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Improvement in Biochemical Parameters in Patients with Type 2 Diabetes After Twenty-Four Sessions of Aerobic Exercise: A Randomized Controlled Trial

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Abstract

Background: Diabetes is a cosmopolitan health problem worldwide, especially in Asia. It is a metabolic disorder originating from insulin secretion deficiency, insulin performance or both. When both factors are involved, abnormal complications may result. Exercise training plays an important role in controlling diabetic parameters, including biomechanical variables.
Objectives: This study aimed at assessing the effectiveness of exercise on biochemical parameters in patients with diabetes.
Methods: This study was a randomized control trial. A total of 30 volunteers met the inclusion criteria and were randomly divided to 2 groups, aerobic and control, by block randomization method. This study was performed during May to October 2016 in Iran. The intervention protocol included 24 sessions (8 weeks) of aerobic exercise on the treadmill with zero slope, 3 days per week for 30 minutes per session. Intensity of training protocol was 50% to 70% maximum heart rate. Measurements of biochemical parameters were done before and after the 24 sessions
Results: There were no significant differences in anthropometric, gender, age, diabetic history, cardiac ejection fraction, and biochemical variables ($P > 0.05$). After 8 weeks, results were as follows: fasting blood glucose (FBS) (130.92 (45.43) Mg/dL), glycosylated hemoglobin (HbA1c) (6.62 (1.52) percent), cholesterol (150.62 (24.07) Mg/dL), triglyceride (119.62 (39.18) Mg/dL), Low density lipoprotein (LDL) (77.23 (26.73) Mg/dL), and very low density of lipoprotein (VLDL) (23.92 (7.90) Mg/dL); these were significantly reduced in the training group ($P < 0.05$), yet, not in the control group. Alternatively, high density lipoprotein (HDL) remained unchanged in the aerobic group (47.85 (17.83) Mg/dL) while it was increased in the control group (42.07 (8.86) Mg/dL). Also, C-reactive protein (CRP)) 2.43 (1.03) Mg/L) and microalbumin (12.32 (1.21) Mg) values didn't change between the 2 groups.
Conclusions: Eight weeks of aerobic exercise was shown to be effective in controlling biochemical parameters. However, longer training duration is needed in order to modify CRP.

Keywords: Exercise, Diabetes Mellitus, Hemoglobin A, Glycosylated, Blood Glucose

1. Background

Type 2 Diabetes (T2DM) is one of the most important human health problems worldwide (1). It has been estimated that, globally, it will be the seventh leading cause of mortality by 2030 (2). The probability of cardiovascular disease in patients with diabetes is 2 to 4 times that of non-diabetics (3). According to the world health organization (WHO) and diabetes federation international (IDF), 1 in 10 adults worldwide had T2DM in 2014 and the cost of treating the complications of diabetes was 8% to 10% of the total cost of treating health problems in the world in 2013 (2, 4).

Hyperglycemia, dyslipidemia, microvascular, and macrovascular complications stem from an absolute or impaired insulin production, which are considered main culprits of diabetes mellitus (5). A 4 to 7 year period is calculated between the onset of the disease and its clinical diagnosis; thus, the probability of damage to the internal organs cannot be ruled out (6). HbA1c is an important indicator of blood sugar control in patients with diabetes and provides better estimations of diabetic complications (7). This traditional biomarker is an independent risk factor for coronary disease and stroke in diabetics and non-diabetics (8). Type 2 diabetes is associated with a reduction in high density lipoprotein (HDL) and an increase in low density lipoprotein (LDL) and triglyceride biomarkers (5).

Increased adipose tissue is a risk factor for insulin resistance in diabetic patients. Increased cytokines, secreted by adipose tissue, causes an increase in C-reactive protein (CRP). Inflammatory factors induce insulin resistance in skeletal muscles, liver, vascular endothelial, and therefore, lead to type 2 diabetes and cardiovascular disease (9). Micro albuminuria in patients with type 2 diabetes is a risk factor for chronic renal failure (10). Mortality from cardiac problems in patients with micro albuminuria and diabetes was 2.5 higher than diabetic patients with a normal microalbumin (11).

Previously, physical activity along with diet and medication was recommended as a treatment for diabetes. In the recent years, due to adverse side effects of drugs, physical activity has been particularly considered in different guidelines (12). Lifestyle interventions aid in enhancement and eventual improvement in anthropometric and metabolic health (13). Different mechanisms decreased blood glucose by exercise, including increased concentration of GLUT4 in plasma membrane, which led to decreased insulin resistance, increased muscle fiber hypertrophy, and subsequently, increased muscle glycogen and glucose (14).

According to previous studies, in order to improve biomarkers, most randomized control studies have included patients with diabetes mellitus and cardiovascular disorders, fewer studies emphasized on the effects of aerobic training in type 2 diabetes. Also, many studies proposed long duration of exercise such as 12 weeks (15, 16), 6 months or more (17-19) of aerobic exercise. The strength of the study was an accurate supervised intervention type, which has obvious advantages. Maximum heart rate was calculated based on the formula 220 - X, where X is the age of the participant or by using the qualitative Borg scale. However, these variables do not provide exact values of maximum heart rate. Therefore, as a novelty of this study, the Bruce protocol was used to obtain maximum heart rate in this study.

Despite the numerous documentations regarding the effectiveness of exercise, the performance of exercise by patients to manage diabetes more efficiently has not been considered thus far. It might be that the length of the exercise is too long to be successfully performed by patients. The primary purpose of this randomized controlled study was to consider the effects of 24 sessions of aerobic exercise on biomarkers. It was hypothesized that aerobic exercise in less time would enhance these biomarkers.

2. Methods

2.1. Subjects

A randomized controlled trial with parallel groups study design was used, in which participants were recruited from all diabetic centers, 2 specialized, and 3 general governmental hospitals through advertisement. This study was performed during May to October 2016 at the Sheikhorreis rehabilitation center, department of physiotherapy, Hamadan University of Medical Sciences, Iran. It was approved by the human ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, which is in accordance with the declaration of Helsinki (IR.SBMU.RETECH.REC.1395.577). This study was registered in the Iranian registry of clinical trials (www.irct.ir) with registration number ID: IRCT2016121831443N1. According to the American diabetes association, diabetes could be diagnosed based on HbA1c and fasting plasma glucose criteria. The other criteria for diabetes disease are fasting lipid profile level (including total, LDL, and HDL cholesterol, and triglycerides), micro albuminuria, body mass index (BMI), weight, and hypertension (15). Six hundred and twenty four patients with diabetes volunteered to participate in this study, who were evaluated based on the inclusion criteria. Inclusion criteria were as follows: 40 to 60 years of age, and male or female with diabetes for a range of 2 to 10 years. Other criteria included HbA1c value of 6% to 10%, BMI of 20 to 30 kg/m^2, inactive lifestyle (less than 30 minutes per week of exercise), non-smoking, non-alcoholic, non-opium user, non-insulin injection use, no history of hypertension or any cardiovascular, muscular, skeletal, neurological, and metabolic disorders. Participant were excluded if they were absent for 2 successive sessions, had respiratory problems during exercise, or if they were reluctant to continue with the protocol for the aerobic group. After initial screening via an interview and examination by a physiotherapist and endocrinology specialist, participants underwent cardiac examination (echocardiography and exercise test) by a cardiologist in order to exclude patients with cardiac problems. The sample size allowed for the detection of the effect of exercise (power of 90%) with 95% confidence interval in each group, which was calculated as 12 individuals, according to Maiorana et al. (16). Sample size requirements was as follow: M = 1.3, SD = 1.8, effect size (delta) = 1.088, Type 1 error (α) = 0.05, and type 2 error (β) = 0.1.

$$\overline{\mu} = \frac{1}{k}\sum\nolimits_{j=1}^{k} \mu_j \tag{1}$$

$$\Delta = \frac{1}{\alpha^2}\sum\nolimits_{j=1}^{k} (\mu_i - \overline{\mu})^2 \tag{2}$$

$$\chi_{k-1}{}^{2}\left(\frac{\chi_{\alpha,\,k-1}{}^{2}}{\lambda}\right)=\beta \quad (3)$$

The 30 volunteers that had the inclusion criteria were entered in the study. Block randomization method was designed to randomize subjects to aerobic and control groups by researchers, and the allocation ratio was 1:1. All the participants filled out and signed the informed consent. Participants were asked to not change their drugs and lifestyle, including activity and diet. Figure 1 shows various stages of this study in a consort diagram. This trial study met the criteria in the consort checklist.

2.2. Exercise Protocol

The training program was done by the first author. Aerobic protocol included 24 sessions (3 days per week) of aerobic exercise on a treadmill (MOTORIZED TREADMILL®, OMEGA GT, USA) with no slope. Each session lasted 30 minutes and the intensity of the training protocol was 50% to 70% max heart rate, which was estimated from the bruce protocol test, and it was increased gradually during the 8-week duration. Target heart rate was also calculated using the carvonen formula.

HRt = HR rest + 50% - 70% (HRmax - HR rest)

Diastolic and systolic blood pressures (Omron®RS2 digital pressure gauge, China) and blood glucose (Accu-Check® performa glocometer, USA) were measured in order to control vital signs before and after starting each session of exercise. If blood pressure was more than 160/90 mmHG, the patient rested for 10 minutes and the blood pressure was measured again. If there was no change in blood pressure, training did not start. Also, if blood glucose level was less than 100 mg/dL, 15 g carbohydrate or food supplements were ingested, and blood glucose was measured again after 20 to 30 minutes. Exercise was started when blood sugar was equal to or greater than 100 mg/dL. Alternatively, it should be mentioned that if the patient's blood suger was higher than 250 mg/dL, exercise didnot begin. Respiratory symptoms and blood glucose were checked during training, and exercise was stopped in case of hypoglycemia. The training intensity was assessed based on the borg scale, every 5 minutes. Heart rate was monitored throughout the training program using digital heart rate meter by placing the belt around the chest and wearing the heart rate monitor like a wrist watch (beurer®PM60 digital pulse meter, Germany). An observer (first author) used the digital pressure gauge, glocometer, and pulse meter to collect all data about vital signs. Before and after each section, all systems were calibrated to zero.

2.3. Measurements

Blood sampling Measurements: Measurments of biochemical parameters were done before and after 24 sessions of intervention (Mahdieh pathology Laboratory, Hamedan, Iran) by blood sampling after overnight fasting in both groups. Also, these biomarkers were measured by an individual blinded to the group allocation.

Serum fasting blood glucose (FBS), LDL, HDL, VLDL, cholestrol, and triglyceride were measured (using an enzymatic method) by biochemistry auto analyzer (Pars Azmoon kit, Biotechnica (BT 3000)®, Italy), while CRP, microalbumin (using an immunometric assey) (Axis-Shield Nyocard®.Norway), and HbA1c (using an affinity chromatography assey) (Axis-Shield Nyocard®.Norway) were measured by the nycocard device .

Body composition measurements: The observer used a digital device to collect anthropometric data. Before and after each intervention, digital devices were calibrated to zero. Weight was recorded on an digital scale (Omron®HN289 digital personal scale, China), height was measured by a stadiometer (WB-800H, Tanita, USA), and BMI was calculated as weight (kg)/height^2 (m).

2.4. Statistical Analysis

The SPSS statistical software 16.0 was used for all the statistical analyses. Statistical analyses were performed based on 'per protocol' approach. To test normality, that is, to verify if the distribution of data was parametric, the Kolmogorov-Smirnov test was used. Independent t test was used to compare baseline and differences in parameters of the 2 groups. Repeated measure analysis of variance (ANOVA) was used to compare variables after 8 weeks of intervention to test within and between effects, simultaneously. The significance level and power of tests were 0.05 and 90%, respectively.

3. Results

From the initial number of participants, 2 patients in the aerobic group were unable to continue the exercise protocol after 12 sessions and were excluded. Thereafter, the study was continued with 28 patients (control: 15 and aerobic: 13). Primary characteristics of participants in the 2 groups are given in Table 1. There were no significant differences at baseline in anthropometric, age, duration of diabetes, cardiac ejection fraction, and biochemical characteristics ($P > 0.05$).

Biochemical values and changes in average plasma serum before and after 8 weeks are shown in Tables 2 and 3. Changes in weight and BMI trends are also presented below (Figures 2 and 3).

After 8 weeks, fasting blood sugar, HbA1c, cholesterol, triglyceride, HDL, LDL, and VLDL were reduced significantly in the training group, yet, they were not significantly different in the control group (Table 2). As shown in Table 3

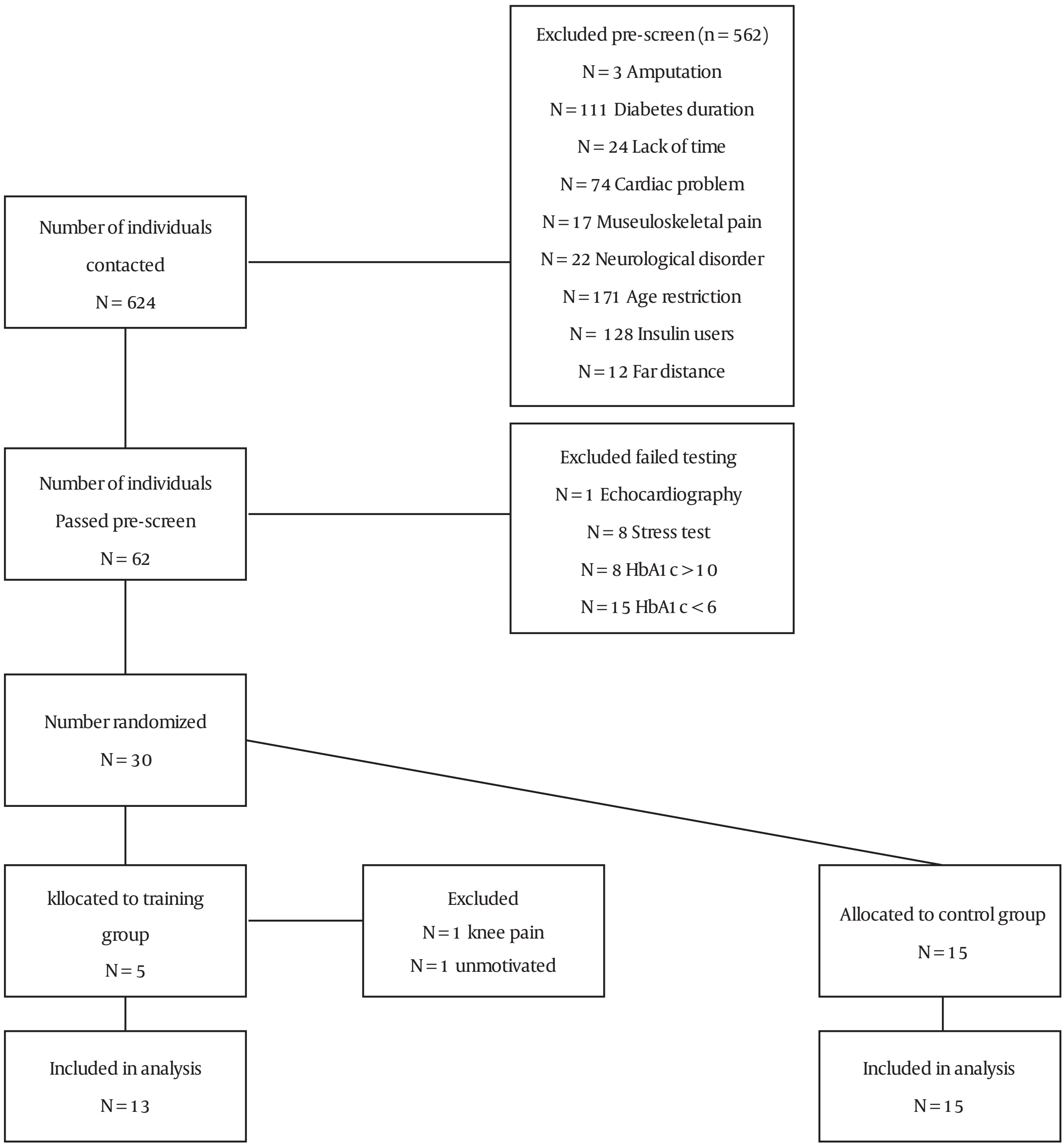

Figure 1. CONSORT Diagram

FBS, HDL, and LDL changes were significantly improved after 8 weeks in the aerobic group (Table 3).

4. Discussion

The findings of this study showed the effect of 8 weeks of aerobic training modified biochemical parameters in such a way that weight and BMI were reduced when compared to pre-intervention in the aerobic group. The HDL and LDL levels were significantly different between the aerobic and control groups. Also, the comparable difference in FBS was close to significance. Many literature reports have considered the impact of exercise on biochemical pa-

Table 1. Baseline Characteristics of the Intervention and Control Groups (mean ± SD)

Variable	Training Group (n = 13)	Control Group (n = 15)	P Value
Age	48.31 (5.02)	48.60 (4.80)	0.876
Height, cm	165.92 (7.84)	166.66 (6.95)	0.792
Weight, kg	75.80 (13.64)	75.03 (9.91)	0.862
BMI, kg/m^2	27.40 (3.65)	26.93 (2.42)	0.692
EF max., %	56.15 (0.02)	56 (0.02)	0.850
Ef min., %	53.08 (0.03)	53.67 (0.02)	0.580
Disease duration, y	4.61 (2.14)	5.33 (1.99)	0.366

Abbreviations: BMI, body mass index; EF max, maximum ejection fraction; EF min, minimum ejection fraction.

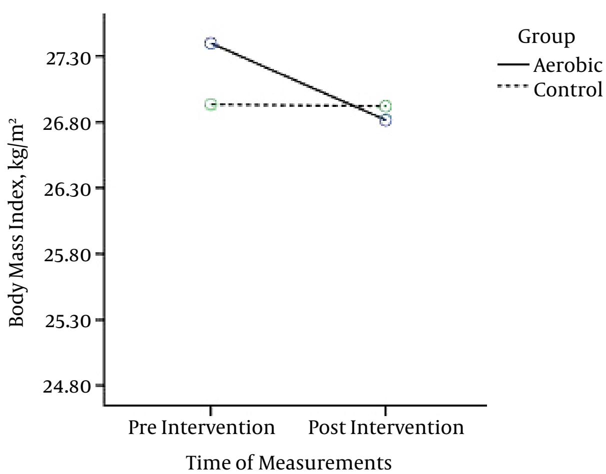

Figure 2. Body Mass Index Changes Before and After Eight Weeks in Aerobic and Control Groups Before and After the Intervention

rameters (17-19). In contrast to other studies, exercise intensity was established by the American diabetes association standard (20). Tessior (18), used 35% to 75% of maximum heart rate (MHR) to asses exercise intensity (17). Maximum heart rate was calculated based on the formula (220 - X) where X is the age of the participant in the previous study; however, this formula does not provide exact value of maximum heart rate. Therefore, the Bruce protocol was used in this study to obtain maximum heart rate. Gordon (15), by using the qualitative Borg scale, determined the exercise intensity and reported decreasing HbA1c after 3 months without any significant changes in BMI after 6 months (15). However, in our study, the FBS, BMI and body weight were reduced by 19%, 2%, and 2%, respectively after 24 training sessions. In some studies, biochemical

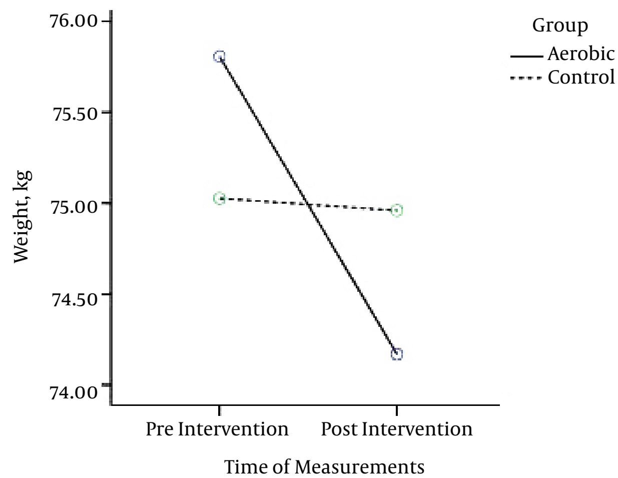

Figure 3. Weight Changes Before and After Eight Weeks in Aerobic and Control Groups Before and After the Intervention

parameters were only reduced after long-term training of 6 months or more (1, 17, 21-23). It seems that exercise duration influences biochemical parameters, and if the duration is less than a threshold, it does not yield a change in biochemical parameters, e.g. 4 exercise sessions were not sufficient to significantly change levels of blood sugar, HDL, and LDL (24). Therefore, due to the low activity of patients with diabetes and unmanaged biochemical parameters after 4 weeks, longer term studies were selected. Control of HbA1C is more important than controlling dyslipidemia in the prevention of micro vascular and macro vascular problems (8). According to the study of Pattyn et al. 1% reduction in HbA1C in the aerobic group led to an 18% decrease in coronary artery disease (25). This was observed in aerobic patients after 24 sessions of training.

Type 2 diabetes is associated with dyslipidemia, which is a risk factor for increasing cardiovascular disease and mortality (24). Therefore, triglyceride, LDL, VLDL, and cholesterol decrease after 24 sessions in the exercise group and yield a positive influence in reducing mortality. Increasing exercise intensity, high lipid level, and longer duration of exercise all are effected by variations in lipid profile. High intensity exercise increased lipoprotein lipase activity in adipose tissue and accelerated turn over and clearance of triglycerides (26). Therefore, high intensity exercise might yield more variations in lipid profile (27).

Furthermore, HDL plays an anti-diabetic role through glucose utilization by skeletal muscles triggering the synthesis and release of insulin from beta cells and cholesterol abscission from macrophages in the arterial wall (28). Physical activity is vital to increase HDL, which consequently controls blood sugar in people with type 2 diabetes

Table 2. Plasma Serum Level Before and After Eight Weeks in the Two Groups (mean ± SD)[a]

Variables	Aerobic	Control	P Value[b]	P Value[c]
FBS, Mg/dL	149.23 (59.12)	138.86 (38.67)	0.553	0.000
HbA1c, %	6.94 (1.41)	7.20 (1.56)	0.632	0.029
Cholesterol, Mg/dL	164.07 (26.70)	155.23 (34.21)	0.344	0.001
Triglyceride, Mg/dL	135.70 (53.24)	151 (92.39)	0.574	0.004
HDL, mg/dL	48.50 (15.98)	47.10 (12.21)	0.756	0.125
LDL, mg/dL	88.15 (27.21)	83.13 (37.23)	0.638	0.299
VLDL, mg/dL	27.15 (10.73)	28.31 (15.74)	0.992	0.000
CRP, mg/L	2.72 (1.04)	2.84 (.40)	0.533	0.243
Microalbumin, mg	12.35 (2.47)	12.83 (4.07396)	0.610	0.737
SBP, mmHg	120 (8.94)	120 (7.55)	0.889	0.837
DBP, mmHg	78.07 (8.00)	77.93 (5.59)	0.919	0.820

Abbreviations: CRP, C- Reactive protein; DBP, diastolic blood pressure; FBS, fast blood sugar; HbA1c, glycosylated hemoglobin; HDL, high density of lipoprotein; LDL, low density of lipoprotein; SBP, systolic blood pressure; VLDL, very low density of lipoprotein.
[a]Values are expressed as mean ± SD (before and after intervention).
[b]P found by the repeated measures ANOVA test (between group).
[c]P found by the repeated measures ANOVA test (inter group).

(29). Although aerobic exercise did not alter the amount of HDL in the aerobic group, the lack of exercise in the control group showed significantly decreased HDL. A decrease in 10 mg HDL in the control group, according to the study of Toth, resulted in an increase of 13% in coronary heart disease (30). Constant HDL, in the exercise group, could be attributed to the normal range of the lipid profile. In this case, the HDL may not be increased (31). Moreover, an increase of 15% in VO_{2max} did not change the amount of HDL because 2-month exercise duration was too short to change it, and therefore, long-term exercise is essential (32); this is consistent with our results. It has been reported that longer duration of exercise, with 70% sub-maximal heart rate, reduces triglycerides, cholesterol, LDL, and increased HDL. This was observed after 10 weeks (33), and low intensity short term exercise did not raise HDL even after 40 weeks. Performing moderate intensity exercises, with 2 to 4 sessions per week lasting 60 minutes, is necessary to increase HDL, considerably. In the current study, medium intensity consisted of three 30-minute exercise sessions per week, which showed that the HDL was not significantly increased at the end of the exercise. The reason behind this was that onlyexercise intensity of more than 80% of maximum heart rate is essential in order to increase HDL (34). The mechanism underlying fat metabolism by exercise is through increasing skeletal muscle capacity for fatty acid oxidization. This is done by increasing enzyme release, which results in an increase in transfer and degradation of adipose tissue (34). Unchanged CRP in this study is consistent with some other documents (Hautonic (35)). However, they used 70% VO_{2max} as an intensity index marker, which is equal to 4 one-hour sessions per week for 3 months (35). C-reactive protein reduction was observed after 6 months with intensity of 50% to 75% in VO_{2max}, 7 months (60% to 70% HRR) and 12 months intervention, respectively (Kadoglou et al. (36), Kondo et al. (37) and Bladucci et al. (38)). In another study, Bladucci reported that the trend in decreasing CRP was observed as follows, combined exercise > high intensity exercise > low-density, respectively. All of those studies stressed on the great influence of exercise duration and secondarily on exercise intensity (38).

Urine samples were taken in the next morning after the last session with the consideration that urine protein increased 24 to 48 hours after exercise (39); unchanged microalbumin after 24 sessions of aerobic exercise was a positive result of this study. Therefore, micro albumin decline could be observed if urine samples were taken 72 hours after exercise in the aerobic group. The main cause of proteinuria after exercise is unclear, however, the renin-angio tension and prostaglandin systems play a major role by increasing angio-tension II during exercise and through the glomerular membrane, which leads to protein filtration (39).

The weakness of this study was the short follow-up period. A long term follow-up was not done in this study because: 1- one of the main limitations of this study was fatigue due to long evaluation period (8 sessions), (initial evaluation visit (2 sessions), endocrinologist (1 session)

Table 3. Plasma Serum Level Before and After 8 Weeks in Two Group (mean ± SD)[a]

Variables	Aerobic (n = 13)	Control (n = 15)	P Value[b]
FBS, mg/dL			
Baseline	167.54 (67.03)	146.00 (30.20)	0.272
At the end	130.92 (45.43)	131.73 (45.58)	0.154
Difference	-36.61 (27.85)	-14.27 (34.06)	0.071
HbA1c, %			
Baseline	7.27 (1.28)	7.37 (1.53)	0.862
At the end	6.62 (1.52)	7.03 (1.64)	0.428
Difference	-0.66 (0.90)	-0.33 (1.28)	0.456
Cholesterol, mg/dL			
Baseline	177.54 (22.65)	165.07 (35.70)	0.289
At the end	150.62 (24.07)	145.40 (30.71)	0.936
Difference	-26.92 (21.12)	-19.67 (39.52)	0.559
Triglyceride, mg/dL			
Baseline	151.77 (61.73)	168.60 (88.31)	0.570
At the end	119.62 (39.18)	133.40 (96.00)	0.930
Difference	-32.15 (27.71)	-35.20 (71.69)	0.887
HDL, mg/dL			
Baseline	47.85 (17.83)	52.13 (13.27)	0.473
At the end	49.15 (14.61)	42.07 (8.86)	0.047
Difference	1.31 (18.87)	-10.06 (9.46)	0.050
LDL, mg/dL			
Baseline	99.08 (23.86)	79.00 (33.79)	0.085
At the end	77.23 (26.73)	87.27 (41.15)	0.110
Difference	-21.85 (30.59)	8.27 (36.39)	0.027
VLDL, mg/dL			
Baseline	30.39 (12.45)	33.67 (17.63)	0.580
At the end	23.92 (7.90)	22.57 (11.41)	0.442
Difference	-6.46 (5.53)	-9.07 (12.30)	0.490
CRP, Mg/L			
Baseline	3.00 (1.00)	2.81 (0.56)	0.663
At the end	2.43 (1.03)	2.88 (0.16)	0.133
Difference	-0.57 (1.50)	-0.31 (1.61)	0.138
Microalbumin, mg			
Baseline	12.38 (3.37)	13.12 (5.82)	0.693
At the end	12.32 (1.21)	12.54 (0.52)	0.520
Difference	-0.06 (3.83)	-0.09 (6.25)	0.789
SBP, mmHg			
Baseline	119.23 (8.62)	120.00 (7.84)	0.810
At the end	120.77 (9.54)	120.00 (7.56)	0.101
Difference	1.54 (9.87)	0.71 (9.54)	0.576
DBP, mmHg			
Baseline	78.46 (5.55)	78.20 (5.56)	0.784
At the end	77.69 (10.13)	78.00 (7.23)	0.903
Difference	-0.77 (9.54)	0.00 (7.84)	0.820

Abbreviations: CRP, C- reactive protein; DBP, diastolic blood pressure; FBS, fast blood sugar; HbA1c, glycosylated hemoglobin; HDL, high density of lipoprotein; LDL, low density of lipoprotein; SBP, systolic blood pressure; VLDL, very low density of lipoprotein.

and cardiologist visits (1 session), lab tests (2 sessions), echocardiography (1 session) and exercise testing (1 session)), and length of the intervention (24 sessions). Overall, there were 32 intervention and evaluation sessions. It has been recommended that high intensity exercise, less number of sessions, and precise monitoring of diet should be employed.

4.1. Conclusions

In conclusion, 24 sessions of aerobic exercise controlled biochemical parameters in control in patients with type 2 diabetes. Constant biochemical parameters of the control group is a warning sign for sedentary patients. Therefore, safe exercise regimen is advised in order to maintain a healthy cardiovascular function and reduce complications in patients with diabetes.

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Footnotes

Authors' Contribution: Data collection: Soulmaz Rahbar and Sedighe Sadate Naimi; data analysis: Abbas Rahimi and Alireza Akbarzadeh Baghban; study design: Sedighe Sadate Naimi, Asghar Reza Soltani, Soulmaz Rahbar, and Hossein Moein Tavakkoli; writing of the manuscript: Sedighe Sadate Naimi and Soulmaz Rahbar; revising of the manuscript: Vahid Rashedi.

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