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Bioscience Research

Print ISSN: 1811-9506 Online ISSN: 2218-3973

Journal by Innovative Scientific Information & Services Network

RESEARCH ARTICLE BIOSCIENCE RESEARCH, 2019 16(3):2450-2458. **OPEN ACCESS**

Effect of high intensity interval training on heart rate variability and aerobic capacity in obese adults with type 2 Diabetes Mellitus

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The purpose of this study was to determine the effect of high intensity interval training (HIIT) on heart rate variability (HRV) and aerobic capacity in obese adults with type 2 diabetes mellitus (T2DM).Forty sedentary obese male subjects diagnosed with T2DM were enrolled in the study. Subjects were randomized into two groups. Group A comprising 20 subjects who performed a 12-week HIIT program and group B comprising 20 subjects as a control group maintained their ordinary activities during the intervention period and did not participate in any exercise program. Anthropometric measures, HRV, peak oxygen consumption (VO_{2peak}), glycated hemoglobin (HbA1c), and blood lipids were measured at baseline and at the end of the exercise program. The HIIT included three 30-min sessions per week. Each HIIT session started with 3 minutes warming-up followed by a 4 high intensity (80-90% heart rate max) periods (four minutes each) interspersed with 4 moderate intensity (50-60% heart rate max) recovery intervals (two minutes each) and ended by 3 minutes cooling down. The HIIT program produced statistically significant improvement in HRV parameters ($p<0.05$) without significant weight reduction. In addition, there were significant improvements in resting heart rate, glycated hemoglobin and total cholesterol ($p<0.05$). The study also showed that the improvement in the overall HRV was positively correlated with the VO_{2peak} changes. HIIT can be considered as a promising exercise mode for reducing cardiovascular risk factors in obese individuals with T2DM through improving cardiovascular autonomic function and aerobic capacity even in the absence of significant weight reductions.

Keywords:interval training, diabetes mellitus, obesity, heart rate variability.

INTRODUCTION

It has been established that obesity is the major risk factor in the incidence of type 2 diabetes mellitus (T2DM). Unfortunately, the prevalence of obesity and T2DM has increased dramatically over the last decades. It has been estimated that more than eighty percent of individuals with T2DM are overweight or obese (Gummesson et al., 2017). Both T2DM and obesity are associated with significant increase in

morbidity and mortality particularly due to cardiovascular disease leading to global health issues (Voulgari et al., 2013; Khajavi et al., 2017).

Diabetic autonomic neuropathy, as a common complication to T2DM, leads to cardiac autonomic neuropathy due to damaged heart autonomic nerve fibers. This causes disruption in the balance between the sympathetic and parasympathetic activity of the cardiac muscle (Voulgari et al.,2013).Cardiac autonomic neuropathy has been found to be associated with about five-fold increase in the risk for cardiovascular mortality. The earliest manifestation of the defective cardiovascular autonomic control is the decreased heart rate variability (HRV) (Serhiyenko and Serhiyenko, 2018).

HRV has been found to be reduced in T2DM patients due to cardiac autonomic neuropathy. Decreased HRV has been considered as a cardiovascular risk factor that might be recognized within 1 year from the onset of T2DM (Pop-Busui, 2010).Likewise, individuals with obesity have been reported to exhibit reductions in HRV that may be caused by sympathetic overactivity in the basal state or defective sensitivity of the adrenergic fibers in response to sympathetic stimuli (Tentolouris et al., 2006). This is supported by improved HRV in obese subjects in response to weight reduction (Sjoberg et al., 2011).

HRV analysis has long been utilized as a practical noninvasive method to assess the cardiac autonomic function. In this method sympathetic and parasympathetic systems balance is evaluated as alteration in the time interval between successive heartbeats. HRV analysis is carried out in time and frequency domains. With respect to frequency domain analysis, high-frequency (HF) component with frequencies from 0.15 to 0.5 Hz represents the parasympathetic activity. Low-frequency (LF) component represents mainly the sympathetic activity and less dominantly the parasympathetic activity. Sympathovagal balance is reflected by the LF:HF ratio. The time domain analysis of HRV considers the intervals between consecutive beats involving root mean sum of squared differences (RMSSD) and standard deviation of the RR interval (SDNN) (Ramos et al., 2017).

T2DM and obese subjects have impaired functional exercise capacity evidenced by reduced peak oxygen consumption (VO_{2peak}) even in the absence of cardiovascular disease. Moreover, VO_{2peak} has been found to be associated with some cardiac autonomic function measures in diabetic patients (Röhling et al., 2017; Abudiab et al., 2013).The reduction in VO_{2peak} may be explained by decreased cardiac output and/or reduced skeletal muscle blood flow due to abnormal peripheral and central vascular dynamics related to the autonomic dysfunction. Abnormal mitochondria biogenesis and impaired oxidative metabolism could be another possible explanation (Szendroedi et al., 2011).

High intensity interval training (HIIT) is a mode of exercise involving short bursts of very intense exercise interspersed with a lower intensity exercise or rest. This type of training, compared to the traditional moderate intensity continuous aerobic training, has the advantage of being more timesaving to overcome the barrier of lack of time and low exercise adherence (Abreu et al. 2018).HIIT has been considered to be more effective than continuous aerobic training at improving aerobic capacity, glucose control in subjects with T2DM (García-Hermoso et al., 2016) and cardiac autonomic function (Kiviniemi et al., 2014).

HRV in healthy population has been found to be improved in response to exercise training (Pichot et al., 2005). Several studies have reported significant HRV improvements as a result of chronic exercise while other studies have shown no effect of exercise training on resting HRV (Figueroa et al., 2007). Whether HIIT can improve HRV in obese subjects with T2DM is uncertain. Thus, the aim of this study was to investigate the effect of HIIT on HRV and aerobic capacity in obese adults with T2DM.

MATERIALS AND METHODS

The experimental design

This is a randomized controlled trial. This study was carried out on obese adults with T2DM to determine the effects of HIIT on HRV and aerobic capacity. The study subjects were randomized into two groups either group A that performed an HIIT program or group B that performed no training and maintained their usual daily activities. HRV, VO_{2peak}, glycated hemoglobin and blood lipids were measured in both groups before and at the end of the training period (12 weeks). The study was carried out over a period of 6 months from November 2017 to April 2018.

SUBJECTS

Fifty sedentary adult male subjects diagnosed withT2DM were enrolled, and 40 subjects completed the study.

All subjects were obese non-smoking adult males without established cardiovascular, respiratory or renal diseases. Also subjects with abundant ectopic heart beats and those on regular medication, except for oral hypoglycemic agents were excluded. All subjects were sedentary exercising less than 150 min/week of moderate intensity exercise for at least the last 6 months. Both groups did not differ in any of the baseline characteristics.

The participants were recruited from local health facilities through advertisements placed in regional hospitals and personal contacts.

Prior to beginning the study procedures, all subjects were evaluated by a physician to exclude subjects not meeting the inclusion criteria and to ensure participants' safety to undergo high intensity exercise program. After an introductory session explaining the detailed evaluation and training procedures used in the study, written informed consent was obtained from participants. All participants were volunteers and they were free to withdraw from the study at any time. The study was approved by the ethical guidelines of Prince Sattam bin Abdulaziz University and in accordance with that established in the Declaration of Helsinki.

Sample size

The sample size estimation was based on the effect size (d = 0.8). G* power 3.0.10 software (University Dusseldorf, Dusseldorf, Germany) was used with power 80% and probability 0.05. The analysis created a sample size 50 participants.

Randomization

Participants were randomized via a computer-generated list (www.randomization.com). An investigator not involved in testing or the delivery of the intervention prepared the randomization assignments. Group assignments were delivered to participants in person in sealed envelopes upon the completion of baseline testing.

Body composition

Anthropometric measures

Height and body mass were measured to the nearest 1 cm and 0.1 kg using a weight and height scale (Detecto, made in USA). Participants were weighed dressed in light clothing and barefoot. Standing height was measured in barefoot condition. Subjects with BMI more than 30 kg/m^2 were selected according to the formula: BMI= weight (kg) / height (m^2).

To measure waist circumference, an inextensible metallic tape was placed directly on the skin between the lower rib margin and the top of iliac crest with the subject at the end of gentle exhalation. Two measurements were done and the average value was considered**.**

Aerobic capacity

VO_{2peak} test was performed for all participants one week before the main study procedures. Participants performed an incremental maximal exercise test according to standard Bruce protocol using a stationary CPET system (Quark CPET, COSMED, Italy) on a motorized treadmill (h/p/cosmos, Pulsar 4.0, Nussdorf-Traunstein, Germany). A 3.0-L syringe was used to calibrate the flow sensor, and CO_2 and O_2 sensors were calibrated against known gases before each test. The test was terminated when subjects reached to the point of volitional exhaustion. For a valid test, subjects had to meet at least two of the following 3 criteria: (a) O_2 consumption plateau (changes <150 mL/min), (b) eventual respiratory exchange ratio ≥1.0, and (c) attainment of 10 b/min within the maximum level of heart rate expected for their ages. Continuous heart rate monitoring throughout the test was carried out using a HR monitor (Polar Electro, Finland).

Sampling and analysis

After a 12-hour overnight fast, subject reported to the laboratory in the morning. Venous blood samples were collected from the medial cubital vein and the serum was separated and analyzed for glycated hemoglobin (HbA1c) concentration (Diabetes Technologies Inc, USA).

The serum lipids including triglycerides, total cholesterol, and HDL cholesterol were measured on in VITROS 5600 auto analyzer (VITROS Chemistry Products, Ortho-Clinical Diagnostics Inc. USA).

Heart rate variability

The assessment of the resting HRV was carried out in the morning after a 12-h overnight fast. ECG signals were recorded using an ECG machine (Magic R Series; Maestros, India). Resting ECG was recorded for 5 min in a quiet dimly lit room with subjects at spontaneous respiration in a supine position after a 15-min rest period.

After automatically deriving the consecutive R-R intervals between QRS complexes they were then exported for analysis in the Kubios HRV software (Biosignal Analysis and Medical Imaging

Group, Joensuu, Finland). Linear interpolation method was used to replace artifacts and ectopic beats from R-R interval recordings. Linear parameters in the time domain standard deviation of normal to normal R-R intervals (SDNN), root mean square of the successive differences (RMSSD) and in the frequency domain (HF power, LF power, HF/HF power ratio) parameters were calculated. Both high frequency (HF) and low frequency (LF) were measured in normalized units.

Interventions

Experimental group

Participants in the experimental group followed a program of HIIT on a treadmill for 12 weeks consisting of three 30-min sessions per week. Each HIIT session started with a 3- minute warm-up period followed by a 4 short maximum-intensity (80-90% heart rate max) efforts (four minutes each) with 4 moderate intensity (50-60% heart rate max) recovery intervals (two minutes each) in-between and ended by a 3-minute cool down period. Participants had to reach the target intensity within the first 2 min of the 4-min interval. All sessions were performed in supervised laboratory conditions.

Control group

All participants in the control group were instructed to maintain their normal daily activity and not to partake in any exercise program during the intervention period.

Statistical Analysis

The values are reported as mean ± standard deviations. Statistical analyses were carried out by IBM SPSS (Statistical Package for Social Sciences (SPSS), Version 23, Chicago, IL). All data were normally distributed checked by Shapiro-Wilk test. The dependent paired t-test was utilized to determine the within group changes from pre- to post-test and independent t-test was conducted to investigate the changes between two groups concerning post-test values. Pearson correlation coefficient was conducted to assess association between VO_{2peak} and HbA1c with SDNN. Statistical significance was accepted at the 5% level.

RESULTS

Subjects that did not complete the trial and those were excluded from the data analysis due to low training adherence (<80% adherence) were 10 participants. Eight participants (16%) from the exercise group dropped out compared with two participants (4%) in the control group. At the end of the intervention period 40 of 50 participants completed the trial (80%). Participants reported no adverse effects or complications with exercise during the training period. The baseline characteristics of the subjects in both groups are shown in table 1.

Table 1. The baseline subjects' characteristics and post-intervention changes

Parameter	Group A (n=20)		Group B (n=20)	
	Pre	Post	Pre	post
Age (years)	52.4±4.6	-	51.8±5.1	-
Weight (kg)	105.2±5.14	102.8±3.6	107.3±5.2	108.8±4.6
Height	172±6.1	-	173±6.5	-
BMI (kg.m-2)	34.8±1.8	33.9±1.7	34.6±1.8	35.1±2.8
Waist circumference (cm)	115.4±3.0	113.9±3.0	115.8±1.6	116.4±1.4
VO2peak (ml.kg−1.min−1)	26.2±2.2	33.6±3.8*	27.1±2.2	27.8±2.0**
HbA1c (%)	7.1±0.5	6.5±0.3*	7.3±0.4	7.5±0.3**
Total cholesterol (mmol/l)	5.5±0.8	4.4±0.7*	5.2±1	5.4±0.8**
LDL (mmol/l)	2.7± 0.8	2.7± 0.8	2.8± 0.7	3 ± 0.6
HDL (mmol/l)	1.3± 0.2	1.2± 0.4	1.3± 0.3	1.4± 0.3
Triglycerides (mmol/l)	1.7± 0.2	1.5± 0.4	1.7± 0.3	1.7± 0.3
Duration of disease (years)	9.6±3.8	-	8.3±4.2	-

Values are presented as mean± SD.

*Significantly different from baseline (P < 0.05). **Significant difference between groups (P < 0.05).

BMI: body mass index; WC: waist circumference; VO2peak: peak oxygen consumption; LDL: low density lipoprotein; HDL: high density lipoprotein.

Table 2. Changes in resting heart rate and heart rate variability parameters

Parameter	Group A (n=20)		Group B (n=20)	
	Pre	Post	Pre	post
HR rest (beats/min)	81.1±2.5	73.9±3.8*	82.4±3.5	84 ±4.2**
SDNN (ms)	34.5±4	44.2±5.1*	33.4±3.7	33.1±3.4**
RMSSD (ms)	23.4±5.1	28.8±3.3*	22±4.9	21.1±4.9**
HF Power (nu)	35.4±0.3	52.7±0.5*	35.3±0.4	35.6±0.4**
LF Power (nu)	58.9±0.2	59±0.3	58.7±0.9	58.5±0.7
LF/HF ratio	1.71±0.2	1.17±0.3*	1.56±0.3	1.46±0.3**

Values are presented as mean± SD. HR rest: resting heart rate.
*Significantly different from baseline (P < 0.05). **Significant difference between groups (P < 0.05).
SDNN: standard deviation of normal to normal R-R intervals, RMSSD: root mean square of the successive differences, HF Power: high frequency power; LF Power: low frequency power, nu: normalized unit, LF/HF ratio high frequency / low frequency.

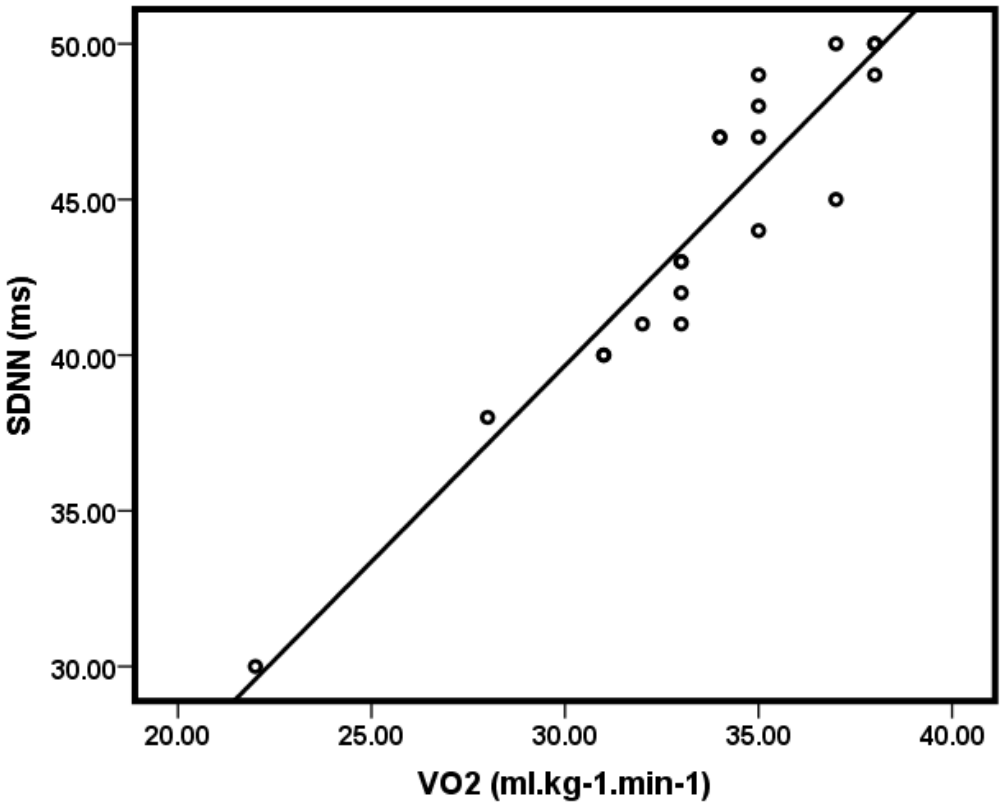

Figure 1: Correlation between VO_{2peak} and SDDN.

There was no within-group change in any measured parameter in group B. The resting heart rate in group A subjects significantly decreased by 9% (p<0.05) from 81.1±2.5 to 73.9±3.8.

The analysis of HRV parameters showed that the two measured time domain parameters in group A subjects SDNN and RMSSD significantly increased by 28% (p<0.05) and 23%(p<0.05) respectively. With respect to frequency domain parameters, LF nu showed no significant change between pre- and post-intervention values (p>0.05). Post-training, HF nu significantly increased by 49% (p<0.05) and LF/HF ratio significantly decreased by 31%.

As shown in figure 1, following the training program in group A, the results revealed a significant positive linear correlation between SDDN and VO_{2peak} (r= 0.94, p=0.001). There was no correlation between improvements in SDDN and improvements in HbA1c (r= -0.4, p=0.9).

DISCUSSION

Recently, there is a large body of scientific literature strongly supporting the role of HIIT as an effective cardiovascular exercise strategy in improving cardiorespiratory function and reducing risk factors of CVD. The present study was designed to determine the effects of HIIT on HRV and aerobic capacity in obese adults with T2DM.

The findings of the current study showed significant improvements in HRV measures and VO_{2peak} in response to 12 weeks of HIIT independent on significant weight changes. Also, there were significant improvements in resting heart rate, glycated hemoglobin and total cholesterol. The study also showed that the improvement in SDDN (which reflects the overall HRV) was positively correlated to the VO_{2peak} changes. The increased value of SDNN after training indicates improvement in the total HRV. The significant increase in SDNN, RMSSD and HF together reflects an increase in parasympathetic modulation and increased vagal activity at rest while the significant decrease in LF/HF ratio indicates decreased sympathovagal balance (Abreu et al., 2018; Ernst, 2017).

These findings are consistent with a recent study that reported HRV (SDNN, RMSSD, HF power) improvements in response to 16 weeks of HIIT in subjects with metabolic syndrome (Ramos et al., 2017). Also, a significant improvement in HRV was reported following a 12-week HIIT program in individuals with T2DM (Parpa et al., 2009). Another study reported significant increase in SDNN, RMSSd and HF by 18.8%, 35% and 47.5% respectively following 6 months of aerobic training at 70–85% HRR in T2DM patients with autonomic neuropathy (Pagkalos et al., 2008). A similar improvement in HF power was found after 2 weeks of HIIT in sedentary middle-age men (Pichot et al., 2005). In contrast, it has been found that 12 weeks of HIIT did not affect HRV parameters in patients with coronary artery disease (Currie et al., 2013). Also, heart rate variability in T2DM subjects did not improve following 16 weeks of endurance training (Figueroa et al., 2007).

In fact there is no consensus on the mechanism by which exercise can affect the cardiac autonomic function. Increase in the plasma volume following HIIT has been postulated to modulate parasympathetic activity and improve HRV (Ramos et al., 2017). Another mechanism purports that the repetitive shear stresses exerted on the vessels walls during HIIT stimulate endothelium for more nitric oxide synthesis, which is in turn, modulates cardiac vagal activity (Green et al., 2011). Furthermore, it has been found that HIIT increases carotid artery distensibility leading to improvements in baroreceptor reflex activity (Heydari et al., 2013). Previous studies reported that improvement in baroreceptor reflex sensitivity is represented by increases in the LF power (Goldstein et al., 2011). However, the findings of the current study do not support this notion as LF power did not significantly increase after training. Moreover, improvement in HRV may be due to alterations in the sinus node as evidenced by significant decrease in HRrest found in the current study (D'Souza et al., 2014). A similar bradycardia during rest in response to exercise training was reported in individuals with T2DM in previous studies (Pagkalos et al., 2008; Loimaala et al., 2003). The working muscles during HIIT may have an indirect role in the autonomic activity regulation through afferent signals from muscular chemoreceptors (Hedelin et al., 2001).

Previous studies have shown that strict glycemic control slows the deterioration of advanced cardiac autonomic dysfunction (Jaiswal et al. 2013). In the same domain, improvement in HRV measures may be due to improved glycemic control. Poor glycemic control and hyperglycemia have been found to cause dysfunction in autonomic nerve fibers innervating the cardiovascular system through accumulation of advanced glycation end products in these cells (Vinik, 2013).Although there was significant improvement in HbA1c after HIIT in the present study, there was no correlation between HRV represented by SDNN and HbA1c. Similar HbA1c improvements were reported in diabetic subjects after HIIT (Hollekim-Strand et al., 2014; Støa et al., 2017). This improvement has been found to be the result of increased glucose uptake in skeletal muscle caused by activation of AMP-activated kinase via increased translocation of GLUT4 (Gibala et al., 2009; Towler et al., 2007).

Interestingly, improvement in HRV in the present study was not accompanied by significant weight reduction even though several studies indicate a relationship between weight reduction and favorable HRV changes. Moreover, it has been found that changes in all measures of HRV to be significantly correlated with the reduction of BMI in overweight and obese adults with T2DM (Sjoberg et al., 2011).However, the absence of significant weight reductions in the present study despite improved HRV is unsurprising as recent studies show that BMI in obese subjects has a

weak relationship with HRV parameters (Yadav et al., 2017). What was expected is significant decrease in BMI in response to 12 weeks of HIIT but the non-significant BMI decrease may be due to the baseline characteristics of the subjects as the majority of the sample were subjects with mild obesity. Also, the absence of change in BMI may be due to an increase in lean body mass and decrease in fat mass. Unfortunately, this cannot be confirmed as changes in body fat percentage have not been measured in the current study. The effectiveness of HIIT in weight loss and improving body composition cannot be rebutted. In fact, body composition changes are affected by several factors including exercise intensity, frequency, diet and lifestyle (Must and Tybor, 2005). HIIT is known to increase fat oxidation, increase excess post-exercise oxygen consumption and decrease post-exercise appetite via increased release of catecholamines (Boutcher, 2011). However, the results of this study revealed no statistically significant reductions in blood lipids except for total cholesterol. This is may be due to normal blood lipid levels in the study subjects before exercise or short exercise duration.

It has been shown that rest vagal modulation following HIIT may be correlated to increased aerobic capacity (VO_{2peak}) (Munk et al., 2010).The results of the present study showed significant improvement in VO_{2peak} following HIIT. In line with this finding, a recent study has reported a 21% increase in VO_{2peak} following HIIT in subjects diagnosed with T2DM (Støa et al., 2017). Similar improvements were found in normal subjects (Helgerud et al., 2007) and those with heart failure (Wisloff et al., 2007). Several mechanisms have been proposed to explain how HIIT can improve aerobic capacity. Still, improved VO_{2peak} is due to increased in oxygen availability through central and/or peripheral mechanisms. Central mechanisms include increased maximum stroke volume induced by enhanced myocardial contractility, increased total hemoglobin and increased blood plasma volume (Astorino et al., 2012). Peripheral mechanisms include increased mitochondrial density and increased skeletal muscle diffusive capacity leading to significant increase in skeletal muscle mitochondrial respiration (MacInnis and Gibala, 2017).

Besides, the results of the present study showed a positive correlation between SDNN and VO_{2peak}. Similarly, previous studies reported a similar positive correlation between HRV and VO_{2peak} both in athletes (Hedelin et al., 2001) and in patients with coronary artery disease (Osterhues et al., 1997). The positive correlation between SDNN and VO_{2peak} found in the present study denotes that the increased aerobic capacity could be one of the mechanisms that explain the improvement in HRV after exercise training. In contrast, baroreflex sensitivity improvement after a 12-month of exercise program in subjects with T2DM correlated significantly with the change in HbA1c, but there was no correlation with changes in VO_{2peak} (Loimaala et al., 2003).

The current study had some limitations. First, is the use of a single gender sample, however using a single gender in the sample was advantageous to avoid any expected differences in HRV responses between genders. Another limitation to the current study is that body fat percentage was not measured and this could help interpret the improvement in HRV parameters and whether it is related to changes in body fats in the absence of weight reduction. A further limitation is that the non-linear HRV indices were not measured. Moreover, measuring HRV only through a 5-min ECG recording could be another limitation. However, this short period of recording could be more reliable than the 24-hour HRV recording which is affected by variations due to circadian rhythms and changes in physical activities. Last, HRV parameters were only measured with subjects breathing spontaneously and not during paced breathing.

CONCLUSION

Upon these findings, it can be concluded that HIIT can be considered as a promising exercise mode for reducing cardiovascular risk factors in obese individuals with T2DM through improvements in cardiovascular autonomic function and aerobic capacity even in the absence of significant weight reduction.

CONFLICT OF INTEREST

The authors declared that present study was performed in absence of any conflict of interest.

AUTHOR CONTRIBUTIONS

AA designed and performed the experiments and also wrote the manuscript. AM performed the medical examination. MW performed the data analysis and exercise prescription. AW and ER monitored the training sessions and reviewed the manuscript. All authors read and approved the final version.

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