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The Effect of High Intensity Interval Training on Lipocalin 2 Gene Expression in Subcutaneous Adipose Tissue and Insulin Function in Obese Rats with Induced Diabetes

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ABSTRACT

Introduction: Genetic evidence indicates the effective role of transcription factors in insulin signaling pathways. The present study was conducted with the aim of determining the effect of high intensity interval training (HIIT) on gene lipocalin2 expression in subcutaneous adipose tissue, as well as glucose and insulin resistance in type 2 diabetic obese rats.

Methods: For this purpose, obesity was induced in 21 male Wistar rats aged 10 by 8 weeks of high-fat diet. Type 2 diabetes was induced in 14 rats by intraperitoneal injection of STZ (25 mg/dL). The rats were divided into obese, diabetic control and HIIT diabetic groups. HIIT group participated in an 8-week HIIT (5 sessions/weekly), sand the control groups did not participate in the exercise program. 48 hours after the last training session, glucose, HbA1C, insulin resistance, and lipocalin2 gene expression in subcutaneous adipose tissue were measured and compared by one-way ANOVA test.

Results: Type 2 diabetes induction increased glucose and insulin resistance (P=0.001) as well as the expression of lipocalin2 (P=0.001) compared to the obese group. On the other hand, HIIT significantly decreased glucose, insulin resistance (P=0.001) as well as lipocalin2 gene expression (P=0.002) in subcutaneous adipose tissue compared to the diabetic control group.

Conclusion: HIIT was associated with improvement of glycemic profile and insulin resistance in diabetic rats, and this may be attributed to the increase in lipocalin2 gene expression in subcutaneous adipose tissue in response to HIIT.

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Introduction

Type 2 diabetes and cardiovascular diseases are increasing in developing countries (1). Recently, the role of hormones secreted from adipose tissue as regulators of skeletal muscle metabolism and the development of insulin resistance and type 2 diabetes has attracted the attention of many researchers today. Some of these adipokines directly or indirectly affect glucose metabolism by regulating insulin secretion and function (2).

Some of them, such as lipocalin-2 have been introduced as one of the important markers related to obesity and effective in glucose homeostasis (3, 4). Lipocalin-2 is a newly known adipokine that is mainly secreted from adipocytes (5). Its secretion increases following the transformation of pre-adipocytes into mature adipocytes and is induced by some inflammatory mediators such as IL-1B and liposaccharides (6). This adipokine or inflammatory cytokine secreted from adipose tissue is expressed by the NF-kB transcription factor through binding to the binding site in its promoter (7). Clinical studies have repeatedly reported an increase in its expression in human adipose tissue and obese animal models or obesity-related diseases such as type 2 diabetes (8, 9), which of course is reversible by some drugs that increase insulin sensitivity (10). Its direct relationship with obesity and insulin resistance has been reported (11). On the other

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hand, factors such as hyperinsulinemia and hyperglycemia are associated with an increase in their systemic levels (11).

Despite these statements, until now the main mechanisms responsible for the response of insulin action in target tissues such as subcutaneous adipose tissue to lipocalin-2 have not been fully defined. Despite the above-mentioned evidences that indicate an increase in lipocalin-2 levels in the presence of obesity, some studies have pointed out that weight loss caused by moderate-intensity exercise is not accompanied by a significant change in lipocalin-2 serum levels (12). Nevertheless, the reduction of its serum levels in response to various training methods has been reported by some researchers (13, 14). In Choi et al study (2009), lipocalin-2 levels in obese women did not change significantly after 12 weeks of moderate intensity aerobic training (12). Meanwhile, clinical studies have indicated a decrease in insulin resistance in response to lower levels of lipocalin-2 (15). However, in Moghadasi et al study (2014), despite the decrease in lipocalin-2 following 8 weeks of resistance and endurance training, insulin resistance did not change (16). On the other hand, in study by Atashak et al (2022), 12 weeks of high-intensity interval training increased lipocalin-2 and also decreased fasting insulin and insulin resistance levels in men with obesity (17). In study by Parker et al (2022) also acute aerobic exercise increases circulating LCN2 for up to 3-h postexercise in young men (18). However, Sabzevari et al (2022) has pointed out that 6 weeks' pilates training resulted in significant reduction in serum concentrations of lipocalin-2, fasting glucose and insulin resistance in in females with overweight and obesity (19).

Apart from the factors affecting the synthesis and secretion of this adipokine from secretory tissues, so far, few studies have reported the effect of training methods on its expression in insulin target tissues, especially subcutaneous adipose tissue. Therefore, considering the high expression of this adipokine in the adipose tissue of type 2 diabetic rats as one of the most important tissues for insulin action on the one hand and the dependence of insulin action or insulin resistance in adipose tissue on it, determining the response of changes in its expression in subcutaneous fat tissue to exercise, especially HIIT, along with measuring insulin resistance and fasting glucose is one of the objectives of this study.

Materials and Methods

Experimental Animals

21 ten-week-old rats with a weight of (220 ± 10 g) were prepare of the animal house of Pastor Institute of Iran. Then, after induction of obesity and T2D, they were randomly divided into 3 groups: 1) obese, 2) control T2D, 3) HIIT T2D. Animals were provided with high fat diet and they were maintained under standardized conditions (12-h light/dark cycle, 25 ± 2 °C & humidity 45-55 %). The rats were left for 1 week for acclimatization prior to the commencement of the experiment.

Ethical Considerations

This study was approved by Committee of Ethics in Research of Islamic Azad University of Islamshahr Branch, Tehran, Iran (Ethic Code: IR.SSU.REC.1398.413) and carried out in accordance with CPCSEA (Committee for the Purpose of Control and Supervision of Experiment on Animal) guidelines.

Induction of Obesity and Type 2 Diabetic

After getting acquainted with the laboratory environment, all rats became obese by a 8 weeks high-fat diet (16), then 7 rats were selected as non-diabetic obese group (obese group, n = 7), and the rest became diabetics. Type 2 diabetic induced by a single intraperitoneal (i.p.) injection of 25 mg/kg streptozotocin (dissolved in citrate buffer, pH 4.5) (20). Diabetic rats were divided into control (n = 7) or HIIT (n = 7) groups. Hyperglycemia was confirmed by elevated blood glucose levels on day 7 after injection and only animals with fasting blood glucose level between 150-400 mg/dl were selected as T2D rats (20).

HIIT Protocol

After induction of diabetes, 14 diabetes rats rats were divided into 2 control T2D (n = 7) and HIIT T2D (n = 7) groups. Subsequently, the rats of the HIIT T2D experienced HIIT for 8 weeks, 5 sessions weekly in the form of interval running on a treadmill (Table 1) (21). The rats of the obese and control T2D groups did not participate in this training program. Finally, 48 hours after the last training session, the studied rats in all 3 groups were dissected after an overnight starvation.

Table 1. HIIT protocol according to speed and time of running in HIIT T2D group

Exercise session	Exercise phase		Resting phase	
(weeks)	**Time** (S)	**Speed** (m/min)	**Time** (S)	**Speed** (m/min)
1 -2	40	20	120	14
3 – 4	40	25	120	14
5 – 6	40	30	120	14
7 - 8	40	35	120	14

** Running time in the exercise phase is 40 seconds and in the active rest phase is 2 minutes and the speed is in meters per minute*

Table 2. Primer sequence

Genes	Primer sequence	Product size	Tm	Gene Bank
Lipocalin-2	**For**: AGCGAATGCGGTCCAGAAAG **Rev**: GACGAGGATGGAAGTGACGTTG	159 bp	60	NM_001191052.1
RNA PolymraseII	**For**: ACTTTGATGACGTGGAGGAGGAC **Rev**: GTTGGCCTGCGGTCGTTC	164 bp	60	XM_008759265.1

Sample Collection and Biochemical Assay

Finally, 48 hours after the lasting exercise session, the fasted rats in all groups (10-12 hours overnight fast) were anesthetized through intraperitoneal injection of 10% ketamine at a dose of 50 mg/kg along with 2% xylosine at a dose of 10 mg/kg, after which they were underwent dissection (22). After the rats were anesthetized, blood samples were collected through cardiac puncture. Then, subcutaneous tissue was removed, then subcutaneous adipose tissue was dissected and immersed in RNA later to analysis and determine gene lipocalin-2 expression. In addition, glucose was determined by the oxidase method (Pars Azmoon kit, Tehran). Insulin was determined by ELISA method (Demeditec, Germany) and the intra-assay and inter-assay coefficient of variation of the method were 2.6% and 2.88 respectively.

RNA Extraction / Real Time – PCR

To purify RNA, 20 milligrams of tissue were ground using a mortar and pestle, and extraction was then performed employing the RNeasy Protect Mini Kit (manufactured by Qiagen Inc. in Germany) according to the manufacturer's protocol (22). In this stage, the One Step SYBR Prime Script RT-PCR Kit (manufactured by the Takara Bio Inc. in Japan) was employed according to the manufacturer's protocol to prepare the reaction product. The thermal cycle program used for the Rotor-Gene Q instrument was as follows: 42˚C for 20 minutes, 95 ˚C for two minutes, and 40 cycles with 94˚C for 10 seconds and 60˚C for 40 seconds. Temperatures from 50 to 99˚C were used for the melting curve after the PCR to study the characteristics of the primers.

Statistical Analysis

All the data are expressed as mean ± SD. Data were analyzed by computer using the Statistical Package for Social Sciences (SPSS) for Windows, version 22.0. One-way ANOVA with Tukey post hoc test was used to compare the variables between the studied groups. Differences were considered to be statistically significant when *p-value* < 0.05.

Table 3. Pre and post-training of body weight of studied groups.

Group	Pre-training	Post-tainting	p-value (paired t test)
Obese	294 ± 7.70	431 ± 8.14	0.001
Control T2D	391 ± 16.12	294 ± 15.76	0.001
HIIT T2D	366 ± 9.37	286 ± 10.94	0.001
P-value (ANOVA)	0.001	0.402	----------

Results

The bodies weight changes before and after training intervention in obese, control T2D and HIIT T2D groups were compared by ANOVA and are presented in Table 3. In addition, intragroup changes in body weight in each group were determined by Paired t-test

Based on ANOVA analysis, A significant difference change was found with regard to Lipocalin-2 expression in subcutaneous adipose tissue between groups (P = 0.001). the findings of Tukey's test showed that T2D induction resulted in significant increase in Lipocalin-2 in the control T2D group compared to obese group (P = 0.001). But HIIT resulted in significant decrease in Lipocalin-2 expression in the HIIT T2D compared to the control T2D group (Figure, 1, P = 0.002). So that, no significant difference was observed with regard to Lipocalin-2 expression between the obese and HIIT diabetic groups (p = 0.811, table 4, Figure 1).

Table 4. The expression of LCN2 in response to diabetes induction and HIIT in the studied groups

Group	Obese	Control T2D	HIIT T2D	Sig (ANOVA)
LCN2 expression	1	1.36 ± 0.27	1.02 ± 0.09	0.001

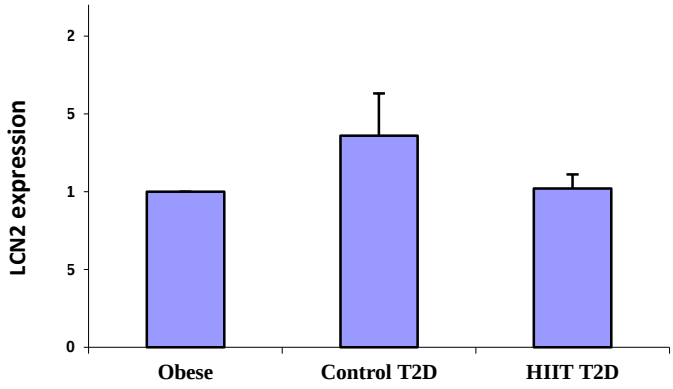

Figure 1. The change pattern of LCN2 expression in subcutaneous adipose tissue of studied groups

Based the results of one-way ANOVA, significant difference was observed with regard to fasting glucose, insulin and insulin resistance between groups (P = 0.001). on the other hand, T2D induction led to an significant increase in insulin resistance and fasting glucose and decrease in serum insulin in control T2D compared to obese group (P = 0.001). But HIIT resulted in significant decrease in insulin resistance (P = 0.001, Figure 2) and fasting glucose (P = 0.001 Figure 3,) and significant increase in serum insulin (P = 0.001, Figure 4) in HIIT T2D compared to control T2D group (Table 5).

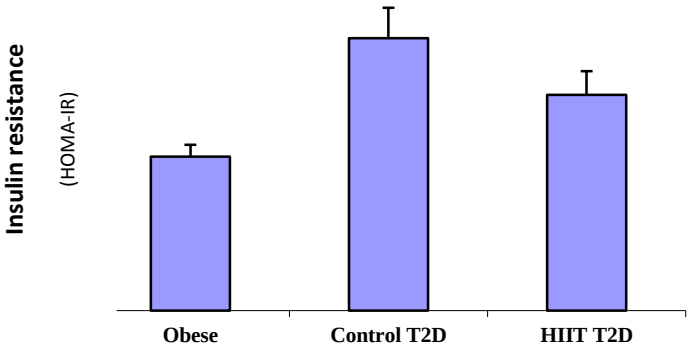

Figure 2. The change pattern of insulin resistance of studied groups

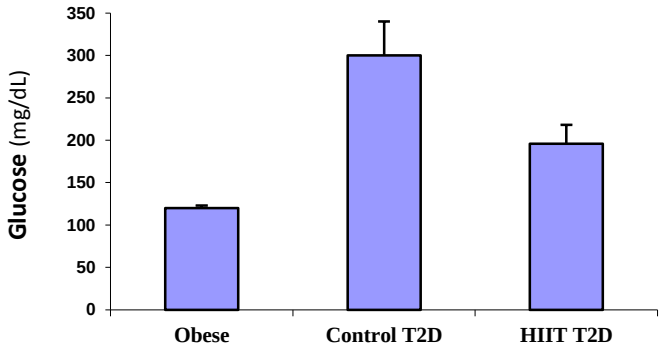

Figure 3. The change pattern of fasting glucose in studied groups

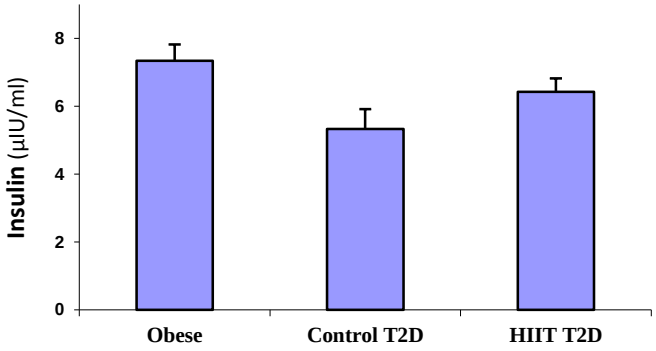

Figure 4. The change pattern of serum insulin in studied groups

Discussion

Decreased lipocalin2 gene expression in subcutaneous adipose tissue in response to HIIT is the main finding of this study. Type 2 diabetes induction in obese male Wistar rats also led to increased lipocalin-2 expression in subcutaneous adipose tissue. HIIT also led to a decrease in serum insulin, an increase in fasting glucose, and an increase in insulin resistance compared to the obese group. The improvement in glucose can be attributed to the reduction of insulin resistance in response to HIIT. In this context, although some studies have reported no change in glucose or glycosylated hemoglobin in response to different training methods (23, 24), some studies consistent with the findings of the present study have shown improvement in blood glucose and insulin resistance in response to exercise training methods in T2D rats (25).

Some other studies have directly attributed the reduction of blood glucose to the increase in insulin action or the improvement of insulin resistance in response to exercise in diabetic rats (20). On the other hand, the improvement of insulin resistance in the studied mice may be attributed to the decrease in lipocalin-2 expression in the subcutaneous adipose tissue in response to intermittent exercise. Nevertheless, in the study of Moghadasi et al (2014), despite the decrease in lipocalin-2 in response to 8 weeks of aerobic and resistance training in inactive young healthy men, CRP and insulin resistance underwent significant changes in response to both training methods (26). On the other hand, Talebi et al (2013) found a significant decrease in lipocalin-2 expression in adipose tissue and a decrease in liver glycogen in 4 and 24 hours after a session of moderate intensity aerobic exercise at a speed of 20 m/min in diabetic rats (27). In Atsek et al.'s study (2017), 8 weeks of resistance

training led to a significant decrease in lipocalin-2 in obese men (28).

In this context, cell and animal laboratory studies have revealed that lipocalin-2 strongly affects insulin signaling pathways and insulin resistance in target tissue such as adipose tissue. In adipose tissue cells, the decrease in lipocalin 2 expression increases insulin-dependent glucose absorption (29, 30). These evidences indicate the role of lipocalin-2 in the formation of insulin resistance of adipocytes and increase in blood glucose. The protective effect of lipocalin 2 deletion on insulin sensitivity is related to the regulation of lipoxygenase 12 and TNF-α in adipose tissue. Thus, the removal of lipocalin 2 in adipose tissue is associated with the improvement of glucose tolerance in male rats that have a high-fat diet (29, 30).

It seems that the decrease of lipocalin-2 in response to internal or external stimuli is also dependent on changes in other cytokines. In this context, Samra et al (2009) for the first time introduced IL-1B as a regulator of the function and lipocalin-2 expression in adipose tissue (31). Mehrabani et al (2014) attributed the decrease of lipocalin-2 in response to aerobic exercise to the decrease of IL-1B and introduced the improvement of insulin resistance as a result of the interaction between lipocalin-2 and IL-1B (32). Inflammatory cytokines TNF-α and INF-γ lead to induction of expression and secretion of lipocalin-2 in adipose tissue (33). On the other hand, it has been mentioned that lipocalin-2 has an anti-inflammatory function by modulating the process of PPARy receptors to decrease NF-kB (34). Nevertheless, some researchers have attributed the reduction of insulin resistance and fasting glucose to the interaction of lipocalin-2 with hepatic insulin sensitivity rather than peripheral insulin sensitivity (35).

In summary, it is pointed out that although the measurement of lipocalin gene expression in subcutaneous adipose tissue in response to HIIT in type 2 diabetic rats is one of the strengths of this study, only the measurement of this genetic component is not enough for a comprehensive conclusion and reaching a general conclusion requires the measurement of other hormonal or genetic components such as FTO, FOXO1, adiponectin or PPARy and their lack of measurement is one of the main limitations of this study.

Conclusion

Improvement of glucose and insulin resistance in this study can be attributed decreased lipocalin-2 gene expression in the subcutaneous adipose tissue in response to HIIT. However understanding the exact mechanisms of these changes requires the measurement of other metabolic, hormonal, and genetic variables.

Declarations

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Ethical Considerations

This study was approved by the Ethics Committee of Islamic Azad University, Islamshahr Branch (Code: IR.SSU.REC.1398.413).

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Authors' Contributions

All authors equally contributed to preparing this article.

Conflict of Interest

There is no conflict of interest.

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