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# Anti-Diabetic Effect of Long-Term Aerobic Training in Type 2 Diabetic Rats with Emphasis on Adiponectin Expression in Subcutaneous Adipose Tissue

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## ABSTRACT

**Background and objectives**: Clinical evidence has demonstrated the important role of adiponectin in insulin signaling pathways in target tissue. The aim of this study was to determine effects of aerobic training on insulin sensitivity, glucose level, and adiponectin expression in subcutaneous adipose tissue of type 2 diabetic rats.

**Methods:** Type 2 diabetes was induced in 14 male wistar rats by intraperitoneal injection of nicotine amide and streptozotocin. The rats were randomly divided into an exercise group (n=7) and a control group (n=7). The rats in the exercise group performed aerobic training in from of treadmill running, five sessions a week, for 12 weeks. Subjects in the control group did not perform any training. Glucose level, insulin level, insulin sensitivity, and adiponectin expression in subcutaneous adipose tissue were determined at baseline and 48 hours after the lasting training session. Independent t-test was used for comparing the variables between the study groups.

**Results**: Aerobic training resulted in a significant increase in serum insulin ($p=0.006$), insulin sensitivity ($p=0.003$), and adiponectin expression in subcutaneous adipose tissue ($p=0.037$) compared with the control group. In addition, the training caused a significant decrease in fasting glucose level compared with the control group ($p<0.001$).

**Conclusion:** Based on these findings, the decrease in blood glucose may be attributed to the improvement of adiponectin-dependent insulin signaling pathways in adipose tissue in response to aerobic training. However, more cellular-molecular studies are needed to understand the mechanisms responsible for these changes.

Keywords: Exercise, Adiponectin, Insulin, Diabetes Mellitus Type 2.

## INTRODUCTION

Diabetes mellitus is one of the common diseases worldwide that currently affects over 451 million people worldwide, and this number is expected to rise to 693 million by 2045 (1). By 2025, the incidence of diabetes in developing and developed countries is expected to increase by 70% and 42% compared to 1995, respectively (2). The global prevalence of type 2 diabetes was estimated to be 8.6% in adults over 20 years and 20.1% in adults over the age of 65 (3).

Among anti-inflammatory cytokines, adiponectin is one of the most important regulators of glucose metabolism and blood lipids (4,5). Adiponectin is a 244-amino acid protein that is mainly secreted by adipose tissue. In humans, adiponectin is encoded by the *AdipoQ* gene on the 3q27 arm of chromosome 17. The human adiponectin gene has three exons that start at exon 2 and end at exon 3 (6). While decreased expression in target tissues (e.g. adipose and muscle tissues) is associated with increased insulin resistance and hyperglycemia, its prolonged overexpression in adipose tissue leads to decreased insulin resistance or increased insulin sensitivity (7).

Plasma adiponectin concentration is directly related to high-density lipoprotein levels and decreased inflammatory markers, suggesting that this anti-inflammatory cytokine affects cardiovascular disease by regulating plasma lipids and reducing chronic inflammation (8). Lower levels of plasma adiponectin have a negative correlation with insulin resistance (9) and are associated with cardiovascular disease (10). In contrast, other adipokines, such as tumor necrosis factor alpha (TNF-α) and resistin, which induce insulin resistance in obese or type 2 diabetic individuals, decrease adiponectin expression (11). A decrease in plasma adiponectin induces the onset of diabetes and decrease in insulin sensitivity in insulin-resistant animal models (12-14). Low plasma adiponectin levels are associated with incidence of type 2 diabetes (13, 14). Low plasma adiponectin has also been observed in other diseases related to insulin resistance, such as cardiovascular disease (15) and hypertension (16). Bidulescu et al. (2020) reported that the effective role of leptin in glycemic control is mediated by decreased adiponectin expression in obese individuals (17). Decreased activity of adiponectin receptors leads to adiponectin dysfunction in insulin-resistant individuals (18). Increased peroxisome proliferator-activated receptor alpha (PPAR-α) is associated with improved adiponectin activity and its receptors in adipose tissue, resulting in increased insulin sensitivity (19). Numerous laboratory studies on independent insulin signaling pathways have reported the insulin-sensitizing effects of adiponectin (20-22). Increasing the expression or consumption of adiponectin agonists, independent of plasma insulin levels, lower blood glucose levels and improve insulin resistance in obese rats (20-23). On the other hand, decreased adiponectin expression leads to increased insulin resistance and hyperglycemia in mice on a high-fat diet (24).

In healthy young individuals, an acute or chronic aerobic exercise session does not appear to affect plasma adiponectin levels (25, 26). However, chronic endurance training increases plasma adiponectin in adolescents or adults (27), obese adults (28), Caucasian whites with impaired glucose tolerance, and patients with type 2 diabetes (29, 30). On the other hand, long-term aerobic training leads to overexpression of adiponectin types 1 and 2 receptors in adipose tissue and skeletal muscle of people with normal glucose tolerance and type 2 diabetic patients (29-31). On the other hand, some studies suggest that aerobic exercise does not alter adiponectin expression in obese individuals (32), insulin-resistant women (33), and type 2 diabetics (34). The inconsistency of findings in this regard may be related to multiple factors such as the study population, pathological conditions, type and intensity of training, duration of training, and type of tissue studied. In the present study, we evaluate effects of a course of aerobic training on glucose levels, insulin sensitivity, and adiponectin expression in subcutaneous adipose tissue of type 2 diabetic rats.

*Blood and tissue sampling*

Forty eight hours after the last training session and after 10 to 12 hours of fasting, the rats were anesthetized by i.p. injection of a mixture of ketamine 10% (50 mg/kg) and xylosine 2% (10 mg/kg). Next, the animals' chest was dissected and a blood sample was taken directly from the animal's heart to ensure minimal animal harm. Subcutaneous adipose tissue was sampled and washed in physiological serum. Then, the samples were

immersed in RNAlater fluid with a ratio of 20% for molecular experiments. Glucose concentration was measured by enzymatic colorimetric method with glucose oxidase (Pars Azmoun kit, Iran). Serum insulin was measured by enzyme-linked immunosorbent assay (ELISA) method using a commercial kit (Demeditec, Diagnostic insulin ELIZA, Germany).

Fasting glucose and insulin levels were used to calculate insulin sensitivity (37) using the following formula: Insulin sensitivity = 1 / [Log (fasting insulin) + Log (fasting Glucose)].

*RNA extraction and Real time–PCR*

RNA extraction was done using the QIAGEN commercial RNeasy mini kit (Cat No: Q74124, QIAGEN, Germany) (38). Adiponectin mRNA level was determined by Real-time PCR by Rotorgen 6000 system using One Step SYBR TAKARA kit (Cat No: BS584-BioBasic). Melting curve analysis was performed at the end of the PCR cycle to determine the validity of the expected PCR product. RNA polymerase II was used as a control gene. Adiponectin gene primer (target gene) and polymerase II as control gene (Housekeeping) were synthesized by Pishgam Biotech Co. (Iran). The Oligo 7 Primer Analysis Software was used to design the primers based on the adiponectin gene (Table 2).

**Table 1- Training time and intensity during the training period**

| Weeks | 1 | 2, 3 | 4, 5 | 6, 7 | 8,9 | 10, 11, 12 |
|---|---|---|---|---|---|---|
| Exercise time (min) | 10 | 20 | 30 | 40 | 50 | 55 |
| Speed of running (m/min) | 18 | 20 | 22 | 22 | 24 | 26 |

**Table 2- Sequence of the primers used in the real-time RT-PCR experiment**

| Genes | Primer sequence | Product size | T m | Gene Bank |
|---|---|---|---|---|
| Adiponectin | For: AGGATGTGAAAGTGAGCCTCTTC<br>Rev: GGAGGAGCATGGAGCCAGAG | 159 bp | 60 | NM_001191052.1 |
| RNA Polymrase II | For: ACTTTGATGACGTGGAGGAGGAC<br>Rev: GTTGGCCTGCGGTCGTTC | 164 bp | 60 | XM_008759265.1 |

*Data analysis*

Data were expressed as mean ± standard deviation. The Shapiro-vilk test was used to ensure normal distribution of data. Comparison of variables between the two groups was performed using independent t-test. All statistical analyses were performed using SPSS (version 16). P-values less than 0.05 were considered significant.

## RESULTS

Aerobic training significantly decreased body weight in the exercise group compared with the control group ($p<0.001$). Based on the results of the independent t-test, adiponectin expression in subcutaneous fatty tissue was significantly higher in the exercise group than in the control group ($p=0.037$) (Figure 1). Aerobic training caused a significant increase in serum insulin ($p=0.009$) (Figure 2) and insulin sensitivity($p=0.003$) (Figure 3) as well as a significant decrease in fasting glucose ($p<0.001$) (Figure 4) compared with the control group.

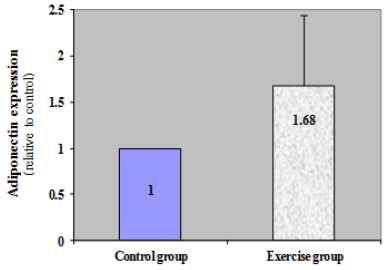


Figure 1. Comparison of adiponectin expression in the gastrocnemius muscle of rats in the exercise and control groups.

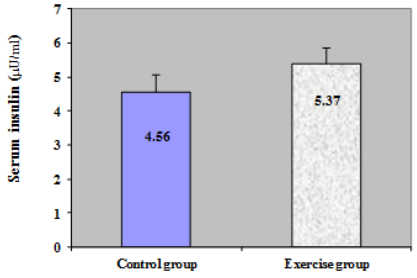


Figure 2. Comparison of serum insulin level between the aerobic training and control groups.

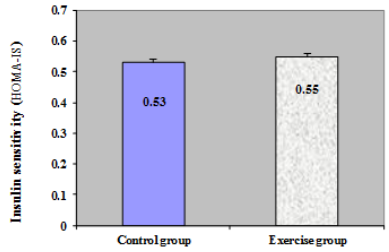


Figure 3. Comparison of insulin sensitivity between the aerobic training and control groups.

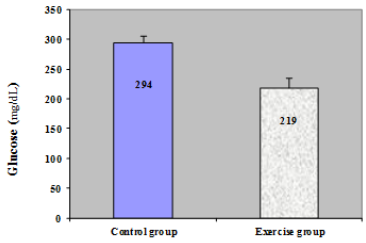


Figure 4. Comparison of fasting glucose levels between the aerobic training and the control

## DISCUSSION

Our results showed increased adiponectin expression in the subcutaneous adipose tissue of diabetic rats in response to aerobic training. In addition, aerobic training was associated with decreased glucose and increased serum insulin and insulin sensitivity levels. The decrease in glucose level and increase in serum insulin can be attributed to increased insulin sensitivity in response to aerobic training. On the other hand, the increased insulin sensitivity itself may be due to adiponectin overexpression in subcutaneous adipose tissue. The results of studies on glucose and insulin homeostasis changes in response to exercise training have been contradictory. Maltais et al. reported no change in insulin and glucose after four months of resistance training (39). In another study, 20 weeks of exercise, three to five sessions a week at intensity of 70% $VO_2$max did not change HbA1C level (40). However, Glans et al. reported a significant reduction in glucose after six months of aerobic and resistance trainings in diabetic patients (41). In another study, increased insulin secretion from isolated pancreatic islets was reported after eight weeks of aerobic swimming (42). In a study by Lopes (2016), decrease in blood glucose after 12 weeks of combined exercise was attributed to increased insulin sensitivity in response to exercise training (43). In the study of Abd El-Kader et al. (2013), the improvement of HbA1C in type 2 diabetic patients after 12 weeks of moderate-intensity aerobic exercise was attributed to insulin function in the target tissue or increased insulin sensitivity (44). Lee et al. also reported an increase in insulin sensitivity in response to 12 weeks of aerobic and resistance trainings (45). Based on the evidence, it can be concluded that the improvement of insulin sensitivity in our study may be attributed to the increased adiponectin expression in subcutaneous adipose tissue in response to aerobic exercise. However, Polak et al. reported no change in plasma levels of adiponectin and adiponectin expression in abdominal subcutaneous adipose tissue (biopsy) after 12 weeks of aerobic exercise in obese women (32). In a study by Dai et al., six months of endurance training, five sessions/week increased serum adiponectin and adiponectin expression in skeletal muscle but did not change adiponectin expression in adipose tissue of Sprague Davley rats (46). Francine et al. also reported increased insulin sensitivity and insulin function in the liver as well as increased plasma levels of adiponectin in response to 10 weeks of aerobic exercise in laboratory rats (47). Min et al. also reported an increase in protein levels and adiponectin expression in adipose tissue and a significant decrease in glucose and insulin resistance after eight weeks of aerobic training in rats fed a high-fat diet (48). Asilah et al. reported that 12 weeks of intermittent exercise resulted in a 2-fold increase in adiponectin 1 receptor expression and a 33% increase in insulin sensitivity in obese individuals (49). Mostowik et al. also reported an increase in serum adiponectin by 12 weeks of aerobic training (50). In a previous study, 12 weeks of aerobic training in form of 40 minutes of jogging/running (at 60-75% of maximum heart rate) resulted in a significant increase in adiponectin expression, insulin sensitivity, $VO_2$max, and serum adiponectin level which were accompanied with a reduction in abdominal obesity in young men. These findings suggest that increased serum levels and expression of adiponectin in blood mononuclear cells through exercise training can improve insulin sensitivity and glucose homeostasis (51).

Experimental evidence indicates a decrease in expression of adiponectin receptors in visceral adipose tissue of humans, experimental rats, and insulin-resistant redonts. This suggests adiponectin dysfunction due to decreased activity of its receptors in insulin-resistant animals (52, 53). In addition, it has been observed that activation of adiponectin agonists by PPARα in diabetic rats stimulates the function of adiponectin in adipose tissue by increasing the expression of adiponectin and its receptors, which results in increased insulin sensitivity (54).

Adiponectin is highly expressed in 3T3L1 adipocytes as a separate type of adipocyte from white and brown adipose tissues in mice. In adipocytes, C / EBP, PPAR, and sterol-binding proteins (SREBP-1C) are involved in accelerating adipogenesis and increasing lipid storage, and insulin-dependent glucose transport (55). Transgenic adiponectin overexpression in ob/ob mice leads to morbid obesity by reducing energy expenditure; however, it significantly improves glucose metabolism by reducing macrophages in adipose tissue and reducing TNF-α expression in adipocytes (7). Genetic studies have shown that adiponectin accelerates IRS1 and AKT phosphorylation by inhibiting p70S6K, resulting in increased insulin sensitivity (25). In parallel, adiponectin reduces the inhibitory effect of the mTOR/p70S6K on insulin signaling pathways by activating the LKB1/AMPK/TSC1/2 pathway (56). On the other hand, increasing the expression or consumption of adiponectin agonists independent of plasma insulin levels lowers blood glucose levels and improves insulin sensitivity (27, 29). Measurement of protein levels or adiponectin expression alone does necessarily indicate the effectiveness of exercise on insulin signaling pathways, and hormonal components such as IL-6, TNF-α and resistin or various transcription factors such as IRS-1, PPARγ, and FOXO1s are involved in this pathway. The lack of measurement of these factors is a limitation of the present study. Apart from the effective role of adiponectin's serum or expression levels, the decrease in glucose level of diabetic rats in our study may be attributed to an increase in serum insulin in response to exercise. Independent of insulin changes in target tissues such as adipose tissue and muscles, increasing serum insulin in response to exercise leads to lower blood glucose and improved glycemic profile. In our study, due to partial destruction of the pancreas by injection of low-dose STZ, the synthesis and release of insulin from pancreatic beta cells was certainly reduced. Studies have shown that continuous exercise can repair pancreatic beta cells, which results in increased synthesis and secretion of insulin (57). In this regard, Eizadi et al. reported an increase in serum insulin with a decrease in blood glucose in response to intermittent aerobic training in type 2 diabetic rats (58).

## CONCLUSION

Eight weeks of aerobic training improved glucose level and increased insulin sensitivity and adiponectin expression in subcutaneous adipose tissue of type 2 diabetic rats. Based on the effective role of adiponectin in insulin function, the decrease in glucose level can be attributed to the improvement of adiponectin-dependent insulin signaling pathways in subcutaneous adipose tissue in response to aerobic training. However, understanding the mechanisms responsible for glucose changes in response to exercise requires further cellular-molecular studies.

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## *DECLARATIONS*

### *Funding*

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### *Ethics approvals and consent to participate*

The study was approved by the Department of Exercise Physiology of Islamic Azad University, Borujerd Branch, Iran (ethical code: IR.IAU.B.REC.1399.010).

### *Conflict of interest*

The authors declare that there is no conflict of interest.

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