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The Effect of *Pistacia Atlantica* Extract and Aerobic Training on the Levels of Triiodothyronine, Thyroxine and Lipid Profile in Streptozotocin-Diabetic Rats

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Abstract

Background: Diabetes is considered as one of the health problems in all societies. Exercise training and herbal medicines are some approaches to improve diabetes. The present study investigated the effect of a six weeks exercise training program and/or *Pistacia atlantica* (mastic) extract on thyroid hormones and lipid profile as well as antidiabetic effects in diabetic rats.

Methods: Forty male Wistar rats were randomly divided into five groups: Healthy control (Ctrl), diabetic control (D), Diabetic + exercise (DE), Diabetic + mastic extract (DM) and Diabetic + exercise + mastic extract (DEM). The six-week period exercise program included aerobic training on a treadmill (five sessions per week, 40 minutes per each session, with a speed of 20 m/min and 5% incline). *Pistacia atlantica* extract was fed 5 days per week (25 mg/kg). Forty eight hours after the last training session, the level of T_3, T_4, triglyceride, cholesterol and HDL were assessed.

Results: Triglyceride levels in DEM group was significantly lower than diabetic group ($p<0.05$). The mean level of cholesterol and HDL (high density lipoprotein) was not significantly different among groups. Plasma concentration of T_3 and T_4 in diabetic control was significantly lower than normal control. Applying mastic extract alone or together with exercise markedly enhanced T4 levels in diabetic rats.

Conclusion: *Pistacia atlantica* extract and exercise training might be good in the improvement of hypothyroidism and hyperlipidemia resulting from diabetes.

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Introduction

Diabetes is a metabolic disorder characterized by hyperglycemia, resulting from inability of the pancreas to secrete insulin and/or increased insulin resistance (1). Hyperglycemia leads to serious complication affecting eyes, kidneys, nerves and heart as well as extensive disorders of metabolism of carbohydrate, lipid, protein, water, and electrolyte (2). On the other hand, diabetes is closely related to other autoimmune diseases, such as thyroid diseases (3). Exercise, proper diet, and insulin prescription are central to the management of diabetes (4).

Since herbal medicines have fewer side effects, the search of new herbal drugs as an alternative to synthetic drugs is increasing (5-7). Herbal remedies have been introduced as a good alternative to chemical drugs due to their lower side effects and increased consumption. The role of medicinal plants such as fenugreek, dill and walnut leaves has been shown to reduce blood lipids (8), while the role of vitamins, minerals and some herbal extracts in the metabolism of thyroid hormones requires further research. *Pistacia atlantica* is a species of pistachio tree known by the English common name Mt. Atlas mastic tree and as the Persian turpentine tree or the so-called Baneh. This plant grows extensively in eastern, central and western parts of Iran (9). This plant contains terpenoid and phenolic compounds, as well as fatty acids and sterols (10). Also, it has been specified that the total phenolic and flavonoid contents of the hull were significantly higher than kernel (11). Flavonoids are molecules with low molecular weight and low solubility in water that have anti-viral, anti-allergic, anti-platelet, anti-inflammatory, anti-tumor, and anti-oxidant activities (12). The biological activity of flavonoids is due to antioxidants activities and by decreasing oxidative stress, they protect the body against reactive oxygen (13, 14). Moreover, flavonoids as the major contents of mastic (Baneh) play an important role in the management of diabetes in different ways such as glucose transport, the activity of insulin receptor and the activation of peroxisome proliferator-activated receptor (15). The positive impact of flavonoids on diabetes treatment is due to an increase in the intracellular levels of vitamin C, prevention of the permeability and rupture of capillaries, and reinforcement of the immune system (16). Mastic oil is characterized by a high nutritional value; it contains a significant amount of unsaturated fatty acids (oleic acid and linoleic acid) and saturated fatty acids (palmitic and stearic) (17). High levels of unsaturated fatty acids can clearly decrease appetite, weight loss and lipid plasma levels (18). On the other hand, since insulin and thyroid hormones are involved in the metabolism of carbohydrates and lipids, a disorder in each of them might affect the activity of the other one (19). Several studies have reported simultaneous prevalence of thyroid disorders and diabetes (20). Peross et al have shown that thyroid disease is more prevalent in women with diabetes type 1 than in men with diabetes type 2 (21). A study carried out by Loucks and Callister (1993) manifested that exercise had no significant effect on the levels of thyroid hormones in women (22). Gonzalez et al (1980) also reported that STZ-induced diabetes resulted in the weight loss of thyroid gland, reduction of its iodine content and hypothalamic TRH which was followed by a reduction in plasma TSH (23). Furthermore, the Saeb et al (2008) indicated that mastic oil had no significant effect on thyroid hormone levels of healthy rats (24).

Regarding the relationship between diabetes and thyroid hormone disorders and also due to thyroid disorders and complications from lipid changes in patients with diabetes, it is important to examine the levels of these hormones. Furthermore, no research has been performed on the effect of mastic on thyroid hormone levels of STZ-induced diabetic rats with diabetes. Accordingly, this study aimed to examine the joint effect of mastic extract and aerobic exercise on lipid profile and thyroid hormones of rats with diabetes.

Animal care and diet

In this study, 40 male Wistar rats (12-14 weeks old, 180-240 g weight) were housed in a clean animal room under a 12-h light and dark cycle at an ambient temperature of 21±2°C, and provided with standard pellet diet and tap water ad libitum throughout the experimental period. All of the experiments were approved by the Ethics Committee of Birjand University of Medical Sciences.

Extract preparation

Pistacia atlantica beans were collected from outskirts of Birjand in Iran and were crushed in an electrical grinder and then 50 g of powder dissolved in 1000 ml ethanol 70% and placed on a shaker for 48 h. Thereafter, the solution was passed through a filter paper and the solvent was removed by rotary evaporation at 40-45°C. The extract (25 mg/kg body weight each day) was orally gavaged for six weeks.

Induction of diabetes

For induction of experimental diabetes, the rats were weighed and then fasted overnight and streptozotocin (STZ) was injected intraperitoneally (40 mg/kg; Sigma Aldrich, St. Louis, MO, USA). STZ solution was prepared in citrate buffer (0.1 mol/l trisodium citrate and 0.1 mol/l citric acid, pH=4.5). Control rats were injected with citrate buffer alone to serve as a normal control group. The rats were tested for hyperglycemia by measuring their blood glucose concentration at 5 days following the STZ injections. Blood was obtained via tail incision and blood glucose was measured using an Accu-chek glucometer. Diabetes was confirmed by plasma glucose level higher than 250 mg/dl (25).

Training program

Animals were exposed to a short-term exercise protocol as previously described (26). Briefly, animals were familiarized for 7 days on a motorized treadmill (0% incline) at 5-10 m/min for 10 min. After one week, the running times and speed were gradually increased to 20 m/min for 40 min at 5% slope. It should be noted that this training intensity for diabetic rats is roughly equivalent to 75 percent of the maximum oxygen consumption. From a total of 40 minutes of training, at the beginning of each session 5 minutes to warm up (the speed of 10 m/min and a slope of zero degrees) and at the end of 5 minutes to cool down the treadmill gradually decreased to reach early speed.

Experimental design

The rats were divided into five groups:

Group 1: normal control (Ctrl)

Group 2: diabetic control (D)

Group 3: D + exercise (DE)

Group 4: D + mastic extract (DM) and

Group 5: D + exercise + mastic extract (DEM)

Biochemical Analysis

Forty eight hours after the last exercise session and 12 hours of fasting, rats were anaesthetized by ether and blood samples were collected into a tube containing anticoagulant (EDTA) by cardiac puncture. Triiodothyronine and thyroxine levels in the plasma were determined by ELISA method using a commercially available kit from Monohyrid, CA, Inc, USA. Glucose, triglyceride, cholesterol and high-density lipoprotein cholesterol (HDL-C) were measured using commercial kits (Pars Azmoon Co, Iran). Plasma insulin was measured using an enzyme-immunoassay (EIA) method by rat insulin ELISA kit (Mercodia AB, Sweden). Homeostatic model assessment of insulin resistance (HOMA-IR) as measure of insulin resistance index was calculated using the following formula: HOMA-IR = (fasting plasma insulin in µg/l × fasting plasma glucose in mg/dl)/405 .

Statistical Analysis

All data were presented as mean ± standard error. The data were analyzed by using one-way ANOVA and least-significance difference was used for the posteriori test. In all statistical analyses, P <0.05 was considered significant (27).

Results

As depicted in Figure 1A, induction of diabetes in rats caused a significant increase in plasma glucose levels compared to the control group. Exercise and/or mastic extract did not reveal a significant decrease in glucose levels compared to the diabetic group, except numerical reduction. Moreover, STZ caused a significant reduction in plasma insulin levels compared to healthy rats (P < 0.05) and application of exercise and/or mastic extract in diabetic rats had no remarkable effect on insulin levels (Figure 1B). To estimate the effect of Exercise and/or mastic extract on insulin resistance in the diabetic rats, we calculated the HOMA-IR. Exercise alone and exercise together with mastic extract were able to significantly ameliorate the insulin resistance that developed in the diabetic rats (Figure 1C, P<0.05).

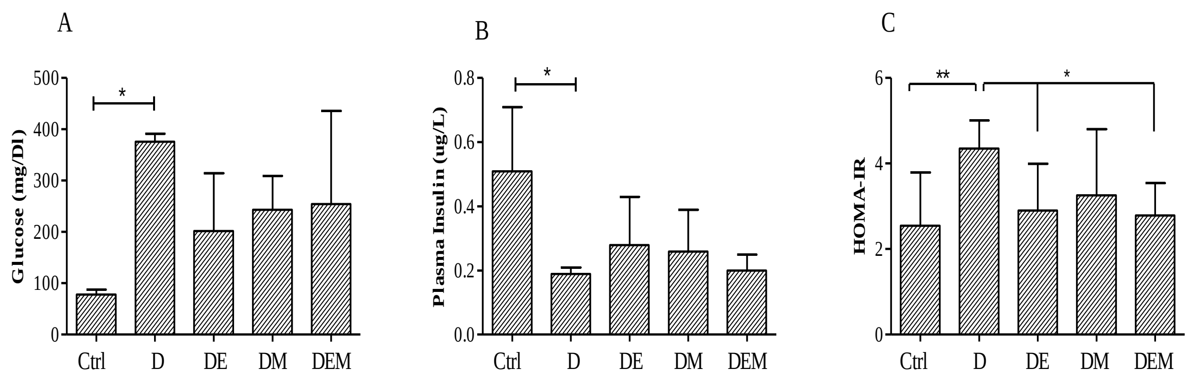

Figure 1. (A) Plasma concentrations of glucose, (B) plasma insulin; and (C) HOMA-IR levels of control rats (Ctrl) or streptozotocin-induced diabetic rats (D) who did or did not receive the intervention of exercise (DE) or mastic extract (DM) and combination of exercise and mastic extract (DEM): *p<0.05, **p<0.01

The assessment of thyroid hormone revealed that the levels of T3 (Figure 2A) and T4 (Figure 2B) were significantly reduced in STZ-induced diabetic rats ($P < 0.001$), but there were no changes in levels of T3 when treated by exercise and/or mastic extract; however, T4 levels were markedly enhanced in diabetic rats receiving mastic extract (DM) or exercising together with mastic extract (DEM) compared to the diabetic control group (D) ($p<0.05$).

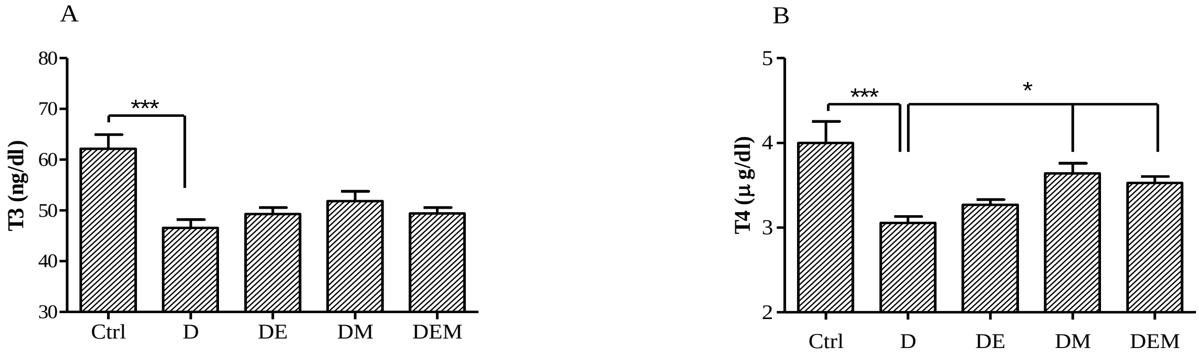

Figure 2. Plasma concentrations of T3 (A) and T4 (B) levels of control rats (Ctrl) or streptozotocin-induced diabetic rats (D) who did or did not receive the intervention of exercise (DE) or mastic extract (DM) and combination of exercise and mastic extract (DEM): *$p<0.05$, ***$p<0.001$

Assessment of lipid profile (Table 1) manifested a significant reduction in triglyceride in the groups of DEM compared to the diabetic control group ($p<0.05$). However, changes in cholesterol and HDL levels in different groups were not significantly changed.

Table 1. The mean and standard deviation of the levels of triglyceride, cholesterol, and HDL

Variable	Ctrl	D	DE	DM	DEM
Triglyceride (mg/dL)	81.13±6.51^{ab}	89.63±11.1^{a}	75.5±11.5^{a}	77.29±13.28^{a}	73.92±5.31^{b}
Cholesterol (mg/dL)	40.25±3.15	44±9.07	43±5.02	42.29±5.52	44.29±4.85
HDL (mg/dL)	23.58±2.32	22.28±2.24	22.9±3.27	22.86±2.2	23.36±1.35

Control rats (Ctrl) or streptozotocin-induced diabetic rats (D) who did or did not receive the intervention of exercise (DE) or mastic extract (DM) and combination of exercise and mastic extract (DEM), Dissimilar letters (a and b) in each row represents that there is a significant difference in the level of $p<0.05$ between groups.

Discussion

The results of this study showed that the use of mastic extract alone and in combination with the training improved insulin resistance in streptozotocin-induced diabetic rats. Moreover, the aerobic exercise in combination with the consumption of mastic extract resulted in significant reduction of blood triglyceride in diabetic rats; however, there were no statistically significant changes in HDL and cholesterol levels. Thyroid hormone levels (T3 and T4) in STZ-induced diabetic rats were markedly decreased and T4 levels significantly increased in STZ-induced diabetic rats receiving exercise alone or in combination with mastic extract, though there was a non-significant increase in the T3 level of diabetic rats treated by exercise and/or mastic extracts.

Diabetes is one of the most prevalent endocrine diseases which is caused by hyperglycemia. The role of reactive oxygen species is very important in the development of this disease (28,29). Streptozotocin is an antibiotic and anticancer drug that is highly cytotoxic for pancreatic B cells. Although the mechanism of beta-cell poisoning has not been fully understood, empirical evidence has shown that some of the damaging effects of STZ help stimulate metabolic processes that increase the production of active oxygen species. STZ-induced diabetes leads to a lack of pancreatic beta cells and therefore reduces insulin secretion (28-30).

In recent years, plants with antioxidant properties have attracted a lot of attention and it is believed that these plants protect the tissues against the harmful effects of free radicals. Researchers suggest that one of the best sources of natural antioxidants is phenolic compounds in plant essential oils (6).

Hyperglycemia-induced generation of free radicals leads to oxidative stress and contribute to the development and progression of diabetes and related contributions. Studies suggest that the consuming foods containing high levels of antioxidant help protect the body against oxidative stress (31-33). Mastic seeds contain various compounds, including terpenoids, phenolic flavonoids compounds, fatty acids, and sterols (34,35). Research has shown that the intake of flavonoids cause a significant decrease in cholesterol levels and thus leads to a reduction in high blood lipid (36, 37). In addition to flavonoids, beta-sitosterol which is considered as the main sterolic compound of mastic is a natural antioxidant source (۳۸). Accordingly, the antioxidant compounds of mastic, by increasing the antioxidant systems, may decrease the lipid peroxidation and, consequently, would reduce the blood triglyceride levels in rats (39). However, decreasing triglyceride levels may be associated with an increase in the lipoprotein lipase (LPL) enzyme, the main enzyme in the metabolism of lipids. This enzyme is synthesized and secreted by adipose tissue and breaks down the triglycerides of VLDL and chylomicrons, change them to monoacylglycerol and free fatty acid (40). The activity of this enzyme can be improved by various factors, such as increased insulin levels and aerobic exercise (21,41). Aerobic exercises indirectly increase LPL activity by augmenting catecholamine stimulation of lipolysis (42). On the other hand, triglyceride is considered as the most important source of energy in aerobic activities (21); therefore, activated LPL under the effect of exercise can increase the breakdown of triglycerides to fatty acids. This will facilitate access to free fatty acids for body energy.

Hypoinsulinemia is associated by extensive endocrine and metabolic disorders which may include growth retardation and hypoactivity of thyroid-pituitary axis, so that subclinical hypothyroidism among type 1 diabetic patients is significantly higher than the normal population (43,44). On the other hand, thyroid hormones, particularly T3, play a pivotal role in the development, differentiation and function of white and brown adipose tissues. T3 hormone stimulates adipocyte differentiation by stimulating lipogenesis pathway enzymes, namely ATP citrate lyase, malic enzyme and enzymes related to fatty acid synthesis (45). The roles of these hormones are lipid storage, lipogenesis and lipolysis as well as the regulation of basal oxygen supply (46, 47). Due to the increased level of thyroid hormones in exercise groups, the effect of thyroid hormones on the reduction of blood triglycerides can be implicated. The results of this study showed that the intake of mastic extract in combination with aerobic exercise can improve the activity of the pancreatic beta cell in diabetic rats. Therefore, increasing levels of insulin and improving its function might improve the level of thyroid hormones. Moreover, Mohammadi Karizno et al (2014) found that the intake of mastic extract and aerobic exercise, either alone or in combination, can result in significant reduction of protein carbonyl (PC) in the liver of diabetic rats (48). Since the formation of the PC is considered as a primary indicator for the oxidation of proteins, reducing PC levels is indicative of improving the antioxidant activity of the liver. As a result, this process affects the metabolism of thyroid hormones and probably improves hypothyroidism caused by diabetes in the examined groups.

In sum, it seems that bennet extract, by reducing the oxidative stress, has protective effects on pancreatic beta cells, and its combination with exercise can improve the function of these cells.

Conclusion

The findings of the present study specify that exercise and oral administration of mastic extract improved blood triglyceride and thyroxine hormone levels of diabetic rats. Therefore, exercise and mastic extract can be used as a complementary treatment to reduce blood lipids and improve hypothyroidism in diabetic rats.

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