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Effect of High-Intensity Interval Training on TCF7L2 Gene Expression in Hepatocytes of Obese Rats

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Abstract

Objective Hepatic glucose release is greatly increased in the presence of obesity and related diseases. The research objective was to explore the impact of high intensity interval training (HIIT) on TCF7L2 gene expression in hepatocytes of obese rats.

Materials and Methods: Out of 21 male Wistar rats aged 10 weeks years (220±10 g), obesity was induced in 14 rats by 8-week high-fat diet. The rats were then divided into normal (n=7), obese control (n=7), and HIIT obese (n=7) groups. Rats in the HIIT group completed 8 weeks of HIIT/5 days weekly, whereas the other groups were inactive. After intervention, TCF7L2 gene expression in hepatocytes, insulin resistance and glucose compared using ANOVA /Tukey's post hoc test between groups by SPSS-22.

Results: Obesity induction led to a significant decrease in TCF7L2 gene expression (*P*: 0.011) and an increase in blood glucose (*P*: 0.009) and insulin resistance (*P*: 0.019) compared with the normal group ($P< 0.001$). On the other hand, interval training led to a significant increase in TCF7L2 gene expression (*P:* 0.029) and a decrease in blood glucose ($P< 0.001$) and insulin resistance ($P< 0.001$) in the obese group compared with the control group.

Conclusion: The observed enhancement in fasting blood glucose levels among obese rats could be linked to increased TCF7L2 gene expression in liver cells, which appears to be a response to interval training intervention. Nevertheless, understanding the main mechanisms responsible for observed changes requires further studies in this field.

Keywords: TCF7L2 expression, Hepatocytes, Interval training, Obesity, Gluconeogenesis

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Introduction

Obesity is one of the most important factors in the pathogenesis of type 2 diabetes mellitus (T2D) (1). By increasing insulin resistance and blood glucose levels, obesity accelerates the spread of some chronic diseases, especially cardiovascular, liver, and type 2 diabetes mellitus (2). Hyperglycemia in obese individuals is caused by inactivity, insulin resistance, and irregular diet. Elevated hepatic glucose production and its subsequent release into the circulatory system are critical factors contributing to the elevated blood sugar levels observed in obese individuals. This phenomenon is primarily attributed to the upregulation of gluconeogenesis in the liver (3). In contrast, several hormonal, metabolic, and inflammatory factors affect hepatic gluconeogenesis (3-5).

Recently, the stimulatory or inhibitory role of transcription factors in protein levels and their expression in the process of gluconeogenesis has been strongly discussed. Among them, although the increased expression of transcription factor 7-like 2 (TCF7L2) in pancreatic beta cells exacerbates the risk of type 2 diabetes by reducing insulin synthesis (6), the decrease in protein levels or its expression in liver hepatocytes leads to increased hepatic glucose production (7). In this context, laboratory science researchers have pointed out, TCF7L2 expression decrease in the pancreas have caused blood glucose levels decrease and improvement in glucose tolerance (6). The role of TCF7L2 on the process of hepatic gluconeogenesis has not been fully determined, but the researchers have concluded that the reduction of blood glucose in the studied subjects is partially because of the reduction of hepatic glucose release due to the deletion of TCF7L2 in the studied mice. (7). It was found that when the TCF7L2 gene was silenced within the hepatocytes in rats, there was a notable elevation in the production of glucose by the liver, ranging from a threefold to fivefold increment relative to the baseline group (7-10).

So far, the effect of exercise training especially high intensity interval training (HIIT) on TCF7L2 gene expression in liver tissue has not been studied. Researchers believe that some optimal adaptations resulting from traditional long-term endurance training are achieved in response to HIIT with a lower volume of the training session much faster (11). For example, it has been found that 2 weeks of HIIT on an exercise bike is associated with a significant reduction in hyperglycemia (12). Also, HIIT in the form of intense walks are associated with improving insulin function and metabolic capacity of skeletal muscles (13) and improving beta cell function (14) in diabetes patients. Based on this evidence, the objective of the current research is to investigate the impact of HIIT on the TCF7L2 gene within hepatic cells. In addition, this study seeks to assess the influence of HIIT on glycemic control and insulin resistance in obese rats.

Material and methods

Experimental animals

In this experimental research, the subject pool comprised the entire cohort of male Wistar rats housed within the Pasteur Institute of Tehran's vivarium, among which 21 rats aged 10 weeks in the weight range of 220 (± 10) grams that were chosen through simple randomized selection process. Out of 21 male Wistar rats, obesity was induced in 14 rats by an 8-week high-fat diet. The rats were then divided into normal (n= 7), obese control (n= 7) and HIIT obese (n= 7) groups. All the studied rats were kept under controlled light conditions with temperature (22± 3 C) and humidity in the range of 30 to 60. In the experimental setup, three rats were housed in transparent acrylic enclosures with a wire mesh entrance. The dimensions of these enclosures were 25, 27, 43 cm. This arrangement provided the subjects with

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unrestricted access to water and high-fat food (obese groups), whereas the control cohort received the standard diet. The study proceeded with the administration of high fat diet (HFD) to the group categorized as obese, whereas the group identified as having normal weight maintained a conventional diet until the conclusion of the research period. HFD and standard diet continued until the end of the study for the obese and normal groups.

Induction of obesity

To induce obesity, HFD was administered for 8 weeks. To prepare high-fat food, standard food was prepared from Pars Animal Feed Company, then kneaded and added to 1% cholesterol powder and 1% 100% pure corn oil and made into pellets again (15).

Training protocol

After the induction of obesity, 14 obese rats were divided into 2 control obese (n= 7) and HIIT obese (n= 7) groups. Subsequently, rats in the HIIT obese group experienced high intense interval training for 8 weeks (5 times/weekly) in the form of interval running on a treadmill (15) (Table 1). Rats in the normal and control obese groups did not participate in this training program. Finally, 48 h after the final exercise session, the studied rats in all 3 groups were dissected after overnight starvation.

Sample Collection and Biochemical Assay

At 48 h after the final training bout, following an overnight fast of 10-12h, all rats were anesthetized by intraperitoneal administration of a solution comprising 10% ketamine at 50 mg/kg and 2% xylazine at 10 mg/kg. Subsequently, hepatic samples were procured from the rats, cleansed with physiological serum, and preserved in microtubes (1.8 ml) containing a 20% solution of RNA stabilizing agent for downstream genetic analyses. The isolation of RNA was performed using the RNeasy Mini Kit provided by QIAGEN. For the quantification of TCF7L2 mRNA levels, reverse transcription-polymerase chain reaction (RT-PCR) was conducted on a Rotorgen 6000 platform, employing the One Step SYBR Green Kit by Takara, according to the manufacturer's protocol. RNA polymerase II served as the endogenous reference gene. The primer sequences utilized are delineated in Table 2.

The quantification of glucose levels was performed using an enzymatic colorimetric approach, employing glucose oxidase as the catalyst (Pars Azmoon, Tehran). The intra- and extra-assay coefficients of variation were 1.74% and 1.19%, respectively. The sensitivity of glucose measurement was 5 mg/dL. Serum insulin concentrations were determined using an ELISA technique in alignment with the specifications provided by the manufacturer of

Table 1. High interval training protocol according to speed and time of running in the interval obese 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 is 40 and 120 s in the exercise and active rest phases, respectively, and the speed is in meters per minute.

Table 2. Primer sequence

Genes	Primer sequence
TCF7L2	**For**: CGTCCATGGTCCCTTCCTC **Rev**: ACTTCAATCAAGCAGGGGCAC
RNA Polymerase Ⅰ Ⅰ	**For**: ACTTTGATGACGTGGAGGAGGAC **Rev**: GTTGGCCTGCGGTCGTTC

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the commercial kit (Demeditec Diagnostic insulin ELISA, Germany). The intra- and extra-assay variation coefficients of insulin were 2.6% and 2.88%, respectively. The sensitivity of insulin measurement was 1.76%. To determine insulin resistance, the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index was determined. This involved applying a specific mathematical model that integrates the concentrations of fasting glucose and insulin in a formulaic computation: (HOMA-IR = [glucose (nmol/L) * insulin (µU/mL)/22.5], using fasting values).

Statistical analysis

To ensure a normal distribution of the data, the Shapiro- Wilk method was employed. Quantitative data were characterized using descriptive statistical measures and graphical representations. Comparative analysis across different groups for the variables in question was conducted using one-way analysis of variance (ANOVA), followed by Tukey's post hoc analysis for detailed pairwise comparisons. The threshold for statistical significance was established at an alpha level below 0.05. All statistical evaluations were performed using SPSS for Windows, version 22.

Ethical considerations

The research received ethical clearance from the Institutional Review Board of the Islamshahr branch of Islamic Azad University (Code: IR.IAU.PIAU.R.1401.010).

Results

Analysis conducted using the Shapiro- Wilk statistical method indicated that the dataset conformed to a normal distribution. Therefore, ANOVA was used to compare the variables. Table 3 delineates the fluctuations in body mass observed in subjects before and after the exercise intervention. At the beginning of the study, the ANOVA results showed a significant difference ($P< 0.001$) in body weight between the studied groups. Based on the findings of Tukey's test, a significant reduction in body weight was observed in the normal group compared with the obese group ($P< 0.001$). On the other hand, the comparison of body mass between the obese control group and those subjected to interval training revealed no statistically significant difference ($P= 0.962$) (Table 4). In addition, in the conditions after the exercise intervention, the findings of the ANOVA test indicate a significant difference in the weight of the rats in the conditions after the study ($P< 0.001$). Based on the results of Tukey's test, a significant difference in body weight was observed between the groups ($P< 0.001$).

Table 3. Pre- and post-training body weights of the three groups (Mean ± SD).

Group	Pre-training	Post-training	*P*-value (Paired T-test)*
Normal	272 (± 10)	282 (± 7)	0.098
Control obese	377 (± 11)	422 (± 15)	< 0.001
Interval training for obese	378 (± 10)	388 (± 7)	< 0.001
***P*-value** (One Way ANOVA)**	< 0.001	< 0.001	

* Represent intra-group changes in body weight in each group by paired T-test
** Represents significant value of body weight difference between groups by ANOVA

Table 4. Results of Tukey test to compare body weight between groups in the pre-training and post-training

Group	Group	Pre-training		Post-training	
		Mean difference	*P*-value	Mean difference	*P*-value
1	2	-105.143*	< 0.001	-140.857*	< 0.001
1	3	-106.571*	< 0.001	-106.857*	< 0.001
2	3	-1.429	0.962	34.000*	< 0.001

Groups: Normal=1, Control obese=2, Interval training=3

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Interval training resulted in a significant reduction in body weight compared with the obese control group ($P< 0.001$) (Table 5).

Determining the impact of interval training on TCF7L2 gene expression in the hepatocytes of obese rats compared with the control obese group was the main aim of this study. The findings of the ANOVA test showed a significant difference in TCF7L2 gene expression between the studied groups ($P< 0.001$) (Table 5). On the other hand, based on the findings of Tukey's test, induction of obesity led to a reduction in TCF7L2 gene expression compared with the normal group ($P< 0.001$). In addition, interval training led to a significant increase in TCF7L2 gene expression in the interval training obese group compared with the control obese group (*P:* 0.029) (Table 6).

Based on the ANOVA results, a significant difference was observed in fasting glucose between the groups ($P< 0.001$) and insulin resistance ($P< 0.001$) (Table 5). Based on the findings of Tukey's test, induction of obesity led to a significant increase in fasting glucose and insulin resistance compared with the normal group ($P< 0.001$). Interval training also significantly reduced glucose levels ($P< 0.001$) and insulin resistance ($P< 0.001$) compared with the obese control group (Table 6).

Discussion

The main finding of this study was increased TCF7L2 gene expression in the liver cells of obese rats. In other words, 8 weeks of interval training led to a significant increase in TCF7L2 gene expression in obese rats induced by HFD compared with the control obese group. Meanwhile, obesity induction decreased TCF7L2 gene expression compared with rats that had a standard diet. The increase in TCF7L2 gene expression in the present study was associated with a decrease in fasting glucose levels in response to interval training. In contrast, insulin resistance also decreased significantly after interval training compared with the control group. It should be mentioned that the effect of intense interval training on genes affecting processes affecting blood glucose, especially in liver cells, is less reported. Although chronic endurance training leads to beneficial physiological changes, similar adaptations can be attained more rapidly through HIIT, which requires a reduced volume and shorter exercise duration (16).

In this context, two weeks of intense interval exercise on a bicycle in diabetics leads to a significant reduction in blood glucose levels (12,17). In addition, interval training in the form of intense running is associated with improved insulin function and glucose metabolism (18). Researchers believe that blood glucose levels in obesity-related diseases such as T2D can be controlled in response to high-intensity training similar to long-term low-intensity exercises (19,20). Based on the evidence that points to the effective role of TCF7L2 in the process of hepatic gluconeogenesis, the decrease in blood glucose following interval training in the

Table 5. Fasting glucose, insulin resistance, and TCF7L2 gene expression in the liver tissue of the studied groups (Mean ± SD)

Variable	Normal	Control obese	HIIT obese	*P*-value
Fasting glucose (mg/dl)	85 (± 7)	120 (± 3)	108 (± 3)	< 0.001
Insulin resistance (HOMA-IR)	1.52 (± 0.17)	2.65 (± 0.16)	2.13 (± 0.14)	< 0.001
TCF7L2 expression	1	0.40 (± 0.09)	0.58 (± 0.18)	< 0.001

Table 6. Results of Tukey test to compare variables between groups

Group	Group	TCF7L2		Glucose		Insulin resistance	
		Mean difference	*P*-value	Mean difference	*P*-value	Mean difference	*P*-value
1	2	0.60000*	< 0.001	-35.429*	< 0.001	-1.13286*	< 0.001
1	3	0.42286*	< 0.001	-23.000*	< 0.001	-0.61000*	< 0.001
2	3	-0.17714*	0.029	12.429*	< 0.001	0.52286	< 0.001

Groups: Normal=1, Control obese=2, Interval training=3

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present study may be attributed to the increased TCF7L2 gene expression in liver cells. The increase in expression in liver cells is associated with a decrease in the expression of enzymes affecting the rate of hepatic gluconeogenesis.

In this context, silencing TCF7L2 by increasing the expression of 3 key gluconeogenesis enzymes, Fbp1, G6Pase, and PEPCK, accelerates this process and increases hepatic glucose production. Meanwhile, TCF7L2 silencing appears to directly affect PEPCK expression (7). In another study, TCF7L2 deletion was associated with a decrease in G6Pase expression in the studied mice (6). Laboratory studies have revealed that the overexpression of G6Pase in liver hepatocytes leads to a multifold increase in the release of glucose from the gluconeogenesis pathway (21,22). On the other hand, the expression of PEPCK increases twofold in the presence of T2D as a disease related to obesity, which greatly increases the production of hepatic glucose from the process of gluconeogenesis (21). Under these conditions, an increase in PEPCK gene expression in a coordinated pattern leads to an increase in G6 Pase expression (21). Hence, increasing their expression or activity by accelerating the process of gluconeogenesis in liver hepatocytes increases the release of glucose from the liver into the bloodstream.

In summary, the decrease in TCF7L2 expression and the increase in the expression of the gluconeogenic enzymes PEPCK and G6Pase play an important role in accelerating gluconeogenesis and its consequence, increasing the release of hepatic glucose into the bloodstream. This process is manifested in the presence of obesity and insulin resistance. Based on this evidence, it appears that the increased TCF7L2 gene expression in response to intense interval training by decreasing the activity and expression of key enzymes of the gluconeogenesis cycle leads to a decrease in the speed of this process in obese rats or obesity-related patient populations, which leads to a decrease in blood glucose levels. On the other hand, the reduction of insulin resistance after exercise training and its direct effects on glucose levels should not be ignored. Steckling et al. (2016) reported a decrease in glucose, glycosylated hemoglobin, and insulin resistance along with an improvement in the inflammatory profile in response to intense interval exercise in obese women (23).

In the present investigation, it is pertinent to observe that the effect of interval training on TCF7L2 gene expression, blood glucose, and insulin resistance was investigated, and the effect of interval training on TCF7L2 gene expression, blood glucose, and insulin resistance was investigated. While intense interval training may have other effects on body health, stress level, inflammation, lipid profile, and blood pressure, the lack of measurement of these effects is one of the limitations of the study. Therefore, to better understand the benefits and side effects of interval training, it is suggested to measure the mentioned variables in future studies.

Conclusions

Intense interval training is associated with improved glycemic profile in obese rats. Based on the evidence supporting the effective role of TCF7L2 in hepatic gluconeogenesis, the improvement in glucose levels in the studied rats may be attributed to the reduction in the speed of this process in response to the increased TCF7L2 gene expression in liver cells by aerobic training. However, understanding the main mechanisms responsible for this process requires more studies.

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Conflict of Interest

The authors have disclosed the absence of any competing interests.

Authors' contributions

A. K: conceived of the presented idea and prepared first drafts of the manuscript.

Y. K: conceived of the presented idea, Conceived and designed the analysis, and Collected the data.

M. E: conceived of the presented idea, planning methodology to reach the conclusion, contributed data and performed the analysis.

S. S: Contributed data or analysis tools and performed the analysis.

S. Gh: Collected the data and analyzed results.

All authors have accepted responsibility for the entire content of this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and approved the version to be published.

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