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Resistance training and glucose profile in obese diabetes rats; the role of gluconeogenic genes expression

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Authors

Salehy Sayed Eshagh[1],
Eizadi Mojtaba[2]*,
Sedaghaty Saeid[3],
Kazemzadeh Yaser[4],
Mirzayan Shanjani Sanaz[5*]

1. PHD Candidate, Department of Exercise physiology, Islamshahr Branch, Islamic Azad University, Tehran, Iran
2. Assistant professor of Exercise Physiology, Saveh Branch, Islamic Azad University, Saveh, Iran
3. Assistant professor of Exercise Physiology, Islamshahr Branch, Islamic Azad University, Tehran, Iran
4. Assistant professor of Exercise Physiology, Islamshahr Branch, Islamic Azad University, Tehran, Iran.
5. Assistant professor of Exercise Physiology, Islamshahr Branch, Islamic Azad University, Tehran, Iran.

***Corresponding authors**:
Eizadi Mojtaba, Department of Exercise Physiology, Saveh Branch, Islamic Azad University, Saveh, Iran

izadimojtaba2006@yahoo.com

ABSTRACT

Objective: Genetic studies point to the effective role of protein levels or expression of gluconeogenic genes in hepatic glucose release in healthy or diseased individuals. This study aimed to assess the effect of resistance training on PEPCK expression in hepatocytes in obese rats with type 2 diabetes (T2D).

Methods: For this purpose, 21 rats obesed by 6 weeks high-fat diet (HFD) were randomly divided to 1) non-diabetic, 2) control T2D, 3) exercise T2D groups. Type 2 diabetes induced by intraperitoneal injection of streptozotocin (STZ: 25 mg/kg) in diabetes groups. The rat of exercise group were completed resistance training for six weeks (5 times weekly) in the form of climbing the ladder by applying resistance. The non-diabetic and control T2D groups did not participate in the exercise program. 48 hours after the lasting exercise session, PEPCK expression in hepatocytes, serum insulin and glucose were compared between groups. Data compared by One-Way ANOVA and Tukey post hoc test ($P< 0.05$).

Results: T2D induction resulted in significant decrease in insulin and increase in fasting glucose and PEPCK expression in hepatocytes compare with non-diabetes rats. Resistance training resulted in significant increase in insulin and decrease in fasting glucose and PEPCK expression in hepatocytes of exercise T2D than control T2D group.

Conclusion: Based on these data, we conclude that resistance training can be improve glucose in diabetes rats and tis effect may be attributed decrease PEPCK expression in response to this training method.

Keywords: Type 2 diabetes, resistance training, Gene expression, Glucose, Gluconeogenesis

Introduction

Circulating glucose as the main fuel of active tissues are regulated by complex processes (1). During short-term starvation, the release of hepatic glucose is accelerated mainly by the breakdown of glycogen into glucose during the

process of hepatic glucogenolysis. On the other hand, following long-term starvation that is associated with the depletion of liver glycogen reserves, a major part of blood glucose is provided by the hepatic gluconeogenesis process. Under these conditions, gluconeogenesis plays a role as the most important effective process in maintaining blood circulation glucose (2). On the other hand, the process of gluconeogenesis is disturbed in the presence of type 2 diabetes, especially in obese diabetics, and the increase in the activity and expression of gluconeogenic enzymes is the main reason for the increase in hepatic glucose release in these patients (3). Therefore, understanding the molecular mechanisms of hepatic gluconeogenesis regulation is one of the most important candidates for maintaining blood glucose, especially in the treatment of diabetes. Regulation of gluconeogenesis is carried out in multiple stages such as hormone secretion, gene transcription and post-translational mechanisms. In response to external stimuli, although the signaling of hormones regulating gluconeogenic pathways such as insulin, glucagon, and glucocorticoids are affected, gene transcription and genes expression involved in gluconeogenesis that control hepatic glucose release are also affected. In this pathway, gluconeogenic genes PEPCK have a key role (2). Thus, the PEPCK promoter activity and transcription requires activation of glucocorticoid receptors and HNF4α transcription (3). The activation of some regulatory transcription factors such as SREBPs by insulin leads to an increase in the lipogenesis rate and inhibition of gluconeogenesis. During hyperinsulinemia, the HNF4α expression in human and rat hepatocytes is reduced by SREBPs (4), which results in a decrease in the activity and expression of gluconeogenic genes such as PEPCK and finally, a decrease in hepatic glucose release by gluconeogenesis (5). Based on this evidence, it is expected that increased insulin levels and decreased activity and expression of gluconeogenic enzyme PEPCK in the hepatocytes of these patients due to external and internal stimuli are associated with inhibition of gluconeogenesis and decreased release of hepatic glucose into the bloodstream. In the meantime, the role of physical activity or exercise training alone or in combination with drug and dietary interventions has been discussed.

In this context, although exercise studies have not been conducted with the aforementioned goals, exercise interventions that change genetic transcription factors or their variants in favor of reducing blood glucose in diabetics or other diseases related to insulin resistance or hyperglycemia have been reported. For example, in the study of Disouzo et al (2010), a swimming training session for 2 hours in the form of 4 stages of 30 minutes led to the reduction of PEPCK expression and the improvement of insulin signaling pathways in insulin-resistant obese mice (6). Some other studies have reported the effect of exercise training on the expression of other transcription factors such as HNF4α in diabetic or non-diabetic laboratory species, in which contradictory findings can be seen. So, in two studies, 10 and 12 weeks of aerobic training have been associated with a decrease in the expression of these gluconeogenic genes in the liver tissue of type 2 diabetic rats (7,8). However, few studies have measured the effect of resistance training on the expression of gluconeogenic genes in liver tissue in obese type 2 diabetic rats. Therefore, the present study aims to determine the effect of resistance training on the expression of gluconeogenic gene PEPCK, as well as glucose and insulin levels in type 2 diabetic obese rats.

Materials and Methods

Experimental animals: 21 ten-week-old rats with a weight of (220 ± 10 g) were prepare of the animal house of Baqiyatallah University of Medical Sciences, Tehran, Iran. Then, after induction of obesity and T2D, they were randomly divided into 3 groups: 1) non-diabetic, 2) control T2D, 3) exercise 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.IAU.PIAU.R.1400.010) 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 6 weeks high-fat diet (9), then 7 rats were selected as non-diabetic obese group (health group, n = 7), and the rest became diabetics. Mice with body mass index greater than 0.68 g/cm2 were selected as obese mice (10). Type 2 diabetic induced by a single intraperitoneal (i.p.) injection of 25 mg/kg streptozotocin (dissolved in citrate buffer, pH 4.5) (11). Diabetic rats were divided into control (n = 7) or exercise (resistance training, 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 (12).

Resistance training protocol: After ensuring diabetic induction, the exercise group was climbed on a stepladder a 26-step, 1 meter vertical ladder with a gradient of 80% without any resistance for 6 times in 3 training sessions in order to learn how to exercise. Then they completed a resistance training lasted 6 weeks for 5 days in weeks. In order to warm and cool the rats before and after the workout, they were climbed and descended the ladder 2 times without any resistance. Each session of resistance training was performed in the form of 5 courses with 4 repetitions on each course, and the resistance was increased through attaching a weight to rats' tails. Breaks between courses and between repetitions were 3 min and 45 sec, respectively. The resistance was increased gradually during training intervention (table 1) (9). Finally, all rats were dissected 48 hours after the last training session following 10 to 12 hours overnight fasting. It should be noted that the non-diabetic and diabetic control rats were not included in the training program during this period.

Table 1: Resistance training protocol based on percentage of body weight

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

Table 1: Resistance training protocol based on percentage of body weight

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 (13). After the rats were anesthetized, blood samples were collected through cardiac puncture. Then, liver tissue was removed and immersed in RNA later to analysis and determine PEPCK 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 (9). 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.

Table 2: Primer sequence				
Genes	**Primer sequence**	**Product size**	**Tm**	**Gene Bank**
PEPCK	**For**: TGCCCCAGGAAGTGAGGAAG **Rev**: CAGTGAGAGCCAGCCAACAG	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 (13). After the rats were anesthetized, blood samples were collected through cardiac puncture. Then, liver tissue was removed and immersed in RNA later to analysis and determine PEPCK 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.

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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.

Results

The bodies weight changes before and after training intervention in non-diabetic, control T2D and exercise T2D groups are presented in Table 3

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

Group	Pre-training	Post-tainting	*p-value* **
Non-diabetes	304 ± 9	401 ± 13	0.001
Control T2D	306 ± 10	387 ± 9	0.001
Exercise T2D	308 ± 11	415 ± 6	0.001
***p-value* ***	0.831	0.001	-------

** inter-group changes: data represented by one way ANOVA (P< 0.05)*
*** intra-group changes: data represented by paired t test (P< 0.05)*

Based one-way ANOVA data, significant difference was observed with regard to PEPCK expression in hepatocytes tissue between groups (P = 0.001). On the other hand, the findings of Tukey's test showed that T2D induction resulted in significant increase in PEPCK in the control T2D group compared to non-diabetes group (P = 0.001). But resistance training resulted in significant decrease in PEPCK expression in the exercise T2D compared to the control T2D group (Fig, 1, P = 0.001). Despite the significant increase in PEPCK expression in response to resistance training compared to the control T2D group, its expression in the exercise T2D remained significantly higher than the non-diabetes group (p = 0.003, table 4).

Group	Non-diabetes	Control T2D	Exercise T2D	*p-value* *
PEPCK expression	1	1.95 ± 0.09	1.37 ± 0.06	0.001

** inter-group changes: data represented by one way ANOVA (P< 0.05)*

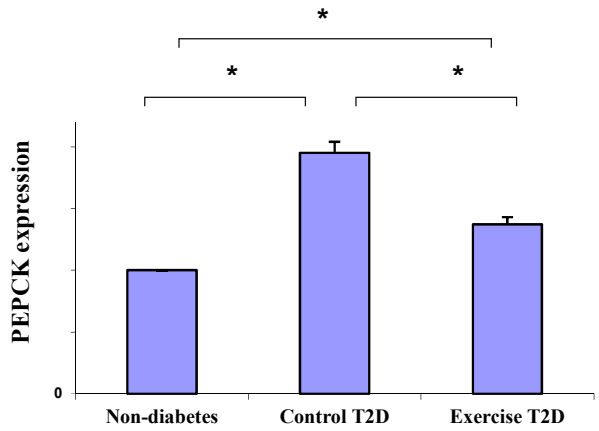

Fig 2: The change pattern of PEPCK expression in hepatocytes tissue of studied groups. T2D induction resulted in significant increase in PEPCK expression in control T2D compared to non-diabetes group. However, Resistance training reduced significantly its levels in the exercise T2D group compared to the control T2D group.

Table 5: Fasting glucose and serum insulin in response to T2D induction and resistance training in the studied groups

Group	Non-diabetes	Control T2D	Exercise T2D	*p-value **
Glucose (mg/dL)	122 ± 3	300 ± 12	*189 ± 17*	0.001
Insulin (µIU/ml)	9.23 ± 0.64	5.97 ± 0.22	6.58 ± 0.15	0.001
** inter-group changes: data represented by one way ANOVA (P< 0.05)*				

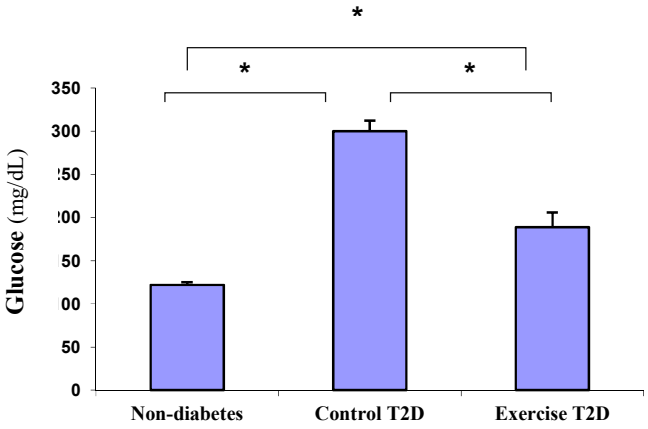

Fig 2: The change pattern of fasting glucose in studied groups

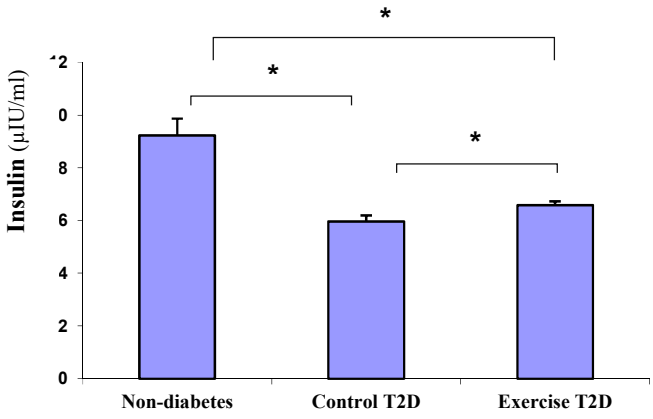

Fig 3: The change pattern of serum insulin in studied groups

Based the results of one-way ANOVA, significant difference was observed with regard to serum insulin, fasting glucose and beta cell function between the study groups (P = 0.001). on the other hand, the findings of Tukey's post hoc test showed that the induction of T2D led to an increase in fasting glucose and decrease in serum insulin levels in control T2D compared to non-diabetes group (P = 0.001, Fig 2). But resistance training resulted in significant decrease in fasting glucose (P = 0.001) and increase in serum insulin (P = 0.043, Fig3) in exercise T2D compared to control T2Dp group (Table 5).

Decreased PEPCK expression by resistance training compared to control T2D rats is the main finding of present study. In other words, 6 weeks of resistance training for 5 sessions weekly led to a decrease in PEPCK expression in the hepatocytes in exercise T2D group compared to control T2D group. Reduction of fasting glucose and increase serum insulin in response to resistance training compared to control T2D rats are other findings of the present study.

These findings are reported while contradicting the findings of the present study, Maltais et al (2016) indicated that despite the reduction of body fat mass, 4 months of resistance training did not lead to a change in glucose levels in overweight elderly men (14). In another study, no change in glycosylated hemoglobin was reported after 20 weeks of exercise training (15). No change in fasting glucose has also been reported after 6 weeks of aerobic training with a 60-80% VO2max (16). Donges et al (2013) also reported no change in insulin function and membrane glucose transport after 12 weeks of resistance training in men with abdominal obesity (17). Contrary to the aforementioned findings, in the research of Chana et al (2015) intense exercise was associated with a significant improvement in blood glucose in diabetic rats (18). Soori and colleagues (2017) also reported a significant decrease in glucose following 12 weeks of resistance training in type 2 diabetic rats (19). In Wei study (2013), 10 weeks of swimming training by rats with a high-fat diet led to an improvement in glucose and lipid metabolism along with a decrease in insulin resistance (20). On the other hand, Lopez et al (2016) have reported a significant decrease in insulin resistance after 12 weeks of combined training in overweight girls (21). Steckling et al (2016) have also attributed the improvement of glucose and HbA1C following 12 weeks of high intensity interval training (HIIT) 3 sessions per week with an intensity of 70 to 90% of the maximum heart rate to a decrease in insulin resistance or inflammatory profile (22).9

The physiological importance of the disturbance in the regulation of hepatic gluconeogenesis genes indicates that the increased expression of some gluconeogenic genes such as PEPCK is associated with glucose intolerance in diabetics. Pastik and his colleagues found in a study on genetically modified mice that increased expression of PEPCK in hepatocytes led to fasting hyperglycemia and peripheral insulin resistance (23). Regarding genetic changes in response to exercise, although studies are limited, Chang et al (2006) have pointed out that 8 weeks of running on a treadmill leads to a significant decrease in protein levels and PEPCK expression (24). Marinho et al (2012) have also pointed out, citing their findings, that long-term endurance training independent of weight loss is associated with the improvement of insulin signaling pathways in liver tissue. These researchers have pointed out that the beneficial effects of exercise on insulin action are associated with a decrease in the expression of gluconeogenic genes, so that long-term endurance training leads to a decrease in PEPCK expression (25). Meanwhile, Nizielski et al (1996) concluded in their study that one-session exercise, even long-term, leads to an increase in the rate of hepatic glucose release through the gluconeogenesis process by increasing the activity of the PEPCK transcriptional signaling pathways (26).

However, it has been found that genes expression involved in gluconeogenesis process decreases significantly after long-term recovery following long-term exercise. Thus, in the study of Ropelle et al (2009), PEPCK expression decreased after 8 hours of recovery following long-term exercise session, and the researchers attributed this decrease to changes in the signaling pathways of other related genes such as liver processes. So, in the aforementioned study, a group of rats performed two 3-hour swimming exercise with a 45-minute rest interval, and the findings showed that the insulin signaling pathways improved after 8 hours of recovery following a long-term endurance exercise session, which decreased PEPCK expression. At the same time, insulin-dependent Akt and Foxo1 phosphorylation is also accompanied by a decrease in PGC-1alpha expression in liver cells (27). Knudsen et al (2015) in their study entitled "Regulation of key factors and enzymes involved in hepatic gluconeogenesis process in the liver tissue of rats" have pointed out that one hour of running on a treadmill leads to an increase in the expression of G6Pase and PEPCK immediately

after exercise, but PEPCK protein levels increase after 10 minutes (28).

Decreased expression of genes involved in hepatic gluconeogenesis can also be attributed to changes in the signaling pathways of other transcription factors. Thus, in the study of Lima et al (2009), researchers attributed the decrease in PEPCK expression to the decrease in TRB3 expression after a long-term recovery following long-term exercise. Thus, in the mentioned study, TRB3 expression in the liver tissue of obese diabetic rats and diabetic rats with leptin resistance decreased significantly in 8 hours after a long swimming session compared to the control group, and the researchers pointed out that the decrease TRB3 expression will lead to a decrease in hepatic glucose release due to the effect on protein levels and PEPCK expression. These researchers have also stated that the production of hepatic glucose after a long recovery following long-term exercise is rooted in the improvement of insulin signaling pathways (29).

Apart from changes in PEPCK expression in liver hepatocytes, resistance training in the present study was also associated with increased insulin levels. In this context, it has been mentioned that the increase of insulin effectively leads to the inhibition of PEPCK transcription within a few minutes (30). The control or genetic regulation of PEPCK by insulin is a complex process involving several chemical mediators, so several studies have evaluated changes in the activity and expression of PEPCK as an indicator of hepatic insulin changes. Under fasting conditions, FOXO1 transcription factor reacts with PGC1-α protein in the promoters of PEPCK, leading to changes in its expression (27). On the other hand, an increase in hepatic insulin leads to the phosphorylation of FOXO1 and TORC2, which leads to their nuclear release and inhibits PEPCK expression (31). In addition, studies on rodents have revealed that hyperinsulinemia in the brain plays an important role in inhibiting gluconeogenic genes expression (32). Based on their findings, these researchers have pointed out that some secondary factors such as the level of liver damage and other parameters such as total body weight can affect the expression of these transcription factors (33). In the end, it is pointed out that the reduction of glucose or the improvement of the glycemic profile cannot be attributed only to changes in the hormonal or genetic components in liver hepatocytes in response to exercise, but this improvement is probably rooted in other changes in insulin synthesis and secretion or insulin function in other target tissues such as muscle tissue or fat, which requires more studies in this field. On the other hand, lack of measurement of other gluconeogenic genes such as HNF4α or G6P are limitations of the study. Also, despite the mentioned results, it should be noted that the absence of a non-diabetic control group is one of the main limitations of the present study, because the comparison of variables in response to resistance training between the diabetic and non-diabetic groups differentiates the effect of exercise on the variables between the two groups.

Conclusion

Resistance training is associated with improvement of hyperglycemia in type 2 diabetic rats. This improvement may be attributed to a decrease in hepatic gluconeogenesis in response to decreased PEPCK expression in hepatocytes. Because this training method led to a decrease in its expression compared to the control group. However, understanding the main mechanisms responsible for the improvement of the glycemic profile in response to exercise requires more molecular cell studies.

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