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ORIGINAL ARTICLE

The Effects of Eight Weeks High-Intensity Interval Training vs. Continuous Moderate-Intensity Training on Plasma Dickkopf-1 and Glycemic Control in Patients with Type 2 Diabetes

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ABSTRACT

Background. Dickkopf-1 (DKK-1) is the most important regulator of the Wingless signaling pathway (Wnt), which plays an important role in inflammation, atherogenesis, and glucose metabolism. Dkk-1 proteins increase with the activation of platelets, and increase of platelet activity plays a role in the progression of progressive atherogenesis in patients with type 2 diabetes. **Objectives.** The aim of this study was the effects of eight weeks high-intensity interval training vs. continuous moderate-intensity training on plasma dickkopf-1 and glycemic control in patients with type 2 diabetes. **Methods.** A total of 57 patients with type 2 diabetes mellitus were randomly assigned to the control (CTR), continuous moderate intensity training (CMIT), and high-intensity interval training (HIIT) groups. Biochemical parameters were measured in all the subjects 48 hours before starting the training program as well as 48 hours after the last session of the training. Both training programs were performed based on specific protocols using a cycle ergometer. **Results.** Both training models could increase VO2peak and decrease glycosylated hemoglobin, insulin resistance, and hypertension in post-test compared to pre-test ($p < 0.05$). The plasma levels of Dkk-1 in the post-test of CMIT and HIIT groups decreased significantly compared to the pre-test values ($p < 0.05$). **Conclusion.** The HIIT and CMIT could decrease blood glucose and insulin resistance and reduce plasma Dkk-1 levels via reducing platelet dysfunction and improving diabetes-related indices.

KEY WORDS: ***Atherosclerosis, Exercise Training, Diabetes Mellitus, Type 2 Diabetes, Dickkopf-1***

INTRODUCTION

Diabetes is a group of complicated metabolic disorders caused by chronic hyperglycemia results from insulin dysfunction. Most patients with diabetes suffer from type 2 diabetes, which is characterized by reduced insulin secretion and increased tissue resistance to Insulin. One of the disorders caused by diabetes is cardiovascular complications and, as a result, the rate cardiovascular mortality is higher in patients with type 2 diabetes than healthy people. In fact, chronic hyperglycemia in type 2 diabetes mellitus is associated with complications such as diabetic neuropathy, diabetic retinopathy, diabetic nephropathy, ischemic heart, and cerebrovascular diseases (1), of which, atherosclerosis is the main mechanism involved in macrovascular diseases in patients with type 2 diabetes in which the thickness of the arterial wall increases, atheroma is formed, and vascular calcification occurs (2). Another factor that seems to play a role in the development of progressive atherogenesis is the increased platelet activation. The platelets of

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patients with diabetes produce more thromboxane in response to various agonists that induce deacylation of arachidonic acid in membrane phospholipids, which is likely to occur due to an increase in the concentration of glucose and lipid in the blood instead of the increased interaction of platelets with the vascular wall (3). In this regard, Dickkopf-1 (Dkk-1) is the most important regulator of the Wingless signaling pathway (Wnt), which plays role in inflammation, atherogenesis, and glucose metabolism. Therefore, platelets appear to be the main supplier of Dkk-1 in clinical conditions. Based on a confirmed hypothesis, Dkk-1 levels in patients with type 2 diabetes may reflect interactions between inflammation, vascular dysfunction, and platelet activation (4). Therefore, it can interfere with an inflammatory intervention between the platelet and endothelium cells in patients with type 2 diabetes.

In total, it is shown that platelets activation increases Dkk-1 proteins, and platelet activation indicators such as Dkk-1 is directly correlated with intima-media carotid layer (as an indicator of atherosclerosis) in patients with diabetes, so that in some studies it is referred to as a new marker for the evaluation of atherosclerosis plaque (5). Physical activity by reducing hyperglycemia, hyperinsulinemia, and hypercholesterolemia can protect heart (6). Nevertheless, a large part of such cardiovascular protective effects caused by exercises are rooted in the improvement of vascular function. On the other hand, the protective effects of exercises on atherosclerosis were confirmed in patients with type 2 diabetes and healthy subjects (7). It was shown that vascular wall thickness and vascular plaque size decrease following aerobic exercise (8). Results of a study showed that the plasma levels of Dkk-1 dropped after an ultra-marathon race (9). On the other hand, Kim et al., showed that a 12-week exercise training reduced Dkk-1 levels in a patient with breast cancer (10). The prolonged period of sedation in an animal model study showed an increase in the expression of Dkk-1 in the brain in a way that long-term, moderate-intensity exercise could cause the negative regulation of Dkk-1 (11).

Although exercise plays an undeniable role in improving vascular health, however, the type of exercise is one of the important points that challenged sports science professionals. Various studies recently showed that high-intensity internal exercises (HIITs) play more effective role in cardiovascular risk factors and improvement of vascular function in hypertensive patients and the ones with type 2 diabetes (6, 12). It seems that HIIT directly affects the vessels by improving the pattern of vascular tension and increasing blood flow (6). In addition, it is shown that HIIT has a better effect than continuous moderate intensity training (CMIT) on health and improvement of vascular function-related indicators including flow-mediated dilation (FMD) (6, 13, 14). For this reason, HIIT is recently considered as one of the favorite interventions by health researchers. One of the most important benefits of HIIT lies in the fact that it allows for extreme sports to be sustained for a longer period than CMIT. Therefore, HIIT triggers a stronger workout than CMIT (15).

Evidence show that HIIT compared with CMIT has the optimal effect on glycemic control, hypertension, and cardiorespiratory fitness in patients with type 2 diabetes. However, the effect of HIIT on plasma Dkk-1 in such patients is not known. Therefore, the present study aimed at investigating the effects of two exercise trainings (HIIT and CMIT) on plasma Dkk-1 level and related parameters such as blood glucose, glycosylated hemoglobin (HbA1c), FMD, and the level of blood pressure in patients with type 2 diabetes mellitus.

MATERIALS AND METHODS

Study Design. The current applied research, semi-experimental study with pretest-posttest design was conducted on patients referring to the Bagheipour specialized Policlinic in Yazd City, Iran in the past two years in order to compare the effects of HIIT and CMIT on atherosclerotic and platelet accumulation in patients with type 2 diabetes.

Participants. To select the study samples, the inclusion criteria were: having type 2 diabetes [according to the American Diabetes Association (2015), the blood glucose level ≥7 mM/L], HbA1c >6%, the age range 60-45 years, pre-hypertensive or early stage of hypertension, or treated hypertension (systolic blood pressure 120-159 mmHg and diastolic blood pressure 80-99 mmHg), at least two years of diabetes, and not attending exercise training in the last six months. The exclusion criteria were fasting blood glucose > 22 mM/L, HbA1c >10%, myocardial infarction, coronary artery bypass graft or angioplasty, chronic heart failure, cardiac arrhythmia, uncontrolled

hypertension [blood pressure above 100/170 mmHg], receiving insulin, functional limitations (e g, osteoarthritis), liver and kidney failure, and smoking and alcohol consumption. For all patients who were eligible to participate in the study, the study process was explained in writing and verbally and the volunteers singed the informed consent form.

After the initial evaluations, 57 subjects, including 24 males and 33 females, were randomly divided into the control (CTR), CMIT, and HIIT groups. Figure 1 shows the flowchart of samples selection.

Measurement of Anthropometric and Biochemical Indices. One week before the beginning of the study, the height and weight of the subjects (using Seca stadiometer and weight scale) and blood pressure (using a mercurial sphygmomanometer) were measured. Blood pressure measurement was also repeated one week after the completion of the intervention. Body mass index (BMI) was calculated by dividing the weight in kilograms by squared height in meters.

Biochemical markers were evaluated in all the subjects 48 hours before the start of the training program and 48 hours after the last training session under a 12-hour fasting condition and in the blood sample drawn from the brachial vein was studied. Blood samples were poured into EDTA-containing tubes and gently mixed. Blood samples were centrifuged at 4°C for 15 minutes at 10,000 rpm and the separated plasma was kept at -70°C and then used to measure the study variables. All measurements were carried out at the same temperature, humidity, ventilation, and ambient light. In addition, the subjects were asked to stop taking alcohol, caffeine, and diuretic drugs for 48 hours before blood sampling. Glucose was measured by the calorimetric enzyme reaction using a chemical analyzer. HbA1c was measured by chromatography. Plasma levels of insulin were measured by ELISA kit (Mercadia AB, Uppsala, Sweden). The serum Dkk-1 (ranged 62.5-4000 pig/mL, internal variation coefficient of 5.4%, external variation coefficient of 8.2%) was measured by ELISA according to the manufacturer's instructions (Lifespan Biosciences, Inc., NO. LS-F2731, Seattle, WA, USA). The insulin resistance index was also measured by the following formula using fasting glucose and insulin levels.

HOMA-IR = [Fasting insulin (mU. L) × fasting glucose (mM. L)] ÷ 22.5

The demographic characteristics of the participants are presented in Table 1.

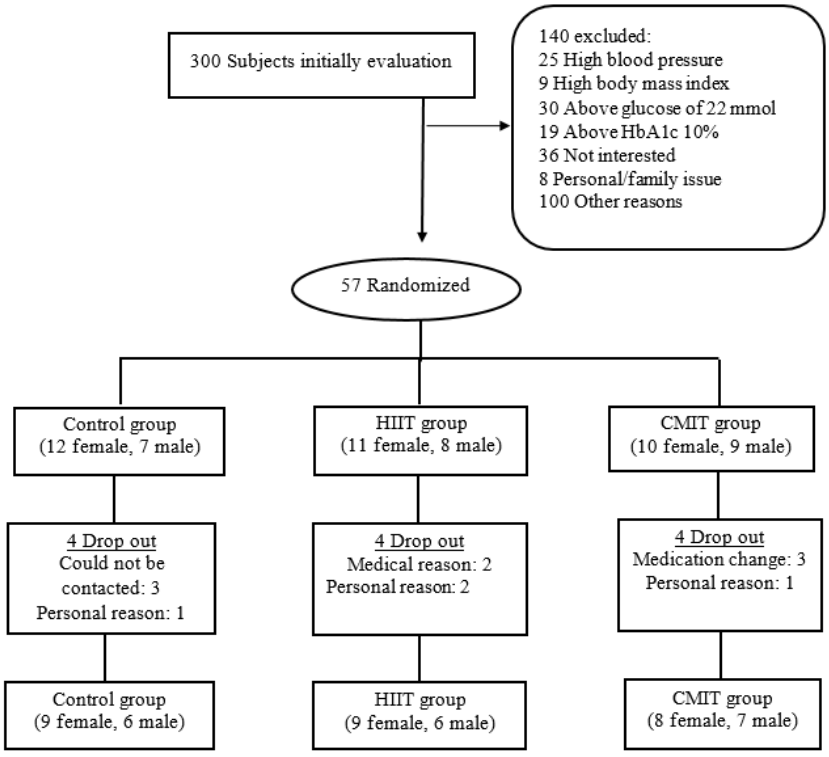

Figure 1. Flowchart of samples selection

Table 1. Demographic characteristics of the study participants

Variable	Control Group	HIIT Group	CMIT Group
Age, yr	54.73 ± 5.73	54.66 ± 6.37	53.40 ± 4.98
Weight, kg	81.50 ± 10.86	83.76 ± 11.57	80.83 ± 11.05
Height, cm	167.47 ± 10.64	169.47 ± 10.05	167.41 ± 10.48
BMI, kg/m2	28.97 ± 1.67	29.05 ± 1.73	28.63 ± 1.86
Blood glucose level, mM/L	10.46 ± 2.14	10.30 ± 2.60	9.95 ± 1.66
Blood insulin, mU/L	8.82 ± 2.33	9.34 ± 2.94	8.97 ± 2.35
Incidence of diabetes, yr	4.86 ± 1.76	3.93 ± 1.38	3.86 ± 1.35
Metformin consumption	(53%) 8	(60%) 9	(53%) 8
Sulfonylurea consumption	(46%) 7	(40%) 6	(33%) 5
Captopril consumption	(20%) 3	(26%) 4	(20%) 3
Atorvastatin consumption	(46%) 7	(53%) 8	(53%) 8

Sports Test. Peak oxygen consumption (VO_{2peak}) and maximal heart rate (HR_{max}) were evaluated one week before and one week after the last training session (HR_{max} was measured along with VO_{2peak}). To carry out these assessments, the Astrand-Rhyming ergometer bike test and the corresponding diagram were used. All subjects were asked to avoid taking caffeine and tobacco for 24 hours prior to the exercise test. In addition, the subjects were also asked to have their last meal at least two hours prior to the start of the test.

Exercise. Each CMIT session included 10 minutes of warming up to 40% of HR_{max}, lasted for 40 minutes at 60%-70% of HR_{max}. At the end of the session, the cooling down exercise was performed for 10 minutes at 40% of HR_{max}. Each session of the HIIT included 10 minutes of warming up to 40% of HR_{max}, performed with ten 1.5-minute intervals at 80%-90% of HR_{max}. Each interval was separated by a 2.5-minute exercise at 50%-60% of HR_{max} from the next interval. At the end of the session, the cooling down exercise was performed for 10 minutes at 40% of HR_{max} (6). The HR_{max} was used to simulate the intensity of exercise (in terms of exercise load) in CMIT and HIIT. The HR_{max} for HIIT was calculated as: (number of intervals × duration of each interval) × percentage of HR_{max} in high intensity interval) + (number of intervals × duration of each interval) × percentage of HR_{max} in a low intensity interval) / total exercise time.

Ethical considerations: Patients were assured about the confidentiality of their information and that their information is used only for research purposes. It should be noted that the study and the intervention protocols were approved by the Ethics Committee of the Research Institute of Sport Sciences (IR.SSRI.REC.1397.345); they were also in accordance with the Declaration of Helsinki.

Statistical Analysis of Data. All data were expressed as mean ± SEM. The Shapiro-Wilk test was used to ensure normal distribution of data. The mixed-ANOVA with Tukey's post hoc test was used to compare the changes induced by exercise intervention. $P < 0.05$ was considered as the level of significance.

RESULTS

The effect of CMIT and HIIT on the level of biochemical parameters measured in the blood sample taken of patients with type 2 diabetes mellitus is presented in Table 2. Based on the results of statistical analyses, both exercise trainings increased VO_{2peak} and decreased HbA1c levels, insulin resistance, and diastolic blood pressure in the post-test compared to the pretest. In addition, both exercise trainings increased VO_{2peak} and decreased HbA1c, insulin resistance and diastolic blood pressure indices compared to the control group (without exercise). Meanwhile, HIIT caused a significant increase in VO_{2peak} and a significant decrease in HbA1c compared to CMIT ($P < 0.05$). None of the HIIT or CMIT significantly changed the systolic blood pressure in different groups of patients with type 2 diabetes.

Table 2. Biochemical and cardiorespiratory fitness indices in pretest and posttest in different groups

Variable	Control Group		HIIT Group		CMIT Group	
	Pretest	Posttest	Pretest	Posttest	Pretest	Posttest
VO_2max; mL/kg/min	24.06±3.82		22.73±4.21	29.26±4.81	22.80±3.86	26.33±3.92**&&
Resistance to insulin	4.20±1.72	4.03±1.66	4.30±1.99	2.54±1.10	3.91±1.06	2.54±0.73**&&
HbA1c, %	8.00±0.75	7.98±0.83	7.38±0.72	6.74±0.60	7.83±0.97	7.32±0.85**&&
Diastolic blood pressure, mmHg	83.20±5.23	83.86±5.13	84.73±5.11	79.73±4.23	84.13±4.67	80.66±3.88*&
Systolic blood pressure, mmHg	138.47±11.71	140.13±11.33	139.93±14.31	133.67±12.27	138.93±14.58	136.18±11.81

Data are expressed as mean ± SEM; HIIT: high-intensity interval training; CMIT: continuous moderate intensity training
***, P < 0.05; **, P < 0.01 in comparison with the control group**
$, P < 0.05; $$, P < 0.01 in comparison with pretest
#, P < 0.05 in comparison with the CMIT group

The results of the effects of HIIT and CMIT on plasma levels of Dkk-1 are presented in Figure 2. Likewise, it was found that the plasma levels of Dkk-1 in the post-test of CMIT and HIIT groups decreased significantly compared to the pretest (P <0.01). Tukey's post hoc test showed that DKK-1 plasma levels decreased significantly in HIIT and CMIT groups compared to control group (P < 0.01). Although the DKK-1 plasma levels of the HIIT group decreased in post-test more than that of CMIT; however, the difference between HIIT and CMIT was not significant (Figure 2).

DISCUSSION

In the current study, it was found that both of the exercises could improve the biochemical parameters of patients with type 2 diabetes by reducing insulin resistance, decreasing HbA1c levels, decreasing diastolic blood pressure and decreasing plasma Dkk-1 levels. Type 2 diabetes mellitus is a complex of metabolic disorders associated with micro- and macrovascular diseases. Although small vessels in type 2 diabetes are the main problematic areas in the affected patients, major vascular dysfunction and cardiovascular stroke are the main causes of death in such patients (16).

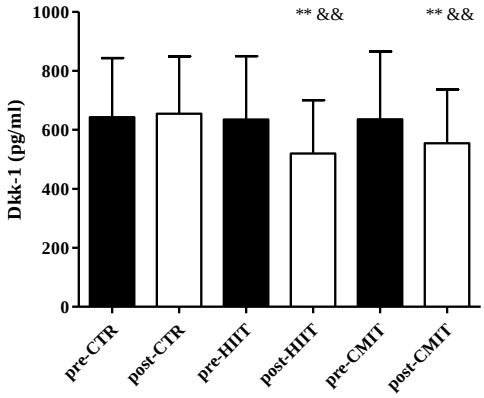

Figure 2. The effect of HIIT and CMIT on plasma DKK-1 levels in the studied groups. Data are expressed as mean ± SEM. CTR, the control; HIIT: high-intensity interval training; CMIT: continuous moderate intensity training
***, P < 0.05; **, P < 0.01 in comparison with the control group**
$, P < 0.05; $$, P < 0.01 in comparison with pretest

Hyperglycemia is the most common cause of vascular disorders in patients with diabetes. Reducing HbA1c levels, which is an index of blood glucose, can reduce retinopathy, nephropathy, and neuropathy in patients with type 2 diabetes (17). The main characteristic of type 2 diabetes is insulin resistance, which means that the response of insulin receptors to insulin decreases, resulting in increased insulin release levels and increased insulin plasma levels (hyperinsulinemia) (16). In the study, both CMIT and HIIT reduced insulin resistance and reduced HbA1c levels.

Exercise improves the effect of insulin and by modifying the homeostasis of glucose and lipids in the blood and blood components contributing to the formation and spread of cardiovascular disease. Exercises do this by influencing glucose metabolism, which stimulates glucose uptake by skeletal muscle. The removal of glucose from the blood by skeletal muscle is mainly done by the glucose transporter type 4 (GLUT4). The placement of this protein in the membrane of the cell is affected by two complex signaling pathways, both of which are controlled by muscle contractions and insulin. Muscle contractions through the signaling of the activating protein kinase by AMPK increase GLUT4 and increase glucose intolerance. Patients with type 2 diabetes mellitus have a disorder of glucose transport in the membrane, and exercise can increase glucose uptake in them (18-20). Another mechanism for the effect of HIIT on the improvement of glucose control in the body is that HIIT call for more muscle fibers and faster muscle glycogen storage and ultimately increases the sensitivity of muscle fibers to insulin after exercise. Because the phenomenon of increased insulin sensitivity following a single HIIT session only lasts for 24 to 48 hours after exercise, regular HIIT may be a good strategy to control acute and/or long-term control of blood glucose level in patients with type 2 diabetes. According to Butcher et al., all studies investigating insulin response to HIIT reported a significant improvement (23% to 58%) in the increased insulin sensitivity. In non-diabetic healthy subjects, improvement in fasting insulin levels and insulin resistance was 23%-33%, while in patients with type 2 diabetes, improvement in fasting insulin and insulin resistance was 46%-58%. On the other hand, it is reported that endurance exercise can improve long-term insulin sensitivity in both young and elderly people. These effects are related to weight loss, increased expression of GLUT4, increased blood flow due to nitric oxide release, and decreased liver glucose production and blood lipids. In general, it can be said that the amount of insulin decreases with exercise, but sensitivity to it intensifies (21-23). The study also showed that both exercise trainings reduced blood glucose and improved insulin resistance in patients.

Recently, many proteins are introduced for the formation of atherosclerotic plaque. For example, in the recent years, the Wingless signaling pathway (Wnt) is introduced; it plays a vital role in physiological processes such as cell differentiation and tissue/organ morphology. Wnt proteins are bound to the Frizzled receptor family and the low-density lipoprotein receptor-related protein 5/6 (LPR-5/6) at the cell surface, then transferred to the nucleus and regulate the expression of the target genes of the Wnt pathway (24). The Wnt signaling pathway is regulated by various antagonistic proteins such as Dkk-1 (25). Increased levels of Dkk-1 in carotid plaques indicate increased interaction between platelets and endothelial cells (26).

Clinical studies show that vascular calcification is modulated by binding Dkk-1 to Wnt receptors and reducing the β-catenin nuclear transfer. By activating platelets, CD40L and Dkk-1 proteins increase. These proteins contribute to atherosclerosis (27). Therefore, in general, diabetes is identified as a factor in the development of atherosclerosis. In the present study, HIIT and CMIT reduced Dkk-1 levels. Possibly, increased platelet activation plays an important role in the incidence of progressive atherosclerosis. Abnormal platelet activity in patients with type 2 diabetes mellitus with chronic hyperglycemia shows that there is a direct correlation between blood glucose control and platelet activation in such patients (28, 29). Therefore, it seems that exercise by controlling the glucose metabolism and decreasing insulin resistance can decrease platelet dysfunction and thereby improve the relative level of diabetes that was also indicated in the present study. In the current study, it was shown that HIIT has a more favorable effect on indices such as VO_{2peak} and HbA1c in comparison with CMIT that is consistent with the results of other studies. For example, Wisløff et al., (2007) reported that HIIT lead to an increase in VO_{2peak} levels compared to CMIT in people with coronary artery disease (30).

As some studies showed that exercise reduces the expression and plasma levels of Dkk-1, the present study also indicated that the HIIT and CMIT exercises can reduce the plasma levels of Dkk-1 in patients with type 2 diabetes. Kim et al., stated that metabolic stress following exercise was one of the factors that led to a decrease in Dkk-1 levels (10). Li et al., in an in vitro and in vivo study showed that the expression of Dkk-1 increases with increased oscillatory tension in the endothelium (31). The shear stress pattern in diabetic patients is associated with increased retrograde and oscillatory tension and decreased anterograde tension (6).

The mechanism of increasing Dkk-1 in patients with type 2 diabetes is still unclear. However, it was shown that increasing the oscillatory and retrograde tension is one of the key factors in increasing Dkk-1. Following the increase in retrograde tension, expression of proteinase-activated receptor-1 (PAR-1) increases. PAR-1 is activated following the increased blood flow and increases cAMP-response element-binding protein (CREB) stimulation. With the transfer of CREB to the nucleus, the expression of Dkk-1 increases (31). On the other hand, 12 weeks of HIIT showed reduced oscillatory and retrograde tension and increased the anterograde tension in patients with type 2 diabetes (6). Therefore, it seems that HIIT can reduce plasma Dkk-1 in patients with type 2 diabetes by adjusting the axillary current.

CONCLUSION

Finally, the study shows that HIIT and CMIT reduce blood glucose and insulin resistance and reduce plasma levels of Dkk-1 by reducing platelet dysfunction and improving indicators related to type 2 diabetes mellitus. However, more studies are needed to determine which one of these exercise trainings can affect platelet disorder associated with type 2 diabetes.

APPLICABLE REMARKS

Regarding the obtained results, HIIT can be used as a non-pharmacological treatment for glycemic control (glucose, insulin, and insulin resistance) and reduction of Dkk-1 (as an atherosclerotic index) in patients with type 2 diabetes.

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