ISSN: 2538-5887; Pathobiology Research. 2026; 29 (1): 7-14
DOI: 10.48311/mjms.2025.117896.82612

The effect of resistance training on MTNR1A gene expression in pancreatic tissue and beta cell function in diabetic rats induced by high-fat diet and STZ

Review History:
Received: 2025-11-23
Revised: 2026-02-17
Accepted: 2026-05-19

Article Type:
Original Research

Authors:
Saeed Karkehabadi[1]
Hasan Matinhomaee[2*]
Shahla Dehghan[3]

1. Department of Exercise physiology, CT.C, Islamic Azad University, Tehran, Iran.
2. Department of Exercise physiology, CT.C, Islamic Azad University, Tehran, Iran.
3. Department of Physical Education and Sport Science, Iz.C., Islamic Azad University, Izeh, Iran.

**** Corresponding author:***
Hasan Matinhomaee

ORCID: 0000-0001-9340-1759
E-mail: hasanmatinhomaee@gmail.com
Tell: +989122319284

ABSTRACT

Introduction: Serum insulin are dependent on hormonal and genetic factors affecting beta cell function. The aim of the present study was to investigate the effect of resistance training on glucose, serum insulin, beta cell function, and MTNR1A expression in pancreatic tissue of type 2 diabetic rats.

Methods: In this experimental study, 14 male Wistar rats were made type 2 diabetic by high-fat diet and intraperitoneal injection of STZ (25 ml/kg). They were then randomly divided into exercise and control groups. The exercise group underwent 8 weeks of resistance training, (5 sessions/weekly), in the form of climbing a step ladder with gradually increasing resistance. 48 hours after the last training session, fasting glucose and serum insulin levels, beta cell function, and MTNR1A gene expression in pancreatic tissue were measured and compared between groups by independent t-test at a significance level of alpha less than 0.5 percent.

Results: Compared to control group, resistance training resulted in significant decrease in fasting glucose (p = 0.001) and MTNR1A gene expression (p= 0.003) in exercise compared with control group. In addition, serum insulin (p= 0.038) and beta cell function (p = 0.001) were significantly higher in the exercise group than in the control group.

Conclusion: In conclusion, resistance training achieved improvements in insulin synthesis in type 2 diabetics which can be attributed to reduced MTNR1A expression in pancreas tissue and improved beta cell function. Further studies are needed to clarify possible mechanisms effective in the insulin synthesis from the pancreas of type 2 diabetics.

Keywords: Diabetes, MTNR1A expression, Beta cell function, Resistance training, Insulin synthesis.

Introduction

Apart from hormonal and metabolic disorders, several environmental factors such as unbalanced diets and physical inactivity have a potential contribution to the occurrence or increase in the severity of type 2 diabetes (1). On the other hand, in the last two decades, the effective role of genetic disorders in protein levels or gene expression in insulin-sensitive tissues or protein synthesis by the pancreas has been considered. In such a way that genetic components pave the way for the occurrence of type 2 diabetes even in the absence of obesity (2). While the main factors of this disease are still not fully understood, scientific sources have confirmed that insulin resistance is the main factor causing it rather than beta cell dysfunction (3). Laboratory studies have indicated that beta cell function in type 2 diabetic patients is reduced by 50 to 60 percent compared to healthy individuals, and the onset of the decrease in the function of these cells dates back approximately 10 to 12 years before the appearance of hyperglycemia (4). Interestingly, some hormonal factors and genetic components do not affect body weight or obesity, but they drastically alter beta cell function and insulin secretion. In other words, independent of obesity, other important factors also play a decisive role in the occurrence of this disease, and genetic studies, especially since 2007 on diabetic or prediabetic individuals, showed that some transcription factors (CDKAL1, CDKN2A/B, IGF2BP2, HHEX, HNF1B, KCNJ11, PPARG,

TCF7L2, SLC30A8, WFS1, ADAMTS9, CDC123, CAMK1D, JAZF1, NOTCH2, THADA, TSPAN8 and LGR5) pave the way for the occurrence of type 2 diabetes even in the absence of obesity (5,6).

Meanwhile, the functional role of melatonin in the synthesis and secretion of insulin from beta cells has been repeatedly proposed. The findings of a study by Li et al. (2018) on laboratory mice revealed that the pineal hormone melatonin affects insulin secretion from pancreatic beta cells through melatonin receptors expressed in pancreatic beta cells. In addition, single nucleotide polymorphisms of the melatonin receptor are strongly associated with type 2 diabetes. These researchers also pointed out that melatonin exerts an inhibitory effect on insulin transcription through its receptors in pancreatic beta cells and the downstream MAPK signaling pathway (7). The effects of melatonin in target tissues are exerted by its two receptors, MTNR1A and MTNR1B, which are encoded by the MTNR1A and MTNR1B genes, respectively. In vitro studies have revealed that both melatonin receptors are expressed in human and rodent pancreatic islets (8,9).

Meanwhile, although the MTNR1B gene is known to be a genetic risk factor for type 2 diabetes (10,11), the MTNR1A gene has been less studied in humans and its role in metabolic diseases is not as well-known as that of MTNR1B (11). In humans, MTNR1A variants are associated with gestational diabetes (12) and obesity-related diseases (13) and insulin synthesis (14). Based on this evidence, the MTNR1A gene has been introduced as a risk gene for type 2 diabetes. However, although some studies have followed the effect of internal and external stimuli on the protein levels or expression of MTNR1B or other genetic and hormonal components effective in the transcription and synthesis of insulin, the response of MTNR1A to exercise training has been less studied.

For example, Eizadi et al (2016) reported a decrease in TCF7L2 expression following 3 months of interval training (15), Ramazani et al (2017) reported an increase in GLP-1R expression following 12 weeks of aerobic training (16), and Rashidi et al (2019) reported a decrease in MTNR1B expression in response to 12 weeks of aerobic training (17) in pancreatic beta cells of type 2 diabetic rats. However, another study reported no change in TCF7L2 expression in pancreatic tissue even in the presence of improved glucose and increased serum insulin in diabetic rats following aerobic training (6). On the other hand, changes in the expression of genes effective in insulin synthesis that were mentioned were associated with increased serum insulin and decreased fasting glucose. Despite the aforementioned evidence, no study has reported the effect of exercise training, especially resistance training, on MTNR1A expression as one of the effective candidates in insulin transcription and synthesis. Based on this limitation, the present study aimed to determine the effect of resistance training on MTNR1A expression as well as glucose, insulin levels, and beta cell function in pancreatic tissue of type 2 diabetic rats.

Materials and Methods

Subjects

The statistical population of this experimental-applied study consists of all male Wistar rats in the animal house of the Pasteur Institute of Iran. Among them, 14 rats aged 10 weeks of old in the weight range of 220 ± 10 grams were randomly selected to participate in the study. Then, after inducing type 2 diabetes, they were randomly divided into control and exercise groups in the eighteenth week (8 weeks of resistance training, 5 sessions/weekly). The studied rats were maintained under controlled light conditions (12 hours of light and 12 hours of darkness, lighting starting at 6 pm and darkness starting at 6 am) at a temperature of (22 ± 3 °C) and humidity ranging from 30 to 50 (%), so that they had free access to water and high-fat food until the end of the study.

Type 2 diabetes induction

To induce type 2 diabetes, a high-fat diet was fed for 8 weeks followed by intraperitoneal STZ injection of (25 ml/kg). To prepare the high-fat diet, 1% cholesterol powder and 1% 100% pure corn oil were added to the standard rat diet (18). One week after diabetes induction, fasting blood glucose was measured and blood glucose between 150 and 400 mg/dL was considered as a criterion for ensuring that the rats developed type 2 diabetes (18).

Training protocol

The exercise group participated in an 8-week

resistance training course, 5 sessions per week (table 1). In each session, resistance training consisted of 5 sets and 4 repetitions in each in the form of climbing a 26-step ladder to a height of 1 meter with a vertical slope of 80%. Rest time between sets was 3 minutes and rest time between repetitions in each set was 45 seconds. Before and after each training session, 2 unresisted ladder climbs were performed for warm-up and cool-down. Resistance was applied by tying weights to the rats' tails equivalent to different percentages of body weight during the training period. (19).

Table 1: Distribution pattern of exercise intensity in resistance training group based on percentage of body weight

Time (weeks)	Resistance (body weight %)
1	30
2	40
3	50
4	60
5	70
6	80
7	90
8	100

Finally, 48 hours after the last training session, the rats were sacrificed and dissected for blood sampling from the heart to measure glucose and insulin, beta cell function, and pancreatic tissue extraction to measure MTNR1A expression (20).

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

Tissue sampling and RNA extraction

48 hours after the last training session (10 to 12 overnight fasting), the rats in each group were anesthetized by intraperitoneal injection of a mixture of 10% ketamine (50 mg/kg) and 2% xylazine (10 mg/kg), and blood samples were taken directly from the animal's heart. Subsequently, the pancreatic tissue of the rats was extracted and after washing in physiological saline, immersed in microtubes containing 20% RNAlater liquid for genetic experiments.

RNA extraction was performed using the commercial RNeasy mini kit from QIAGEN. mRNA gene determination was performed by RT-Real time PCR using the Rotorgene 6000 system using the One Step SYBR TAKARA kit from Takara according to the company's instructions. RNA Polymerase was used as a control gene. The primer sequence patterns are shown in table 2.

Statistical Methods

Shapiro-Wilk test was used to ensure the normal distribution of data. Descriptive statistics were used to describe data and graphs. Independent t-test was used to compare each variable between groups. The significant level was considered to be an alpha of less than 5 percent. All statistical analyses were performed using SPSS/Win version 22 software.

Results

Table 3 shows the pattern of body weight changes before and after the intervention in the study groups.

Based on the results of the independent t-test, a significant difference was observed in serum insulin and glucose levels between the control and exercise groups. Resistance training resulted in a significant decrease in fasting glucose (P = 0.001, Figure 1) and a significant increase in serum insulin (P = 0.038, Figure 2) in the exercise group compared to the control group (table 4). A significant difference was also observed in beta cell function between the two groups (P = 0.001, Figure 3). In other words, beta

Table 2: The primer sequence

Genes	Primer sequence	Product size	T m	Gene Bank
MTNR1A	For: TTGCTGTGGTGTCCTTTTGC Rev: GCAAGGCCAATACAGTTGAGG	159 bp	60	NM_001191052.1
RNA PolymraseII	For: ACTTTGATGACGTGGAGGAGGAC Rev: GTTGGCCTGCGGTCGTTC	164 bp	60	XM_008759265.1

Table 3: Body weight (g) in before and after training intervention in the study groups

Group	Pre-training	Post-training	Sig (intra-group)
Control	403 ± 9	435 ± 6	0.011
Exercise	401 ± 8	415 ± 6	0.038
Sig (inter-group)	0.544	0.035	----

Table 4: Fasting glucose and other variables after exercise intervention of exercise and control groups (Mean ± SD).

Variable	Control group	Exercise group	sig
Fasting glucose (mg/dl)	287 ± 28	214 ± 22	0.001
Serum insulin (µU/ml)	5.06 ± 0.51	6.34 ± 1.10	0.038
Beta cell function (HOMA-BF)	8.27 ± 1.57	15.46 ± 6.62	0.001
MTNR1A gene expression	1	0.71 ± 0.19	0.003

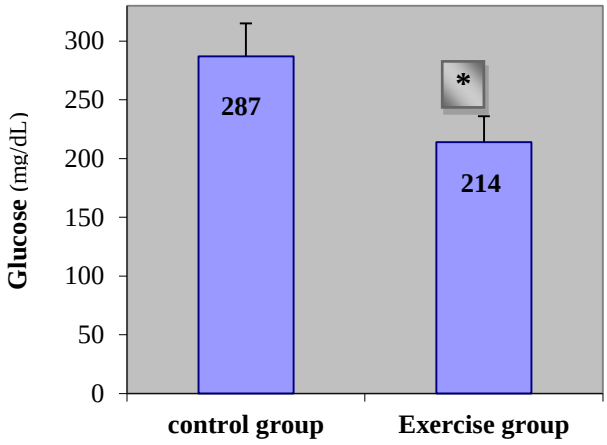

Figure 1: Changes in fasting glucose following resistance training compared to the control group

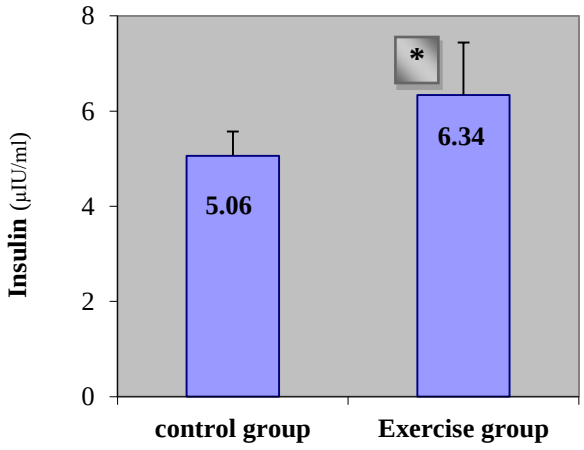

Figure 2: Changes in serum insulin following resistance training compared to the control group

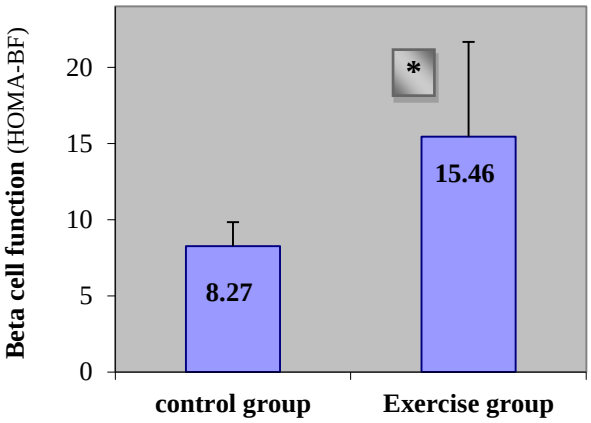

Figure 3: Changes in beta cell function following resistance training compared to the control group

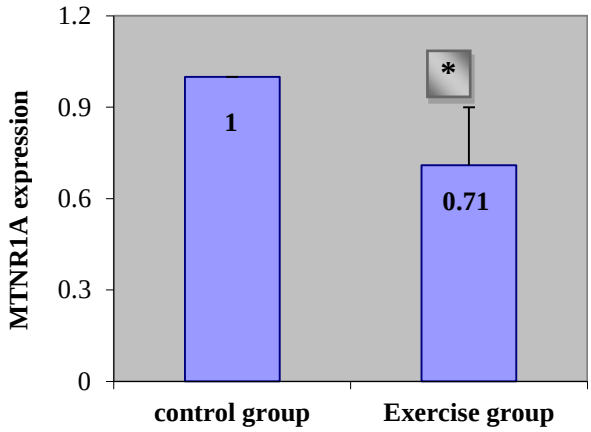

Figure 4: Changes in MTNR1A expression following resistance training compared to the control group

cell function increased significantly in the exercise group following resistance training compared to the control group. In addition to the aforementioned changes, resistance training resulted in a significant decrease in MTNR1A gene expression in the pancreatic tissue of the exercise group compared to the control group (P = 0.003, Figure 4).

Discussion

The decrease in MTNR1A expression in pancreatic tissue of type 2 diabetic rats is the most important finding of the present study. In other words, resistance training for 8 weeks with 5 sessions per week led to a significant decrease in expression in pancreatic tissue compared to the control group that did not participate in training. On the other hand, the decrease in fasting glucose along with an increase in serum insulin and beta cell function following resistance training are other findings of the study. Although the effect of exercise training on MTNR1A expression in the pancreas has not been studied so far, the response or adaptation of other hormonal and genetic variables to exercise training has been reported many times, and these results are also contradictory. For example, in the study of Ghasemalipour et al (2015), although 3 months of aerobic training led to a decrease in weight and body fat percentage in type 2 diabetic patients, the serum TNF-α level did not change (21). In another study, 12 weeks of aerobic training led to a decrease in glucose and insulin resistance in type 2 diabetic men (22). In the study by Behkar et al (2023), an increase in serum insulin was observed along with a decrease in fasting glucose and an increase in PKBα expression in the pancreatic tissue of type 2 diabetic rats following 8 weeks of interval training, but GLP-1R expression did not change compared to the control group (23). However, Ramazani et al (2017) reported an increase in GLP-1R expression in pancreatic tissue and serum insulin along with a decrease in fasting glucose in type 2 diabetic rats following 12 weeks of aerobic training (16).

The increase in serum insulin following resistance training in the present study is probably due to improved beta cell function. Several studies have attributed the decrease in serum insulin in diabetics to a decrease in beta cell function in these patients (15). In this context, it has been stated that beta cell function in type 2 diabetics is reduced by up to 80% compared to healthy individuals, depending on various influencing factors (24,25). On the other hand, a study reported a 40 to 60% decrease in beta cell mass in type 2 diabetics compared to non-diabetics (26).

The response or adaptation of beta cell function to exercise training has been less studied. However, scientific sources suggest that both diet and exercise increase insulin secretion, although the mechanisms of action of each are independent of the other. A high-fat diet increases beta cell mass through hypertrophy to overcome insulin resistance, while exercise increases beta cell mass through hyperplasia and reduced cell death (27).

In support of this evidence, both interval and resistance training in the present study led to increased beta cell function in diabetic rats compared to the control group. Some studies have also reported increased beta cell function following exercise training (28). Also, in diabetic populations, regular exercise training is associated with increased insulin response to hyperglycemia, which implies the effect of exercise on beta cell

function (28). Based on the aforementioned evidence, regardless of the potential effect of exercise training that has been shown to increase insulin sensitivity or decrease insulin resistance in target tissues to exercise training, the increase in serum insulin and decrease in blood glucose in the present study can be attributed to improved beta cell function in response to interval and resistance training. This hypothesis has been previously confirmed by some other studies (29). In this regard, Eizadi et al (2012) also attributed the increase in serum insulin in response to exercise training in type 2 diabetic patients to improved beta cell function (30).

Some studies have reported improved beta cell function in response to reduced fat mass resulting from continuous exercise or dietary modification (31,32). Other training methods, such as treadmill running or swimming, have been reported to preserve beta cell function (33,34). In this regard, it has been suggested that exercise training accelerates insulin transcription and synthesis pathways by changing protein levels or expression of some transcription factors affecting insulin synthesis in pancreatic beta cells. Eizadi et al, in two independent studies in 2016 and 2017, showed that increased serum insulin following interval and resistance training leads to decreased expression of the TCF7L2 gene as the most important transcription factor affecting insulin synthesis in type 2 diabetic rats, and attributed the increased beta cell function and serum insulin in response to these training methods to decreased TCF7L2 in pancreatic beta cells of type 2 diabetic rats (15,35). Despite the aforementioned evidence, no study has been reported to date that follows the protein levels or expression of MTNR1A in response to exercise training in diabetic rats or other healthy and diseased populations.

Despite these limitations, the findings of the present study indicate a significant decrease in MTNR1A expression in response to resistance training. In other words, 8 weeks of resistance training significantly reduced MTNR1A expression in pancreatic tissue of type 2 diabetic rats, and this decrease was associated with increased beta-cell function and serum insulin. However, genetic studies have supported the effective role of melatonin and its receptors in the pancreas in insulin synthesis. Thus, increased melatonin and its receptor expression in the pancreas of diabetic rats leads to a decrease in insulin transcription and synthesis (8,9,14).

Some other studies have indicated that MTNR1A, another melatonin receptor, is expressed in pancreatic beta cells independently of MTNR1B and has been introduced as a genetic risk factor for type 2 diabetes by affecting insulin synthesis and secretion, such that its increased expression in pancreatic beta cells leads to a decrease in insulin synthesis by affecting insulin transcription signaling pathways (36). Mühlbauer et al (2012) have also stated, citing laboratory studies, that increased melatonin inhibits insulin synthesis primarily through MTNR2A and MTNR1A receptors in INS-1 cells of rats and isolated islets of mice (37). Based on the observations of the present study, although measuring the expression of MTNR1A in pancreatic tissue is one of the strengths of the study, measuring these transcription factors alone does not indicate the mechanisms responsible for insulin synthesis in response to exercise, and measuring oxidative stress markers and other transcription factors such as TCF7L2, FOXO1 or GLP-1R are limitations of the study.

Conclusion

Resistance training improves glucose in type 2 diabetic rats. This improvement can be attributed to increased serum insulin in these patients. On the other hand, based on the findings of the study and other laboratory evidence that support the effective role of melatonin receptors on insulin transcription and synthesis in beta cells, the increase in serum insulin in diabetic rats is likely to be due to the reduction in MTNR1A expression and increased beta cell function following this training regimen. Further study will be needed to clarify the mechanism of the regulation of the insulin secretion of beta cells by exercise training.

Acknowledgments

The authors wish to thank the Islamic Azad University of Central Tehran Branch For their support and assistance.

Funding

This research was funded by Islamic Azad University, Central Tehran Branch.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

References

1. Yarmohammadi M, Behboudi L, Eizadi M. The Effect of 12 Weeks Resistance Training on FOXO1 Expression in Hepatocytes, Glucose and Insulin in Diabetic Rats- A Brief-Report. IJDO. 2019; 11 (3):193-195.
2. Ruchat SM, Rankinen T, Weisnagel SJ, Rice T, Rao DC, Bergman RN, et al. Improvements in glucose homeostasis in response to regular exercise are influenced by PPARG Pro12Ala variant: results from the HERITAGE Family Study .Diabetologia. 2010 Apr; 53(4):679-89.
3. Schmid DA, Held K, Ising M, Uhr M, Weikel JC, Steiger A. Ghrelin stimulates appetite, imagination of food, GH, ACTH, and cortisol, but does not affect leptin in normal controls. Neuropsychopharmacology. 2005 Jun; 30(6):1187-92.
4. Levy J. Beta-cell deterioration determines the onset and rate of progression of secondary dietary failure in type 2 diabetes mellitus: the 10-year followup of the Belfast Diet Study. Diabet Med. 1998, 15: 290– 296.
5. Villareal DT, Robertson H, Bell GI. TCF7L2 variant rs7903146 affects the risk of type 2 diabetes by modulating incretin action. Diabetes 2010, 59:479–485.
6. Eizadi M, Ravasi AA, Soori R, Baesi K, Choubineh S. Effect of three months aerobic training on TCF7L2 expression in pancreatic tissue in type 2 diabet es rats induced by streptozotocin- nicotinamide. Feyz 2017; 21(1): 1-8.
7. Li Y, Wu H, Liu N, Cao X, Yang Z, Lu B, Hu R, Wang X, Wen J. Melatonin exerts an inhibitory effect on insulin gene transcription via MTNR1B and the downstream Raf-1/ERK signaling pathway. Int J Mol Med. 2018 Feb; 41(2):955-961.
8. Mulder H, Nagorny CL, and Lyssenko V, Groop L. Melatonin receptors in pancreatic islets: good morning to a novel type 2 diabetes gene. Diabetologia. 2009 Jul; 52(7):1240-9.
9. Lyssenko V, Nagorny CL, Erdos MR. Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat Genet. 2009; 41:82–88.
10. Tan X, Ciuculete DM, Schiöth HB, Benedict C. Associations between chronotype, MTNR1B gen-otype and risk of type 2 diabetes in UK Biobank. J Intern Med. 2020; 287: 189-196.
11. Owino S, Sánchez-Bretaño A, Tchio C, Cecon E, Karamitri A, Dam J, et al. Nocturnal activation of melatonin receptor type 1 signaling modulates diurnal insulin sensitivity via regulation of PI3K activity. J Pineal Res 2018; 64(3): 10.
12. Li C, Qiao B, Zhan Y, Peng W, Chen ZJ, Sun L, et al. Association between ge-netic variations in MTNR1A and MTNR1B genes and gestational diabetes mellitus in Han Chinese women. Gynecol Obstet Invest 2013; 76: 221-227.
13. Xu XH, Kou LC, Wang HM, Bo CM, Song XC. Ge-netic polymorphisms of melatonin receptors 1A and 1B may result in disordered lipid metabolism in obese patients with polycystic ovary syndrome. Mol Med Rep 2019; 19: 2220-2230.
14. Shaaban Z, Khoradmehr A, Amiri-Yekta A, Nowzari F, Jafarzadeh Shirazi MR, Tamadon A. Pathophysiologic mechanisms of insulin secre-tion and signaling-related genes in etiology of polycystic ovary syndrome. Genet Res (Camb) 2021; 2021: 7781823.
15. Eizadi M, Ravasi AA, Soory R, Baesi K, Choobineh S. The Effect of Three Months of Resistance Training on TCF7L2 Expression in Pancreas Tissues of Type 2 Diabetic Rats. Avicenna J Med Biochem. 2016 June; 4(1):e34014.
16. Ramazani Rad M, Hajirasouli M, Eizadi M. The effect of 12 weeks of aerobic training on GLP-1 receptor expression in pancreatic tissue and glycemic control in type 2 diabetic rats. Qom Univ Med Sci J. 2017; 11(6):36-45.
17. Rashidi M, Eizadi M. The effect of an interval exercise period (HIIT) on MTNIR1B gene expression, insulin and glucose levels in type 2 diabetic rats. Journal of Knowledge & Health 2019; 14(1):28-35.
18. Eizadi M, Mirakhori Z, Farajtabar Behrestaq S. Effect of 8-Week Interval Training on Protein Tyrosine Phosphatase 1B Expression in Gastrocnemius Muscle and Insulin Resistance in Rats with Type 2 Diabetes. Avicenna Journal of Medical Biochemistry. 2019 December; 7(2):51-56.
19. Eizadi M, Mirakhori Z, Amini A. The effect of 8-week resistance training on IRS-1 gene expression in gastrocnemius muscle and glycemic profile in diabetes rats. Arch Med Lab Sci. 2019; 5(1):23-30.
20. Marita AR, Sarkar JA, Rane S. Type 2 diabetes in non-obese Indian subjects is associated with reduced leptin levels: Study from Mumbai, Western India. Mol Cell Biochem. 2005; 275(1-2): 143-51.
21. Ghasemalipour H, Eizadi M, Hajirasouli M. The Effect of Regular Aerobic Training on Tumor Necrosis Factor-Alpha (TNF-α) in Males with Type II Diabetes .Avicenna J Med Biochem. 2015 March; 3(1): e26908.
22. Yazdanpazhooh S, Banaeifar A, Arshadi S, Eizadi M. Six Weeks Resistance Training Effect on FTO Expression in Type II Diabetes Rats. IJDO. 2018; 10(4) :216-222.
23. Behkar M, Eizadi M, Sedaghaty S, Kazemzadeh Y, Moslehi M. Impact of High-Intensity Interval Training on GLP-1R/ PKBα Axis in Pancreatic Tissue of Diabetic Rats Induced by High-Fat Diet and STZ. IJDO .2023; 15(4): 201-207.

24. Ferranninin E, Castalldeli A, Miyazaki Y, Matsuda M, Mari A, DeFronzo RA. Beta cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: A new analysis. J Clin Endocrinol Metabolism. 2005; 90(1): 493-500.

25. DeFronzo RA. From the triumvirate to the ominous octet: A new paradigm for the treatment of type 2 diabetes mellitus. Diabetes. 2009; 58(4): 773-795.

26. Withers DJ, Gutierrez JS, Towery H, Burks DJ, Ren JM, Previs S, Zhang Y, Bernal D, Pons S, Shulman GI, Bonner-Weir S, White MF. Disruption of IRS-2 causes type 2 diabetes in mice. Nature. 1998; 391: 900 –904.

27. Sunmin P, Sang MH, Ji EL, So RS. Exercise improves glucose homeostasis that has been impaired by a high-fat diet by potentiating pancreatic β-cell function and mass through IRS2 in diabetic rats. Journal of Applied Physiology November. 2007; 103(5): 1764-1771.

28. Dela F, von Linstow ME, Mikines KJ, Galbo H. Physical training may enhance beta-cell function in type 2 diabetes. Am J Physiol Endocrinol Metab. 2004 Nov; 287(5): 1024-31.

29. Gumbiner B, Polonsky KS, Beltz WF, Griver K, Wallace P, Brechtel ,G et al. Effects of weight loss and reduced hyperglycemia on the kinetics of insulin secretion in obese non-insulin dependent diabetes mellitus. J Clin Endocrinol Metab. 1990; 70: 1594-1602.

30. Eizadi M, Behboudi L, Zahedmanesh F, Afsharmand Z. Effect of Acute and Chronic Exercise on Beta-Cell Function in Diabetic Patients. Knowledge and Healths. 2012; 6(4): 15-19.

31. Davies MJ, Metcalfe J, Day JL, Grenfell A, Hales CN, Gray IP. Improved beta cell function, with reduction in secretion of intact and 32/33 split proinsulin, after dietary intervention in subjects with type 2 diabetes mellitus. Diabet Med. 1994; 11: 71-78.

32. Hosker JP, Kumar S, Gordon C, Bhatnagar D, France M, Boulton AJ. Diet treatment of newly presenting type 2 diabetes improves insulin secretory capacity, but has no effect on insulin sensitivity. Diabet Med. 1993; 10: 509-513.

33. Pold R, Jensen LS, Jessen N, Buhl ES, Schmitz O, Flyvbjerg A, Fujii N, Goodyear LJ, Gotfredsen CF, Brand CL, Lund S. Long-term AICAR administration and exercise prevents diabetes in ZDF rats. Diabetes. 2005; 54: 928 –934.

34. Rhodes CJ, White MF. Molecular insights into insulin action and secretion. Eur J Clin Invest. 2000; 32, Suppl 3: 3–1.

35. Eizadi M, Soory R, Ravasi A, Baesy K, Choobineh S. Relationship between TCF7L2 Relative Expression in Pancreas Tissue with Changes in Insulin by High Intensity Interval Training (HIIT) in Type 2 Diabetes Rats . JSSU. 2017; 24 (12): 981-993

36. Amin M, Gragnoli C. Melatonin receptor 1A (MTNR1A) gene linkage and association to type 2 diabetes in Italian families. Eur Rev Med Pharmacol Sci. 2023 May; 27(10):4688-4692.

37. Mühlbauer E, Albrecht E, Bazwinsky-Wutschke I, Peschke E. Melatonin influences insulin secretion primarily via MT_1 receptors in rat insulinoma cells (INS-1) and mouse pancreatic islets. 2012; 52(4): 446-459.