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Effects of High-Intensity Interval Training on Transcription Factor 7-Like 2 / Glucagon-Like Peptide-1 Axis in Pancreatic Tissue of Obese Diabetic Rats

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ABSTRACT

Background and objectives: Genetic studies have indicated the effective role of transcription factors in insulin synthesis and secretion, especially in the case of diabetes. This study aimed to assess the effects of high-intensity interval training on transcription factor 7-like 2/ glucagon-like peptide 1 (TCF7L2 / GLP-1) axis in pancreatic tissue of obese rats with type 2 diabetes mellitus (T2DM).

Methods: For this purpose, obesity was induced in 21 male Wistar rats (weighting 220±10 g) by exposure to a high-fat diet for six weeks. Then, the rats were randomly assigned to a non-diabetic, a control T2DM, and an exercise diabetic group. Next, T2DM was induced by intraperitoneal injection of streptozotocin (25 mg/kg). The rats in the exercise group participated in a HIIT program, five times a week, for six weeks. After the intervention, TCF7L2 and GLP1 expression in the pancreas tissue was determined by real-time PCR. Serum insulin, glucose, and beta cell function were compared between the study groups. Data were analyzed using one-way ANOVA and Tukey post hoc test at a significance level of 0.05.

Results: Induction of T2DM increased glucose level and TCF7L2 expression but decreased insulin, beta cell function, and GLP-1R expression. In addition, HIIT significantly decreased TCF7L2 expression as well as glucose level, serum insulin, and beta cell function; however, it did not significantly change GLP-1R expression compared with the control diabetes rats.

Conclusion: Based on the findings, the improvement of serum insulin and glucose level following HIIT may be attributed to the decrease in TCF7L2 gene expression in the pancreatic tissue of diabetic rats.

Keywords: Insulin, Exercise, Gene expression.

INTRODUCTION

Obesity and type 2 diabetes are now recognized as global epidemics. Type 2 diabetes is the most common endocrine disease caused by glucose intolerance due to an imbalance between insulin synthesis and insulin demand (1). While the underlying causes of this disease are not yet fully understood, studies have confirmed that insulin resistance is one of the primary causes of this type of diabetes rather than beta cell dysfunction (2). However, some studies have suggested that beta cell dysfunction plays an important role along with insulin resistance in the incidence and severity of the disease (3). Based on a prospective study by the British Diabetes Association, beta cell function decreases by 50-60% in type 2 diabetic patients, and the function of these cells decreases approximately 10 to 12 years before the onset of hyperglycemia (4). Several studies have reported no evidence of hyperglycemia in the absence of beta cell dysfunction (5, 6). On the other hand, studies of the last two decades have attributed the defect or decrease in beta cell function to genetic disorders (7).

Meanwhile, it has been recently found that transcription factor 7-like 2 (TCF7L2) gene polymorphisms are associated with type 2 diabetes (8). In fact, its overexpression in the pancreas increases the risk of type 2 diabetes by 1.46-fold (9). The gene codes for a T-cell transcription factor that plays an important role in the Wnt cell signaling pathway, which is essential for regulating cell proliferation and differentiation (10). Some studies have reported a 5-fold increase in the expression of this gene in pancreatic cells of patients with type 2 diabetes compared to healthy individuals, which has been associated with decreased insulin secretion (11). On the other hand, a close relationship between glucagon-like peptide-1 (GLP-1) secretion and TCF7L2 in the regulation of pancreatic islet function has been reported (12). Moreover, TCF7L2 controls the transcription of the proglucagon gene (13), which encodes both glucagon and GLP-1 and controls the production of each hormone by post-translational cleavages of L cells and pancreatic alpha cells (14). GLP-1 stimulates beta-cell proliferation and inhibits apoptosis and cell death. In addition to direct effects on insulin secretion, they stimulate glucose uptake as well as transcription and release of insulin stimuli (15).

Based on the available evidence, it is hypothesized that decreased TCF7L2 expression as well as increased GLP-1R expression in the pancreas due to internal or external interventions leads to increased insulin secretion from these cells. However, changes in the expression of these genes in pancreatic tissue or their downstream pathways in response to pharmacological or non-pharmacological interventions such as exercise interventions have been less studied.

In this regard, Eizadi et al. (2016) reported a decrease in TCF7L2 expression in the pancreatic tissue of diabetic rats in response to long-term resistance training (16). In another study, increased GLP-1R expression was reported after 3 months of aerobic training in normal-weight type 2 diabetic rats (17). Despite this evidence, there is no study on the effects of high-intensity interval training (HIIT) on the expression of TCF7L2 and GLP-1R in the pancreatic tissue of obese type 2 diabetic rats. In this context, it has been pointed out that some adaptations in response to HIIT are achieved much faster than long-term endurance training (18). Considering the effective role and interaction of TCF7L2 and GLP-1R in insulin synthesis, the present study aimed to evaluate the effects of a HIIT program on the expression of TCF7L2 and GLP-1R as well as glucose level, serum insulin level, and beta cell function in obese type 2 diabetic rats.

MATERIALS AND METHODS

Twenty-one 10-week-old rats with a weight of 220 ± 10 g were enrolled in the study. After induction of obesity and type 2 diabetes, the rats were randomly divided into three groups: 1) non-diabetic, 2) control type 2 diabetic, and 3) exercise type 2 diabetic. The animals were provided with a high-fat diet and maintained under standardized conditions (12-h light/dark cycle, 25 ± 2 °C, and humidity of 45-55%). The rats were familiarized with the laboratory conditions for a week. The study received approval from the Committee of Research Ethics of Islamic Azad University of Islamshahr, Iran (approval code: IR.IAU.PIAU.R.1400.011) and was carried out per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals.

After induction of obesity by exposure to a high-fat diet for six weeks (19), seven rats were selected as a non-diabetic obese group (n=7), and the rest became diabetics. Lee index was used to diagnose obesity (20). Type 2 diabetes was induced by a single intraperitoneal injection of 25 mg/kg streptozotocin (dissolved in citrate buffer, pH 4.5) (19). Diabetic rats were divided into a control (n=7) and an exercise (n=7) group. Hyperglycemia was confirmed by the detection of elevated blood glucose levels on day 7 post-injection, and only animals with fasting blood glucose levels between 150-400 mg/dl were identified as diabetic (16, 21).

From the 18th week, the exercise group participated in HIIT training for six weeks, five sessions a week (27 minutes weekly) in the form of running on a treadmill. The training was carried out with 40-second repetitions and 2-minute active rest between each repetition (22).

Table 1-Details of the exercise protocol

Weeks	Exercise Running speed (m/min)	Active rest walking speed (m/min)	Treadmill slope (degree)
1	25	10	5
2	25	10	10
3	28	10	10
4	32	10	10
5	35	10	10
6	35	10	10

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.

After an overnight fast and 48 hours after the last training session, the rats were anesthetized by intraperitoneal injection of 10% ketamine (50 mg/kg) along with 2% xylosine (10 mg/kg), after which they underwent dissection (16). Then, blood samples were collected through cardiac puncture. Pancreatic tissue was removed to determine TCF7L2 and GLP-1R expression. Insulin level was assessed using an ELISA kit (Demeditec, Germany). The intra-assay and inter-assay coefficient of variation of the method for insulin assessment were 2.6% and 2.88, respectively. Glucose level was determined using a glucose oxidase method (Pars Azmoonf kit, Tehran). Beta cell function (HOMA-BF) was determined using the following formula (23):

$$\text{HOMA-B} = \frac{20 \times \text{Fasting Insulin } (\mu U/ml)}{\text{Fasting Glucose (mmol/l)} - 3.5}$$

RNA extraction was done using the QIAGEN commercial RNeasy mini kit (Cat No: Q74124, QIAGEN, Germany) (16). Next, TCF7L2 and GLP-1 mRNA levels were determined by real-time PCR using the Rotorgen 6000 system (QIAGEN GmbH, Germany) and One Step SYBR TAKARA kit (Cat No: BS584-BioBasic, Takara, Japan). Melting curve analysis was performed at the end of the PCR cycle to determine the validity of the expected PCR products. TCF7L2 and GLP-1 gene primers and polymerase II as the control gene were synthesized by Pishgam Biotech Co., Iran. The Oligo 7 primer analysis software was used to design the primers based on the gene. To purify RNA, 20 mg of tissue were ground using a mortar and pestle. Extraction was performed using the RNeasy Protect Mini Kit (Cat. No. / ID: 74124, QIAGEN, Netherland) according to the manufacturer's protocol (16). In this stage, the One Step SYBR Prime Script RT-PCR Kit (Takata, Japan) was employed according to the manufacturer's protocol to prepare the reaction product. The thermal cycle program was as follows: 42 ˚C for 20 minutes, 95 ˚C for two minutes, 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.

Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows, version 22.0. Data were expressed as mean ± standard deviation. One-way ANOVA with the Tukey post hoc test was performed to compare the variables between the groups.

A *p*-value of less than 0.05 indicated a statistically significant difference.

RESULTS

Table 2 summarizes the data and significant changes in body weight within and between the study groups.

Based on the results of one-way ANOVA, TCF7L2 expression in pancreatic tissue differed significantly between the study groups (p= 0.001). Based on the findings of the Tukey

post hoc test, induction of type 2 diabetes significantly increased TCF7L2 expression in the control diabetic group compared to the obese control group (p=0.001). On the other hand, HIIT significantly decreased TCF7L2 expression compared to the control diabetic group (p=0.032). However, its expression in the exercise group remained significantly higher than in the obese control group (p=0.003) (Table 3 and Figure 1). The results also showed that GLP-1R expression in the pancreatic tissue differed significantly between the study groups (p=0.001). The induction of type 2 diabetes significantly decreased GLP-1R expression in the control diabetic group compared to the obese control group (p=0.001). However, HIIT did not affect GLP-1R expression compared with the control diabetic group (p=0.221) (Figure 2). Based on the results of one-way ANOVA, serum insulin, fasting glucose, and beta cell function differed significantly between the study groups (p=0.001). According to the results of the Tukey post hoc test, serum insulin level and beta cell function in the control diabetic group were significantly lower compared with the obese control group (p=0.001).

On the other hand, HIIT significantly increased serum insulin (p=0.031) and beta cell function (p=0.001) compared with the control diabetes group (Table 3). Also, the fasting glucose level in the control diabetic group was significantly higher than that in the obese control group. However, HIIT significantly decreased glucose levels (p=0.001).

Table 2- Pre- and post-intervention values of body weight in different groups

Groups	Pre-training	Post-tainting	*p*-value (paired t-test)
Obese control	**304 ± 9**	**401 ± 13**	**0.001**
Control diabetes	**306 ± 10**	**387 ± 9**	**0.001**
Exercise diabetes	**309 ± 11**	**356 ± 10**	**0.001**
***p*-value (ANOVA)**	**0.725**	**0.001**	**-------**

Table 3- Expression of TCF7L2 and GLP-1R and diabetes determinants in pancreatic tissue of rats in different study groups

Variables	Obese control	Control diabetes	Exercise diabetes	Sig (ANOVA)
TCF7L2 expression	**1**	**1.29 ± 0.05**	**1.17 ± 0.11**	**0.001**
GLP-1R expression	**1**	**0.38 ± 0.09**	**0.48 ± 0.14**	**0.001**
Glucose level (mg/dL)	**122 ± 3**	**300 ± 12**	***202 ± 9***	**0.001**
Insulin level (µIU/ml)	**9.23 ± 0.64**	**5.97 ± 0.22**	**6.63 ± 0.19**	**0.001**
Beta cell function (HOMA-BF)	**57 ± 4.55**	**9 ± 0.59**	**17 ± 1.55**	**0.001**

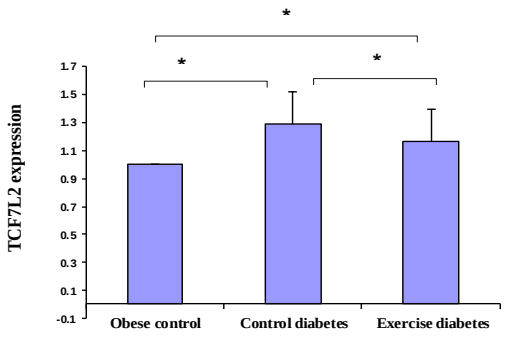

Figure 1- The pattern of TCF7L2 expression changes in pancreatic tissue of rats in different study groups

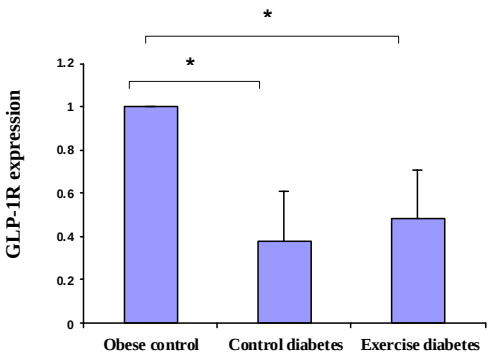

Figure 2- The pattern of GLP-1R expression changes in pancreatic tissue of rats in different study groups

DISCUSSION

The present study aimed to determine the effects of HIIT on TCF7L2 and GLP-1R expression in the pancreatic tissue of type 2 diabetic rats. Decreased TCF7L2 expression in response to HIIT is a key finding of the present study. In other words, six weeks of HIIT, five sessions a week, reduced the expression of TCF7L2 in the pancreatic tissue of obese diabetic rats. However, the expression of GLP-1R did not change significantly in response to HIIT compared with the diabetic control group. However, blood glucose decreased and serum insulin and beta cell function increased significantly compared with the diabetic control group. Eizadi et al. (2016) reported a decrease in TCF7L2 expression in the pancreas of type 2 diabetic rats in response to long-term resistance training (16). Significant reductions in blood glucose and glycosylated hemoglobin following long-term exercise have been reported by several studies (24, 25). On the other hand, increased serum insulin in response to exercise in type 2 diabetics or obese people have been reported by some studies (26) but not all (27, 28). Some studies have also demonstrated an increase in beta cell function in response to aerobic training (29).

Among the multiple factors affecting insulin synthesis, studies in the past two decades have constantly pointed out the role of genetic factors in the destruction of beta cells (30). Impaired expression of these genetic factors, especially TCF7L2, is associated with decreased function of beta cells or dysfunction of other pancreatic cells, which results in decreased insulin secretion (30). Some studies have supported the notion that TCF7L2 overexpression in the pancreas is the strongest genetic factor involved in reduced insulin secretion (31).

Evidence suggests that TCF7L2 affects insulin secretion by the glucose-stimulated insulin secretion pathway, inhibiting insulin-stimulating incretins, or converting proinsulin to insulin (32). Thus, the increase in insulin levels in response to prolonged exercise may be attributed in part to changes in TCF7L2 expression in the pancreatic tissue. Nevertheless, in the present study, no change in GLP-1R expression was observed in response to HIIT. This may be attributed to the small number of subjects or the scattering of GLP-1R changes in the studied rats.

It has been reported that TCF7L2 reduces GLP-1 secretion from the small intestine and reduces the expression of GLP-1R in the pancreas (33). On the other hand, TCF7L2 is also required for some functions of GLP-1 in the transcription and synthesis of insulin in the pancreas. For example, the internal secretory capacity of GLP-1 to stimulate pancreatic beta cells is associated with a factor that increases the translation levels of several genes in the Wnt signaling pathway, including the cyclin D1 and c-Myc cell cycle regulators (14). Genetic studies have shown that type 2 diabetes is associated with the expression of TCF7L2 and its polymorphisms due to impaired insulin secretion (34). In addition, the reduction of insulin exocytosis due to vascular graft defect may be a result of impaired expression of exogenous 2 proteins (35).

Despite numerous studies, the exact mechanisms through which different training methods affect insulin secretion and beta cell function are not clear. In a recent study, prolonged aerobic exercise decreased blood glucose and increased serum insulin levels and beta cell function in type 2 diabetic rats, while TCF7L2 expression remained unchanged (36). It seems that the type, intensity, duration, and frequency of training might affect insulin secretion differently. Considering the inhibitory role of TCF7L2 on insulin synthesis in beta cells, it seems that the decrease in TCF7L2 expression in response to HIIT leads to an increase in the synthesis and secretion of insulin from these cells, which ultimately decreases blood glucose in diabetic patients. However, understanding the mechanisms responsible for GLP-1 expression changes in response to exercise requires further studies.

CONCLUSION

Based on the results, HIIT increases serum insulin and beta cell function in obese diabetic rats. This improvement may be attributed to the decreased expression of TCF7L2 in response to this type of training. Despite the lack of change in GLP-1R expression, increased serum insulin and beta cell function following interval training may be attributed to other TCF7L2-dependent genetic pathways, suggesting the need for further studies on this subject.

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DECLARATIONS

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Ethics approvals and consent to participate

The study received approval from the Committee of Research Ethics of Islamic Azad University of Islamshahr, Iran (approval code: IR.IAU.PIAU.R.1400.011) and was carried out per the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest regarding the publication of this article.

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