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THE EFFECT OF RESISTANCE TRAINING ON PARAOXONASE-1 IN WOMEN WITH TYPE 2 DIABETES

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ABSTRACT

Introduction: There are limited data on the effect of exercise on paraoxonase-1 levels in patients with type 2 diabetes. The objective of this study was to examine the effect of resistance exercise on plasma concentrations of paraoxonase-1 levels and some metabolic indices in diabetic status. Methodology: Twenty-five adult women with type 2 diabetes were randomly assigned to resistance exercise (n=12) and control (n = 12) groups. The resistance exercise program included 3 sessions per week for 8 weeks. Concentrations of paraoxonase-1, glucose, insulin, and insulin resistance index were measured before and after intervention. T-test was used for intra-group assessment of variables and t-independent t-test was used for the comparison of the variables. Results: Intra-group analysis results showed that the changes of paraoxonase-1 and glucose levels in both groups were not significant. After 12 weeks of resistance exercise, insulin levels and insulin resistance index decreased significantly in the experimental group, and after 12 weeks of resistance exercise, significant difference was seen in insulin levels and insulin resistance index in the experimental group compared to those in control group. Conclusion: Based on the results of this study, after 12 weeks of circular resistance exercise, non-significant increase was seen in serum paraoxonase-1 concentration level and significant decrease was seen in insulin levels and insulin resistance index. Given significant decrease in insulin resistance index in the experimental group and its non-significant change in control group, it can be stated that insulin resistance in the experimental group improved.

Keywords: Resistance Exercise, Paraoxonase-1, Insulin, Type 2 Diabetes

INTRODUCTION

An increase in the prevalence of type 2 diabetes has caused this disease to be considered as one of the health problems. This metabolic disease is associated with an increase in the concentration of hyperglycemia. Hyperglycemia in the long term leads to many pathological changes such as neuropathy, retinopathy, gastrointestinal dysfunction, immune system deficiency, vascular damage, and tissue repair disorder (Balducci et al., 2012). Researchers believe that insulin resistance plays a major role in the pathophysiology of type 2 diabetes. Patients with diabetes are highly susceptible to cardiovascular complications, so that cardiovascular diseases are considered as the most important cause of death in these patients. The most common of these factors are increased triglyceride levels, reduced HDL levels, high LDL, obesity and high blood pressure (Belfiore et al., 2011). One of the factors involved in regulating lipid oxidation is the paraoxonase enzyme. Paraoxonase-1 is calcium-dependent esters, discovered for the first time in 1946. It is produced in the liver (Boule et al., 2001).

Paraoxonase is an enzyme established on HDL, which can play an important role in the antioxidant and anti-thyrogenic properties of lipoproteins. It also prevents oxidation of lipoproteins and formation of oxidized LDL in vitro conditions (Belfiore et al., 2011). Other roles of paraoxonase-1 include hydrolyzing and inactivating of toxic metabolites of homocysteine thiolactone. It also plays role in pathogenesis of various diseases such as diabetes, chronic renal failure, obesity and metabolic syndrome (Boule et al., 2001). Moreover, the clinical importance of this enzyme has not yet been proven, since conflicting results have been reported in epidemiologic studies in order to determine the relationship between the activity of this enzyme and coronary artery disease in obese people (Boule et al., 2001).

One of the factors involved in the diabetes is an increase in insulin levels, which is due to an increase in blood glucose concentration. Insulin causes the growth of body tissues through various mechanisms, which the most important of them is the regulation of lipoprotein lipase (LPL) (Boule et al., 2001). Insulin shows lipogenic effects. It is also a strong inhibitor of lipolind in the liver and fatty tissue. In addition, insulin inhibits hormone-sensitive lipase. Insulin also lowers the concentration of free fatty acids in the plasma (Brites, et al., 2000). Diabetes and aging are associated with reduced muscle strength and metabolic control, leading to reduced muscle mass. Despite the beneficial effects of aerobic activity on cardiovascular and metabolic parameters, some patients with type 2 diabetes, especially old and obese people, have difficulty in performing these types of exercises (Costa et al., 2005). Increasing exercise activity, especially resistance exercise, in patients with type 2 diabetes, can be effective in increasing physical function, controlling blood glucose, and preventing plasma lipids and blood glucose levels (Costa et al., 2005; Dunstan et al., 2002), decreased oxidative stress (Ernst et al., 2010) and increased insulin sensitivity (Eves et al., 2006), increased strength and mass Muscle and also bone density can and control of blood glucose and can be effective in preventing sarcopenia and osteoporosis through reducing the plasma lipid levels and blood glucose (Flack et al., 2010). Increasing insulin, using glucose, and muscle mass caused by muscle contraction make exercise resistance a suitable tool for people with diabetes. This type of exercise is also effective and safe for obese and elderly people (Dunstan et al., 2002). Little research was conducted on the effect of exercise on paraoxonase-1 levels as an effective factor in insulin sensitivity. With regard to the effect of physical activity on the paraoxonase enzyme, researchers found that in subjects with metabolic syndrome, performing exercises with moderate severity increased serum paraoxonase-1 during three months (Fuhrman, 2012). In contrast, results of other studies showed that in patients with coronary artery disease and in subjects with metabolic syndrome, aerobic and resistance exercise led into an increase in paraoxonase-1 levels in serum (Costa et al., 2005). Based on the studies, few studies have been conducted on the effect of resistance exercise on plasma concentrations of paraoxon-1 in patients with type 2 diabetes, especially in adult women. Thus, the objective of this study was to examine the effect of resistance exercise on plasma concentration of paraoxon-1 in adult women with type 2 diabetes.

METHODOLOGY

Subjects

The study was a quasi-experimental design with a pre-test and post-test design. Twenty-four adult women with type 2 diabetes in Zanzan city participated in the study. The inclusion criteria of subjects included having at least one-year history of type 2 diabetes and blood glucose higher than 100 mg / ml, and no history of cardiovascular, renal, and hepatic disease, infection, surgery, injuries, and not taking alcohol and tobacco agents. During the study period, the subjects consumed metformin and chlorpropamide capsules twice per day, based on prescription of physicians, which due to ethical considerations, there was no possible to discontinue medications. After the examinations, written consent was taken from the participants. Then, subjects were randomly divided into experimental and control groups (age = 47.75 ± 7.04 years, weight = 90.9 ± 9.6 kg, n = 10) and control group (age = 49.08 ± 6.48 years, weight = 84.12 ± 5.86 kg, n = 12).

Resistance exercise protocol

The experimental group exercises for 12 weeks, 3 days per week, one session per day for 60 minutes, with intensity of 50-80% of a maximal repeat. Accordingly, the subjects of the experimental group exercised with intensity of 50-70% of a maximal repeat for 6 weeks and 10-15 repetitions for each movement, and in the 6th week to the end of the exercise period. Since second 6 weeks up to end of exercise period, they exercises with intensity of 70-80% of a maximal repeat and with 8 to 10 repetitions for each movement. The program of each session included 3 turns and each turn also included 8 stations. The activity time at each station was 45-60 seconds, the rest time between stations was 30-60 seconds and the rest time between two turns was 120-180 seconds (Ghosh *et al.*, 2009; Goldhammer *et al.*, 2007). The specifications of the exercise protocol are presented in Table 1.



Table 1: Specifications of the resistance exercise protocol

Time	Number of sessions per week	Exercise intensity (One maximum repetition)	Number of period	The number of repetitions at each station	Time of each station	Rest time between each station (Second)	The rest time between each period (Second)
The first 6 weeks	3 sessions	50-70%	3	10-15	45-60	30-60	120-180
The second six weeks	3 sessions	70-80%	3	8-10	45-60	30-60	120-180

Stations include breast press, knee opening, knee flexion, Lat Pull Down, arm bending, seated rowing, heel lifting, and arm opening. The principle of overload was designed in such a way that, after four weeks of practice, one maximal repeat test was performed for each person at each station and the weight was adjusted accordingly. It should be noted that these movements were performed with circular bodybuilding equipment in circular (Goldhammer *et al.*, 2007). The total time of each exercise session included warming up very light and without resistance for 10-15 minutes, an exercise program with weight and cooling for 10 minutes.

The method of measurement of variables

First, height was measured by a height meter with precision of 0.1 cm, the weight was measured by using a digital scale with precision of 0.1 kg and the organ circumference was measured with strip meter. The percentage of body fat was also obtained using a body composition analyzer. Table 1 shows the physical and functional characteristics of the subjects before and after 12 weeks of resistance exercise. Then, the values of one maximal repeat of 10 activities of the subjects were determined. In order to determine one maximal repeat of considered movements, the subjects were first invited to the test site a few days before the main exercise to be acquainted with the desired movements and one maximal repeat of the movements to be obtained. Subjects first performed each movement with 8 to 10 repeats and 50% of their maximal expected repeat. Then, the subjects rested for one minute. Then, the subjects performed the considered movements with 3 to 5 repeats and 75% of their maximal expected repeat. Then, they rested for a minute. After performing the above steps, the subjects increased the weight from 1.25 to 4.5 kg to reach a maximal expected repeat. This process was performed until voluntary fatigue time. The weight through which the subjects reached voluntary fatigue was determined as a maximal expected repeat of the considered movements (Hordern et al., 2012). Blood sampling was performed 48 hours before the first exercise session and 48 hours after the last exercise session. Subjects were asked to avoid using these foods for 12 hours before blood sampling. To simulate the sampling time in order to control circadian rhythm, sampling was performed at the beginning and the end of the study at 8 am. In this study, 10 cc of blood was taken from arm vein of right hand of the subjects and the samples were collected in tubes containing Ethylene Diamine Tetra Acetic Acid (EDTA) and centrifuged (at 2000 rpm for 10 minute) and the plasma was stored at freezing temperature at -80°C . Serum concentration of paraoxonase -1 and insulin was determined by ELISA method and by using human specific kits. They were purchased from China and Mercodia AB, Uppsala, Sweden, respectively. The concentration of glucose was determined by enzymatic-dyeing method using glucose oxidase technology and glucose kit (Pars Test Company, Iran). To evaluate the insulin resistance, HOMA-IR index was used. The fasting glucose and insulin were measured based on the following formula:

$$\text{HOMA-IR} = \text{glucose concentration} \times \text{insulin concentration} \div 22.5$$

Statistical methods

After confirming the normal distribution of the data using the Kolmogorov-Smirnov test, dependent t-test was used for statistical analysis and intra-group comparison of the variables, and independent t-test was used for the comparison of the variables among the groups. In addition, Pearson correlation coefficient was used to determine the relationship between vaspin and other measured variables. All data are presented in mean and standard deviation. The calculations were performed using SPSS20 statistical software and the significance level of the tests was considered as $P \leq 0.05$.

RESULTS

A. Results of physical and functional indices

The results of examining the physical and functional characteristics of the experimental and control group are presented in Table 1. Intra-group examination of subjects showed that the mean values of weight was significantly reduced after exercise by 8.47% ($p = 0.03$) after the exercise period ($p = 0.03$), while it was non-significantly reduced in the control group by 3.44% ($p = 0.13$). In the experimental group, intra-group examination showed that mean BMI values decreased in the post-test stage compared to those in pre-test and increased in the control group, but the change was not significant (p -value was 0.18 and 0.28 in experimental and control groups, respectively).

Table 2: Mean comparison of physical and functional characteristics of the experimental and control groups after the resistance exercise period

Variables	Group	Baseline	8 weeks	dependent t	P value	P value
Age (years)	Experimental	47.75±7.04	~	~	~	~
	Control	49.08±6.48	~	~	~	
Anthropometric measurement						
Height (cm)	Experimental	169.9 ± 7.39	~	~	~	~
	Control	171.7 ± 5.76	~	~	~	
Weight (kg)	Experimental	90.9±9.6	83.2 ± 14.6	2.40	0.03*	0.87
	Control	84.2±5.86	81.3 ± 7.5	1.60	0.03*	
BMI (kg/m ²)	Experimental	28.1±4.4	26.7 ± 3.9 *	4.41	0.18	0.43
	Control	27.5±3.6	27.8 ± 3.2	1.13	0.28	

The values are presented as mean ± standard deviation. Cm: centimeter. kg/m²: kilogram per square metre. Kg: kilogram. BMI (Body mass index): calculated by dividing weight (kg) by height squared (m²). * Significant difference in compare to Pre values ($p \leq 0.05$).

B: Results of paraoxonase-1 and insulin resistance index

The results of examining the concentration of measured variables are presented in Table 3. The serum concentration of paraoxonase-1 increased by 8.43% in the experimental group, while it decreased by 6.26% in the control group. The intra-group analysis showed no significant changes in any of the groups (p value in the groups was 0.76 and 0.83, respectively). Inter-group analysis showed that after 12 weeks of resistance exercise, serum paraoxonase-1 concentration in the experimental group was not significantly different from that of the control group ($p = 0.50$). Intra-group study examination showed that the mean blood glucose levels decreased by 6.22% in the experimental group, while it increased by 24.1% in the control group, but the decrease and increase in the experimental and control groups were not statistically significant (P -value was 0.09 and 0.09 in the experimental and control groups, respectively). In contrast, inter-group examination showed that blood glucose levels were significantly different in the experimental group and control group ($p = 0.05$).

The results of intra-group analysis showed that after 12 weeks of resistance exercise, insulin levels and insulin resistance index decreased significantly in the experimental group in the post-test stage compared to those in pre-test (p -value in the experimental group and control group was 0.07 and 0.003, respectively). Moreover, after 12 weeks of resistance exercise, no significant difference was seen between insulin levels and insulin resistance index of experimental group and those of control group.



Table 3: Comparison of the mean biochemical indices of the experimental and control groups before and after the resistance exercise period

Variables	Group	Baseline	8 weeks	P value
paraoxonase-1 (nm/l)	Experimental	293.25 ± 70.92	318 ± 254.59 *	0.50
	Control	272.41 ± 227.04	255.33 ± 183.88 *	
FPG (mg/dL)	Experimental	257.92 ± 83.95	216.08 ± 43.04 *	0.005 **
	Control	207.50 ± 77.24	257.33 ± 82.70	
Insulin (µU/mL)	Experimental	17.22 ± 11.95	8.68 ± 3.82 *	0.002 **
	Control	16.19 ± 9.19	18.68 ± 3.82	
HOMA-IR	Experimental	10.65 ± 7.22	4.59 ± 2.23 *	0.006 **
	Control	8.07 ± 3.65	12.27 ± 9.48	

The values are presented as mean ± standard deviation. nm/l: nanomole per litre. mg/dl: milligram per deciliter. µU/mL: microunits per milliliter. FPG: fasting plasma glucose concentration. HOMA-IR: homeostatic model assessment of insulin resistance. * P < 0.05; *Significant difference in compare to Pre values (p≤0.05). ** P≤ 0.05, Significantly different between groups.

DISCUSSION

One of the important results of this study showed non-significant increase in paraoxonase levels in the experimental group. Studies have shown that one of the characteristics of paraoxonase-1 inhibits LDL oxidation and can play a protective role in cardiovascular disease in vitro conditions. Previous studies have shown that increasing the levels of paraoxonase-1 plasma is a useful response to cardiovascular disease and in people with metabolic syndrome. However, its mechanism is still unknown (Hordern et al., 2011). In the present study, the intra-group analysis showed that paraoxonase-1 in the experimental group increased non-significantly. In contrast, it decreased in control group, while its reduction was not statistically significant. Moreover, inter-group analysis did not show significant difference between the two groups in terms of paraoxonase-1 levels. Based on knowledge of the researchers of this study, there is little and contradictory information on the effect of aerobic exercises on serum paraoxonase-1 concentrations in patients with type 2 diabetes. Thus, the information will be very limited. There are controversial views on the effects of exercise on the plasma paraoxonase-1 concentration and especially the effects of long-term exercise on plasma paraoxonase-1 concentrations and its relationship with other metabolic parameters. In studies conducted on animal samples, Romani et al (2009) reported that paraoxonase-1 levels did not change significantly after aerobic exercise on a treadmill with an intensity of 65% of maxima oxygen consumption (Ibanez et al., 2005). In addition, in studies on human samples, Goldhammer et al. (2007) observed a significant increase in plasma paraoxonase-1 levels after 12 weeks of aerobic exercise in subjects with coronary artery disease (Knowler et al., 2002). Otocka-Kmiecik (2010) also reported a significant increase in paraoxonase-1 levels following one session of acute aerobic exercise on treadmill in young male athletes (Kraus et al., 2002). The results of this study are in line with those of other researchers (Ibanez et al., 2005). However, the contradictory results of the studies do not clarify that plasma paraoxonase-1 concentrations increase or decrease in patients with type 2 diabetes (Kraus et al., 2002). The contradictory results in studies might be due to the different ages of subjects. The type of response and adaptation in age groups to the physiological conditions in which they are located might be different. The results of the study indicated that age is a determining factor in paraoxonase-1 activity .

The results of studies on humans showed that paraoxonase-1 serum activity is very low at birth and increases over time. Paraoxonase-1 activity of people remains almost constant over time when he or she reaches adulthood. Paraoxonase-1 activity may decrease in middle-aged people by expansion of oxidative stress conditions (Hordern *et al.*, 2011). In addition, the status of type 2 diabetes disease in subjects may be important in this study. It should be noted that type 2 diabetes is a complex metabolic disorder, which may be a disruptive factor in the activity of paraoxonase-1 enzyme (Ibanez *et al.*, 2005). There is no accurate information on paraoxonase-1 polymorphism and the race of the participants in the study (Hordern *et al.*, 2011). The inconsistency of results of this study with those of other studies might be attributed to this fact. Some researchers argue that paraoxonase-1 is more affected by genetic and racial differences (Knowler *et al.*, 2002). In this study, researchers have shown that paraoxonase-1 activity is not significantly different between patients with cardiovascular disease and the control group, and they argue that this supports racial differences in paraoxonase-1 polymorphism (Kraus *et al.*, 2002). In order to clarify all aspects of the effect of physical activity on paraoxonase-1 activity, the effect of intense and heavy exercises on this factor was also studied. In a 16-week study, Thomas *et al.*, found that paraoxonase-1 activity was reduced in half, one, two hours after an intense exercise and the paraoxonase-1 activity in subjects returned to initial level after 24 hours in subjects at the beginning of the protocol and 16 weeks after aerobic exercise (Kraus *et al.*, 2002). Based on the report of these researchers, response time pattern of paraoxonase-1 in an intense physical activity session varies according to genotype PON1-192. The results of these studies with regard to paraoxonase-1 activity and the effect of physical activity on it, it is concluded that physical activities have a significant effect on paraoxonase-1 activity. However, desired physical fitness of people can affect the paraoxonase-1 activity (Ibanez *et al.*, 2005). Researchers showed that modification in lifestyle (including alcoholic beverages, smoking, and lack of physical inactivity) are important factors affecting the changes in paraoxonase-1 activity (Kulkarni *et al.*, 2014). It also seems that one of the reasons for reducing paraoxonase-1 in the control group to be type of diet of the subjects. Studies have shown that high-fat diet can lead to obesity and metabolic syndrome in the long terms and ultimately result in a decrease in paraoxonase-1 levels. The researchers found paraoxonase-1 activity decreased by about 27% after 8 hours in healthy men after consuming a high-fat diet, but it returned to normal value after 12 hours. Replacing the saturated dietary fat decreased paraoxonase-1 activity by about 6% in healthy males and females (Hordern *et al.*, 2011). However, further studies are required to clarify the molecular mechanism of paraoxonase-1 and its changes in the body as a result of exercises. This study also revealed a significant reduction in glucose levels, serum insulin levels and HOMA-IR. This result is in line with that of other studies (Kwon *et al.*, 2010).

Insulin resistance is a biological response to insulin concentration in the body. Physical activity has a beneficial effect on insulin sensitivity in people with type 2 diabetes. Studies showed that endurance exercise improved the insulin sensitivity; since muscular contractions increased glucose uptake and muscle mass (Flack *et al.*, 2010). Recent studies have revealed that resistance exercise, like endurance exercise, improved insulin resistance. In a study conducted by Kwon *et al.*, a significant change in insulin resistance was observed following 12 low intensity resistance exercises 40-50% of one maxima repeat) in women with type 2 diabetes (Otocka-Kmiecik *et al.*, 2010). In contrast, in the study conducted by Hordern *et al.*, insulin resistance and plasma



glucose did not change significantly in patients with type 2 diabetes after 4 weeks of resistance exercises (Praet et al., 2009). In contrast, Abanez et al showed that the insulin sensitivity was significantly increased and glucose levels were significantly decreased following 16 weeks of progressive resistance exercise with an intensity of 50-80% of one maxima repeat in elderly men with type 2 diabetes (Fuhrman, 2012). The difference between results of these studies may be attributed to the characteristics of the subjects and the type of exercise (intensity and duration of exercise). Resistance exercise includes the activity of individual muscular groups, and they require rest between the repeats due to the metabolic metabolism of the body, and less than half of time of each resistance exercise session involves active muscle contraction (Shavandi et al., 2010). Increasing the muscles' GLUT4 levels, insulin receptors, protein kinase B, and glycogen synthase after exercise, muscle contraction improves glucose levels and insulin sensitivity (Tomás et al., 2002). Glucose transporting to skeletal muscle is performed through glucose transporter proteins, and GLUT4 is the most important isoform in skeletal muscle, which its activity is affected by contraction and insulin (Shavandi et al., 2010). Following exercise, GLUT4 levels increase in the exercised muscle, leading to improved insulin effect on glucose metabolism. When the level of insulin secretion decreases, the base insulin and glucose-stimulated insulin levels would decrease, resulting in decreased insulin resistance in the tissues.

While this study tried to select homogeneous subjects in order to prevent the effectiveness of some of the factors on the results of the research, one of the limitation of the present study was that its subjects included patients with type 2 diabetes, whose diet was monitored by specialist physician. Thus, in order to observe ethical considerations in the research, the diet was not controlled by the researcher and this issue can be considered in future research by researchers who want to control all variables affecting the research results. Undoubtedly, the controlled implementation of such protocols, diet control, and the examining the paraoxonase 1 changes in subcutaneous fatty tissue can be more appropriately resolve some of the uncertainties on the mechanisms of paraoxonase-1. Given the results of this study, non-significant increase was seen in serum concentration of paraoxonase-1 and significant reduction was seen in the level of glucose, insulin and insulin resistance index following 8 weeks of resistance exercise. Given significant decrease in insulin resistance index in the experimental group and lack of its significant change in control group, it can be stated that insulin resistance in the experimental group was improved. Thus, circular resistance exercise can be used as an effective factor in improving insulin sensitivity in patients with type 2 diabetes.

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