



Aerobic Exercise Ameliorates Glycemic Control by Improving Beta Cell Function regardless of Insulin Resistance in Diabetic Rats

Running title

Aerobic training and glycemic profile in diabetes

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ABSTRACT

Objective: Improving glycemic profile in diabetic patients is rooted in several metabolic, hormonal, and genetic factors. The aim of this study was to determine the effect of aerobic training on blood glucose level in diabetic rats with emphasis on insulin resistance and beta cell function.

Methods: For this purpose, 14 male Wistar rats were divided into two aerobic training (running on a treadmill for 10 weeks, five sessions per week, n=7) and control (n=7) groups after induction of type 2 diabetes by intraperitoneal injection of nicotinamide and streptozotocin (STZ). Fasting blood glucose, serum insulin level, insulin resistance, and beta cell function in both groups were measured after the last exercise session and compared by independent T test at a significant alpha level of less than 5% ($p < .05$).

Results: Despite no change in insulin resistance ($p = .458$), aerobic training resulted in a significant decrease in fasting blood glucose ($p < .001$) as well as a significant increase in serum insulin level ($p < .001$) and beta cell function ($p = .011$) compared to the control subjects.

Conclusion: Despite no change in insulin function in target tissues, the improvement in glycemic profile of type 2 diabetic rats in response to aerobic training may be attributed to increased synthesis or secretion of insulin, or in other words, increased beta cell function. Understanding the mechanisms responsible for altering insulin function at cellular levels in response to exercise requires further studies in this area.

Keywords: Aerobic exercise, Glycemic profile, Insulin resistance, Beta cell function, Type 2 diabetes

Introduction

Type 2 diabetes is caused by glucose intolerance due to an imbalance between insulin reserves and demand (1). Researchers have found that type 2 diabetes is the most common metabolic disorder caused by complex interactions between hormonal, genetic, and environmental factors that may affect lipid and glucose metabolism, leading to impaired hepatic and muscular insulin function, insulin secretion, adipose tissue metabolism, and whole body lipolysis as well as possibly metabolic defects in other organs of the body (2). Meanwhile, although some transcription factors regulating protein or gene expression affect insulin secretion by pancreatic cells or glucose synthesis through hepatic gluconeogenesis, others affect insulin signaling pathways, responsible for glucose and fat homeostasis, in target tissues such as adipose and muscle tissues.

Insulin resistance is a pathological condition in which cells fail to normally respond to insulin hormone, which often occurs in the presence of obesity, high blood pressure, high cholesterol, and type 2 diabetes (1). Insulin resistance due to impaired transmission of insulin signals in target tissues is a common cause of type 2 diabetes. Adipose tissue plays an important role in insulin resistance through the irregular production and secretion of a number of inflammatory or anti-inflammatory cytokines. Thus, increased secretion of TNF- α or resistin as inflammatory cytokines or decreased secretion of adiponectin as an anti-inflammatory cytokine in adipose tissue increases insulin resistance (3). On the other hand, in addition to reduced insulin function in target tissues, pancreatic beta cell damage also plays a key role in the pathogenesis of this disease (4).

But the exact mechanisms by which beta cell function is reduced in these patients have not yet been fully understood. Among the factors that may be involved in this disorder are insulin receptors regulating beta cell function and beta cell mass (5). Therefore, longitudinal studies have always emphasized beta cell dysfunction as an important and influential factor in the prevalence and severity of type 2 diabetes. Based on the available evidence, researchers are always looking for ways to improve insulin function in

target tissues or increase insulin synthesis and secretion in the pancreas in these patients.

In the meantime, the role of exercise and physical activity has always been important. It has been hypothesized that increased cardiovascular fitness leads to increased insulin function while decreasing body fat mass (6); however, some other studies have reported that increased cardiovascular fitness affects insulin function regardless of changes in body weight and target tissue composition (7).

A significant reduction in insulin resistance by interval training was reported in a study by Racil et al. (2013) (8). Lopes et al. (2016) also attributed the decrease in blood glucose level after 12 weeks of combined training to the reduction in insulin resistance in response to exercise (9). However, Donges et al. (2013) reported a significant decrease in fasting blood glucose after 12 weeks of aerobic training with no change in insulin resistance (10). On the other hand, while Maltais et al. (2016) reported no change in serum insulin level after prolonged resistance training (11), Eizadi et al. (2017) based on their findings pointed out that decreased fasting blood glucose in response to aerobic training was due to increased serum insulin level and beta cell function (12). Based on the evidence, there is a discrepancy regarding the association between changes in blood glucose level and insulin function in target tissues or insulin secretion by pancreatic cells in response to various training methods, and no general consensus has yet been reached. Regarding this contradiction, the present study aimed to investigate the effect of aerobic training as one of the common methods of exercise on both insulin resistance and beta cell function as well as on blood glucose and insulin levels in type 2 diabetic rats.

Materials and Methods

In this experimental study, 14 male Wistar rats (aged 10 weeks, weighting 210 ± 20 g) were purchased from Pasteur Institute, Tehran, Iran. The type 2 diabetes was induced by intraperitoneal injection of nicotinamide and streptozotocin (STZ) in all rats, which were then randomly assigned into aerobic (10 weeks of aerobic exercise, five sessions per week) and

control (no exercise) groups. Rats under study were kept in Plexiglas cages with mesh door and 25×27×43 cm dimensions under controlled light conditions (12 hours in light and 12 hours in darkness) at 22 ± 3 °C and 30 to 50% humidity with free access to water and food. This study was approved by the Ethics Committee of Islamic Azad University, Semnan Branch, Iran (Ethic Code: IR.IAU.SEMNAN.REC.1400.001).

Type 2 diabetes induction: Intraperitoneal injection of nicotinamide and STZ was performed to induce type 2 diabetes in rats. At first, nicotinamide solution at a dose of 110 mg/kg of body weight was injected intraperitoneally. After 15 minutes, freshly prepared STZ solution in citrate buffer (pH=4.5) at a dose of 60 mL per kg of body weight was injected intraperitoneally (10). One week after diabetes induction, fasting blood glucose (10-12 hours of overnight fasting between 8 pm to 9 am) was measured, and blood glucose level between 150 and 400 mg/dL was considered as the development of type 2 diabetes in mice (10).

Training protocol: The aerobic group participated in an aerobic training program. The training program was performed by running on a treadmill for 10 weeks, five sessions per week, with a gradual increase in speed (18 to 26 meters per minute) and time (10 to 55 minutes)(12). The control group did not participate in the training program during the course. All rats were dissected 48 hours after the last training session.

Table 1. Aerobic exercise program by week and running speed in aerobic group

Exercise Sessions (Weeks)	Running Speed (m/min)	Running Time (min)
1	18	10
2 - 3	20	20
4 - 5	22	30
6 - 7	22	40
8 - 9	24	50
10 - 12	26	55

Blood sampling and biochemistry

About 48 hours after the last training session (10-12 hours of overnight fasting between 8 pm to 9 am), rats in both groups were anesthetized by intraperitoneal injection of a mixture of 10% ketamine at a dose of 50 mg/kg and 2% xylosine at a dose of 10 mg/kg. The animal's chest was

then dissected, and a blood sample was taken directly from the animal's heart. Glucose concentration was measured by glucose oxidase technology (Pars Azmoun-Tehran) as an enzymatic method. Serum insulin level was measured by ELISA method in accordance with the standards of the commercial kit (Demeditec Diagnostic insulin ELIZA) made in Germany. Fasting blood glucose and insulin were measured and used to calculate insulin resistance (HOMA-R) and beta cell function (HOMA-B) (13, 14).

$$\text{HOMA-R} = \frac{\text{Fasting Insulin } (\mu\text{U/ml}) \times \text{Fasting Glucose (mmol/l)}}{22.5}$$

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

Statistical analysis: Shapiro-Wilk test was used to ensure the normal distribution of data. Comparison of variables between the two groups was performed using independent t-test. All statistical analyzes were performed using SPSS/Win software Version 22. Changes less than 5% were considered as significant.

Results

Body weight changes in both groups before and after the exercise intervention are summarized in Table 2. The results of independent t-test showed that there was no significant difference in body weight between the two groups before the study ($p=.166$). On the other hand, intragroup changes investigated using t-test showed that body weight at the end of the study in both aerobic ($p<.0001$) and control ($p<.0001$) groups significantly increased compared to the beginning of the study. Also, the results of independent t-test indicated that body weight in the aerobic group was lower than in the control group after the intervention ($p<.0001$).

Table 2. Body weight (g) before and after the intervention in the study groups

Group	Pre-Intervention	Post-Intervention	Sig. (Intragroup)
Control	220 ± 3.34	254 ± 5.96	< .0001
Aerobic	225 ± 2.61	241 ± 2.24	< .0001
Sig. (Intergroup)	.166	< .0001	----

On the other hand, there was no significant difference in insulin resistance index between the aerobic and control groups. In other words, aerobic training caused no significant change in insulin resistance index in the aerobic group compared to the control group not participating in the exercise program ($p=.458$). However, fasting blood glucose in the aerobic group was significantly lower ($p<.0001$), and serum insulin

level was significantly higher ($p<.0001$) compared to the control group. On the other hand, aerobic training was associated with a significant increase in beta cell function in the aerobic group compared to the control group ($p=.011$) (Table 3).

Table 3. Determinant markers of type 2 diabetes in the aerobic and control groups			
Variable	Control Group	Aerobic Group	Sig.
Fasting glucose (mg/dL)	294 ± 11	240 ± 14	< .0001
Serum insulin (μU/mL)	4.06 ± 0.21	5.11 ± 0.25	< .0001
Insulin resistance (HOMA-IR)	2.95 ± 0.12	3.03 ± 0.19	.458
Beta cell function (HOMA-BF)	6.34 ± 1.14	10.43 ± 2.21	.011

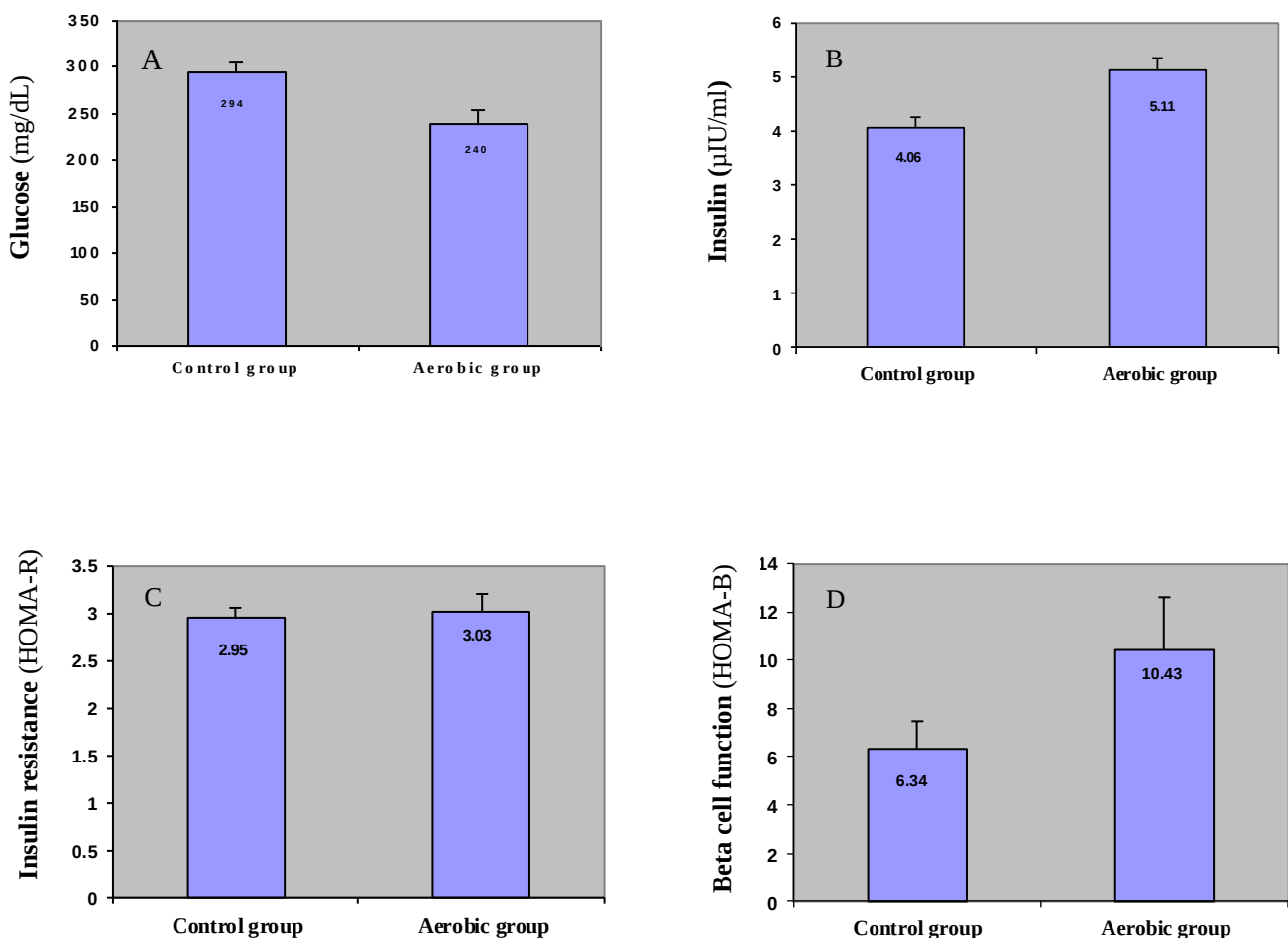


Figure 1: Change in fasting glucose (A), Serum insulin (B), Insulin resistance (C) and Beta cell function. Compared to control subjects, aerobic training resulted in significant decrease in glucose ($P < 0.0001$) and increase in serum insulin ($P < 0.0001$) and beta cell function ($P = 0.011$) without change in insulin resistance ($P = 0.458$)

Discussion

Decreased fasting blood glucose along with increased serum insulin level and beta cell function in response to aerobic exercise were the main findings of the present study, while aerobic training was not associated with a significant change in insulin resistance. In other words, a 10-week aerobic training intervention resulted in a significant decrease in fasting blood glucose and a significant increase in serum insulin level and beta cell function in type 2 diabetic rats with no significant change in insulin resistance compared to the control group in which animals did not participate in exercise. In this regard, although some researchers have reported no significant changes in insulin resistance, serum insulin level, or beta cell function (10, 11), in other studies by Eizadi (2017) and Rashidi (2019), increased serum insulin level and beta cell function and decreased insulin resistance in response to exercise have been reported (12, 15). Despite the presence of evidence for the effect of aerobic exercise on beta cell function, in a study by Karstoft et al. (2014), four months of walking interval training, in five 60-min sessions per week, significantly increased insulin sensitivity in type 2 diabetics but had no effect on insulin secretion (16). Contrary to the findings of the present study, in a study by Omid et al. (2017), aerobic training for eight weeks improved insulin resistance without affecting beta cell function in obese diabetic women (17). It should be noted that the effect of exercise training on insulin function in target tissues is partly mediated by a decrease in body fat mass, and this effect is often felt in obese subjects. The difference between the Omid's study and the present study results could be due to the difference in fat mass and body weight of the participants, as the study population in Omid's study was obese women. Exercise, especially long-term exercise, is associated with body weight and fat mass loss. Type 2 diabetes in the present study was caused by direct destruction of pancreatic cells rather than insulin resistance due to weight gain or a high-fat diet. Therefore, the discrepancy in the findings of the mentioned study and ours may be attributed to the type of population studied.

In type 2 diabetes, insulin secretion increases in response to insulin resistance, but this response

does not last for a long time. This type of diabetes affects all people with insulin resistance and usually a relative (not absolute) insulin deficiency (18). While the underlying causes of this type of diabetes have not yet been fully understood, insulin resistance is one of the primary causes of this type of diabetes rather than beta cell dysfunction (19). Insufficient insulin produced by the pancreas to maintain the normal function of the body's cells and impaired use of insulin by the body's cells for unknown reasons are the main features of this type of diabetes. In response to increased insulin resistance, insulin secretion by beta cells increases. This continuous adaptation eventually leads to the development of hyperinsulinism and a gradual increase in insulin resistance, especially in type 2 diabetic patients (20). However, it should be noted that the period of adaptation of beta cells to the phenomenon of insulin resistance in diabetic patients is much shorter than in non-diabetic obese people and leads to the inability of these cells to adequately secrete insulin (21). For example, one study found that beta cell mass in type 2 diabetic patients was 40 to 60% lower compared to the non-diabetic group (21).

According to a prospective study by the British Diabetes Association, beta cell function is reduced by 50 to 60% in type 2 diabetes, and the reduction in these cells function dates back to about 10 to 12 years before the onset of hyperglycemia (22). Several studies have reported that in the absence of beta cell dysfunction, no evidence of hyperglycemia is observed (23).

Increased activity of beta cells to overcome insulin resistance in individuals genetically unable to compensate for insulin resistance due to insufficient secretion of excess insulin, leads to the phenomenon of glycolipid toxicity of membrane lipid molecules. Continuation of these conditions gradually leads to a decrease in insulin gene expression and beta cell mass over time, depending on the severity of insulin resistance, resulting in increased levels of glucose and free fatty acids (23). Consistent with some previous studies (12, 15), aerobic exercise in the present study resulted in a significant increase in serum insulin level and beta cell

function in type 2 diabetic rats. In this regard, it could be mentioned that both diet and physical activity increase insulin secretion, while their functional mechanisms are independent of each other. Diet increases beta cell mass through hypertrophy to overcome insulin resistance, while exercise increases beta cell mass through hyperplasia, which is displayed as increased beta cell proliferation and reduced apoptosis (24). Beta cell mass expands by hyperplasia through increased replication and neogenesis via the recruitment of progenitors and hypertrophy to establish and sustain hyperinsulinemia, resulting in glycemic storage (25).

It has been suggested that changes in beta cell function are due to mechanisms such as changes in the stimulation threshold of insulin secretion in response to blood glucose level compared to other insulin stimuli such as arginine or glycine chlamydia, reduced or absence of the first phase of insulin secretion, prolongation of the secondary phase of insulin secretion, and gradual irreversible damage to cellular components of insulin secretion (23, 26).

Longitudinal studies in humans have clearly shown that beta cell function deteriorates over time and with age. There is some evidence showing that in the early stages or before the onset of diabetes, beta cell function decreases steadily but slowly by about 2% per year. After an increase in blood glucose or the development of hyperglycemia, the destruction or inability of beta cells significantly increases (18% per year), and this degradation in beta cell function could be visible even in the presence of treatment regimens (27,28). Imbalances in metabolic responses due to increased glucose and free fatty acids and increased beta cell degradation lead to apoptosis or cell death and do not appear to be improved by compensatory processes such as increasing beta cell mass to overcome insulin resistance. Finally, it is associated with a decrease in beta cell mass (29).

In the present study, 10 weeks of aerobic training was associated with improved glycemic profile in type 2 diabetic rats. However, it has been suggested that progressive aerobic exercise has more metabolic benefits than moderate aerobic exercise (30, 31). On the other hand, increased insulin secretion in response to long-term aerobic

training in humans and animal models with type 2 diabetes has also been reported by other researchers (32). Findings of a recent study showed that seven sessions of aerobic exercise led to a significant improvement in beta cell function in the elderly with impaired glucose tolerance (33); in this study, although increased beta cell function was not associated with changes in body weight and blood glucose concentration (33), but in another study, increased beta cell function was reported to be associated with decreased body weight, body fat percentage, blood glucose concentration, and TG (34). On the other hand, in a recent study, eight weeks of HIIT training increased the ability of the pancreas to secrete insulin to compensate for insulin resistance compared to baseline levels (16). Both diet and exercise increase insulin secretion, while their functional mechanisms are independent of each other according to scientific sources. To overcome insulin resistance, a high-fat diet increases beta cell mass through hypertrophy, while exercise increases beta cell mass through hyperplasia and reduces cell death (24).

Conclusion

Aerobic exercise improves glycemic profile without altering insulin resistance in type 2 diabetic rats. Based on the available evidence, this improvement may be attributed to an increase in serum insulin level due to improved beta cell function in response to aerobic exercise. However, understanding the mechanisms responsible for altering insulin function in target tissues in response to training interventions requires further cellular-molecular studies in this area.

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