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Effects of two types of exercises on MCT1 and GLUT4 expression in visceral white adipose tissue in type I diabetic rats

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White adipose tissue plays an important role in controlling the body's metabolism. In type I diabetes mellitus (T1DM), the function of this tissue is severely impaired. The beneficial effects of exercise have been shown in this condition. In this study, we investigated how exercise can benefit on T1DM. Thus, we studied the effects of moderate-intensity endurance training (MIET) and high-intensity interval training (HIIT) on MCT1 and GLUT4 levels in visceral white adipose tissue (vWAT) of T1DM rats. Twenty-eight male rats were divided into four groups: control, T1DM, T1DM+HIIT, and T1DM+MIET. The expression of MCT1 and GLUT4 mRNAs was evaluated in vWAT after 12 weeks of training. The mRNA levels of MCT1 and GLUT4 decreased in T1DM but increased in both the exercised groups. The effects of HITT and MIET on these genes were similar. MIET and HIIT led to increasing levels of MCT1 and GLUT4 mRNA in white adipose tissue. This can probably improve adipose tissue health and ultimately glucose homeostasis in T1DM.

Keywords: Diabetes mellitus, Endurance training, Exercise, Glucose transporter, Lactate transporter

Type 1 diabetes mellitus (T1DM) is an autoimmune disease characterized by a lack of insulin production due to the destruction of the beta cells of the islets of Langerhans in the pancreas[1]. Although the pathophysiology of type 1 diabetes may seem simple, nowadays we know that it is the result of a complex interplay between several factors and despite advances in treatment and management of these patients, glycemic control in most of them is not optimized[2].

Adipose tissue is the central organ in lipid and glucose metabolism and also produces many hormones and cytokines[3]. Lactate production from glucose and its release has recently been identified as a new function of adipose tissue. It has been shown that even in the presence of oxygen, white adipose tissue produces high amounts of lactate[4,5]. Lactate, as the end product of glycolytic metabolism, mediates the completion of carbohydrate oxidation through oxidative phosphorylation[6]. Lactate released from adipose tissue is later oxidized in other tissues or used in the hepatic gluconeogenesis[7]. Furthermore, it can act as a signaling molecule[8].

Lactate transport is one of the main functions of adipocytes. Monocarboxylate transferases (MCTs) are a family of transporters that carry lactate, pyruvate, ketone bodies, ketoacids, and some drugs across the plasma membrane (15 of Baily). In most cells, these MCT1 and MCT4 are expressed and they are the main lactate influx an efflux pathway. MCT1 has a high affinity while MCT4 has a low affinity for lactate[9,10]. MCT1 plays an important role in the uptake of lactate from adipose tissue and its transport across the cell membrane into the bloodstream[11]. It was shown during maturation of preadipocytes into adipocytes, MCT1 expression and thus lactate flux increases[12]. In addition, it is considered as a marker of browning of adipocytes[13].

Glucose is the body's main source of energy. Adipose tissue has the highest percentage of glucose stored in the form of glycogen and triglycerides[14]. There are several glucose transporters in humans called GLUT1 to GLUT12[15]. GLUT4 was cloned for the first time in the late 1980s. It is expressed in skeletal muscle, cardiac muscle, and adipose tissue and is responsible for glucose transport into these tissues[15]. It is the most abundant glucose transporter

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in adipose tissue. Deletion of GLUT4 in adipose tissue can lead to insulin resistance in both muscle and liver[16,17]. One possible explanation for this is the elevated levels of retinol-binding protein 4 or other adipokines in the bloodstream[18]. Interestingly, individuals with obesity and type 2 diabetes have been found to have reduced expression of GLUT4 in their adipose tissue[19,20]. On the other hand, the overexpression of GLUT4 in adipose tissue has been shown to improve glucose tolerance and increase insulin action[21,22]. Furthermore, this overexpression results in higher levels of novel lipids that have antidiabetic effects[23]. GLUT4 is insulin-dependent and its expression increases in response to insulin[24] Thus, in T1DM that the insulin is absent its expression can decrease and thus the metabolic function of adipose tissue can disrupt.

Some investigations in T1DM patients have shown that increased physical activity can lead to increased life expectancy and reduced risk of complications[25,26]. Desire to do more intense exercise is increasing. Studies have shown that although all exercises improve glucose tolerance, their effects on glucose kinetics are different[27]. Therefore, it is possible that the beneficial effects of exercises with different intensities are exerted through different mechanisms.

Considering the importance of adipose tissue in controlling the body's metabolism and the beneficial effects of exercise on diabetes, and to better understand the underlying mechanisms, here, we investigated the effect of two types of exercise [moderate-intensity endurance training (MIET) and high-intensity interval training (HIIT)] on the expression of MCT1 and Glut4 mRNA in adipose tissue of rats with type 1 diabetes.

Materials and Methods

Animals and diabetes induction

Twenty-eight male Wistar rats (250-300 g) were purchased from Kerman Physiology Research Center and divided into 4 groups (7 in each group). Control (Con Gr. I); type 1 diabetes (T1DM Gr. II); Diabetes + Moderate Intensity Endurance Training (T1DM + MIET Gr. III); and Diabetes + High-Intensity Interval Training (T1DM + HIIT Gr. IV). They were kept under a 12 h light/dark cycle, with free access to standard rat chow and water. All experiments were performed in accord with the national guidelines for animal studies. The study was approved by the Ethics Committee of the Kerman University of Medical Sciences (IR.KMU.REC.1399.563). To induction type 1 diabetes (T1DM) in groups 2 to 4, a single dose of STZ (60 mg/kg) was intraperitoneally injected. In controls, the equivalent volume of the vehicle was injected. Rats with fasting blood sugar (FBS) more than 300 mg/dL (measured by Accu Chek Active, Germany) were included in the study. The body weight and FBS of animals were measured weekly.

Exercise protocol

The exercise began one week after the induction of diabetes and lasted for 12 weeks 5 days a week Given that we had no dietary restrictions, the animals had free access to food and water during the entire period. They did not have access to food only during exercise training, which was between 9 a.m. and 12 a.m.

with a motor-driven treadmill. The first week of the MIET group consisted of 20 min running at speed of 15-20 m/min. After familiarization, the speed and duration of exercise increased up to 28 m/min for 60 min[28]. The first week of the HIIT group consisted of 10-20 min running at speed of 15m/min that gradually increased to 30 m/min. After familiarization, the treadmill exhaustion test was done. The HIIT protocol consisted of 6 (first week) to 12 (12^{th} week) steps. Each step was composed of a 2-min interval interspersed with 1 min of rest. In the first week the intensity of intervals was set at 70% of the peak speed reached in the exhaustion test and after that increased 10% each week[29].

Blood and tissue collection

After 24 hours of the last exercise session, animals were euthanized in deep anesthesia. Immediately, the abdominal adipose tissue (omental) was removed, immersed in liquid nitrogen, and stored at –80°C. Blood samples were collected to measure serum lactate levels.

MCT1 and GLUT4 mRNA evaluation

Relative expression levels of GLUT4 and MCT1 mRNA were analyzed using Step One Plus real-time PCR system (Applied Biosystems Corporation, Foster City, California, USA) and with 2X Master Mix Green with high ROXO (Ampliqon company, Denmark). Briefly, 50 mg of adipose tissue was taken and homogenized. The total RNA was extracted using EZ-10 RNA Mini-Preps (Bio Basic, Canada) and according to the RNA kit protocol. With 1000 ng of RNA, cDNA synthesis was performed using cDNA Synthesis kit (REVERT AID RT KIT (K1621), THERMO Fisher Company, Germany-Darmstadt) and according to the kit protocol. The following

primers were used: MCT1 forward: GCTGTCATGT ATGCCGGA, MCT1 reverse: CAATCATAGTCAG AGCTGG[30], GLUT4 forward: GGCCATGAGCGAT GAGTTTC, GLUT4 reverse: GGCGGAGGATTGTT GAGATG[30], 18S forward: GTCGGCATCGTTTATGG TCG, 18S reverse: GTTGGTTTTCGGAACTGAGGC[30]. The temperature conditions were as follows: initial denaturation step at 95°C for 10 min, 40 cycles of denaturation at 95°C for 15 s, and annealing for 30 s. MCT1 and GLUT4 mRNA expression levels were normalized in relation to 18S mRNA using CT and $2^{-\Delta\Delta CT}$ method. We used 18S as an internal control.

Statistical analysis

Statistical analysis was performed using SPSS 20. Data are presented in the Figures and Table as the means ± SEM. One-way ANOVA test followed by Tukey's *post-hoc* analysis for comparison among the studied groups. To investigate the relation between body weight and serum FBS, linear regression was used. All *P* values were two-tailed, and $P < 0.05$ was considered as the significance level.

Results

FBS, serum lactate levels, and body weight

Both exercises led to a significant decrease in FBS after 12 weeks. Animal body weights at the biggening of the experiments weren't significantly different. But after 12 weeks, all diabetic groups had significantly lower weight than control group. Body weight in T1DM+MIET group was significantly more than T1DM group at week 12. In addition, the weight of all diabetic groups was lower at the end of the studies than in the first week, which indicates that diabetes leads to weight loss. Serum lactate levels in T1DM rats were significantly more than control group at the end of experiments. But, in exercise groups it was similar to control group. (Table 1).

Table 1 — Blood glucose and lactate levels and weights of animals in different groups

	Con	T1DM	T1DM + MIET	T1DM + HIIT
FBS				
wk 1	64±2.1	484±25.7***	478±19.1***	496±16.3***
wk 12	62±2.0	410±23.3***	170±23.5***	209±19.7***
Lactate wk 12	1.7±0.15	2.3±0.15*	1.8±0.17	1.7±0.18
Weight				
wk 1	248±12.6	247±13.5	252±5.2	250±4.1
wk 12	305±11.7	197±10.5***	234±20.6**#	215±6.2***

[Data are expressed as mean ± SEM. *P <0.05 *vs*. control group, **P <0.01 *vs*. control group, ***P <0.001 *vs*. control group, #P >0.05 *vs*. T1DM group, Con: Control, T1DM: type 1 diabetes mellitus, MIET: moderate-intensity exercise training + T1DM, HIIT: high-intensity interval training+ T1DM]

MCT1 and GLUT4 mRNA expression

MCT1 mRNA level in vWAT of T1DM group significantly downregulated compared to control (non-diabetic) group. Both two types of exercises (MIET and HIIT) upregulated its mRNA level in vWAT. The MCT1 mRNA levels in T1DM+MIET and T1DM+HIIT groups significantly upregulated (P <0.05) compared to both the T1DM group and the control group. (Fig. 1A)

The levels of GLUT4 mRNA downregulated significantly in the T1DM group compared to control (P <0.01). It upregulated significantly in MIET and HIIT groups *vs*. T1DM and non-diabetic rats (P <0.05). (Fig. 1B)

Correlation between body weight and FBS

Weight improvement observed in MIET+T1DM was not seen in HIIT+T1DM. Also, tendency to increase in blood sugar of animals in HIIT+T1DM

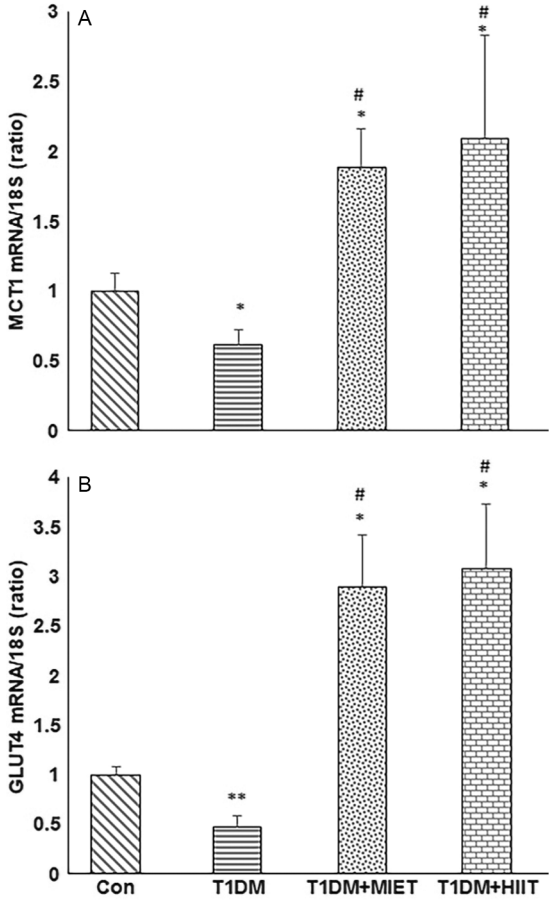

Fig 1 — (A) MCT1 mRNA; and (B) GLUT4 mRNA expression in the visceral white adipose tissue of studied groups (n=7). [*P <0.05 *vs*. control group, **P <0.01 *vs*. control group, #P>0.05 *vs*. T1DM group. [Con: Control, T1DM: type 1 diabetes mellitus, MIET: moderate-intensity exercise training + T1DM, HIIT: high-intensity interval training+ T1DM]

was lower than MIET+T1DM. Hence, linear regression was performed to determine if there was a relationship between weight and blood sugar. The results showed that there was a significant relationship between them (P <0.001, r=0.644). Regression formula:

$$FBS_{(week\ 12)} = 627.8 - (1.718 \times Weight_{(week\ 12)}).$$

Discussion

Type 1 diabetes significantly reduced the expression of MCT1 and GLUT4 genes in white adipose tissue of Wistar rats. Both HIIT and MIET led to a significant increase in the expression of these genes.

Having healthy adipose tissue is essential for maintaining glucose homeostasis. Adipokines secreted from adipose tissue under normal and healthy conditions maintain glucose homeostasis, whereas inflamed adipose tissue secretes hyperglycemic adipokines, which ultimately leads to a vicious cycle of hyperglycemia and inflammation[31]. In T1DM patients, the absolute absence of insulin leads to severe fat loss and adipose tissue degeneration. On the other hand, due to the general inflammation, adipose tissue is also inflamed[31,32]. Thus, in most T1DM patients, little adipose tissue remains which are dysfunctional and can lead to worsening of the disease by producing hyperglycemic adipokines and inflammatory cytokines. Therefore, maintaining the health of adipose tissue in these patients is very important.

Lactate is an important mediator in cell bioenergetics[33]. There is an interaction between white adipose tissue and lactate. White adipose tissue can convert significant amounts of metabolized glucose to lactate[34]. Lactate, on the other hand, can regulate the biology and metabolic activity of adipocytes through autocrine and paracrine pathways. Lactate similar to insulin inhibits lipolysis in adipose tissue. Lactate transfer in white adipose tissue cells is mediated by MCT1[35]. In this study, we showed that the expression of the MCT1 gene (the main transporter of lactate in adipose tissue) is significantly increased by HIIT and MIET in T1DM rats. It has been shown the lactate flux through this transporter is bidirectional. This bidirectional flux is involved in fine-tuning the metabolic activity of adipocytes according to extracellular metabolic conditions and thus efficient glucose utilization. Furthermore, MCT1 can be considered as an indicator of adipocytes' beigeing[35]. Some studies have shown that increasing the production of some myokines during exercise can induce adipocytes' beigeing[36]. Beige adipocytes are batches of brown-like adipocytes in WAT[37]. It has been shown that brown adipose tissue transplantation to T1DM mice led to normal blood sugar, reduced tissue inflammation, and normal glucose tolerance, which was associated with increased IGF-1 levels suggesting that healthy adipose tissue could improve glucose homeostasis by increasing IGF-1 production[38]. Therefore, it is possible that HIIT and MIET exert their beneficial effects on adipose tissue by producing myokines and through mechanisms dependent on increasing MCT1 expression and adipocytes beigeing (batches of brown-like adipocytes in WAT).

An essential step in lipid synthesis is the entry of glucose into cells and the production of triglycerides[39]. GLUT4 is the most abundant glucose transporter in adipose tissue. Its K_m of glucose is in the physiological range and is about 5 mmol / L, so it is the rate-limiting stage in glucose transfer[40]. Therefore, an increase in GLUT4 will be associated with an increase in glucose uptake and fat production in adipose tissue. Increased adipose tissue can be accompanied by an increase in adipokines involved in glucose homeostasis, and thus a decrease in blood glucose. We showed that GLUT4 expression decreased in the vWAT of the T1DM group, but increased in MIET and HIIT groups. Therefore, increased expression of GLUT4 in vWAT may be one of the mechanisms of beneficial effects of exercise in type 1 diabetes. This is in line with other studies in type 2 diabetes that showed exercise can increase GLUT4 in adipose tissue[41]. Furthermore, it has been shown that transgenic mice with increased GLUT4 expression in their adipose tissue are more sensitive to insulin and have better glucose tolerance. Conversely, GLUT4 knockout in mice was associated with insulin resistance and glucose intolerance[20,42].

The animal body weights at the beginning of the study were similar in the groups, but at the end of the study, they are significantly different. After 12 weeks, the weight of the animals in the diabetic groups decreased. However, weight loss was lower in the MIET group. As mentioned above insulin is essential for lipogenesis. In type 1 diabetes, lipogenesis is inhibited due to a lack of insulin[43]. Exercise by increasing GLUT4 can increase the entry of glucose into cells and thus increase lipogenesis in adipocytes. In addition, due to the increased expression of MCT1

in adipose tissue, the exchange of lactate through adipocytes is also increased. Lactate in a paracrine manner can bind to GPR81 and inhibit lipolysis by reducing cAMP in adipocytes. The improvement in weight loss observed in the MIET group was not observed in the HIIT group. In T1DM patients, HIIT exercise can lead to a greater increase in plasma norepinephrine than MIET exercise[44]. It is possible that norepinephrine prevented weight gain in this group by increasing lipolysis in adipose tissue.

In cardiovascular patients, it has been shown that high-intensity exercise has a more beneficial effect than moderate exercise[45]. In our study, the expression of MCT1 and GLUT4 in adipose tissue and reduction of blood glucose were similar in HIIT and MIET groups but the weight of animals at the end of the study was lower in HIIT than MIET. Furthermore, linear regression showed that there was a significant reverse correlation between FBS and weight at the end of the study. Thus, it is possible that if HIIT is adjusted so that the weight is kept within the normal range, it can have a greater effect than MIET exercise.

The limitation of our research was that we did not examine the protein levels of these genes. It is true that protein expression can change at the post-translational level, but it has been shown that there is a good relationship between gene and protein expression in conditions where mRNAs express differentially[46]. Another limitation of our study was that we did not examine food consumption pattern in animals. Although this issue is important, but our purpose of this study was to investigate the impact of exercise on MCT1 and Glut4 levels in vWAT rather than specifically analyzing food consumption patterns.

Conclusion

The above study has demonstrated that both moderate-intensity endurance training (MIET) and high-intensity interval training (HIIT) can upregulate MCT1 and GLUT4 mRNA expression in visceral white adipose tissue (vWAT). This can improve vWAT health in type I diabetes mellitus (T1DM) rats. It suggests that the increased expression of these genes could be one of the mechanisms yielding beneficial effects of exercise in T1DM, particularly MIET.

Ethical approvement

The study was approved by the Ethics Committee of the Kerman University of Medical Sciences (IR.KMU.REC.1399.563).

Conflict of interest

Authors declare no competing interests.

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