The 8-week aerobic exercise reduces the blood sugar HbA1c and cholesterol levels in women with type 2 diabetes: A Single Blind Randomized Controlled Clinical Trial

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Article Type: Original Article

Article History:
Received: 18 Jul 2020
Revised: 2 Aug 2020
Accepted: 6 Aug 2020

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Abstract
Background and objective: The effect of aerobic exercise (AE) on cardiovascular (CVD) related risk factors are still debatable. Therefore this randomized controlled clinical trial (RCT) was performed with unique and specific AE protocol to investigate the effect of eight-week AE only on female subjects with type 2 diabetes.

Material And Method: A controlled RCT was performed on 30 women with type 2 diabetes aged 30 - 50. They were randomly divided into two groups, intervention and control by block randomization method. The intervention group received an incremental AE for eight weeks, three sessions per week, max heart rate (55-75%) and rating of perceived exertion (RPE) 12-13 for 150 minutes per week. Blood samples were taken before and after each intervention for both groups to be evaluated for fasting blood sugar (FBS), lipid profile [triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C)] and hemoglobin A1c (HbA1c).

Result: Eight-week AE intervention led to a significant decrease in HbA1c level (p = 0.025) in experimental group compared to control however no significant differences was observed in terms of FBS and lipid profile (total cholesterol (TC), triglyceride (TG), LDL-C and HDL-C) between control and experimental group (p> 0.05). The results of paired t-test showed that FBS, TC and HbA1c levels were significantly reduced within experimental group after intervention compared to pre-test (p = 0.038, p = 0.05, p = 0.002, respectively). There was no significant difference between TG, LDL-C, and HDL-C levels within experimental group between pre and post-test (p>0.05).

Conclusion: It can be concluded that AE has been effectively reduce FBS, HbA1c and TC in women type 2 diabetes.

Keywords: Exercise, Glycated Hemoglobin A, lipid, Diabetes Mellitus Type 2
Introduction

Diabetes is a chronic metabolic disorder associated with insufficient insulin production and elevated blood sugar levels (hyperglycemia) as a result. Type 2 diabetes (T2D) is associated with many cardiovascular diseases (CVD) related risk factors such as obesity, hypertension, hyperlipidemia, lack of physical activity, elevated FBS, smoking and elevated glycosylated hemoglobin (hemoglobin A1c) (1-3). T2D causes 2-4 fold higher risk factor for CVD related death (4). Regular AE is considered as a treatment program for CVD and reduces CVD related complications (5). Regular physical activity (PA) also improves glucose and lipid metabolism by increasing insulin sensitivity. PA increases HDL-C and reduces TG and LDL-C levels. PA can increase the body's response to insulin and increases insulin sensitivity and found to be useful in preventing T2D, FBS management (6). Recent studies found that AE improves blood sugar by reducing HbA1c levels, increases insulin sensitivity, and plays an important role in controlling diabetes and preventing subsequent cardiac complications (7-10).

Aerobic exercise (AE) increases insulin receptor uptake and glucose transportation into muscle tissue (7). The American Diabetes Association (ADA) recommends 30-min moderate aerobic activity for 5 days of a week or 150 minutes per week (11). Previous studies show that AE is effective in term of controlling diabetes by activating AMPK pathway and increasing glucose uptake. AMPK activity increases glucose transport by increasing the serum GLUT4 level in insulin-resistant skeletal muscle and mediates the effects of GLUT4 expression.

So far many investigations have been performed on the effect of AE on T2D subjects and one meta-analysis reviewed 21 articles on this topic (12). According to this met-analysis the most common reason for exclusion of studies was lack of control group. Most of the studies prescribing AE three days per week, 50 and 85% Vo2 peak, 55 and 85% maximum heart rate, and the length of AE intervention ranged between 8 weeks to 1 year. Results on the effect of AE on diabetics are still heterogeneous, and more controlled randomized trials with different AE protocols on different populations are needed to reach more conclusive conclusions with less heterogeneity. Therefore the present controlled randomized clinical trial designed to investigate the effect of 8-week AE on FBS, A1c (HbA1c) and lipid profile [triglyceride (TG), total cholesterol (TC), low density lipoprotein cholesterol (LDL-C) and high density lipoprotein cholesterol (HDL-C)] in T2D female patients. The female population was actually selected because they were more accessible. To the best of our knowledge this study is unique in term of AE protocol (HR max (55-75%, three sessions AE per week for 8 weeks, each session 50 minutes with moderate-intensity AE) and study population (only female diabetic subjects were considered).

Materials and Methods

This was a randomized controlled clinical trial carried out on selected 30 women with type 2 diabetes (age = 30-50 years). Inclusion criteria included the presence of T2D based on the criterion of the world health organization (WHO). FBS (≥7 mmol / L, (126 mg / dL) and 1HbA1c values (≥11mmol/mol), having diabetes for more than three years, undergoing treatment only with oral drugs and no insulin administration, absence of
The 8-week aerobic exercise reduces the blood sugar…

Amini Najafabadi B. et al.

Statistical power 1-\(\beta\) = 0.80
Reliability = 0.95

A random block was used to determine the sample for each group and the blind method was one-way.

Experimental design

Prior to the study, the groups were compared matched for age, height, and weight and no significant difference were found between them. Subjects were then randomly divided into two groups: experimental group consisted of 15 diabetic women participating in moderate-intensity aerobic exercise and control group consisted of 15 diabetic women who did not engage in regular exercise.

Interventions

The control group did not do any AE. The exercise program in the intervention group included aerobic exercises, 3 sessions per week for 8 weeks. Moderate-intensity AE (walking), was performed at HR max (55-75%). HR max was estimated using Karvonen formula (Maximum Heart Rate: 220- your age) and heart rate of the subjects during exercise were controlled by taking the pulse from the carotid area. These exercises were performed with perceived exertion ratings between 12 to 13 for 150 minutes per week and 50 minutes per session. The warm-up program included 10 minutes of jogging, combined arm and leg movements, and stretching exercises. Aerobic exercises were performed for 35 minutes in the first two weeks and 5 minutes were added to the training time once every two weeks by observing the principle of progressive overload. Also, to return the body to its initial state, cooling movements were performed for 10 minutes. Exercises were performed in a gym at a temperature of 25 °C. The exercise protocol was implemented according to the research conducted by Horden et al. (2012) and Mendes et al. (2016) (Table 1)(13, 14).

Table 1: Exercise protocol

<table>
<thead>
<tr>
<th>Week</th>
<th>Period</th>
<th>Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>The first and second week</td>
<td>35</td>
<td>%55-60</td>
</tr>
<tr>
<td>Third and fourth week</td>
<td>40</td>
<td>%60-65</td>
</tr>
<tr>
<td>Fifth and sixth week</td>
<td>45</td>
<td>%65-70</td>
</tr>
<tr>
<td>Seventh and eighth week</td>
<td>50</td>
<td>%70-75</td>
</tr>
</tbody>
</table>

Anthropometrics

In this study, the height of people was measured by means of a SECA (US) portable stadiometer with a 0.1cm precision and weight variable was also measured based on kilograms by Beurer model scales while people had the least clothes and no shoes.

Blood analysis
The subjects were introduced to Nabi Akram Laboratory in Najafabad where they were asked to rest in a sitting position for 20 minutes. Blood samples were taken from the brachial vein (5ml) to measure glycemic index and lipid profile after 12 hours of overnight fasting in the pre-test and in the post-test (48 hours after the last exercise session). The centrifuged blood samples and collected serum were then stored for further analysis. Lipid profile levels were measured by an autoanalyzer (BA400) using a Biosystem kit and peroxidase method. FBS level was measured by a biosystem kit and an autoanalyzer (BA400) using glucose oxidase method. HbA1C level was also measured by Axzshzld kit and autoanalyzer (BA400) using immunoturbidimetry method.

**Statistical analysis**

Descriptive data were reported as mean ± standard deviation. Intergroup and intragroup changes were compared using Independent t-test and paired t-test, respectively. P ≤ 0.05 was considered as the significance level and data analysis was performed using SPSS ver. 22.

**Result**

Table 2 shows statistical data related to the demographic characteristics of the subjects and the mean of glycemic indexes and lipid profile at the baseline (pre-test) in the research groups. The results of independent t-test showed no significant difference between the two groups in terms of height, weight and age (p> 0.05) and the two groups are homogeneous in all of the above cases. The results of this test also showed no difference between the two groups in terms of the mean , BMI , HbA1c, FBS, TG, TC, LDL-C, HDL-C and levels at the beginning of the study and the two groups were homogeneous in terms of these indices (p>0.05).

**Table 2. Demographic information of research subjects**

<table>
<thead>
<tr>
<th>Variable</th>
<th>group</th>
<th>M± SD</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Control</td>
<td>51±7</td>
<td>0.186</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>50±3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Control</td>
<td>1.61±0.04</td>
<td>0.230</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>1.59±0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>Control</td>
<td>70.1±6.2</td>
<td>1.505</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI (pree-xam)</td>
<td>Experimental</td>
<td>69.5±6.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>27.10±2.33</td>
<td>-0.701</td>
<td>0.489</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>27.65±2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FBS (pree-xam)</td>
<td>Control</td>
<td>174.93±59.03</td>
<td>-0.575</td>
<td>0.57</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>186.60±51.85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (pree-xam)</td>
<td>Control</td>
<td>7.68±1.53</td>
<td>-0.213</td>
<td>0.83</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>7.82±1.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglyceride (pree-xam)</td>
<td>Control</td>
<td>152.53±61.05</td>
<td>0.375</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>128.13±65.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (pree-xam)</td>
<td>Control</td>
<td>152.53±61.05</td>
<td>0.723</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>163.87±34.33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L.D.L (pree-xam)</td>
<td>Control</td>
<td>101.60±21.71</td>
<td>0.979</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>88.40±31.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL (pree-xam)</td>
<td>Control</td>
<td>49±6.86</td>
<td>-</td>
<td>0.26</td>
</tr>
<tr>
<td></td>
<td>Experimental</td>
<td>47.47±4.57</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Mann-Whitney test was used to evaluate this index*
First, paired t-test was used to compare intragroup changes in lipid profile (LDL-C, TG, TC), BMI, FBS and HbA1c in the pre-test and post-test phases. Wilcoxon test was also used for HDL index.

The results of paired t-test showed that the mean FBS and HbA1c levels in experimental group were significantly lower in the post-test phase (p = 0.03) as compared to the pre-test phase (p = 0.002), however, the mean of these parameters showed a significant increase in the control group in post-test (p = 0.03) as compared to the pre-test phase (p = 0.05). Cholesterol (TC) level did not change significantly within the control group but its amount within the experimental group decreased significantly after AE (p= 0.05). There was no significant difference between the control and experimental groups in terms of BMI, TG, LDL-C, and HDL-C levels before and after the intervention (p> 0.05).

Independent t-test was also used to compare intergroup changes in terms of LDL-C, TG, TC, HbA1c, FBS .BMI and Mann-Whitney was also used to compare changes in HDL-C level between the two groups. The results of these tests showed significant difference between the two groups in terms of mean values of HbA1c and FBS levels in the post-test (p <0.05). Figure 1-7.
Discussion

The results of the present study showed a significant difference in terms of HbA1c and FBS both inter- groups (between the control and experimental groups) and within intervention group. However, there was no significant difference between the control and experimental groups in terms of mean lipid profile (LDL-C, TC, TG, BMI and HDL-C). The results of paired t-test for within group differences showed that the mean FBS, TC and HbA1c levels were significantly lower within the intervention group over time. However, the mean of these parameters increased significantly within the control group over the time. No significant intra-group differences were found for BMI, LDL-C, HDL-C and TG.

Several studies with different AE protocol and/or duration with our study also showed a significant decrease in the HbA1C level followed by PA (15, 16) which is consistent with the results of our study. HbA1C level showed significant reduction after eight weeks and sixteen weeks of AE at intensities between 50 to 85% VO2 in subjects with T2D (17, 18). In the study by Dixit. et al. the 8-week AE with different protocols from our study and different study populations, mostly male, showed similar results with our study (19) in terms of HbA1C. HbA1c is an important indicator of long-term blood sugar control (20). According to epidemiological studies HbA1c is also known as an important risk factor for CVD (21). Studies have shown that the best treatment goal in people with diabetes is to modulate HbA1c. Studies by Segalet al. (2007) ،Marcus et al. (2008), and
The 8-week aerobic exercise reduces the blood sugar…

Church et al. (2010) are among the studies that confirm these results (22-24). However, these results contradict the results of Bilo et al. (2011) which they did not see any significant change in HbA1c levels after 8 weeks of AE in diabetic patients. In their study, mean age and BMI of subjects was 30-70 years and 25-40 kg/m². These discrepancies may be due to high differences in age and BMI values (25) as well as their relatively less intensive exercises compared to the previous studies and the present study. Also, the type and method used to measure HbA1c are different in different studies (electrometry, calorimetry, chromatography), which can affect the results (26). AE can increase glucose transporters, which improves insulin function and glucose metabolism, and can lower HbA1c.

PA also ensures homeostasis of glucose and glycemic factors by decreasing FBS levels. The results of the present study showed a significant decrease in FBS values both inter-group and also intra-group over time which is consistent with the results of Misra et al (2008), Cauza et al (2005), Shenoy et al (2009) (27-29). Tekmadikis et al. during a different AE protocol (4-16 weeks AE) found a significant decrease in FBS levels and an improvement in insulin sensitivity in type 2 diabetic subjects (30). On the other hand, Cauza et al. did not show any significant reduction in blood sugar after 4 months of AE. It might be due to the fact that the duration of AE in each session (15-30 minutes) was relatively short in their study (28). In a study by Rahbar et al. with very similar AE duration time (8 weeks) and AE protocol (3 sessions per week, intensities between 50%- 70%) with our study significant changes in HbA1c and FBS inter-group were observed however contrary to our study they also found significant changes in cholesterol, LDL-C and TG compared to control. They interestingly reported the elevation of HDL-C in control group compared to intervention (31). Considering the similar AE protocol between their study with our the difference in the effect of intervention on lipid profile needs more research.

One possible mechanism that explains the role of AE in controlling and lowering blood sugar (FBS and HbA1c) in type 2 diabetes is an increase in Glut4 counts, which will be resulted in increased glucose uptake into muscle cells and glucose uptake. Muscles expend large amounts of glucose at two times, one during insulin-dependent PA and another one about 2-3 hours after each meal. Frequent muscle contractions during exercise have an insulin-like effect and send large amounts of glucose into the cell to produce energy. These frequent contractions increase the number of Glut4 molecules and increase transportation of glucose across the cell membrane. It also allows muscle fibers to have low glycogen concentrations for a relatively long period of time (32). On the other hand, muscle cells try to regenerate their glycogen reserves after exercise, and for this reason, the blood glucose concentration is at a low level for several hours after exercise. Research shows that Glut4 levels in young athletes are higher than non-athletes people. Approximately, 80% of patients with type 2 diabetes are obese and obesity is a major cause of insulin resistance (33). On the other hand, fatty acids produced by adipose tissue disrupt the transfer of Glut4 to the cell surface (34). Exercise may prevent fatty acids from accumulating in muscle cells by increasing oxidation. Increased capillary density, increased sensitivity of insulin receptors, changes in phospholipid composition of sarcolemma, increased activity of oxidative...
enzymes, and increased activity of glycogen synthase are also among the important factors in lowering blood sugar (29). A study showed that 8-week AE improved insulin resistance within the experimental group and also between the groups significantly (35).

Optimal LDL-C levels for adults with diabetes are <100 mg/dl (2.60 mmol/l); HDL-C are >40 mg/dl (1.02 mmol/l); and TG levels are <150 mg/dl (1.7 mmol/l). In women, who tend to have higher HDL cholesterol levels than men, an HDL goal 10 mg/dl higher may be appropriate (36). The results of the present study showed no significant difference between the groups in terms of lipid profile following AE. However, the results of paired t-test for intra group analysis showed that TC level decreased significantly within the experimental group over time. There was no significant difference inter-group or intra group within experimental group in terms of TG, LDL-C, and HDL-C in our study which might be due to the insufficient intensity and duration of AE in our protocol, lack of dietary fat restriction and diet, or could be due to the genetically factors, along with environmental influences. A review of 51 articles on the effect of PA intervention on non-diabetic subjects showed a mean increase in HDL cholesterol of 4.6 % however different study and meta-analysis on the effect of PA on diabetic subjects did not confirm this improvement in HDL-C (12, 35).

Although our study population was only female diabetic patients and a study showed that the level of performing PA is lower in women than in men (37) the results of the present study were consistent with a number of various reports that have not seen positive effect of applying AE diabetic patients on TG, LDL-C, and HDL-C levels (22, 25, 28, 38). There is strong evidence that high-intensity exercise exerts significant positive effects on lipid profile and decreases mortality rate by more than double over a decade (39). The intensity, duration, and frequency of exercises can be considered as the reason for achieving these results. Also, the reduction of saturated fats, diet, and weight loss has been considered to affect lipid changes (40, 41). Contrary to the results of the present study, Baharloo et al. (2014) stated that a 12-week aerobic exercise led to a significant decrease in TG, LDL, and HDL levels. Researchers believe that the lipid profile levels at the beginning of exercise are influential, so that the higher the level of blood lipids, the more noticeable changes will be shown (17, 42, 43). The absence of any change in the lipid profile in the present study may be attributed to the low initial levels of this variable.

The mostly used measure of cholesterol is ‘total cholesterol’ or TC, which includes LDL-C and HDL-C (44). We found a significant decrease in TC level following aerobic activity. Elevated TC level increases risk of CVD related problems approximately twice in non-diabetic patients (45) and the mean annual CVD related mortality as three times in patients with elevated cholesterol levels (>220 mg/dL)(46). therefore, these results confirm the cardio-protective effect of PA for this group of patients (47).

The mechanism by which exercise activity improves fat metabolism may be due to changes in the activity of lipase enzymes, including lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL). One of the possible reasons for the decrease in TC in the present study is increased LPL activity (48). Researchers have found that long-term PA has a greater effect on lowering blood cholesterol levels than intense and short-term exercises. Every diabetic patient should engage in at least 150 min moderate intensity PA per week, at least 3 days/week, with no

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The 8-week aerobic exercise reduces the blood sugar…

Amini Najafabadi B. et al.

more than two consecutive days without activity (49).

Conclusion

The results of present study support the undeniable beneficial effects of physical activity in patients with type 2 diabetes. In this study, aerobic exercises played a significant role in reducing HbA1c and FBS levels in inter-group and intra-group analysis. Aerobic exercise also led to a decrease in TC level in intervention group over time. However, the results showed no beneficial effect for 8-week aerobic exercises in term of TG, LDL-C and HDL-C. Based on the results of this study it can be concluded that aerobic exercises has blood glucose management and cardiovascular protective activity.

Due to the existing limitations such as: budget, it was not possible to measure insulin and insulin resistance in the subjects. Therefore, it is suggested that serum insulin and insulin resistance be evaluated in diabetics simultaneously with the evaluation of glycemic index.

Acknowledgments

This article is part of a student dissertation. Hereby, the author would like to express their gratitude to the staff working in Janan Diabetes Center and the Nabi Akram Laboratory in Najafabad as well as all the diabetic women participating in this research project.

Declarations

A written informed consent was obtained from all participants. The study was approved by randomized clinical trial at the Iranian Clinical Trial Registration Center. The registration code number is IRCT20200803048287N1 and ethics code was: IR.IAU.NAJAFABAD.REC.1399/083.

References


The 8-week aerobic exercise reduces the blood sugar... Amini Najafabadi B. et al.

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The 8-week aerobic exercise reduces the blood sugar... Amini Najafabadi B. et al.


How to cite: