Inflammatory, antioxidant and glycemic status to different mode of high-intensity training in type 2 diabetes mellitus

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Abstract

Background Exercise has traditionally been used and prescribed as an effective and suitable way to treat type 2 diabetics Mellitus (T2DM). In this regard, we compared inflammatory, antioxidant, and glycemic status to different kinds of high-intensity interval training (strength training, HIIT, and HIIT + ST) in patients with T2DM.

Methods and results Fifty-nine 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. Inflammatory, antioxidant, glycemic factors, and anthropometric parameters were evaluated at baseline and after the 12 weeks of interventions. Training HIIT groups significantly improved antioxidant factors, lipid profile, and glycemic parameters (P ≤ 0.05). Interleukin 6 (IL-6), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α) significantly decreased in the three training groups. As a result of training, the overall inflammatory and antioxidant status were improved considerably in all three training groups compared to the CON group (P ≤ 0.05). In addition, there were significant differences in CRP at the follow-up values between ST and CON groups (P ≤ 0.05). Exercise time and TC were significantly improved in HIIT than in the CON group (P ≤ 0.05). The results showed a significant difference between the HIIT + ST group and the CON group in VO2peak (P ≤ 0.05).

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

Keywords T2DM · HIIT · Oxidative stress · Inflammatory markers

Introduction

Epidemiological results indicate that 488 million adults aged 20–99 years living with diabetes in 2019 and expected to increase to more than 700 million by 2045 [1]. T2DM is characterized by high blood glucose, insulin deficiency, and insulin resistance [2]. Several studies have found that T2DM triggers oxidative stress by increasing free radicals and reducing antioxidant status [3, 4]. Simultaneously reactive oxygen species (ROSs) may also contribute and accelerate insulin resistance development and decline antioxidant levels associated with β-cell dysfunction and insulin resistance [5]. In mitochondria, hyperglycemia-induced the generation of intracellular ROS during oxidative respiration [6]. Additionally, increased oxidative stress-induced inflammation is another mechanism in the progression and pathogenesis of T2DM [6]. Thus, it seems that systemic inflammations have a critical mediator role in the pathogenesis of T2DM. Previously, inflammatory markers, in specific CRP, IL-6, and TNF-α, are increased in T2DM [7]. According to hs-CRP levels, diabetics can be categories as low, intermediate, and high risk in cardiovascular events [8]. Moreover, inflammatory cytokines directly induce vascular dysfunction, possibly by increasing ROS, changing calcium channel expression and activity, and increasing cyclooxygenase expression (7).

On the other hand, exercise interventions have been considered a proper non-pharmacological method for T2DM management [9]. Previous studies showed that aerobic training
improved hemoglobin A1c (HbA1c), fasting glucose, and insulin sensitivity in T2DM [10, 11]. Moreover, it suggested that high-intensity aerobic exercise is superior to lower-intensity exercise in the improvement of cardiorespiratory fitness in T2D patients [12]. Regular physical activity (PA) increases insulin sensitivity, possibly by decreasing ROS and inflammatory factors production [6]. Studies found that regular exercise training improves antioxidant capacity and attenuates the basal oxidative damage caused by ROS [7]. Long-term exercise is related to decreased pro-inflammatory factors such as IL-6, TNF-α, CRP, and elevated anti-inflammatory markers [13, 14].

However, a lack of time has been identified as one of the critical barriers preventing patients from achieving the recommended PA level. Therefore, patients must participate in more time-efficient training programs to achieve optimized outcomes. HIIT appears to be a feasible and time-efficient alternative exercise protocol. Støa et al. [15] showed that 12 weeks of supervised HIIT significantly improved VO2peak and decreased HbA1c compared to moderate-intensity continuous training. In addition, a medium-term intervention (4-month) study [16] reported more significant improvements in body weight, fat mass, and glycemic control in HIIT than continuous training in T2D patients. Similarly, Mitranun et al. [11] also found that HIIT (12 weeks) improved HbA1c, maximal aerobic capacity in T2D patients, even if the total exercise time was reduced to half of that recommended.

Therefore, training intensity is the primary factor to increase metabolic effects in T2DM patients [17]. However, interval duration and work/recovery intensity plays a significant role in HIIT training effectiveness. Interestingly, strength training (ST) can be 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 diabetes patients [18]. Thus, it seems that combined training such as ST + HIIT may provide health advantages, as glycemic control, cardiorespiratory fitness, and body composition. Although exercise training benefits in diabetic people have been detected, understanding the molecular basis needs more investigation. In this regard, a limited number have compared the effect of HIIT, ST, and HIIT + ST on inflammation, antioxidant, and glycemic control in T2DM. Hence, this study examined the different HIIT protocols on inflammatory, antioxidant, and glycemic status in T2DM patients.

Method

Subjects and study design

T2DM subjects referred to Oxygen medical center, Tehran, were selected to participate in this study. Eligibility criteria were as follows: fasting blood glucose (FBG) higher than 7 mmol/L, 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 total 59 eligible subjects were categorized to HIIT (n = 16), ST [15], HIIT + ST (n = 15), or CON (n = 13) with an online randomization statistical service method.

The current research confirmed by the ethical committee of Tehran University (Ethic No: IR.UT.SPORT.REC.1399.004), conducted to the standards set by the Declaration of Helsinki. All subjects provided written informed consent before participating. At the beginning and following the 12-week intervention period, blood samples, Cardiopulmonary Exercise Test (CPET), and subjects characteristics were evaluated and analyzed. In addition, before the beginning of the study, daily nutrition intake was assessed by a food frequency questionnaire on three consecutive days. Data were analyzed using the Nutritionist IV software.

Main and secondary outcomes

The primary outcome was the change in HbA1c values following three months of different types of training. Secondary outcomes were changes in glycemic control (e.g. fasting glucose, and fasting insulin); lipid profile, antioxidant status (e.g. SOD, GPx, MDA, and TAC), inflammatory status (e.g. TNF-α, IL-6, and CRP), body composition (e.g. body weight, BMI); and cardiorespiratory fitness (e.g. HRmax, VO2peak, and exercise time).

Training protocols

HIIT sessions were performed on cycle ergometers, containing 10 × 60-s cycling intervals at the 85% to 90% maximal heart rate (HRmax) intensity, divided by 1 min active recovery [18]. Warm-up (5 min) and cool-down (5 min) performed in ~40% HRmax each session. All subjects use a heart rate monitor (Polar Beat, Polar Electro) throughout exercise training.

ST protocol consisted of three sets performed at the maximum weight that participants could move eight times with good technique in following exercises: bench press, leg curl, leg press, leg extension, lat pull-down, and shoulder press [19]. Furthermore, an abdominal crunch exercise was performed at three sets of 15 repetitions. The resting period between sets was established to 1-min.

Combined intervention participants performed firstly ST, followed by HIIT, totaling 70 min. According to previous researches, this order (ST before HIIT) of protocols improved glycemic stability. In addition, it attenuates the
severity and duration of hypoglycemia after exercise in contrast with the reverse order [18]. All protocols were carried out three times per week. To adjust exercise intensity, all participants performed CPET and strength tests every four weeks 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.

**CPET and dynamic strength test**

The CPET on an ergometer cycle (Vyntus CPX, CareFusion, Germany) was performed to determine VO2peak. All Subjects were asked to avoid caffeinated beverage consumption, smoking, and intense exercise 24 h before the exercise test. Warm-up included 3-min cycling at the 25 W intensity, and the next intensity (power output) was enhancement 10 W/min until exhaustion. During CPET, a chest belt (Polar Beat, Polar Electro) was monitored and recorded the heart rate. The following criteria considered to record the value of peak oxygen uptake (VO2peak) as the highest during CPET: (1) RER (respiratory exchange ratio) more than ≥ 1.1, (2) reaching 90% of the HRmax according to age, and (3) plateau in VO2 contrary to the increment of exercise intensity. Moreover, the Borg 6–20 scale was applied to detect the rate of perceived exertion during CPET.

A submaximal test has been performed in leg extension, leg press, bench press, and lat pull-down using an exercise machine to calculate the one-repetition maximum (1-RM). First, 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.

**Anthropometric data and blood sample analyses**

Bodyweight and BMI were measured by a body composition analyzer (InBody 570, Korea). Height measured with a portable stadiometer (InBody, InLab S50, Korea).

Blood samples from the brachial vein have been collected 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, four °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) [20] using 1,1,3,3-tetra-ethoxypropane as the standard.

**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). In case of significant interaction, one-way ANOVA was applied to test main factors, followed by posthoc analysis Bonferroni test (P < 0.05). The normality and homogeneity of variances’ assumptions for all data were verified using Shapiro–Wilk and Levene’s tests. The chi-squared test was used to determine the differences between medication variables. Mean ± SEM has been used to report all values.

**Result**

**Baseline characteristics**

Table 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 one-way ANOVA, there was no significant difference between intakes of carbohydrate, protein, and total fat at baseline among the 4 study groups (P ≥ 0.05).

**Cardiorespiratory fitness (CRF)**

The two-way ANOVA showed no statistically significant interaction effects (group × time) for weight, BMI, HRmax, and SBP (P ≥ 0.05).

The results showed a statistically significant interaction between the groups and time on VO2peak exercise time, and DBP (P ≤ 0.05). According to the follow-up tests, significant differences in VO2peak were observed at the follow-up values between the HIIT + ST group with ST and CON groups (P ≤ 0.05). In addition, there were significant differences in exercise time at the follow-up values between HIIT with CON group (P ≤ 0.05) (Table 2).
Glycemic and Profile Lipid status

The two-way ANOVA result showed no statistically significant interaction effects (group × time) for HOMA-IR, HbA1c, insulin, fasting glucose, and TG (P ≥ 0.05) (Table 2). The results showed a statistically significant interaction between the groups and time on HDL, LDL, and TC (P ≤ 0.05). According to the follow-up tests, significant differences in IL-6 were observed at the follow-up values between training groups and the CON group (P ≤ 0.05). Moreover, there were substantial CRP differences at the follow-up values between ST and CON groups (P ≤ 0.05). As well, the result showed a statistically significant decrease in IL-6 and CRP from pre- to post-test (P ≤ 0.05) in all training groups, whereas these remain unchanged in the CON (P ≥ 0.05) (Fig. 1).

Antioxidant status

The results showed a statistically significant interaction between the groups and time in SOD (P ≤ 0.05). Furthermore, the follow-up tests showed significant differences in SOD at the follow-up values between all training groups with the CON group (P ≤ 0.05). The results showed a statistically significant interaction between the groups and time on GPX and TAC (P ≤ 0.05). The follow-up tests showed significant differences in GPX and TAC at the follow-up values between all training groups with the CON group (P ≤ 0.05). The result showed a statistically significant interaction between the groups and time on IL-6 and CRP (P ≤ 0.05). According to the follow-up tests, significant differences in IL-6 were observed at the follow-up values between training groups and the CON group (P ≤ 0.05). Moreover, there were substantial CRP differences at the follow-up values between ST and CON groups (P ≤ 0.05). As well, the result showed a statistically significant decrease in IL-6 and CRP from pre- to post-test (P ≤ 0.05) in all training groups, whereas these remain unchanged in the CON (P ≥ 0.05) (Fig. 1).
| Table 2  | Anthropometric, exercise test and biochemical variables outcome at baseline and follow-up of training periods |
|----------|------------------------------------------------------------------------------------------------------|
|          | Within-group comparison                                                                                       | Between-groups comparison                                                                 |
|          | HIIT (16)                                               | ST (15)                                                  | HIIT + ST (15)                              | CON (13)                               | HIIT* ST | HIIT* HIIT + ST | HIIT* CON | ST* HIIT + ST | ST* CON | HIIT + ST | ST* CON |
| Weight (kg)                                | 78 ± 6.38                                             | 81.33 ± 6.49                                             | 78.86 ± 5.27                               | 75.61 ± 4.75                          | 3.33 ± 2.09 | 0.86 ± 2.09 | 2.38 ± 2.17 | 2.46 ± 2.12 | 5.71 ± 2.2 | 3.25 ± 2.2 |
| Follow-up                                  | 76.82 ± 5.75*                                          | 79.54 ± 5.34*                                             | 76.93 ± 4.74*                              | 75.07 ± 4.61                          | 2.72 ± 1.85 | 0.10 ± 1.75 | 1.74 ± 1.92 | 2.61 ± 1.88 | 4.47 ± 1.95 | 1.85 ± 1.95 |
| BMI (kg m⁻²)                                | 28.01 ± 2.72                                           | 28.69 ± 2.76                                             | 25.65 ± 2.32                               | 26.58 ± 2.58                          | 0.67 ± 0.93 | 1.46 ± 0.93 | 1.42 ± 0.97 | 2.13 ± 0.95 | 2.1 ± 0.98 | 0.03 ± 0.98 |
| Follow-up                                  | 27.59 ± 2.58*                                          | 28.06 ± 2.45*                                             | 25.89 ± 2.15*                              | 26.40 ± 2.60                          | 0.46 ± 0.88 | 1.70 ± 0.88 | 1.19 ± 0.91 | 2.16 ± 2.89 | 1.65 ± 0.92 | 0.5 ± 0.92  |
| VO₂peak (mL/kg min)                         | 24.93 ± 3.17                                           | 24.4 ± 2.52                                              | 26.8 ± 3.5                                 | 24.84 ± 2.82                          | 0.53 ± 1.09 | 1.86 ± 1.09 | 0.09 ± 1.13 | 2.4 ± 1.11 | 0.44 ± 1.15 | 1.95 ± 1.15 |
| Follow-up                                  | 27.06 ± 2.99*                                          | 25.93 ± 2.6*                                              | 29.4 ± 3.37*                               | 25.65 ± 2.49                          | 1.12 ± 1.04 | 2.33 ± 1.04 | 1.4 ± 1.08  | 3.46 ± 1.06 | 0.27 ± 1.1  | 3.74 ± 1.1*  |
| HRmax (bpm)                                 | 125.43 ± 7.53                                          | 126.6 ± 7.53                                             | 128.13 ± 8.04                              | 129.23 ± 6.11                         | 1.16 ± 2.65 | 2.69 ± 2.65 | 3.79 ± 2.75 | 1.53 ± 2.69 | 2.63 ± 2.79 | 1.09 ± 2.79 |
| Follow-up                                  | 133.43 ± 5.16*                                         | 135.2 ± 5.14*                                            | 135.13 ± 5.82                              | 131.6 ± 6.29                          | 1.76 ± 2.01 | 1.69 ± 2.01 | 2.12 ± 2.08 | 0.06 ± 2.04 | 3.89 ± 2.11 | 3.82 ± 2.11 |
| DBP (mm Hg)                                 | 83.81 ± 3.46                                           | 84.24 ± 3.24                                             | 84.66 ± 3.24                               | 84.42 ± 3                             | 0.18 ± 1.08 | 0.85 ± 1.08 | 1.57 ± 0.32 | 0.66 ± 1.1  | 1.38 ± 1.14 | 0.71 ± 1.14 |
| Follow-up                                  | 82.31 ± 2.33                                           | 83.93 ± 2.78                                             | 82.46 ± 4.24                               | 86.3 ± 2.25                           | 0.62 ± 1.08 | 0.15 ± 1.08 | 3.99 ± 1.12 | 0.46 ± 1.1  | 3.37 ± 1.14 | 3.84 ± 1.15* |
| SBP (mm Hg)                                 | 127.06 ± 6.75                                          | 124.26 ± 6.69                                            | 129.93 ± 6.23                              | 126.32 ± 5.13                         | 2.79 ± 2.34 | 2.87 ± 2.37 | 1.06 ± 2.43 | 5.66 ± 2.38 | 1.73 ± 2.46 | 3.93 ± 2.46 |
| Follow-up                                  | 125.31 ± 4.86                                          | 125.46 ± 5.71                                            | 125.2 ± 6.13                               | 128.46 ± 5.31                         | 0.15 ± 1.98 | 0.11 ± 1.98 | 3.3 ± 2.06  | 0.26 ± 2.01 | 2.99 ± 2.09 | 3.26 ± 2.09 |
| Exercise time (min)                         | 7.44 ± 0.92                                            | 7.23 ± 1.03                                              | 7.16 ± 0.87                                | 7.05 ± 0.99                           | 0.21 ± 0.34 | 0.28 ± 0.34 | 0.38 ± 0.35 | 0.07 ± 0.34 | 0.17 ± 0.36 | 0.1 ± 0.36   |
| Glucose (mmol/L)                            | 9.62 ± 0.98*                                           | 8.96 ± 1.27*                                             | 9.46 ± 0.8*                                | 8.48 ± 1.4*                           | 0.65 ± 0.4 | 0.16 ± 0.4  | 1.14 ± 0.42 | 0.49 ± 0.41 | 0.48 ± 0.42   | 0.97 ± 0.42 |
| Insulin (mU/L)                              | 9.99 ± 1.38                                            | 10.03 ± 1.41                                             | 9.63 ± 0.85                                | 9.85 ± 1.19                           | 0.04 ± 0.44 | 0.36 ± 0.44 | 0.14 ± 0.46 | 0.4 ± 0.45  | 0.18 ± 0.46   | 0.22 ± 0.46 |
| Follow-up                                  | 8.56 ± 1.37*                                           | 8.4 ± 1.31*                                              | 8.2 ± 1.09*                                | 9.4 ± 1.14                            | 0.16 ± 0.44 | 0.36 ± 0.44 | 0.83 ± 0.46 | 0.2 ± 0.45  | 0.99 ± 0.47   | 1.19 ± 0.47 |
| HOMA-IR                                    | 3.72 ± 0.79                                            | 3.94 ± 0.94                                              | 3.77 ± 0.83                                | 3.72 ± 0.48                           | 0.22 ± 0.28 | 0.05 ± 0.28 | 0.16 ± 0.47 | 0.03 ± 0.46 | 0.23 ± 0.47   | 0.19 ± 0.47 |
| Follow-up                                  | 2.74 ± 0.7*                                            | 3.02 ± 0.91*                                             | 2.86 ± 0.67*                               | 3.42 ± 0.44                           | 0.27 ± 0.25 | 0.11 ± 0.25 | 0.67 ± 0.26 | 0.16 ± 0.26 | 0.4 ± 0.27   | 0.56 ± 0.27  |
| HbA1c (%),                                  | 7.73 ± 1.06                                            | 7.73 ± 0.97                                              | 7.59 ± 0.58                                | 7.28 ± 0.77                           | 0.00 ± 0.31 | 0.14 ± 0.31 | 0.45 ± 0.32 | 0.13 ± 0.32 | 0.44 ± 0.33   | 0.31 ± 0.33 |
| Follow-up                                  | 6.82 ± 0.79*                                           | 6.71 ± 0.76*                                             | 6.73 ± 0.43*                               | 7.18 ± 0.73                           | 0.1 ± 0.25 | 0.08 ± 0.25 | 0.35 ± 0.26 | 0.01 ± 0.25 | 0.46 ± 0.26   | 0.44 ± 0.26 |

*Significant differences compared to baseline within the group at p < 0.05.
Table 2 (continued)

|                  | Within-group comparison                      | Between-groups comparison                     |
|------------------|----------------------------------------------|----------------------------------------------|
|                  | HIIT (16) ST (15) HIIT + ST (15) CON (13)    | HIIT* ST HIIT* HIIT + ST HIIT* CON ST* HIIT + ST ST* CON HIIT + ST *CON |
| Baseline         | 1.21 ± 0.02 1.25 ± 0.42 1.24 ± 0.03 1.26 ± 0.03 | 0.00 ± 0.01 0.02 ± 0.01 0.00 ± 0.01 0.01 ± 0.01 0.00 ± 0.01 0.01 ± 0.01 |
| Follow-up        | 1.44 ± 0.04* 1.36 ± 0.11* 1.45 ± 0.03* 1.27 ± 0.03 | 0.08 ± 0.02* 0.00 ± 0.02 0.17 ± 0.02* 0.09 ± 0.02* 0.08 ± 0.02* 0.17 ± 0.02* |
| LDL (mmol/L)     |                                             |                                             |
| Baseline         | 3.56 ± 0.48 3.44 ± 0.59 3.55 ± 0.38 3.72 ± 0.44 | 0.12 ± 0.17 0.01 ± 0.17 0.15 ± 0.18 0.1 ± 0.17 0.27 ± 0.18 0.17 ± 0.18 |
| Follow-up        | 2.95 ± 0.35* 2.87 ± 0.43* 2.74 ± 0.32* 3.68 ± 0.45 | 0.00 ± 0.17 0.00 ± 0.14 0.94 ± 0.14≠ 0.00 ± 0.14 0.94 ± 0.14≠ 0.94 ± 0.14≠ |
| TC (mmol/L)      |                                             |                                             |
| Baseline         | 4.8 ± 0.74 4.99 ± 0.65 4.81 ± 0.53 4.83 ± 0.64 | 0.18 ± 0.23 0.00 ± 0.23 0.02 ± 0.24 0.18 ± 0.23 0.15 ± 0.24 0.02 ± 0.24 |
| Follow-up        | 4.25 ± 0.45* 4.65 ± 0.66 4.32 ± 0.38* 4.75 ± 0.44 | 0.39 ± 0.17 0.06 ± 0.17 0.49 ± 0.18≠ 0.33 ± 0.18 0.1 ± 0.18 0.43 ± 0.18 |
| TG (mmol/L)      |                                             |                                             |
| Baseline         | 1.89 ± 0.16 1.97 ± 0.21 1.85 ± 0.2 1.84 ± 0.15 | 0.07 ± 0.06 0.03 ± 0.06 0.04 ± 0.07 0.11 ± 0.06 0.12 ± 0.07 0.01 ± 0.07 |
| Follow-up        | 1.58 ± 0.16* 1.53 ± 0.11* 1.49 ± 0.15* 1.66 ± 0.53 | 0.04 ± 0.1 0.08 ± 0.1 0.08 ± 0.1 0.03 ± 0.1 0.12 ± 0.1 0.16 ± 0.1 |

The data are expressed as the mean ± SEM. Two-way repeated ANOVA and one-way ANOVA were used for calculated P values for variables. Values are means ± SD. The data in the between-groups comparison show the mean difference between the groups at baseline and follow-up.

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

*Statistical analysis indicates the significant difference between baseline and follow-up: p ≤ 0.05
≠ Statistical analysis indicates the significant difference between groups at follow-up: p ≤ 0.05
The two-way ANOVA showed no statistically significant interaction effects (group × time) for MDA (P ≥ 0.05) (Fig. 2).

**Discussion**

The purpose of this study was to evaluate the effectiveness of different types of HIIT (ST, HIIT, and HIIT + ST) on some inflammatory factors, antioxidant profile, glycemic control, and cardiorespiratory fitness in T2DM patients to provide information on an ideal type of HIIT program. The principal finding of this study is that there were significant differences between all training groups with the CON group in terms of DBP, LDL, HDL, IL-6, SOD, GPX, and TAC (P ≤ 0.05). In addition, there were significant differences in CRP at the follow-up values between ST and CON groups (P ≤ 0.05). Exercise time and TC were significantly improved in HIIT than in the CON group (P ≤ 0.05). The results showed a significant difference between the HIIT + ST group and the CON group in VO2peak (P ≤ 0.05). Therefore, type 2 diabetes patients should perform regular exercise training, especially at a high intensity, to improve the antioxidant profile, glycemic control, cardiorespiratory fitness, and attenuate the inflammatory factors (Fig. 3).

The current study showed significant differences between the HIIT + ST group with CON group in VO2peak. However, there were no significant differences in exercise time, BMI, and HRmax between the training and the CON groups. It has been found that T2DM patients have
lower cardiorespiratory fitness (CRF) than healthy individuals [15, 21]. Studies have emphasized more significant advantages of HIIT on CRF than other types of exercise training in T2DM patients. Støa et al. demonstrated three months of HIIT training contain 4 × 4 min with 85–95% of HRmax improved VO2max and BMI in T2DM [15]. Hansen et al. also were found a 16% (75% VOpeak) and 8% (50% VOpeak) increased in VO2max following two months of HIIT training [22]. Similarly, Ghardashi-Afousi et al. showed that 12 weeks of HIIT improved VO2peak around 6.2 ml/kg/min than the control group in patients with T2DM [23]. The lower CRF level in T2DM might be associated with low capillary density, increased blood viscosity, higher blood glucose levels [24]. Exercise training intervention can improve the CRF in T2D patients and decrease cardiovascular mortality. In that regard, an increase of VO2max around 3.5 mL/min/kg is associated with a 12% increase in survival [25].
Fig. 3  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) percent change from baseline to follow-up. Data are means ± SEM. HIIT, high-intensity training group; ST, strength training group; HIIT + ST, high-intensity training + strength training group; CON, control group. The results showed significant differences between ST and CON groups in CRP (P ≤ 0.05). In addition, the results of TNF-α showed substantial differences between the three training groups with the CON group (P ≤ 0.05). ≠ Statistical analysis indicates the significant difference between groups: p ≤ 0.05

≠ Statistical analysis indicates the significant difference between groups: p ≤ 0.05
Studies have found that exercise intensity plays an essential factor in CRF improvements [26]. However, this study showed no significant differences between training groups in VO₂peak, exercise time, and BMI. Recently a narrow review found that short and medium-term HIIT interventions are an efficient stimulus to improve CRF and body composition in
individuals with T2DM [27]. It seems that increased CRF in HIIT compared to low-intensity exercise training associated with creating a more significant challenge to the heart, changes in the stroke volume, cardiac contractility [28], and skeletal muscle oxidative capacity [26]. Moreover, an increase of VO2peak is associated with improving glycemic control and insulin-stimulated glucose uptake rate [29].

There were no significant differences between the four groups in glycemic control, HOMA-IR, HbA1c, insulin, and fasting plasma glucose. Previous researches have studied the effect of HIIT on %HbA1c in a patient with T2DM. Mitranun et al. showed HIIT (3 sessions per week for three months) decreased 11% HbA1c in T2D patients [11]. Cassidy et al. found that HbA1c reduced after 12 weeks of HIIT [28]. Ghardashi-Afousi et al. showed that HIIT for 4 min at high intensity and 3 min at low intensity was associated with a 14% decreased in HbA1c [23]. The present study showed that HIIT, ST, and HIIT + ST decreased the %HbA1c by around 11%, 13%, and 11%, respectively. In line with our results, T2DM patients who performed 12 weeks of supervised HIIT training with 85%–95% HRmax showed a non-significant change in insulin. However, a significant reduction in HbA1c has been found in HIIT training compared to moderate-intensity continuous training [15]. A systematic review recently reported that combined aerobic/resistance training seems superior to only aerobic training to improve %HbA1c [30]. Furthermore, it has been demonstrated that each 1% reduction in HbA1c levels was related to a 14% decrease of myocardial infarctions and a 21% reduction in risk of of-death associated with diabetes [31] (Fig. 4).

The results showed that insulin and HOMA-IR significantly decreased in all training groups from baseline to follow-up. In this regard, 4-months strength training (70%–80% 1RM) improved IR (~15%) and metabolic markers on diabetic subjects [32]. Additionally, ST (more than 85% 1RM) significantly improved insulin sensitivity in people with diabetes, while the effect of endurance training was moderate [33].

In T2DM patients, insulin levels were significantly decreased following four months HIIT walking exercise compared with continuous walking training [34]. Similar to the current study, HIIT significantly decreased FBG in T2DM patients [35, 36]. In another study, subjects performed 33 sessions of cycle-ergometer HIIT and reported lower FBG [36]. Sixteen weeks of HIIT (jogging/running) decreased FBG in adults with T2DM [35]. Despite the lack of differences among groups in the current study, these results emphasize the HIIT as an effective strategy to have significant effects on glycemic status in T2DM patients. The mechanisms associated with exercise training and glycemic control are not completely clear. However, improved glycemic control by HIIT seems to be related to the increase of insulin signaling, insulin-stimulated glucose disposal rates, glucose transporter protein levels, skeletal muscle blood flow, and glucose delivery [37]. These mechanisms seem to depend on intensity, and theoretically, HIIT appears to be more effective [38].

There were significant differences in HDL, LDL, and DBP values among the three training groups with the CON group. Besides, TC was significantly improved in HIIT than CON group. These results are in line with prior investigations, which found only the HIIT + RT group improved TC and LDL compared to the control group [39]. Amri et al. showed a significant improvement of lipid profile following ten weeks of HIIT compared to the control group in diabetics Wistar rats [40]. Moreover, TG, HDL, LDL, and SBP improved following the HIIT intervention [8, 11].

Exercise training has heterogeneous effects on blood pressure. A significant reduction in SBP has been shown after resistance training in T2DM patients [41]. Similar to this study, Jorge et al. showed decreased blood pressure in combined training (resistance + aerobic) after 12 weeks in T2D [10]. However, another study did not find any blood pressure reductions after exercise training [42]. It seems that the lack of significant differences in blood pressure, TC, and TG between the groups in the current study was likely due to the absence of significant differences in weight loss, as hypothesized by previous researches [10, 42].

In the current study, we demonstrate the significant differences in concentration of SOD, GPX, TAC, and IL-6 in all training groups with the CON group (P ≤ 0.05). There were significant differences in CRP at the follow-up values between ST and CON groups. Previous studies reported a significant association between inflammation and oxidative stress, referred to as the oxidative-inflammatory cascade in T2DM. On the other hand, the anti-inflammatory and oxidative stress effect of exercise has been discussed recently. In this regard, Mohammadi Zadeh et al. demonstrated that 12 weeks of HIIT decreased pro-inflammatory parameters and improved anti-inflammatory factors in T2DM [43]. Khanna et al. (2017) shown that combined exercise (aerobic + resistance) has more effects on a decrease of TNF-α, CRP, IL-1β and, IL-6 compared to aerobic or resistance training alone [44]. In overweight/obese individuals, short (2 weeks) and medium-term (16 weeks) of HIIT significantly
decreased IL-6 [45, 46]. But, two other short training period studies reported no significant effects on IL-6, TNF-α, and CRP in T2DM [47].

The exact mechanism of the anti-inflammatory effect of HIIT is not clear. According to the previous investigation, it seems that weight loss is required to moderate inflammatory factors [48]. Inflammatory cytokines, including TNF-α and CRP, decreased insulin sensitivity and increased diabetic complications [6]. However, after an exercise intervention, visceral fat mass reduction and muscular anti-inflammatory myokines production have been proposed to improve inflammatory status [49].

Pro-inflammatory factors associate with ROS increase and induce more significant oxidative stress in T2DM [50]. On the other hand, exercise training such as HIIT increases antioxidant capacity [18]. In the current study, there were significant differences between all training groups with the CON group regarding SOD, GPX, and TAC. A similar study in T2DM subjects demonstrated the different types of training (strength training, aerobic training, and combined training) provided significant increases in antioxidant enzymes in T2DM [51]. Mitranun et al. reported increased GPx and decreased MDA after the HIIT training, but not traditional exercise training [11]. Mallard et al. showed that HIIT training was able to upregulate antioxidant capacity while continuous training did not, suggesting a superior HIIT effect when performed in the long term [47]. 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 increasing the antioxidant defense systems [52]. 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 [53].

**Strengths and limitation**

The current study showed that HIIT is an effective exercise method to improve the antioxidant profile, glycemic control, cardiorespiratory fitness, and attenuate the inflammatory factors in T2DM. The public health message recommended focusing on increasing regular PA, particularly at a high intensity. Despite the encouraging results observed, there is some limitation in this study that should be addressed. The number of participants was small in our study, which may have limited the power of the study to clear differences between groups. In addition, nutritional status and energy consumption did not control during the study, affecting outcomes.

**Conclusion**

In conclusion, our investigation found that various physiological and biochemical advantages resulted from HIIT, regardless of the training protocol type. The current study showed that DBP, LDL, HDL, IL-6, SOD, GPX, and TAC significantly improved in training groups compared to the CON group. Moreover, there was a significant difference between the HIIT + ST group with CON group in terms of VO2peak. Therefore, from a practical clinical perspective, the performance of HIIT + ST may be advised for additional benefits for T2DM patients.

**Author contribution** MS, EH, FS designed the study. PP, MS, and EH collected the data. MS and FS revised the final version of the manuscript. All authors read and approved the manuscript.

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**Declarations**

**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.

**Consent to publish** Patients signed informed consent regarding publishing their data and photographs.

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