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Aerobic exercise program reduces oxidative stress and cardiometabolic risks in elderly diabetic patients

Aisha A. Hagag[1,2],Ayat R. Abdallah[3,4],Taha T. Abdelgawad[2,5] ,Samah M. Ismail[1,2] ,Abdullah M. Al-shenqiti[6]

[1]Department of Physical Therapy for Cardiovascular/Respiratory Disorders and Geriatrics, Faculty of Physical Therapy, Cairo University, **Egypt**.
[2]Department of respiratory therapy, college of medical rehabilitation sciences, Taibah University, **Kingdom of Saudi Arabia**
[3]Department of Epidemiology and Preventive Medicine, National Liver Istitute, Menoufiya University, Egypt.
[4] Department of Family and Community Medicine, College of Medicine, Taibah University, **Kingdom of Saudi Arabia**
[5]Chest Medicine Department, Faculty of Medicine, Mansoura University, Mansoura, **Egypt**
[6]Physical therapy departments, college of medical rehabilitation sciences, Taibah University, **Kingdom of Saudi Arabia**

***Correspondence:** aishahagag73@gmail.com **Received 04-02-2020, Revised: 04-03-2020, Accepted: 05-03-2020 e-Published: 09-03-2020**

Aerobic exercises have been shown to be a simple and economical therapeutic modality that may be considered as a beneficial adjuvant for type 2 diabetics. This study investigated the effect of aerobic exercise program on biochemical oxidative stress indicators and cardio- metabolic risks in patients with type 2 diabetes. This controlled randomized study included 20 type 2 diabetic patients who participated in an aerobic exercise program and a similar number of type 2 diabetic patients in the control group. Cardio- metabolic risk factors such as glycosylated hemoglobin, serum total cholesterol, triglycerides, low-density lipoprotein, high-density lipoprotein, resting heart rate, and resting blood pressure were determined at baseline and after 12 weeks. The oxidative stress indicators (malondialdehyde and oxidative status (superoxide dismutase and catalase activities) were measured. In the aerobic exercise group there were significant reductions in glycosylated hemoglobin, total cholesterol, triglycerides, and low density lipoprotein-cholesterol with significant increase in high density lipoprotein-cholesterol. Lipid peroxidation as indicated by malondialdehyde significantly decreased in the aerobic exercise group, while the activity of superoxide dismutase, catalase and total reactive antioxidant potential significantly increased. ($p<0.05$) The study demonstrates the efficacy of aerobic exercises on cardiometabolic risks, oxidative stress markers and antioxidant status in patients with type 2 diabetes and suggests that aerobic exercises may have therapeutic preventative and protective effects on type 2 diabetes mellitus by decreasing oxidative stress and improving antioxidant status.

Keywords: aerobic exercises, cardio- metabolic risks, oxidative stress, type 2 diabetes

INTRODUCTION

Diabetes mellitus is a significant healthcare concern that affects more than 165 million individuals and leads to cardiovascular disease, retinopathy, nephropathy, and diseases of both central and peripheral nervous systems.(Maiese et al, 2007) Hyperglycemia is associated with the complications of type 2 diabetes mellitus. High rates of glucose utilization are accompanied with increased formation of free radical and protein modification. (Shah and Brownlee, 2016)

The imbalance resulting from the increase of reactive oxygen species, with a concomitant lowering of antioxidant defenses results in micro- and macro- vascular complications of diabetes. (Vlassara and Uribarri, 2014) The relationship of hyperglycemia with increased peroxidation of lipids has been reported. (Kesavulu et al, 2002) increased levels of thiobarbituric acid reactive substances (TBARS) were found in the blood of type 1 and type 2 diabetes. (Davi G et al, 2003)

Oxidative stress is oxidative modification of biological components such as lipids, proteins and nucleic acids by reactive oxygen species, which induces several organ dysfunctions. The "free radical theory of aging" stated that the accumulation of these injuries is a cause of decline in biological functions in elderly. (Yuji Naito et al, 2010)

In Anti-Aging Medicine, which contributes to improvement of Quality of Life and promotion of health, it is important to detect risk factors of aging as early as possible in order to undertake aggressive interventions to solve them. (Naito Y et al, 2005) Exercise training can counteract many of the physiological effects of aging and can decreases the risk for many diseases linked to excessive oxidative stress (Church et al, 2002). Previous studies show that regular exercise training can prevent the increase in membrane lipid peroxidation in several tissues which is associated with age. (Radak et al ,2004)

The human body has anti-oxidative enzymes such as glutathione peroxidase (GSH), superoxide dismutase (SOD), and catalase, which remove free radicals. These enzymes contribute a preventive type of anti- oxidative network. (Naito Y, 2006) High levels of free radicals with simultaneous decline of antioxidants defense mechanism lead to increased lipid peroxidation, damage of cellular organelles, and development of insulin resistance. This promotes the appearance of diabetic complications. (M Alipour et al, 2012; Rubanyi GM and Vanhoutte, 1986)

The ability to transfer oxygen from ambient air to the mitochondria of skeletal muscle during sustained exercise is known as cardiorespiratory fitness. A low cardiorespiratory fitness represents a greater risk factor for the development of type 2 diabetes mellitus (T2DM).(Florez. & Castillo-Florez, 2012) Subjects with T2DM have a decreased exercise performance compared to healthy subjects. In addition, an exercise intervention can improve cardiovascular risk and blood glucose control in T2DM.(Fang et al ,2005; Jill, 2002)

Cardiorespiratory fitness is assessed by cardiopulmonary exercise testing. Different protocols are used; the functional capabilities and the purpose of the test determine the choice of protocol. Both bicycle and treadmill protocols can be used, however treadmill walking is a more familiar activity than cycling, it involves a larger muscle mass and more work against gravity.(K Albouaini, 2007)

Most studies on the effects of exercise in T2DM were based on short-term interventions and not included an elderly subjects.(Solomon, 2013, Church et al , 2010, Boule et al ,2001)

In this study, we tested the hypothesis that 12 weeks of aerobic exercise training on elderly subjects with T2DM can positively affect antioxidant defense and cardio- metabolic risk factors.

MATERIALS AND METHODS

Participants included forty adult male and female subjects with T2DM. They were recruited from the outpatient clinic of diabetes at kasr Al -Ainy teaching hospital. Their age ranged from 60 to70 yrs old, with body mass index ranged from 25 to 34.9 (overweight and class 1 obesity) and duration of diabetes from 2 to 7 years. They were nonsmokers and did not receive any antioxidant supplements.

All subjects received standard medical care aimed at achieving optimal glycemic, lipid, blood pressure and body weight targets, including glucose-, lipid- and blood pressure lowering agents and a dietary regimen prescribed by the diabetologist. No further nutritional intervention was given throughout the study.

Medications were adjusted throughout the study to account for potential reduced. The exclusion criteria were: the use of insulin, HbA1c above 9.0%, dyslipidemia, hypertension or having a diagnosis of any complications of diabetes mellitus and any musculoskeletal disorders that interfere with the exercise program. Participants were randomly assigned into two groups that were equal in numbers; the study group (n=20) who participated in an aerobic exercise program for 12 weeks plus their oral hypoglycemic; and control group (n=20) who only received the oral hypoglycemic, the study protocol was approved by ethics committee of faculty of physical therapy, Cairo university. All subjects gave a written, informed consent before participation.

Study design:

This study was a parallel group randomized controlled trial (RCT). Initially, physical evaluations were carried out including interview with an expert physician to rule out any contraindications to exercise testing and any exclusion. After that, participants attended the outpatient clinic for:

1-Anthropometric evaluation:

The following anthropometric parameters were evaluated: weight, height, body mass, waist and hip circumferences. Body mass (kg) and height (m) were determined by a digital scale coupled to a stadiometer Welmy® (W 110 H, Santa Bárbara d'Oeste, SP, Brasil), with accuracy of 0.1 kg and 0.01 cm, respectively.

Body mass index (BMI, kg/m^2) and waist-to-hip ratio were calculated

According to World Health Organization.(WHO, 2000).

2-Blood collection and biochemical analysis:

Venous blood samples were taken at 8:00 a.m after at least 12 hours fasting and 48 hours from the last exercise bout from the antecubital vein in EDTA coated (for plasma) or plain (for serum) tubes using standard aseptic techniques. Total cholesterol, HDL-cholesterol, LDL-cholesterol fraction and triglycerides were measured by enzymatic colorimetric assays; Glycated hemoglobin (HbA1C) was measured by an immunoassay; plasma antioxidant properties were assessed by total reactive antioxidant potential (TRAP), determined by chemiluminescence .(Lissi E, et al, 1995)

The SOD activity was determined by inhibition of pyrogallin (formed due to auto-oxidation of pyrogallol) .(Marklamd S and Marklamd G, 1974) and catalase activity was measured by ultraviolet method, based on the transformation of hydrogen peroxide.(Beer RF and Sezar IW, 1952) Malondialdehyde concentration in the serum was measured spectrophotometrically according to Yagi .(Yagi, 1987)

3-Submaximal treadmill exercise testing:

Before conducting the exercise tolerance test, all subjects had to visit the laboratory to be familiarized with the equipment in order to be cooperative during conducting the test. Each subject underwent continuous progressive exercise tolerance test according to modified Bruce protocol (exercise treadmill test). The first two stages of the modified Bruce Test were performed at a 1.7 mph with 0% grade inclination and 1.7 mph with 5% grade inclination, and the third stage corresponds to the first stage of the Standard Bruce Test protocol with 10% inclination, These modifications in protocol are important for older and deconditioned populations(Bruce et al,1963)

All high intensity sub-maximal tests were performed in the morning, 2 h after the subject's usual breakfast. Volunteers were asked not to have high-intensity physical activity, caffeine consumption 24 h before the tests.(Ribeiro JP, et al, 1986)

The parameters obtained from the test were: Systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), and the peak heart rate at as a percent from the age-predicted maximum (220- age). (Midgley AW et al, 2007)

Symptoms at sub-maximal exercise that result in test termination include muscle fatigue, intermittent claudication, exhaustion, extreme dyspnea, A decrease in systolic blood pressure below the resting pressure, or the participant reaches 95% of the age-predicted maximum (220-age).(Bruce et al,1963; Midgley AW, et al, 2007)

The aerobic exercise training program:

The aerobic treadmill-based training program was started with a 5-minute warm-up phase performed on the treadmill (YY>9028D made in china with input voltage AC220-240 v/50-60 HZ) at a low load(25% of peak heart rate achieved at submaximal exercise test), Active phase of the training session was gradually increased from 20 to 40 minutes in the form of walking on electronic treadmill with zero inclination three times per week for twelve weeks. The intensity of exercise session was determined by using karvonen equation "(training heart rate =[% (peak heart rate- resting heart rate)] + resting heart rate)" the intensity was gradually increased from 60% to 70%.

The peak heart rate is the maximum heart rate achieved at the submaximal exercise testing performed according to a modified Bruce protocol. This rate was defined as the training heart rate (THR).(Sharon; and Denise , 2007)training heart rate was measured using pulsometer watch and treadmill speed ranged from 2 to 5 kilometer per hour throughout the session. Training sessions were performed in a hospital-based setting and supervised by personal trainers with specialist degree in physical therapy at fitness and rehabilitation Centre at Kasr Al- Ainy hospital, Cairo university.

Statistical Analysis:

Data has been collected and entered to the computer using SPSS (Statistical Package for Social Science) program for statistical analysis, (version 21; Inc., Chicago. IL).

Two types of statistics were done:

1.Descriptive statistics:

Where quantitative data has been shown as mean, and Standard deviation SD, while qualitative data was expressed as frequency and percent.

2.Analytical statistics:

where Chi- square test has been used to measure association between qualitative variables. Student t-test has been used to compare mean and SD of 2 sets of quantitative normally distributed data, while Mann Whitney test was used when this data is not normally distributed.

Paired t-test has been used to compare mean and SD of paired quantitative normally distributed data, while Wilcoxon test was used when this data is not normally distributed.

P-value will be considered statistically significant when it is less than 0.05**.**.

RESULTS

Figure 1: shows the flow diagram of patient recruitment and randomization. Of 94 individuals who interested to participate in the study, 54 were excluded based on the adopted criteria. In total, 40 individuals (19 male, 21 female) performed all baseline assessments, and all subjects completed the intervention.

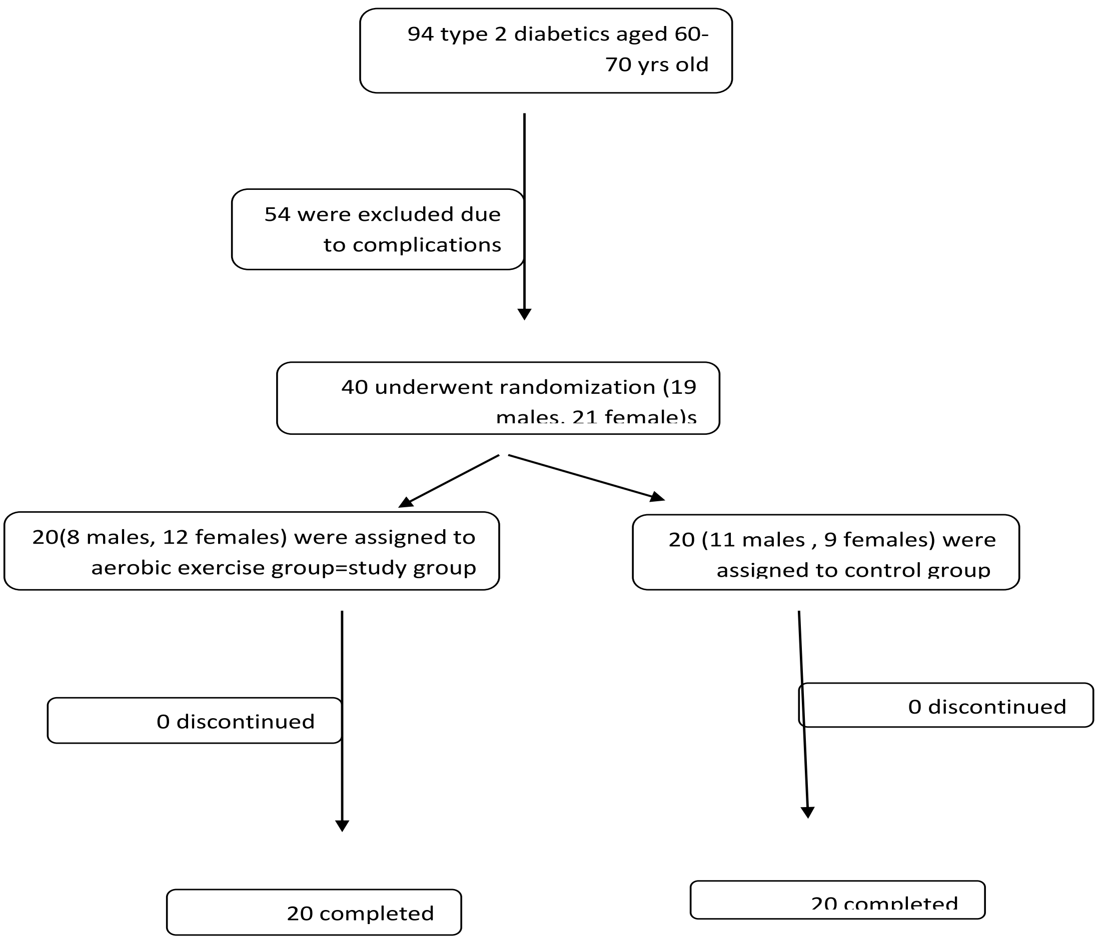

Figure 1: flow diagram of patient recruitment and randomization

Baseline data:

In the present study as shown in (Table 1a) there were non-significant (P≥0.05) differences in age, weight, BMI and duration of diabetes between both groups. Table (1b) showed that there were no significant differences concerning sex distribution in both groups.

Comparisons of cardiometabolic parameters in both groups:

Between group comparisons:

In the current study as shown in (table 2), there were no significant differences (p>0.05) concerning HbA1C, serum triglycerides, Total Cholesterol, HDL-cholesterol, LDL-cholesterol, HR peak, HR resting, SBP and DBP pre-intervention while there were significant differences (p<0.05) in these parameters post-intervention in favor of the study group.

Within group comparison:

In the study group :As shown also in (table 2) there was a significant decrease in HbA1C, serum triglycerides, Total Cholesterol, LDL-cholesterol, resting HR, SBP and DBP, while there was a significant increase in HDL-cholesterol, and HR peak.

In the control group: The obtained data in (table 2) revealed that there was no significant differences concerning the serum triglycerides, Total Cholesterol, LDL-cholesterol, HDL-cholesterol, resting HR, SBP and DBP while there was a significant decrease in HbA1C.

Comparisons of oxidative stress biomarkers in both groups:

Between group comparisons:

Data obtained in (table 3) revealed that there were no significant differences concerning TRAP, SOD, Catalse and MDA pre-intervention, while there was a significant difference concerning these variables post- intervention in favor of the study group.

Within group comparisons:

In the study group: As shown in (table 3) there was a significant increase in TRAP, SOD, Catalse while there was a significant decrease in MDA

In the control group: The obtained data in (table 2) revealed that there were no significant differences concerning TRAP, SOD, Catalse and MDA

Table (1a) baseline characteristics of both groups:

Variable	Study group: (n=20) Mean ± SD	Control group: (n=20) Mean ± SD	p-value
Age(yrs)	64.35±2.8	62.96±5.23	0.08
Weight(kg)	82.27 ± 5.6	80±3.8	0.09
BMI(kg/m^2)	30.4±2.6	28±3.1	0.11
Diabetes duration(yr)	4.3±2.1	5.2±1.4	0.15
Waist-to-hip ratio :			
• **Males:**	0.95 ± 0.07	0.97±0.04	0.12
• **Females:**	0.81 ± 0.08	0.84±0.02	0.16

Values are presented as mean ± standard deviation; p- Value > 0.05: There were no differences between groups in their general characteristics

Table (1b): sex distribution in both groups

Gender	Study group (n=20) Number (%)	Control group (n=20) Number (%)	Total (n=40) Number (%)	χ^2	p-value
males	9 (45%)	10 (50%)	19 (47.5%)	0.43	0.5
Females	11 (55%)	10 (50%)	21(52.5%)		
χ^2 : Chi squared value	p value: Probability value				

Table 2: Cardiometabolic parameters in baseline (pre) and after 12 weeks(post) in both groups

Variable	Study group (n=20) Mean ± SD	Control group (n=20) Mean ± SD	p-value
HbA1c (%)			
Pre	7.76±0.45	7.89±0.5	0.083
Post	6.52±0.32	6.98±0.43	0.001*
p-value	0.013*	0.012*	
Triglycerides (mg/dl)			
Pre	154.23± 35.7	158.34± 42.3	0.123
Post	138± 0.41	156.53± 32.5	0.023*
p-value	0.012*	0.89	
Total Cholesterol(mg/dl)			
Pre	182.9 ± 48.6	185.4 ± 32.3	0.63
Post	178.4 ± 41.3	182.4 ± 41.3	0.003*
p-value	0.002*	0.923	
HDL-cholesterol(mg/dl)			
Pre	49.7 ± 15.9	52.7 ± 12.3	0.341
Post	55.7 ± 13.4	51.7 ± 15.7	0.014*
p-value	0.011*	0.501	
LDL-cholesterol(mg/dl)			
Pre	110 ± 32.6	114 ± 35.6	0.812
Post	107.0 ± 28.6	111 ± 37.6	0.011*
p-value	0.021*	0.734	
HR peak (b/m)			
Pre	138 ± 12.42	134.87 ± 10.42	0.781
Post	140.87 ± 14.42	133.27 ± 8.4	0.011*
p-value	0.0231*	0.92	
Resting HR:(b/m)			
Pre	81.71± 8.12	82.23± 5.42	0.901
Post	77.23± 6.42	81.76± 6.42	0.001*
p-value	0.015*	0.654	
SBP(mmHg)			
Pre	131.43± 8.12	134.63± 6.13	0.671
Post	125.76± 5.41	135.86± 4.41	0.001*
p-value	0.002*	0.912	
DBP:(mmHg)			
Pre	82.9± 5.12	84.9±3.11	0.056
Post	78.45± 6.89	85.45± 5.23	0.005*
p-value	0.006*	0.006	

Values are presented as mean ± standard deviation; b/m: beat per minute; SBP: systolic blood pressure; DBP: diastolic blood pressure; * a significant difference ($p<0.05$).

Table 3: variables of oxidative stress biomarkers in pre and post study in both groups.

Variable	Study group (n=20)	Control group (n=20)	p-value
TRAP (contains/min)			
Pre	147.239 ±48.643	148.32±23.65	0.123
Post	154.661±51.148	143.26±21.34	0.0001*
p-value	0.001*	0.543	
SOD (U/mL)			
Pre	11.25 ± 0.86	11.43±0.98	0.311
Post	14.34±0.65	11.87±0.32	<0.001*
p-value	0.001*	0.276	
Catalase (U/mL)			
Pre	82.28 ± 6.59	84.16±2.11	0.326
Post	90.56±8.11	85.11±5.12	<0.001*
p-value	0.002*	0.121	
MDA (nmol/L)			
Pre	2.43 ± 0.15	2.87±0.12	0.212
Post	1.54±0.18	2.56±0.16	0.004*
p-value	0.001*	0.112	

Values are presented as mean ± standard deviation; TRAP: total reactive antioxidant potential; SOD: superoxide dimutase; MDA:malodialdhyde; * significant difference (p<0.05)

DISCUSSION

The present study confirmed the positive effects of aerobic training on cardiometabolic risks and biochemical oxidative stress markers in type 2 diabetics. Forty participants with type 2 diabetes were engaged in an areobic exercise program, 3 times per week for a total study period of 12 weeks.

In the current study, 12 weeks of aerobic exercise program showed that Malondialdehyde (MDA) concentration, a lipid peroxidation product of oxidative stress significantly decreased. Total reactive antioxidant potential (TRAP), and the activities of SOD significantly increased which was accompanied by a significant increase in catalase in the aerobic exercise group compared with the control.

Results of this study showed that aerobic exercises significantly reduced serum TC, LDL-cholesterol and serum triglycerides with significant increase in HDL-cholesterol (p<0.05), and it revealed also a significant reduction of HbA1c, resting heart rate , resting systolic and diastolic blood pressure (p<0.05), In the aerobic exercise group following 12 weeks of treatment in comparison to the control.

I order to maintain various cell functions, physiological levels of reactive oxygen species (ROS) are important although an overload of ROS which exceeds the capacity of the antioxidant system induce oxidative stress.(Dro¨ge, W,2002) Oxidative stress plays a key role in both initiation and complications of type 2 diabetes mellitus(T2DM).(Chang & Chuang 2010) Oxidative stress also is a high risk factors for aging. (Yoshikawa, 1990)

Exercise training is known as an effective modality in type 2 diabetes mellitus to increase insulin sensitivity; also regular exercise can reduce oxidative stress and strengthen antioxidant defenses. (Laaksonen, 2000; Kim et al, 1996) The improved antioxidant defense system due to aerobic exercise training may be due to the adaptive reduction of free radical production and increased enzyme biosynthesis. (Lui, 1993)

Lipoprotein abnormalities contribute a role in the pathogenesis of diabetic atherosclerosis. (Lewis and Steiner, 1996) Morbidity and mortality in patients with type 2 diabetic mellitus associated with dyslipidemia in which there is elevated triglyceride and LDL, and decreased HDL cholesterol concentrations. (Loh et al , 1996; Steiner, 1999)

Several studies found that exercise training can improve glycaemic parameters, lipid profile, and blood pressure in diabetics. (Connie et al , 2009)

In agreement with the current study Shehab MA, 2011 concluded that aerobic exercise training is an accepted therapeutic modality in management of type 2 diabetes mellitus for its beneficial effects that exercise improves diabetic status and reduces the metabolic risk factors, insulin sensitivity and lipid profile, so adults with diabetes are advised to perform at least 150 min/week of moderate intensity aerobic physical activity (50–70% of maximum heart rate), through at least 3 days/week.

The current study comes in agreement with that of Vinetti G and colleagues who demonstrated that supervised exercise training of 1-year duration can affect positively insulin sensitivity and blood levels of LDL cholesterol. Increased cardiorespiratory fitness and a healthier body composition were probably the underlining causes. (Vinetti, 2015)

In our opinion, however, too long session duration used by Vinetti G and colleagues was not suitable for the selected old population, in addition it is considered time consuming which may affect patient adherence and encourage withdrawal. Hence, seeking for effective exercise session duration was in our purposes in the current study.

Previous studies and meta-analyses showed that areobic exercise training improves physical fitness in subjects with T2DM, along with a reduction of HbA1c.(Balducci, S. et al, 2012; Boule, 2003)

In an agreement with the current study, Atalay and Laaksonen considered that the regular exercises are of major importance in treatment of diabetes. Although exhausting exercise may increases the oxidative stress, their study showed that antioxidant defense can be regulated by regular physical activity. (Atalay, M., & Laaksonen, 2002)

Clinical findings demonstrate that therapeutic benefit of exercising, so patients with diabetes mellitus should be encouraged to participate in an structured intervention programs.(Praet, S. F., & van Loon, 2009)

Exercise intensity is expressed in terms of maximum oxygen consumption (VO2max), ratings of perceived exertion and/or heart rate (HR). (Borg, 1970) VO2max is accepted as the criterion measure of cardio-respiratory capacity. (American College of Sports Medicine, 1991) One of the limitations of the current study is the lack of investigation VO2max for reasons of budgetary constraints that the measurement of VO2max is restricted to sophisticated research equipment required. In this study, heart rate was used as valid indicators of exercise intensity.

There is a strong relationship between heat rate and the aerobic capacity. Therefore, it is possible to assess the aerobic capacity with no expensive laboratory equipment by using heart rate as a strong predictor to estimate VO2 max. (Ehsanollah Habibi et al , 2014)

Finally in agreement with our study Mihriban Arslan et al concluded that, A three-weekly, 12-week, aerobic-training program, reduces blood pressure and was associated with significant decrease in MDA levels in type 2 diabetic individuals. (Mihriban Arslan et al, 2014)

CONCLUSION

The findings of the study demonstrated the efficacy of aerobic training on cardiometabolic risks, oxidative stress markers and antioxidant status in patients with type 2 diabetes. These findings suggest that aerobic training has therapeutic preventative and protective effects in type 2 diabetes. This may have direct impact on the use of aerobic training as a safe therapeutic modality in diabetes mellitus.

CONFLICT OF INTEREST

There are no conflicts of interest

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AUTHOR CONTRIBUTIONS

All authors contributed in all parts of this study

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