Orginal Article Open Access
Iranian Journal of Diabetes and Obesity (IJDO)

Relationship between Changes in Serum Insulin with Hepatic Expression of *PEPCK*, *G6Pase* and *HNF4α* in Response to Resistance Training in Diabetic Rats with High-Fat Diet and STZ

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Abstract

Objective: Genetic studies indicate that available insulin influences the activity or expression of hepatic gluconeogenic genes. This study aimed to assess the effect of resistance exercise program on gluconeogenic genes expression and their change relation with insulin in response to training.

Materials and Methods: 18 male wistar rats by 6 weeks high-fat diet were studied. Type 2 diabetes was induced by intraperitoneal injection of STZ (25 mg/dl) in 14 rats. Finally, the studied rats were selected into 3 groups: 1) non-diabetic, 2) control diabetic, 3) resistance diabetic. Rats in the resistance group participated in a 6-week resistance training in the form of climbing a step ladder with resistance and other groups remained none-training. ANOVA statistical test used to compare glucose, insulin and hepatic expression of *PEPCK*, *G6Pase* and *HNF4α* between groups. Correlation between insulin changes and gene expression was determined by Spearman's correlation test.

Results: Serum insulin significantly increased following resistance training intervention (P= 0.043). A significant decrease was also observed in fasting glucose (P= 0.001) and hepatic expression of *PEPCK* (P= 0.001), *G6Pase* (P= 0.001) and *HNF4α* (P= 0.011) compared to control diabetes rats. Significant inverse correlation was observed in the change of insulin with *HNF4α* (P= 0.001), *PEPCK* (P= 0.013) and *G6Pase* (P= 0.043) in response to resistance training.

Conclusion: Resistance training is associated with changes in the expression of gluconeogenic genes, and these changes can probably be attributed to changes in serum insulin.

Keywords: Diabetes, Resistance Training, Gluconeogenic genes, Insulin

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Citation: Eizadi M, Salehi S S, Rashidi M. Relationship between Changes in Serum Insulin with Hepatic Expression of PEPCK, G6Pase and HNF4α in Response to Resistance Training in Diabetic Rats with High-Fat Diet and STZ. IJDO 2025; 17 (1) :40-47

URL: https://ijdo.ssu.ac.ir/article-1-933-en.html

10.18502/ijdo.v17i1.18032

Article info:
Received: 26 December 2024
Accepted: 29 January 2025
Published in February 2025

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[DOI: 10.18502/ijdo.v17i1.18032]

Introduction

For many years, insulin resistance and beta cells dysfunction, or in other words, defects in insulin secretion have been introduced as the main causes of type 2 diabetes(T2D) (1-3). Increased fasting glucose of these patients is also the result of hepatic glucose release more than normal (4).

Gluconeogenesis is a process in which glucose is synthesized from non-sugar precursors such as fat or amino acids, and this process is accelerated in the presence of T2D, which leads to an increase in hepatic glucose release, especially in T2D (5). In this regard, it has been stated that the of gluconeogenesis rate is regulated by gluconeogenic enzymes such as Fructose-1,6-bisphosphatase (*FBPase*), phosphoenolpyruvate carboxykinase (*PEPCK*), and glucose-6-phosphatase (*G6Pase*) (6,7).

In this context, it has been stated that the overexpression of hepatocyte *G6Pase* leads to a multifold increase in hepatic glucose release induced by gluconeogenesis (8,9). On the other hand, the expression of *PEPCK* doubles in the presence of T2D, which significantly enhancing hepatic glucose production via gluconeogenesis. Under these conditions, an upregulation of the *PEPCK* gene expression in a coordinated manner results in elevated expression of *G6Pase* (8). It has also been stated that the activity and transcription of *PEPCK* and *G6Pase* promoters require activation of glucocorticoid receptors and Hepatocyte nuclear factor 4 alpha (*HNF4α*) transcription (10). In other words, *HNF4α* acts as a stimulus for the activity or expression of gluconeogenic genes *PEPCK* and *G6Pase* through some of its key cofactors such as peroxisome proliferator-activated receptor co-activator-1α (*PGC1α*) (10).

On the other hand, the genetic coding of these proteins is affected by some key hormones such as glucagon, insulin, adrenaline and glucocorticoids. Among these hormonal components, Insulin is the most effective regulatory marker of gluconeogenesis inhibition hepatic glucose release (7,11,12). In fact, insulin signaling pathways are crucial in regulating the expression of genes involved in gluconeogenesis, including *G6Pase* and *PEPCK* (11). In other words, the activity or expression of these components is affected by insulin levels (12).

On the other hand, under hyperinsulinemia conditions, the expression of *HNF4α* in human and rat hepatocytes is reduced by sterol regulatory element–binding proteins (*SREBPs*) (13), which leads to the inhibition of *PGC1α* activation by *HNF4α*, and the result is a reduction in the activity and expression of *G6Pase* and *PEPCK* gluconeogenic genes. And finally, the reduction of hepatic glucose release is caused by hepatic gluconeogenesis (11). Based on the aforementioned evidence, it seems that the increase in insulin leads to a reduction in the activity or expression of the gluconeogenic genes *G6Pase* and *PEPCK*, as well as *HNF4α* by decreasing the rate of hepatic gluconeogenesis, which leads to a decrease in hepatic glucose release. But so far, few studies have followed the effect of therapeutic interventions such as drug therapy or exercise interventions on insulin levels and gluconeogenic genes expression. For example, Eizadi et al, (2017) have reported an increase in circulating insulin along with a reduction in glucose after 12 weeks of aerobic training in T2D rats (14). In another study, Nikseresht et al (2022) attributed the increase in hepatic glucokinase expression following interval training in diabetic rats to the increase in insulin following interval exercise (15).

Nevertheless, the effect of resistance training on the mentioned components is less reported. Based on this research gap, in the present study, in addition to determining the effect of resistance training on fasting glucose and insulin and the hepatic expression of *PEPCK*, *G6Pase* and *HNF4α* genes, the relationship between insulin changes and the expression of the mentioned genes in response to this training method is also determined.

[DOI: 10.18502/ijdo.v17i1.18032]

Material and Methods

18 male rats aged 10 weeks (220±10 grams) were purchased from the Baqiyatullah University of Medical Sciences and obesed by 6 weeks of high-fat diet (16). Rats exhibiting a body mass index exceeding 68% g/cm2 were classified as obese (17). Then T2D induced by intraperitoneal injection of STZ in 14 rats. Finally, the studied rats were separated into three distinct groups: 1) non-diabetic, 2) Diabetic control, 3) Diabetes + Resistance Training.

T2D induction

To induce type 2 diabetes, a high-fat diet was used for 6 weeks and intraperitoneal injection of STZ (25 ml/kg) in citrate buffer (pH=4.5) was used (16). To create a high-fat diet, the standard feed was supplemented with 1% cholesterol powder and 1% pure corn oil (16). One week following the initiation of diabetes, fasting blood glucose levels were assessed, with readings ranging from 150 to 400 mg/dL serving as the benchmark for confirming Type 2 Diabetes (18).

All rats were kept under controlled conditions of light (12 hours of light and 12 hours of darkness, start of lighting at 6 in the evening and start of shutdown at 6 in the morning), temperature (22± 3°C), and humidity (30-50%). All rats were maintained in a regulated environment with a light-dark cycle (12:12), temperature (22± 3°C), and humidity levels (30-50%) (18).

Resistance training protocol

Resistance training was conducted six weeks, with sessions held five times each week. The pattern of distributing training intensity by progressively augmenting resistance, achieved by attaching weights to the tails of rats, corresponds to various percentages of their body weight. Each training session consisted of five sets, each comprising four repetitions (Table 1), the rest between sets is set at 3 minutes, while the rest for each repetition within a set is 45 seconds (16).

Blood sampling and gene expression analysis

48 hours following the final training session, all rats underwent dissection after fasting overnight. Intraperitoneal injection of 10% ketamine and 2% xylazine was used to anesthetize the rat. A blood sample was directly drawn from the heart to assess fasting glucose levels and serum insulin concentrations. Fasting glucose was measured by glucose oxidase (Pars Azmoun-Tehran) method and serum insulin (Demeditec Diagnostic insulin ELIZA, German) was measured by ELISA method.

Also, liver tissue was extracted and immersed in nitrogen in 1.8 ml microtubes immediately after washing in physiological serum. RNA extraction was performed by the commercial kit RNeasy mini kit of QIAGEN Company. The quantification of gene mRNA was performed using RT-Real Time PCR on a Rotrogen 6000 system, employing the Takara One Step SYBR kit as per the manufacturer's guidelines. To analyze the characteristics of the primers, a range of temperatures between 50 and 99 degrees Celsius was applied to generate the melting curve. Table 2 presents the sequence pattern of the primers. RNA Polymerase II served as the control gene.

Data analysis

The Kolmogorov-Smirnov test and Levine's test were employed to verify the normality of distribution and the homogeneity of variances, respectively. For mean comparisons, one-way ANOVA and Tukey's post hoc test were utilized, with a significance threshold set at $P< 0.05$.

Spearman's correlation test was used to determine the relationship between insulin changes and studied genes in response to

Table 1. Protocol for resistance training based on a percentage of body weight

Time	First week	Second week	Third week	Forth week	Fifth and six week
Resistance (body weight %)	30	50	70	90	100

[DOI: 10.18502/ijdo.v17i1.18032]

resistance training. Statistical analysis was conducted using SPSS version 22.

Ethical considerations

The approval of the research ethics committee of Shahid Beheshti University with code: (IR.IAU.PIAU.R.1400.010).

Results

The results of ANOVA test indicate a significant difference in fasting glucose, serum insulin and hepatic genes expression of *PEPCK*, *G6Pase* and *HNF4α* between groups. Data by Tukey post hoc test showed that T2D induction resulted in significant increase in fasting glucose (*P*= 0.001) and genes expression of *PEPCK* (*P*= 0.001), *G6Pase* (*P*= 0.001) and *HNF4α* (*P*= 0.025) and significant decrease in serum insulin (*P*= 0.001) in diabetic control compared to non-diabetes groups (Table 3).

Based on Spearman's correlation test, a significant inverse relationship was observed between changes in serum insulin with changes in the expression of *HNF4α* (*P*= 0.001, r= -0.986), *PEPCK* (*P*= 0.013, r= -0.868) and *G6Pase* (*P*= 0.043, r= -0.750) in response to resistance training. In other words, a significant inverse correlation was observed between their changes.

Discussion

The findings of the current study indicate the effectiveness of resistance training on the expression of hepatic genes effective in gluconeogenesis. In other words, 6 weeks resistance exercise intervention led to a reduction in the expression of *PEPCK*, G6Pase and *HNF4α* in the hepatocytes of T2D rats. Resistance training also resulted in a significant reduction in fasting glucose. Therefore, based on the theoretical foundations that have been previously reported regarding the role of hepatic glucose release induced by gluconeogenesis, especially in diabetic patients (5-7), the improvement of blood glucose in the studied diabetic rats can be attributed to the reduction in the expression of *PEPCK*, *G6Pase* and *HNF4α* in response to attributed resistance exercises. In this context, although limited studies are available, in the study of Chang et al (2006), aerobic training led to a significant decrease in *PEPCK* protein and expression compared to the control group (19). Nevertheless, in the study of Nikseresht et al (2022), despite the increase in serum insulin in response to 6 weeks of interval training, the expression of *G6Pase* did not change (20).

It has been noted that exercise decreases *HNF-4α* and subsequently decreases hepatic *PEPCK*, which plays an important role in suppressing hepatic gluconeogenesis by Akt

Table 2. The sequence pattern of the primers

Genes	Primer sequence	Product size	Time	Gene Bank
G6Pase	For: GGTTGGGATACTGGGCTGTG Rev: TTGTAGATGCCCCGGATGTG	159 bp	60	NM_001191052.1
PEPCK	For: TGCCCCAGGAAGTGAGGAAG Rev: CAGTGAGAGCCAGCCAACAG	164 bp	60	XM_008759265.1
HNF4α	For: GCAGAGATGAGCCGTGTGTC Rev: TTGATCTTGCCTGGGTCACTC	159 bp	60	NM_001191052.1
RNA PolymraseII	For: ACTTTGATGACGTGGAGGAGGAC Rev: GTTGGCCTGCGGTCGTTC	164 bp	60	XM_008759265.1

Table 3. The fasting glucose, serum insulin and gene expression in response to T2D induction and resistance intervention (Data by One Way ANOVA)

Variables / Groups	**Glucose** (mg/dL)	**Serum insulin** (µIU/ml)	***PEPCK* expression**	***G6Pase* expression**	***HNF4α* expression**
Non-diabetes	122 (±3)	9.23 (±0.64)	1	1	1
Diabetic control	300 (±12)	5.97 (±0.22)	1.95 (±0.09)	1.94 (±1.22)	1.75 (±0.08)
Diabetes + Resistance Training	189 (±17)	6.58 (±0.15)	1.37 (±0.06)	1.40 (±0.21)	1.25 (±0.05)
Sig (ANOVA)	0.001	0.001	0.001	0.001	0.001

[DOI: 10.18502/ijdo.v17i1.18032]

phosphorylation. In this context, although few studies have followed the effect of resistance training on the expression of *HNF-4α* in diabetic rats, but in line with the current study, Yadgari et al (2018) have reported 12 weeks of regular aerobic exercise (21). A decrease in hepatic *HNF-4α* expression along with a decrease in glucose and an increase in serum insulin following interval training has also been reported by these researchers (21). In this context, it has been mentioned that *PGC-1α* controls the transcription of gluconeogenesis enzymes such as *PEPCK* and *G6Pase* through *HNF-4α* and *FOXO1* (22). Based on these evidences, it is concluded that the reduction of *HNF-4α* expression related to resistance training by inhibition of gluconeogenic genes leads to the reduction of hepatic glucose release related to gluconeogenesis in T2D rats.

In the current study, although lack of glucagon measurement is one of the main limitations, the increase in serum insulin in response to resistance exercise intervention is one of the main findings. On the other hand, an inverse relationship between serum insulin and the expression of *HNF-4α*, *PEPCK* and *G6Pase* was observed in response to resistance training. Based on the evidence mentioned below, the change in the expression of the measured genes can be somehow attributed to the increase in insulin in response to the training intervention. In confirmation of these statements, De 'Souza et al (2010) also attributed the reduction of *G6Pase* expression after 2 hours of endurance swimming in the form of 4 sets of 30 minutes to the increase of insulin signaling pathways in non-diabetic rats (23). Marinho et al (2012) have also pointed out their findings that long-term endurance training independently of weight loss is associated with improving insulin signaling pathways in hepatocytes. These researchers have pointed out that the beneficial effects of exercise on insulin function in the liver tissue are associated with a decrease in the expression of gluconeogenic genes, so long-term endurance exercises lead to a decrease in the expression of *PEPCK* and *G6Pase* (24).

It has been found that genes expression involved in the process of gluconeogenesis decreases significantly after long-term recovery following long-term exercise. Thus, in the study of Ropelle et al (2009), the expression of hepatic genes *PEPCK* and *G6Pase* decreased after 8 hours of recovery after a long-term exercise, and the researchers attributed this decrease to a change in the signaling pathways of other related genes such as liver processes. The findings showed that the insulin signaling pathways are improved after 8 hours of recovery following a long-term endurance exercise session that is associated with a reduction in the expression of hepatic gluconeogenesis genes such as *PEPCK*, simultaneously with an increase in insulin-dependent *Foxo1* phosphorylation, as well as a decrease in the expression of *PGC-1α* in cells (25).

A transient increase in intravenous insulin similar to the postprandial conditions results in rapid inhibition or suppression of hepatic glucose production from gluconeogenic or glycogenolytic sources. The evidence obtained from the isolated liver in the cellular-molecular studies on rats have revealed that the inhibition of insulin-dependent hepatic gluconeogenic process is facilitated through the regulation of the transcription of rate-limiting enzymes of this process (26). Recent observations on rodents indicate that even hyperinsulinemia in the brain leads to a decrease in hepatic glucose release due to the negative regulation of the expression of gluconeogenic genes (27). On the other hand, physiological hyperinsulinemia in humans and dogs is associated with long-term inhibition of hepatic glucose release dependent on hepatic gluconeogenic pathways (28).

Insulin interacts with receptors in the liver to control signaling pathways that trigger the activation of enzymes involved in both the uptake and release of glucose during gluconeogenesis, glycolysis, and glycogen metabolism. During starvation, the increase of *PGC-1α* along with other gluconeogenic proliferation factors such as *FOXO1* and *HNF4α* leads to strengthening the activity and

[DOI: 10.18502/ijdo.v17i1.18032]

expression of hepatocytes *PEPCK* and *G6Pase* (29). On the other hand, the presence of insulin in the liver stimulates glucokinase (30) and decreases the expression of *G6Pase* and *PEPCK* (31), which leads to long-term changes in glucokinase and *G6Pase* and *PEPCK* proteins that facilitate the release and absorption of glucose. The genetic regulation of *G6Pase* and glucokinase changes rapidly in response to hepatic insulin changes in rats (1369) and dogs (32) but it has been observed that changes in their protein levels in response to insulin changes in dogs take several hours (33).

Apart from the effects of *PEPCK* and *G6Pase* on insulin, the decrease in *HNF4α* expression following resistance training may be attributed to the increase in insulin. In this context, it has been pointed out that in hyper-insulinemic conditions, a decrease in the expression of *HNF4α* in human and rat hepatocytes is observed under the influence of *SREBPs* (34), which inhibits the activation of *PGC1α* by *HNF4α* and ultimately reduces the activity and expression of *G6Pase* and *PEPCK* leads, which results in the reduction of hepatic glucose release by gluconeogenesis (35). On the other hand, the stimulation of some transcription regulatory factors such as *SREBPs* by insulin leads to the acceleration of the lipogenesis process and the reduction of gluconeogenesis (34). Researchers of genetic sciences believe that in type 1 diabetes patients and those patients with T2D who are faced with a decrease in insulin secretion due to beta cells destruction, the decrease in insulin levels increases *HNF4α* expression and, as a result, increases the activity and expression of gluconeogenic enzymes which ultimately causes the acceleration of gluconeogenesis and the increase of hepatic glucose release, and this is the main cause of which is the main reason for increased fasting insulin in these patients (10,36).

Conclusion

Resistance training leads to a decrease in fasting glucose in T2D rats, which is probably due to a decrease in hepatic glucose release. Based on study results, resistance exercise intervention leads to a decrease in the expression of gluconeogenic genes *PEPCK*, *G6Pase* and *HNF4α*, which is probably due to a decrease in insulin levels. However, knowing the main mechanisms responsible for hepatic glucose release in response to exercise requires more studies.

Acknowledgments

The authors thank the genetics laboratory of Pasteur Institute of Tehran for their cooperation in gene analysis.

Funding

None.

Conflict of Interest

The authors declared no conflict of interest.

Authors' contributions

M.E.: conceived and design the analysis and wrote the paper.

S.S.S.: collected the data and performed the analysis.

M.R.: contributed data or analysis tools and wrote the paper.

All the authors critically revised the manuscript, agree to be fully accountable for the integrity and accuracy of the study, and read and approved the final manuscript.

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[DOI: 10.18502/ijdo.v17i1.18032]

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[DOI: 10.18502/ijdo.v17i1.18032]