Protective Effect of aerobic exercise training along with hydroalcoholic cinnamon extract on inflammatory indicators and oxidative stress in rats fed a high-fructose drink

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Abstract

Background: Inflammatory indicators and oxidative stress play an important role in insulin resistance. The aim of this study was to investigate the effect of aerobic training with cinnamon extract on inflammatory indicators and oxidative stress in rats fed a high-fructose drink.

Methods: Thirty-six Wistar male rats divided into groups: control (n=9), aerobic exercise (n=9), cinnamon extract (n=9), and aerobic exercise –cinnamon extract (n=9). Insulin-resistance status induced by %10 fructose solutions. Exercise groups subjected to a 5-day per week aerobic exercise program (with 75-80% VO2max) for 8 weeks. Extract groups subjected was Injected 200 mg/kgBW/day cinnamon extract. Data were analyzed using one-way ANOVA and statistical significance was set at p<0/05.

Results: The results showed that aerobic training with or without extract caused to a significant decrease in serum TNF-α, IL-6 and CRP (p<0/05). Indeed, in all three experimental groups, SOD and GPX increased significantly compared to control (P<0.05). MDA levels also decreased significantly in experimental groups compared to control group (P<0.05).

Conclusion: Results of this study indicated that aerobic exercise and cinnamon reduced inflammatory indicators and oxidative stress in rats fed a high-fructose drink. Also, cinnamon extract with aerobic exercise has a greater effect on these indicators.

Keywords: Exercise, Cinnamon, Insulin resistance, Inflammation and oxidative stress

1. Introduction

Insulin resistance is a pathological condition in which the sensitivity of liver and peripheral tissues to the effects of insulin decreases. Insulin resistance is the main pathogenic factor in the development of diseases such as type 2 diabetes, obesity and cardiovascular diseases. Oxidative stress plays an important role in the development of insulin resistance and is the cause of insulin resistance (1). One of the complications of insulin resistance is chronic inflammation. Various signaling cytokines are activated during insulin resistance, obesity and type 2 diabetes (2). TNF-α and IL-6 play an important role in inflammatory and immune responses, and it has been shown that their expression increases in conditions of insulin resistance. Dysregulation of TNF-α and IL-6 leads to the inhibition of hepatic insulin receptors and the reduction of insulin signaling effects in vivo and hinders the cellular effects of insulin. In addition, TNF-a causes cell damage through excessive production of oxidants (3). When fructose is eaten as a carbohydrate source alone in rats, it leads to complications similar to insulin resistance. Studies show that animals fed fructose suffer from oxidative damage and inflammation. Li et al showed that in fructose-fed hamsters, the levels of cytokines TNF-α and IL-6 were higher than in the control group (4). It seems that aerobic exercise is one of the best ways to deal with metabolic complications caused by high fructose consumption (5). In a study by Stanišić et al. on Wistar rats that received 10% fructose, it was shown that running on a treadmill decreased insulin and insulin resistance (6). Also, in another study, it was shown that the activity of inflammatory proteins in insulin-resistant rat decreased after aerobic exercise (5). In addition, oxidative stress is also affected by sports activities, its intensity and duration. Abdi et al observed that aerobic exercise caused a significant increase in total antioxidant, superoxide dismutase and catalase levels in diabetic male rats (7). Inadequate response to some common treatments for diabetes has caused that in America, about 2 to 3.6 million people use complementary and alternative medicine methods to treat diabetes, the most attention being paid to herbal and food treatments (8). Some studies have shown that plants also have anti-inflammatory properties. Cinnamon has antioxidant and anti-diabetic properties due to its polyphenols. Research has shown the positive role of antioxidants in reducing inflammatory cytokines. Cinnamaldehyde in cinnamon reduces inflammatory mediators in macrophages and monocytes (9). It has also been shown that treatment with cinnamon extract led to the reduction of inflammatory symptoms and markers (10) and oxidative stress (11) in rat. Since the use of fructose in beverages and foods is high nowadays, and the consumption of fructose increases food intake in animal studies, and this probably increases obesity and damages signaling pathways in liver cells (12). And on the other hand, considering the role of sports activities and cinnamon in reducing and modifying inflammation and the beneficial effects of oxidants, as well as the role of inflammation and free radicals in the development of metabolic syndrome; This research intends to study the simultaneous effect of cinnamon consumption and aerobic exercise on inflammatory indicators and oxidative stress in insulin-resistant rat.

2. Material and methods

All animal experiments were performed in accordance with animal welfare policies (based on the Helsinki Convention policies) and the National Institutes of Health guidelines for the care of laboratory animals were followed. A number of 36 male rats (4-6 weeks old,

weighing 154.67±10.95 g) from the Wistar breed were selected as samples from Pasteur Amel Institute and transferred to the research center. After one week of adaptation to the environment, insulin resistance was induced using 10% fructose solution for 5 weeks (13). Then insulin resistant rat were randomly divided into four equal groups (control group, exercise group, extract group, exercise-extract group). The tested rat were kept in groups of four and five rat in transparent polycarbonate cages, in an environment with a temperature of 20-24 °C, humidity of 45-55% and a light-dark cycle of 12:12 hours.

Rats in exercise and exercise-extract groups trained 5 days a week for 8 weeks. The entire training period was divided into three phases: familiarization, overload and maintenance or stabilization of work intensity. In the familiarization stage (first week), the rat walked on the special treadmill for 10-15 minutes at a speed of 10 m/min every day. In the overload stage (second to fourth week), the rats first walked for 15 minutes at a speed of 12 m/min, and the intensity and duration of the activity gradually increased over the course of 3 weeks until it reached the final amount determined for each group. In the maintenance or stabilization stage, from the fifth to the eighth week, the rats ran on the treadmill for 4 weeks with a determined intensity of 28 m/min, equivalent to 75-80% of the maximum oxygen consumption, and for 60 minutes. In addition, from the total activity time, 5 minutes were considered for warming up and 5 minutes for cooling down the rat at a speed of 7 m/min (14).

The bark of the cinnamon tree was powdered using a grinder and 24 g of the prepared powder was dissolved in 20 cc of 96% medical ethyl alcohol. The obtained mixture was kept at room temperature (25 °C) for 24 hours. Next, the resulting mixture was thoroughly mixed using a magnetic stirrer for 4 minutes, and it was smoothed on a Whatman paper, where the initial weight was recorded. The paper and powder remaining on it were dried in an oven at 50 °C for 1.5 hours. The amount of dissolved powder was determined by the difference in the weight of dry powder remaining on the filter paper and the initial amount of cinnamon. The extract extracted in this way contains a large amount of alcohol (about 20 ml). In order to remove alcohol, the extract is placed in an environment free of any pollution for 48 hours until the excess alcohol evaporates and its amount reaches the minimum possible (5 ml). Next, the volume of the extract was increased to 150 ml using 9% physiological serum (injectable normal saline). Each mouse was injected with 200 mg/kg body weight (0.5 ml) per day of the obtained solution (15).

Insulin resistance was induced in rat using 10% fructose solution for 5 weeks. To make a 10% solution, 9 liters of water was mixed with 1 kg of food crystal fructose (Merck company, Germany) and was given freely to the subjects. After 5 weeks of acclimatization to the environment and making the rat insulin resistant, for glucose measurement, blood was taken from the retina behind the eyes of the samples in fasting state (16). In this study, animals whose blood glucose level was higher than 170 mg/dl were considered as insulin resistant rat (17).

72 hours after the end of the last training session, the rats were anesthetized by intraperitoneal injection of a combination anesthetic of ketamine (30-50 mg/kg) and xylazine (3-5 mg/kg) and then killed. At first, blood was taken from the right ventricle. After centrifuging the blood samples and separating the serum, the amounts of the studied enzymes

were measured using the spectrophotometric method and standard animal kits of Erel (China). TNF-α, IL-6 and CRP levels were measured using an ELISA kit (R&D Systems, Sydney, NSW, Cusabio Biotech China and R&D Systems Europe, Abingdon, UK, respectively). To avoid the effect of circadian rhythm, sampling started at 8:00 and ended at 11:30.

After confirming the normal distribution of the data using the Shapiro-Wilk test, one-way analysis of variance and Tukey's post hoc test were used for statistical analysis. All data are presented as mean ± standard deviation. The calculation was done using SPSS v.16 statistical software and the significance level was considered $P \leq 0.05$.

3. Results

The weight changes of the subjects as well as the mean and standard deviation of the research variables are listed in Tables 1 and 2.

Table number 1: Body weight of rat

		control group (n = 9)	Training group (n = 9)	Extract group (n = 9)	Training-Extract group (n = 9)
weight (kg)	Pre-test	152.11±6.56	161.33 ± 9.57	157.11 ± 9.90	148.11±13.41
	Post-test	303.89±6.02	292±18.62	314.22 ± 21.06	294 ± 21.36

Table No. 2: The results of changes in variables in different research groups

	control group (n = 9)	Training group (n = 9)	Extract group (n = 9)	Training-Extract group (n = 9)
Insulin (mU/l)	14.25 ± 5.07	8.35 ± 3.76*	10.55 ± 2.76	8.54 ± 1.91*
Glucose (mg/dl)	196.22 ± 22.38	181.22 ± 32.26	172.89 ± 43.39	138.78 ± 38.63*
TNF-α (pg/ml)	70.67 ± 6.78	52.22 ± 10.73*	53.56 ± 11.05*	41.78 ± 7.75*
IL-6 (pg/ml)	257.89 ± 15.35	201.56 ± 25.62*	178.33 ± 27.87*	162.56 ± 23.73*
CRP (ng/ml)	524.00 ± 98.18	350.11 ± 93.45*	410.33 ± 74.27*	299/67 ± 73/30†*
SOD (Ug/gr Hb)	758.44 ± 104.21	1001 ± 166.45*	971.33 ± 185.77*	159/75 ± 1133/56†*
GPX (Ug/gr Hb)	28.01 ± 2.19	35.74 ± 2.70*	31.66 ± 2.31*±	38.51 ± 2.85†*
MDA (nmol/ml)	1.461 ± 0.14	1.038 ± 0.24*	1.106 ± 0.24*	0.957 ± 0.35*

* Difference with the control group, ± Difference with the training group† Difference with the extract group

The results of analysis of variance showed that aerobic training with cinnamon extract has caused a significant decrease in the serum levels of TNF-α, IL-6 and CRP compared to the control group ($p<0.05$). There was a significant decrease in IL-6 in the training -extract group compared to the training group ($p=0.007$) and CRP in the training -extract group compared to the extract group ($p=0.046$). The results of analysis of variance showed that SOD increased significantly in the exercise, extract and exercise-extract groups compared to the control group ($p=0.009$, $P=0.034$ and $p=0.000$, respectively). The increase of SOD in the exercise-extract group was also significant compared to the extract group ($P=0.005$). Also, GPX of experimental groups showed a significant increase compared to the control group ($P=0.000$, $P=0.022$ and $P=0.000$, respectively). The increase of GPX in the exercise and exercise-extract group was significant compared to the extract group ($P=0.009$ and $P=0.000$, respectively). Finally, the MDA of the exercise group, extract and exercise-extract had a significant decrease compared to the control group ($P=0.009$, $P=0.032$ and $P=0.002$, respectively).

4. Discation

The findings of the present study showed that aerobic exercises and consumption of cinnamon extract caused a significant decrease in serum inflammatory indices in insulin-resistant rat. Perhaps the most important cause of metabolic disorders is hyperinsulinemia. It seems that increased insulin decreases energy consumption in animal models and increases dependence on fats and leads to inflammation in several tissues (18). Protocols that reduce circulating insulin can reduce inflammation (19). As a key marker of inflammation, TNF-α is the first known cytokine capable of causing insulin resistance, which can inhibit the function of pancreatic beta cells by affecting glucose and fat metabolism and with a regulatory decrease in insulin signaling in fat cells, a decrease in GLUT4 transmission and a decrease in glucose consumption lead to insulin resistance (20). Studies have shown that aerobic exercise activity can reduce insulin resistance in diabetic patients by modulating the produced cytokines such as TNF-α (21). IL-6 also has pro-inflammatory or anti-inflammatory effects depending on the target tissue. In the absence of exercise activities, high levels of this cytokine can cause inflammatory responses that interfere with several key processes of glucose homeostasis regulation and cause insulin resistance (22). In line with the findings of this study, Botezelli et al showed in a study on rat fed with high fructose that strength sports activity reduced inflammatory indicators such as IL-6 and TNF-α (5). Sports activity can directly reduce the production of cytokines in fatty tissue, muscle and mononuclear cells, and indirectly by increasing insulin sensitivity and improving endothelial function, it can also reduce the level of CRP in the blood circulation (23).

IL-6, TNF-α and CRP levels increase in metabolic syndrome diseases that are accompanied by inflammation. It seems that fructose causes oxidative stress and inflammation and increases the level of CRP in rat that have eaten fructose, which indicates the involvement of inflammatory protein in metabolic syndrome diseases (24). In the present study, the group that consumed cinnamon extract had significantly lower levels of inflammatory indicators than the control group, which indicates the ability of cinnamon to control inflammation in rat fed with high fructose. In line with this study, Tuzcu et al. showed that cinnamon polyphenol extract inhibits hyperlipidemia and inflammation in rats with high-fat diets (25). Also, Qin et al found that cinnamon extract decreases the expression of IL-1β, IL-6 and TNF-α and increases the expression of insulin receptor in animal samples (26). One of the ways to increase inflammatory factors is to increase NF-κB. NF-κB is activated in hypoglycemic conditions or when reactive oxygen species are increased (27). A study showed that cinnamon reduces inflammatory factors by inhibiting NF-κB (28).

Among the other results of the present study was the increase of SOD and GPX levels as well as the decrease of MDA serum levels as a result of a period of aerobic exercise with the consumption of cinnamon extract in rats. In line with this research, Dehghan et al showed in a research that 8 weeks of endurance training with cinnamon supplement increased the activity of catalase and GPX in rats. Also, the amount of TCA increased and protects rats against oxidative stress (29). Also, in a research, it was shown that cinnamon extract and aerobic exercise provide protection against heart diseases by reducing the serum levels of MDA in rats (30). In the present study, the oxidant capacity of the samples improved after aerobic sports activities. Aerobic sports activities are associated with the production of free radicals due to the consumption of more oxygen by the organs (31). However, evidence

shows that free radicals can act as signals to stimulate adaptive processes during sports activities (31).

According to some reports, antioxidant capacity decreases in diabetic people or animal models. However, Li et al showed that the polyphenols in cinnamon are able to protect against the oxidant effects caused by metabolic syndrome diseases (11). There are many studies that show that SOD and GPX are important enzymes that destroy reactive oxygen species and protect the pancreas against oxidative stress damage (32). In addition, the level of MDA indicates the level of lipid peroxidation and cell damage. Studies have shown that cinnamon polyphenol is able to increase the activity of SOD and GPX in the pancreatic tissue of diabetic rats and reduce the amount of MDA (11). SOD, CAT, and GPx are the first line of cellular defense against oxidative damage, breaking down O2 and H2O2 before they are converted to hydroxyl radicals. In animals that consumed fructose, the level of activity of SOD, CAT and GPx decreased and increased O2 (33). In the present study, the consumption of cinnamon extract caused a significant increase in the amount of SOD, GPX and a decrease in MDA, which may be due to the effects of this extract to eliminate free radicals. Cinnamon is rich in strong antioxidants such as polyphenols, which, with polyphenolic compounds, increase the uptake of glucose by various body cells and reduce the level of oxidative stress (34). Badalzadeh et al showed the positive effect of 200 mg of cinnamon on MDA values (30). Many studies have reported that cinnamon bark, leaf and fruit extracts have high phenol content and high ability to eliminate free radicals (35). These effects are caused by the presence of phenolic hydroxyl group in cinnamon (36). Another mechanism by which cinnamon reduces lipid peroxidation is increasing the expression of Nrf2 and HO-1 proteins in May rats (25). The transcription factor Nrf2 is one of the most important antioxidant defense mechanisms that protect cells and tissue from various oxidative stresses (37). Also, HO-1 has many effects against oxidative stress and damage (38). In the present study, a significant increase in the amount of SOD and GPX was observed in the aerobic exercise-cinnamon extract group compared to the extract group. It seems that when aerobic sports activities are combined with adequate consumption of antioxidants, they help to control metabolic syndrome better than either of them alone (33).

Among other results of the present study, the increase of antioxidant indices was associated with the decrease of inflammatory indices in different groups. Oxidative damage has been reported in rats after consuming a high-fructose diet. Oxidative stress can increase the expression and activity of NFjB, and NFjB can lead to the synthesis of IL-6 and TNF-α (39). NF-κB activation increased the expression of a large number of inflammatory cytokines and stimulated the inflammatory cascade in fructose-fed rat (27). In a study, it has been shown that cinnamon extract reduces the expression of NF-κB and improves pancreatic beta cells of insulin-resistant rat and causes normal insulin secretion (11). TNF-α production can be modulated by ROS. Sports activities are able to increase antioxidant activity through the upregulation of SOD, GPX and catalase and lead to anti-inflammatory conditions (40). Also, reducing the level of triglycerides and cholesterol following sports activities causes adjustment in the level of CRP. Studies have shown that exercise reduces the effects of IL-6 signaling on cells (41). Due to the fact that the creation and treatment of metabolic syndrome naturally requires a long process and time, the length of the research period was one of the

limitations of the present study. In longer protocols, the effects of exercise and cinnamon extract can be more carefully studied.

5. Conclusion

The results of the present study showed that aerobic exercise alone and combined with cinnamon hydroalcoholic extract has a positive effect in rats fed with high fructose by changing some biochemical variables that cause inflammation in the body and also improving the oxidant capacity. Also, the effect of combining exercise with cinnamon extract on improving inflammatory indices and antioxidant capacity was better than the effect of cinnamon extract. Therefore, it is recommended to use the combination of aerobic exercises with cinnamon in insulin resistant models to reduce the effects of metabolic syndrome.

Declarations

Ethical Considerations

Compliance with ethical guidelines

This research was carried out with the approval of the Ethics Committee of the Research Institute of Physical Education and Sports Sciences.

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Authors' contributions

Conceptualization: Ahmad Abdi, Fatemeh Hosseini, Shiva Haibi, Rostam Abdi; Methodology: Ahmad Abdi, Fatemeh Hosseini, Shiva Haibi; Formal analysis: Ahmad Abdi; Investigation; Writing: Ahmad Abdi; Funding acquisition: Fatemeh Hosseini, Shiva Haibi, Rostam Abdi.

Conflicts of interest

The authors declare that they have no competing interests.

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