ORGINAL ARTICLE

Effects of High Intensity Interval Training and Combined Training on Serum Apelin Levels and pancreatic β-cell function in Overweight Type 2 Diabetes Women

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Received: 01 January 2019

Accepted: 21 February 2019

Published in May 2019

Abstract

Objective: Physical exercise is a well-established therapeutic method in type 2 diabetes treatment. The purpose of this study was to investigate the effects of eight weeks combined and High Intensity Interval Training on serum apelin levels and pancreatic β-cell function in overweight women with type 2 diabetes mellitus.

Materials and Methods: Fifty-two overweight female patients with type 2 diabetes (aged 45-60 years old, BMI> 30) with HbA1c>6.5% participated in the study voluntarily. The participants were assigned to High Intensity Interval Training (HIIT) group (n= 17), combined training group (n= 17), and control group (n= 18) according to their HbA1c levels. The exercises included 12 weeks of combined training and HIIT. Levels of HbA1c and fasting glucose and insulin were measured.

Results: There was a significant decrease in the fasting blood glucose in the HIIT groups (*P*-value: 0.001). Serum insulin levels showed significant increases in the HIIT (*P*-value: 0.001) and combined training groups (*P*-value: 0.001). Changes in apelin level were not significantly different within HIIT and combined training groups (*P*-value: 0.13 and 0.09, respectively). The data showed significant differences in pancreatic β-cells function in HIIT ($P <$ 0.001) and combined training groups (P= 0.003). Furthermore, the ANCOVA test showed that there were no significant differences in fasting blood glucose concentrations (F= 1.853, *P*-value: 0.171), apelin (F= 0.511, *P*-value: 0.12). However, significant differences were observed between groups in insulin (F= 3.622, *P*-value: 0.036), and β-cell function (F= 4.243, *P*-value: 0.003).

Conclusion: Physical exercise is an effective training method to improve glycemic control in woman with type 2 diabetes.

Keywords: Apelin, pancreatic β-cells function, Diabetes mellitus, High intensity interval training, Combined training

Introduction

Obesity and noninsulin-dependent diabetes mellitus are globally epidemic (1). Type two diabetic mellitus (T2DM) occurs due to a combination of peripheral insulin resistance (skeletal muscle, liver, and adipose tissue) and ultimately due to a failure of beta cell mass to compensate for this resistance (2).

During the last decade, a growing number of adipokines have been identified, including leptin adiponectin, resistin and lipokine. These adipokines play a role in the physiological settings of fat stores, metabolism, and nutritional behavior as well as obesity-related disorders. It has been reported in recent years that adipose tissue secretes an adipokine called aplein, which plays a role in carbohydrate metabolism and insulin function (3). Apelin is a peptide hormone that has been introduced as an endogenous ligand for the APJ receptor, similar to the angiotensin receptor coupled to the coupled G protein. Apelin levels change with changes in insulin levels in the blood and it seems to prevent insulin secretion in the pancreas. Obviously, decreasing the amount of insulin produced or even preventing its effect on glucose metabolism will reduce its blood loss. Give this condition causes hyperglycemia and in the long term leads to type 2 diabetes (3).

Apelin plasma levels increase in obesity, along with insulin resistance and hyperinsulinemia (rats and humans) (3). In a study, diabetic patients and patients with impaired glucose tolerance, levels of apelin increased significantly and stated that there was a potential relationship between aplein and the pathogenicity of insulin resistance and type 2 diabetes(4). Researchers have reported that insulin sensitivity decreases in the pleura muscle of mice with apelin deficiency. As a result, those mice are affected by insulin resistance and, eventually, by type 2 diabetes. Subsequently, apelin injection to subjects increased muscle glucose uptake and Akt phosphorylation and ultimately improved insulin sensitivity. The researchers concluded that this effect of Apelin is mediated by the protein-dependent protein G and AMPK.

Physical activity can stimulate insulin signaling by affecting glucose function and affect blood glucose and its long-term effects (3,5). In some clinical studies, Apelin levels have been reported to increase in obesity and insulin resistance, and aplein levels decrease with body weight loss (3). Physical exercises also increase levels of Glucose transporter type 4 (GLUT-4) as an agent. It is effective in preventing insulin resistance.

Exercise improves blood glucose control in type 2 diabetes, reduces cardiovascular risk factors, contributes to weight loss, and improves well-being (6,7). The challenges related to blood glucose management vary with diabetes type, activity type, and presence of diabetes-related complications (9,10). Physical activity and exercise recommendations, therefore, should be tailored to meet the specific needs of each individual. The activity that involves a larger muscle mass has better results for patients with T2DM (11). One of the important immediate effects of an aerobic exercise is improving insulin function, so that in most people 2 to 72 hours after the session of exercise with moderate intensity, blood glucose levels decrease. Gorman et al., for example, showed that blood glucose reduces for 16 hours after an aerobic exercise session, and signaling pathways involved in glucose uptake into skeletal muscle are active (12). Blood glucose reduction depends on the duration and intensity of the exercise, the training status and the state of diabetes. Although exercise generally increases glucose uptake and stimulates fat oxidation, long-term and severe physical activity improves longer-term insulin function (13).

Lack of time and a decrease in blood glucose observed in continuous exercises are important barriers in diabetes to do sports activities (14). Other studies have shown that Sprint Interval Training (SIT), as a High Intensity Interval Training (HIIT) protocol, has beneficial effects on health such as cardiovascular health and fat loss in T2DM patients (15).

Ghasemi Karam et al. (16) compared the effect of HIIT and slow continuous exercises on insulin resistance in overweight men. Insulin resistance and fasting glucose significantly decreased in both training groups compared to the control group. The results of this study showed, there were no significant difference between the two types of exercises on insulin resistance. It seems that improvement in insulin resistance does not depend on the type of exercise, and a regular exercise program in terms of timing and repetitions can change insulin resistance (16).

Apelin is a beneficial adipocytokine with anti-obesity and anti-diabetes properties and a glucose hemostasis regulator (17). Eight weeks endurance training regulate apelin gene expression in obese subjects, however, in response to exercise, there is no change on the level of serum apelin (18). Kadoglou et al. (19) showed, 12 weeks of aerobic training increases apelin level in T2DM patients (19).

Given that the factors contributing to the inability of beta cells and the increased prevalence of diabetes in obese individuals have not yet been fully understood. Therefore, we assumed that combined exercises and high intensity exercises could produce beneficial effects for diabetic patients. Therefore, the aim of this study was to investigate the effects of different HIIT and combined (strength and aerobic) exercises on apelin serum levels and β-cell function in women with T2DM.

Materials and Methods

This research is semi-experimental, which was done in both the field and laboratory. After initial negotiations with the Shahrekord Diabetes Association Centers and announcements distributed in Shahrekord City, qualified individuals were invited to participate in the study. Among 60 patients who were referred to the clinic, 52 T2DM women between 45 to 60 years old, fasting blood glucose (FBG) greater than 126 mg / dl (20,21), an HbA1c > 6.5% , and body mass index (BMI) between 25-30 kg / m² were selected. The sampling method was convinient. Twenty-seven subjects consumed thiazolidinedione and metformin, 20 patients with insulin injections, and 5 subjects received insulin and oral medication. The participants were assigned to HIIT group (n= 17), combined training group (n= 17), and control group (n= 18) according to their HbA1c levels. They filled out the consent form, the medical background questionnaire, and preparation questionnaire for starting the physical activity, and they had no cardiovascular, articular and neuromuscular diseases, diabetic foot ulcers, and nephropathy in past medical history. First, during a meeting, the volunteers became familiar with the type of study, its objectives, and method of implementation. The volunteers were assured that the information received from them would be completely private. They were allocated to three groups by simple randomization. At the end, 42 subjects completed the study period and 10 were excluded due to some illness and absence in the training sessions. About 24 hours before the start of the training and 48 hours after the last training session, the subjects' blood samples were taken in identical conditions.

The current training course was held for eight weeks and three sessions per week. The combined group program was performed according to Table 1. The combined exercise group had two sessions per week, resistance training with 70% of one maximum repetition and aerobic exercise with 60-70% of maximum heart rate and one session per week only aerobic exercise (a total of three session per week). The combined exercise group

Table 1. The combined training (strength-aerobic) protocol

Week	Strength training					Aerobic training		
	Set	Repetition	Recovery time between each set (min)	Weight (IRM percent)	Number of sessions per week	Duration (min/day)	Intensity (MHR percent)	Repetition (day/week)
Introduction (Week 1)	1	15	2-3	15	2	15	60	3
Introduction (Week 2)	2	15	2-3	15	2	20	60	3
1-2	3	15	2-3	12	2	25	70	3
3-4	3	12	2-3	12	2	30	70	3
5-6	3	12	2-3	12	2	30	70	3
7-8	3	10	2-3	10	2	30	70	3

initially exercised the strength training program and, after five minutes rest, they performed an aerobic exercise program. In order to personalize the exercise, if a person could have three sets of exercises with eight more repetitions, that is, a total of 20 repetitions at one session, 2.5 to 5 kg were added to the weight (22). In an aerobic exercise, if the person could practice two consecutive sessions with the same intensity as recommended, 5 to 10 % was added to the percentage of heart rate in which the activity was performed (23,24). In the HIIT group, the main exercise consisted of 4-10 repetitions of a 30 seconds Wingate test on an ergometer with maximum effort. The participants in this group performed a riding activity in the Wingate test lasted for 30 seconds with a resistance equivalent to 7.5% of their body weight. The number of performances of the Wingate test was increased during each training week (25), and if the subject could complete three repetitions at a specified speed and load in two consecutive sessions, 10% was added to the amount of load. The recovery time between each repetition was four minutes of inactive rest. The total activity time for this practice was considered to be 20 to 40 minutes (26). The control group did not participate in any regular activity.

Before the start of the research protocol and after the eight weeks, the subjects came to the clinic, and their weight, height and body mass index were measured.

In order to estimate the maximum power, the subjects first warmed up with a lighter weight and then, the subjects selected a weight based on their own estimations that they could lift up perfectly and correctly at least once and maximally 10 times. By placing the weight value and number of repetitions in the following formula, the maximum power of the subject was obtained in each movement (27).

1 RM= Weight ÷ (1.0278 - (0.0278 × Number of repetitions))

The thickness of the subcutaneous fat was measured using calipers. The fat thickness of each point was measured three times in a rotary manner and its mean was used in the formula:

Body density= 1.0994921 - 0.0009929 (X) + 0.0000023 (X^2) - 0.0001392 (age)

Fat percentage= (4.95÷ Body density - 4.5) ÷100

X: indicates the thickness of the subcutaneous fat of the three points of the thigh, the upper pelvis and the triceps brachii in millimeters (28).

To measure the thickness of the subcutaneous fat, the Harpenden caliper was used with an accuracy of 0.1 mm.

In order to measure serum glucose, insulin and apelin, 24 hours before the start of exercise protocol and 48 hours after the last session, 10 cc of blood was taken from the subjects after 12 hours of fasting. Serum glucose and apelin levels were measured by ELISA method using Pars kit manufactured in Iran. Serum level of insulin was measured by ELISA method using Diaplus kit manufactured in the USA.

IR formula was used to calculate the β-cell function.

β-cell function =(20 ×fasting serum insulin (ml / ml) ÷ (3.5× fasting serum glucose (mg / dl)).

Descriptive statistics were used to calculate the mean and standard deviation (SD) of the research variables. The protocol was registered in the Iranian clinical trial registry, IRCT: IRCT20141118019995N1. The ethics committee of Shahrekord University (code no: sku94/210) granted the ethical approval of study. The Kolmogorov-Smirnov test was also used to evaluate the normal distribution of data. The differences between the groups were dependent on the T-test and to determine the differences between the groups, the analysis of covariance (ANCOVA) was used and the significance of the LSD test was used to determine the difference between the groups. All statistical calculations were performed using SPSS software version 17 and at the significance level of 0.05.

Results

Anthropometric and physiological features as well as serum glucose, apelin, and insulin and β-cell function in the subjects were shown in Table 2. Comparison of intra-group changes showed no significant reduction in the percentage of fat, hip circumference, waist to hip ratio, BMI, and mean blood pressure in both training groups, while body mass in the combined group decreased significantly. However, there was no significant difference between the pre- and post-test findings in the control group. Reduction of FBG was insignificant after the combined training and significant in the HIIT group. No significant decrease in FBG was observed in the control group. Apelin levels in both training groups did not decrease significantly. The inter-group outcomes did not show significant difference in FBG and apelin variables.

Serum insulin decreased significantly in both training groups. β-cell function increased significantly in both training groups The inter-group results showed a significant difference between the HIIT group and control group in serum insulin and β-cell function (Table 3).

Table 2. Comparison of intra-group and inter-group changes in three training groups

Variable		HIIT Mean (±SD)	Combined training Mean (±SD)	Control Mean (±SD)	Inter-group F	Inter-group P
Body mass (kg)	Pre-test	73.06± 21.62	76.30± 9.58	71.26± 13.20	1.69	0.197
	Post-test	77.00± 12.34	75.55±9.23	71.44± 13.06		
	Intra-group t	-0.914	2.407	-0.481		
	P-value	0.377	0.032	0.639		
Body mass index (kg/m2)	Pre-test	29.57±2.77	29.85± 2.97	29.13± 4.17	0.51	0.603
	Post-test	28.97± 3.39	29.99± 8.61	29.70± 4.41		
	Intra-group t	1.211	-0.421	-1.386		
	P-value	0.248	0.680	0.189		
Body fat percent (%)	Pre-test	42.64± 2.23	31.32± 4.63	43.92± 2.49	0.60	0.550
	Post-test	41.14± 4.34	27.99± 2.36	42.64± 4.95		
	Intra-group t	1.042	-0.976	0.911		
	P-value	0.317	0.347	0.379		
Waist to hip ration	Pre-test	1.01± 0.13	1.01± 0.25	1.01± 0.018	0.17	0.837
	Post-test	0.93± 0.06	0.97± 0.07	0.98± 0.070		
	Intra-group t	1.455	0.653	1.107		
	P-value	0.170	0.525	0.288		
Mean blood pressure (MmHg)	Pre-test	9.548± 1.141	9.500± 1.32	6.707± 1.19	14.31	0.000
	Post-test	9.185± 0.53	9.200± 1.15	6.650± 0.97		
	Intra-group t	1.047	1.144	2.357		
	P-value	0.314	0.273	0.189		
Apelin	Pre-test	256/65± 25.12	286.56± 42.12	302.44± 38.03	0.511	0.12
	Post-test	279.12± 50.08	266.26± 56.00	312.23± 63.03		
	Intra-group t	0.980	2.452	0.450		
	P-value	0.13	0.09	0.73		
FBG	Pre-test	210.07± 32.90	216± 63.08	177.28± 47.09	1.853	0.171
	Post-test	147.92± 41.17	163.85± 71.47	183.28± 60.70		
	Intra-group t	5.34	2.04	-0.408		
	P-value	0.000	0.062	0.690		
Insulin	Pre-test	7.72± 2.63	9.10± 2.62	6.58± 1.61	3.622	0.036
	Post-test	4.96± 1.30	5.93± 2.24	6.21± 2.06		
	Intra-group t	4.95	4.31	0.912		
	P-value	0.000	0.001	0.378		
β-cell function	Pre-test	47.34± 15.21	45.88± 10.61	47.87± 14.25	4.243	0.003
	Post-test	57.63± 11.18	54.36± 9.13	48.63± 12.43		
	Intra-group t	3.35	4.65	0.365		
	P-value	0.000	0.000	0.530		

Table 3. LSD follow-up test results in Insulin and Insulin resistance variables

Group	Inter-group difference	Insulin *P*-value	Insulin resistance *P*-value
HIIT group	Combined group	0.539	0.144
	Control group	0.012	0.001
Combined group	HIIT group	0.539	0.144
	Control group	0.070	0.168

Discussion

According our findings, during intense HIIT and combined exercises, the decrease of FBG was only significant in the HIIT group. Insulin significantly decreased in HIIT and combined groups. β-cell function significantly increased in HIIT and combined groups Apelin had no significant reduction in intra-group and inter-group. Inter-group outcomes showed no significant difference in training groups, except for insulin and β-cell function, which is consistent with the results of some studies and inconsistent with some others.

In general, the performance indicator for pancreatic beta cells is influenced by the ratio of FBG and insulin levels. Physical activity seems to be effective in improving the performance index of pancreatic beta cells by lowering insulin and blood glucose levels and improving blood glucose control in type 2 diabetic patients. In this regard, Cathie et al. reported that short-term aerobic activity (7 consecutive days, 1 hour per session with 60-70% of maximum heart rate) in elderly people with impaired glucose tolerance improved 59% in insulin sensitivity and 31% in the function of pancreatic beta cells. Overall, their results indicated that short-term sports activities in elderly people with impaired glucose tolerance improve insulin resistanceand the function of pancreatic beta cells (29). Cris et al. reported that aerobic exercise was performed for 8 months in overweight men with sedentary lifestyle (first group: low mileage training 12 miles per week and moderate severity of 40 to 55 percent oxygen consumption, group 2: Exercise with low mileage 12 miles per week and high intensity 65-80 percent of consumed oxygen, third group: 20-mile-long exercise and high intensity 65-80 percent of oxygen consumption) lead to improvement of the function of pancreatic beta cells in three aerobic training groups, but this improvement was higher in the moderate intensity group (30). Exercise in addition to lowering insulin levels of the plasma improves insulin receptor at the cell surface. Exercise by reducing the levels of glucose and fasting insulin leads to improved function of the pancreatic beta cells.

There was an insignificant increase in serum apelin levels in HIIT group and an insignificant decrease in the combined group. Apelin can be considered as a good adipokine. Apelin can reduce body fat, insulin and triglyceride levels (31). Our research results are incompatible with the results of Kadoglou et al. (19), which showed a significant increase in serum apelin level after aerobic exercise intervention in diabetic patients (19). Although Kadoglou et al. (19) found that aerobic exercise is effective on apelin levels, even in the absence of a significant decrease in the weight of T2DM women. Sheibani et al. also reported 8 weeks aerobic training was effective in reducing serum apelin levels, BMI and body fat mass in obese women (32).

As the results showed, there was a significant improvement in serum insulin and β-cell function in the HIIT and combined groups compared to the control group. Therefore, physical exercises more than 12 weeks with different training practices (a combination of aerobic, resistance and HIIT trainings versus non-training) have beneficial effects on adipocytokine factors in people with T2DM. During the 12 weeks of exercise, BMI, body fat percentage and WHR in the HIIT and combined groups were significantly decreased compared to the control group. An insignificant decrease observed in the level of apelin in the combined training group may be due to the insufficient stimulus in the present study.

In a study conducted by Alizadeh et al. (33), 27 overweight or obese women were divided into three groups. One group performed a continuous exercise of jogging with moderate intensity for 40 minutes per day, and another group performed a continuous exercise with moderate intensity. It was concluded that there was no significant difference in FBG and lipid profile in the three groups (33).

In a study by Kadoglou et al. (19) 132 subjects with BMI> 25 kg / m2 were divided into four groups. One group performed self-care exercises, the other group performed aerobic exercises four days a week, with 60-75% of maximum heart rate, and the third group performed resistance training, with 60-80% of a maximum repeat. There was also a control group. The results of the study showed that all the active groups had significant improvements in their blood glucose, insulin, insulin sensitivity and triglyceride levels compared to the control group. Since obesity is the most important factor in the progression of insulin resistance, reducing fat percentage can improve insulin sensitivity (19). In the present study, the fat percentage of the subjects in both training groups was decreased but not significantly. Reducing fat percentage by reducing the production of glucose in the liver, increases insulin secretion from pancreas and decreases insulin resistance. It can be said that in both exercises, decreasing the percentage of fat in subjects resulted in significant changes in insulin and insulin resistance.

Cuff et al. (34) studied the effect of multi-interval physical activity on insulin resistance in type 2 diabetic women. A total of 28 postmenopausal women with T2DM were randomly assigned to one of the three groups and exercised for 16 weeks: control, aerobic training, and aerobic training along with resistance training. Only the combined group had an improvement in insulin sensitivity and insulin and a significant increase in muscle density (34). In this study, improvement in insulin resistance was attributed to improvement in body mass index, while the BMI in our study decreased in both training groups, but not significantly. There is a relationship between the duration of the training period and the BMI, so that the duration of the exercise increases the insulin sensitivity, which can be interpreted by increasing the receptor of insulin signaling, or the level of glucose transporting protein and genes, activating glycogen synthesis and hexokinase, or by increasing the reciprocation of muscle glucose and variation in the composition of the muscles (34). The duration of the training period in Cuff's research was longer than our research, and perhaps the insignificance of the BMI could be attributed to the short duration of the training period. However, it seems that a decrease in BMI has been effective in improving insulin and insulin resistance.

Conclusions

Regarding the results of this study on the effect of two types of exercises on glucose metabolism and glycemic indexes, it can be suggested that both types of exercises have the same capability and efficiency to improve these indices, therefore, People with limited time and also have unwanted effects of continuous exercises can use this effective method of HIIT to improve their glycemic conditions. Also, coaches and specialists in the rehabilitation of people with T2DM can also be these types of exercises with the same efficiency as compared with continuous training in their safe use.

Acknowledgments

Thanks to all of the subjects of this research and Pars Sport Rehabilitation Center in Shahrekord.

Funding

All the costs of this research were provided by the research authors

Conflict of Interest

No case was reported by the authors.

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