



The impact of aerobic training on insulin resistance with emphasis on changes in adropin and fetuin-A in sedentary overweight females



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ABSTRACT

Introduction: Disruption of inflammatory profile in the presence of obesity and overweight is associated with reduced insulin action in target cells. In the present study, the effect of aerobic training on insulin resistance is evaluated with an emphasis on possible changes in adropin and fetuin-A in overweight women.

Methods: For this purpose, 24 overweight adult females ($26 \leq \text{BMI} \leq 30$) were randomly assigned into experimental ($n=12$) or control ($n=12$) groups. The experimental group underwent an 8-week aerobic training of 3 sessions weekly, and the control group did not participate in the training. 24 hours before and 48 hours after exercise training, fasting blood sample was taken to measure serum levels of adropin, fetuin-A and insulin resistance in the 2 groups. Data were compared between the two groups by independent and paired sample t test at a significance level of less than 0.5 percent.

Results: No significant difference was observed in all variables between groups at baseline ($p < 0.05$). Aerobic training resulted in significant increase in serum adropin ($p = 0.001$) and decrease in Fetuin-A ($p = 0.001$) and insulin resistance ($p = 0.019$) in experimental groups. All variables remained without change in control group ($p < 0.05$).

Conclusion: The improvement in insulin resistance following aerobic training may be attributed to a decrease in fetuin-A and an increase in adropin in response to this type of exercise. However, further studies are needed to understand the underlying mechanisms responsible for these changes.

Keywords:

Aerobic training, Overweight, Adropin, Fetuin-A, Insulin resistance.

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1. Introduction

Obesity, especially abdominal obesity, has been identified as a potential predictor of increased mortality. The increased morbidity and mortality in individuals with general and abdominal obesity is largely attributed to the increased incidence of type 2 (T2D) diabetes and cardiovascular disease in these individuals (1). Inactivity or

decreased physical activity, as well as increased calorie intake, along with genetics, are among the most important factors in the prevalence of obesity and overweight, which lead to systemic inflammation and disruption of inflammatory cytokines and adipokines (2). Insulin resistance and, subsequently, T2D have been identified as the major

complications of overweight and obesity (3). On the other hand, the phenomenon of insulin resistance occurs in response to disruption of the inflammatory profile and imbalance of active adipokines, especially in the presence of overweight and obesity (4).

Among them, Fetuin-A, in response to increased inflammatory cytokines and decreased anti-inflammatory cytokines, provides a basis for increased insulin resistance, especially in the presence of obesity (5), as a direct relationship between its serum levels and BMI has been reported (6). Fetuin-A is a 60-kDa glycoprotein that was first identified in the evaluation of advanced kidney disease (7). Fetuin-A induces insulin resistance in rodents by inhibiting insulin receptors. On the other hand, it has been identified as an endogenous ligand for the TLR4 receptor, through which saturated fatty acids induce proinflammatory signaling and insulin resistance. Circulating Fetuin-A levels are increased in obesity, metabolic syndrome, and type 2 diabetes, and are associated with hepatic steatosis in humans. Increased systemic levels predict the risk of type 2 diabetes, as well as myocardial infarction and stroke (8).

On the other hand, adipon, a 76-amino acid peptide hormone mainly expressed by the liver and brain, has been introduced as a beneficial regulator related to insulin sensitivity and energy homeostasis in glucose homeostasis and control of metabolic diseases such as type 2 diabetes and insulin resistance (9). The role of nutrition in controlling serum levels of adipon is undeniable from the liver, which is responsible for glucose and lipid homeostasis, and its effective role in preventing cardiovascular pathologies, controlling cardiac metabolism and vascular function has been reported (10). On the other hand, a decrease in adipon is associated with increased insulin resistance, especially in the presence of obesity, and a negative correlation between adipon and age and BMI has been reported (11).

Based on the above evidence, increased

serum Fetuin-A and decreased serum adipon are associated with increased insulin resistance, especially in obese individuals. Therefore, it seems that normalizing their levels in response to weight loss or other therapeutic interventions increases the tendency to improve insulin resistance in obese or overweight individuals. In this context, although Schultes et al, (2010) have indicated that serum Fetuin-A levels do not change in response to weight loss in obese women (12), its decrease in response to weight loss in obese children has been reported by Reinehr et al. (2008) (13). However, Bagheri et al. (2024) reported no change in Fetuin-A following resistance training (14). On the other hand, it has been noted that adipon secretion can be increased by manipulating diets, exercise training, and other therapeutic interventions (15). In another study, 8 weeks of interval training reduced insulin resistance in obese rats fed a high-fat diet (16). However, the response or simultaneous adaptation of serum Fetuin-A levels, adipon, and insulin resistance to exercise training, especially aerobic exercise, in overweight women is still not well defined. Based on this limitation, the present study aimed to determine the effect of relatively long-term aerobic exercise on serum levels of Fetuin-A, adipon, and insulin resistance, as well as changes in weight and body fat percentage in inactive overweight women.

2. Materials and Methods

2.1. Subjects

The current research employed a quasi-experimental methodology, utilizing both pre-test and post-test evaluations. The demographic under study comprised overweight females aged 30 ± 5 years of old. A total of 24 participants, all overweight women ($26 \leq \text{BMI} \leq 30$) were selected and randomly assigned to control ($n=12$) or experimental group ($n=12$). Over an 8-week, the experimental group engaged in aerobic training 3 times weekly, while the control group did not participate in aerobic training.

2.2. Inclusion and exclusion criteria

Overweight or in other words BMI between 26 and 30 kilograms per square meter, is the main criterion for inclusion in the study. The participants in the study are individuals who do not engage in athletics, do not smoke, and are not pregnant. They have also not been involved in any consistent training programs for the past six months. Additionally, these subjects have not followed any specific diet, and their weight has remained relatively stable, with less than one kilogram of fluctuation. Inclusion criteria for the study include a review of medical histories specifically looking for any instances of kidney diseases, cancer, or seizure disorders. Exclusion criteria encompass regular participation in training programs or the presence of any health conditions that could influence the study's dependent variables. Also, if the individual develops a disease during the training period that requires the use of medications that affect the dependent variables, they will be excluded from the study.

2.3. Anthropometric measurements

Anthropometric measurements were taken for both groups before and after the exercise program. Height was recorded using a wall-mounted caliper, with participants barefoot, to a precision of 0.1 cm. Measurements of hip and abdominal circumferences were taken at their widest points following a normal exhalation, using a non-stretchable measuring tape with a measurement error of less than 0.1 cm. Weight was assessed using a Seca scale, accurate to 0.5 kg. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. The percentage of body fat was determined using an OMRON body composition analyzer from Finland.

2.4. Training protocol and blood sampling

Following the anthropometric

Table 1: Distribution of exercise duration and intensity in minutes and percentage of maximum heart rate, respectively

Weeks	Exercise intensity (%HRmax)	Time of running (min)
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measurements, participants were instructed to visit the blood laboratory for sample collection following an overnight fast of 10 to 12 hours, scheduled between 8 and 9 a.m. They were also advised to avoid engaging in strenuous physical activities for 48 hours prior to the sampling. The blood draws involved taking 5 ml from the left hand vein of each seated and resting participant. After the serum was separated, it was stored at -80 degrees Celsius until the analysis of the variables could be conducted (pre-test)

Aerobic exercises were performed for 8 weeks, 3 sessions per week. The exercise protocol was a modified version of the Ciolac et al. protocol, which started with 55% of maximum heart rate in the first and second weeks, and the intensity of aerobic exercises was increased by 5% every two weeks, and finally reached 70% of maximum heart rate in the eighth week. Each session was performed for 25 to 45 minutes, so that in the first two weeks, the duration of the subjects' activity was 25 to 30 minutes, and every two weeks, 5 minutes were added to this duration, which finally reached 40 to 45 minutes in the eighth week (table 1) (17,18).

48 hours following the conclusion of the final training session, another round of blood samples was collected under identical conditions to those of the pre-test. The fasting glucose levels were determined using the glucose oxidase technique, while serum insulin levels were quantified through the ELISA method. Additionally, levels of adipon and fetuin were also assessed using ELISA kits from Sunlang, Korea, and Eastbiopharm, China, respectively. Insulin and glucose levels were used for the homeostasis model assessment of insulin resistance $\text{Insulin resistance (HOMA-IR)} = [\text{fasting insulin } (\mu\text{g/ml}) \times \text{fasting glucose (mmol/l)}] / 22.5$ (19).

1	55	25 - 30
2	55	25 - 30
3	60	30 - 35
4	60	30 - 35
5	65	35 - 40
6	65	35 - 40
7	70	40 - 45
8	70	40 - 45

Table 2: Pre and post-training of anthropometrical indexes of 2 groups (Mean $\pm$ SD)

Variables	Exercise group			Control group		
	Pre-training	Post-training	<i>P value</i>	Pre-training	Post-training	<i>P value</i>
Weight (kg)	79.4 $\pm$ 4.21	76.1 $\pm$ 7.14	0.009	78.7 $\pm$ 3.31	79.3 $\pm$ 5.33	0.321
AC (cm)	89 $\pm$ 5.11	86 $\pm$ 6.24	0.021	90 $\pm$ 3.28	90.4 $\pm$ 5.31	0.416
BMI (kg/m ²)	27.76 $\pm$ 2.44	26.61 $\pm$ 3.47	0.014	27.91 $\pm$ 2.67	28.12 $\pm$ 2.54	0.213
Body fat (%)	33.68 $\pm$ 3.54	28.75 $\pm$ 3.98	0.006	33.28 $\pm$ 3.41	33.41 $\pm$ 2.69	0.423

AC, abdominal circumference; BMI: body mass index

3. Data analysis

Statistical evaluations were conducted using the statistical software package (SPSS, Version 22.0, SPSS Inc, USA). The Kolmogorov-Smirnov test was utilized to evaluate the normality of distribution. Comparisons of variables between groups at baseline were analyzed using an independent t-test. Paired t-test used to assess the intra-group changes of variables in each group. The statistical significant level was ≤ 0.05 .

4. Ethical Considerations

This study was approved by the Ethics Committee of Islamic Azad University, South Tehran Branch, (Code: IR.IAU.SARI.REC.1403.272).

5. Results

The mean and standard deviation of each of the anthropometric indices in response to aerobic exercise and the control group are summarized in Table 2. No significant difference was observed in the baseline levels of each of these indices in the pre-

test condition between the two groups ($p > 0.05$). On the other hand, the results of the paired t-test revealed that aerobic exercise led to a significant decrease in each of these indices in the experimental group, while none of the variables changed significantly in the control group ($p > 0.05$).

In the pre-test condition, no significant difference was observed in the levels of Fetuin-A ($p = 0.235$), adiponin ($p = 0.411$) and insulin resistance ($p = 0.635$) between the experimental and control groups. However, based on the results of the paired t-test, aerobic training resulted in a significant decrease in Fetuin-A compared to the pre-test in the experimental group ($p = 0.001$, Fig 1). On the other hand, serum adiponin levels increased significantly following aerobic training in the experimental group ($p = 0.001$, Fig 2). The insulin resistance index also increased significantly following aerobic training in the experimental group ($p = 0.019$, Fig 3). However, none of these variables changed significantly in the control group ($p > 0.05$).

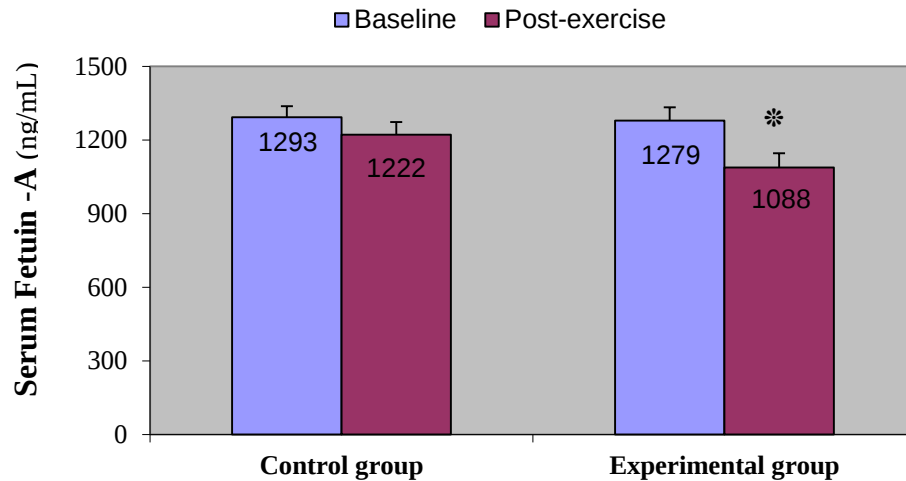


Figure 1: The changes pattern of serum Fetuin-A concentration in control and experimental groups of studied subjects. Aerobic training leads to significant decrease in serum Fetuin-A in experimental group, while this variable remained without change in control group. (* represent significant difference with baseline.)

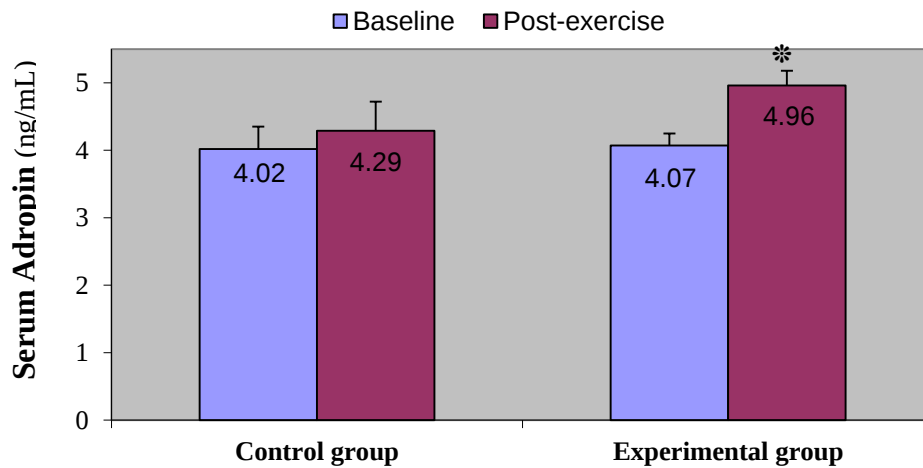


Figure 2: The changes pattern of serum Adropin concentration in control and experimental groups of studied subjects. Aerobic training leads to significant increase in serum Adropin in experimental group, while this variable remained without change in control group. (* represent significant difference with baseline.)

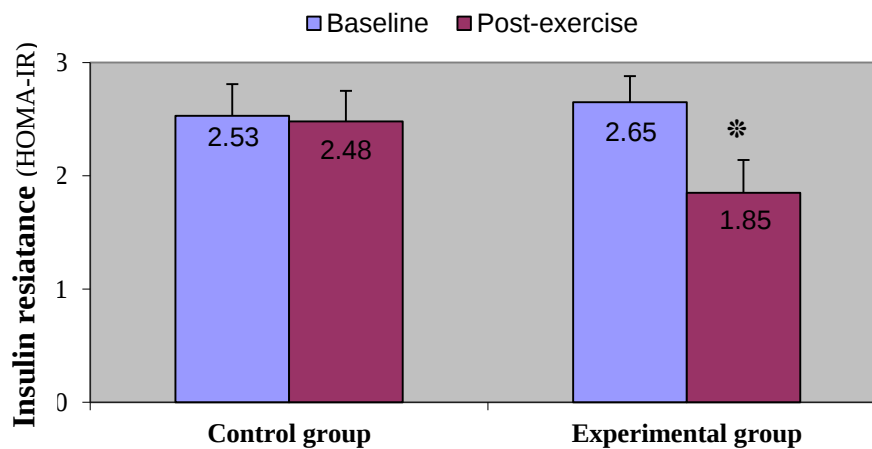


Figure 3: The changes pattern of insulin resistance in control and experimental groups of studied subjects. Aerobic training leads to significant decrease in insulin resistance in experimental group, while this variable remained without change in control group. (* represent significant difference with baseline.)

6. Discussion

The findings of the study indicate a significant reduction in insulin resistance following aerobic training in overweight women. In other words, 8 weeks of aerobic training in the form of 3 sessions per week led to a significant reduction in insulin resistance in overweight women who previously had a sedentary lifestyle. This evidence supports an increase in insulin function in target tissues such as skeletal muscle, adipose tissue, and liver in response to this type of exercise. Based on what was stated in the introduction, the reduction in insulin resistance, or in other words, the improvement in insulin function in the study subjects, may be attributed to changes in Fetuin-A and adropin in response to aerobic training. In this context, it is noted that aerobic training in this study led to a decrease in Fetuin-A and an increase in adropin, which supports the aforementioned cases. If we want to refer to previous studies on Fetuin-A, the results of the present study are inconsistent with the results of Khalafi (2023) in combined exercise and Bagheri (2024) in resistance exercise (14,20). In contrast, it is consistent with the findings of Vizvari (2020) and Ren (2021) in aerobic training (21,22).

Clinical laboratory studies have revealed that Fetuin-A, on the one hand, leads to a decrease in vascular calcification by forming stable colloidal complexes with calcium (23) and, on the other hand, by downregulating the glucose transporter GLUT4 and its membrane transport as well as reducing the activity or expression of protein kinase B (AKT1), resulting in a decrease in membrane glucose uptake (24). On the other hand, Fetuin-A increases insulin resistance by inhibiting the membrane tyrosine kinase of insulin receptors (25). On the other hand, clinical studies have revealed that Fetuin-A facilitates the interaction between the liver and target organs. By inhibiting insulin receptors stimulated by insulin tyrosine kinase, it causes insulin resistance. It has also been identified as an endogenous ligand for the TLR4 receptor, through

which saturated fatty acids induce pro-inflammatory signaling and insulin resistance (8). Based on this evidence, it seems that aerobic training improves insulin function in target tissues by inhibiting or reducing hepatic Fetuin-A secretion. In this context, it has been suggested that exercise training may lead to a decrease in Fetuin-A expression and secretion from the liver by improving the inflammatory profile, and to a decrease in serum Fetuin-A levels and subsequent improvement in insulin resistance by reducing weight and body fat mass in overweight individuals (26).

The findings of the present study also indicate a significant increase in adropin following aerobic training, while its serum levels did not change in the control group. Physical activity has been reported as an effective strategy to improve glucose intolerance and insulin function, especially in obese or high-fat populations (27). In this regard, although Sanchis et al, (2015) reported no change following a season of soccer-specific training (28). In contrast, an increase in its serum levels after 12 weeks of aerobic training with calorie restriction in sedentary obese women was reported in another study (29). An increase in its levels after a single aerobic exercise session in diabetic rats was also reported by Sato et al, (2017) (30).

The effective role of adropin in metabolic homeostasis, especially insulin function and inhibition of dyslipidemia in adropin-deficient mice has been reported (31). On the other hand, increasing serum adropin improves glucose oxidation by increasing pyruvate dehydrogenase activity. On the other hand, by reducing carnitine palmitole transferase B activity, it leads to a decrease in fat oxidation in skeletal muscles, which ultimately leads to improved metabolism and glucose intolerance (32). Studies on laboratory mice have clearly shown that exercise improves the gradual age-related decline in systemic adropin and leads to an increase in its serum levels (33). Considering the effective role of adropin in insulin function and the effectiveness of exercise training on its

serum levels, the possible role of its changes in response to exercise training in weight loss and prevention of type 2 diabetes in inactive individuals has been pointed out. In this context, Rezaei-Manesh et al, (2022) have pointed out a significant decrease in serum adiponectin along with a decrease in BMI and insulin resistance following interval aerobic training (34). Shirovieh et al, (2022) have also attributed the decrease in insulin resistance following aerobic training in overweight men to an increase in serum adiponectin in response to this training method (35). Although measuring Fetuin-A and adiponectin changes as hormonal components affecting insulin action are among the strengths of the present study, understanding the main mechanisms responsible for insulin action is not possible by measuring these hormonal components alone, and measuring other hormonal, enzymatic, and genetic components is also required, and the lack of measuring them is one of the limitations of the present study.

Conclusion

Aerobic training reduces Fetuin-A and increases serum adiponectin in overweight women. Based on in vitro evidence supporting the role of these hormonal components in insulin action, the reduction in insulin resistance following aerobic training in overweight women can be attributed to the change in Fetuin-A and adiponectin in response to this training method. However, insulin action is not solely dependent on these hormonal components, and further cellular-molecular studies are needed to understand the main mechanisms responsible for these changes.

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Declarations

Authors declare that they have no competing interests.

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