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The effect of nonlinear resistance training with dill extract on serum adropin levels and its relationship with insulin resistance in type 2 diabetic patients

Leila Ahmadi[1*]
1. Master of Exercise Physiology, Azad University, Lamerd Branch

* Corresponding author: Leila Ahmadi
Email:

***Abstract*— the aim of this study was to investigate the effect of nonlinear resistance training with dill extract on adropine and its relationship with insulin resistance in type 2 diabetic patients. 32 patients with type 2 diabetes were divided into four groups: resistance training, supplementation, resistance training + supplementation, and placebo. Interventions were performed for 12 weeks. Consumption of dill included 300 mg / kg body weight per day. Nonlinear resistance training, consumption and their combination significantly reduced blood sugar and insulin resistance and significantly increased adropine levels (P <0.05). These changes were significantly greater in the exercise and dill combination groups. The relationship between adropine changes and insulin resistance was also significant and negative (P <0.05). Adropine may play a role in reducing insulin resistance following nonlinear resistance training. Consumption can increase the effects of exercise.**

Keywords*— *Diabetes, Dill, Resistance training, Adropine, Insulin resistance

Introduction

Diabetes is one of the most common metabolic disorders of the present century, which is becoming epidemic (1). Prolonged exposure to high glucose levels is known to be one of the major causes of diabetes (2). Environmental factors such as lack of exercise along with obesity, stress and genetic factors are other causes of diabetes (3). Increased insulin resistance can lead to type 2 diabetes and increase the risk of atherosclerosis, high blood pressure and cardiovascular disease (4). Adropine, on the other hand, is a hormonal peptide discovered in 2008 by Kumar et al. This protein consists of 76 amino acids and is originally considered a secretory peptide. Its amino acid sequence is the same in humans, mice and rats. Although current knowledge about the exact physiological role of this peptide is weak and needs further studies, recent data show an important role for it in energy homeostasis and control of glucose and fatty acid metabolism (5). This protein is encoded by the Enho gene, which is mainly expressed in the liver and central nervous system. Adropine is a membrane-bound protein that mediates cell-cell communication. In addition, adropine has been identified in various tissues and body fluids, such as the brain, cerebellum, liver, kidney, heart, pancreas, small intestine, endothelial cells, and so on. Previous studies have shown that the level of this protein varies under different physiological and pathological conditions. Adropine is

involved in fat and carbohydrate metabolism, metabolic diseases, central nervous system function, endothelial function, and cardiovascular disease. Information on the exact role and mechanism of action of this interesting protein is not yet complete (5). Recently, adropine has been shown to be important in the choice of skeletal muscle fuel (6). Adropine has been shown to increase pyruvate dehydrogenase activity to increase glucose oxidation (7). Therefore, it is possible that increasing adropine by increasing glucose metabolism leads to a decrease in blood sugar and thus a decrease in insulin resistance. This effect can prevent diabetes in the elderly and also reduce the risk of heart disease. Adropin also reduces the oxidation of muscle fatty acids in parallel by inhibiting carnitine, a key enzyme that transports fatty acids to mitochondria (6). In addition, adropine can reduce exercise-induced vascular stiffness by increasing nitric oxide (NO) (8). However, not much research has been done on the effect of exercise on adropine, and it seems that studies on the effect of exercise on this peptide, which was discovered in 2008 and its discovery life is not yet 10 years. Fuji et al. (2015) reported that 8 weeks of aerobic exercise significantly increased serum adropin levels in middle-aged and elderly adults (8).

On the other hand, physical activity is not only useful for treating various diseases such as obesity, diabetes and hyperlipidemia, but also for maintaining good health (9). Although different types of aerobic activity are considered a good treatment for patients, especially diabetics, because diabetics are usually obese and have a sedentary lifestyle, these exercises are not possible for all patients. Such people do not have enough motivation and strength for aerobic physical activity. Physical activity in diabetics and obese people requires a certain amount of muscle strength and endurance that can be achieved through resistance training (10). Resistance training is a growing treatment tool that has the potential to increase muscle strength, endurance, flexibility, body composition and reduce risk factors for cardiovascular disease (11). Also, resistance training with sufficient intensity and duration can reduce glucose and glycosylated hemoglobin (HbA1c) alone (12). Resistance training can improve muscle mass, strength and power and can be considered a healthy treatment tool. Resistance training can also increase insulin sensitivity and daily energy expenditure and improve quality of life (13, 14). Resistance training is associated with increased force production, muscular hypertrophy, especially in fast-twitch fibers, recall of large number of motor units, and nerve impulses (15). On the other hand, resistance training preferentially improves glucose uptake by increasing the size of each muscle fiber, all of which together have a greater effect on the amplitude of the action potential (16). In a review study of 30 selected studies, it was reported that HbA1c, fat mass and systolic blood pressure were significantly reduced due to resistance training programs (17). However, there are many types of resistance training that require further study. Nonlinear resistance training, meanwhile, can be a viable option because it has a similar metabolism to aerobic exercise but also develops resistance training adaptations. In any case, more studies are needed in this area. On the other hand, the role of nutritional interventions along with exercise programs is very important. If exercise programs are combined with nutritional interventions, they will have a more positive effect. In this regard, recently, a lot of attention has been paid to medicinal plants due to their naturalness and lack of side effects. Among them, dill (Anethum graveoleus) is a plant of the umbrella family and contains dilatosides, coumartin, camphorol and other flavonoids and phenolic acids. The hydroalcoholic extract of this plant can be effective in lowering blood sugar. The antioxidant compounds in dill are effective in glucose uptake and can also be involved in repairing and regenerating damaged beta cells (18).

The aim of this study was to investigate the effect of nonlinear resistance training with dill extract on adropine and its relationship with insulin resistance in type 2 diabetic patients.

Methodology

This research is a quasi-experimental study with pre-test and post-test design with placebo group which was performed in two groups of blinds. 32 women with type 2 diabetes with a body mass index (BMI) of 30 and above were randomly assigned to four groups of nonlinear resistance training, supplemental nonlinear resistance training + supplementation and placebo (10 people in each group). Before starting the research, the nature, goals and risks of this study were explained to the subjects in a face-to-face meeting

and written consent was obtained from them to participate in this study. He was present at the sampling session 24 hours before the start of training and blood samples were taken from four groups in the 12-hour fasting position. After that, the interventions were performed for 12 weeks. The resistance training + supplement group received both nonlinear resistance training and dill supplementation interventions. During this period, the placebo and supplement groups performed daily activities and normal life without participating in regular exercise. The supplement group took 300 mg / kg body weight daily as capsules. The placebo group also took 300 mg / kg body weight per day in capsule form. Capsules of both supplement and placebo groups were used in the same shape and size. The nonlinear resistance training program includes weight training at different intensities with an emphasis on muscle endurance and a flexible timing pattern. This exercise program has been presented in advance by Nikseresht and his colleagues and its full description is given in Tables 1 and 2 (19).

48 hours after the end of training, the subjects were present in the second sampling and blood samples were taken from all four groups in a 12-hour fasting state. For each sample, levels of insulin and adropine were measured and insulin resistance was calculated. In addition, weight and body mass index were measured and calculated. Glucose was obtained by turbidimetric colorimetric method using an elitech kit made in Italy. Insulin was obtained by ELISA method using a microcalorimetry kit from Monobind, USA. Insulin resistance calculated using glucose and insulin concentrations and Homeostasis Model Assessment formula. Insulin (HOMA-IR) was calculated as follows:

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

Adropine was measured using an ELISA kit made in the USA by ELISA method and spectrophotometer. Height was measured with a German-made Seca height gauge on which a person stands barefoot. Weight was measured with a digital scale made in Germany, without ordinary shoes and clothes. Body mass index was also calculated by dividing weight in kilograms by height squared in meters. In order to compare and evaluate the changes of variables in four research groups and in two blood sampling times, the statistical test of mixed-variance analysis of intra-subjects in a 4×2 design (4 groups and 2 times) was used. If a significant difference was observed, Tukey post hoc test was used. A significance level of $P \leq 0.05$ was considered.

Results

The results of mixed analysis of variance are reported in Table 1. The results of Tukey's post hoc test are also summarized in Table 2. The results of the Pearson correlation coefficient test are also presented in Table 3.

Table1. Results of mixed variance analysis

Variables	Groups	Before	After	F	P	Effect size
Glucose ()	training	124.62 ± 10.80	106.25 ± 10.00	16.86	0.001 *	0.64
	dill	119.12 ± 5.11	106 ± 10.00			
	training + dill	126.37 ± 10.05	89.50 ± 9.00			
	placebo	106.87 ± 6.08	113.87 ± 6.00			
Insulin ()	training	17.17 ± 2.17	14.70 ± 2.52	15.12	0.001 *	0.61
	dill	16.15 ± 3.05	13.70 ± 3.30			
	training + dill	16.36 ± 2.70	10.80 ± 2.34			
	placebo	14.70 ± 2.02	14.70 ± 1.78			
Insulin resistance	training	5.28 ± 0.85	3.94 ± 0.88	22.91	0.001 *	0.71
	dill	4.69 ± 0.98	3.70 ± 1.02			
	training + dill	5.06 ± 1.07	1.89 ± 0.68			
	placebo	3.86 ± 0.52	4.12 ± 0.55			
Adropine ()	training	2.26 ± 0.30	3.84 ± 0.57	23.21	0.001 *	0.71
	dill	2.59 ± 0.43	3.81 ± 0.99			
	training + dill	2.36 ± 0.35	4.79 ± 0.55			
	placebo	2.41 ± 0.25	2.38 ± 0.32			

*significant at the level of P≤0.05

Table2. Tukey's post hoc test results

Pairwise comparison	Glucose	Insulin	Insulin resistance	Adropine
Training / dill	0.83	1	0.82	0.65
Training / training + dill	0.02 *	0.005 *	0.001 *	0.035 *
Training / placebo	0.002 *	0.028 *	0.003 *	0.001 *
Dill / training + dill	0.004 *	0.004 *	0.001 *	0.002 *
Dill / placebo	0.015 *	0.030 *	0.028 *	0.002 *
Training + dill / placebo	0.001 *	0.001 *	0.001 *	0.001 *

*significant at the level of P≤0.05

Table3. Pearson correlation coefficient test results

Correlation matrix	Glucose	Insulin	Insulin resistance	Adropine
Glucose	-	r= 0.83 p= 0.001 *	r= 0.93 p= 0.001 *	r= - 0.73 p= 0.001 *
Insulin	r= 0.83 p= 0.001 *	-	r= 0.94 p= 0.001 *	r= - 0.67 p= 0.001 *
Insulin resistance	r= 0.93 p= 0.001 *	r= 0.94 p= 0.001 *	-	r= - 0.72 p= 0.001 *
Adropine	r= - 0.72 p= 0.001 *	r= - 0.68 p= 0.001 *	r= - 0.73 p= 0.001 *	-

*significant at the level of P≤0.05

Nonlinear resistance training, consumption and their combination significantly reduced serum glucose (P = 0.001). Glucose reduction was significantly higher in the exercise and dill combination group (P <0.05). The relationship between changes in adropin and serum glucose was also significant and negative (P = 0.001, r = - 0.73). Nonlinear resistance training, consumption and their combination significantly reduced serum insulin (P = 0.001). Insulin reduction was significantly greater in the exercise and dill combination groups (P <0.05). The relationship between changes in serum adropine and insulin was also significant and negative (P = 0.001, r = - 0.67). Nonlinear resistance training, consumption and their combination significantly reduced insulin resistance (P = 0.001). The decrease in insulin resistance was significantly greater in the exercise and dill combination groups (P <0.05). The relationship between changes in serum adropine and insulin was also significant and negative (P = 0.001, r = - 0.72). Also, nonlinear resistance training was consumed and their combination significantly increased serum adropine (P = 0.001). The increase in adropine was significantly higher in the exercise and dill combination groups (P <0.05).

Discussion

According to the findings of the present study, 12 weeks of nonlinear resistance training, consumption and their combination significantly reduced blood sugar and insulin resistance in type 2 diabetic patients and significantly increased their adropin levels. However, these changes were significantly greater in the combination of exercise and dill groups than in the exercise group alone and dill alone. Among them, the relationship between changes in adropin and insulin resistance was also significant, so that with increasing adropin, insulin resistance decreased. Significant reductions in blood sugar (20) and significant reductions in insulin resistance (21) have been reported in various studies. In line with the present results, a decrease in insulin resistance has been reported along with a decrease in BMI (22). One of the most important reasons for hypoglycemia following exercise is an increase in glucose transporter called GLUT-4 through the mechanism of cellular calcium increase due to muscle contractions, which leads to more blood glucose transfer into the cell, resulting in lower blood sugar and insulin resistance. (23). Mechanisms such as increasing insulin signal inhibitors such as Insulin receptor substrate-1, increasing mRNA, glucose transporter proteins GLUT-4, increasing the activity of glycogen synthetase and hexokinase enzymes in skeletal muscle, reducing release and increasing the uptake of free fatty acids

Plasma and increased glucose uptake and changes in muscle composition are involved in this adaptation (23).

So far, various studies have examined the effect of physical exercise on insulin resistance and lipid profiles, but a number of studies have examined the possible mechanisms involved (the effect of exercise on insulin resistance and profile). Lipids) are not high. In this study, in addition to insulin resistance and lipid profile, we studied adropine, a new peptide of hepatic origin that affects lipid and carbohydrate metabolism, and the results showed a significant increase in this peptide with 12 weeks of nonlinear resistance training Patients had type tow diabetes. But the previous findings in this regard are not many. However, consistent with the present findings, Fuji et al. (2015) reported that 8 weeks of aerobic exercise significantly increased serum adropin levels in middle-aged and elderly adults (8). Adropine, on the other hand, is a regulator of endothelial nitric oxide synthetase and NO release, which decreases with age. However, the effect of aerobic exercise on circulating adropin levels in middle-aged and elderly adults remains unclear. Fuji et al. (2015) concluded that adropine may be involved in reducing stiff exercise due to arterial stiffness (8). Although few studies have shown that serum adropine levels increase with aerobic exercise (8) the source of exercise-induced increase in adropine is still not well understood. Adropine is produced in vascular endothelial cells, brain, heart, kidney, liver, pancreas, skeletal muscle, and small intestine (24, 25). An in vitro study showed that adropine increased NO production in venous endothelial cells by increasing the phosphorylation of the eNOS protein (26). In this regard, in connection with water training for the elderly, Tanabe et al showed that aerobic swimming training increases the expression of aortic mRNA and eNOS protein in older mice (27). Therefore, since exercise-induced increase in adropine may help regulate arterial eNOS levels through the effect of autocrine or paracrine in endothelial cells, adropine expression in endothelial cells may lead to increased circulating adropine following exercise. Be (8). However, we do not yet know what happens to the expression of the adropin gene following physical exercise, and future research should be conducted on the effect of nonlinear resistance training on the expression of adropin mRNA in older men. Recent clinical studies have shown a decrease in adropine in cardiovascular patients such as coronary artery disease, cardiac X syndrome and angina pectoris (28, 29, 30). Also, in patients with type tow diabetes, low adropine levels have been reported with endothelial dysfunction (31). Therefore, adropine can be a new biomarker for endothelial function associated with diabetes and heart disease (31). In this connection, adropine has been reported to regulate lipid and carbohydrate metabolism (32) and its secretion is regulated by dietary sugar and fat intake (33). Adropine leads to weight loss and improved glucose tolerance and hepatic lipid metabolism (32, 33, 34). As in the present study, weight and body mass index also decreased significantly in the nonlinear resistance training group. The effect of adropine on carbohydrate metabolism probably depends on the activation of pyruvate dehydrogenase, which increases the use of sugar as a fuel in skeletal muscle, which increases glucose oxidation and insulin signaling activity (35). Previous studies have shown that adropine is needed to prevent obesity-induced insulin resistance (32, 33). If the concentration of adropine decreased in insulin resistance, impaired glucose metabolism and obesity were reported (34, 36).

The findings of this study also showed that consumption of dill extract at a rate of 300 mg / kg body weight per day has similar effects to the effect of exercise and its addition to exercise, leads to a further increase in adropine and a further decrease in resistance to It becomes insulin. The hypoglycemic effect of dill extract is probably related to its flavonoid composition (quercetin). One of the possible mechanisms of action of this plant in lowering blood sugar is the effect on glucose uptake. Plant antioxidant compounds reduce glucose uptake in the intestine. This effect is achieved by inhibiting digestive enzymes such as alpha amylase and alpha glucosidase, which are involved in the hydrolysis of carbohydrates, inhibiting the transfer of glucose from the folded membrane of the small intestine, and delaying the emptying of gastric contents into the small intestine. On the other hand, plant antioxidants also have an insulin-like effect and increase glucose uptake into peripheral tissues. Another possible mechanism of action of this plant is its effect on beta cells and repair and regeneration of damaged cells and stimulation of these cells to insulin secretion.

Conclusion

It is concluded that nonlinear resistance training improves diabetes and prevents its complications by reducing insulin resistance in type 2 diabetic patients. Adropine also appears to play a role in these exercise-induced changes. Consumption of 300 mg / kg body weight of dill extract may also have similar effects to exercise due to its flavonoid compounds, including quercetin. Extract this dose of dill and exercise will probably increase the effect of exercise.

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