasting glucose has been reported after a long-term aerobic exercise despite no significant change in serum adiponectin levels (35-36). Most scientific references have noted that adiponectin increases glucose metabolism particularly in skeletal muscles and improves insulin sensitivity (33,36). Furthermore, adiponectin reduces blood glucose concentration and improves glycemic control and insulin sensitivity through reduction of hepatic glucose production by direct inhibition of hepatic gluconeogenesis enzymes i.e. phosphoenolpyruvate carboxy kinase and glucose 6-phosphate (37). This anti-inflammatory cytokine reduces fatty acids oxidation in skeletal muscles and unsaturated fatty acid delivery to the liver that reduces hepatic triglyceride synthesis and secretion of VLDL (38). Another finding of the current study is the increase in insulin sensitivity through exercise. Researchers have attributed the increase in insulin sensitivity to the increase in blood adiponectin levels (7). Available evidence suggests that the relationship between aerobic exercise and increase in insulin sensitivity due to adiponectin is most likely dependent on expression levels of adiponectin receptors in skeletal muscles (30). Researchers have attributed one of the mechanisms of increase in insulin through exercise to increased capillary density between muscle fibers and improvement in insulin intracellular signals (39).

Multiple confounding factors such as diet, duration and intensity of exercise and changes in body fat percentage are effective in systemic adiponectin levels through exercise. In this regard, several studies have reported increased expression levels of adiponectin receptors in human skeletal muscles and animal models. These studies have reported deferent increases in expression levels of adiponectin and its receptors through exercise depending on the intensity and duration of the exercise (41-40). In this regard, Zhang et al. suggest that changes in adiponectin levels are dependent on the intensity and duration of exercise (42). Some other studies also suggest that reduction in adiponectin only occurs when the diet or exercise is associated with weight loss or fat mass loss (43). In the present study, reduction in serum adiponectin was associated with body weight loss, fat mass loss as well as body mass index reduction. Despite the mentioned findings, a study showed that 4 weeks of aerobic exercise led to 97% increase in adiponectin in obese people and 86% increase in people with type II diabetes without a significant decrease in body weight (40). In another study, following a 10-week aerobic exercise program, two-fold increase in adiponectin was observed without weight loss (44). Some researchers have noted that the lack of increase in blood adiponectin through exercise could possibly be due to simultaneous increase in other cytokines and hormones that are effective in reducing adiponectin levels (45-46).

**Conclusion**

In general, it can be said that adiponectin levels and insulin sensitivity with hyperglycemia are less in diabetic patients than healthy subjects. Exercise is an effective non-pharmacological treatment to increase adiponectin level and decrease hyperglycemia in patients with type 2 diabetes. Although the basic mechanisms involved in changes in adiponectin levels through exercise have not yet been fully understood, negative energy balance appears to be more effective in adiponectin increase. However, according to findings...
of other studies, it seems that changes in other confounding factors such as other cytokines and plasma volume changes in adiponectin response to exercise may be effective, which requires more studies.

Acknowledgment
Hereby, all healthy subjects and diabetic patients participating in this study as well as Islamshahr Diabetes Society who sincerely collaborated during the study are sincerely appreciated.

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