Diets along with interval training regimes improves inflammatory & anti-inflammatory condition in obesity with type 2 diabetes subjects

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Received: 29 August 2018 / Accepted: 1 November 2018 / Published online: 28 November 2018
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Abstract

Background Different physical activities and diets change the regulation of inflammations in both type 2 diabetes (T2D) patients and obese individuals, but the effect of both (Physical activity and diet) on pro/anti-inflammations has remained unknown. We investigated pro/anti-inflammations control, cardiovascular function, and total physiological parameters before and after 24 weeks of low volume high intensity interval training (HIIT) on a cycle ergometer along with four dietary regimes in obesity with T2D patients.

Methods 33 non-active obesity T2D patients (BMI ≥ 30) midges (47 yrs. ± 5) were volunteered to participate and randomly divided into three experimental ($n = 11$) [(1) LCD = low Carbohydrate Diet, (2) LFD = Low Fat Diet and (3) HFD = High Fat Diet] and one control ($n = 9$) [ND = normal diet] groups. The whole groups performed underwent 8-week dietary regimes and then performed 3 days/weeks (3 set 10×60 s) HIIT on a cycle ergometer for 12 weeks, which followed by a 4-week diet period again. Also, prior to and after 8 weeks diet-12 weeks High Intensity Interval Training (HIIT) and 4 weeks diet 2-h oral glucose tolerance test (OGTT), resting blood pressure, incremental maximal oxygen uptake (VO_{2peak}) cycle ergometer test and blood sample was collected from the subjects in order to measure pro/anti-inflammatory cytokines (IL-6, TNF- α , leptin, resistin, adiponectin, and FGF21).

Results After 24 weeks of intervention, the results indicated that the highest improvement in the percentage of changes in glucose happened in LCD (−34.76), insulin in ND (+16.43), cholesterol in LCD (−33.35), LDL in LFD (−9.14), HDL in LCD (+41.81), TG in LCD (−40.71), weight in LCD (−12.49) and HOMA-IR in HFD (−6.82). The results also indicated that after 24 weeks of HIIT and diet interventions, highest benefit percentage change IL-6, resistin and leptin occurred in LCD (−32.10, −28.29 and −53.92, respectively), TNF- α , FGF21 and adiponectin in LFD (−48.06, +55.30 and +42.32, respectively). However, these changes were observed in other groups.

Conclusions These results demonstrated that HIIT along with low carbohydrate regimes improves overall cardiovascular parameters and reduce pro-inflammatory markers and increase anti-inflammatory markers in type 2 diabetic patients. Additionally, as with HIIT along with low carbohydrate, HIIT coupled with low fat would improve inflammation markers, though these effects were less significant. These findings suggest that HIIT along with low carbohydrate is a beneficial exercise and dietary strategy in T2D patients.

Keywords Pro/anti-inflammatory · T2D patients · Obesity · Adipokines · HIIT

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Abbreviations

HIIT	High Intensity Interval Training
LCD	Low Carbohydrate Diet
LFD	Low Fat Diet
HFD	High Fat Diet
FGF21	Fibroblast growth factor 21
T2D	type 2 diabetic
ND	Normal Diet
OGTT	oral glucose tolerance test

Introduction

Obesity is increasingly recognized as a serious global public health problem and plays a key role in type 2 diabetes (T2D) [1]. Obesity and T2D are common disorders characterized by excess visceral adiposity, associated with hyperglycaemia, hypertension, insulin resistance and dyslipidemia, which together are termed “metabolic syndrome” [2, 3]. A considerable amount of literature has reported that the risk of development of T2D, obesity, and cardiovascular diseases are related to increase metabolic disorders [4, 5].

Some previous studies have suggested that metabolic disorders involve a pro-inflammatory condition in which both hypertrophied adipocytes and adipose tissue-resident immune cells, such as primarily lymphocytes and macrophages contribute to increased circulating levels of proinflammatory cytokines [5–8]. Moreover, several studies have suggested that obesity and a T2D may affect metabolic dysfunctions through several mechanisms including effects on inflammatory pathways, which include altered plasma levels of specific pro-inflammatory proteins and cytokines, a phenomenon known as “systemic low-grade inflammation” [6, 7, 9].

Indeed, adipose tissue in obesity and T2D individuals is considered as a complex and highly active metabolic endocrine organ which produces various cytokines and is a well-known source of inflammation [8, 10]. Increased levels of adipokines and pro-inflammatory cytokines, such as leptin, adiponectin, resistin, apelin, visfatin, tumor necrosis factor- α , and interleukin-6, have prominent roles in the pathogenesis of the metabolic syndrome [4, 11].

Several pathomechanisms in the development of obesity in primary and secondary T2D are closely linked with inflammatory processes. They can be influenced by a several factors, of which dietary components, physical inactivity, smoking, alcohol consumption, and other lifestyle factors are most commonly investigated [12–14].

Medical nutrition therapy is recommended for treating diabetes. However, these recommendations have not been updated to target the inflammatory components, which can be affected by diet and lifestyle. Considerable amount of literature has been published about associations between diet, inflammation, and T2D. However, the distinct themes of these studies have implied different diets low in fat, but many other studies of those diets found significant reductions in inflammatory markers. These included the Dietary Approaches to Stop Hypertension (DASH) diet [15], the low-fat, the Diabetes Prevention Program (DPP)-style diet, the low-energy low-protein diet [16], the vegan and American Diabetes Association (ADA) diets [17], the high-protein low-fat diet [18], and both the high-protein and low-protein diets [19]. These studies also supported the hypothesis that the high- Monounsaturated fatty acids (MUFA) diet decreased inflammation [20]. Jonasson et al. [21] demonstrated that

following a low-carbohydrate diet (LCD) has a favorable impact on low-grade inflammation in type 2 diabetes compared with advice to following a low-fat diet (LFD), where only LCD was found to significantly improve the subclinical inflammatory state in type 2 diabetes [21]. Further, several studies have concluded that reducing carbohydrate content, rather than glycemic index, is a better strategy for lowering glycemia in adults at risk of diabetes [22].

Recent evidence has mainly focused on the effects of lifestyle interventions (diet, exercise and training) on inflammation, lipid profile and glycemic factors. Notwithstanding, the fact that they are recommended in mix together [23], however, few investigators have tested diet, exercise in mix together.

Several human studies, both clinical and experimental, have been assessing the role of regular physical activity (training) on metabolic disorders, including on diabetes. The results from these studies clearly suggested that the beneficial effect of exercise seems to be related to its ability in lowering inflammatory cytokines levels and/or elevating the anti-inflammatory levels both in obesity and type 2 diabetes. Several new publications have appeared in recent years documenting the health-beneficial effects of different high intensity interval training (HIIT) regimens for T2D. Their novel findings include improved overall glycemic control and pancreatic β cell function in T2D patients following 8 weeks of HIIT on cycle ergometer [24]. It is positively involved in complicated systems of metabolically processes [25], improving performance [26] improving HbA1c [27]. Madsen et al. indicated that following 8 weeks of HIIT on cycle ergometer, the circulating anti-inflammatory cytokines concentrations increased among inactive T2D patients [4].

There is no study about the direct effect of exercise training (especially HIIT) and dietary combination on inflammation, anti- inflammation, and glycemic control in individuals with obesity and T2D. hence, due to the limited availability of data for analysis on this topic, this research seeks to address the following objectives: The first objective is to assess the cumulative effects of HIIT and diets (low carbohydrate and low fat) in a long-term (24 weeks) lifestyle intervention program on the control parameters of inflammation and pro-inflammation adipokines in obesity with T2D subjects. The second objective is to describe the effects of this program on other parameters (glycemic and insulin sensitivity statuses, impaired fasting glycemia; insulin sensitivity or resistance) in obesity with T2D subjects [28].

Materials and methods

Subjects and procedures

Participants were recruited through local advertisements and evening sessions at the Centre for physiological laboratory in

Education of Bushehr City, where the study was conducted. The patients were 65 T2D and obese men who volunteered for, and enrolled in, an ongoing study designed to have their inflammation as well as anti-inflammation markers and glycemic status examined. Finally, 42 obese with T2D were eligible for the study. The patients were randomly divided into 4 groups.

In the first group ($n = 11$) who underwent HIIT and consumed Low CHO diet regimens. The second group ($n = 11$) who underwent HIIT and consumed Low Fat diet regimens. The third group ($n = 11$) who underwent HIIT and consumed high Fat diet regimens. Finally, the last group ($n = 9$) underwent HIIT and consumed normal diet regimens, as shown in Diagram 1.

three participants (one patient from each experimental groups) dropped out of the study during the interventions (exercise training and diet regimes) and plasma samplings. The inclusion criteria for the patient's study were BMI 30–39 kg/m², diagnosis of type 2 diabetes treated with diet without additional oral glucose-lowering medication (incretin-based therapy or insulin), age 36–58 years, sedentary lifestyle (no regular exercise more than once per week), glucose intolerance, family history of obesity in at least one first-degree relative, and no use of medications affecting body composition or metabolism. There were weight or age exclusion criteria (age ≤ 35 years and weight ≤ 85 kg). Also, patients who had difficulties understanding the Persian language, suffering from severe mental disease or malignant disease, or who were abusing drugs could not participate in the study. All participants were nonsmokers. The study was approved by the institutional review board for Human Use at the Isfahan University of Medical Sciences. All subjects filled informed consent from before participating in the study.

Nutrition interventions

The patients were randomized (Randomization was not stratified and was based on drawing blinded ballots) to Low-Carbohydrate Diet (LCD), Low-Fat Diet (LFD), High-Fat Diet (HFD), and Normal Diet (ND) groups. The four groups consumed an energy content of 1800 kcal/day. The nutrient composition used in our study was similar to the one traditionally recommended for treating obese patients with T2D in Iran. ND group had an energy content for whom 35% of

energy (E %) came from fat, 50 E% from carbohydrate and 15 E% from protein. The LCD group, they received 45% energy (E %) from fat, 20 E% from carbohydrate and 35 E% from protein. The LFD group received 30 E% from fat (less than 10 E% from saturated fat), 50 E% from carbohydrate and 20 E% from protein. Finally, the HFD group had an energy content where 60% energy (E %) came from fat, 30 E% from carbohydrate, and 10 E% from protein. The nutrient composition and dietary advice were given by physicians on a group basis at baseline and during examination. They were standardized with regard to energy content and nutrient composition. One dedicated dietician provided all participants with suitable recipes at each group meeting and was also available for questions from participants during the whole study period.

Exercise training program

Exercise training sessions consisted of 10 intervals of supervised (10×1 min ergocycle (1 min = 15 s with 75% HRmax, 15 s with 85% HRmax and 20s with 90 HRmax) 60-min weekly sessions of HIIT. HIIT prescription was based upon the results of the baseline maximal treadmill exercise test, estimated maximal aerobic power, and maximal heart rate test. HIIT sessions were performed on ergocycle (Monark, model 849 E, Sweden) under supervision of a physician and consisted of a 5-min warm-up at 50 W, followed by 10 intervals of 1 min of repeated bouts of 15 s with 75% HRmax, 15 s with 85% HRmax, and 30s with 90 HRmax (≈ 180 – 185 W, in the first weeks and 5–10% overload in following weeks) interspersed by 60s to 90 s periods of active rest (30% HRmax (≈ 50 – 75 W) in the first four weeks, 35% HRmax in the second four weeks (≈ 60 – 85 W), and 40% HRmax in the last four weeks (≈ 70 – 95 W), with finally a 5-min cool down at 50 W. The targeted Borg rating of perceived exertion (RPE) was set at 18 during the exercise sessions. The total exercise time was 20 min per HIIT session as presented in Diagram 2.

Procedures

In this investigation, 33 elderly obese (BMI between 30 and 38 kg/m²) men with T2DM (with 12 months history of T2D) were volunteered to participate in the present study. The participants' selection according to eligibility criteria included

Diagram 1 Interventions used in obesity with T2D patients

Diagram 2 Exercise training program

fasting hyperglycemia $>126 \text{ mg}\cdot\text{dL}^{-1}$ and glycated hemoglobin (HbA1c) $\geq 6.5\%$, no drug therapy during the previous 6 months, sedentary or insufficiently active lifestyle (according to the International Physical Activity Questionnaire previously validated in Iranian population), non-involvement in regular physical activity or exercise program during the previous six months, and family history of T2DM (mother and/or father). In the next stage, the patients took apart in a screening visit. After a 12-h fasting period, body weight (kg), height (cm), and abdominal circumference (cm) were measured. Venous blood samples (10 mL) were obtained for insulin analysis. A capillary blood sample was collected for determining the blood fasting glucose concentration (Accu-check Advantage, Roche, Germany). Glycated hemoglobin (HbA1c) was estimated as proposed by Rohlfing et al. [29]. The insulin resistance index, HOMA-IR (< 2.71), was estimated according to Matthews et al. [30]. This study was performed in three phases. In the first phase, to meet our primary objective, participants were randomized and divided into four groups as mentioned above. In this phase, the physician educated the participants how to conduct diet recommendations and nutrition program during 8 weeks and report their diet to the physician every three days to control them and modify the program if required. Finally, all participants completed this phase correctly. In the second phase, the participants took part in experimental session in the laboratory under the supervision of a cardiologist and physician in order to undergo a maximal incremental test (IT) to determine the maximal heart rate and to establish the exercise intensity in 12-week high intensity interval training on a cyclergometer (as mentioned above). In the last visits in the second phase, the participants were familiarized with the exercise training program and with schedule design and study objectives. In this phase, the participants continued their diet recommendations. All sessions (12 weeks) began at 8 AM. At the beginning of each

experimental session, blood glucose was measured (AccuChek Advantage) and, if the values were outside the 100 mg/dL and 300 mg/dL range, the experimental session did not occur and the session was rescheduled for the upcoming week [31]. Then, the participants performed exercise on a cyclergometer after 90 min of carbohydrate ingestion, and hence they were hyperglycemic. By the end of this phase, three participants dropped out from study (1 person per experimental groups). In the third phase, following 8 weeks of diet and 12 weeks exercise + diet, participants restarted a nutrition program for 4 weeks as presented in Diagram 3.

Assays

All analyses were conducted in the central Laboratory of Abadan and Free Zone Arvand College of Medical Sciences. All baseline blood samples were taken in the morning after an 8–9 h overnight fasting. The blood samples were centrifuged for 10 min at 4°C and plasma samples were stored at 80°C for subsequent analyses. The blood samples were collected 72 h before the start of the diet training program and 48 h after the last exercise and diet regimens session.

Basal fasting glucose (Pars kit, made in Iran), insulin (Diaplus kit, made in USA), insulin resistance (HOMA-R), total cholesterol, LDL-cholesterol, HDL-cholesterol, plasma triglycerides concentration and adipokines (leptin, adiponectin, resistin and IL-6, TNF- α , FGF21) levels were measured at the start of the trial and repeated after 24 weeks of four dietary and exercise training interventions. Weight, height, tetrapolar bio impedance and blood pressure were measured at the start of the trial and repeated after 24 weeks of four dietary and exercise training interventions. These measurements were performed at the same time of the day. Adipokines were analyzed using high-sensitivity enzyme-linked immunosorbent assays (ELISAs) kits. TNF- α was analyzed by high-sensitivity ELISA kit

(eBioscience, Vienna, made in Austria); leptin was assayed via high-sensitivity ELISA kit (Mediagnost, Reuttlinger, made in Germany); IL-6 was assayed through high-sensitivity ELISA kit (EK0410, Boster, made in china); resistin was assayed via high-sensitivity ELISA kit (Boster, made in USA); adiponectin was assayed by high-sensitivity ELISA kit (Millipore Corporation, Billerica, MA, made in USA); FGF21 was assayed through high-sensitivity ELISA kit (Boster, made in USA), and total cholesterol, LDL-cholesterol, HDL-cholesterol, plasma triglycerides concentration were assayed utilizing photometric method using pars Azmoon CO. kit. The Ethical Committee of the Isfahan University of Medical Sciences approved the study with the Ethical code of IR.UI.REC.1396.062.

Statistical analysis

Descriptive statistics were computed for each treatment group (diet only, diet/HIIT) at baseline and following 24 weeks of interventions. The results were expressed as mean $\pm$ standard deviation. The distribution of variables was analyzed by Kolmogorov–Smirnov test. All data were analyzed using SPSS (version 21). Overall comparisons of the change in baseline and the 8 weeks of diet, 12 weeks of exercise and 4 weeks of diet were performed using repeated-measures ANOVA. For all analyses, a P value <0.05 was considered statistically significant.

Results

Table 1 presents the baseline characteristics for participants in the study. There were no significant baseline demographic

differences between the four groups at baseline. The mean age was 46 years. Among the groups was no statistical difference in the initial HbA1c and other indexes (Table 2).

Effects of chronic diet and HIIT regimens treatment on fasting plasma glucose, insulin, insulin resistance (HOMA-R), Total cholesterol, LDL-cholesterol, HDL-cholesterol, plasma triglycerides, and weight

After 24 weeks of diet and HIIT regimens, Two-way repeated ANOVA on fasting plasma glucose (Treatment $\times$ Time as repeated measures) indicated significant main effects of time ($F_{5,190} = 21.72$; $P < 0.001$; Partial $\eta^2 = 0.36$), between the four groups ($F_{3,38} = 9.80$; $P < 0.001$; Partial $\eta^2 = 0.43$), and a significant interaction between the two factors (Treatment $\times$ Time) ($F_{15,190} = 3.55$; $p < 0.001$; Partial $\eta^2 = 0.21$) on accumulated Fasting Plasma Glucose (FPG) (Fig. 1a). Post-hoc analysis identified some significant differences in FPG following regimens between the four groups. A one-way ANOVA test revealed that there are some significant differences in the mean scores of 24 weeks of the diet and HIIT regimens across the 4 groups, as demonstrated in Fig. 1a. The results of two-way repeated ANOVA on Insulin indicated a significant main effect of time ($F_{5, 195} = 77.37$; $P < 0.001$; Partial $\eta^2 = 0.671$). However, there was no significant main effect of groups ($F_{3, 38} = 2.12$; $P > 0.114$; Partial $\eta^2 = 0.143$), while there was a significant interaction between time and groups, ($F_{15, 195} = 10.52$; $P < 0.001$; Partial $\eta^2 = 0.454$). Post-hoc analyses using Bonferroni indicated that during the interventions, the mean number of time for the 4 groups was significantly different (Fig. 1b). The results of two-way repeated ANOVA on HOMA-IR demonstrated significant main

Diagram 3 24-week program including 8 weeks for diet, 12 weeks for diet plus exercise training (HIIT) and 4 weeks for diet

Table 1 Baseline characteristics of subjects in study (subjects who completed and included in per protocol analysis)

	Normal Diet+ HIIT	Low Carbohydrate+ HIIT	Low Fat +HIIT	High Fat +HIIT
Number of subjects	9	11	11	11
Age	44.82 ± 6.21	47.08 ± 7.04	49.31 ± 8.09	44.66 ± 7.58
Diabetes(years)	8	6	7	7
Height (cm)	174.09 ± 7.31	174.44 ± 6.9	174.7 ± 5.75	176.98
Weight (kg)	100.45 ± 9.06	100.45 ± 8.22	107.61 ± 12.94	104.6 ± 7.84
BMI (kg/m ²)	33.15 ± 2.35	32.99 ± 1.57	35.23 ± 3.52	33.40 ± 2.42
Waist circumference	102.87 ± 6.10	104.09 ± 8.99	106.02 ± 8.78	106.35 ± 7.56
Total cholesterol (mmol/dl)	5.8 ± 0.9	5.72 ± 0.87	6.9 ± 0.83	5.9 ± 0.77
HDL-cholesterol (mmol/dl)	1.46 ± 0.26	1.13 ± 0.34	1.49 ± 0.35	1.49 ± 0.31
LDL-cholesterol (mmol/dl)	3.63 ± 0.62	3.44 ± 0.72	3.59 ± 0.65	3.14 ± 0.71
Total cholesterol/HDL ratio	4.09 ± 1.11	5.27 ± 1.01	4.41 ± 1.6	4.12 ± 1.14
Fasting Triglycerides	2.54 ± 0.30	2.50 ± 0.49	2.23 ± 0.36	2.50 ± 0.39
Fasting glucose (mmol/dl)	6.60 ± 0.62	6.36 ± 1.04	5.93 ± 0.96	6.06 ± 0.95
HbA1c (%)	6.89 ± 0.53	6.87 ± 0.51	7.04 ± 0.64	7.00 ± 0.53
Systolic BP (mmHg)	141.74 ± 9.19	137.49 ± 8.57	137.79 ± 10.74	137.25 ± 11.01
Diastolic BP (mmHg)	87.97 ± 6.06	86.45 ± 6.69	85.51 ± 6.25	87.18 ± 6.61

effects of time ($F_{5, 190} = 39.413$; $P < 0.001$; Partial $\eta^2 = 0.509$), between the four groups ($F_{3, 38} = 3.937$; $P < 0.001$; Partial $\eta^2 = 0.237$), and a significant interaction between the two factors (Treatment $\times$ Time) ($F_{15, 190} = 5.170$; $p < 0.001$; Partial $\eta^2 = 0.290$). Bonferroni post-hoc analysis identified some significant differences of time in HOMA-IR following regimens between four groups. One-way ANOVA revealed that there are some significant differences in the mean scores on 24 weeks of the diet and HIIT regimens across the four groups as shown in Fig. 1a, c. The results of two-way repeated ANOVA on Total Cholesterol showed significant main effects of time ($F_{5,190} = 19.552$; $P < 0.001$; Partial $\eta^2 = 0.340$) between the four groups ($F_{3,38} = 99.101$; $P < 0.001$; Partial $\eta^2 = 0.887$), and a significant interaction between the two factors (Treatment $\times$ Time) ($F_{15,190} = 2.362$; $p < 0.004$; Partial $\eta^2 = 0.157$); on LDL-Cholesterol, it showed significant main effects of time ($F_{5,190} = 5.16$; $P < 0.001$; Partial $\eta^2 = 0.120$), groups ($F_{3,38} = 10.27$; $P < 0.001$; Partial $\eta^2 = 0.448$), and interaction Treatment $\times$ Time ($F_{15,190} = 3.757$; $p < 0.004$; Partial $\eta^2 = 0.229$); on HDL-Cholesterol, it indicated significant main effects of time ($F_{5,190} = 5.43$; $P < 0.001$; Partial $\eta^2 = 0.125$), groups ($F_{3,38} = 6.68$; $P < 0.001$; Partial $\eta^2 = 0.346$), and no significant difference in the interaction Treatment $\times$ Time ($F_{15,190} = 0.745$; $p < 0.737$; Partial $\eta^2 = 0.056$); and on Plasma Triglycerides, it revealed significant main effects of time ($F_{5,190} = 15.26$; $P < 0.001$; Partial $\eta^2 = 0.28$), groups ($F_{3,38} = 39.65$; $P < 0.001$; Partial $\eta^2 = 0.758$), and interaction Treatment $\times$ Time ($F_{15,190} = 3.012$; $p < 0.001$; Partial $\eta^2 = 0.19$). Bonferroni Post-hoc analysis identified some significant differences of time in Total Cholesterol, LDL-Cholesterol, HDL-Cholesterol, and Plasma Triglycerides following regimens between the four groups. One-way ANOVA revealed

that there are some significant differences in the mean scores on 24 weeks of the diet and HIIT regimes across Total Cholesterol (Fig. 1d), LDL-Cholesterol (Fig. 1e), HDL-Cholesterol (Fig. 1f), Plasma Triglycerides (Fig. 1g). The results of two-way repeated ANOVA on weight showed significant main effects of time ($F_{5, 195} = 4.61$; $P < 0.002$; Partial $\eta^2 = 0.108$). There was not any significant main effect of groups ($F_{3, 38} = 45.06$; $P > 0.001$; Partial $\eta^2 = 0.781$). On the other hand, there was also a significant interaction between time and group, ($F_{15, 195} = 3.44$; $P < 0.001$; Partial $\eta^2 = 0.214$). Post-hoc analyses using Bonferroni indicated that in the interview times, the mean number of times for the four groups are significantly different. One-way ANOVA indicated that there are some significant differences in the mean scores of 24 weeks of the diet and HIIT regimes across the four groups, as illustrated in Fig. 1h.

Effects of chronic diet and HIIT regimes treatment on IL-6, TNF- α , leptin, Resistin, adiponectin, FGF21

The results of two-way repeated ANOVA on TNF- α indicated significant main effects of time ($F_{5,190} = 23.62$; $P < 0.001$; Partial $\eta^2 = 0.384$) between the four groups ($F_{3,38} = 124.89$; $P < 0.001$; Partial $\eta^2 = 0.90$), and a significant interaction between the two factors (Treatment $\times$ Time) ($F_{15,190} = 14.376$; $p < 0.001$; Partial $\eta^2 = 0.532$); on IL-6, it showed significant main effects of time ($F_{5,190} = 7.534$; $P < 0.001$; Partial $\eta^2 = 0.165$), groups ($F_{3,38} = 8.298$; $P < 0.001$; Partial $\eta^2 = 0.396$), and did not show any significant interaction Treatment $\times$ Time ($F_{15,190} = 1.059$; $p < 0.397$; Partial $\eta^2 = 0.077$); on Leptin, it revealed significant main effects of time ($F_{5,190} = 17.766$; $P < 0.001$; Partial $\eta^2 = 0.319$), groups ($F_{3,38} = 98.48$; $P <$

Table 2 Percentage of change in obesity diabetes-related pro-inflammatory/anti-inflammatory adipokines and physiological parameters

Parameters		Pro-inflammation/anti-inflammation						Physiological parameters							
Group/Treatment	weeks	IL-6	TNF- α	Leptin	Resistin	adiponectin	FGF21	Glucose	Insulin	cholesterol	LDL	HDL	Triglyceride	weight	HOMA-IR
normal	4 Weeks	-4.08	-5.10	-1.11	-1.91	+1.02	-5.00	-11.26	-6.62	-2.75	-9.11	-3.93	-17.37	-0.82	-8.69
	8 Weeks	+2.09	-8.52	+1.62	-1.68	+1.10	-7.05	-9.75	-13.17	-1.14	-9.32	+6.80	-10.30	+1.05	-14.63
	14 Weeks	-1.77	+2.31	-1.06	-0.51	+4.38	-4.51	-17.03	+7.65	-8.95	+3.05	-4.00	-16.84	-1.56	+2.57
	20 Weeks	-2.14	+9.22	-1.67	-5.67	+4.25	+17.03	-19.77	+29.15	-16.79	+0.15	+4.08	-18.24	-2.50	+21.62
Low CHO	24 Weeks	-4.23	+11.69	-1.99	-1.30	+4.59	+21.66	-17.27	+16.43	-15.70	+1.92	+11.18	-14.57	-0.76	+10.96
	4 Weeks	-2.31	-2.11	-5.28	-10.63	+11.12	-1.32	-3.78	-16.04	-15.06	-9.17	+15.81	-14.50	-2.90	-15.82
	8 Weeks	-4.89	-19.23	-27.74	-5.89	+16.76	+0.66	-12.47	-33.41	-22.13	-9.43	+10.51	-26.82	-8.87	-34.30
	14 Weeks	-14.64	-34.88	-48.71	-13.13	+21.11	+36.46	-19.26	+30.04	-18.88	+0.89	+17.09	-44.23	-10.95	+15.49
Low FAT	20 Weeks	-35.10	-50.31	-64.84	-29.04	+17.33	+55.29	-28.21	+35.35	-29.40	-38.46	+23.43	-54.99	-13.97	+23.68
	24 Weeks	-32.10	-18.69	-53.92	-28.29	+18.10	+55.86	-34.76	+11.54	-33.35	-7.95	+41.81	-40.71	-12.49	+0.07
	4 Weeks	+3.32	-10.00	-7.37	-6.30	+15.30	-4.15	-8.17	-11.78	-6.41	-9.47	+3.21	-14.12	-4.31	-21.63
	8 Weeks	-4.38	-18.44	-16.97	-12.31	+20.81	+19.58	-7.55	-19.26	-12.55	-17.96	+10.67	-6.35	-5.53	-19.75
High FAT	14 Weeks	-19.12	-24.91	-29.25	-14.19	+28.96	+29.28	-20.37	+4.53	-12.25	-27.22	-30.69	-39.71	-13.72	-1.07
	20 Weeks	-44.90	-62.90	-35.96	-13.89	+36.42	+32.17	-15.14	+17.40	-23.13	-26.67	+15.80	-31.59	-9.57	+12.47
	24 Weeks	-24.97	-48.06	-30.26	-15.27	+42.32	+52.30	-13.81	+6.94	-23.29	-9.14	+21.13	-32.70	-9.23	+2.99
	4 Weeks	+15.36	-1.93	-1.35	-1.99	+9.83	+1.22	-10.28	+1.36	+1.24	-6.15	-10.01	-11.12	-3.05	-1.14
	8 Weeks	-2.11	+7.57	+1.07	-13.60	-7.13	-18.80	-0.97	-13.93	+4.24	-4.39	+5.52	+7.17	+2.97	-12.72
	14 Weeks	-12.68	-1.35	-7.44	-9.40	+1.59	+4.87	-4.49	-3.94	+5.95	-1.64	+6.43	+2.93	+2.01	-4.71
	20 Weeks	-14.37	-7.23	-4.07	-16.04	+4.61	-12.27	-10.16	+1.76	+2.07	-0.89	+10.86	-14.75	+2.43	-0.72
	24 Weeks	-18.67	+0.66	+0.11	-9.18	+1.84	-13.43	-7.46	-5.24	-4.07	-6.18	+9.47	-0.14	+5.74	-6.82

0.001; Partial $\eta^2 = 0.88$), and interaction Treatment $\times$ Time ($F_{15,190} = 5.15$; $p < 0.001$; Partial $\eta^2 = 0.289$); on adiponectin, it indicated significant main effects of time ($F_{5,190} = 7.373$; $P < 0.001$; Partial $\eta^2 = 0.162$), groups ($F_{3,38} = 40.58$; $P < 0.001$; Partial $\eta^2 = 0.762$), and interaction Treatment $\times$ Time ($F_{15,190} = 2.98$; $p < 0.001$; Partial $\eta^2 = 0.19$); on FGF21, it demonstrated significant main effects of time ($F_{5,190} = 6.194$; $P < 0.001$; Partial $\eta^2 = 0.14$), groups ($F_{3,38} = 8.59$; $P < 0.001$; Partial $\eta^2 = 0.404$), and interaction Treatment $\times$ Time ($F_{15,190} = 2.264$; $p < 0.006$; Partial $\eta^2 = 0.152$); finally, on Resistin, it presented significant main effects of time ($F_{5,190} = 10.58$; $P < 0.001$; Partial $\eta^2 = 0.218$), groups ($F_{3,38} = 8.08$; $P < 0.001$; Partial $\eta^2 = 0.39$), and interaction Treatment $\times$ Time ($F_{15,190} = 2.49$; $p < 0.006$; Partial $\eta^2 = 0.165$). Bonferroni Post-hoc analysis identified some significant differences of time in IL-6, TNF- α , Leptin, Resistin, Adiponectin, FGF21 following regimens between the four groups. One-way ANOVA revealed that there are some significant differences in the mean scores on 24 weeks of the diet and HIIT regimes across IL-6 (Fig. 1i), TNF- α (Fig. 1j), Leptin (Fig. 1k), Adiponectin (Fig. 1m), FGF21 (Fig. 1n) Resistin (Fig. 1l).

Discussion

In this study, we analysed the influence of obesity-induced T2D on pro-inflammatory and anti-inflammatory adipocytokines (TNF- α , IL-6, adiponectin, leptin, FGF21 and resistin) as well as physiological markers (Fasting Plasma Glucose, Insulin, Insulin Resistance (HOMA-R), Total Cholesterol, LDL-Cholesterol, HDL-Cholesterol, Plasma Triglycerides and weight). This led to increased/ decreased risk for T2D patients and might be a target for preventive obesity-reducing interventions.

The effects of diet and HIIT interventions on circulating concentrations of metabolic factors

The main findings of the current study suggested that the diets with the HIIT interventions were effective in decreasing/increasing Fasting Plasma Glucose, Insulin, Insulin Resistance (HOMA-R), and Total Cholesterol, LDL-Cholesterol, HDL-Cholesterol, Plasma Triglycerides, and weight. In this regard, following 24 weeks of diet and HIIT intervention, we observed that in Fasting Plasma Glucose, the lowCHO group ($\% \Delta$: -34.76), in insulin, the ND group ($\% \Delta$: +16.43), in Total Cholesterol, the lowCHO group ($\% \Delta$: -33.35), in LDL-Cholesterol, the LFD group ($\% \Delta$: -9.14), in HDL-Cholesterol, the LCD group ($\% \Delta$: +41.81), in Plasma Triglycerides, the LCD group ($\% \Delta$: -40.81), in HOMA-IR, the HFD group ($\% \Delta$: -6.82) and in loss weight, the LCD group ($\% \Delta$: -12.49), indicated an improving trend. On the

Fig. 1 Effects of 24 weeks of diet or HIIT on (a) fasting blood glucose (a) fasting serum insulin (b). The data are expressed as means $\pm$ SEM. α : Significantly different between normal diet and low CHO; β : Significantly different between normal diet and low FAT; χ : Significantly different between normal diet and high FAT; δ : Significantly different between low CHO and low FAT; Φ : Significantly different between low CHO and high FAT; γ : Significantly different between low FAT and high FAT

other hand, other groups also showed slight improvements. Totally, the greatest improvements were seen in the LCD group than in other groups in obese Type 2 Diabetic subjects.

The most important clinical studies conducted on the effects of diet or HIIT interventions on Fasting Plasma Glucose [32–35], Insulin [33, 36–39], Insulin Resistance (HOMA-R) [10, 36, 37], Total Cholesterol [35], LDL-Cholesterol [10, 35, 36, 40–42], HDL-Cholesterol [35, 36, 38, 41, 43–45], Plasma Triglycerides [35, 36, 41, 46], and weight [35, 46–49] in obese Type 2 Diabetic subjects have reported improvements, particularly advocating a low carbohydrate or low glycemic intake.

These studies suggested that the glucose lowering effect can be attributed to weight loss. In reviewing the literature, no data was found on the effect of simultaneous diet and HIIT on physiological parameters in this study. However, in a review conducted by Aguiar et al. [38], it has been suggested that multi-component lifestyle interventions can prevent T2DM, which include a dietary intervention along with both aerobic and resistance exercise training. They are modestly effective in inducing weight loss, improving impaired fasting glucose, improving glucose tolerance, and improving dietary and exercise outcomes in at-risk and prediabetic adult populations [38]. In another study, Feinman et al. (2014) reported that dietary carbohydrate restriction reliably reduces high blood glucose, does not require weight loss (although is still best for weight loss), and leads to reduction or elimination of medication. Notably, it has never shown side effects comparable to those seen by use of many drugs [50].

When studying physiological responses in obese Type 2 Diabetes, Juanola-Falgarona reported that at weeks 16 and 20 and at the end of the intervention, changes in BMI differed significantly between intervention groups. Reductions in BMI were greater in the low-glycemic index group than in the low-fat and high-GI diet group, whereas in the high-GI diet group, reductions in BMI did not differ significantly from those in the other 2 groups. The decrease in fasting insulin, homeostatic model assessment of insulin resistance, and homeostatic model assessment of β cell function was also significantly greater in the low-GI diet group than in the low-fat and high-GI diet groups. Despite this tendency for a greater improvement with a low-GI diet, the three interventions were not observed to have different effects on hunger, satiety, lipid profiles, or other inflammatory and metabolic risk markers [51]. Juanola-Falgarona's theory for these results was that a low-GI and energy-restricted diet containing moderate amounts of

Fig. 1 (continued)

carbohydrates may be more effective than a high-GI and low-fat diet at reducing body weight and controlling glucose and insulin metabolism [51]. In this case, the percent study indicated that, LCD and LFD were almost equally effective in improving physiological responses especially fasting glucose. In other study, three nutritional beverages (500 mL skim-milk, macronutrient control, or flavored water placebo) were consumed after a 12-week low-volume HIIT intervention. The results showed significant main effects of time, but no difference was observed between the groups (Milk, Macronutrient control, Placebo) for CGM¹ 24-h mean glucose, HbA1c, body fat percentage, and lean mass. These findings further support the idea that in type 2 diabetes, high-intensity interval training

is a potent stimulus for improving several important cardiovascular risks and metabolic factors [10].

Although in our study improved metabolic factors were present and sustained in both the LFL and LCD groups, the differences when compared to the ND and HFD groups were significant. Changes (improvements) in metabolic factors for the LCD group were far greater than those of other groups. These differences are likely to be linked to the decreased carbohydrate intake and hence glucose utilization and the subsequent increase in fat metabolism to compensate for intracellular energy requirements (Fig. 1a, b, c, d, e, f, g and h).

A substantial and significant improvement at all timed (diet or HIIT+diet or dietary interventions) of baseline metabolic factors was observed in all of the four studied groups, but none of them appeared to be superior (except for LCD), which is

¹ -Continuous Glucose Monitoring

similar to the studies by [15, 17, 19, 36, 52–55]. On the other hand, the findings in our cohort study were incongruent with the research by Oliveira et al. 2012; [42, 45]. Overall, in our investigation, we found that simultaneous dietary and interval training regimens especially LCD and LFD compared with ND or HFD improved impaired metabolic factors in obese Type 2 Diabetic men. The present findings support these prior reports.

The information now available concerning the effects of aerobic and resistance training in diabetic patients are of great interest to the medical and scientific community. However, there are several studies that suggesting the beneficial effects of physical activity on metabolic profile, while the effects on mechanisms of pro-inflammation and anti-inflammation underlying diabetes are now starting to be elucidated.

The effects of diet and HIIT interventions on circulating concentrations of adipokines

Our data showed significantly decreased levels of IL-6, TNF- α , leptin and resistin as pro-inflammation markers across all four groups, but these reductions were more remarkable in LCD and LFD groups. Moreover, considering anti-inflammation markers, the data indicated significantly increased levels of adiponectin and FGF21 in three groups except for the HFD group. Decreased and increased levels of pro-inflammation and anti-inflammation adipokines in our findings were not in accordance with previous studies. A study by Khanna et al. (2017) found that combined exercise has greater anti-inflammatory effects than aerobic or resistance exercise alone causing a considerable decrease in CRP, IL-6, IL-1b, TNF- α , leptin, and resistin levels and a greater increase in anti-inflammatory cytokines such as IL-4, IL-10, and adiponectin [56]. Clinical studies investigating the effects of diets alone and aerobics, resistance and their combination both on anti-inflammatory and pro-inflammation alone are sparse, but results that are in line with our findings (Simultaneous Dietary and Interval Training Regimens) have not been reported. Certainly, the changes observed in the adipocytokines do not reflect the results of previous studies. Nevertheless, the number of dietary and exercise training interventions reporting anti-inflammatory and pro-inflammation markers is limited and a large number of theories have been extrapolated from animal and laboratory studies rather than clinical scenarios. Overall, These findings in present study support contentions that diet and HIIT affects insulin sensitivity and inflammatory markers and that changes in resistin, IL-6, TNF- α , leptin, FGF21, Adiponectin may be correlated with some of these changes.

Several studies have documented that chronic inflammation is an important cause of cardiovascular disease and is strongly associated with obesity and metabolic dysfunction. The results from these studies clearly demonstrated that

adipose tissue macrophage density grows with obesity, thereby reducing production of anti-inflammatory adipokines, and increasing secretion of pro-inflammatory cytokines. Prior investigations have provided a clear picture that diets only or exercise only can improve the imbalance between anti-inflammatory and pro-inflammation markers in obesity-related T2D. Nevertheless, lack of HIIT and diet combination in the majority of these studies has been a major limitation when trying to identify the dependent effects of exercise and diets on pro/anti-inflammation. In this study, we studied four diets+ HIIT groups in order to determine whether the addition of exercise to ND, LCD, LFD and HFD diets would result in greater improvements in anti-inflammatory and pro-inflammation markers and metabolic factors compared to a diet or HIIT alone. Overall, the results provide evidence that an LCD and LFD diet and HIIT intervention can ameliorate the increase in serum metabolic risk factors and inflammation seen in obesity with type 2 diabetes associated with an unhealthy diet and physical inactivity. However, LCD and LFD diet and HIIT intervention can acts in an anti-inflammatory manner to inhibit proinflammatory pathways and stimulate anti-inflammatory pathways.

Prior studies have noted that Adiponectin and leptin are probably the two most studied hormones as they have been identified for many years. Current evidence suggests that adiponectin plays an important role in the pathogenesis of obesity, type 2 diabetes mellitus, atherosclerosis, and inflammation [57]. It is inversely linked to BMI, waist-hip ratio, hypertension, insulin resistance, dyslipidemia, and coronary artery disease. A comprehensive study by Jorge et al. investigated a range of systemic inflammatory markers over the course of 3 months in T2DM participants (men and women aged 30–70 years diagnosed with T2DM and with a body mass index between 25 and 40 kg/m²) with the following results: Control: light stretching exercise; Aerobic: up to lactate threshold; Resistance: load not described; Combination: aerobic and resistance training with the same intensity of the other training groups and half of the exercise volume on each category. The results from the studies by Jorge et al. mentioned above clearly demonstrated reduced hsCRP serum levels across all groups, including control after the intervention. The changes in adiponectin, resistin, TNF- α were not significant, however. In another study, Vetter et al. evaluated the effect of a low-carbohydrate diet versus a low-fat calorie-restricted diet on adipokine levels in obese diabetic participants. The changes in adiponectin, resistin, TNF- α , or IL-6 were insignificant in either groups after intervention. The both studies were incongruent to our results and did not find any differences in adiponectin and leptin after 26 weeks. This contrast has been shown to be related probably due to differences in the type of diet or exercise training. Indeed, as interval training is better structured and more interesting for patients than other types of exercise training, and better tolerated due

to changes in the intensity during training without interruption [25]. In the present study, elevated adiponectin serum levels were in line to improve in profile of lipedema ($\downarrow$ LDL, $\uparrow$ HDL). Thus, Adiponectin anti-inflammatory actions have been associated with improvement of cardiometabolic profile, which might be due, at least in part, to the regulatory actions on other factors, including on TNF- α , IL-6 and CRP levels [10]. Note that diet along with HIIT had to be sustained over a long period of time and the different diets here were sustained over long periods of time than those in many short-term studies. These differences may have contributed to our ability in detecting a significant effect of the diets and HIIT on adiponectin and leptin [58].

Many human studies have suggested that adipokines are involved in the pathogenesis of obesity, atherosclerosis, inflammation, and type 2 diabetes mellitus. Of those adipokines, IL-6 and TNF- α are considered as potential markers for the treatment of obesity, type 2 diabetes mellitus, atherosclerosis and inflammation. TNF- α and IL-6 are pro-inflammatory cytokines not only produced mainly by immune cells, but also by adipocytes, and therefore the levels of TNF- α and IL-6 are associated with obesity and type 2 diabetes mellitus (Tong et al. 2017; [59]). We found that following 24 weeks of dietary and HIIT interventions, the IL-6 levels dropped among all obese diabetic patients (except for patients with ND diet) and were significantly lower in lowCHO (-32.10), low FAT (-24.97) and high FAT (-18.67) compared with ND (-4.23). We also found a reduction in TNF- α levels for lowCHO (-18.69) and low FAT (-48.06) compared to high FAT ($+11.69$) along with ND ($+0.66$) and non-obese healthy subjects. The finding of this study are similar to the results of [60, 61]. However, they are incongruent with the results of [36, 52, 62]. Further, the HIIT improved liver insulin sensitivity independently of reductions in liver TAG/DAG/ceramide levels. HIIT also improved adipose tissue insulin sensitivity independently of adipocyte cell size, macrophage accumulation in adipose tissue, adipose tissue inflammation, or markers of adipose tissue browning. Importantly, improvements in adipose and liver insulin sensitivity occurred independently of ACC phosphorylation, (Marcinko et al. 2015). These differences were observed between these studies and ours, since the above-mentioned studies have used aerobics and resistance or combination training, but no HIIT. Some authors have reported a correlation between IL-6 and IR [11, 59]. In a study, there was augmented inflammation in T2DM in Pakistani patients which plays a significant role in higher insulin resistance in these patients. TNF- α levels grow with longer duration of the disease. [63]. The results of a meta-analysis conducted by Jelleyman et al. suggested that HIIT is effective at improving measures of insulin resistance compared to continuous exercise and a non-exercising control group. Importantly, the largest effects were seen in those with Type 2 diabetes or metabolic syndrome. Furthermore, in those with Type 2 diabetes or

the metabolic syndrome, there was a 0.92 mmol.L $^{-1}$ reduction in fasting glucose and a 0.47% (5 mmol.L $^{-1}$) reduction in HbA1c when compared to studies with a non-exercising control group [63, 64]. Mohammadi et al. also reported that patients with MetS had a significantly greater serum IL-6 and TNF- α levels than the controls, supporting the evidence that inflammation plays an important role in the immunopathogenesis of the disease. Additionally, IL-6 and TNF- α serum levels may predict MetS. The lack of association between IL-6 and TNF- α serum levels and MetS components remains to be investigated by further research. However, this study demonstrates that in addition to changes in diet, the exercise intervention is also believed to be a mediator of anti-inflammatory effects, since increases in physical activity correlate with reductions in inflammation, due to this study suggesting that there may be a direct effect of physical activity independent of adiposity, mediating the reduction in inflammation.

Fibroblast growth factor 21 (FGF21) is amino acid hormone 181 from FGF family which induces hyperglycemia and functions as anti-fat and heat producer. FGF21 is expressed in adipocytes, liver, skeletal muscles, and pancreas [65]. In our study, FGF21 levels following 24 weeks of diets and HIIT interventions rose among all obese diabetic patients (except for patients with HFD diet) and were significantly higher in lowCHO ($+55.86$), low FAT ($+52.30$) and ND ($+21.66$) compared with HFD (-13.43) which decreased. Regarding resistin, we also found significantly diminished levels in lowCHO (-28.29) and low FAT (-15.27) compared to high FAT (-9.18) and ND (-1.30). Some authors have reported that FGF21 is a metabolic hormone which affects energy balance along with fat and glucose metabolism. The omission of FGF21 causes disturbance in glucose hemostasis and leads to fatness. Studies suggest that the overweight have higher levels of FGF21. However, it seems that FGF21 has anti-fat effects which contribute to losing weight through the increase in fat uptake and reduction in fat mass. Tofighi et al. showed that HIIT program elevated the serum levels of FGF21 and Irisin in sedentary obese women ($P < 0.05$). Also, the results of independent t-test showed a significant difference between HIIT group and control group in terms of FGF21 and Irisin levels. In line with our investigation, Karimi and Banitalebi indicated that after 8 weeks of training, despite the increase in FGF21 in sprint interval training (SIT) and combination groups, there was no significant difference between the pretest and posttest groups in SIT ($P = 0.158$), combination ($P = 0.279$) and control ($P = 0.834$) groups. The comparison between the groups revealed no significant difference between the exercise groups ($P = 0.819$). They also indicated no significant changes in any of the groups. However, the significance of SIT in achieving this result can be caused by short duration, age and fitness level of the participants, though, the need for longitudinal studies in this field remains essential. However, the mechanisms through which HIIT can increase FGF21 are unknown, but

mechanisms such as AMPK's activation, elevated FGF21 via activating P13/AKT signaling pathway by Insulin, and FGF21 levels have a direct link with BMI, visceral adiposity, and pericardial adiposity, controlling the body weight by activating mTORC1, increasing the absorption of glucose, controlling the liver lipogenesis and raising FFA lipolysis when the person is hungry, increasing energy consumption by modifying AMPK activity and SIRT1 through LKB1 in adipose tissue, and oxidation of free fatty acids and glycolysis have been suggested for justifying the elevation of FGF21 and its physiologic effects. [66]. One or more of the abovementioned reasons may reduce FGF21 in type 2 diabetic patients following regimens used in our study.

Nowadays, one of the important adipocytokines involved in the metabolism of lipids and carbohydrates is resistin which has a particular role in the development of insulin resistance [67]. Over the past years, some studies in humans have examined the relationship between circulating resistin levels and obesity as well as diabetes. The results of these studies have been contradictory and difficult to interpret due to inconsistencies in the target epitopes used in resistin assays, as well as in ethnicity and clinical background of the subjects investigated. We demonstrated that plasma resistin concentrations are higher in non-obese T2D patients when compared with healthy non-obese control subjects [11]. Some studies have reported the same results as ours, confirming higher circulating resistin levels in diabetic patients. Several studies have suggested that increased resistin in T2D was not associated with markers of insulin resistance [11]. Therefore, based on available data, this research was performed as a first kind in order to clarify the effect of HIIT along with diets on resistin, one of the pro-inflammatory factors, in obesity-related T2D.

Our findings add to a growing body of evidence that weight loss in obese T2D participants promotes a reduction in markers of inflammation. Moreover, improve in diet and HIIT induced lipids profile, insulin sensitive/resistance likely reason significantly promote markers of pro/ anti inflammation. However, this study also showed that adiponectin and FGF21 increased significantly in response to diet and HIIT induced weight loss. Obviously, more research is needed to determine the effects of diet and/or exercise-induced weight loss on pro/ anti inflammation before conclusions can be drawn.

Conclusions

In conclusion, the present study showed that the levels of adiponectin, TNF- α , IL-6, resistin and FGF21 can be significantly modulated during the development of obesity with type 2 diabetes in response to improve in diet and HIIT induced weight loss and lipids, glycemic profile. However, some of lipids and glycemic profile were not significantly affected and changes did not correlate with markers of body

composition, glucose homeostasis and pro/ anti inflammation markers. The interventions used in the present study might influence cardiovascular risk though significant changes in adipocytokines and inflammatory markers in T2D patients. However, this study was limited in that we only investigated the impact on a relatively small cohort of men adhering to this particular exercise and diet intervention, due to there may be sex differences in cardiovascular risk response to a diet and exercise intervention. Finally, following the proper use of HIIT (low volume) and diets (lowCHO and low FAT), increase in anti-inflammatory adipocytokines, and decrease in pro-inflammatory cytokines, could possibly modulate the pathogenesis of obesity and type 2 diabetes mellitus, and might serve as a prognostic marker and a therapeutic intervention for obesity-related type 2 diabetes mellitus. Therefore, the use of dietary intervention and high intensity interval training, and subsequently diet, can improve obese patients with type 2 diabetes. Nevertheless, additional research needs to be conducted with larger sample size in men and women adhering to different types of HIIT and diet interventions to further assess the impact of weight and/or fat loss on pro/ anti inflammation markers.

Acknowledgements We highly appreciate Professors Mehdi kargarfard and Syed Mohamad Marandi for their great support with data collection. Further, we feel obliged to thank the patients who participated in this study.

Funding This study was supported by the Faculty of Physical Education and Sports Sciences, Isfahan University, Iran.

Compliance with ethical standards

Conflict of interests The authors declare that there is no conflict of interest associated with this manuscript.

Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of Ethics Committee in College of Medicine, Isfahan University, Iran as well as with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Approval of the study was issued by the Ethics Committee at College of Medicine, Isfahan University, Iran.

Informed consent Informed consent was obtained from all individual participants taking part in the study.

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