Inflammatory, Antioxidant and Glycemic Status to Different Mode of High-Intensity Training in type 2 Diabetes Mellitus

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Abstract

Background: Exercise is considered to improve metabolic markers in type 2 diabetics Mellitus (T2DM). In this regard, we compared inflammatory, antioxidant, and glycemic status to a different mode of high-intensity interval training in patients with T2DM.

Methods and Results: 59 T2DM patients (age= 45-60 yrs) were randomly divided to strength training (ST) (n=15), high intensity interval training (HIIT) (n=16), HIIT+ST (n=15) or served as control (CON) (n=13) groups. Experimental groups performed three training sessions/week for 12 weeks. Blood biochemistry and anthropometric parameters were evaluated at baseline and after the 12 weeks of interventions.

All training protocols ameliorated antioxidant factors (total antioxidant capacity, glutathione peroxidase, superoxide dismutase, and malondialdehyde activities), lipid profile (TC, TG, HDL and, LDL,) and glycemic parameters. Moreover, interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) significantly decreased in three training groups; however, these change was more pronounced in the ST+HIIT group. As a result of training, the overall concentration of inflammatory and antioxidant status was improved significantly in all three groups than the CON group and baseline values ($P \leq 0.05$). Moreover, non-substantial differences were found among groups on and measured glycemic variables.

Conclusions: Our results showed improvement in inflammatory factors, antioxidants, and glycolytic indices in all groups regardless of their type. However, for more benefits in T2DM patients, combination exercises can be suggested.

1. Introduction

Estimates show that the global number of T2DM patients will reach about 366 million in 2030 (1). T2DM leads to several macro and microvascular complications related to long-term damage and various organ-system failure (2). In this regard, several studies have indicated that T2DM triggers oxidative stress by the production of free radicals and a reduction in antioxidant status (3, 4). Reactive oxygen species (ROSs) and simultaneously decline in antioxidant levels have been indicated in causing β-cell dysfunction and insulin resistance, which are hallmarks of T2DM (5). It has been shown that there are several sources of oxidative stress formation under diabetic conditions such as mitochondrial and non-mitochondrial origins (6). In mitochondria, hyperglycemia has been induced the generation of intracellular ROS during oxidative respiration through the increment of electrons transfer by the electron transport chain (7). On the other hand, enzymatic and non-enzymatic antioxidant cellular systems have improved to maintain homeostasis by protecting the body against free radicals (8).

Additionally, increased oxidative stress-induced-inflammation is another mechanism in the progression and pathogenesis of T2DM (7). It seems that systemic inflammations have a critical mediator role in the pathogenesis of T2DM. Previous research has indicated that CRP and inflammatory markers, in specific IL-6 and TNF-α, are increased in subjects with T2DM (6), resulting in insulin resistance and, subsequently, development diabetic complications (7). CRP is considered the link between inflammation and

atherosclerosis, an independent predictor of cardiovascular diseases, and the outcome of acute coronary syndromes (9). In this regard, according to hs-CRP levels, diabetics can be categories at low, intermediate, and high risk in cardiovascular events (10). Moreover, inflammatory cytokines also directly induce vascular dysfunction, possibly through the increment of ROS, changing calcium channel expression and activity, and/or increasing cyclooxygenase expression (6).

On the other hand, diabetes demonstrates a primary challenge to the health care system; efficient and providential methods are necessary for its therapy. Physical activity and regular exercise have been considered a useful non-pharmacological method for T2DM management (11). Regular physical activity ameliorates insulin sensitivity and status of metabolic possibly through decrement of ROS and inflammatory factors production and enhancement of ROS-detoxification (7) and decrements the risk of cardiovascular events (12). Studies indicated that regular exercise training improves antioxidant capacity and attenuate the basal oxidative damage against ROS (6). Furthermore, long-term exercise is related to a decrement of pro-inflammatory factors such as IL-6, TNF-a, and CRP levels, besides elevated anti-inflammatory markers (13, 14). In this regard, previous researches presented that HIIT has a significant effect on inflammatory and oxidant status in T2DM. It is reported that hyperglycemia and muscle mitochondrial capacity improved following only two weeks of HIIT in patients with T2DM (15).

Additionally, several studies have shown that HIIT is more advantageous compared to continuous training in improving metabolic status, cardiovascular risk factors, and insulin sensitivity in individuals with T2DM (16, 17). Therefore, training intensity is the primary determinant for enhancing metabolic effects in patients with T2DM, even when performed in a short period (18). However, determining HIIT training effectiveness, interval duration, and work/recovery intensity play a significant role. Interestingly, strength training (ST) can be considered an effective method to improve the glycemic status and insulin sensitivity and mitigate the loss of strength and skeletal muscle mass, which generally exist in the individual with diabetes (19). Therefore, it seems that combine training such as ST + HIIT may provide health advantage, as glycemic control, cardiorespiratory fitness, and body composition. Moreover, although exercise training benefits in diabetic people have been detected, understanding the molecular basis needs to be more investigated. In this regard, a limited number have compared the effect of HIIT, ST, and HIIT + ST on inflammation and antioxidant state in T2DM. Hence, this study examined the different HIIT protocols on inflammatory, antioxidant, and glycemic status in T2DM patients.

1. Procedures

1.2. Subjects and study design

T2DM subjects who were referring to Oxygen medical center, Tehran, according to eligibility criteria, were elected to participate in the study. Eligibility criteria were as follows: fasting blood glucose (FBG) higher than7 mmol/L, glycosylated hemoglobin (HbA1c) upper 6%, at least two years of T2DM history, 45–60 years of age, no regular exercises during the previous six months. Exclusion criteria were: HbA1c above 10%, FBG > 22 mmol/L, previous myocardial infarction or stroke, cardiovascular disease history, cardiac

arrhythmia, renal and liver failure, smoking, and any contraindications to exercise. A number of 59 eligible subjects were randomized to HIIT (n = 16), ST (15), HIIT + ST (n = 15), or CON (n = 13) with an online randomization statistical service method. The current research was accepted by the Tehran University Ethics Board, conducted to the standards set by the Declaration of Helsinki, and all subjects provided written informed consent before participating. At the beginning and following the 12-week intervention period, blood collection, CPET, dynamic strength test, and body mass index (BMI) data were evaluated and analyzed. Intake of daily nutrition was evaluated by a food frequency questionnaire on three consecutive days, representing each item they ate and drank as precisely as possible. Data were analyzed using the Nutritionist IV software.

Table 1

Characteristics of subjects at baseline

	HIIT (16)	ST (15)	HIIT + ST (15)	CON (13)	P value
Gender (Men/woman)	9/7	7/8	10/5	6/7	NS
Age (years)	52.02 ± 4.59	51.31 ± 4.47	52.53 ± 4.80	52.28 ± 3.16	NS
Height (cm)	167.06 ± 6.26	168.6 ± 6.08	172.53 ± 4.86	168.92 ± 5.37	NS
Weight (kg)	78 ± 6.6388	81.33 ± 6.49	78.86 ± 5.27	75.61 ± 4.75	NS
BMI (kg.m-2)	28.01 ± 2.72	28.69 ± 2.84	26.55 ± 2.32	26.58 ± 2.58	NS
VO2peak (mL kg $^{-1}$ min – 1)	24.93 ± 3.17	24.4 ± 2.52	26.8 ± 3.5	24.84 ± 2.82	NS
HbA1C (%)	7.73 ± 1.06	7.73 ± 0.97	7.59 ± 0.58	7.28 ± 0.77	NS
Duration of diabetes (years)	7.25 ± 2.38	7.4 ± 2.5	7.06 ± 2.46	6.76 ± 2.65	NS
Medication	8 (50%)	6 (40%)	7 (46%)	5 (38%)	NS
Diuretic	5 (31%)	7 (46%)	6 (40%)	6 (46%)	NS
ACE inhibitors	6 (37%)	9 (60%)	8 (53%)	7 (53%)	NS
CCI	10 (62%)	11 (73%)	9 (60%)	8 (61%)	NS
Metformin	8 (50%)	7 (46%)	7 (46%)	5 (38%)	NS
Sulfonylureas	4 (25%)	6 (40%)	5 (33%)	5 (38%)	NS
DPP-4 inhibitors	9 (56%)	6 (40%)	8 (53%)	7 (53%)	NS
Statins	263.89 ± 31.48	265.67 ± 24.42	252.59 ± 27.46	256.44 ± 25.44	NS
Macro Nutrition	70.6 ± 12.84	67.28 ± 9.66	73.27 ± 12.09	72.6 ± 9.77	NS
Carbohydrate (g/d)	1.49 ± 0.25	1.32 ± 0.24	1.36 ± 0.22	1.21 ± 0.12	
Fat (g/d)					
Protein (g/kg/d)					

The data are presented as the mean ± SEM. Independent t-test and chi-squared test applied to calculated P values for demographic characters and medication variables, respectively. HIIT, high-intensity training group; ST, strength training group; HIIT + ST, high-intensity training + strength training group; CON, control group; BMI, body mass index.

1.3. Training Protocols

HIIT sessions were carried out on cycle ergometers, containing 10×60-s cycling intervals at the 85–90% maximal heart rate (HRmax) workload, divided by 1 min active recovery (19). The intensity of ~ 40% HRmax has been considered for warm-up (5 min) and cool-down (5 min) in each session. To confirm

suitable intensity, all subjects use a heart rate monitor (Polar Beat, Polar Electro) throughout exercise training.

Patients in the ST group performed bench press, leg curl, leg press, leg extension, lat pull-down, and shoulder press in three sets with maximum weight that could lift eight reps (20). Furthermore, abdominal crunch exercise was performed at three sets of 15 repetitions. 1-min has been considered a rest time sets.

Combined intervention participants performed firstly ST, followed by HIIT, totalizing 70 min. Moreover, according to previous researches, this order (ST before HIIT) of protocols improves glycemic stability. It attenuates the severity and duration of hypoglycemia after exercise in contrast with the reverse order (19). All protocols were carried out three times per week. Additionally, to adjust exercise intensity, every four weeks, all participants underwent CPET and strength tests to characterize their new HRmax and strength records, respectively.

Subjects in the CON group were asked to continue their routine activities without participating in any exercise program throughout the study.

1.4. CPET and dynamic strength test

The CPET, through indirect calorimetry respiratory gas exchange, has been performed to determine VO2peak on an ergometer cycle (Vyntus CPX, CareFusion, Germany). All Subjects were asked to avoid caffeinated beverages or smoking consumption and intense exercise for 24 h before the exercise test. The cycling workload adjusts to 25 W for 3-min warm-up, and the next intensity (power output) was enhancement 10W/min until exhaustion. Heart rate was monitored and recorded during CPET through a chest belt (Polar Beat, Polar Electro). The following criteria consider to record the value of Peak oxygen uptake (VO2peak) as a highest during CPET: (1) RER (respiratory exchange ratio) more than ≥ 1.1, (2) reaching to 90% of the HR_{max} according to age, and (3) plateau in VO2 contrary to the increment of exercise intensity. Moreover, the Borg 6–20 scale applied to detect the rate of perceived exertion in CPET.

A submaximal test has been carry-out in leg extension, leg press, bench press, and lat pull-down using an exercise machine to calculate the one-repetition maximum (1-RM). Moreover, 50% of the expected 1-RM has been used for a short warm-up (10–12 reps). Then, on a trial-and-error base up to 3 times, it determined a load that subjects could lift ten reps until exhaustion.

1.5. Anthropometric data and blood sample analyses

Using standardized procedures, body weight was measured by a body composition analyzer (InBody 570, Korea) and height have been evaluated with a portable stadiometer (InBody, InLab S50, Korea), and the BMI was computed.

Blood samples from the brachial vein have been gathered between 8:00 am and 10:00 am in overnight fasting conditions at the beginning and after the exercise training period. The collected samples were directly centrifuged (2000 g, 10 min, 4°C). The plasma and serum were placed in liquid nitrogen and transferred to the laboratory for further analysis. General biochemistry including glucose, low-density

lipoprotein (LDL), total cholesterol (TC), high-density lipoprotein (HDL), and triacylglycerol (TG) values were distinguished using an automated analyzer (CobasC111; Roche Diagnostics, Indianapolis, IN, USA). Anion exchange chromatography has been performed to calculate the HbA1c. Plasma levels of IL-6, TNF-α (East Bio-Pharm, China), CRP (Diagnostic Biochem Inc, Canada), SOD (Abcam, Germany) and GPX (Abcam, Germany), and insulin (Mercodia, Sylveniusgatan 8A, Sweden) were measured by ELISA, based on the guidance of manufacture. The colorimetric method used to evaluate the plasma TAC (Cayman, Ann Arbor, USA) is based on manufacturing guidance. The plasma MDA was measured using Draper et al. (1993) (21) using 1,1,3,3-tetra-ethoxypropane as the standard.

1.6. Statistical Analysis

Statistical analysis of the data from each experiment was performed with IBM SPSS statistics 21 software (SPSS, Inc., Chicago, IL, USA), using Two-way repeated ANOVA (group × time), ($P < 0.05$) followed by posthoc analysis Bonferroni test ($P < 0.05$). To determine the differences between medication variables, the chi-squared test was used. Mean ± SEM has been used to report all values.

2. Result

Baseline characteristics

Tables 1 presented the baseline characteristics of the subjects in the study. In the 4 study groups, all the baseline characteristics (demographic characteristics and medication) were similar. Moreover, according to independent t-tests tests, there was no significant difference between intakes of carbohydrate, protein, and total fat at baseline among the 4 study groups.

Demographic characteristics and Cardiorespiratory fitness (CRF)

Table 2 present the results of demographic characteristics and cardiorespiratory fitness at the baseline and after the training periods. The two-way ANOVA exhibit substantial interaction effects (group × time) for weight, BMI, HR_{max}, $VO2_{peak,}$ and exercise time following the training periods ($P \leq 0.05$). Based on baseline measures, weight, BMI, HR_{max}, $VO2_{peak,}$ and exercise time considerably improved in 3 experimental groups, as well as, only exercise time significantly increased in the CON group ($P \leq 0.05$). Posthoc results showed significantly greater values for $VO2_{peak}$ in the HIIT + ST group in contrast to CON and ST groups (Table 2, $P \leq 0.05$). Additionally, only HIIT + ST produced a significant decrement in SBP following 12 weeks of intervention ($P \leq 0.05$).

Glycemic and Profile Lipid status

After 12 weeks of training periods, a substantial group × time interaction was shown for HOMA-IR, HbA1c, insulin, and fasting glucose (Table 2, $P \leq 0.05$). Significant differences were seen in fasting glucose, insulin, HOMA-IR, and HbA1c after the intervention period in training groups ($P \leq 0.05$). Moreover, posthoc results showed non-differences among groups, significantly ($P \geq 0.05$). Furthermore, plasma HDL, LDL, TC (except ST group), and TG concentrations improved significantly in the HIIT, ST, and HIIT + ST groups

after training periods ($P \leq 0.05$), without a change in the CON group ($P \geq 0.05$). According to the post hoc results, there was a substantial difference in HDL and LDL concentration among three training groups with the CON group ($P \leq 0.05$). Besides, differences were significant among ST with HIIT and HIIT + ST groups in HDL and LDL levels ($P \leq 0.05$).

Inflammatory status

The two-way ANOVA presented considerable interaction effects (group × time) for TNF-α, IL-6, and CRP after the intervention periods ($P \leq 0.05$). According to baseline measures, TNF-α, IL-6, and CRP significantly improved in 3 experimental groups. Besides, TNF-α concentration showed a significant reduction in the CON group ($P \leq 0.05$). Bonferroni posthoc results illustrate a significant reduction of IL-6 in the HIIT, ST, and HIIT + ST groups than the CON group ($P \leq 0.05$). Moreover, a significant difference has been detected among ST and CON groups in CRP after the intervention (Fig. 1, $P \leq 0.05$).

Antioxidant status

The 2-way ANOVA for SOD, GPx, MDA, and TAC activity showed significant interaction effects (group × time) followed by the intervention period ($P \leq 0.05$). As a result of training, the overall concentration of SOD, GPx, MDA, and TAC were improved considerably in all three groups in contrast to baseline levels (Fig. 2, $P \leq 0.05$). As well as, SOD decreased substantially in the CON group ($P \leq 0.05$). According to the post hoc test, the HIIT, ST, and HIIT + ST groups presented a significantly higher SOD, GPx, and TAC levels than the CON group ($p < 0.05$). A significant difference has been reported among HIIT + ST and HIIT groups in plasma SOD levels following 12 weeks of intervention ($p < 0.05$). Moreover, differences were not significant among the four groups in MDA values ($P \geq 0.05$).

Table 2

Anthropometric, exercise test and biochemical variables outcome at Baseline and follow-up of training periods

	HIIT (16)	ST (15)	HIIT + ST (15)	CON (13)	P-value
Weight (kg)					
Baseline	78 ± 6.38	81.33 ± 6.49	78.86 ± 5.27	75.61 ± 4.75	0.115
Follow-up	76.82 ± 5.75*	79.54 ± 5.34*	76.93 ± 4.74*	75.07 ± 4.61	
BMI (kg.m-2)					
Baseline	28.01 ± 2.72	28.69 ± 2.76	26.55 ± 2.32	26.58 ± 2.58	0.071
Follow-up	27.59 ± 2.58*	28.06 ± 2.45*	25.89 ± 2.15*	26.40 ± 2.60	
VO2peak (mL kg $^{-1}$ min − 1)					
Baseline	24.93 ± 3.17	24.4 ± 2.52	26.8 ± 3.5	24.84 ± 2.82	0.027
Follow-up	27.06 ± 2.99*	25.93 ± 2.6*	29.4 ± 3.37*	25.65 ± 2.49	
HRmax (bpm)					
Baseline	125.43 ± 7.53	126.6 ± 7.53	128.13 ± 8.04	129.23 ± 6.11	0.785
Follow-up	133.43 ± 5.16*	135.2 ± 5.14*	135.13 ± 5.82*	131.6 ± 6.29	
Exercise time (min)					
Baseline	7.44 ± 0.92	7.23 ± 1.03	7.16 ± 0.87	7.05 ± 0.99	0.159
Follow-up	9.62 ± 0.98*	8.96 ± 1.27*	9.46 ± 0.8*	8.48 ± 1.4*	
Fasting glucose (mmol/L)					
Baseline	9.99 ± 1.38	10.03 ± 1.41	9.63 ± 0.85	9.85 ± 1.19	0.495
Follow-up	8.56 ± 1.37*	8.4 ± 1.31*	8.2 ± 1.09*	9.4 ± 1.14	
Insulin (mU/L)					
Baseline	8.37 ± 1.47	8.77 ± 1.17	8.73 ± 1.35	8.54 ± 0.91	0.519
Follow-up	7.22 ± 1.53*	7.95 ± 1.27*	7.77 ± 1.06*	8.24 ± 0.93	

The data are expressed as the mean ± SEM. Two-way repeated ANOVA was used for calculated P values for variables. HIIT, high-intensity training group; ST, strength training group; HIIT + ST, high-intensity training + strength training group; CON, control group; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL, High-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, Triglycerides.

	HIIT (16)	ST (15)	HIIT + ST (15)	CON (13)	P-value
HOMA-IR					
Baseline	3.72 ± 0.79	3.94 ± 0.94	3.77 ± 0.83	3.72 ± 0.48	0.589
Follow-up	2.74 ± 0.7*	3.02 ± 0.91*	2.86 ± 0.67*	3.42 ± 0.44	
HbA1c (%)					
Baseline	7.73 ± 1.06	7.73 ± 0.97	7.59 ± 0.58	7.28 ± 0.77	0.982
Follow-up	6.82 ± 0.79*	6.71 ± 0.76*	6.73 ± 0.43*	7.18 ± 0.73	
DBP (mm Hg)					
Baseline	83.81 ± 3.46	84 ± 2.47	84.66 ± 3.24	84.42 ± 3	0.009
Follow-up	82.31 ± 2.33	83.93 ± 2.78	82.46 ± 4.24	86.3 ± 2.25	
SBP (mm Hg)					
Baseline	127.06 ± 6.75	124.26 ± 6.69	129.93 ± 6.23	126 ± 6.32	0.463
Follow-up	125.31 ± 4.86	125.46 ± 5.71	125.2 ± 6.13*	128.46 ± 5.31	
HDL cholesterol (mmol/L)					
Baseline	1.21 ± 0.02	1.25 ± 0.42	1.24 ± 0.03	1.26 ± 0.03	0.001
Follow-up	1.44 ± 0.04*	1.36 ± 0.11*	1.45 ± 0.03*	1.27 ± 0.03	
LDL cholesterol (mmol/L)					
Baseline	3.56 ± 0.48	3.44 ± 0.59	3.55 ± 0.38	3.72 ± 0.44	0.001
Follow-up	2.95 ± 0.35*	2.87 ± 0.43*	2.74 ± 0.32*	3.68 ± 0.45	
TC (mmol/L)					
Baseline	4.8 ± 0.74	4.99 ± 0.65	4.81 ± 0.53	4.83 ± 0.64	0.317
Follow-up	4.25 ± 0.45*	4.65 ± 0.66	4.32 ± 0.38*	4.75 ± 0.44	

The data are expressed as the mean ± SEM. Two-way repeated ANOVA was used for calculated P values for variables. HIIT, high-intensity training group; ST, strength training group; HIIT + ST, high-intensity training + strength training group; CON, control group; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL, High-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, Triglycerides.

	HIIT (16)	ST (15)	HIIT + ST (15)	CON (13)	P-value
TG (mmol/L)					
Baseline	1.89 ± 0.16	1.97 ± 0.21	1.85 ± 0.2	1.84 ± 0.15	0.626
Follow-up	1.58 ± 0.16*	1.53 ± 0.11*	1.49 ± 0.15*	1.66 ± 0.53	

The data are expressed as the mean ± SEM. Two-way repeated ANOVA was used for calculated P values for variables. HIIT, high-intensity training group; ST, strength training group; HIIT + ST, high-intensity training + strength training group; CON, control group; DBP, diastolic blood pressure; SBP, systolic blood pressure; HDL, High-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, Triglycerides.

The effect of a different mode of HIIT on inflammatory status in T2DM patients. Tumor necrosis factor-alpha (TNF-α) (A), high-sensitive C-reactive protein (CRP) (B), and Interleukin 6 (IL-6) (C) at baseline (black) and after the training periods (gray). Data are means ± SEM. HIIT, high-intensity training group; ST, strength training group; HIIT + ST, high-intensity training + strength training group; CON, control group. According to baseline measures, TNF-α, IL-6, and CRP significantly improved in 3 experimental groups ($P \leq 0.05$). Bonferroni posthoc results illustrate a significant reduction of IL-6 in the HIIT, ST, and HIIT + ST groups than the CON group ($P \leq 0.05$).

The effect of a different mode of HIIT on antioxidant status in T2DM patients. Superoxide dismutase (SOD) (A), Malondialdehyde (MDA) (B), Glutathione peroxidase (GPx) (C), and total antioxidant capacity (TAC) (D), at baseline (black) and after the training periods (gray). Data are means ± SEM. HIIT, high-intensity training group; ST, strength training group; HIIT + ST, high-intensity training + strength training group; CON, control group. As a result of training, the overall concentration of SOD, GPx, MDA, and TAC was improved substantially in all three groups compared to baseline values ($P \leq 0.05$). According to the post hoc test, the HIIT, ST, and HIIT + ST groups presented a significantly higher for SOD, GPx, and TAC levels in contrast to the CON group ($p < 0.05$).

3. Discussion

The current study indicated a significant increase in $VO2_{peak}$, exercise time, and improvement of BMI and HR_{max} in three training groups. It has been found that T2DM patients have lower cardiorespiratory fitness (CRF) in contrast to healthy individuals (22, 23). Previous research has indicated that HIIT results in more significant CRF improvements than traditional training at lower intensities among individuals with chronic diseases such as metabolic syndrome (24, 25). It has been considered that the lower level of CRF shown in T2DM might be associated with low capillary density, increased blood viscosity, higher blood glucose levels, and presence of neuropathic and vascular complications in T2DM (26), besides plays as a significant predictor for cardiovascular mortality. However, T2DM patients shown lower CRF, exercise training intervention can ameliorate CRF and decrease cardiovascular mortality. In that respect, as every 3.5 mL/min/kg increment of $VO2_{max}$ has been shown to a 12% improvement in survival (27).

Moreover, studies have found that exercise intensity plays an essential factor in CRF improvements (24). Studies have emphasized the potent efficacy of HIIT on CRF, with more significant advantages than other exercise training types in T2DM patients. Støa et al. demonstrated three months of HIIT training contain 4×4 min with 85–95% of HR_{max} improved VO2max and BMI in T2DM (22). Furthermore, Hansen et al. also were found 16% (75% VOpeak) and 8% (50% VOpeak) improvements in VO2max following two months (28). In the current study, the more remarkable improvement of $VO2_{peak}$, exercise time, and BMI decrease were found in the combined training group. Recent reviews recommend that HIIT interventions, short and medium-term, are an efficient stimulus to improve CRF and body composition characters in individuals with T2DM (29). It seems that mechanisms involved in the superiority of HIIT, despite mode, maybe due to creating a more significant challenge to the heart, changes in the stroke volume induced by an increment of cardiac contractility (30), and skeletal muscle oxidative capacity, which improves mitochondrial function (24), thus increasing CRF. Enhancing of VO2peak has been related to improved glycemic control, insulin-stimulated glucose uptake rate (31), and blood pressure in T2DM individuals (17).

Moreover, we demonstrated a decrement of TG, TC, and LDL and an increase in HDL after 12 weeks of intervention in all training groups. There was a significant difference in HDL and LDL concentration among three training groups with the CON group. Besides, significant differences have been found between ST with HIIT and HIIT + ST groups in HDL and LDL values. Moreover, due to training, DBP and SBP decreased in experimental groups, but only HIIT + ST a substantial decrement in SBP following 12 weeks of intervention. Exercise training has heterogeneous effects on lipid profile and blood pressure. Although these results are in line with prior investigations, which found only the HIIT with RT group improved TC and LDL-C compared to the control group (32). In another study, improvements for TG, HDL, and SBP has been found following the HIIT intervention (8). Similarly, Mitranum et al. showed that HIIT training improved LDL, HDL, TG, and SBP, although the changes were associated with the pre-intervention values (17). Previous researches also described decreases in blood pressure phenomena. Jorge et al. demonstrated that combined training (aerobic, resistance) significantly decreased blood pressure (33).

Additionally, a significant reduction in SBP has been shown after resistance training in T2DM patients (34). However, another study did not find any blood pressure reductions after exercise training (35). It seems that the lack of significant differences in blood pressure, TC, and TG among the groups in the current study was likely due to the absence of significant differences in weight loss, as hypothesized by previous researches (33, 35).

In glycemic status, HOMA-IR, HbA1c, insulin and, fasting plasma glucose had improved significantly in HIIT, ST, and HIIT + ST groups, with no differences among the four groups. HbA1c is a long-term indication of glycemic status that is substantially attenuated following HIIT training, despite mode. Previous researches have studied the effect of HIIT on %HbA1c in a patient with T2DM. In that respect, T2DM patients who carry out a HIIT program with 85–95% of HR_{max} showed a significant reduction in HbA1c compared to moderate-intensity continuous training, though insulin was not changed significantly (22). Karstoft et al. found more significant improvements in glycemic control in HIIT compared to the

continuous-walking training in T2DM patients (36). A recent meta-analysis illustrated that HIIT is more efficient than moderate-intensity continuous training for improving insulin sensitivity in healthy individuals (37). It has been demonstrated that each 1% reduction in HbA1c levels was related by a 14% decrease of myocardial infarctions and a 21% reduction of risk of-death associated with diabetes (38).

Moreover, we demonstrate that insulin and HOMA-IR, known as insulin resistance, significantly decreased in all experimental groups. In insulin resistance (IR), the biological function of insulin is decreased in peripheral target tissues. IR resulted in a disproportionate insulin value to the glycemic level. Thus, IR is associated with a hyperinsulinemia status (39). The present results tend to be in line with previous observations, where a cohort study demonstrated significantly improved IR (~ 15%) and metabolic markers after 4-month strength training (70–80% 1RM) on diabetic subjects (40). Additionally, ST (more than 85% 1RM) resulted in ameliorating insulin sensitivity in people with diabetes, while the effect of endurance training was moderate (41).

Moreover, in T2DM patients, insulin levels were substantially decreased following chronic HIIT performed by walking exercise (42). HIIT significantly attenuates FPG in T2DM patients (43, 44), similar to the current study. Winding et al. performed 33 sessions of cycle-ergometer HIIT and reported lower fasting plasma glucose (44). Moreover, 16 weeks of HIIT (jogging/running) decreased fasting plasma glucose in adults with T2DM (43). Despite the lack of differences among groups, these results emphasize the HIIT as an effective strategy to produce significant effects on glycemic status in T2DM patients. The mechanisms for ameliorated glycemic status related to exercise training are not completely clear. Improved glycemic control induced by HIIT seems to be associated by the increment of insulin signaling, insulin-stimulated glucose disposal rates, glucose transporter protein levels, and improved skeletal muscle blood flow, enhancing the glucose delivery (45), and local factors related with exercise training (15). Although all of these processes seem intensity-dependent, theoretically HIIT appears to be more effective (46).

Previous research has presented a significant association among inflammation and oxidative stress that could be referred to as the oxidative-inflammatory cascade (OIC) in T2DM. On the other hand, the anti-inflammatory and oxidative stress effect of exercise has been discussed recently. In the current study, we demonstrated that the overall concentration of SOD, GPx, MDA, TAC, TNF-α, IL-6, and CRP significantly improved in 3 experimental groups, besides, TNF-α and SOD concentration showed significant reduction and increased in the CON group, respectively. In this regard, Mohammadi Zadeh at al. demonstrated that HIIT decrement pro-inflammatory parameters and improved anti-inflammatory factors in T2DM people (47). Khanna et al. (2017) shown that combined exercise (aerobic + resistance) has more effects on decrement of TNF-α, CRP, IL-1β and, IL-6 compared to aerobic or resistance training alone (48). In our investigation, the combined training group showed greater improvement in inflammation factors comparison to the others. Similar results to the ones in our study were presented with decreased CRP levels while using a different protocol of HIIT, either alone or combined with RT in T2DM patients (9).

Moreover, two short types of research reporting no substantial effects on IL-6, TNF-α, and CRP in T2DM (49). Moreover, in a meta-analysis with T2DM individuals, aerobic exercise was related to reducing CRP, while strength or combined training was not (50). According to the previous investigation, it seems that weight loss is required to moderate such factors (51). Inflammatory cytokines, including TNF-α and CRP, were leading to decreased insulin sensitivity and the evolution of diabetic complications (7). The exact mechanism of the anti-inflammatory effect of HIIT is not precise. However, the reduction of visceral fat mass and muscular anti-inflammatory myokines production, such as IL-6 (52), has been proposed to improve inflammatory status after an exercise intervention.

Furthermore, pro-inflammatory factors resulting from the IR state induce increment in ROS and free radicals and induce more significant oxidative stress in T2DM (53). On the other hand, the exposure to pro-oxidant inducers such as HIIT increases antioxidant capacity (19). In the current investigation, three HIIT types increase significantly antioxidant enzymes and decreased the MDA levels, with no differences between the groups. A similar study in T2DM subjects demonstrated the different modes of training (strength training, aerobic training, and combined training) provided significant increases in antioxidant enzymes, which may have attenuated oxidative stress of diabetes (54). In the study by Mitranun et al., increases in GPx were reported along with decreases in MDA after the HIIT training, but not traditional exercise training (17). Moreover, HIIT training was able to upregulate antioxidant capacity while continuous training did not suggest a superior effect of HIIT when performed in the long term (49). The impact of long-period exercise training on oxidative stress in T2DM patients has not been thoroughly examined. It has been reported that exercise duration and intensity play an essential role in enhancing the antioxidant defense system (55). In this regard, HIIT activates an activated protein kinase that is significantly associated with cellular energy homeostasis and induces the expression of peroxisome proliferator-activated receptor coactivator-1α (PGC-1α). PGC-1α works as a regulator of mitochondrial biogenesis and helping to improve the VO2max and less oxidative stress (56).

Conclusions

In conclusion, our investigation found that various physiological and biochemical advantages resulted from HIIT, regardless of the training protocol type. However, it should be noted that the non-difference among groups on most variables may be associated with the small sample size, the intake of different drugs, which may affect on exercise outcomes. Moreover, there was no control on the energy intake of the subjects during the training period. More researches with a similar period will be required to investigate whether differences exist in response to distinct type HIIT exercise in patients with T2DM.

Declarations

Compliance with ethical standards

Funding: Any institutes did not fund this study.

Conflict of interest: The authors declare no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were by the ethical standards of the ethical committee of Tehran University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate: Informed consent was obtained from all individual participants included in the study.

Author Contribution: MS and FS designed the study. PP, SS, and MS collected the data. FS and PP revised the final version of the manuscript. All authors read and approved the manuscript.

Consent to Publish: Patients signed informed consent regarding publishing their data and photographs.

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Figures

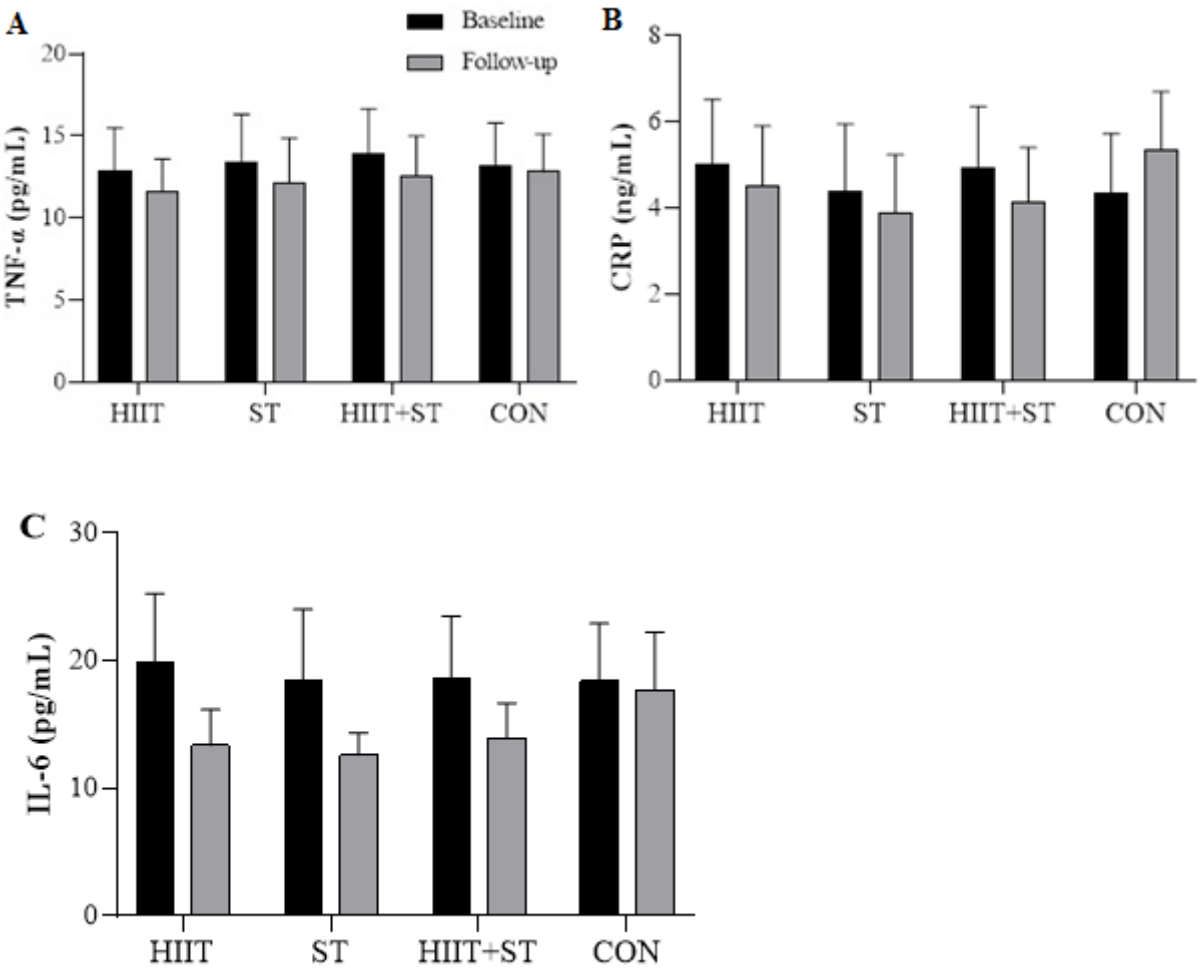

Figure 1

The effect of a different mode of HIIT on inflammatory status in T2DM patients. Tumor necrosis factor-alpha (TNF-α) (A), high-sensitive C-reactive protein (CRP) (B), and Interleukin 6 (IL-6) (C) at baseline (black) and after the training periods (gray). Data are means ± SEM. HIIT, high-intensity training group; ST, strength training group; HIIT+ST, high-intensity training+ strength training group; CON, control group. According to baseline measures, TNF-α, IL-6, and CRP significantly improved in 3 experimental groups ($P \leq 0.05$). Bonferroni posthoc results illustrate a significant reduction of IL-6 in the HIIT, ST, and HIIT+ST groups than the CON group ($P \leq 0.05$).

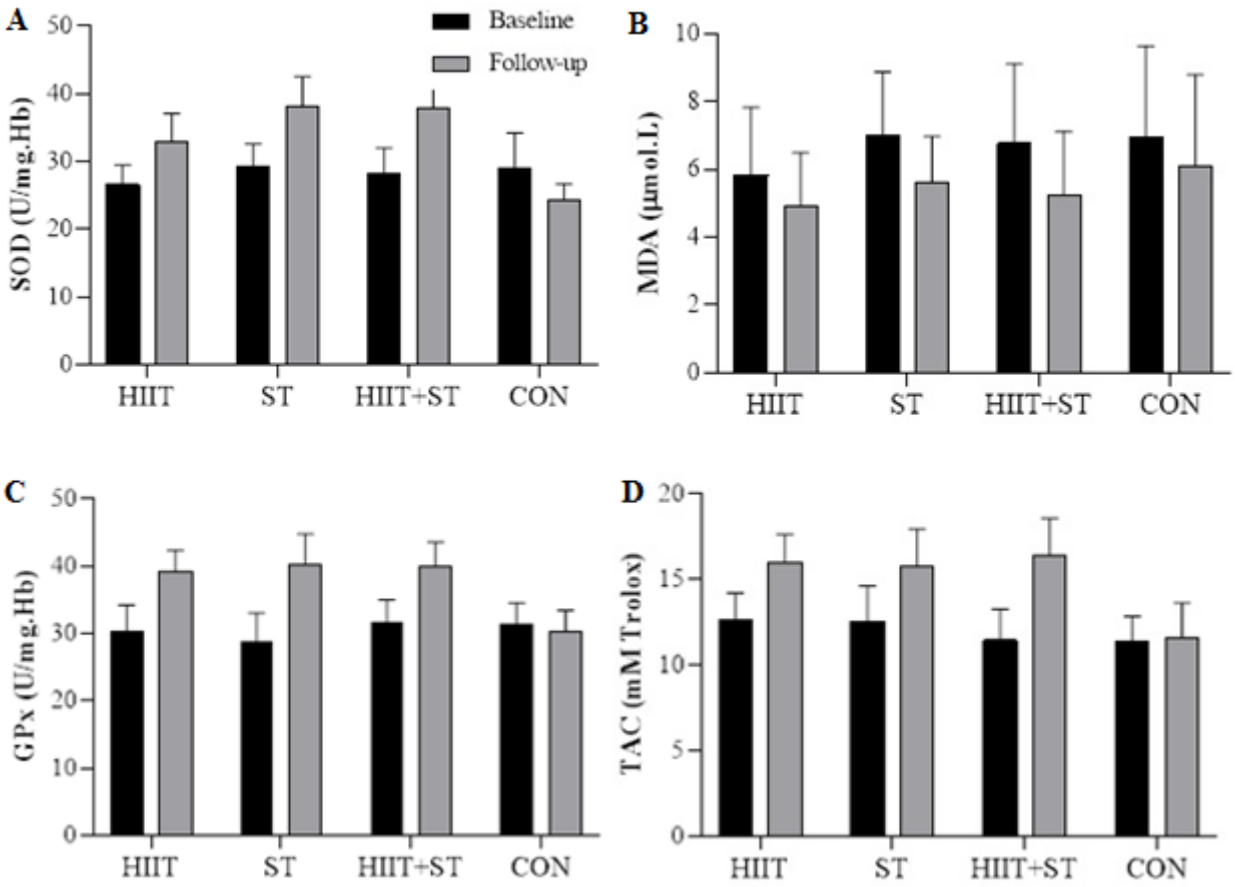

Figure 2

The effect of a different mode of HIIT on antioxidant status in T2DM patients. Superoxide dismutase (SOD) (A), Malondialdehyde (MDA) (B), Glutathione peroxidase (GPx) (C), and total antioxidant capacity (TAC) (D), at baseline (black) and after the training periods (gray). Data are means ± SEM. HIIT, high-intensity training group; ST, strength training group; HIIT+ST, high-intensity training+ strength training group; CON, control group. As a result of training, the overall concentration of SOD, GPx, MDA, and TAC was improved substantially in all three groups compared to baseline values ($P \leq 0.05$). According to the post hoc test, the HIIT, ST, and HIIT+ST groups presented a significantly higher for SOD, GPx, and TAC levels in contrast to the CON group ($p < 0.05$).