High-Intensity Interval vs. Continuous Endurance Training: Preventive Effects on Hormonal Changes and Physiological Adaptations in Prediabetes Patients

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Abstract

Safarimosavi, S, Mohebbi, H, and Rohani, H. High-intensity interval vs. continuous endurance training: Preventive effects on hormonal changes and physiological adaptations in prediabetes patients. *J Strength Cond Res* 35(3): 731–738, 2021—The aim of this study was to examine the effects of a 12-week high-intensity interval training (HIIT) intervention, or an isocaloric continuous endurance training (CET) intervention on insulin resistance indices and change in irisin and preptin in patients with prediabetes. Thirty-two prediabetic male patients (age = 38.7 ± 4; body mass index = 26.9 ± 1.4 kg·m^{-2}; and $\dot{V}O_2$peak = 2.49 ± 0.22 L·min^{-1}) were randomly assigned into 3 training groups (N = 8). These groups were matched based on the required energy expenditure (EE) for completing each protocol: (a) HIIT (10 × 60 seconds at 90% peak oxygen uptake [$\dot{V}O_2$peak], 1: 1 work to recovery at 50 W), (b) CET at an intensity equivalent to maximal fat oxidation (Fatmax) (CETFAT) (pedaling for a duration that expends an equivalent EE to an HIIT session [E ≈ HIIT]), (c) CET at an intensity equivalent to anaerobic threshold (CETAT) (E ≈ HIIT), and (d) the control group (CON): continued to perform their daily activities. After intervention, blood glucose levels were significantly ($p < 0.05$) lower in the HIIT group compared with CETAT group. Exercise training improved the insulin resistance index by 35, 28, and 37% in CETFAT, CETAT, and HIIT groups, respectively. Irisin concentrations in the HIIT and CETAT groups was significantly ($p < 0.05$) decreased compared with the pre-training values. Also, HIIT and CETFAT resulted in significant ($p < 0.05$) changes in preptin concentration compared with baseline. This study demonstrated that both HIIT and CETFAT protocols had similar effects on the insulin resistance index of prediabetic patients. Also, the intensity and type of exercise were effective factors in changing irisin and preptin concentrations.

Key Words excess postexercise oxygen consumption, training techniques, intermittent exercise, pedaling, $\dot{V}O_2$peak

Introduction

Prediabetes, typically defined as blood glucose concentrations higher than normal, but lower than diabetes thresholds, is strongly linked to the development of type 2 diabetes (T2D) (11,36). It is estimated that ~35% of all US adults have prediabetes and are therefore at higher risk of future development of T2D and cardiovascular disease (36). Regular exercise can help prevent the progression of prediabetes to T2D (7). Studies have shown that lifestyle interventions incorporating 150 minutes of moderate-intensity physical activity (PA) (primarily walking) per week can reduce the incidence of T2D by ~58% (18). However, it has been shown that only 15–20% of adults adhere to these recommendations. Hence, alternative forms of physical activities such as high-intensity interval training (HIIT), which may increase exercise adherence and may therefore be attractive for the prevention of T2D, have been recommended accordingly (18). However, different forms of continuous endurance training (CET) have been developed, which in turn have specific and beneficial effects on the prevention and management of T2D (3,8,27,38).

As the precursor to T2D, prediabetes is determined by impaired fasting glucose (IFG; fasting plasma glucose concentration of 100–125 mg·dl^{-1}) and impaired glucose tolerance (IGT; 2 hours glucose 140–199 mg·dl^{-1}) or both (11). Impaired glucose tolerance is associated with disorders in fat metabolism and impairments related to insulin actions such as glucose transfer, glycogen synthesis, and glucose metabolism (4,11). In humans, glucose homeostasis is regulated indirectly by the interactions of other

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Table 1. Anthropometric and physiological characteristics of the subjects ($N = 8$ for each group).*†

Characteristics	CON	CETFAT	CETAT	HIIT
Age (y)	37.4 ± 3.2	39.1 ± 4.0	39.8 ± 3.9	38.6 ± 4.5
Body mass (kg)	83.9 ± 7.4	81.6 ± 7.0	82.2 ± 5.6	81.8 ± 6.1
BMI ($kg \cdot m^{-2}$)	27.0 ± 2.2	26.7 ± 3.0	26.6 ± 2.9	27.3 ± 3.3
$\dot{V}O_2$peak ($L \cdot min^{-1}$)	2.4 ± 0.2	2.5 ± 0.2	2.6 ± 0.2	2.5 ± 0.3

*CON = control; CETFAT = continuous endurance training with intensity equivalent to fatmax; CETAT = continuous endurance training with intensity equivalent to anaerobic threshold; HIIT = high-intensity interval training; BMI = body mass index; $\dot{V}O_2$peak = peak oxygen uptake.
†Data are mean ± (*SD*).

hormones, such as insulin, that are important for glucose regulation, or directly through storage and release, and the modulation of glucose uptake (29). In this regard, irisin and preptin play an important role in carbohydrate and fat metabolism (1). The stimulation of browning of white adipose tissue by irisin leads to increased energy expenditure (EE), reduced fat mass, improved glucose homeostasis, and improved insulin sensitivity (29). Moreover, irisin-induced increases in oxidative metabolism, peroxisome proliferator–activated receptor gamma coactivator 1 alpha (PGC1α) gene expression, mitochondrial transcription factor, and glucose transporter 4 (GLUT4) lead to increased mitochondrial biogenesis (37).

Preptin is included in the insulin family and, like insulin-like growth factor 2 (IGF2) hormone, is synthesized and secreted in pancreatic beta cells (9). Because of impact on phosphorylase C (PLC) and protein kinase C (PKC) through concentration with the IGF2 receptor, preptin is considered as a strong stimulator for insulin secretion (10). Serum levels of preptin in diabetic patients are higher than those in healthy individuals. This high level of preptin is positively related to diastolic blood pressure, triglycerides, hemoglobin A1c (HBA1c), and the insulin resistance index and is negatively correlated with very-low-density lipoprotein (39). These characteristics of preptin might be an important factor in the etiology of insulin resistance (10).

Physical activity plays a major role in prevention of IFG, IGT, and type 2 diabetes (36). Depending on the type, intensity, and duration, PA is a strong physiological stimulus affecting substrate oxidation and hormone secretion (27). Low to moderate exercise intensities can lead to the highest rate of fat oxidation and by contrast, higher intensities decrease this rate (35). Undertaking exercise at an intensity that is proportional to maximal fat oxidation (Fatmax) is well known to increase fat metabolism capacity (38) Understanding specialized forms of this exercise methods may be helpful for improving insulin resistance, adiponectin levels, and lipid profiles simultaneously in obese individuals (3).

Exercise training at the intensity equivalent to anaerobic threshold (AT) is another training method that is commonly used by athletes. The individual AT represents the individual physiological breakpoint between the aerobic and anaerobic systems. It has been reported that exercises performed at this

Table 2. Matching groups based on EE during and after exercise oxygen consumption.*†

		Energy expenditure				
		During exercise		EPOC ($kcal \cdot min^{-1}$)		
Protocols	Exercise time (min)	kcal	$kcal \cdot min^{-1}$	Fast component	Slow component	Total
HIIT	20	237 ± 14.1	11.85 ± 1.4	4.06 ± 0.61	2.17 ± 0.17	2.54 ± 0.32
CETAT	28 ± 3.2	236 ± 1.2	8.63 ± 1.3	3.5 ± 0.39	2.03 ± 0.21	2.31 ± 0.19
	35 ± 4.4	301 ± 16.3‡	8.82 ± 1.3	3.61 ± 0.31	2.1 ± 0.17	2.4 ± 0.26
CETFAT	37 ± 5.1	237 ± 1.5	6.39 ± 0.77	2.89 ± 0.27	1.88 ± 0.11	2.09 ± 0.24
	55 ± 5.7	354 ± 13.2‡	6.54 ± 0.93	3.01 ± 0.34	1.96 ± 0.2	2.17 ± 0.17

*EE = energy expenditure; EPOC = excess postexercise oxygen consumption; HIIT = high-intensity interval training; CETAT = continuous endurance training with intensity equivalent to anaerobic threshold; CETFAT = continuous endurance training with intensity equivalent to Fatmax.
†In CETAT and CETFAT groups, first rows denote pedaling for a duration that expends an equivalent EE to an HIIT session without same postexercise EE as HIIT. Second rows denote pedaling for a duration that expends an equivalent EE to a HIIT session in such a way that postexercise EE is almost equal to that of HIIT.
‡Significantly different change compared with HIIT group ($p < 0.05$).

Table 3. Daily nutritional profile of the subjects ($N = 8$ for each group).*†

Variable	CON	CETFAT	CETAT	HIIT
Carbohydrate ($g \cdot d^{-1}$)	457 (46)	468 (36)	475 (41)	463 (31)
Fat ($g \cdot d^{-1}$)	79 (17)	74 (19)	76 (19)	78 (22)
Protein ($g \cdot d^{-1}$)	121 (27)	103 (19)	106 (21)	99 (17)
Energy intake ($kcal \cdot d^{-1}$)	3,094 (184)	2,996 (179)	3,066 (197)	3,002 (169)

*CON = control; CETFAT = continuous endurance training with intensity equivalent to Fatmax; CETAT = continuous endurance training with intensity equivalent to anaerobic threshold; HIIT = high-intensity interval training.
†Data are mean ± (*SD*).

intensity decreases glycogen stores in skeletal muscles (27). Bruce and Hawley (8) demonstrated that the aerobic exercise (performed at AT) improved insulin sensitivity and mitochondrial biogenesis. Thus, CET with these methods could be useful strategies for regulation of metabolic diseases (34).

It has also been shown that exercise at higher intensities may be more effective for improving glycemic control in patients with T2D (22). It has been reported that HIIT induces greater metabolic adaptations than regular endurance training (21). Findings by Little et al. (22) indicated that HIIT can improve glucose control and induce rapid adaptations in skeletal muscle linked to betterment of metabolic health in patients with T2D.

Compared with the duration and type of exercise, the intensity of exercise is arguably the most important factor in influencing excess postexercise oxygen consumption (EPOC) (13). Generally, when the exercise bout is controlled for volume, regardless of exercise mode, higher intensities produce higher EPOC than lower intensities (5). Thus, exercising at higher intensities may be central to assuring that EPOC can have a significant effect on the energy balance equation (14). As such, a higher EPOC after HIIT could be effective in obtaining different results compared with the CET intervention at an intensity equivalent to the anaerobic threshold (CETAT) and CET at an intensity equivalent to maximal fat oxidation (CETFAT). Therefore, the aim of this study was to investigate and compare the effects of a 12-week HIIT intervention, an isocaloric CETFAT, and CETAT on insulin resistance indices, irisin, and preptin in patients with prediabetes. We hypothesized that, in comparison with CET, the higher EE after HIIT would be the central factor for specific physiological adaptations to this protocol. We also hypothesized that if the superior EPOC is compensated by the higher exercise session time commitment of CET, the effects of both training methods would be equivalent.

Methods

Experimental Approach to the Problem

Before the baseline measurements, subjects made several familiarization visits to the laboratory to become orientated with the testing procedures and training devices. 48–72 hours before the start, and after the end of training sessions at first, fourth, and eighth weeks, the subjects performed a progressive exercise test to determine peak oxygen uptake ($\dot{V}O_2peak$), Fat_{max}, and AT. Subjects completed all pretraining and post-training tests at approximately the same time of the day under similar laboratory conditions. They were also asked not to participate in any PA 24 hours before the testing sessions. After baseline measurements, the subjects were randomly assigned into 4 groups: HIIT, CETFAT, CETAT, and control (CON). These protocols were matched based on the required EE for completing each. Subjects completed exercise training 4 sessions per week for 12 weeks. Each exercise session started with a 5-minute warm-up and finished with a 5-minute cool down. Heart rate (HR) was recorded during each exercise session using Polar HR monitor (Polar type A300). Blood samples were collected 48 hours before the start and after the end of the training period.

Subjects

Thirty-two prediabetic male patients (mean ± *SD*: age = 38.7 ± 4; body mass index [BMI] = 26.9 ± 1.4 $kg \cdot m^2$; and $\dot{V}O_2peak = 2.49 \pm 0.22\ L \cdot min^{-1}$) volunteered to participate in this study. Anthropometric and physiological characteristics of the subjects are presented in Table 1. Subjects were medication-free and before the study, all the experimental procedures, benefits, and risks of the study were explained fully to all subjects, and they signed the written informed consent. Additional exclusion criteria included high fasting blood glucose (fasting blood glucose of >100 $mg \cdot dl^{-1}$), previous history of respiratory problems, coronary heart disease, and daily smoking. The study was approved by the Human Investigation Committee of the Sport Sciences Research Institute (IR.SSRI.REC.1395.122).

Procedures

Anthropometric Measurements. Body mass (Wt) and stature (Ht) were measured to the nearest 0.1 kg and 0.1 cm, respectively, using a calibrated Seca Alpha (model 220; Seca, Birmingham, United Kingdom) scale and a Seca Alpha stadiometer. Body composition was analyzed using bioimpedance (Venus 5.5; Korea). Height (m) and body mass (kg) were used to calculate their BMI ($kg \cdot m^{-2}$).

Graded Exercise Test. Subjects performed an incremental exercise test on a cycle ergometer to evaluate cardiorespiratory values. Subjects warmed up for 5 minutes at a constant workload of 20 W. The incremental test began at 25 W;

Table 4. Pre-training vs. post-training values for peak fasting glucose ($mg \cdot dl^{-1}$), fasting insulin ($mU \cdot L^{-1}$), HOMA-IR, HbA1c (%), and OGTT after 75 g glucose (2 hours).*†

	Group			
CON	CETFAT	CETAT	HIIT	
Fasting glucose ($mg \cdot dl^{-1}$)				
Pre	112.2 ± 3.7	110.8 ± 5.6	113.7 ± 3.8	111.0 ± 5.9
Post	114.8 ± 4.1	97.3 ± 3.7‡§	101.1 ± 5.4‡§‖	93.8 ± 4.8‡§
Fasting insulin ($mU \cdot L^{-1}$)				
Pre	14.4 ± 1.2	15.2 ± 1.8	15.5 ± 2.0	14.1 ± 1.2
Post	15.1 ± 1.5	11.3 ± 1.7‡§¶	12.5 ± 1.5‡§	10.5 ± 1.0‡§¶
HOMA-IR				
Pre	4.01 ± 0.4	4.19 ± 0.6	4.36 ± 0.6	3.88 ± 0.5
Post	4.28 ± 0.6	2.71 ± 0.4‡§	3.13 ± 0.5‡§‖	2.43 ± 0.3‡§
HbA1c (%)				
Pre	5.72 ± 0.2	5.77 ± 0.2	5.81 ± 0.2	5.82 ± 0.2
Post	5.78 ± 0.2	5.68 ± 0.3	5.67 ± 0.3	5.62 ± 0.2‡
OGTT after 75 g glucose (2 hours)				
Pre	162.1 ± 13.0	166.3 ± 17.1	174.2 ± 19.4	172.1 ± 19.0
Post	165.7 ± 17.2	151.8 ± 18.3‡§	163.8 ± 13.1‡	149.8 ± 16.1‡§

*CON = control; CETFAT = continuous endurance training with intensity equivalent to Fatmax; CETAT = continuous endurance training with intensity equivalent to anaerobic threshold; HIIT = high-intensity interval training; HOMA-IR = homeostasis model–estimated insulin resistance.
†Data are mean (±*SD*).
‡Significantly different compared with pre-training value ($p < 0.05$).
§Significantly different change compared with CON group ($p < 0.05$).
‖Significantly different change compared with HIIT group ($p < 0.05$).
¶Significantly different change compared with CETAT group ($p < 0.05$).

thereafter, workload increased 25 W every 3 minutes up to a respiratory exchange ratio of ≥1.00. After that, it was increased by the same increments with 1-minute intervals until volitional fatigue (31). During the tests, $\dot{V}O_2$, and $\dot{V}CO_2$ were measured using a gas analyzer system (ZAN600 CPET, Oberthulba, Germany), calibrated according to the manufacturer's instructions. Fat oxidation rates were calculated using the following stoichiometric equation (17):

$$\text{Fat oxidation rate } \left(g \cdot min^{-1}\right) = 1.695\ \dot{V}o_2\ \left(L \cdot min^{-1}\right) - 1.701\ \dot{V}co_2 \left(L \cdot min^{-1}\right)$$

Highest fat oxidation rate was considered as Fatmax, which was calculated using aforementioned equation. The $\dot{V}O_2$peak was determined based on the average $\dot{V}O_2$ from the final 20 seconds of the incremental test. The individual AT was determined using modified V-slope method (2).

Isocaloric Workouts. To match all training groups, subjects' EE were measured during the exercise session and for 5 hours thereafter. Indirect calorimetry was applied during each intervention and each 30 minutes during the 5 hours after exercise. Subjects were permitted to remove the facemask at fixed time points only to drink water periodically during the 5 hours after exercise (19). After completing their activation, subjects sat on a chair and their acute and prolonged EPOC were measured during 0th–30th, 60th–90th, 120th–150th, 180th–210th, and 240th–270th minutes (after the activation) using the gas analyzer. Due to the higher EE of HIIT, EE in HIIT was considered as the basic value for calculating that of CETFAT and CETAT groups. The duration of exercise sessions in the other training groups was determined by the time it took an individual to achieve an equivalent EE to HIIT (E ≈ HIIT) (Table 2).

Blood Analysis. Venous blood samples were collected from the forearm with subjects in a seated position. All blood samples were collected between 7:00 and 10:00 AM Blood samples were collected in EDTA-containing tubes and immediately centrifuged at 3,000 rpm at 4° C for 15 minutes. The resulting serum and plasmas were aliquoted and stored at −80° C for analysis. Plasma glucose concentration was determined using the enzymatic colorimetric method (glucose oxidase-amino antipyrine [GODPAP]). Fasting insulin and Hemoglobin A1c (HbA1c) were assessed using electro chemiluminescence and high-performance liquid chromatographic methods, respectively. Homeostasis model–estimated insulin resistance was calculated using the formula (Fasting insulin [$\mu U \cdot ml^{-1}$] × Fasting glucose [$mmol \cdot L^{-1}$]/22.5) (27). Serum irisin and preptin concentrations were measured using a commercially available enzyme-linked immunosorbent assay (ELISA; Phoenix Pharmaceuticals, Inc., Burlingame, CA).

Control of Diet and Physical Activity. All subjects were instructed to maintain their accustomed dietary and PA habits throughout the study. They were also asked to record and analyze food diaries 3 days before baseline testing using

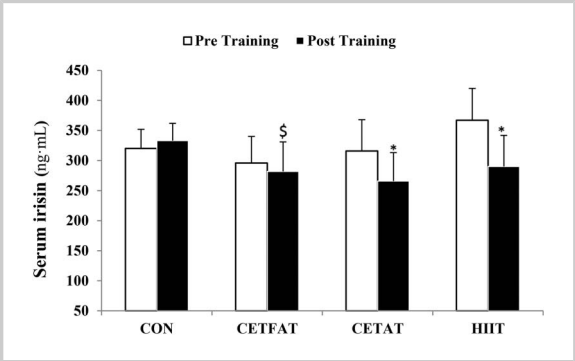

Figure 1. Changes in serum irisin levels at pre-training and post-training for control (CON), continuous endurance training with intensity equivalent to Fatmax (CETFAT), continuous endurance training with intensity equivalent to anaerobic threshold (CETAT), and high-intensity interval training (HIIT). *$p < 0.05$ vs. pre-training; \$$p < 0.05$ vs. HIIT group.

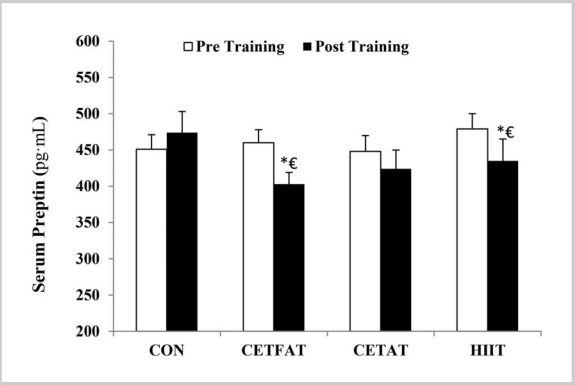

Figure 2. Changes in serum preptin levels at pre-training and post-training for control (CON), continuous endurance training with intensity equivalent to Fatmax (CETFAT), continuous endurance training with intensity equivalent to anaerobic threshold (CETAT), and high-intensity interval training (HIIT). *$p < 0.05$ vs. pre-training; €$p < 0.05$ vs. CON group.

software (COMP EAT 4.0; National Analysis System, London, United Kingdom) and to replicate this diet before the post-training test session (Table 3). In addition, subjects were asked to record their daily energy intake in a random manner during the training period. During the study, the habitual lifestyle of subjects was unchanged, and they were asked refrain from alcohol and caffeine and not to participate in any PA 24 hours before each testing session.

Training Programs. The HIIT group performed 10 × 60-second cycling intervals interspersed with 60 seconds of recovery. Individual workloads were selected to elicit oxygen consumption of 90% $\dot{V}O_2$peak during the intervals (12). During recovery, subjects were allowed to rest or pedal slowly against a resistance of 50 W. The CETFAT and CETAT groups performed continuous cycling at Fatmax and AT intensities, respectively. Duration of exercise sessions for CETFAT and CETAT was determined for each subject individually (pedaling as long as required to achieve an EE equivalent to an HIIT session [E ≈ HIIT]). Training session started with a 5-minute warm-up, and finished with a 5-minute cool down. Subjects also completed a graded exercise test at fourth and eighth weeks to recalculate the prescribed exercise intensities and durations to ensure that all these programs were performed at the preferred intensities during the training period.

Statistical Analyses

All analyses were performed using the SPSS software (version 20.0; USA), with α set at 0.05. Results were expressed as mean ± *SD*. A 1-way analysis of variance compared the effects of HIIT, CETFAT, and CETAT on all variables among groups. Tukey's post-hoc test compared differences among groups when a significant *F*-ratio was observed. A paired pre-post Student's *t*-test was run separately in each specific training group to determine whether each specific training program had any effect on the dependent measures. Pearson product-moment correlations were used to examine relationships between variables.

Results

There were no significant differences in baseline anthropometric and physiological characteristics among groups. The average time and EE of exercises were as follows: HIIT, 20 minutes and 11.8 ± 1.4 kcal·min^{-1}; CETAT, 35.0 ± 4.4 minutes and 8.8 ± 1.3 kcal·min^{-1}; and CETFAT, 55 ± 5.7 minutes and 6.5 ± 0.9 kcal·min^{-1}, respectively. Energy expenditure during exercise in CETFAT and CETAT groups were significantly higher than in HIIT group ($p \leq 0.05$). However, there was no significant difference in EE between groups when total EE (EE during exercise + EPOC) was considered (Table 2).

When expressed as percentages of the $\dot{V}O_2$peak, there were significant differences in the exercise intensities between HIIT and CETFAT groups (90.0 ± 3.4% vs. 41.0 ± 4.5%; $p = 0.001$), HIIT and CETAT (90.0 ± 3.4% vs. 64.0 ± 6.6%; $p = 0.001$), and CETAT and CETFAT (64.0 ± 6.6% vs. 41.0 ± 4.5%; $p = 0.001$). Also, no significant differences were observed in mean energy intake among groups (Table 3).

As shown in Table 4, after the 12-week training program, blood glucose ($p = 0.004$, $p = 0.007$, $p = 0.001$), insulin ($p = 0.002$, $p = 0.003$, $p = 0.001$), oral glucose tolerance test (OGTT) ($p = 0.025$, $p = 0.039$, $p = 0.002$), and insulin resistance index ($p = 0.001$, $p = 0.001$, $p = 0.001$) were significantly lower in HIIT, CETFAT, and CETAT groups compared with pre-training values, respectively. Also, the effect of exercise training on blood glucose and the insulin resistance index was significantly higher in HIIT group compared with CETAT groups ($p = 0.033$ and $p = 0.028$, respectively). There was a significant difference in the effect of exercise training on the OGTT index between CETFAT and CON ($p = 0.031$), and HIIT and CON ($p = 0.001$). HbA1c significantly decreased with HIIT (5.82 ± 0.24 vs. 5.62 ± 0.21%; $p = 0.001$) and remained unchanged in

CETFAT, CETAT, and CON groups from pre-training to post-training with no significant difference between groups.

Serum level of irisin significantly decreased in HIIT and CETAT groups ($p = 0.003$, 0.001, respectively) compared with pre-training, whereas there was a nonsignificant reduction in the CETFAT group. The change in irisin level was significantly ($p = 0.035$) higher in HIIT group compared with CETFAT group (Figure 1).

After the training period, preptin concentration was significantly lower in HIIT and CETFAT groups ($p = 0.001$ and 0.013, respectively), but not in the CETAT group. Moreover, there was a significant difference in post-training preptin concentration between HIIT and CON ($p = 0.004$), CETFAT and CON ($p = 0.001$), with no significant difference between training groups ($p > 0.05$) (Figure 2).

Discussion

The major findings from this study that used 3 isocaloric protocols were that, although HIIT had a greater postexercise EE (EPOC) compared with the other groups, the EE of CETFAT and CETAT groups during exercise were higher than that of the HIIT group. After the 12-week training program, blood glucose, insulin, OGTT, and the insulin resistance index were significantly lower in HIIT, CETFAT, and CETAT groups compared with pre-training values. High-intensity interval training showed greater effects on blood glucose and insulin resistance index compared with the CETAT group. The post-exercise OGTT index in CETFAT and HIIT groups was significantly different compared with the CON group. HbA1c significantly decreased for HIIT group compared with pre-training. Serum level of irisin significantly decreased in HIIT and CETAT groups and changes in its level were greater in HIIT compared with the CETFAT group. Preptin concentration was significantly lower in HIIT and CETFAT groups when compared with pre-training. Moreover, there was a significant difference in preptin concentration with HIIT and CETFAT compared with CON group.

The main objective of measuring EPOC in this study was to ensure that all 3 protocols were conducted in an isocaloric manner. Higher EPOC is result of restoration of phosphocreatine, lactate removal, increased circulating catecholamines, and body temperature as classically proposed (23). Our results indicated that after 3 isocaloric exercises (HIIT, CETFAT, and CETAT with EE equivalent to 237 kcal), the HIIT group had greater postexercise EE compared with the 2 other training groups. In support of this, Borsheim and Bahr (5) demonstrated that higher exercise intensities produce higher EPOC than lower intensities of exercise. However, contrary to our findings, it has been shown that higher exercise duration has greater EPOC compared with lower-duration exercises with the same intensities. Gore and Withers (13) reported that by enhancement of duration of exercise with an intensity equivalent to $\geq$50% $\dot{V}O_2$max, EPOC increases consequently. The lower intensities used in the CETFAT may explain the discrepancies in our findings.

In this study, we aimed to clarify which protocol is more effective in reducing blood glucose and insulin resistance indexes in prediabetes patients. It showed that regardless of the type and intensity of exercise, 12 weeks of various training programs reduced blood glucose concentrations and the insulin resistance index in patients with prediabetes. In our experiment, blood glucose levels and the insulin resistance index were significantly lower in the HIIT group compared with the CETAT group and no difference was observed between the HIIT and CETFAT. This demonstrates that when HIIT and CETFAT are isocaloric, their effects on the aforementioned variables are equivalent. Interestingly, HbA1c only reduced with HIIT, but there were no between-group differences in change in HbA1c. High-intensity interval training is now commonly used as an alternative to longer-duration endurance training with similar or superior improvements in health-related variables (32). In this context, previous studies of HIIT and moderate-intensity continuous training (MICT) have produced contradictory results regarding improvements in insulin resistance and glucose concentrations. Some studies have reported positive effects (7,24,32), whereas others showed no effects (32). Consistent with our findings, Mitranun et al. (24) found that HIIT and MICT significantly reduced fasting blood glucose concentration and insulin resistance; however, HbA1c decreased significantly only in the HIIT group in patients with T2D (24). Our results are in line with those of Boulé et al. (7) suggesting that exercise intensity is a more important factor than exercise volume for improving HbA1c. Factors such as subjects characteristics, intensity, volume, and frequency of the prescribed protocol might also explain the differences in results. In subjects with insulin resistance, there is metabolic inflexibility (5), i.e., the reduced ability of tissues to adapt their metabolism to changes in physiological conditions. Generally, metabolic inflexibility is a consequence of an impairment in the capacity of tissues to shift from lipid to glucose oxidation when passing from low-insulin fasting conditions to high-insulin glucose-stimulated conditions. Seemingly, glucose is likely to decrease in T2D subjects with exercise, especially after submaximal aerobic exercise training. This is because the exercise-induced increase in uptake of blood glucose by skeletal muscles is greater than the production of hepatic glucose (26). The cellular energy sensor AMP-activated protein kinase (APMK), nitric oxide synthase, calcium/calmodulin-dependent protein kinase, and expression of PGC-1α might be activated through signaling pathways that increases insulin sensitivity, thus leading to the improvement of several key factors (26) such as raised GLUT4 content, increased aerobic enzyme capacity, and mitochondrial biogenesis (32). It has also been mentioned that a greater EPOC, resulting in higher EE, may lead to greater improvements in health-related factors such as weight loss (19). Thus, matching of EE, when including the EPOC component in the HIIT, CETFAT, and CETAT protocols, may explain the differences between our findings and those of others.

In this study, irisin concentrations reduced in all 3 training groups. However, this decrease was statistically significant only in the HIIT and CETAT groups. Moreover, the change in irisin level was significantly different between the HIIT and CETFAT groups. These findings support other investigations reporting decreases in the irisin levels of plasma after an intermittent sprint-type running protocol (16) and a 12-week period of endurance training (70% $\dot{V}O_2$max) (28). However, our findings were contrary to the findings of Miyamoto-Mikami et al. (25) who indicated that levels of circulating irisin increases after 8 weeks of cycling endurance training (60–70% $\dot{V}O_2$peak) in healthy middle-aged/older adults. The authors attributed their subjects' increased irisin levels to the reduction in visceral fat after endurance training. It has been reported that levels of irisin remain unchanged after 26 weeks of aerobic training (60% of HR reserve) in healthy adults (15), which could be supportive of our demonstration, and suggests that using low-intensity exercise (41.0 ± 4.5% $\dot{V}O_2$peak) could be a plausible reason for unchanged irisin levels in the CETFAT group. Irisin is not only a myokine liberated by muscle tissue, but also an adipokine released by adipose tissue, and given the fact that chronic exercise training is in close relationship with body fat reduction and body mass, a decrease in irisin level as a result of chronic exercise training could be expected (30,33). Cross-sectional investigations have demonstrated positive correlations between circulating irisin and homeostatic indices such as fasting blood glucose and insulin resistance (30,33). Glucose and fatty acids might be involved in the regulation of irisin secretion in individuals with T2D (20). Irisin is therefore assumed to have an increased and compensatory release by adipose/muscle tissue to overcome an underlying irisin resistance, and may counteract the physiological effects of deteriorated insulin function (30). Irisin also stimulates glucose uptake by enhancement of GLUT 4 through activation of AMPK (29). Collectively, the overall interpretation of the aforementioned studies leads to the conclusion that ameliorated insulin resistance, which is associated with chronic exercise training, diminishes circulating irisin as a consequence.

The results of this study showed that after a 12-week training period, preptin levels significantly decreased in the HIIT and CETFAT groups. This study is the first to examine the difference between the effect of HIIT and MICT on changes in preptin in patients with prediabetes. In agreement with previous research (39), our results also indicated a positive correlation between serum levels of preptin and OGTT, insulin resistance, and fasting insulin level. Moreover, a positive relationship was observed between serum levels of preptin and fasting glucose concentration. By contrast, there was a negative correlation between preptin level and HbA1c. Bu et al. (6) reported that higher levels of glucose concentration in patients with prediabetes lead to higher preptin levels than in those with normal glucose tolerance. Preptin secretion as a result of elevated glucose concentration activates PKC and PLC, leading to insulin secretion through calcium-dependent pathway (10). Although the precise mechanism responsible for the changes shown in our experiment is not clear, the observed decrease in glucose concentration after performed protocols could be a plausible reason.

In conclusion, our results indicated that irrespective of type and intensity of the protocol, a 12-week exercise intervention (either HIIT, CETFAT, or CETAT) resulted in a significant decrease in insulin and glucose concentration in patients with prediabetes. Also, we concluded that intensity and type of protocol are 2 effective factors on changes in irisin and preptin levels. According to these findings, continuous training with low-to-moderate intensity is a preferred method for those unable to perform exercise with higher intensities. Moreover, compared with CET, HIIT may expend the same energy and may have the same effect on insulin resistance but with the time commitment equal to half that of CET.

Practical Applications

The most striking finding from this study was that a CET intervention with an intensity equivalent to Fatmax, or a 12-week HIIT intervention, induced remarkable changes on physiological variables related to glucose control in patients with prediabetes. These findings suggest that CET with low-to-moderate intensity (especially Fatmax) is an effective protocol for the modulation of insulin resistance. These prescriptions could be applied as a practical method to reduce the incidence of type 2 diabetes in patients with prediabetes. Moreover, the greatest effect on irisin and preptin were found in the HIIT and CETFAT groups, respectively, suggesting that the mechanisms of effect for hormonal changes are different based on training volume and intensity. Accordingly, both HIIT and CETFAT programs could be useful exercise protocols depending on the priority of specific physiological requirements.

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