

## Effect of Resistance and Interval Training on Serum Melatonin and Expression of Its Receptors (MTNR1A and MTNR1B) in the Pancreas Tissue of Diabetic Rats

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### Abstract

**Objective:** In addition to controlling seasonal and circadian rhythms, melatonin has been recognized as a potential gene associated with type 2 diabetes (T2D). This study aimed to investigate the impact of resistance and interval training on serum melatonin and its receptors expression (MTNR1A, MTNR1B) in pancreatic tissue of type 2 diabetic rats.

**Materials and Methods:** To achieve this, T2D was established in 21 male Wistar rats through an 8-week high-fat diet followed by an intraperitoneal injection of STZ (25 ml/kg), then were divided to control (no exercise), resistance (resistance training), and interval (interval training) groups. Exercise interventions lasted 8 weeks (5 time/weekly). Fasting glucose, serum insulin and melatonin, beta cell function, MTNR1A and MTNR1B expression in pancreatic tissue were assessed 48 hours following lasting exercise and analyzed among groups using a one-way ANOVA test.

**Results:** Both resistance and interval training led to significant increase in insulin and beta cell function and significant decrease in glucose, serum melatonin, MTNR1A and MTNR1B expression in pancreatic tissue compared with control group ( $P < 0.05$ ). Significant difference were not observed in all variables between interval and resistance groups ( $P > 0.05$ ).

**Conclusion:** Resistance and interval training are associated with increased insulin in T2D rats, and this improvement may be attributed to decreased melatonin and its receptor expression in pancreatic beta cells. Additional research is required to elucidate alternative mechanisms that contribute to elevated insulin levels.

**Keywords:** Type 2 diabetes, Melatonin receptors expression, Exercise training, Beta cell function

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## Introduction

Clinical research has demonstrated that insulin resistance plays a central role in the onset of type 2 diabetes (T2D) (1). However, some studies have pointed out that 50 to 60% of beta cell function is reduced in these patients, and have introduced increased insulin synthesis and secretion as the first step in improving this disease (2). In the last decade, gene linkage studies have revealed a broad association between genetic factors and T2DM and other metabolic diseases (3). These studies have introduced a list of transcription factors that are closely related to the prevalence of T2DM, which has attracted a lot of attention from health science researchers. Interestingly, most of these genetic factors affect the prevalence or severity of diabetes mainly by affecting beta cell function. Among them, melatonin (N-acetyl-5-methoxytryptamine), a hormone produced by the pineal gland has been introduced as one of the candidate genes for T2DM (4). Its circadian secretion changes in the presence of diabetes, and a significant negative correlation between its systemic levels and insulin has been reported in the presence of T2DM (5).

Although melatonin is known as a regulator of circadian rhythms in mammals, it affects various metabolic functions such as glucose homeostasis (6). On the other hand, it has been shown that both melatonin receptors MTNR1A and MTNR1B are expressed in human and rodent pancreatic islets (7). Although some studies have indicated differences in melatonin receptor levels in rodents (8,9), there is no difference in melatonin receptor levels in human pancreatic islets (7). In other words, in rodent and human models, MTNR1B protein is predominantly expressed in beta cells and MTNR1A protein is also predominantly expressed in beta cells (7). Although the role of the MTNR1B gene as a genetic risk factor in the predisposition to

T2DM has been reported (10), fewer studies have been conducted on the MTNR1A gene and its role in the prevalence or severity of diabetes has been studied less. On the other hand, the association of its variants with gestational diabetes (11) and obesity-related hyperglycemia and insulin synthesis (12) introduces MTNR1A as the second melatonin receptor effective in insulin synthesis.

The laboratory studies have indicated the inhibitory effect of melatonin on insulin synthesis and secretion from the pancreas (7,12). On the other hand, increasing the level and its receptors expression in beta cells by sensitizing these cells to melatonin leads to the inhibition of insulin synthesis, especially in diabetic individuals (13). Based on these concepts, it seems that the expression of melatonin receptors in pancreatic tissue is associated with increased insulin synthesis and secretion. However, there are limited reports available on the effect of internal or external stimuli on the expression of melatonin receptors in the pancreas of healthy or diabetic populations. On the other hand, some other studies reported the effect of exercise training as a non-pharmacological treatment on some genetic components affecting insulin transcription and synthesis in diabetic rats. For example, Karimi et al. (2019) reported increased FOXO1 pancreatic expression of T2D rats along with increased serum insulin and decreased fasting glucose following 6 weeks of interval training (14). Eizadi et al. (2017) also attributed the increased insulin of T2D rats following resistance and interval training to decreased TCF7L2 expression in pancreatic tissue (15,16). Rashidi et al (2019) also reported decreased MTNR1B expression in pancreatic tissue and increased insulin in T2DM rats following long-term interval training (17). However, no study has been reported to date to compare the effects of interval and resistance training on serum

melatonin and MTNR1A and MTNR1B expression. Based on these limitations, our study aimed to determine and compare the effects of resistance and interval training on serum melatonin levels and the expression of its receptors (MTNR1A, MTNR1B) in the pancreas of T2DM rats, as well as serum melatonin, beta cell function and systemic insulin.

## Materials and methods

### Subjects

The statistical population for this experimental-applied research comprised all male Wistar rats housed at the Pasteur Institute. From this population, 21 rats aged 10 weeks were randomly chosen to participate in the experiment. Following the type 2 diabetes induction, the animals were assigned to one of three groups: control (no exercise), resistance training (8 weeks resistance exercise), and interval training (8 weeks interval training). Throughout the study, the rats were kept under regulated environmental conditions, with lighting scheduled from 6 p.m. to 6 a.m., temperature maintained at (22± 3°C), and humidity controlled between 30% and 50%. The animals had unrestricted access to water and a high-fat diet.

### Diabetes induction

T2D induced by administering an 8 weeks of high-fat diet (HFD), followed by an intraperitoneal injection of STZ (dose of 25 ml/kg) (18). One week after the injection, animals exhibiting fasting glucose ranging from 150-400 mg/dl were identified as type 2 diabetes (18).

### Training protocols

The resistance group was climbed on a 26-step stepladder with a gradient of 80% (1 meter vertical ladder) (19). Then they completed a resistance training (8 weeks, 5 days/weekly). Exercise sessions was performed in 5 courses (4 repetitions in each course). The resistance was increased by

attaching a weight to rats' tails. Rest between course was 3 min and between repetitions 45 sec. The resistance increased gradually during intervention (Table 1). In the interval group, training was performed for 8 weeks (5 time/weekly) in the form of treadmill running with active rest between repetitions according to Table 2 (18).

### Tissue sampling and RNA extraction

48 hours followed by lasting exercise session (10-12 overnight fasting), all rats were anesthetized by intraperitoneal injection of ketamine (10%, 50 mg/kg) and xylazine (2%, 10 mg/kg), and Blood samples for glucose, insulin, and melatonin measurements 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. Glucose levels were determined using an enzymatic colorimetric assay based on glucose oxidase, employing a glucose kit supplied by Pars Azmoun Company, Tehran. Serum concentrations of insulin and melatonin were quantified via the ELISA method, following the protocols provided with the commercial kit (Demeditec Diagnostic Insulin ELISA, Germany). Beta cell function was also calculated by substituting fasting insulin and glucose values into the relevant formula (20).

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

RNA extraction was performed using a QIAGEN kit (commercial RNeasy mini kit). The identification of mRNA genes was carried out via RT-Real time PCR on the Rotorgene 6000 platform, utilizing the One Step SYBR TAKARA kit from Takara, following the manufacturer's protocol. RNA polymerase was used as a control gene. The primer sequence patterns are shown in Table 3.

## Statistical analysis

Statistical comparisons were performed using SPSS/Win version 22. To compare each variable between groups, one-way ANOVA statistical test was used along with Tukey's post hoc test. The significant level was considered to be an alpha of less than 0.5 percent.

## Ethical considerations

The Research Ethics Committee of Islamic Azad University granted approval for this study under the ethics code IR.IAU.SARI.REC.1403.215.

## Results

Table 4 presents the circulating, fasting blood glucose and the other biochemical marker targeted in this study. Based on results by ANOVA test, significant difference were

observed in serum insulin ( $P= 0.017$ ), glucose ( $P= 0.001$ ), melatonin ( $P= 0.001$ ) and beta cell function ( $P= 0.001$ ) between groups. Based on Tukey's test results, to compared with control group, both resistance and interval intervention led to a significant increase were observed in serum insulin ( $P= 0.038$ ,  $P= 0.027$ ; respectively) and beta cell function ( $P= 0.001$ ,  $P= 0.001$ ; respectively) as well as significant reduction in glucose ( $P= 0.001$ ,  $P= 0.001$ ; respectively) and serum melatonin ( $P= 0.001$ ,  $P= 0.001$  respectively). However, there was no significant difference between interval and resistance groups with regard to serum insulin ( $P= 0.983$ ) and glucose ( $P= 0.953$ ), melatonin ( $P= 0.744$ ) and beta cell function ( $P= 0.998$ ).

The medical history of the patients revealed that 61.4% had a history of high blood pressure. The table results indicated that the

**Table1. Pattern of exercise intensity distribution in the resistance training group according to body weight percentage**

Time (weeks)	Resistance (body weight %)
First	30
Second	40
Third	50
Fourth	60
Fifth	70
Sixth	80
Seventh	90
Eighth	100

**Table2. Pattern of exercise intensity distribution in the interval training group based on speed and time of running in exercise and resting phase**

Exercise session (weeks)	Exercise phase		Resting phase	
	Time (S)	Speed (m/min)	Time (min)	Speed (m/min)
First-second	40	20	2	14
Third-fourth	40	25	2	14
Fifth-sixth	40	30	2	14
Seventh-eighth	40	35	2	14

**Table 3. Primer sequence pattern**

Genes	Primer sequence	Product size	T m	Gene bank
MTNR1A	For: TTGCTGTGGTGTCTTTTGC Rev: GCAAGGCCAATACAGTTGAGG	159 bp	60	NM_001191052.1
MTNR1B	For: TTGCTGTGGTGTCTTCCTG Rev: GCAAGGCCAATACAGTGGTTCG	159 bp	60	NM_001191052.1
RNA PolymraseII	For: ACTTTGATGACGTGGAGGAGGAC Rev: GTTGGCCTGCGGTCGTTC	164 bp	60	XM_008759265.1

mean P-R interval was  $0.15 (\pm 0.03)$ , the mean Q-T interval was  $0.39 (\pm 0.02)$ , and the mean QRS voltage was  $0.83 (\pm 0.14)$ , all of which fell within the normal range. Furthermore, the height of the S-T segment showed that 86.3% were normal, while 10.8% were elevated and 2.9% were depressed.

Based on what was mentioned earlier, the main objectives of this study are to assess the impact of interval and resistance training on MTNR1A and MTNR1B expression in pancreas tissue. The results of the ANOVA test indicate a significant difference in both MTNR1A ( $P= 0.002$ ) and MTNR1B ( $P= 0.001$ ) between groups (Table 5). So that, both interval and resistance training led to a significant decrease in MTNR1A ( $P= 0.006$ ,  $P= 0.003$ ; respectively) and MTNR1B ( $P= 0.001$ ,  $P= 0.001$ ; respectively) expression compared to the control group. However, significant difference were not observed between interval and resistance groups in MTNR1A and MTNR1B expression ( $P= 0.963$ ,  $P= 0.897$ ; respectively).

## Discussion

The findings of the study indicated a reduction in the expression of MTNR1A and MTNR1B receptors of pancreatic tissue in T2D rats response to interval and resistance training. So that, 8 weeks of resistance and interval training, 5 sessions per week, independently of each other, led to a reduction in the expression of MTNR1A and MTNR1B in the pancreatic tissue compared to a group of

them that did not participate in the training period. These changes were also accompanied by a decrease in glucose and melatonin and an increase in insulin of 2 groups. Although there are few findings regarding the impact of exercise training on serum melatonin levels in diabetic populations, reports on other variables have been presented in recent years. As Lopes et al (2016) reported a significant reduction in glucose along with an increase in insulin sensitivity following 12 weeks of combined training (resistance + aerobic) (21). However, Maltais et al (2016) reported no significant change in glucose and insulin following 4 months of resistance training (22). In another study, 20 weeks of aerobic training at an intensity of 70% of maximal oxygen consumption did not lead to any change in HbA1C (23).

The observed elevation in serum insulin following both interval and resistance training in this study is likely due to enhanced beta-cell function. Notably, improvements in beta-cell performance among obese individuals with T2DM after weight reduction provide substantial evidence that obesity and its related metabolic disturbances contribute to beta-cell impairment (24). Scientific literature indicates that while both dietary interventions and physical activity stimulate insulin secretion, they do so via distinct mechanisms. Specifically, a high-fat diet promotes an increase in beta-cell mass through hypertrophy as a compensatory response to insulin resistance, whereas exercise facilitates beta-

**Table 4. Mean and SD of biochemical marker of studied groups**

Group	Control	Interval	Resistance	P-value*
Glucose (mg/dL)	287 ( $\pm 28$ )	218 ( $\pm 25$ )	214 ( $\pm 22$ )	0.001
Insulin ( $\mu$ IU/ml)	5.06 ( $\pm 0.51$ )	6.43 ( $\pm 0.97$ )	6.34 ( $\pm 1.10$ )	0.017
Melatonin (pg/ml)	86.14 ( $\pm 4.30$ )	74.14 ( $\pm 2.55$ )	72.71 ( $\pm 3.77$ )	0.001
Beta cell function	8.27 ( $\pm 1.55$ )	15.37 ( $\pm 3.78$ )	15.46 ( $\pm 3.62$ )	0.001

\*ANOVA

**Table 5. Relative expression of MTNR1A and MTNR1B in the intervention groups**

Group	Control	Interval	Resistance	P-value
MTNR1A relative expression	1	0.62 ( $\pm 0.21$ )	0.66 ( $\pm 0.16$ )	0.002
MTNR1B relative expression	1	0.73 ( $\pm 0.16$ )	0.71 ( $\pm 0.19$ )	0.001

\*ANOVA

cell expansion through hyperplasia and by decreasing apoptosis (25).

Consistent with these findings, the current research demonstrated that both interval and resistance training resulted in greater beta-cell function in diabetic rats compared to controls. Additional studies have similarly documented enhanced beta-cell activity following exercise interventions (26).

Furthermore, in individuals with diabetes, consistent exercise has been linked to enhanced insulin responses during episodes of hyperglycemia, suggesting a positive influence of physical activity on beta cell function (26).

Drawing from this evidence, it can be inferred that, beyond the well-established effects of exercise on increasing insulin sensitivity or reducing insulin resistance in target tissues, the observed elevation in insulin and reduction in glucose levels in the current study may be due to improved beta cell function resulting from interval and resistance training. This interpretation is supported by findings from previous research (27). Also Eizadi et al (2012) reported that the rise in serum insulin following exercise training in patients with T2DM was attributable to enhanced beta cell function (28).

Conversely, laboratory investigations have demonstrated that while certain reversible factors can influence beta cell function, the fundamental impairment and insufficiency of insulin secretion by beta cells is primarily rooted in genetic factors (29). Research conducted over the past decade has also linked reductions in fasting glucose levels and elevations in serum insulin following exercise training to the activity of transcription factors involved in insulin synthesis within beta cells. Consequently, it has been suggested that both beta cell functionality and insulin production are, to some extent, regulated by transcription factors that play key roles in the insulin signaling pathways of these cells (29). In this context, exercise training is reported to enhance the pathways responsible for insulin transcription and synthesis by modulating the

protein levels or expression of specific transcription factors critical for insulin production in pancreatic beta cells. Supporting this perspective, Eizadi et al have reported that both interval and resistance exercise result in decreased expression of the TCF7L2 gene recognized as a major transcription factor influencing insulin synthesis in type 2 diabetic rats. They attributed improvements in beta cell function and increased serum insulin observed after these exercise interventions to reduced TCF7L2 expression in the pancreatic beta cells of these animals (15,16).

These findings are reported while in the study of Behkar et al. (2023) 6 weeks of interval training in the absence of changes in GLP-1R expression as another transcription factor affecting insulin synthesis in beta cells led to a reduction in serum insulin in T2DM rats (30). However, in another study by these researchers, an increase in PKB $\alpha$  expression in pancreatic beta cells was reported along with an elevation in insulin following interval training in T2DM rats (31).

This study demonstrated the beneficial impact of both interval and resistance training on the regulation of genetic factors involved in insulin production within the pancreatic tissue in diabetic rats. Nonetheless, there is a lack of studies examining how exercise influences the protein levels or gene expression of MTNR1B and MTNR1A in the pancreas. While Rashidi et al (2016) observed a reduction in MTNR1B pancreatic expression, accompanied by elevated serum insulin and reduced fasting glucose following interval training (17), there remains a lack of research specifically addressing changes in MTNR1A protein levels or gene expression after exercise in diabetic rats or other populations. Furthermore, the influence of interval training on MTNR1B expression has not been extensively documented. Despite these gaps, the present study provides evidence that both interval and resistance training significantly reduce in the pancreatic expression of MTNR1A and MTNR1B in T2D rats. Eight weeks of either

training modality, performed five times per week, resulted in decreased expression of these receptors, which was associated with improved beta cell function and increased serum insulin levels. These findings align with genetic studies highlighting the critical role of melatonin and its receptors in pancreatic insulin synthesis, as increased melatonin receptor expression has been linked to diminished insulin transcription and production in diabetic rats (7,12). Additionally, variants in *MTNR1A* have been implicated in gestational diabetes (11) and other conditions related to impaired insulin synthesis (12).

In this context, some other studies have indicated that *MTNR1A*, another melatonin receptor, is expressed independently of *MTNR1B* in pancreatic beta cells 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 is associated with decrease in insulin synthesis by affecting insulin transcription signaling pathways (32). 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 (33). An inverse relationship between serum levels of melatonin and insulin has been reported (34), and this relationship is much more evident in T2DM rats (35).

In vitro evidence has revealed that the inhibitory effect of melatonin on insulin transcription in pancreatic cells is mediated by *MTNR1B* receptors and a decrease in MAPK activity-dependent signaling pathways, such that increased melatonin and overexpression of *MTNR1B* lead to a decrease in MAPK activity-dependent signaling pathway, which ultimately leads to a reduction in insulin transcription and synthesis in pancreatic beta cells (36).

It has also been noted that melatonin inhibits glucose-dependent insulin synthesis and

secretion in beta cells (37). Thus, following the silencing of *MTNR1B*, the inhibitory effect of melatonin on insulin transcription and insulin gene expression in beta cells is reduced (36). The binding of melatonin receptors to  $G_{i\alpha}$  proteins on the one hand (38) and also the reduction of melatonin protein by reducing or inhibiting the production of cAMP and protein kinase A (PKA) in pancreatic beta cells lead to a decrease in insulin secretion (7).

It also showed that the association of the *NEUROD1* gene with *MTNR1B* risk variants, especially *MTNR1B* rs10830963, leads to increased *MTNR1B* mRNA expression, which leads to increased melatonin transcription and signaling in pancreatic cells, and its increase, through a decrease in cAMP, leads to decreased insulin secretion from the pancreas, which ultimately leads to increased fasting glucose and the risk of T2DM (39). In conclusion, based on the results of our study and citing the effective role of melatonin and its receptors in the pancreas on insulin gene transcription and expression as well as beta cell function, which have been mentioned in previous studies, the increase in beta cell function and insulin in response to both resistance and interval training in our study can be attributed to the decrease in melatonin and the expression of *MTNR2A* and *MTNR1A* receptors in pancreatic tissue in response to these training methods.

On the other hand, the study findings revealed that long-term exercise training results in these changes regardless of the type of exercise, as the study findings indicate no difference in the effectiveness of interval and resistance training on the aforementioned variables. In this context, some previous studies have also indicated that exercise training leads to increased beta cell function through both hypertrophy and hyperplasia in beta cells (25).

## Conclusions

Interval and resistance training lead to a decrease in fasting glucose and serum insulin

in T2DM rats. Based on evidence supporting the effective role of melatonin and its receptors in the pancreas on insulin transcription and synthesis, the increase in insulin may be attributed to a reduction in melatonin and the expression of MTNR2A and MTNR1A in pancreatic beta cells in response to these training methods. So that, the findings revealed that, regardless of the type or method of training, both interval and resistance training affect this process and there is no difference in their effectiveness. Despite these findings, further investigation at the cellular and molecular levels is necessary to elucidate the primary mechanisms underlying this alteration in response to exercise training.

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### Conflict of Interest

No conflict of interest.

### Author contributions

H.M: Conceptualization, Project administration, Methodology, Investigation, collecting the data, Writing-Review & Editing. S.K: collecting the data. Methodology, Investigation, Writing-Review & Editing. S.D.G: Formal Analysis, Investigation, Writing-Review & Editing.

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