The Effect of 8 weeks Aerobic Training and Glycogon Consumption on Serum Apelin and Insulin Resistance in Women with Type 2 Diabetes

Mahboobeh Ramezani[1], Farzaneh Taghian[2*]

1. MSc, Department of Physical Education and Sport Science, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran.
2. PHD, Department of Physical Education and Sport Science, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran.

***Correspondence:**
Farzaneh Taghian, Department of Physical Education and Sport Science, Isfahan (Khorasgan) Branch, Islamic Azad University, Isfahan, Iran.
Tel: (98) 0913 308 0241
Email:
mahbouberamezni730@gmail.com

Received: 24 August 2019

Accepted: 05 December 2019

Published in January 2020

Abstract

Objective: Apelin is a novel adipokine that plays an important role in regulating energy homeostasis and improving insulin resistance. The purpose of the present study was to compare the effect of eight weeks aerobic interval training and glycogon consumption on serum apelin levels and insulin resistance in women with type 2 diabetes.

Materials and Methods: This is a quasi-experimental study. Forty diabetic women with mean age (48.08± 6.14) weight (72.61± 11.51) kg, height (156.33± 6.36) cm, body mass index (BMI) (29.73 ± 4.62) kg / m 2 were selected. Samples were randomly divided into four groups: aerobic interval training (n= 10), glycogon consumption (n= 10), combination (n= 10) and control (n= 10). To measure low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride (TG), fasting blood glucose, cholesterol, insulin, apelin and insulin resistance were measured. Then the aerobic and combination group participated in an aerobic interval training program (8 weeks, 3 sessions per week, 1 hour session, 40-60% of maximal beat intensity). Glycogel 3 capsules of 145 mg daily were used. After eight weeks, all variables were measured in four groups. T-test and analysis of variance were used.

Results: The findings of this study showed that the level of apelin decreased significantly in all three groups (*P*-value=0.018). Changes in glucose (*P*-value=0.16) and insulin (*P*-value=0.31) in groups were not significant .Insulin resistance was significantly decreased in the combination and glycogel groups (*P*-value=0.03).

Conclusion: Aerobic interval exercises and glycogon consumption can be used to reduce some of the risk factors for diabetes in people with diabetes.

Keywords: Apelin, Diabetes, Glycogon, Aerobic interval training, Insulin resistance

Introduction

Today, diabetes has become a growing health problem around the world. The rapid changes in lifestyle caused increase of the type 2 diabetes mellitus (T2DM) prevalence, especially in developed and developing countries (1). The adipose

tissue, as an active endocrine gland, secretes many chemicals that are involved in regulation of physiological processes. These chemical messengers such as adiponectin, leptin, resistin and visfatin are known as adipokines (2). Inflammation caused by disturbance of pre- and anti-inflammatory cytokine concentrations is one of the main causes of metabolic syndrome and T2DM. In recent years, the role of hormones secreted by adipose tissue as regulators of skeletal muscle metabolism and the development of insulin resistance, and ultimately T2DM has attracted many researchers (3).

Imbalanced production of adipokines is involved in the development of diabetes and pro-inflammatory factors in metabolic diseases (4). The adipose tissue secretes an adipokine called apelin that plays a role in carbohydrate metabolism and insulin function (5) apelin is secreted as Pro-apelin as a 77-amino acid precursor and then divided into several smaller bioactive peptides, including apelin 36 and apelin 13 (6). Apelin is a peptide that acts in conjunction with the Apj receptor. Reports suggest that apelin is associated with insulin resistance. For example, apelin levels change with changes in insulin levels in the blood (7-10). Stopping insulin secretion by decreasing cAMP in beta cells through phosphodiesterase- dependent phosphatidylinositol 3 kinase activity (PI3K) is considered as one of apelin's functions (11,12).

The apelin injection to the insulin-resistant obese mice stimulate glucose uptake and improves insulin sensitivity, as well as decreases triglycerides (TG), free fatty acid and insulin, and thus decreases body weight and improves obesity (13,14). Hyperglycemia is the key to a series of biochemical events that elevates oxidative stress, causing oxidation of low density lipoproteins (LDL) molecules, activation of coagulation processes, as well as stimulating the adhesion of leukocytes and platelets, which contribute to thrombus formation, leading a predisposed environment to endothelial dysfunction development (15). Regular exercise can play a major role in reducing the complications of diabetes, including obesity, hypertension, hyperalpidemia and hyperinsulinemia, and increasing insulin sensitivity in the target tissue, increasing the levels of carrier proteins (GLUT4) and decreasing the insulin resistance (16,17).

Recently, a collection of three herbs of sage, granadillo and ginseng has been prepared as Glycogol to reduce blood glucose in diabetic patients (18). Therefore, the purpose of this study was to compare the effect of Glycogol intake with aerobic interval training on serum levels of apelin and insulin resistance in women with T2DM.

Materials and Methods

This is a clinical trial study with pre-test and post-test design. The participants in this study were 40 women with T2DM and the age range of 35-55 years old in Yazd with a fasting blood glucose greater than 200 mg/dl. At first, referring to the Yazd diabetes research center of and reviewing medical records of patients and calling them, sending recall and poster placement in clinics on the implementation of information research. Then, the volunteers participating in the research were enrolled.

Subsequently, eligible participants were selected based on the criteria for entering the study. The inclusion criteria in this study were the age group of patients (35-35 years), female, the blood glucose level between 126 to 400 mg /dl, the history of at least two years of T2DM. The exclusion criteria of this study were severity of illness (renal failure, chronic liver disease, decompensated heart failure, pulmonary infections and proliferative diabetic retinopathy), pregnancy and lactation, known history of drug allergy, diabetic foot ulcer, and a desire to change a specific exercise program or diet. Eventually, 40 participations were selected to participate in the study. The subjects were divided into four groups using random number table. The four groups consisted of the aerobic exercise group (n= 10), the Glycogol group (n= 10), the aerobic

exercise and Glycogol group (n= 10) and the control one (n= 10). At the beginning of the research process, the participants signed a written consent form for participating in sports exercises. In addition, the physical activity readiness questionnaire (PAR-Q) was used to determine the level of suitability of participants for beginning an exercise program. Training protocol and Glycogol capsule consumption

Before the beginning of the exercise program, in several sessions, the participants became acquainted with the exercises, principles for safety training materials, and the way to use of the training devices. In each session, the main components of aerobic exercise consisted of three sections: warm-up, training and cool-down. Stretching and slow jogging was performed during warm-up for 15 minutes. The main exercise training in the first session was 20 minutes with 40 to 45% of maximum heart rate, every two weeks, 5 minutes were added to the time of exercise, and exercise training intensity was increased by 5%. The cool-down activities focus on slow movements. The training group and the exercise plus Glycogol group did aerobic exercise three sessions per week for 12 weeks. The pressure and the number of repetitions of each exercise were determined based on the participants' abilities and physical fitness.

The participants were asked if they felt any pressure or inability in doing the exercises, they did the repetitions that they could easily perform. The amount and severity of the aerobic training program were designed based on the performed research and prescribed guidelines for diabetic patients (3,19,20). The control group continued the same daily activities during the study period.

The daily-recommended intake of Glycogol capsule (The Goldaru Pharmaceutical Company, Isfahan) was three capsules of 145 mg for 8 weeks after each meal. The Glycogol capsule contains herbal ingredients, including sage, fenugreek, cinnamon, and ginseng- a combination of blood glucose lowering plants. No special side effects have been yet reported. Since the extraction of Salvia officinal is was carried out with water solvent, there were no side effects of the products containing hydroalcoholic extracts of this plant. During the study, in order to keep the calorie intake constant, the participants' dietary information was recorded by the 24-hour dietary recall questionnaire in three days (Saturday, Sunday, and Friday) in the first, sixth and final weeks. The aerobic exercise group and the Glycogol group performed aerobic exercise for 8 weeks, three sessions per week for 60 minutes followed by daily Glycogol intake.

Biochemical Measurements

Blood samples were taken at 5:00 am in the anterior part of the left ventricle in two steps, 24 hours before the first training session and 24 hours after the last exercise session, at 8:00 am. Blood samples were collected in sterile tubes and then for separation of plasma, blood samples were centrifuged (for 10 minutes at 3000 rpm) at -70 °C. After collecting samples in the post-test and according to the pre-test, all the blood samples were removed from the freezer in one day and the tests were performed according to the relevant protocol. In both two steps of blood sampling, the participants were fasting for at least 12 hours (8 p.m. to 8 a.m.). In addition, the experimental group was asked to have no exercise or long walk for 24 hours after the end of the training. The participants were asked to not use the capsule 24 hours before blood sampling. Glucose measurements were performed using the Pars test kit and photometric methods. Monobind Inc. kit was used to measure insulin by immunoassay. Insulin measurement was performed by immunoassay. Apelin was measured by ELISA method using an AP kit with sensitivity of 5.21 pg / ml. To measure LDL and HDL cholesterol and triglyceride, the Pars test kit was used. The insulin resistance index was also calculated using the HOMA-IR equation (29). HOMA-IR = Fasting serum insulin (U / mlμ) × Fasting blood sugar (mmol / L) divided by 22.5 after eight weeks of

intervention. All variables measured in the pre-test were re-measured.

Descriptive statistics were used to examine and describe the characteristics of the participants, including age, height, weight, body mass index (BMI), fat percentage, fasting blood glucose and fasting insulin, insulin resistance index, serum apelin, LDL and HDL cholesterol as well as TG in four groups. The Kolmogorov-Smirnov was used to test for the normal distribution of data, the one-way ANOVA and Tukey's post hoc used to examine the difference between the groups and to compare means of two or more samples the T-test was used. For data analysis using SPSS version 21 software was used (*P*-value= 0.05).

Ethical considerations

This study was approved in Ethics Committee of Biomedical School of Islamic Azad University, Isfahan branch (Khorasgan). The ethical code for this study is 23821404931026 (http://pajoohesh.khuisf.ac.ir/showcodpayan.aspx)

Results

Table 1 presents the central indices related to general characteristics of subjects at pretest and posttest including age and BMI.

The results of Table 1 show that the research groups are homogeneous based on the variables such as age, and body mass index there were no significant differences among these variables in the groups before applying the independent variable. The results of Kolmogorov-Smirnov test also showed that the distribution of data in the pre-test was normal. Table 2 Comparing the Apelin, Glucose and insulin before and after exercise in the four groups.

The results of ANOVA revealed that there is significant difference in apelin (*P*-value= 0.1) and Glucose (*P*-value= 0.2) and Insulin (*P*-value= 0.82) the four groups. Table 3 Comparing Lipid profile variables before and after exercise in the four groups.

In the comparison of intragroup, the T-test results showed that fasting glucose post-test scores in combination groups (*P*-value= 0.005) decreased significantly after intervention, while in aerobic training group (*P*-value= 0.16) and Glycogol (*P*-value= 0.14) there were not significantly different. Intergroup (analysis of variance) showed that the difference between the groups in the glucose variable was not significant (*P*-value≤0. 05).

Discussion

The results of the study showed that in the intragroup comparisons in fasting glucose level, only the combination group (*P*-value= 0.005) decreased after the intervention.

Table 1. Comparing the mean age and BMI in the four groups

Variable \ Group	Aerobic exercise M (± SD)	Glycogol M (± SD)	Combined M (± SD)	Control M (± SD)	F	*P*-value
Age (year)	50.07 (±7.52)	52.44 (±8.26)	51. 2 (±5.9)	49.4 (±2.91)	1.39	0.26
BMI (kg/m^2)	31.05 (±3.9)	28.79 (±2.69)	29.41 (±3.39)	29.67 (±7.98)	1.17	0.33

Table 2. Comparing the apelin, glucose and insulin before and after exercise in the four groups

Variable	Step	Group				*P*-value (ANOVA)
		Aerobic exercise	Glycogol	Combined	Control	
Apelin (ng/ml)	before	1418.48 (±1126.14)	914.81 (±1625.36)	1269.83 (±1806.69)	326.43 (±1224.16)	0.1
	after	1797 (±1282.14)	1049.58 (±1969.66)	1289.03 (±2033.50)	316.86 (±1233.20)	
	P (paired T-test)	0.018	0.003	0.002	0.77	
Glucose (mg/dl)	before	217.9 (±72.9)	189.66 (±65.95)	195.10 (±45.47)	148.2 (±36.79)	0.2
	after	198.7 (±52.25)	167.33 (±55.29)	153.4 (±47.75)	148.46 (±39.8)	
	P (paired T-test)	0.16	0. 14	0.005	0.56	
Insulin (mIU/L)	before	12.18 (±2.98)	16 (±11.22)	11.59 (±8.75)	7.46 (±5.16)	0.82
	after	7.13 (±5.84)	12.45 (±8.57)	6.76 (±3.78)	6.11 (±4.4)	
	P (intragroup paired T-test)	0.44	0.15	0.057	0.28	

Table 3. Comparing lipid profile variables before and after exercise in the four groups

Variable	Step	Group				*P*-value (ANOVA)
		Aerobic exercise	Glycogol	Combined	Control	
Cholesterol (mg/dl)	before	218.25 (±62)	220.50 (±95.6)	146.37 (±17.57)	153.6 (±37.10)	0.009
	after	212.40 (±53.52)	192 (±44)	139.75 (±14.76	154 (±36.38)	
	p (paired T-test)	0.54	0.57	0.003	0.79	-
Triglyceride (mg/dl)	before	188.60 (±69.84)	199.44 (±71.22	195.10 (±45.47	132 (±59.7)	0.02
	after	183.80 (±48)	198.2 (±47.55)	153.40 (±47.75)	128.6 (±51.45)	
	p (paired T-test)	0.67	0.93	0.002	0.42	-
HDL (mg/dl)	before	45.7 (±4.71)	44.44 (±6.69)	43.30 (±7.25)	42.2 (±7.88)	0.63
	after	43.4 (±4.45)	45.33 (±14.071)	40.9 (±4.14)	42.80 (±7.85)	
	p (paired T-test)	0.25	0.78	0.25	0.30	-
LDL (mg/dl)	before	133.20 (±50.72)	108 (±27.03)	135.8 (±48.8)	87.40 (±30.68)	0.04
	after	136.60 (±48.02)	104 (±34.37)	118 (±34.37)	85.80 (±30.76)	
	p (paired T-test)	0.54	0.4	0.02	0.19	-

In a study by Behradmanesh and colleagues entitled "The effect of Glycogol capsules on blood glucose in type 2 diabetic patients", there was a significant decrease in blood sugar level in diabetic patients (18), which was not consistent with the current study. The possible reason of this difference was referred to the length of the research. In the Behradmanesh study, the length of his research was 3 months.

The levels of insulin in the Glycogol group were *P*-value= 0.15, in the combination group *P*-value= 0.05 and in the aerobic exercise group *P*-value= 0.44, respectively. Therefore, the mean difference after the intervention in the combination group was decreased. In the intragroup comparison, the p-value was 0.82. It means that the independent variable (aerobic exercise, Glycogol and combination) have not shown a significant effect on insulin reduction in all three groups. None of the variables in the control group also showed any significant difference. The results of the present study have been inconsistent with the results of some research.

Hemati and co-workers (2013) conducted a study entitled "the effect of highly periodic exercise (HIIT) on plasma levels of adiponectin, resistance and insulin sensitivity in inactive young men." In this study, 18 volunteers participated randomly in two experimental and control groups. The experimental group performed high intensity periodic exercise protocol for six weeks (three sessions per week). Each session consisted of four to six repetitions of running at maximum speed in a 20-meter area with 30 seconds of recovery. The results of this study showed that serum concentrations of insulin, fasting glucose and insulin resistance decreased in the experimental group; insulin sensitivity and beta cell function increased, but these changes were not statistically significant (22).

The reasons for the inconsistency of the results of Hemati and co-workers study with the present study were related to the gender of the participants, the type of exercise and the method of research. Taghian colleagues (2013) also showed that after 12 weeks of aerobic exercises, insulin and glucose levels did not change significantly in obese women (23). The reasons for the inconsistency of this research with the current study may be due to the type of exercise, sex of participants, or commercial kits measuring insulin and glucose.

In the intragroup comparison, in the case of insulin resistance, the p-value was 0.03 and 0.03 in Glycogol and combination groups, therefore, therefore, the mean difference before and after the intervention was significant. Kazemi and co-workers (2014), in a study entitled "effects of aerobic training on plasma concentration of apelin and insulin resistance in type 2 diabetic rats" showed a significant decrease in plasma concentrations of glucose and insulin as well as insulin resistance in the aerobic training group compared to the control group. In addition, there was a significant negative correlation between apelin plasma concentration and insulin resistance after 6 weeks of aerobic training, which is similar to the current study (24).

during a bout of exercise the increased contraction-stimulated glucose uptake is linked to increases in AMP-activated protein kinase (AMPK), which results in the phosphorylation of the RabGTPase-activating protein TBC1D1.It appears that a slightly different pathway is used to regulate glucose uptake at rest, and involves TBC1D4 (also known as AS160), the prologue of TBC1D1. TBC1D4 is involved in the insulin stimulated regulation of GLUT4 translocation and glucose uptake in adipocytes and myocytes (25). Insulin promotes the phosphorylation of TBC1D4 causing its deactivation and thereby increasing GLUT4 activity. TBC1D4 is also involved in the regulation of glucose uptake post exercise, when increases in SI are associated with elevated intracellular kinase Akt, which results in the phosphorylation of TBC1D4. TBC1D4 has similar properties to TBC1D1 and produces similar effects, in that the active form TBC1D4 promotes the hydrolysis of GTP to GDP on Rab proteins, thereby preventing the translocation of GLUT4 to the cell membrane (26).

In the present study, the glucose level decreased in the combination group. One of the components of Glycogol capsules is fenugreek, and in animal studies, the effect of this plant on type 1 and type 2 diabetes has been proven (27). Because of its high antioxidant effect, fenugreek reduces lipid peroxidation; fenugreek contains saponins, carbohydrates, steroids and alkaloids such as trigonella, trigonometry, all of which have a decreasing effect on blood glucose level. Fibers found in fenugreek reduce glucose uptake. Hydroxyisolucine, which is an amino acid found in fenugreek seed fiber, stimulates insulin secretion and increases the number of insulin receptors. Saponins in fenugreek also inhibit intestinal absorption of lipids (28,29).

Apelin in mice increases the displacement of GLUT4 from the cytoplasm to the plasma membrane. However, it is still not clear whether apelin is actively intermediate in regulating insulin sensitivity. Studies on mice injected with apelin showed that this cytokine could improve glucose uptake in insulin-resistant cells. Furthermore, apelin can act as a factor in increasing insulin sensitivity. The underlying mechanism of the apelin effects on insulin resistance remains unclear, but studies on mice showed that apelin specifically improved the displacement of GLUT4 due to insulin action (30). In the study of Kadoglou, it was shown that the AMP-activated protein kinase made the proposed link between insulin sensitivity with exercise mediation and apelin changes (31).

In the apelin variable, the mean difference before and after the intervention in the Glycogol capsules, aerobic exercise and combination groups was significant. Apelin serum levels increased significantly in three groups. Obviously, obesity is one of the risk factors for diabetes, which may lead to significant changes in plasma apelin levels. In a study conducted by Kazemi and colleagues entitled "effects of aerobic training on plasma concentration of apelin and insulin resistance in type 2 diabetic rats" it was emphasized on the effect of six weeks of aerobic training on the increase of apelin blood (24), which was consistent with the results of the present study. In a study by Haghighi (25) , titled "Changes in plasma apelin levels and insulin resistance index after an aerobic exercise program in overweight healthy women", the results of the effect of aerobic exercise on apelin was not inconsistent with our research. Probably the increase of apelin in this study is due to the research on diabetic participants that their fasting blood glucose levels are the stimulating factor for apelin. The results showed that aerobic exercise and Glycogol capsule consumption were effective in weight loss. Therefore, weight loss seems to be one of the main mechanisms for reducing plasma apelin after aerobic exercise.

In this study, insulin levels in the combination group significantly decreased. This change is justifiable by examining the relationship between cytokine and insulin. The rapid phosphorylation of insulin receptor substrate (IRS) is one of the main mechanisms for the

development of insulin resistance. Reducing insulin production improves insulin sensitivity and decreases insulin resistance (32).

On the other hand, some of the anti-inflammatory effects of exercise may be associated with a reduction in cytokines produced by adipose tissue. Long-term aerobic exercise reduces the production of atherogenic cytokines, while increasing the production of antiatherogenic cytokines. In some studies, it was shown that the produced insulin stimulates apelin production by adipose tissue. On the other hand, plasma apelin levels decrease with body weight loss (33). In the present study, the weight of the participants was significantly decreased, which is to some extent explained by the results obtained. One of the limitations of this study is the lack of strict control over the nutrition of the subjects.

Conclusions

Based on the findings of the present study, weight and BMI decreased in the aerobic exercise and combination groups. Perhaps you can get better results with the length of the training period. In other dependent variables, such as triglyceride, cholesterol, LDL, HDL, glucose and insulin resistance, there was a significant decrease in the combination group, which was not seen in other groups. It can be concluded that among the four groups, there was a significant change in the combination group, and the taking Glycogol capsules as well as exercise activities in parallel were considered the cause of this positive change. Moreover, the use of the Glycogol capsules and aerobic exercise activities as well as their combinations increase blood apelin levels in the post-test compared to the pre-test. This suggests a positive effect of taking Glycogol and exercise on people with diabetes.

Acknowledgments

The authors would like to appreciate all participants and those who helped us. This research was done by personal budget of the corresponding author and there was no conflict of interests in this research.

Funding

No grant.

Conflict of Interest

The authors declare that there is no conflict of interests.

References

1. Istek N, Karakurt P. Effect of activities of daily living on self-care agency in individuals with type 2 diabetes. Journal of Diabetes Mellitus. 2016;6(04):247.
2. Bahram ME, Mogharnasi M. The Effect of Twelve weeks High Intensity Training Interval (HIIT) on Leptin Levels and Obesity Dependent Factors among Female Students Suffering Overweight. Journal of Sport Biosciences. 2015;21;6(4):451-65.
3. Zarei M, Hamedinia M, Haghighi A, Noorafshar R, Amini S. Effect of three combined aerobic-resistance exercise training protocols with different intensities on metabolic control and visfatin levels in men with type 2 diabetes. Iranian Journal of Diabetes and Metabolism. 2016;16(1):63-76. (in Persian)
4. Santangelo C, Filesi C, Varì R, Scazzocchio B, Filardi T, Fogliano V, et al. Consumption of extra-virgin olive oil rich in phenolic compounds improves metabolic control in patients with type 2 diabetes mellitus: a possible involvement of reduced levels of circulating visfatin. Journal of Endocrinological Investigation. 2016;39(11):1295-301.
5. Heinonen MV, Laaksonen DE, Karhu T, Karhunen L, Laitinen T, Kainulainen S, et al. Effect of diet-induced weight loss on plasma apelin and cytokine levels in individuals with the metabolic syndrome. Nutrition, Metabolism and Cardiovascular Diseases. 2009 Nov 1;19(9):626-33.
6. O'Harte FP, Parthsarathy V, Hogg C, Flatt PR. Acylated apelin-13 amide analogues exhibit enzyme resistance and prolonged insulin releasing, glucose lowering and anorexic properties. Biochemical pharmacology. 2017;146:165-73.
7. Yue P, Jin H, Aillaud M, Deng AC, Azuma J, Asagami T, et al. Apelin is necessary for the maintenance of insulin sensitivity. American journal of physiology-endocrinology and metabolism. 2010;298(1):E59-67.
8. Boucher J, Masri B, Daviaud D, Gesta S, Guigné C, Mazzucotelli A, et al. Apelin, a newly identified

adipokine up-regulated by insulin and obesity. Endocrinology. 2005;146(4):1764-71.
9. Brame AL, Maguire JJ, Yang P, Dyson A, Torella R, Cheriyan J, et al. Design, characterization, and first-in-human study of the vascular actions of a novel biased apelin receptor agonist. Hypertension. 2015;65(4):834-40.
10. Cavallo MG, Sentinelli F, Barchetta I, Costantino C, Incani M, Perra L, Capoccia D, Romeo S, Cossu E, Leonetti F, Agati L. Altered glucose homeostasis is associated with increased serum apelin levels in type 2 diabetes mellitus. PLoS One. 2012;7(12).
11. Dray C, Knauf C, Daviaud D, Waget A, Boucher J, Buléon M, et al. Apelin stimulates glucose utilization in normal and obese insulin-resistant mice. Cell metabolism. 2008;8(5):437-45.
12. Boucher J, Masri B, Daviaud D, Gesta S, Guigné C, Mazzucotelli A, Castan-Laurell I, Tack I, Knibiehler B, Carpéné C, Audigier Y. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology. 2005 Apr 1;146(4):1764-71.
13. Glassford AJ, Yue P, Sheikh AY, Chun HJ, Zarafshar S, Chan DA, et al. HIF-1 regulates hypoxia-and insulin-induced expression of apelin in adipocytes. American Journal of Physiology-Endocrinology and Metabolism. 2007;293(6):E1590-6.
14. Winzell MS, Magnusson C, Ahrén B. The apj receptor is expressed in pancreatic islets and its ligand, apelin, inhibits insulin secretion in mice. Regulatory peptides. 2005;131(1-3):12-7.
15. Marmett B, Nunes RB. Resistance and aerobic training in the treatment of type 2 diabetes mellitus. J Diabetes Metab Disord Control. 2017;4(5):00126.
16. Delavar R, Heidarianpour A. The effect of aerobic exercise training on plasma apelin levels and pain threshold in T1DM rats. Iranian Red Crescent Medical Journal. 2016;18(9).
17. Kim HJ, Lee JS, Kim CK. Effect of exercise training on muscle glucose transporter 4 protein and intramuscular lipid content in elderly men with impaired glucose tolerance. European journal of applied physiology. 2004;93(3):353-8.
18. Behradmanesh M, Ahmadi M, Rafieian-Kopaei M. Effect of glycogol on blood glucose level of patients with type II diabetes. Iranian Journal of Endocrinology and Metabolism. 2012;14(2):163-8.
19. Hordern MD, Dunstan DW, Prins JB, Baker MK, Singh MA, Coombes JS. Exercise prescription for patients with type 2 diabetes and pre-diabetes: a position statement from Exercise and Sport Science Australia. Journal of Science and Medicine in Sport. 2012;15(1):25-31.
20. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RRet al. Exercise and type 2 diabetes: the American college of sports medicine and the American diabetes association: joint position statement. Diabetes care. 2010;33(12):e147-67.
21. Ïzadi M, Soheli S, Khorshidi D, Doali H. The Relationship between Serum Ghrelin with Beta-Çell Function Ïndex and Ïnsulin Resistance in People with Type 2 Diabetes. J Mazandaran Univ Med Sci. 2011; 21 (82) :18-25.(in Persian).
22. Hemmatinafar M, Kordi M, Choopani S, Choobineh S, Gharari Arefi R. The Effect of High Intensity Interval Training (HIIT) on Plasma Adiponectin Levels, Insulin Sensitivity and Resistance in Sedentary Young Men. Journal of Advances in Medical and Biomedical Research. 2013;21(84):1-12. (in Persian) Taghian F, Zolfaghary M, Hedayati M. Effect of 12 weeks aerobic exercise on visfatin level and insulin resistance in obese women. Razi Journal of Medical Sciences. 2014;20(116):35-44. (in Persian).
23. Kazemi F, Ebrahim K, Asl SZ. Effects of aerobic training on plasma concentration of apelin and insulin resistance in type 2 diabetic rats. Journal of Tabriz University of Medical Sciences and Health. 2014;36(3):62.
24. Haghighi Amir Hossein. The Effect of Aerobic Training and Green Tea Supplement on Serum Leptin and Insulin Resistance in Overweight and Obese Men. Journal of Faculty of Sport Biosciences 2013;4(15):23-43.
25. Bird SR, Hawley JA. Update on the effects of physical activity on insulin sensitivity in humans. British Journal of Sports Medicine (BJSM).. 2017;2(1):e000143.
26. Xue WL, Li XS, Zhang J, Liu YH, Wang ZL, Zhang RJ. Effect of Trigonella foenum-graecum (fenugreek) extract on blood glucose, blood lipid and hemorheological properties in streptozotocin-induced diabetic rats. Asia Pac J Clin Nutr. 2007;16(1):422-6.
27. Sauvaire Y, Ribes G, Baccou JC, Loubatieres-Mariani MM. Implication of steroid saponins and sapogenins in the hypocholesterolemic effect of fenugreek. Lipids. 1991;26(3):191-7.
28. Eidi M, Eidi A, Zamanizadeh H. Effect of Salvia officinalis L. leaves on serum glucose and insulin in healthy and streptozotocin-induced diabetic rats. Journal of ethnopharmacology. 2005;100(3):310-3.
29. Zhu S, Sun F, Li W, Cao Y, Wang C, Wang Y, et al. Apelin stimulates glucose uptake through the PI3K/Akt pathway and improves insulin resistance in 3T3-L1 adipocytes. Molecular and cellular biochemistry. 2011;353(1-2):305-13.
30. Kadoglou NP, Vrabas IS, Kapelouzou A, Lampropoulos S, Sailer N, Kostakis A, et al. The impact of aerobic exercise training on novel adipokines, apelin and ghrelin, in patients with type 2 diabetes. Medical science monitor: international medical journal of experimental and clinical research. 2012;18(5):CR290.

31. Esposito K, Nappo F, Giugliano F, Di Palo C, Ciotola M, Barbieri M, et al. Meal modulation of circulating interleukin 18 and adiponectin concentrations in healthy subjects and in patients with type 2 diabetes mellitus. The American journal of clinical nutrition. 2003;78(6):1135-40.

32. Gielen S, Adams V, Möbius-Winkler S, Linke A, Erbs S, Yu J, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. Journal of the American College of Cardiology. 2003;42(5):861-8.