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Effect of Eight-Week High Intensity Interval Training on Omentin-1 Gene Expression and Insulin-Resistance in Diabetic Male Rats

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ABSTRACT

Background. Omentin-1, a novel adipokine expressed in visceral adipose tissue, is negatively correlated with insulin-resistance and obesity. **Objective(s).** The aim of this study was to investigate the effect of eight weeks of high-intensity interval training on omentin-1 gene expression in visceral adipose tissue and insulin-resistance in male wistar rats. **Methods.** A total of 26 male Wistar rats (mean weight = 110±10 gr) were purchased from Pasteur Institute in Iran. At first, six rats were separated as base control group and, after eight weeks of feeding with normal diet, were dissected and their visceral adipose tissues were sampled. The remaining rats were given a high-fat diet for eight weeks. After this, seven rats were separated into the non-diabetic fat group (obese HIIT). Then, diabetes was induced on the remaining animals. After eight weeks, diabetic rats were divided into two groups—diabetic control group (n=6) and diabetic HIIT exercise group (n=7). The exercise group ran on treadmill for eight weeks—five days a week with a speed of 29–36 m/min and intensity of 90% of VO₂ max. The activity was repeated five times in the first week, which increased to 12 times in the last week. A total of 48 hours after last session, fasting blood glucose and insulin were measured. Omentin gene expression was measured from visceral adipose tissue. **Results.** Results showed that omentin-1 gene expression was increased significantly after eight weeks of HIIT. Blood glucose and insulin-resistance decreased significantly in training groups (p=0.001). **Conclusion.** It can be concluded that eight weeks of HIIT induce high omentin-1 gene expression and reduce fasting glucose level and insulin-resistance in diabetic male wistar rats.

KEY WORDS: *High Intensity Interval Training, Insulin Resistance, Omentin-1, Gene Expression, Type 2 Diabetes.*

INTRODUCTION

Diabetes is a metabolic disorder that is characterized by increase in blood glucose due to deficiency in insulin secretion, resistance to insulin, or both. The prevalence of diabetes is expected to rapidly increase from 171 million individuals (2.8% of the world's population) in

2000 to 366 million (4.4% of the world's population) by 2030 (1). Treatment goals in this disease include the decrease in insulin-resistance via nutrition control, exercise, drug treatment, and stimulation of insulin secretion (2). Adipose tissue plays a central role in energy haemostasis

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control, which it performs by producing hormones called adipokines (3). Therefore, perturbation in their secretion might be effective in metabolic and inflammatory disorders (4, 5).

Omentin-1 is a novel fat depot-specific adipokine that was discovered from visceral adipose tissue (6). Omentin gene is located in chromosomal region of q₂₂-q₂₃. This chromosomal region is related to Type II diabetes in various populations (7-9). Decrease in omentin-1 levels has been reported in patients with impaired glucose control (10), type 1 (11) and Type 2 diabetes (10, 12). These findings indicate that blood omentin-1 levels may play an important role in the pathogenesis of diabetes. On the other hand, lower omentin-1 levels in diabetic patients might indicate perturbation in omentin biosynthesis or in response to hyperglycaemia and hyperinsulinemia (13). It has been reported that augmentation in the adipokine's level is accompanied by increase in insulin sensitivity (14). Recent research works have demonstrated that blood level of omentin-1 and its gene expression have an inverse relationship with obesity, body mass index, waist-to-hip ratio, insulin-resistance, and leptin level, and have direct relationship with adiponectin and HDL levels (15-17). Omentin enhances insulin-stimulated glucose uptake and phosphorylation in subcutaneous fat and in visceral adipocytes, but has no effect on basal glucose uptake (6). It has been proved that insulin-stimulated GLUT4 translocation, through the activation of Akt signalling, plays an important role in maintaining glucose homeostasis (15). Tan *et al.* reported in 2008 that insulin and glucose significantly reduce omentin production and its mRNA expression in omental adipose tissue, while hyperinsulinemia reduces serum omentin-1 levels significantly in healthy subjects (11). Previous studies have also shown that omentin has anti-inflammatory, anti-atherogenic, and anti-diabetic properties (18).

Sedentary habits are one of the main factors that develop Type 2 diabetes (19). It has been demonstrated that augmentation of omentin-1 gene expression after one training session can control hyperglycaemia in diabetic rats (20). Increment in omentin-1 level after 12 weeks of aerobic training in obese males (21) and no change in its level after four weeks of resistance

training in male wistar rats (22, 23) have been reported.

High-intensity interval training (HIIT) has been proposed as a time-efficient exercise intervention that may bring about similar benefits to moderate-intensity aerobic exercise. It has been reported that steady state exercise with duration of 30 mins and moderate intensity in most days a week resulted in no fat reduction compared to HIIT, indicating high efficiency of HIIT for high fat oxidation and reducing fat tissue (24). HIIT is an appropriate training program for reducing body fat percent and for improving anthropometric indices in inactive young females (25). While HIIT tends to have a potent effect on cardio-respiratory fitness in a variety of populations, benefits to omentin-1 gene expression, obesity and markers of metabolic health — such as glucose regulation and insulin sensitivity— are less well-defined. It involves a significant decrease in visceral (intra-abdominal) adipose tissue in overweight and obese participants because of weight reduction due to physical activity, decreased caloric intake, or both. Also the energy expenditure during HIIT training was positively associated with the percent change in visceral fat per week; so it might be good intervention to improve metabolic indices in diabetic overweight peoples. Therefore, this study, for the first time, was conducted to investigate the effect of eight weeks of HIIT exercise on omentin-1 gene expression and on insulin-resistance in diabetic male rats.

MATERIALS AND METHODS

This study was approved by the Ethical Committee of Tehran University. All animals received humane care according to the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Sciences and published by the National Institutes of Health (NIH publication 86-23 revised 1985).

Animals. A total of 26 wistar male rats with an average weight of 110±10 gr and age (five to eight weeks) were purchased from Pasteur Institute in Iran. At first, six rats were separated as base control group and after eight weeks' feeding with normal diet, visceral adipose samples were obtained. The remaining 20 rats were fed with high-fat diet for eight weeks. Three rats were kept

in each cage made of polyethylene with metal doors and dimension of 20*20*40 cm and in controlled conditions with mean temperature of 24±4 °C and humidity of 50-65 per cent. All 20 rats had free access to food and water.

Diabetes was induced by the injection of streptozotocin dissolved in citrate buffer (0.1 M) with pH=4.5 and amount of 30 mg per kilogram of body weight. The diabetic criteria were blood glucose level higher than 300 mg/dl (26). Four weeks after injection, blood samples were taken from rats' tails and blood glucose concentration was measured by Glucometer. Diabetic rats were divided into two groups—diabetic control group (six rats with mean weight of 239.4±15.15 gr) and diabetic HIIT group (seven rats with mean weight of 249.3 ±11.55 gr). Seven non diabetic obese rats considered as obese HIIT group (n=7) and performing same eight week HIIT training program.

HIIT protocol. After becoming diabetic, rats in diabetic HIIT group and obese HIIT group were familiarized with protocol for one week and then trained for eight weeks—five days a week. They ran on treadmill with 90% of VO_2 max with duration of 15 to 30 second and velocity of 29 meter per minute in the first week and 36 meter per minute in the last week. Rest time

between intervals was one minute. at the task was repeated five times in the first week and 12 times in the last week. Warming and cooling down time was five minutes (27).

Blood sampling and Biopsy. A total of 48 hours after last training session, while animals were on fast for 12 hours, they were anesthetized using Ketamine+Xylazine (KX) (75 mg Ketamine per kg and 10 mg Xylazine per kg body weight) via intraperitoneal injection and then blood samples were taken directly from animal's heart. Blood was collected into a vacuum tube with EDTA and then centrifuged at 3000 rpm for 10 min. The serum was transferred to appropriate containers and stored at -80 °C to be used for subsequent measurement. Visceral adipose biopsy was also done. Samples were washed in isotonic saline solution and placed immediately in microtubes free of RNAase and DNAase and were frozen using liquid Nitrogen.

Measurement of blood insulin, glucose, and insulin resistance. Plasma insulin and glucose levels were determined using ELISA kit (made of Sweden) and the photometric method with 1mg/dl sensitivity, respectively. To determine insulin resistance, HOMA-IR formula was used (28).

$$\text{HOMA-IR} = \text{fasting plasma insulin (microunit/ml)} \times \text{fasting plasma glucose (mg/dl)}/405$$

Measurement of Omentin-1 gene expression. Omentin-1 gene expression was measured by real-time quantitative polymerase chain reaction (RT-PCR).

Extraction of RNA. RNA was extracted according to the Stratec kit made in Germany. A total of 25 mg frozen adipose tissue was taken from micro-tubes after defrosting and crushed using a razor. Extraction was continued until the preparation of purified RNA was completed.

Preparation of cDNA and RT-PCR. To make cDNA from the total RNA, Random Hexamer was used as a primer due to long strand of RNA sequence. In order to replicate omentin-1 cDNA, the following primers were used (24). In the present study, Hypoxanthine phosphoribosyl transferase was selected as the housekeeping gene.

Forward-omentin -1: 5`-CAAGGAAATCAAGGAGGAG-3`

Reverse- omentin -1: 5`-CAGGGTTCTTGTAGTCATC-3`

In order to construct cDNA, directions of the American THERMO kit were followed and RT-PCR was performed using cyber Green. ΔC_t

Livak method was used to calculate changes in the relative expression of omentin gene by applying following equations.

$$\begin{aligned} \Delta C_t &= C_t \text{ target gene} - C_t \text{ housekeeping gene} \\ \Delta \Delta C_t &= \Delta C_t \text{ test sample} - \Delta C_t \text{ control sample} \\ \text{Relative fold change in gene expression} &= 2^{-\Delta \Delta C_t} \end{aligned}$$

Statistical Analysis. Results are presented as means \pm standard deviation (SD). Kolmogorov-smirnov test (k-s) was used for checking normality of distributions. To compare the three groups, one-way ANOVA and post hoc Tukey test was used. Significant level was set at $p < 0.05$.

RESULTS

The results showed that there was no significant difference between the weights of the four groups at base time ($p = 0.64$). Within

the group, results demonstrated that after eight weeks of training, the rats' weight did not change significantly compared to base time in diabetic control group ($p = 0.86$) and diabetic HIIT group ($p = 0.27$). Mean values for rat's body weight in each group are presented in Table 1.

There was significant difference in omentine-1 gene expression ($P = 0.001$), glucose level ($P = 0.001$), insulin level ($P = 0.001$) and insulin resistance (HOMA, $p = 0.001$) between the four groups. These results have been shown in Figure 1.

Table 1. Subject's Body Weight (gr) in 4 groups of study

Group	Base control	Diabetic control	HIIT Diabetic	HIIT Obese
Primary	130.8 \pm 14.7	135 \pm 11.3	131 \pm 10.4	132 \pm 13.2
After 8 Weeks diet sacrificed		309.6 \pm 17.5	304.2 \pm 17.4	310.2 \pm 17.2
After inducing diabetes	255.8 \pm 22.5	255.2 \pm 21.9	340.2 \pm 17.1
Final	231.6 \pm 55.6	252.5 \pm 18.6	324.4 \pm 10.8

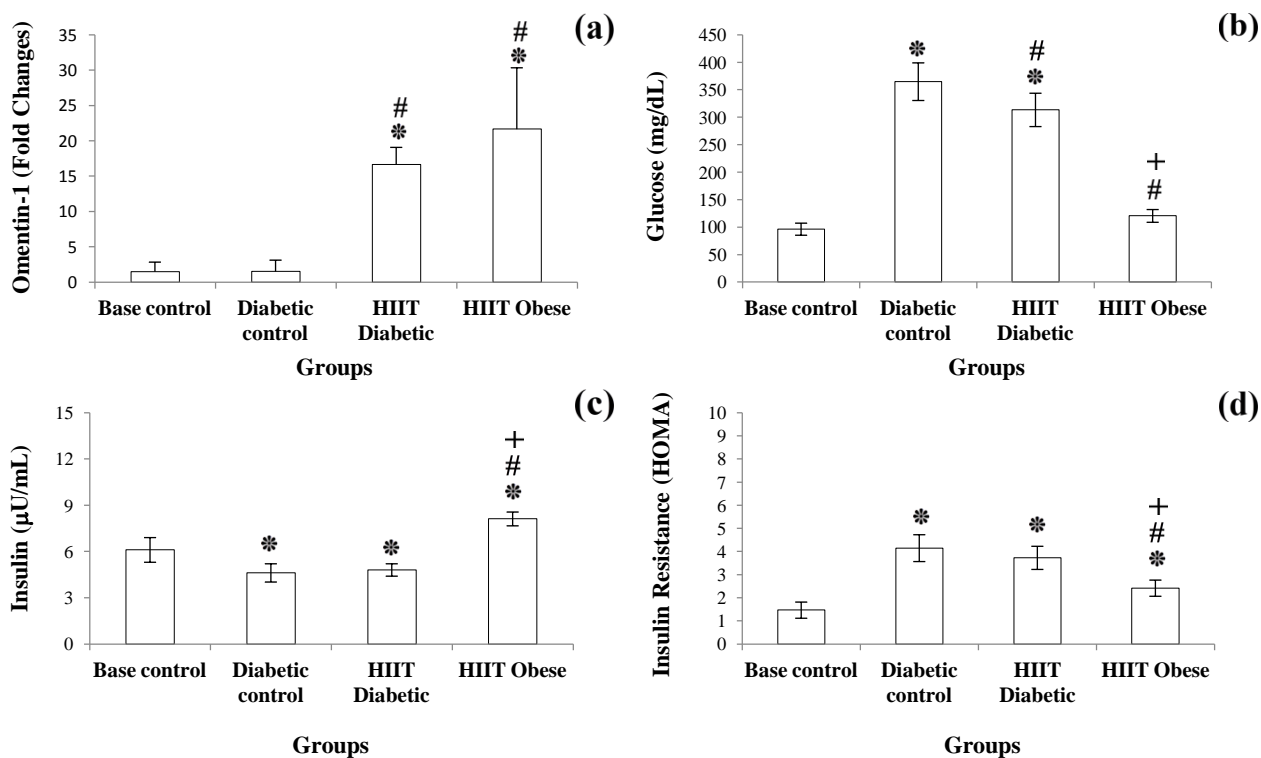


Figure 1. Between groups differences of (a) Omentin-1, (b) Glucose, (c) Insuline, and (d) Insulin Resistance after eight weeks HIIT training. *: Significant difference with Base control, #: Significant difference with Diabetic control, +: Significant difference with HIIT Diabetic.

As can be seen in Figure 1-a, HIIT training induced an increase in omentin-1 gene expression ($p=0.001$). Also, post-hoc analysis showed that omentin-1 gene expression of diabetic HIIT and obese HIIT were significantly higher than base and diabetic control groups.

There was significant difference in glucose level ($P=0.001$) between the four groups. Also, post-hoc analysis showed that glucose level was decreased in HIIT group compared to the diabetic control group ($p=0.01$) (Figure 1-b). Glucose level of diabetic HIIT and obese HIIT groups were significantly decreased compared to the diabetic control group.

There was a significant difference in plasma insulin level between base control group and diabetic control group ($p=0.002$) and between base control group and HIIT group ($p=0.004$), but there was no significant difference ($p=0.836$) between HIIT group and diabetic control group (Figure 1-c).

There was significant difference in insulin resistance (HOMA, $p=0.001$) between four groups. Post-hoc analysis showed that insulin resistance was higher in diabetic control group ($p=0.001$) than HIIT diabetic and obese groups ($p=0.001$). However, in spite of the fact that there was no significant difference between diabetic control and HIIT diabetic groups ($p=0.297$), insulin resistance in obese HIIT group was significantly decreased comparing with the HIIT diabetic group (Figure 1-d).

DISCUSSION

The aim of this study was to investigate the effect of eight weeks of HIIT training on omentin-1 gene expression and on insulin resistance in streptozotocin-induced diabetic male rats. The main finding of this study was that omentin-1 gene expression was increased after eight weeks of HIIT in both diabetic and obese groups.

It has been reported that in addition to the energy storage and release, adipose tissue is an active endocrine organ that synthesizes and secretes a wide range of hormones and cytokines, that involve in Insulin sensitivity (Adiponectin and Omentin), fat metabolism (Cholesterylester transfer protein), inflammation (TNF α), and food intake (Leptin) (29-32). Omentin-1 is an adipocytokine that is mainly secreted from

omental adipose tissue. It was discovered by Yang et al. in 2003. Omentin gene is related with Type 2 diabetes in various populations (7, 8, 33).

Physical activity can improve intake and uptake of glucose during and after exercise via different mechanisms. Some of these mechanisms are increasing in muscular blood flow, increasing in insulin binding to its receptor, increasing in transformation of the insulin receptor and increasing in glucose transport by stimulating of GLUT4 displacement to muscle cell surface (34, 35). In addition to anti-inflammatory properties, presumably omentin-1 plays a role in carbohydrate metabolism and makes consumption of blood glucose by muscles. Therefore, it supplies muscle glucose consumption and reduces body weight by fat lipolysis in adipose tissue (36).

Previous studies have shown that omentin enhances insulin signal transduction via activation of Akt/protein kinase B and improves insulin-stimulated glucose uptake in human adipocytes (6). On the other hand, insulin-stimulated GLUT-4 translocation via activation of AKT signalling is important in maintaining glucose homeostasis. Therefore, it is thought that omentin will improve glucose homeostasis and insulin sensitivity by AKT signalling. A total of 80 to 85 percent of blood glucose is consumed by skeletal muscles and omentin plays a role in stimulating of insulin receptor and glucose uptake in skeletal muscle. Thus, it seems increasing omentin gene expression after exercise is important in the control of hyperglycaemia (15).

Results of present study showed that HIIT induces an increase in omentin gene expression and significant decrease in blood glucose level in diabetic rats. These results are consistent with results of previous studies (7, 12, 13, 20, 21).

In fact, Yang et al. in 2006 demonstrated that recombinant omentin-1 enhances insulin-stimulated glucose uptake and Akt phosphorylation in human adipocytes. Also, circulating omentin-1 levels are negatively correlated with metabolic risk factors, including body mass index, waist circumference, and insulin resistance (HOMA) (1). In accordance with increase in omentin-1 in both exercise groups, insulin resistance (HOMA) decreased in HIIT diabetic and obese groups. Therefore, one

probable mechanism for metabolic improvement of exercise in diabetic people is elevation in omentin-1 levels. Also, HIIT exercise training can be optimal stimulus to change omentin-1 levels.

Effect of one session aerobic exercise on omentin-1 gene expression was investigated in male wistar rats (20). In this study, after induction of diabetes, rats were divided into four groups (one control and three training groups). All training groups ran on treadmill for 45 min with velocity of 20 meter per minute. Biopsy time was different in three experimental groups; biopsy was done immediately after exercise in Group 1, four hours after exercise in Group 2, and 24 hours after exercise in Group 3. Omentin-1 gene expression was measured in adipose tissue. Results showed that omentin-1 gene expression was higher in Groups 2 and 3 compared to control group. Effect of low intensity resistance exercise on serum omentin-1 concentration and on adiponectin in streptozotocin-induced diabetic rats was studied and results showed that resistance exercise induces an increase in serum adiponectin but makes no significant change in glucose concentration, insulin and omentin-1 levels (37). This result is inconsistent with our results. Low intensity exercise and short duration might be the reason for different results of two studies.

Auguet et al. in 2011 studied adiposal omentin-1 gene expression and plasma omentin level in obese women. It was revealed that plasma omentin level is significantly lower in obese women compared to control group and it was correlated inversely with glucidic metabolism parameters. Omentin circulating levels correlated inversely with the metabolic syndrome. Omentin gene expression in visceral adipose tissue was significantly lower in obese women than in control (38). Results of the present study also showed that augmentation in omentin gene expression was associated with decreased blood glucose level after HIIT. It has been reported that omentin mRNA expression was low in overweight and obese people and is related to Type 2 diabetes. Therefore, omentin expression has negative correlation with insulin, HOMA-IR and with BMI (12).

Hyperinsulinemia has inhibitory effect on omentin production and in fact insulin has down regulatory effect on omentin production (11). In the present study, plasma insulin and HOMA decreased but not significantly. This result is

consistent with results of the study performed by Kordi et al. in 2013 but is not consistent with other studies (12, 39). The reason for inconsistency might be different subjects, time and type of activity.

Adiponectin is one of peptides secreted from adipose tissue that has important role in glucose and lipid metabolism (40). Low adiponectin level is related to insulin resistance and Type 2 diabetes (41). However exercise-induced increase in insulin sensitivity is independent of plasma adiponectin level (42). Inverse relationship between plasma omentin-1 levels and obesity and insulin resistance has also been reported (7, 43). Induction of diabetes in rats resulted in reduction in serum omentin-1, adiponectin and insulin level and increase in glucose level (6, 37). It has been shown that exercise-induced increase in insulin sensitivity is lower in people with normal weight than overweight people (44). Subjects of the present study did not become fat after induction of diabetes, thus no change in insulin resistance is consistent with result of study performed by O'Donovan et al. in 2005.

CONCLUSION

The results of the present study suggested that eight weeks' HIIT induces an increase in omentin-1 gene expression and reduction in fasting glucose level and insulin resistance in diabetic male rats. Therefore, it seems that HIIT is an effective exercise method to decrease disorders of obesity and diabetes at least by increase in omentin-1 gene expression and reduction in fasting glucose levels of diabetic people.

APPLICABLE REMARKS

- HIIT training resulted in an improvement in glucose level and insulin resistance in obese participants, and this improvement was accompanied by increased omentin-1 concentrations.
- High-intensity interval training (HIIT) has been proposed as a time-efficient exercise intervention that may bring about similar benefits to other types of exercise.

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