ORGINAL ARTICLE

Effect of Different HIIT Protocols on the Glycemic Control and Lipids Profile in Men with type 2 diabetes: A Randomize Control Trial

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Abstract

Objective: : High intensity interval training (HIITs) can induce weight control, lowering blood pressure and beneficial effects on cardiovascular health in type 2 diabetic patients. The effect of different volumes of these exercises is unclear in type 2 diabetic patients. The aim of this study was to compare the effect of low volume and high volume of short-term intensive training on glycemic indexes of men with type 2 diabetes.

Materials and Methods: Thirty type 2 diabetes male patients who were referred to Yazd diabetes research center (30 - 46 years old) were selected and randomly divided into 3 groups of low and high volume HIITs groups and control group. The intensity of the exercises in low volume was up to 110% and in high volume up to 80% of the maximum heart rate. The two training groups performed exercises 3 days of week for 8 weeks. Glycemic factors and lipids profile were measured before and after the last training session. Data were analyzed by covariance and paired T-test.

Results: Low volume HIIT exercises significantly decreased the glucose (*P*-value: 0.01), HbA1c (*P*-value: 0.01), insulin (*P*-value: 0.005), insulin resistance (*P*-value: 0.001), and triglyceride (*P*-value: 0.04). Low volume HIIT in the insulin resistance had a significant difference with the control group (*P*-value: 0.04). High density lipoprotein in high volume group had a significant difference with the control group (*P*-value: 0.021).

Conclusion: Low-volume HIIT exercises can be a non-pharmacological approach to improving glycemic factors in type 2 diabetic patients.

Keywords: Glycemic factors, Low-volume HIIT, High volume HIIT, Type 2 diabetes

Introduction

Diabetes mellitus (DM) and related risk factors are associated with obesity, high blood pressure and lipid disorders as a worldwide pandemic. DM and metabolic disorders are costly (1,2).

Epidemiological studies showed that the prevalence of DM is increasing in developed and developing societies. DM increases the morbidity and mortality of heart disease, stroke, blindness, kidney failure and foot ulcer,

and also has a significant impact on the quality of life (3).

Obesity and DM are inseparably linked; more than 80% of type 2 diabetes (T2DM) patients are overweight or obese according to body mass index (BMI) (4). The insulin resistance is the main cause of T2DM (5,6). One of the main causes of obesity and T2DM is the imbalance between intake and consumption of energy (7,8). In general, physical activity with a diet and weight control is essential for diabetes prevention and management. Exercises training are one of the most effective methods for increasing cardiovascular fitness in T2DM patients (9). Exercise and physical activity in diabetics create beneficial adaptations in the adipose tissue and skeletal muscle, resulting in increased the GLUT4, decreased blood glucose levels, increased insulin sensitivity, reduced low density lipoprotein (LDL) and increased High density lipoprotein (HDL) (10,11). The maintenance of normal blood glucose at rest and during exercise depends on the coordination and integration of the sympathetic nerves system and the endocrine system. Muscle contraction increases delivery of glucose to the muscle, although blood glucose levels are commonly produced by glucose production through the process of gluconeogenesis and liver glycogenolysis and recall other energy sources, including free fatty acids (12). Several factors affect the use of energy sources during exercise; of course the most important are intensity and duration of activity. Physical activity changes the substrata from free fatty acids (the main source during rest) to glucose, muscle glycogen, fat and amino acids (13).

By increasing the intensity of exercise, dependence on carbohydrates (in the blood and muscle) increases. In early exercise time, glycogen provides a large amount of active muscle energy, so that glycogen stores are evacuated, and glucose uptake from blood and fatty acids released from adipose tissue increases. Intra muscular fat stores are the most available source of fat during long-term sports activities. As the duration of exercise continues, the production of glucose from the glycogenolysis of the liver is changed to gluconeogenesis (12). There are two well-known pathways for stimulating glucose uptake by the muscle. During rest, glucose is delivered to the muscle dependent to insulin and its main role is the restoration of muscle glycogen stores. During exercise, muscle contractions increase blood glucose uptake to help muscle glycogenolysis. Since both pathways are separate from each other, in T2DM patients whose insulin-dependent absorption is defective, absorbing blood glucose into the active muscle is doing. Absorption of glucose into the muscle even after exercise is also high because glucose uptake pathways persist after exercise (14). Physical activity increases the amount of basal metabolism, improves blood circulation throughout the body, improves health and decrease risk of cardiovascular disease, retinopathy, nephropathy and renal complications of diabetic patients (15).

Due to optimizing time and lack of adherence and motivation to doing exercises and long-term activities among the general population and patients, the role of short-term exercises has been highlighted in the health of people (16,17).

The recent studies on sport sciences, using a combination of speed training (ST) and interval training (IT), devised a new method of exercises called high intensity interval training (HIIT), which improved both aerobic and anaerobic systems. HIIT is repetitive short time workout (up to 60s) with intense near to maximum HR (90 to 110%) or peak VO2 activity (VO2 peak $\geq$ 90%). Regarding the intensity of the exercises, an HIIT attempt may take from several seconds to several minutes, with various interventions separated by a few minutes of rest or activity with low intensity (18,19). Given the wide range of HIIT studies in which researchers used 5 seconds to 4 minutes of activity as HIIT, the activities are divided into two categories:

Low-volume HIIT: Less frequent activities, or up to 60 seconds, with intensity equal to or

near maximum power or velocity, are considered to be intense low volume exercises. (20).

High-volume HIIT: Activities with longer activities, from 1 to 4 minutes known as HIIT, but less intense than low volume HIIT (20).

As the mechanism of these exercises, HIIT increases the concentration of energy substrates and the activity of enzyme linked to the metabolism, hence increasing the frequency of high intensity repetitions and alternating it with a recovery between the activity changes the need of muscle cells and metabolic pathways, which simultaneously involves the development of aerobic and non-aerobic energy production in ATP reconstruction. Therefore, by using these training, we can expect a wide range of metabolic and functional adaptations (21). Due to immobility and low average levels of physical activity among people with metabolic diseases due to lack of enough motivation, optimizing time, short-term physical activity can play an effective role in improving their health. The results of Trap et al. showed that 15 weeks of HIIT exercises had a significant decrease in the percentage of total body fat, subcutaneous fat of abdomen, and insulin resistance in young women in compared with the traditional exercises (22). Considering the available information on the positive effects of HIIT exercises and the lack of similar research, the study of the effect of different volumes of these exercises on the health-related indices of T2DM patients seems necessary. However, despite the lack of complete recognition of the cellular-molecular mechanisms of HIIT exercises, it is necessary to study the unclear and unknown points. The aim of this study was to evaluate the effect of HIIT training on glycemic factors and lipid profiles in T2DM patients.

Materials and Methods

The present study was a randomized control trial study with pretest and post-test design with control group. The statistical population of this study included all non-athletic T2DM

men in Yazd city. The sample size was calculated by using G*power software based on the mean and standard deviation of previous studies for blood glucose, insulin and insulin resistance, and the minimum required number of 9 samples for each group was estimated (alpha= 0.05, power= 0.8 and effect size= 0.25), which for a higher statistical power of 10 samples per group was chosen. Thirty T2DM patients as the studied sample were selected from Yazd diabetes research center. They were divided into three groups by simple randomization: high volume HIIT training (10 subjects), low volume HIIT (n= 10) and control group (n= 10). During the study, the training groups participated in the HIIT training protocols for an extended period of 8 weeks, and the control group did not receive any interventions during this period, and only had their daily and normal activities. Subjects were evaluated for physical health, history of cardiovascular, respiratory, orthopedic problems and diabetic neuropathy under supervision of physicians before intervention. All subjects completed the PAR-Q questionnaire and medical assessment and signed informed consent. Subjects were non-athletic and non-insulin dependent with age range of 29 to 46 years and body mass index (BMI) rang of 23 to 36. The severity of the disease in these subjects were in terms of fasting blood glucose (FBG) levels between 126 - 350, 2-hour glucose (2hpp) between 200 - 400, and HbA1c higher than 6.5.

The exercises done on stationary bicycle, the Chinese classic model bike made in China and Heart rate was recorded by means of a heart rate monitor (Polar Equine S-610i, Polar®) to control the intensity of exercise during workout.

Method of measuring blood variables

According to the previous literature, 24 hours before the first training session and 48 hours after the last session, we collected 10 cc venous blood samples from the pre-arm venous in the fasting state (at 8:30 am). Blood samples were immediately poured into special

tubes and then centrifuged at room temperature of 3000 rpm for 5 minutes. The serum was stored for further measurements at -80 °C. The serum levels of FBG, 2hpp, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG) and total cholesterol (TC) were measured using a Biosystems kit manufactured in Italy and colorimetric method using the Biosystems B400 machine. HbA1c levels were also measured using Japan's HPLC (TOSOH G8) device. In order to measure serum insulin levels, the Monobind kit of the United States was used manually. The MR96A (Mindray) device was also used to read the test results. The HOMA-IR formula was used to calculate insulin resistance (23).

HOMA-IR= Insulin fasting serum (mg/ ml) × Fasting glucose (mg/ dL) / 22.5

Exercise protocols
Regarding the nature of HIIT training and increasing the intensity of exercise as well as overweight in diabetic patients, the implementation of the exercise protocol for these patients on stationary bike was more secure than the exercise on the treadmill, according to the training program included two protocols of HIIT exercises with high volume and low volume, which was performed for 8 weeks and 3 consecutive days each week. Regarding the high intensity of this kind of training and lack of fitness of patients, the first six sessions in both groups included familiar exercises and fitness. Each training session included 5 minutes of warming up (stretching and cycling on a bike) and 5 minutes of cool down (very low intensity) at the end. In order to control the intensity of the exercises, we used resting heart rate of the patients.

Low volume HIIT Protocol
This training program included 24 sessions for 8 weeks and three non-consecutive days per week. The exercises began in the first six sessions to create adaptability and training with very low intensity. The sets of the training increased since the fourth session,

from 2 sets to 6 sets in the final session, and the duration of each set increased from 10 seconds to 20 seconds. In order to comply with the principle of overload, the intensity of exercise was controlled by increasing heart rate from 90% HR in the third week to 110% HR in the eighth week.

High volume HIIT Protocol
This training program included 24 sessions for 8 weeks and three non-consecutive days per week. The exercises began in the first six sessions to create adaptability and training with very low intensity. The sets of the training increased from 2 sets to 6 sets at the last session, the duration of the sets was 60 seconds. The intensity of exercise was controlled by increasing heart rate from 70% HR in the third week to 80% HR in the eighth week.

Statistical analysis
Normality was assessed for each group using the Shapiro–Wilk test. Paired T-test was used to compare the pre-test and post-test values for time effect. The covariance test was used for comparing the groups, and for post hoc LSD was used. Statistical significance for all data analysis was set at 0.05. All data was analyzed using IBM SPSS Statistics Version 21.

Ethical considerations
This study was approved by Committee of Ethics in Research of Shahid Sadoughi University of Medical Sciences, Yazd, Iran with number of IR.SSU.REC.1396.103, then was registered in the Iranian Clinical Trial Registration Center (www.irct.ir) with IRCT20180827040887N1 code. At first session, all subjects sign the inform consent.

Results
The demographic information of the subjects including the mean and standard deviation (SD) of age, weight, height, and BMI were reported in Table 1.
In control group, as shown in Table 2, insulin resistance, FBG, TG and LDL did not change

Table 1. Demographic characteristics of subjects including mean and standard deviation of age, weight, height and BMI

Variables	Age	Weight (kg)	Height (cm)	BMI (kg/m^2)
Control	5.78 (±37.5)	86.5 (±14.76)	0.07 (±1.71)	3.27 (±29.51)
High Volume	3.77 (±37.80)	12.95 (±85.12)	0.06 (±1.70)	3.14 (±29.85)
Low Volume	5.10 (±39.30)	13.51 (±87.99)	0.04 (±1.73)	3.80 (±29.22)
P-values	0.688	0.888	0.370	0.970

Table 2. Mean (SD) of glycemic indexes and lipid profiles in pretest and post-test in three groups

Groups	Variables	Pre-test Mean (± SD)	Post-test Mean (± SD)	*p*-value
Control	FBG (mg/dl)	177 (±53.39)	177.80 (±54.95)	0.918
	2hrpp (mg/dl)	248 (±88.81)	245.10 (±78.44)	0.850
	HbA1c	7.80 (±1.86)	7.81 (±1.92)	0.971
	Insulin (μU/ml)	5.49 (±3.32)	7.18 (±5.05)	0.223
	HOMA-IR	39.72 (±20.61)	52.77 (±37.66)	0.162
	TG (mg/dl)	241.20 (±94.35)	229 (±82.07)	0.655
	TC (mg/dl)	158.40(± 26.16)	158.30 (±23.75)	0.993
	LDL (mg/dl)	66.90 (±16.59)	78.50 (±16.22)	0.424
	HDL (mg/dl)	37.90 (±2.64)	33.10 (±3.48)	0.007[b]
	Fat%	22.18 (±5.92)	23.53 (±4.05)	0.289
High volume	Glucose (mg/dl)	162.90 (±65.63)	157.50 (±35.28)	0.835
	2hrpp (mg/dl)	244.60 (±72.25)	232.20 (±95.11)	0.616
	HbA1c	7.30 (±2.30)	7.49 (±2.25)	0.262
	Insulin (μ U/ml)	8.10 (±5.06)	6.09 (±3.71)	0.217
	HOMA-IR	50.46 (±29.20)	40.23 (±23.17)	0.375
	TG (mg/dl)	213.80 (±81.25)	194.80 (±65.16)	0.443
	TC (mg/dl)	179.80 (±29.41)	181.50 (±18.20)	0.868
	LDL (mg/dl)	97.90 (±26.03)	105.20 (±21.38)	0.169
	HDL (mg/dl)	39.20[a] (±4.52)	37.70[a] (±5.77)	0.193
Low-volume	Fat%	22.72 (±2.60)	20.34 (±2.69)	0.001*
	Glucose (mg/dl)	181.7 (±30.79)	160.50 (±35.39)	0.015*
	2hrpp (mg/dl)	270.40 (±65.91)	217.50 (±89.67)	0.091
	HbA1c	7.96 (±1.08)	7.22 (±1.23)	0.014*
	Insulin (μU/ml)	5.72 (±2.63)	4.79 (±2.16)	0.005*
	HOMA-IR	45.06 (±19.31)	34.68[a] (±17.96)	0.001*
	TG (mg/dl)	237.8 (±75.91)	202.90 (±80.64)	0.049*
	TC (mg/dl)	180 (±35.40)	173.60 (±32.16)	0.542
	LDL (mg/dl)	89.80 (±21)	87.20 (±18.64)	0.392
	HDL (mg/dl)	39 (±4.76)	38.50 (±2.06)	0.098
	Fat%	22.69 (±4.74)	19.80 (±2.70)	0.035*

* Significant decrease compared to the pre-test
a Significant difference with the control group
b Significant unexpected decline in pre-test

significantly in post-test compared to the pre-test in the control group, except for the unexpected decrease in HDL.

There were no significant differences between three groups by using ANCOVA after removing pre test scores, but we found some two by two comparisons (post hoc) difference which mentioned in follow.

High volume HIIT group
Among glycemic variables and lipid profiles, only a significant reduction in fat percentage was observed in the high volume group. In other variables, no significant difference was observed between pre-test and post-test. Comparing the between group of HDL different only between the groups of high HIIT and control group (*P*-value: 0.021). In term of insulin resistance, due to the small number of subjects, this group had a border line significant difference with the control group (*P*-value: 0.09).

Low-volume HIIT group
According to graph 1 and table 2, paired T-test showed a significant decrease in TG. In glycemic indices, FBG, insulin, insulin resistance and HbA1c decreased significantly.
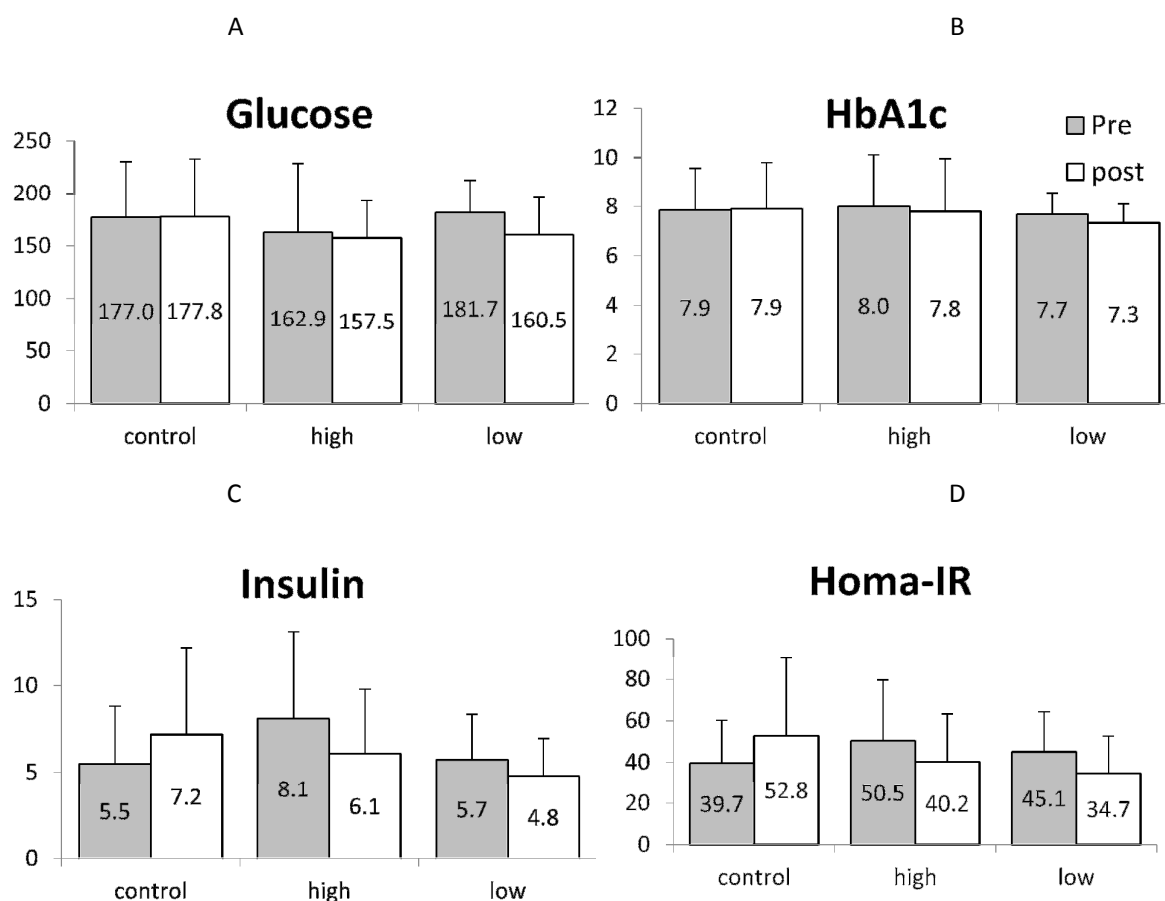
Figure 1. The means and standard deviations of fast blood sugar (A), HbA1c (B), Insulin (C) and Insulin resistance (D) in three groups at pre test and post test
*   significant differences with pretest
\#   significant differences with control

Also, ANCOVA and LSD post hoc showed, the insulin resistance index was significantly different only between the groups of low HIIT and control group (*P*-value: 0.049).

Discussion
In this study, 30 men with T2DM were selected and randomly divided into three groups: control, low-volume HIIT, and high volume HIIT groups. In low volume, the intensity of exercise was near to maximum (95% max. HR) and over maximum (up to 110% max. HR), and intensity of exercise in high volume group was less than low volume group (up to 85% max. HR). Both groups trained three days per week for 8 weeks (24

sessions) (stationary bike cycling). The results showed that high volume HIIT training had a significant effect on reducing body fat percentage, while low volume HIIT training in terms of lipid profile reduced body fat percent and TG as well. For glycemic indices, glucose, insulin, insulin resistance and HbA1c significantly reduced.

Lipid profile
Both training groups of low volume and high volume HIIT reduced the percentage of body fat significantly. Previous studies, such as Shaban (29), also reported similar results in HIIT training (4 sets of 30 seconds), and they mention this exercise, in terms of time effects,

is an effective factor for reducing body fat percentage.

Low volume and high intensity training in this study showed better results in TG reduction. Blood TG is one of the important components of lipid profile. Insulin resistance and impaired insulin function can lead to dyslipidemia in diabetic patients. Increasing the concentration of TG, LDL and lowering the HDL concentration is a feature of dyslipidemia in patients with T2DM, which are also a major risk factor for atherosclerosis and cardiovascular disease. Some studies have also been described high TG as an independent risk factor for myocardial infarction. High levels of TG may result in elevated lipoproteins, including chylomicrons, various VLDL subunits, or moderate-density lipoprotein (IDL cholesterol).

Researchers have described the period of exercise training as one of the factors influencing lipid profile changes (60). The literature also support high body weight loss or body composition changes to improve TG status. In other words, exercise significantly affects the lipid profiles of individuals who have higher TG and LDL levels (17). There is also evidence of a relationship between pre-exercise TG concentration and the magnitude of post-exercise exercise changes. In other words, people with higher serum TG levels prior to exercise showed higher reductions after exercise, while those who had low levels of TG before exercise changed less or not significantly. In the present study, the TG of subjects in both experimental groups was high (high volume group, 213 mg/ dL and low volume, 237 mg/ dL). The exercise especially HIIT have better result in subjects with higher rates of blood TG. Past studies have also shown that in response to a one session exercise, the amount of TG in the blood decreases until 2 days after an exercise session, and this is beneficial even in men with hyperlipidemia.

Due to the close-to-meaning decrease in the exercise group, a low volume of exercise (a decrease of about 35 units), which used more

intense exercises compared with the high volume exercises (decreasing about 19 units), the effect of exercise intensity and also the initial levels of TG may be a potential factor in reducing the level of TG levels. At the same time, according to the research background regarding the effect of exercise on serum TG levels in different individuals, one of the reasons for not significantly altering the serum levels of TG can be due to the duration of the training period.

Glycemic factors
In the present study, FBG and 2hpp in both groups were decreased in post-test compared to the pre-test, which was statistically significant only in the low volume HIIT group for FBG. Previous studies have also reported the effects of low-volume HIIT exercises on reducing blood glucose, including Sandwi et al. (24), Fex et al. (25), Trapp et al. (26), Richard et al. (27), and Adamson et al. (28), which almost their training protocols (including 5 to 10 sets of 30 seconds) were similar to our study's low-volume protocol. In contrast studies of Shaban et al. (29), the effect of HIIT was not significant, but their training was 4 sets of 30 seconds of running 20 meters for 6 weeks, which differed in intensity, duration and type of activity.

In diabetic patients, impaired glucose metabolism is usually due to impairment of GLUT-4 function or impaired insulin signaling. Considering the fact that in this study, FBG and HbA1c showed a significant decrease, it can be concluded that the low-volume HIIT exercise protocols in this study have been able to positively change the amount of carrier proteins GLUT-4. Also, it should be noted that high volume HIIT training have been effective in reducing blood glucose, but low HIIT exercises have had a greater reduction in FBG and has been statistically significant. It can be said that blood glucose changes are probably correlated with intensity of exercise. Little et al. (30) investigated the effect of 2 weeks of HIIT on FBG and mitochondrial capacity of skeletal

muscle in T2DM patients. The exercise protocol used 2 weeks of HIIT on a stationary bike, each containing 10 sets of 1 minute cycling with 90% of the maximum oxygen consumed. The exercise protocol of this study is similar to the HIIT protocol of the present study, which has been shown to decrease the mean blood glucose and glucose levels in T2DM patients. Regarding the duration of training and intensity, it can be said that both of the time and the intensity are important variables in the effect of exercise on blood glucose. On the other hand, the role of exercise and muscle contractions during exercise have been shown to improve insulin sensitivity (27).

Generally, exercising activity increases the amount of glucose transporters in the exercised muscles, which improves insulin action and glucose metabolism and can decrease the amount of glycosylated hemoglobin. One of the reasons for the insignificant decrease in HbA1c due to high volume HIIT exercises in this study is that HbA1c is an indicator that indicates the average blood glucose in the last 3 months and the duration of exercise in this study was eight weeks. It's been a week that this time. This short duration of training may not be sufficient for a meaningful change in the level of HbA1c in high volume HIIT exercises. And we can also point out that lower intensity of high volume training than low volume training group could be deduced that high volume training can be due to insignificant HbA1c between pre-test and post-test.

Limitations

An important limitation of the study is that we did not blind the investigators and were unable to control for physical activity and diet external to the sessions, like most training studies. In additional, due to the effect of menstrual cycles on some biochemistry factors and also any cultural restrictions, only males were recalled in the study.

Conclusions

The research findings support the superiority of the low-volume HIIT exercise protocol on the high-volume HIIT protocol in influencing the improvement of variables related to men with T2DM, so it can be argued that low-volume HIIT exercises, according to lower volume need to less time compared to high-volume protocols is a more appropriate option for recommend to T2DM patients, especially for the improvement of some glycemic and triglyceride factors.

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Conflict of Interest

All authors declare there were no conflicts of interest.

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