The effect of regular moderate exercise, on cardiac hypertrophy and blood glucose level in diabetic adult male rats

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ABSTRACT: Diabetes mellitus comprises a group of common metabolic disorders that hyperglycaemia is the common phenotype of its. Although, insulin and other glucose-lowering drugs are the most common method for treating diabetes, but also beneficial effects of exercise in regulating glucose metabolism, have been proved. Considering the effective role of exercise in diabetic patients, in this study the impact of different periods of regular moderate exercise on cardiac hypertrophy and blood glucose level were examined, to presenting a suitable pattern of exercise for diabetic patients. 60 male Wistar rats (300±50g) were randomly divided into six groups (n=10): sedentary control, control with fifteen day exercise, control with sixty day exercise, sedentary diabetic, diabetic with fifteen day exercise and diabetic with sixty day exercise. Diabetes was induced by injection of streptozotocin (60 mg/Kg). The treadmill exercise 5 days a week for an hour with 22 (m/min) speeds were begun, a week after induction of diabetes. The results of this study showed that the mean blood glucose level is significantly decreased (P<0/05) by increasing the day of exercising. And also, regular moderate exercise has prevented cardiac hypertrophy that was observed in the sedentary diabetic group. The fifteen day regular moderate exercise was not significantly reduced the blood glucose and by continuing it, blood glucose was closer to normal. Also, this type of exercise, was prevented from hypertrophy of the heart that caused by diabetes.  

Key words: Regular moderate exercise, Diabetes, Blood glucose, Hypertrophy.

Introduction

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production. Two main categories of diabetes mellitus named as type 1 and 2 (Longo, et al. 1991). Recent studies reported the number of diabetic people will increase in 2030 (Shaw, et al. 2010). Insulin administration and blood glucose decreasing drugs are the most common method for treating diabetes, but the beneficial effects of exercise on glucose metabolism proved (Bidasee, et al. 2008). Generally, regular moderate exercise has contributed in preventing of diabetes complications (Zinnman, et al. 2003). Exercise; by decreasing the blood glucose level and increasing the insulin sensitivity of cells, exerts its effect. Exercise by increasing the glucose transporter 4 (GLUT4), insulin receptor substrate (IRS) and muscle mass, improve the body's response to insulin (Praet, et al. 2006). There are limited studies on the effects of physical activity, and influence of different intensity of treadmill exercise in type I diabetes, also there is inconsistency among these studies. Considering previous studies the effect of regular moderate exercise on cardiac hypertrophy and blood glucose level were examined.
MATERIALS AND METHODS

Animals
Adult male Wistar rats (300±50 g) were obtained from the Animal House of the University of Tabriz. The rats maintained in a 12-h light/dark cycles at 22 ± 2 °C and were allowed to free access to standard laboratory chow and water. Additionally, care was taken to use the minimum number of animals possible in each experiment.

Experimental designs
Animals were randomly divided into six groups (10 each): 1- Sedentary Control group (SC), 2- Sedentary Diabetic group (SD), 3- Healthy Control with 15-day Exercise group (H15E), 4- Healthy control with 60-day Exercise group (H60E), 5- Diabetes with 15-day Exercise group (D15E), 6- Diabetes with 60-day Exercise group (D60E). Diabetic animals were housed triad in cages.

Experimental protocols
Diabetes type I in rats was induced by intraperitoneal injection of 60 mg/kg Streptozotocin (STZ) (Sigma, St Louis, MO) (Ozkaya, et al. 2007). STZ was dissolved in citrate buffer (1:1 mixture of 0.1 M citric acid and 0.2 M Na₂HPO₄) just before injection. Rats in the control groups received an intraperitoneal injection of an equal volume of citrate buffer instead of STZ. Forty-eight h after STZ injection, blood samples were obtained from the tail vein and blood glucose concentrations were measured with a Surestep glucometer. Successful induction of diabetes was defined as a blood glucose level of 250mg/dl (Ozkan, et al. 2005). Also polyuria and polydipsia were observed in diabetic rats.

Exercise protocols
Before beginning the formal 15 and 60 day exercise protocol, animals were habituated to treadmill running (5–20 min/day) for 5 consecutive days. After this period of habituation, the exercised animals performed 5 days of consecutive treadmill exercise (60 min/day) with 22 m/min speeds (Taylor, et al. 2003). At the beginning of 60 minute exercise, to warm up the rats, treadmill speed had been set at 5 m/min and progressively increased to 22 m/min. At the end of 60 minute exercise, the speed progressively decreased to 5 m/min to cool down. Mild electrical shock was used sparingly to motivate animals to run. Control animals did not perform treadmill exercise but were placed on a non-moving treadmill for 60 min/day for 5 days a week. Exercised animals were studied 24 h after their last exercise session.

Measurement of blood glucose level
The blood glucose concentrations of diabetic rats were measured in blood collected from the tail vein in the morning, at the first, middle and end of each experimental period. The body weight of all rats was measured.

Sample collection
After the experimental periods, all of the rats (control and diabetic groups) were anesthetized by intraperitoneal injection of 100mg/kg ketamine and 5 mg/kg xylazine (Atalay, et al. 2004). Hearts of rats were immediately removed and washed with cold 9% normal saline, left ventricles excised from hearts, and heart and left ventricular weights were measured.

Data Analysis and statistics
Data were analyzed by using one- way analysis of variance. The post hoc tukey were performed to determine which condition differed significantly from each other.

RESULT

GLUCOSE RESULTS

At the end, the means of fasting blood glucose level in the sedentary control group in comparison with sedentary diabetic group showed a significant difference (p<0.05) (table 1). It should be noted that the means of fasting blood glucose level in sedentary diabetic rats during the examination period, showed a significant increase (Figure 1).

At the beginning of exercise period there is no difference in fasting blood glucose level among the sedentary control group, healthy control with 15-day exercise group and healthy control with 60-day exercise group (table1).
The means of fasting blood glucose level in diabetes with 60-day exercise group indicates a significant difference on days 30 and 60 of the 60-day exercise protocol. Also the means of final blood glucose level showed a significant decrease in comparison with initial blood glucose level in diabetes with 60-day exercise group (P<0.05) (Figure 1).

There is no significant difference in the means of fasting blood glucose level in diabetes with 15-day exercise on days 7 and 15 (P<0.05). The means of blood glucose at days 7 and 15 after 15 day exercise did not significantly reduce.

At the end of the experimental period, there is a significant difference in the means of fasting blood glucose level between diabetes with 60-day exercise and diabetes with 15-day exercise groups (P<0.05) (Table 1).

60-day exercise decline the means of fasting blood glucose level in diabetes with 60-day exercise group in comparison with a sedentary diabetic group (P<0.05) (Table 1).

Table 1. General characteristics of STZ-induced diabetic and healthy rats. Sedentary Control group (SC), Sedentary Diabetic group (SD), Healthy Control with 15-day Exercise group (H15E), Healthy Control with 60-day Exercise group (H60E), Diabetes with 15-day Exercise group (D15E), and Diabetes with 60-day Exercise group (D60E). Data are means±S. E. M. Data statistically compared with Tukey (P<0.05).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SC</th>
<th>SD</th>
<th>H15E</th>
<th>D15E</th>
<th>H60E</th>
<th>D60E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial Blood Glucose</td>
<td>85.3±4.3</td>
<td>378.8±39.1</td>
<td>89.0±4.4</td>
<td>390.3±41.1</td>
<td>91.3±5.2</td>
<td>324.8±17.7</td>
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<tr>
<td>(mg/dl)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final Blood Glucose</td>
<td>88.3±5.2</td>
<td>455.5±33.8</td>
<td>88.5±3.8</td>
<td>317.3±26.9</td>
<td>81.5±3.4</td>
<td>175.8±34.8</td>
</tr>
<tr>
<td>(mg/dl)</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Final Body Weight</td>
<td>280.1±8.1</td>
<td>183.0±10.9</td>
<td>279.8±8.6</td>
<td>261.8±14.0</td>
<td>259.1±9.7</td>
<td>288.8±23.5</td>
</tr>
<tr>
<td>(g)</td>
<td></td>
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</table>

Figure 1. Blood glucose level: Sedentary Control group (SC), Sedentary Diabetic group (SD), Diabetes with 15-day Exercise group (D15E), and Diabetes with 60-day Exercise group (D60E).

* Significantly different from initial Blood Glucose (P<0.05).

**Hypertrophy index**

At the end of the study period, the means of heart weight between the sedentary control and sedentary diabetic groups showed a significant difference (P<0.05) (Table 2).

There is a significant difference in the means of heart weight among the sedentary diabetic, diabetes with 60-day exercise and diabetes with 15-day exercise groups, but no significant difference was shown in diabetic exercise groups.
The means of heart weight between the healthy control with 15-day exercise and sedentary control is not significant, but it is significant with healthy control with 60-day exercise, also there is no significant difference between healthy exercise groups (Table 2).

The means of left ventricular weight in the experimental groups are not significantly different between the sedentary control group, sedentary diabetic group and healthy control with 15-day exercise group, diabetes with 15-day exercise group and diabetes with 60-day exercise group. But the means of left ventricular weight among the healthy control with 60-day exercise group is significant with other five groups (p<0.05) (Figure 2).

A significant differences were observed in the means of heart weight to body weight ratio among sedentary diabetic group in comparison with other groups (P<0.05) (Table 2).

There is no significant difference in the means of left ventricular weight to body weight ratio among experimental groups (Table 2).

**Table 2. Cardiac hypertrophy index.** Sedentary Control group (SC), Sedentary Diabetic group (SD), Healthy Control with 15-day Exercise group(H15E), Healthy Control with 60-day Exercise group (H60E), Diabetes with 15-day Exercise group (D15E), and Diabetes with 60-day Exercise group (D60E). Data are means±S.E.M. Data statistically compared with Tukey (P<0.05).

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<th>D15E</th>
<th>H60E</th>
<th>D60E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart weight (g)</td>
<td>1.032±0.02</td>
<td>0.821±0.04</td>
<td>1.065±0.04</td>
<td>1.028±0.07</td>
<td>1.794±0.04</td>
<td>1.037±0.3</td>
</tr>
<tr>
<td>Left ventricular weight (g)</td>
<td>0.184±0.01</td>
<td>0.162±0.01</td>
<td>0.194±0.02</td>
<td>0.181±0.01</td>
<td>0.261±0.02</td>
<td>0.203±0.02</td>
</tr>
<tr>
<td>Heart weight to body weight ratio (mg/g)</td>
<td>3.62±0.03</td>
<td>4.27±0.09</td>
<td>3.79±0.19</td>
<td>3.87±0.14</td>
<td>3.81±0.15</td>
<td>3.87±0.12</td>
</tr>
<tr>
<td>Left ventricular weight to body weight ratio (mg/g)</td>
<td>0.688±0.03</td>
<td>0.793±0.03</td>
<td>0.730±0.04</td>
<td>0.750±0.07</td>
<td>0.830±0.03</td>
<td>0.745±0.05</td>
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**CONCLUSION**

The blood glucose level was increased in rats that received STZ (Table 1). These findings are in line with other studies (Atalay, et al. 2004, DeBlieux, et al. 1993). STZ enters to beta cells and by induction of necrosis in the pancreatic beta cells depleted insulin level and increased blood glucose level (Schnedl, et al. 1994).

The results of the present study showed that 15-day regular moderate exercise training not only decreases the blood glucose level in the diabetic running group but also by continuing the exercise blood glucose level be closer to normal level (Table 1). These results are consistent with findings of 60-day voluntary exercise treatment (Howarth, et al. 2007), also Salem et al. (2007) was shown that exercise improved glycemic control in diabetic patients, but it is in contrast with some other studies (Howarth, et al. 2010). The reason for this difference could be due to the type, intensity and duration of exercise. So that glucose uptake in sport muscles is more than the maximum amount of insulin stimulation uptake (Praet, et al. 2006). Furthermore, exercise plays an important role in reducing blood glucose level by increasing the sensitivity of GLUT4 in muscle and also insulin receptor substrate (Dengel, et al. 2004).

In the present study it was shown that regular moderate exercise has a role in long-term blood glucose regulation, as the means of blood glucose level was significantly decreased by increasing the days of exercise. These results are inconsistent with the findings of other investigators (Naatalli, et al. 2002). The reason for this discrepancy may be due to the type and intensity of exercise, because studies have shown that heavy and long-term exercise by increasing hepatic glucose output can cause the blood glucose rises (Praet, et al. 2006).

In the present study, a significant reduction in heart weight between the sedentary diabetic and sedentary control groups can be seen, that these results are consistent with other relative researches (Howarth, et al. 2008. Kawaguchi, et al. 1997).

In this study heart weight to body weight ratio were considered as hypertrophy markers. The indices show in the sedentary diabetic rat heart get hypertrophy (Table 2). These results are also in line with the findings of other studies (Kawaguchi, et al. 1997). Microvascular damage seen in diabetic patients provides the necessary background for the damage to the myocardium, fibrosis and hypertrophy of the heart (Hileeto, et al. 2002). In addition, other factors involved in the development of cardiac hypertrophy are upregulation of vasoactive factors such as endothelin-1 (Lehmann, et al. 1997). In this study, regular moderate exercise prevents heart hypertrophy in diabetic exercise groups (Table 2). Cardiovascular risk factors such as high cholesterol and other lipids provide the context for microvascular disease in diabetic patients. Many studies have reported the exercise has an important role in reducing risk factors for heart disease such as cholesterol (Park, et al. 2000). Endothelin-1 is also increased in diabetic patients (Van Guild, et al. 2007). Upregulation of this gene in diabetic patients leads to hypertrophy of the heart. However, regular aerobic exercise in healthy
men reduces blood endothelin-1 level (De Angelis, et al. 2000). From all the above mentioned, we can conclude that probably, Exercise by reducing the level of cholesterol, other lipids and endothelin-1 prevents the occurrence of hypertrophy and heart failure in diabetic patients.

REFERENCES


