The effect of high intensity interval training and moderate intensity continuous training on the levels of cardiotrophin-1and insulin resistance in women with type 2 diabetes

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Abstract

Introduction: Cardiotrophin-1 (CT-1) plays an important role in promoting the obesity related disorders including insulin resistance. The aim of present study was to investigate the effect of high intensity interval training (HIIT) and moderate intensity continuous training (MICT) on the levels of CT-1 and insulin resistance in women with type 2 diabetes.

Materials and Methods: Thirty-six women (average age of 46.95±3.49 years old, average weight of 79.5±5.7 kg) with type 2 diabetes randomly assigned in three equal groups including HIIT, MICT and control groups. Both training program conducted for 12 weeks and three session per week. Blood samples collected before and after intervention and serum levels of CT-1 and insulin were measured by ELISA method.

Results: Between group analysis indicated a significant decrease of CT-1 levels in HIIT (P=0.002) and MICT (P=0.016) groups compared to control group, but no significant difference observed between HIIT and MICT groups (P=1.000). Paired t test analysis indicated that serum levels of CT-1 significantly decreased in both HIIT and MICT groups (P<0.001). Moreover, insulin resistance significantly decreased in HIIT and MICT groups compared to control group (P<0.001). Intragroup analysis indicated a significant decrease of insulin resistance in HIIT and MICT groups (P<0.001).

Conclusion: It seems that, positive effects of HIIT and MICT protocols including improvement the insulin resistance are exerted by decreased the serum levels of CT-1. In addition, HIIT was no superior compared to MICT for observed changes in CT-1 levels and insulin resistance.

Keywords: Exercise training, Type 2 diabetes, Cardiotrophin-1

Introduction

Overweight and obesity result in increased the risk of type 2 diabetes, hypertension, hypercholesterolemia, cardiovascular disease and some type of cancers (1). Type 2 diabetes is highly prevalence chronic metabolic disease worldwide, which recognized as a new global health problem, and its estimated that type 2 diabetic population will double until the 2030 years (2). Type2 diabetes is characterized by high glucose levels and insulin resistance due to dysfunction of pancreatic beta cells, which result in elevated blood glucose and free fatty acid levels, increased free radicals, beta cell dysfunction,

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induce the oxidative stress and inflammatory pathways and more inflammatory damage (3). The effects of obesity in type 2 diabetes pathogenesis exerted by various mechanisms, including the expression of some mediators such as cardiotrophin-1 (CT-1) by adipose tissue, and also increase its circulation levels (4).

CT-1 is a member of interleukin 6 (IL-6) cytokine family with a molecular weight of 21.5 kDa that exerts its cellular effects on peripheral tissues via glycoprotein 130 (gp-130) (4). CT-1 is significantly expressed in different tissue including muscle, heart, liver and white adipose tissue and play several protective effects (5). Its reported that CT-1 is one of the major regulators of energy metabolism, and mice with CT-1 knockdown showed a decreased in energy expenditure and increase in the incidence of obesity, hypercholesterolemia and type 2 diabetes, which were exactly the same as the metabolic syndrome. Accordingly, researchers have suggested that CT-1 modulates fat and glucose metabolism and could be a potential treatment for obesity and insulin resistance (6). However, CT-1 levels increase in some pathological conditions, such as hypertension and coronary artery disease (7) and obesity (8). In addition, its suggested that plasma CT-1 levels are significantly higher in subjects with impaired glucose tolerance and recently diagnosed type 2 diabetes compared to healthy individuals (9), which CT-1 upregulation probably is due to increased CT-1 secretion by various organs in these conditions, especially in obesity. The metabolic, cardio-protective, and antihypertensive properties reported for CT-1, represented that observed CT-1 up-regulation in above mentioned pathologies may be a protective mechanism to counteract the onset of obesity related disorders such as type 2 diabetes or cardiovascular diseases (6), and increased the levels of CT-1 in type 2 diabetes is associated with simultaneously increases in levels of other inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and IL-6 (10). According to these findings, it seems that modulation of CT-1 levels is one of the important mechanisms to decrease its pathological effects in diabetic patients. Its reported that exercise training may affected the levels of CT-1, and researchers indicated the increased CT-1 levels in hypertensive patients after 12 weeks resistance training, but there was no significant difference between control and trained groups (11). In addition, Rendo et al (2013) suggested that weight loss program (nutritional intervention and physical activity) result in decreased serum levels of inflammatory mediators including leptin and CT-1 levels which was associated with significant decrease of insulin resistance (12). Different type of exercise training including resistance and aerobic training play an important role in modulation of insulin resistance in type2 diabetic patients (13). However, its observed that HIIT resulted in similar or even further improvements in body composition, physical fitness, and glycemic control compared to continuous endurance training and therefore concluded that HIIT is time-efficient treatment for type2 diabetic individuals (14). In contrast, some researchers suggested that HIIT induces cardiometabolic adaptations similar to those of MICT in prediabetes and type2 diabetes (15). Despite these findings, there was no information about the different exercise training effect including HIIT and MICT on the levels of CT-1 as a key regulator of lipid and glucose metabolism (6). Therefore, the aim of present study was to compare the effect of HIIT and MICT on the levels of CT-1 and insulin resistance in type2 diabetic women.

Materials and Methods

After informing in Tehran diabetes association, type2 diabetes patients were

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recruited for take part in present study and among them, the 36 volunteers women age ranging 35 to 50 years old with type2 diabetes selected as a subject for participate in the present research.

Inclusion criteria were the confirmed diabetes by physician and average glucose levels >126 mg/dl, no kidney, pulmonary and cardiovascular disease, body mass index between 25-35 $kg.m^2$, no menopause, non-addiction to drugs or alcohol, don't take part in regular physical activity in the last year, no injuries or physical limitation, no medical prohibition to participate in exercise training, signing a written informed consent, and lack of different types of malignancies (cancer). Exclusion criteria consisted of no regular participation in training program sessions, injuries during exercise and inability to continue training program, unwillingness to continue research protocol, consumption certain drugs or supplements during research period. Subjects' characteristics including age, height, and body mass index (BMI) in different groups were reported in Table1.

Table1. Subjects' characteristics in different groups.

Variable	Control	MICT	HIIT
Age (years)	46.35±4.25	47.64±2.73	46.87±3.49
Height (cm)	157.62±4.12	158.45±4.79	159.37±5.84
Weight (kg)	80.15±6.21	79.62±6.52	78.76±4.60
BMI ($kg.m^2$)	32.24±1.87	31.38±2.57	31.45±2.72

Data are shown as mean ± SD. HIIT: High Intensity Interval Training, MICT: Moderate Intensity Continuous Training.

The present study was conducted according to the principals of the Declaration of Helsinki and the study protocol was approved by the ethics committee of Islamic Azad University- Science and Research Branch (Ethical codes: IR.IAU.SRB.REC.1399.011).

The present research was randomized double-blind placebo-controlled trial, which documented in the Iranian registry of clinical trials (registration number: IRCT20200729048252N1). The present study conditions and possible side effect or benefits of exercise training was explained to all subjects and among those who agreed with present study conditions, 36 subjects were randomly selected. All subjects participated in the present study voluntarily. After baseline testing, participants were matched based on weight, height, and BMI and randomly were divided into three equal groups (12 subjects in each group) including control, HIIT and MICT groups, which the HIIT and MICT groups received 12 weeks training program. Previously researchers suggested that exercise training as a HIIT or MICT is safe and effective for patients with type2 diabetes (15). Subjects were asked to don't change the nutritional and lifestyle habits. It should be noted that all subjects consumed blood glucose-lowering and anti-diabetic drugs such as metformin, glibenclamide and sulfonylureas. All patients were asked not change the dose and type of medication taken during 12 weeks intervention, and any change in the dose and type of medication should be done only in consultation with a physician.

Body Fat and VO2max Measurement

In order to evaluate the body fat percentage in subjects, the body composition analyzer was used. Maximal oxygen uptake (VO_{2max}) was analyzed through the Rockport Walk Test (RWT) according to previous researches (16).

HIIT and MICT Protocol

Exercise training program in both HIIT and MICT groups conducted on treadmill as a walking or running. HIIT protocol consist of 4×4-min intervals at 85–95% of HRmax followed by 3 min active recovery (walking or jogging at 50–60% of HRmax) in between the intervals. The MICT group walked

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continuously on treadmill for 47 min in each session at 60–70% of HRmax (17, 18). Before conducting main part of HIIT and MICT protocol, 10 min warm-up period at 50–60% of HRmax and finally 5 min cool-down period conducted respectively. The subjects heart rate during training session were monitored by Polar belt. During 12 weeks intervention period, subjects in control group continued their daily routine life.

Blood Samples Collection

Blood sampling performed in both pre and posttest stages by physician. The first fasting blood sample was taken 72 hours before first training session and the second blood sample was taken 72 hours after last training session from the subject's forearm vein. Blood samples were immediately poured into falcon tubes without anticoagulant agent. In next step, blood samples centrifuged at 3000 rpm for 10 minutes and obtained serum were stored at -70 °C for next laboratory measurements.

Biochemical Analysis

The ELISA method was used for measurement the serum levels of cardiotrophin-1 (Elabscience, Catalog number: E-EL-H0651, Sensitivity: 9.38 pg.ml, both intra-CV and inter-CV was < 10%) and insulin (Demeditec, Catalog number: DE2935, Sensitivity: 1.76 µIU/ml) according to Manufacturer's instructions. Glucose levels were also measured by Pars Azmoun kit with a sensitivity of 5 mg/dL. Moreover, insulin resistance calculates with following formula (19):

Fasting insulin {µU/mL} × Fasting glucose {mg/dL} /405

Statistical Analysis

Data analysis performed by SPSS-24 software. First, the distribution of data was examined. Since the results of Shapiro-Vilk test showed that the data have a normal distribution (P>0.05), analysis of covariance test was used to compare between groups changes and if the between groups difference was significant statistically, Bonferroni post-hoc test was used to compare different groups together. Moreover, within group difference were determined by paired t test. For all tests, the significance was considered at P<0.05 and if p value was less than 0.05, the changes were considered significant statistically.

Results

Analysis of covariance test for insulin resistance (HOMA-IR) represented a significant difference between group (P<0.001), and Bonferroni post hoc test indicated a significant decrease of HOMA-IR in HIIT and MICT groups compared to control group (P<0.001), but no significant difference noted between HIIT and MICT groups (P=0.399). Moreover, significant decrease of HOMA-IR was noted from pre- to post training for HIIT and MICT groups (P<0.001) and no significant change for control group (P=0.301) (Table2).

Due to significant between group difference for percent body fat and BMI (P<0.001), its observed that percent body fat and BMI in HIIT and MICT groups significantly decreased compared to control group (P<0.001). However, percent body fat (P=0.368) and BMI (P=1.000) showed no significant difference between HIIT and MICT groups. Intragroup analysis by paired t test indicated a significant decrease of percent body fat and BMI in HIIT and MICT groups (P<0.001), although the changes for percent body fat (P=0.306) and BMI (P=0.228) wasn't significant for control group. VO_{2max} data analysis by analysis of covariance test noted a significant difference between research groups (P<0.001), and VO_{2max} significantly increased in HIIT and MICT groups compared to control group (P<0.001), but the VO_{2max} changes after 12

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weeks intervention wasn't significant between HIIT and MICT groups (P=0.074). In addition, significant increase in VO_{2max} were observed from pre- to post 12 weeks training for HIIT and MICT groups (P<0.001) and there was no significant change for control group (P=0.226) (Table2). Analysis of covariance test indicated that, there was significant difference between control, MICT and HIIT groups for CT-1 levels (p=0.002). Bonferroni post hoc test indicated a significant decrease of CT-1 levels in HIIT (p=0.002) and MICT (p=0.016) groups compared to control group, but no significant difference observed between HIIT and MICT groups (p=1.000). Moreover, paired t test indicated that serum levels of CT-1 significantly decreased in both HIIT and MICT groups (p<0.001), but there was no significant difference for control group (p=0.229 (Figure1).

Table 2. The variables levels before and after 12 weeks intervention (HIIT or MICT).

Variables	Test stage	Control	MICT	HIIT	Between groups P value
Glucose (mg/dl)	pre test	172.1±22.04	167.4±17.68	181.2±17.47	<0.001
	post test	170.8±22.82	146.3±10.97	149.4±12.25	
Paired t test P value		0.424	<0.001	<0.001	-
Insulin (mU/ml)	pre test	9.7±1.12	9.2±0.91	10.3±1.44	<0.001
	post test	9.6±1.05	8.1±0.69	8.7±0.85	
Paired t test		0.455	<0.001	<0.001	-
HOMA-IR	pre test	4.1±0.41	3.8±0.45	4.6±0.76	<0.001
	post test	4.0±0.53	2.9±0.30	3.2±0.53	
Paired t test P value		0.301	<0.001	<0.001	-
Percent body fat (%)	pre test	34.4±2.35	32.6±3.48	33.1±2.85	<0.001
	post test	34.7±2.44	30.7±3.13	30.5±2.96	
Paired t test P value		0.306	<0.001	<0.001	-
BMI ($kg.m^2$)	pre test	32.2±1.87	31.3±2.57	31.4±2.72	<0.001
	post test	32.3±1.94	30.8±2.47	30.9±2.61	
Paired t test P value		0.228	<0.001	<0.001	-
VO_{2max} (ml.kg.min)	pre test	28.3±2.68	29.1±3.43	27.8±2.76	<0.001
	post test	28.1±2.91	32.7±3.84	32.4±3.29	
Paired t test P value		0.226	<0.001	<0.001	-

Data are shown as mean ± SD. HIIT: High Intensity Interval Training, MICT: Moderate Intensity Continuous Training, HOMA-IR: Homeostatic Model Assessment for Insulin Resistance, BMI: Body Mass Index.

Discussion

Present study conducted aimed to compare the effect of 12 weeks exercise training as a HIIT and MICT on the levels of CT-1 and insulin resistance in type2 diabetic patients. Main preset study findings were that 12 weeks HIIT and MICT result in significant decrease of CT-1 levels compared to control group, but no significant difference observed between HIIT and MICT groups. In addition, a significant decrease of insulin resistance in HIIT and MICT groups compared to control group were observed, and like as CT-1, no significant difference noted between HIIT and MICT groups for insulin resistance. It reported that CT-1 levels upregulated in obesity and insulin resistance condition, which probably high circulating levels of CT-1 in obesity and type2 diabetes derives more from skeletal muscle than from white adipose tissue (WAT) and increased its expression in skeletal muscle in these condition, represent a protective mechanism to counteract fat accumulation and to facilitate glucose uptake by the muscle acting in an autocrine or paracrine manner (20).

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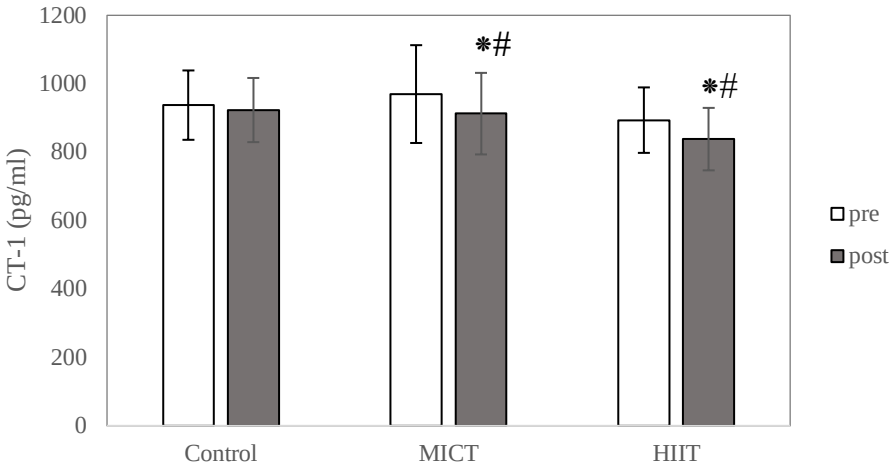


Figure 1. Serum cardiotrophin-1 (CT-1) levels (expressed as mean ± SD) before and after 12 weeks HIIT and MICT protocols. * Denote significant decrease compared to the pre-test stage. # Denote significant decrease compared to control group.

CT-1 may cause insulin resistance in adipocytes. CT-1 like as other IL-6 cytokines family members, induces the expression of suppressor of cytokine signaling 3 (SOCS3), which inhibited the insulin receptor substrate (IRS)-1 phosphorylation and downstream insulin signaling through binding to insulin receptor (21). In addition to obesity and type2 diabetes, CT-1 involved in hypertension (7), and diabetes-induced damage and cardiovascular risk (22). Therefore, CT-1 recognized as a new target for many pathological conditions (23). Present study findings, indicated for first time that different exercise training type including HIIT and MICT is associated with significant decrease of CT-1 levels. Although, there is no similar study about the effect of exercise training especially in diabetic patients on the levels of CT-1, Marti et al (2017) confirmed present study findings and reported a significant decrease of CT-1 expression in peripheral blood mononuclear cells (PBMC) after 10 weeks lifestyle intervention (calorie-restriction and physical activity) in obese children. However, in contrast to present study represented no changes in serum levels of CT-1 after intervention, which simultaneously insulin resistance remained unchanged (24). Probably shorter and different type of intervention compared to present study, and also different subjects' characteristics is responsible for these contradictory results. These results probably emphasize the positive correlation between CT-1 levels and insulin resistance, as in present study, decrease of insulin resistance with HIIT and MICT protocol was associated with significant decrease in serum levels of CT-1. Accordance with our findings, researchers suggested that higher circulating CT-1 levels were associated with increased insulin resistance and impaired glucose tolerance (9).

In another study and agreed with present findings, Rendo et al (2013) observed a significant decrease of CT-1 levels after 12 weeks weight loss program (nutritional and physical education ”endurance training” intervention), which was associated with simultaneous weight loss, decrease in body fat percentage, BMI, WHR, and insulin resistance, and researchers concluded that decreased serum levels CT-1 are associated with a lower risk of developing the metabolic syndrome in overweight and obese children (12). Decrease CT-1 levels in present study was associated with decrease body fat

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percentage and BMI, which suggested that probably decrease in CT-1 levels after exercise training and weight loss program could occur as a result of a decrease in fat mass. Some researches confirmed this hypothesis and suggested that adipocytes are an important source for CT-1 secretion under hyperglycemic conditions (4).

Another finding of present study was that despite decrease in insulin resistance with HIIT and MICT protocol, there was no significant difference between HIIT and MICT groups and they were equally effective in reducing insulin resistance. These results are consistent with the study conducted by Wormgoor et al (2018), which reported that 12 weeks HIIT effects is equivalent to MICT in glucose control, cardiometabolic risk, and microvascular complication markers in men with type2 diabetes (25). In addition, regarding to fasting glucose, HbA1c, blood pressure, BMI, lipid profile (total cholesterol, HDL, LDL, triglycerides), and waist to hip-ratio, the two exercise modalities induced similar effects (15). Although some researchers have stated that higher-intensity training compared to lower-intensity training leading to greater improvements in HbA1c, higher-intensity exercise training did not cause further reductions in fasting glucose compared to lower-intensity training (26). Other researchers reported that increase in cardiorespiratory fitness after HIIT is approximately double the increase after MICT (27). In present study, VO_{2max} increased in HIIT group compared to MICT group was non significantly higher and VO_{2max} in HIIT and MICT group respectively increased 16.54 and 12.37 percent. However, HIIT and MICT effectiveness pathways and the exact mechanisms for exercise training effect (including HIIT and MICT) in the lowering CT-1 levels are remarkably unknown and more studies are needed to answer the existing questions.

Conclusion

In conclusion, according to present study findings, HIIT and MICT result in significant improvement in insulin resistance probably by lowering CT-1 concentration and HIIT is no superior compared to MICT for observed changes in CT-1 levels and insulin resistance in type2 diabetic patients. Decrease CT-1 levels by HIIT and MICT can be attributed to decrease body fat mass as an important source for CT-1 secretion and production in obese individuals.

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Conflicts of Interest

The authors declare that there is no conflict of interest.

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