https://doi.org/10.46389/rjd-2025-1672
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2025; volume 32, issue 4, pages 417–426

Original Article

Simultaneous effect of interval training and lipoic acid on adropin and vascular endothelial growth factor-C in skeletal muscle of type 2 diabetic male rats

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Received: 29 May 2025 / Accepted: 9 September 2025

Abstract

Type 2 diabetes mellitus (T2DM) is a serious chronic metabolic disorder that has a significant impact on the health, quality, and life expectancy of patients as well as the health care system of communities. The study aimed to investigate the simultaneous effects of high-intensity interval training (HIIT), low-intensity interval training (LIIT), and lipoic acid (LA) on Adropin and vascular endothelial growth factor-c (VEGF-C) in the skeletal muscle of type 2 diabetic male rats. Twenty-one three-week-old diabetic male Wistar rats in seven groups were included in this study. An intense interval training program with a VO_2 max intensity (maximum oxygen consumption) of 85–90% and a low VO_2 max intensity of 65–70% VO_2 max was performed for six weeks. The LA supplement was administered orally once a day for 6 consecutive weeks at a dose of 20 mg/kg. At the end of the training period, the posterior skeletal muscle tissue of their legs was removed. Fasting blood glucose (FBG), insulin, Adropin and VEGF-C levels were measured. Our results showed that low-intensity interval training programs and high-intensity interval training programs alone and with LA supplementation significantly decreased and increased FBG and insulin, respectively (P<0.01). There was a significant increase in the levels of VEGF-C (P=0.001) and Adropin (P=0.001) compared to the diabetic control group (P<0.001). Performing interval exercises with low and high intensities, along with lipoic acid supplementation, played a significant role in increasing diabetes-modulating parameters.

Keywords: low interval training, high interval training, lipoic acid, adropin, vascular endothelial growth factor C, Type 2 Diabetes Mellitus

Introduction

In type 2 diabetes mellitus (T2DM), impaired insulin signaling and insulin resistance lead to increased hepatic glucose production, contributing to a global health crisis characterized by high prevalence and increasing incidence [1]. Exercise Training (ET) is recognized as one of the cornerstones of treating hyperglycemia in type 2 diabetes mellitus (T2DM) [2]. The use of physical activity in the treatment of type 2 diabetes is recommended as a non-pharmaceutical strategy [3]. Lipoic acid (LA) is an organic compound found in plant and animal tissues. It is known as an essential cofactor in regulating energy metabolism and supporting the enzymatic breakdown of nutrients [4]. In the body, it is produced in very small amounts by the *de novo* synthesis of fatty acids (FA) and cysteine. Considering that LA is synthesized in small amounts in the human body, its therapeutic efficacy likely depends on dietary absorption and supplementation to enhance its

bioavailability [5]. Despite the anti-diabetic and anti-lipid properties of LA reported in some clinical trials, several studies have found that LA does not improve blood glucose control or lipid profiles.

Additionally, two studies report that LA supplementation can reduce body mass index and weight, as well as inflammatory markers. The effectiveness of LA supplementation in improving the glycemic status and lipid fractions is, therefore, controversial [6]. Ardropin (Ad), a newly identified protein, is encoded by a gene related to energy homeostasis (Enho). It is released in a variety of tissues, including vascular endothelial cells, the brain, kidneys, liver, pancreas, and skeletal muscle [7]. It has been found that type 2 diabetic patients have lower serum levels of Ad than non-diabetics. Angiogenesis and circulating Ad levels have been linked to exercise in numerous studies [8]. The identified VEGFs, known by the names VEGF-A, VEGF-B, VEGF-C, and VEGF-D, possess structural characteristics typical of the VEGF family but exhibit diverse biological activities [9]. Serum VEGF has been investigated in relation to other biochemical and demographic variables, including triglycerides (TGs), body mass index (BMI), total cholesterol (TC), and the glycosylation of hemoglobin A1c (HbA1c), high-density lipoprotein (HDL), glucose uptake and low-density lipoprotein (LDL) [10]. Here, we aimed to assess the simultaneous effects of exercise training and lipoic acid on Ad and Vascular Endothelial Growth Factor-C (VEGF-C) in skeletal muscle of type 2 diabetic male rats.

Material and methods

Animals

Twenty-one male Wistar rats (mean weight: 159±30 g) were housed in cages with a 12-hour light/dark cycle and controlled humidity (60 percent). The rats had free access to food and water. All animal interventions were carried out in accordance with the ethical guidelines of the National Institutes for the Care and Use of Laboratory Animals, approved by the ethics committee of Aliabad Azad University of Katul (IR.IAU.AK.REC.1399.010).

Induction of type 2 diabetes

To develop a T2DM rat model After a week of adaptation and 12 hours of fasting, a single injection of Streptozotocin (STZ) at a dose of 65 mg/kg (manufactured by Sigma-Aldrich, USA) dissolved in citrate buffer (0.1 M pH=4.5) followed 15 minutes later by an intraperitoneal injection of 120 mg/kg Nicotinamide (NA; Sigma-Aldrich, USA) dissolved in normal saline. Rats' blood glucose levels are measured three times: prior to STZ injection, 48 hours after injection, and six weeks after beginning aerobic exercise and a 10-hour fast. A blood glucose level of more than 250 mg/dl is the threshold for diabetes. Diabetes developed in all of the rats given STZ. The same volume of 0.1 M citrate buffer was administered intraperitoneally to the control group to equalize its impact.

Animal study design

21 three-week-old male Wistar rats were divided into seven groups, 3 rats in each group, which includes: 1) healthy control; 2) Diabetic control; 3) Diabetic + lipoic acid; 4) Diabetic + high-intensity exercise; 5) diabetic + low-intensity exercise; 6) Diabetic + high-intensity exercise + lipoic acid; 7) diabetic + low-intensity + lipoic acid. In order to supplement LA, 20 mg of liposomal lipoic acid supplement (Lipoic acid supplement manufactured by Sigma Aldrich, USA) was dissolved in methylcellulose and given to rats one hour after exercise by gavage and one meal per day. The thin-layer coating method was used for the Lipoic Acid supplement, where lecithin phospholipid (L-a-a-phosphatidylcholine) was first dissolved in chloroform to obtain the initial solution. Then, cholesterol was dissolved in chloroform, and the second solution was obtained. In the next step, the two solutions were mixed in a ratio of four to one. Then, this compound was evaporated under vacuum in a rotary evaporator at a temperature of 50°C and a speed of 150 rpm. With the formation of a thin lipid film, the evaporation continued for at least two hours. Then, LA was dissolved in distilled water and added to the solution. To homogenize the suspension and produce nanovesicles, the obtained samples were homogenized for 15 minutes with an ultrasound homogenizer. Then, the homogenized suspension was placed in the vicinity of nitrogen and subjected to lipid transfer heat for one hour. Then, the produced product was centrifuged, and a clear suspension of nanoliposomes was obtained and stored at 4°C until use.

Training protocol

The animals of the training and supplementary groups were trained on how to use the special treadmill for the activity for a week prior to the start of

https://doi.org/10.46389/rjd-2025-1672

the training protocol. After that, in order to determine the maximum physical capacity and the intensity of sports exercises, the maximum speed test was performed on the treadmill: thus, after 10 to 20 minutes of warming up with an intensity of 40 to 50% VO_2 max, the speed of the treadmill every two minutes 0.03 m/s increased until the animal was unable to run further. The maximum rate of oxygen consumption was determined to be when the blood lactate level exceeded 6 mmol/L. There were two main types of training programs for the training groups: High-intensity interval training (HIIT) groups, according to the modified Sangstad et al. method [11], included 6 weeks of training, 5 sessions per week that contained 10 intervals for 4 minutes with an intensity of 85–90% of VO_2 max running on a treadmill. Active rest between intervals was also in the form of 2-minute runs with an intensity of 5–10 m/min. Low-intensity interval training (LIIT) groups consisted of 6 weeks of 5 sessions per week, each including 13 intervals of 4 minutes at an intensity of 65–70% of VO_2 max, performed on a treadmill. Active rest between intervals was also in the form of 2-minute runs with an intensity of 5–10 m/min. The rats were warmed up with an intensity of 5–10 m/min for 5–10 minutes, and then the main training phase was performed with two specified intensities, followed by the cooling phase at an intensity of 5–10 m/min. It was done for 5–7 minutes, and the exercise was over.

Sampling

Rats were anesthetized with a mixture of Ketamine and Xylazine at a ratio of 5:2 in resting conditions (48 hours after the last training session) and then sacrificed. The rats' skeletal muscle was separated, and immediately after washing with deionized water, they were placed in liquid nitrogen and then frozen at -75°C. To measure the biological indicators of the tissue, the skeletal muscle was first homogenized using liquid nitrogen in a manual powder mortar. Then, 0.1 g (100 mg) of the powder was homogenized with 1 mL of phosphate-buffered saline (PBS) buffer. Then, the solution obtained was centrifuged for 15 minutes at 5000 rpm at 4°C in a refrigerated centrifuge, and the supernatant obtained was used to measure the research indicators.

Laboratory methods

The Fluorescent immunohistochemical technique was used to investigate the VEGF-C protein (SC-374628) and Adropin protein levels (LS-B10139) in the skeletal muscle of rats. To perform chemical staining and determine the amount of protein, the muscle was cut to a thickness of 10 µm. After cutting the muscle tissue, fixation was performed using either Bouin's solution or 10% formalin. To dehydrate the tissue, the sample was placed in alcohol, and then, to clarify the sample, it was placed in xylene. In the next step, the sample was placed inside the melted paraffin, and the sample covered with paraffin was placed inside the mold filled with melted paraffin. While freezing the paraffin, the sample was also sectioned inside the rest and prepared. A microtome device cut the sample with the paraffin mold with a thickness of 5 to 10 microns. The cut on the slide contains albumin to stick on the slide. The slides were placed in the oven at 90°C for 20 minutes to melt the paraffin in the sample. To remove the paraffin inside the sample, the samples were placed in Xylene. Slides are inserted into Haematoxylin dye and washed for 15 minutes with running water, and then immersed in Eosin several times, washed with running water and then put in 70%, 80%, 90%, and 100% alcohol to dehydrate it well, and then put it in Xylene to denature it and make it clear. The samples were washed with PBS in four steps, each at a 5-minute interval. To recover the antigen, two normal hydrochloric acids were added to the samples and left for 30 minutes. A borate buffer was added to neutralize the acid for 5 minutes. Cells were washed with PBS.

Triton 0.3% was added for 30 minutes to permeabilize the cell membrane, and then the cells were washed with PBS. 10% Normal Goat Serum was added for 30 minutes to block the secondary antibody reaction and serve as an additional color in the background. The primary antibody (code: SC-271255, manufactured by the Santa Cruz company, USA), diluted (1:100 ratio) with PBS, was added to the sample and placed in a refrigerator at a temperature of 2 to 8 degrees for one night. The next day, the tissue was washed 4 times with PBS for 5 minutes each time. A secondary antibody (code: SC-271255, manufactured by Santa Cruz, USA) was added to the sample at a dilution of 1:150 and then incubated in an incubator at 37°C for 1 hour and 30 minutes in the dark. After that, the sample was transferred from the incubator to the darkroom, and after washing four times, DAPI was added to it, immediately removed, and then poured onto the PBS sample. In the final step, the sample is observed using an Olympus fluorescent microscope with a 400 mm lens to confirm the presence of the markers. Blood glucose level was measured using a kit (Pars Azmon) and insulin by the ELISA method (Mercodia).

Statistical analyses

An independent t-test was used to compare the means of two healthy and diabetic control groups, and one-way ANOVA was used to compare the diabetic groups, and Tukey's post hoc test was used to compare the two groups. SPSS version 20 software was used for data analysis. The minimum level of significance in the test is $P \leq 0.05$.

Results

In Figure 1A shows a comparison of the amount of VEGF-C (ng/ml) protein expressed between the control and diabetic groups. Figure 1B shows a comparison of the amount of VEGF-C expressed in skeletal muscle tissue in different study groups.

Figure 2 shows the comparison of the amount of VEGF-c protein expressed in skeletal muscle in different study groups. The amount of VEGF-C protein was the highest in diabetic + lipoic acid + high-intensity exercise and diabetic + lipoic acid + low-intensity exercise when compared to the diabetic control (the lowest amount of VEGF-C protein).

In Figure 3A shows a comparison of the amount of Ad (pg/ml) protein expressed between the control and diabetic groups. Figure 3B shows a comparison of the amount of Ad protein expressed in skeletal muscle in different research groups. In Figure 1A and Figure 3A show the comparison of the control and diabetic groups. There was a significant increase in the amount of VEGF-C and adropin in the control group compared to the diabetic group, respectively. In Figure 1B and Figure 3B show the comparison of different study groups. The results showed that the highest to lowest amounts of VEGF-C and adropin were in the diabetic + lipoic acid + high-intensity exercise, diabetic + lipoic acid + low-intensity exercise, diabetic + high-intensity exercise, diabetic + low-intensity exercise, and diabetic + lipoic acid and diabetic groups, respectively.

Figure 4 shows a comparison of the amount of Ad protein expressed in skeletal muscle tissue in different study groups. The amount of Ad protein was the highest in diabetic subjects supplemented with lipoic acid and low-intensity exercise, as well as in diabetic subjects supplemented with lipoic acid and high-intensity exercise, compared to the diabetic control.

Figure 5A and Figure 3B show the insulin and glucose levels in different study groups. The levels of both parameters were significantly different in the healthy control group compared to the diabetic group. Figure 5A shows that the highest insulin level was significantly observed in the diabetic group supplemented with lipoic acid and high-intensity exercise, as well as in the diabetic group supplemented with lipoic acid

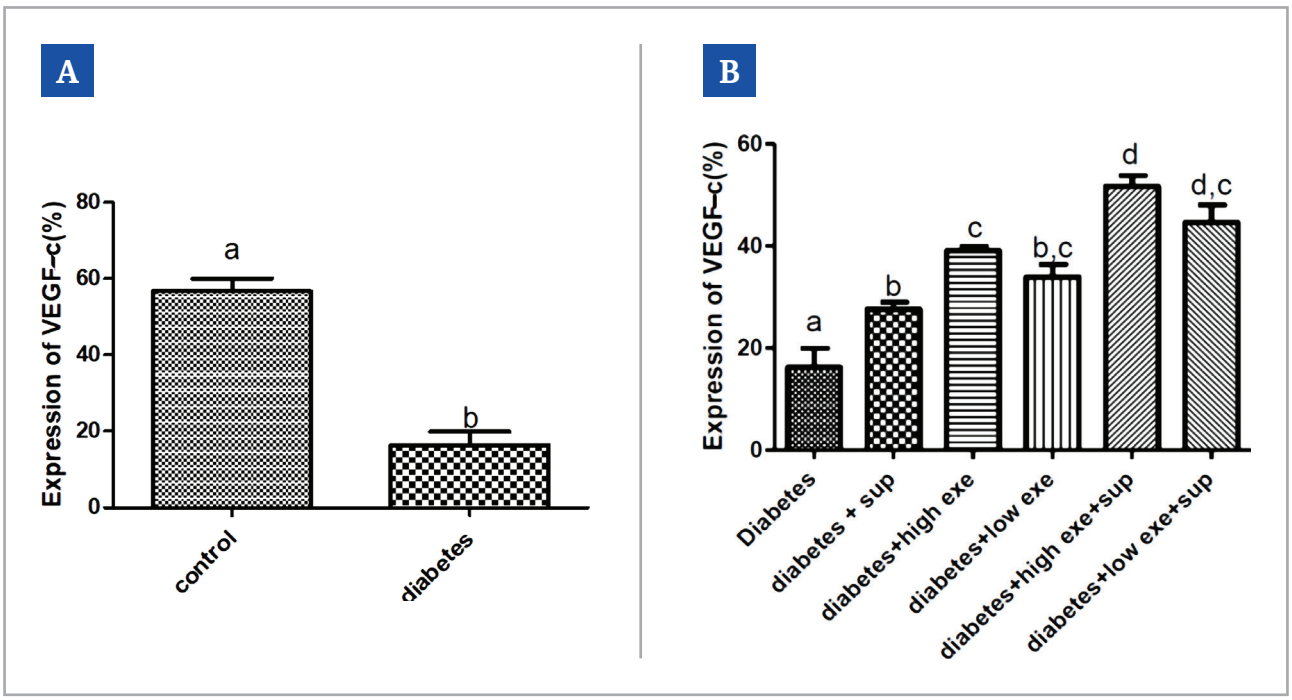

Figure 1: A – Comparison of the amount of VEGF-C (ng/ml) protein expressed between the control and diabetic groups; B – Comparison of the amount of VEGF-C expressed in skeletal muscle tissue in different study groups. * – P-value lower than 0.05 was considered significant.Sup – supplement (Lipoic acid); Exe – exercise.

https://doi.org/10.46389/rjd-2025-1672

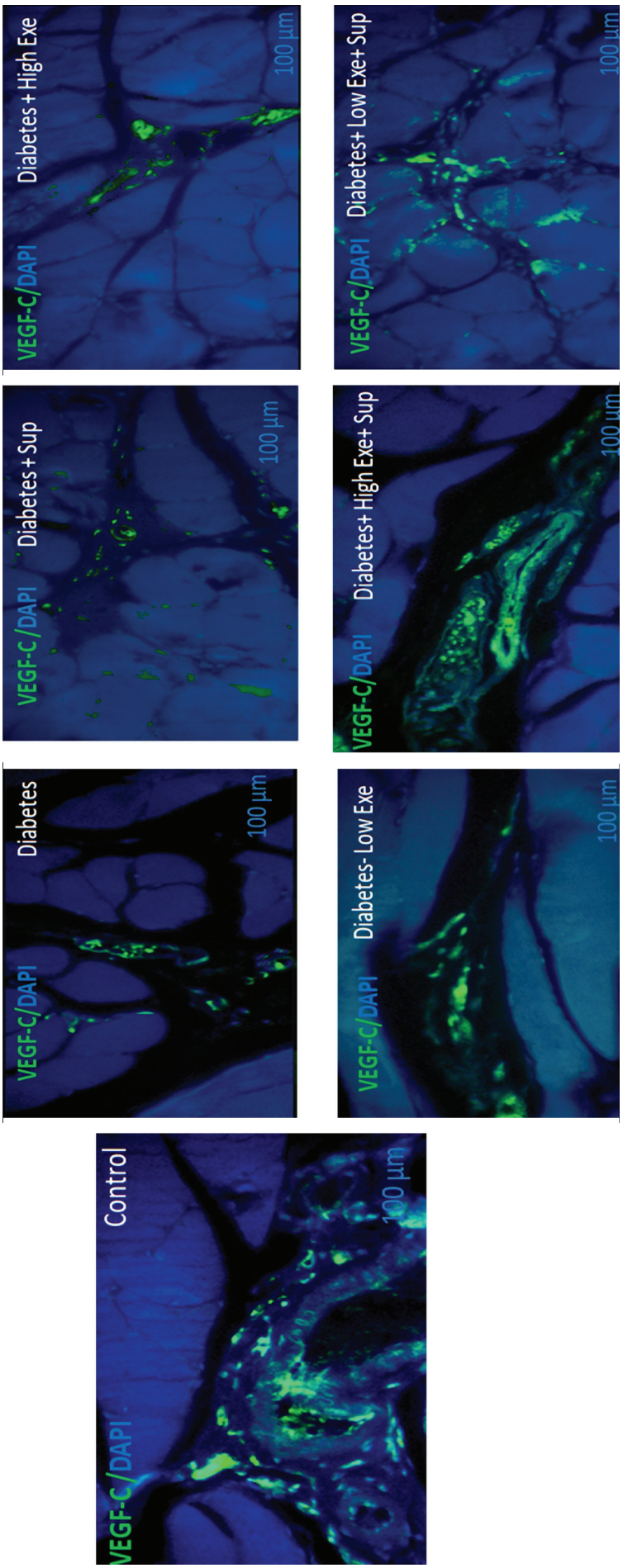

Figure 2: Comparison of the amount of VEGF-C protein expressed in skeletal muscle tissue in different study groups (The amount of VEGF-C protein is marked with green color). DAPI: is a blue fluorescent stain, Sup: supplement (Lipoic acid), Exe: exercise, DAPI: 4′,6-diamidino-2-phenylindole.

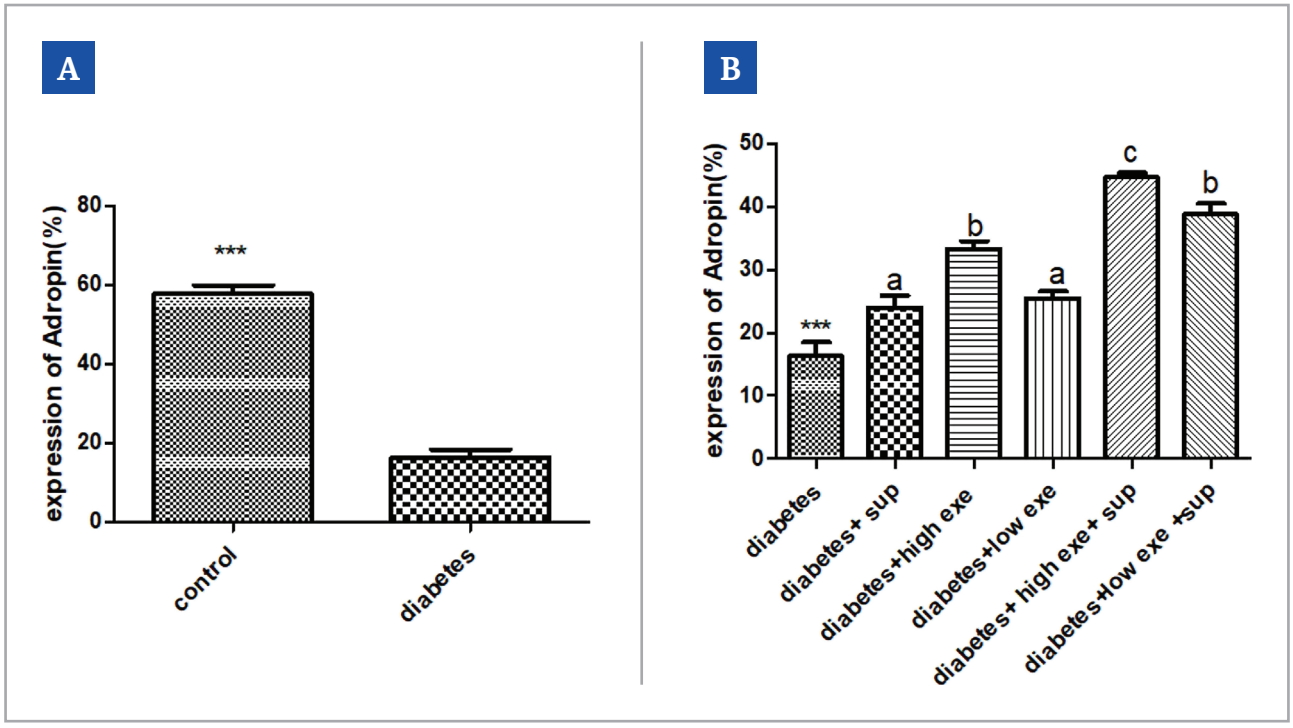

Figure 3: A – Comparing the amount of Adropin (pg/ml)protein expressed between the control and diabetic groups. * – P-value lower than 0.05 was considered significant. B – Comparison of the amount of Adropin protein expressed in skeletal muscle in different research groups. *** – Significant compared to intervention groups with lipoic acid and with low and high-intensity exercise. Sup – supplement (Lipoic acid); Exe – exercise.

and low-intensity exercise. The lowest level of insulin was observed in the diabetic control. Regarding blood glucose, the lowest level was observed in the diabetes group supplemented with high-intensity exercise and lipoic acid, and the highest average was associated with the control diabetes group (Figure 5B).

Discussion

Six weeks of low-intensity interval training (LIIT) and high-intensity interval training (HIIT) alone, and in combination with lipoic acid, resulted in a significant increase in the serum levels of Ad (13.7%) and vascular endothelial growth factor ligand in Wistar type 2 diabetic male rats compared to the control group. There is probably a direct relationship between Ad concentration and type 2 diabetes. It has been indicated that the serum level of adropin in type 2 diabetes patients is lower than in non-diabetic subjects. Exercise may affect the secretion of adropin and play an important role as a physiological regulator of its function and secretion. Some studies have confirmed that hyperglycemia is the most important factor in the occurrence and progression of vascular complications in both type 1 and type 2 diabetes [12].

Due to the strong connection between vascular function and insulin sensitivity, researchers hypothesized that Ad may have a direct effect on the endothelium [13]. The expression of Ad in endothelial cells may play a significant role in increasing the circulating levels of Ad. Recent advances in lymphatic research have determined that exercise stimuli cause adaptive changes in the behavior of primary lymphatics and unregulated lymphangiogenesis. Increasing evidence shows that muscle disorders are closely related to lymphatic dysfunction, growth, and regeneration. During these processes, VEGF-C plays a crucial role as an important regulator of muscle lymphangiogenesis.

Further studies are necessary to elucidate the structural and molecular plasticity of mammalian muscle lymphatics in response to endurance exercise and pathological events. Exercise is known to induce skeletal muscle angiogenesis in the body; however, its effect on lymphangiogenesis remains unclear. Although the effect of regular aerobic exercise on VEGF levels has been investigated, the impact of aerobic exercise intensity has not been thoroughly examined to date. Although the benefits of regular exercise for people with diabetes are well proven, the type of exercise recommended for these health benefits remains unknown for many reasons. In recent years, studies have

https://doi.org/10.46389/rjd-2025-1672

Figure 4: Comparison of the amount of adropin protein expressed in skeletal muscle tissue in different research groups. The amount of adropin protein is marked with green color. DAPI is a blue fluorescent stain. Sup – supplement (Lipoic acid); Exe – exercise. DAPI: 4',6- diamidino-2-phenylindole.

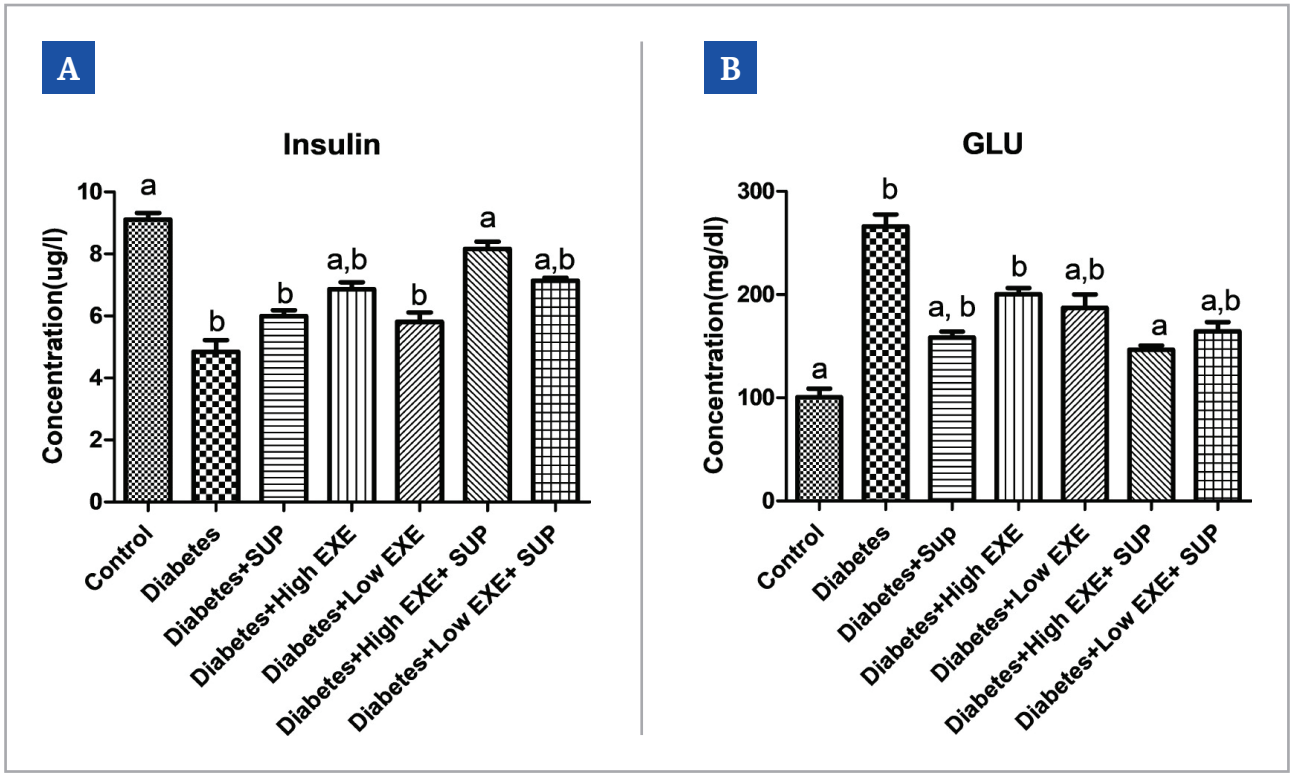

Figure 5: A – The level of insulin in different study groups; B – The level of glucose in different study groups. * – P-value lower than 0.05 was considered significant. Sup – supplement (Lipoic acid); Exe – exercise.

investigated the primary role of VEGF in normal or abnormal growth and the nature of the veins [14].

In our study, the highest mean VEGF-C protein level was observed in the Diabetes+High EXE+ supplemental group, and the lowest was in the diabetic control group. The effect of exercise can vary depending on its components, including type, duration, frequency, and intensity. Therefore, to illustrate the effect of regular exercise training, various aspects must be examined. Shakhchizadeh et al. demonstrated that resistance training had no significant effect on VEGF levels [15], whereas Gavin et al. reported significant changes in VEGF levels after resistance training [16]. Kraus et al. revealed that after two and four hours of aerobic activity, VEGF levels increased in both active and inactive individuals [17]. Dong et al. also examined the impact of exercise on VEGF in rats. At the end of the first, third and sixth week, VEGF increased [18]. Skeletal muscle is the primary site of glucose disposal; increasing muscle mass enhances insulin sensitivity through the physiological improvement of muscle and related vessels, regardless of the method used, whether through calorie restriction, aerobic exercise, resistance training, or a combination of lifestyle factors. Reducing body fat appears to improve insulin sensitivity [19].

The results of the current study indicated a significant decrease in fasting blood glucose levels (29.9%), insulin (37.9%) and insulin resistance (56.7%) in the training group. As blood glucose levels decrease, its entry into red blood cells will decrease, because the higher the blood glucose level, the higher the glycation rate of red blood cells, and the percentage of HbA1C increases [20]. Several studies have investigated the effectiveness of each type of resistance and aerobic exercise on fasting blood glucose, insulin, and the insulin resistance index in diabetics. In this regard, Cauza et al. investigated blood glucose control in patients with type 2 diabetes. The resistance training program in this study consisted of 3 sessions per week of weight training, which began with 3 sets in the first weeks, targeting large muscles, and increased to 6 sets in the final weeks. Aerobic exercise also included pedaling on a treadmill at an intensity of 60% of the maximum oxygen consumption for 15–30 minutes. These researchers reported that aerobic exercise had no significant effect on fasting blood glucose and insulin resistance index, but resistance exercise decreased these indices [21].

As stated earlier, according to studies, aerobic exercise can increase the response of skeletal muscles to insulin by increasing the expression and/or activity of proteins involved in glucose metabolism and insulin signaling. Additionally, low-intensity aerobic exercises may enhance glycogen synthase activity and increase

https://doi.org/10.46389/rjd-2025-1672

GLUT4 protein expression. On the other hand, fat oxidation is also a major aspect in improving insulin performance, and aerobic exercise increases fat storage in muscle and fat oxidation capacity. Additionally, aerobic exercise increases the utilization of fat during a period of low-intensity aerobic activity after exercise, which also leads to a decrease in muscle glycogen and blood glucose [22].

Therefore, the discrepancy in the results of Cauza et al. [23] regarding the effectiveness of aerobic exercise can be attributed to the difference in the type and program of aerobic exercise, as the Cauza et al. study [23] involved treadmill-based aerobic exercises. In addition, the overload applied in that research appears to be low, ensuring that the exercise intensity remained constant throughout the research period. The duration of each exercise session was increased to a maximum of 30 minutes in the final week. Based on the available evidence, the duration and intensity of exercise are effective factors in reducing blood glucose levels. Therefore, by controlling blood glucose in the normal range, HbA1C values also decrease. Improving glycemic control in diabetic patients may prevent or delay the development of complications associated with this disease and reduce the risk of cardiovascular problems, such as arterial stiffness.

In a study, Laura Mandolesi et al. investigated the effect of 3 different methods of exercise (aerobic, resistance and combined) on metabolic control and insulin resistance. Combined exercises were more effective and took the beneficial effects of both types of resistance and aerobic exercises [24]. Additionally, Yavari et al. investigated the effects of aerobic and resistance exercises, as well as a combination of both, on blood glucose control, cardiovascular risk factors, and body composition in patients with type 2 diabetes. Both aerobic and resistance exercises are effective interventions for managing the complications of type 2 diabetes, but combined exercises are associated with more positive changes [25].

Hence, the findings of the present study were consistent with those of some other studies [15] and contrary to the results of other studies [26, 27]. Study of Liu et al showed that the effect of 12 weeks of combined aerobic-resistance exercises (aerobic with an intensity of 40–60% of maximum oxygen consumption, resistance with an intensity of 50–60% of one maximum repetition) on blood glucose control, insulin and resistance index led to a significant reduction in fasting glucose levels and insulin resistance compared to the control group [28].

Other findings [28] also showed that after 4 weeks of aerobic training (running and cycling for 40 minutes, 3 sessions per week, at 60–70% of maximum oxygen consumption) in healthy controls, the training significantly reduced HbA1C, fasting blood glucose, insulin, and insulin resistance [28]. The American Diabetes Association and the American College of Sports Medicine reported that exercise programs for healthy, obese, or overweight people, as well as diabetic patients, should be a combination of aerobic and resistance exercises, to include the beneficial effects of both types of exercise [29]. The duration, intensity, and type of aerobic and resistance exercises are crucial for reaping the beneficial effects of both types of exercises. Fujie et al. [30] demonstrated a positive relationship between aerobic exercise training and changes in plasma Ad levels. They demonstrated that aerobic exercise resulted in an increase in the serum level of Ad in both healthy and elderly adults. The reason for the difference between the results of this study and other findings may be the type of training protocol, duration, and level of physical fitness of the participants.

Findings by Alizadeh et al. [23] indicated the effect of aerobic activity with an intensity proportional to maximum fat oxidation on Adiposity and insulin resistance in overweight women. Their results showed significant changes in insulin factors and insulin resistance between the test group and the control group. However, no significant changes were observed for glucose and Ad. Due to the effect of the fasting state on the increase of Ad or insufficient duration and intensity of activity, no significant changes were observed in the level of Ad. There were limitations in our study, including the difficulty in strictly controlling the exercise program and diet, as well as the lack of similar research in sports.

Conclusion

In type 2 diabetic rat models, performing intense and low-interval sports activities along with lipoic-acid supplementation played a significant role in increasing the amount of diabetes modulating indicators containing lymphangiogenic growth factors and Ad and also insulin and reducing blood glucose.

Conflict of interest

The authors declare no conflict of interest.

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 https://doi.org/10.46389/rjd-2025-1672