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# Lipid- lowering Effects of Endurance Training and Cinnamon Extract in Streptozotocin- induced Diabetic Rats

Sepideh Dolati[1*], Rokhsare Rostami[2], Seyed Ali Hosseini[2], Aleme Hariri Far[3], Abdossaleh Zar[4]

1. Department of Nutrition, Ministry of Health, Tehran, Iran.
2. Department of Sport Physiology, Marvdasht Branch, Islamic Azad University, Marvdasht, Iran;
3. Department of Community Nutrition, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran.
4. Department of Sport Physiology, Persian Gulf University, Bushehr, Iran.

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ABSTRACT

**Introduction:** Diabetes is a disease caused by a lack of insulin secretion or a decrease in tissue sensitivity to insulin. The aim of this study was to investigate the lipid-lowering effects of endurance training (ET) with cinnamon (C) extract in streptozotocin (STZ)-induced diabetic rats.

**Methods:** Thirty-two diabetic rats were divided into four groups of 8 rats, including 1) cinnamon, 2) training, 3) training+cinnamon and 4) sham groups. During four weeks, groups 1 and 3 received daily 100 mg/kg C perennially, and groups 2 and 3 ran on treadmill five times per week for 60 minutes each session at a speed of 8 to 16 m/min. Data were analyzed using paired sample t test and one way ANOVA and Tukey's *post-hoc* tests (p≤0.05).

**Results:** Cinnamon powder, training and training+cinnamon significantly reduced TG, LDL and VLDL levels as well increased HDL (P=0.001) in compare with sham group, training+cinnamon significantly reduced Cho and VLDL (P=0.001) in compare with sham group; training+cinnamon had more effect on decrease of Cho (p=0.02) and LDL (p=0.002) as well as increase of HDL (P=0.004) rather than training. Also cinnamon (P=0.03) and training (P=0.04) significantly reduced VLDL in compare with sham group.

**Conclusion(s):** Although training and cinnamon have lipid-lowering effect in diabetic rats, nevertheless it seems training simultaneously with cinnamon administration has better effect on improving lipid profile compare to training alone.

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## Introduction

Diabetes mellitus describes a group of metabolic disorders characterized by high blood glucose levels. Diabetes patients are at risk for a number of serious health problems that can result in high medical care costs, reduced quality of life and increased mortality (1). The global prevalence of diabetes in adults has been increasing in recent decades as well as eating style and sedentary lifestyle seems to be some of the underlying causes of diabetes (2). According to available statistics, in 2017, 451 million people aged 18 to 99 years worldwide had diabetes, which is estimated to reach 692 million by 2045 (1). Studies show that an active lifestyle in adults reduces the risk of developing impaired glucose tolerance, insulin resistance and type 2 diabetes (3). Changes in circulating lipid profile, such as triglycerides (TG), low density lipoprotein (LDL), very low density lipoprotein (VLDL) and high density lipoprotein (HDL), are complications of high levels of persistent blood glucose (2, 4). LDL is atherogenic lipoprotein that is associated with cardiovascular diseases (5). It is well known that the endurance training (ET) is an important part of lifestyle modification for the treatment of hyperlipidemia (6-8). ET increases bearing load intensity and resistance to fatigue during long-time workouts by enhance the muscle strength (8). Different effects of ET on lipid profile has been reported in existing literature, it is shown. For example, in a meta-analysis study, ET increased HDL (5 %) as well as decreased LDL and TG (5 and 4%, respectively), Also ET reduced total cholesterol (TC) (3- 16%) and LDL (5- 39%) as well as increased HDL (14- 27%) (8, 9). According to the results of an animal study in diabetic rats, physical activity increased HDL,

* *Corresponding author:* Sepideh Dolati, Department of Nutrition, Ministry of Health and Medical Education, District 2, Eyvanak Blvd of Industry Square, Tehran, 1467664961, Iran. Tel: +982181454977; Email: sd.dolati@gmail.com.

and decreased TG or VLDL by change of fat-regulator enzymes, increase of fat intake as fuel, decrease of lipid protein transfer (LPT) and increase of LDL and LCAT (lecithinease of LDL aacyltransferase) (10). In another study, 12 weeks of moderate intensity ET significantly reduced LDL and increased HDL levels. According to this study, it seems that the minimum time required for ET to cause significant changes in serum lipid profile is 60-90 minutes (11), So it appears that moderate-intensity ET for at least 60 minutes might improve lipid profile status. So the role of exercise in obesity and diabetes in improving insulin sensitivity and lipid profile have been well established (9). Although the results of an animal study showed that 6 weeks of aerobic exercise had no effect on reducing insulin in diabetic rats (10). Despite the above, diet therapy is generally considered as the first step in the treatment of diabetic patients. The administration of herbal medicine has been common in ancient civilizations since ancient times, and today herbal medicine in various forms, including the use of herbal products or their complete extracts, is common all over the world (12). Because with the industrial development of the pharmaceutical industry, many synthetic drugs have entered the market, which have often many adverse effects. In traditional medicine, Cinnamon (C) has been considered for its ability to enhance of disease such as diabetes and its complications, including hyperlipidemia (12). C is from the Lauraceae family and derived from the bark of Cinnamomum trees and has two main species Cinnamomum zeylanicum and Cinnamon cassia. C is native to the Indian and Sri Lankan regions (13) and is most commonly used in spices in Asia, Australia and South America. The most important component of C is Cinnamaldehyde, which known as (E)-3-phenyl-2-propenal or 3-phenylacrylaldehyde (14, 15). Human studies have shown that C has many therapeutic properties, including lowering triglycerides, LDL, TC, anti-inflammatory properties, thereby reducing cardiovascular disease (16, 17) and lowering blood glucose (18-20). In animal studies phenolic antioxidants of C extract have been found to be effective in reducing hyperlipidemia, oxidative stress, anti-inflammatory properties, and improving cognitive function (12, 21). In a study on 28 high-fat diet obese rats, lipid profile was improved in rats receiving 12-week polyphenol C supplementation (21). The results of a meta-analysis study showed that the rate of change in lipid profile variables is depended on the amount and duration of C administration. Longer supplementation is associated with lower levels of TC, LDL and TG. There was no significant relationship between HDL changes and duration of C supplementation (12). In today's society, due to the high cost of treatment as well as the side effects of using synthetic drugs, people tend to use healthier and less complicated treatment methods such as exercise and also use traditional medicine and herbs to treat diseases. According to reported studies, most of researches investigate the lipid lowering effect of exercise (8, 22) and C administration (12, 17) separately and less studies have been reported the effects of ET simultaneously with C administration in diabetes disease, Therefore, there is a high need to investigate the simultaneous effect ET and C administration as special factors in decreasing blood lipids, which is one of the common complications of diabetes. The results of present study can provide a clear view of the synergistic effects of ET and C administration on lipid profile. If C administration could enhance the lipid lowering effects of ET in diabetes statue, this substance can be used as a beneficial natural supplement to improve diabetes along with ET to prevent further diabetes disorders. Therefore present study was designed to investigate the effect of ET simultaneously with C administration on serum lipid profile in streptozotocin (STZ) - induced diabetic rats.

## Materials and Methods

In this experimental study, 32 adult male Sprague- Dawley rats with mean age of eight weeks were purchased and transferred to the laboratory. Rats were kept in the laboratory environment in standard situation (5 rats in a cage, temperature of 23 ± 2 °C; light/dark cycle of 12:12 and humidity of 45 to 55 %) for eight days during the adaptation period.

### *Diabetes Induction*

For diabetes induction all rats were injected intra- peritoneally with 60 mg/kg STZ (sigma chemical, st Louis, MO, USA) at a rate of. Four days later, fasting blood glucose was measured glucometer and the rats with blood glucose levels above 300 mg/dL selected as statistical sample.

### Grouping

Rats base on blood glucose (23) were divided into four groups of eight rats including 1) C, 2) ET, 3) ET+C and 4) sham. Groups 1 and 3 received 100 mg/kg C extract intra- peritoneally (24) and rats in groups 2 and 3 ran on treadmill three sessions per week and 60 minutes each session with moderate intensity (25). Forty eight hours after last training session and C administration, the rats were anesthetized by ketamine and xylazine, and then blood samples were gathered. For blood sampling operation, first animals first anesthetized with Ketamine and xylosine. Then blood samples gathered directly from the left ventricle of animals. Lipid profile (HDL-C, TG and Cho) was measured enzymatically using commercial biochemistry kits prepared by Pars Azmoon Inc, Tehran, Iran and also LDL-C was calculated using Friedwald equation. VLDL-C was calculated by dividing TG by five.It should be noted that the entire research period was four weeks.

### Endurance Training Protocol

At first rats were placed on the treadmill to learn how to run (running at speed of 8 m/min with a 0 degree slope for 10 min). At the end of the treadmill a very weak electric shock was inserted to force the rats to run. To prevent possible damage by electric shock, the animals were conditioned from the beginning by gently tapping the treadmill and producing a relatively weak sound or by touching the tail of the animal. In present study, endurance training consisted of four weeks of incremental running on a slope treadmill (0% slope) at a speed of 8 to 16 m/min for 60 minutes per session and five sessions per week. To warm up the rats during training sessions, the rats were first run on the treadmill for eight minutes at speed of 8 m/min and then the training program was performed. At the end of the training program; for cooling down the speed inversely reduced in order to run the machine to zero. The cooling down program lasted about five to seven minutes (25).

### Cinnamon Preparation

The C sample was powdered by mechanical grinding. For each 100 g of cinnamon powder, 300 ml of distilled water was used as the solvent. After 24 hours extraction was carried out by Buchner funnel and then the solvent was concentrated by rotary apparatus (24).

### Ethical Review

The project was *approved by the Ethical Committee* at the Azad University – Marvdasht Branch and registered in the Iranian Registry of Clinical Trials (NO: IR.IAU.REC.1399.025) and written informed consent was taken from all participants.

### Statistical Analysis

Kolmogorov–Smirnov test was used to review the normality of the findings as well as paired sample t test and one way ANOVA with Tukey's post- hoc tests were used to analyze data with SPSS software version 21 (p≤0.05).

## Results

### Research Sample

The weights of the rats in the pre- test and post- test are presented in Table 1 as well as lipid profile levels in the four groups of study are reported in Table 2 and figures 1-2.

**Table 1.** The weights of the rats in the pre- test and post- test (mean ± standard deviation)

| Group | Pre- test (gram) | Post- test (gram) | P |
|---|---|---|---|
| **Sham** | 179.55±19.43 | 172.55±23.47 | 0.23 |
| **C** | 171±18.97 | 183.45±16.14 | 0.03 |
| **ET** | 159.77±21.01 | 168.33±26.70 | 0.04 |
| **ET+C** | 167.62±18.74 | 175.28±27.23 | 0.04 |

**ET:** Endurance Training**, C:** Cinnamon**; ET+C:** Endurance Training with Cinnamon

### Primary Findings

The results of paired sample t test in Table 1 showed that weight of rats in post- test significantly increased in C (P=0.03), ET (P=0.04) and ET+C (0.04) groups but did not changed in sham group.

The results of One-way ANOVA test showed that there was significant differences in TG (P=0.001), HDL (P=0.01) Cho (P=0.001), VLDL (P=0.001) and LDL (P=0.001) levels of STZ- induced diabetic rats.

The results of the Tukey's *post- hoc* test showed that C, ET and ET+C significantly decreased TG and VLDL levels as well as increased HDL levels (P=0.001) in compare with sham group; ET+C significantly decreased Cho and LDL (P=0.001) in compare with sham group; ET (P=0.04) and C (P=0.03) significantly decreased LDL in compare with sham group also ET+C had a greater effect on decrease of Cho (P=0.02) and LDL (P=0.002) as well as increase of HDL (P=0.004) compare to ET (Figures 1 and 2).

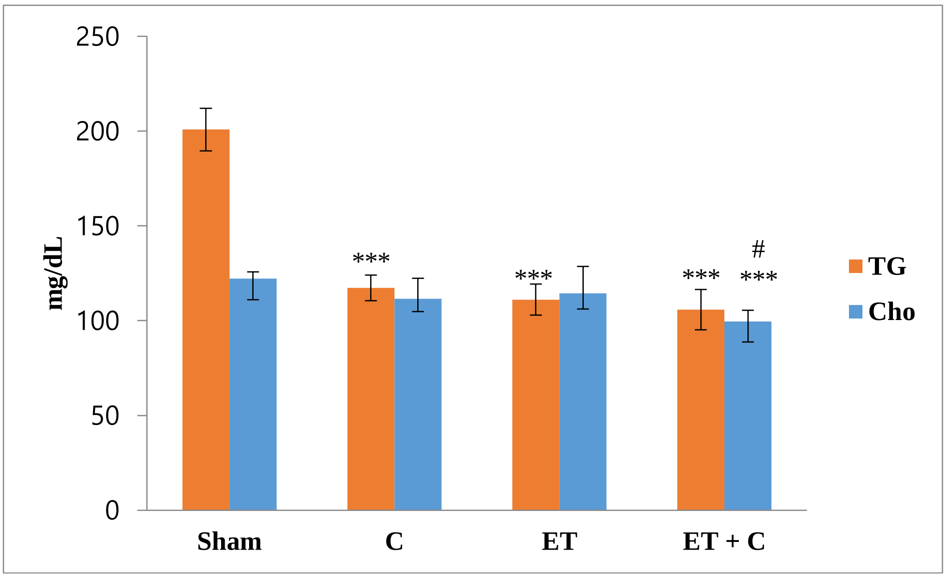


**Figure 1.** TG and Cho serum levels in diabetic rats
*** P<0.001 Significant decrease compare to Sham group; # P<0.05 Significant decrease compare to ET group; (ET: Endurance Training, C: Cinnamon; ET+C: Endurance Training with Cinnamon)

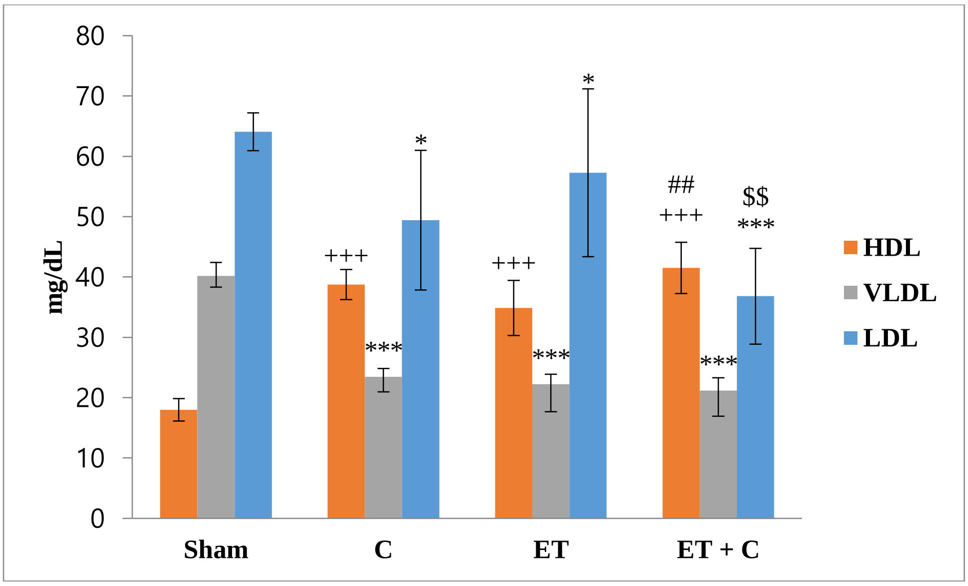


**Figure 2.** HDL, VLDL, and LDL serum levels in diabetic rats
*** P<0.001, * P<0.05 Significant decrease compare to Sham group; $$ P<0.01 Significant decrease compare to ET group; + + + P<0.001 Significant increase compare to Sham group; ## P<0.01 Significant increase compare to ET group; (ET: Endurance Training, C: Cinnamon; ET+C: Endurance Training with Cinnamon)

## Discussion

### *Summary of the Primary Research Results*

Findings showed that four weeks of ET decreased significantly serum Cho and LDL as well as increased HDL levels in STZ-induced diabetic rats. Four weeks of C administration reduced TG and LDL levels significantly as well as increased HDL levels in STZ-induced diabetic rats. Four weeks of ET with C administration decreased significantly TG and LDL levels as well as increased HDL in STZ-induced diabetic rats and in compare to ET had greater effect on reduction of Cho and LDL levels as well as increase of HDL levels.

***Discussion of the Primary Research Results***

Findings showed that four weeks of ET significantly decreased serum Cho and LDL as well as increased HDL levels in STZ-induced diabetic rats. Some findings suggest that ET enhanced lipid profile, which is consistent with the results of present study (26). According to the current guidelines of the American Diabetes Association (ADA), combining aerobic and resistance training is probably the most effective way to control glucose and lipids in type 2 diabetes (3). On the other hand, one study showed compared to calorie restriction, ET had less effect on the lipid profile of obese diabetic rats and more effective on glycemic indices, inflammation, and body composition (27). Perhaps one reason for decline in cholesterol after aerobic exercise in diabetic rat is the change in fat-regulating enzymes and increase in fat intake during exercise (10). The mechanism of improve of lipid profile factors by ET is still unknown (26). But according to the findings of a meta-analysis, the mechanism of the effect of ET on adipocytokinase levels may be one of the factors altering lipid profile levels in cardiovascular patients (26). One of the suggested mechanisms for changes in lipid profile after physical activity is physical activity increases LDL and LCAT and decreases LTP (lipid transfer protein). As a result, HDL increases and TG or VLDL decreases (10). It should be noted that LCAT is involved in regulating fat metabolism and the binding of free cholesterol to HDL (28). In line with present study four weeks of swimming training (22), six weeks of swimming training (29), eight weeks of ET (30) and six weeks of resistance training (10) significantly improved lipid profile in diabetic rats. The consistency in the findings may be also due to similar types of diabetes induction, exercise and time duration. Regarding lipid profile changes due to exercise, it should be noted that HDL is one of the important factors contributing to the transmission of cholesterol, and is increased according to the intensity and duration of the exercise (22). It has been determined that plasma HDL elevation has a close relationship with plasma Triglyceride levels; these changes will improve insulin sensitivity (22). However, there are mechanisms, such as reduced insulin sensitivity, that lead to changes in blood lipid and lipoprotein levels. These mechanisms may be the cause of changes in fat profiles due to exercise (22). In this study, one of the possible mechanisms of increase in HDL is the increase in lipoprotein lipase due to regular exercise and subsequently, the catabolism of lipoproteins (31). On the other hand, in addition to LDL, lecithin-cholesterol Acyltransferase (LCAT), converts cholesterol into HDL particles. Increasing this enzyme may be responsible for increasing HDL due to exercise. LCAT has been shown to be greatly increased in some exercise activities. Exercise also appears to increase lipolysis and reduce fatty acids in the muscles (32).

Also, in the present study, four weeks of C administration significantly reduced TG and LDL levels as well as increased HDL levels in STZ-induced diabetic rats. In one animal study, C extract reduced hyperlipidemia (12) and in another study, 12-weeks C extract (28 obese rats) reduced serum LDL and TG, in addition, increased HDL levels (21). The results of these two studies are in line with the findings of present study. According to the meta-analysis on 13 randomized controlled trials with 750 participants, C supplementation significantly decreased LDL, Cho, and TG, but increase of HDL was not significant (12). According to the results of this study, C supplementation over a longer period was associated with a significant decrease in LDL, Cho and TG, but its effect on HDL was not significant. Thus, the amount and duration of supplementation is important in its effectiveness (12). In one animal study, C extract significantly reduced dyslipidemia compared to dexamethasone and, helped maintain atherogenic indices (Cho, LDL, and HDL) in atherosclerotic rats (13). The possible mechanism of the effect of C on serum lipids in animal studies, inhibition of hepatic HMG-CoA reductase activity, and consequently cholesterol depletion in high fat rats. Another possible mechanism for C to reduce triglycerides is to inhibit the activity of the enzymes involved in carbohydrate metabolism (pancreatic α-amylase and α- glucosidase), stimulate cellular glucose uptake by GLUT-4 membrane translocation and glycogen synthesis (17). There are two suggested mechanisms for lowering blood TG concentration; C polyphenols increase glycogen synthesis and decrease glycogenolysis (33) as well as decrease glucose uptake by the small intestine and regulate peroxisome proliferator-activated receptor gamma (PPARγ) (12). Thus, a decrease in chylomicron uptake and a possible increase in triglyceride uptake by adipocytes may explain our findings. Possible activation of peroxisome proliferator-activated receptor alpha (PPARα) by C may help to lower blood cholesterol levels. Another possible mechanism could be that the vitamin may be responsible for the increase in fat metabolism (12).

The results of the present study showed that four weeks of ET with C administration significantly decreased TG and LDL levels as well as increased HDL in STZ-induced diabetic rats and in compare to ET had greater effect on reduction of Cho and LDL levels as well as increase of HDL levels. It seems the combination of C polyphenol supplementation and ET can be used as an effective drug to improve the lipid profile of diabetic rats, so that each one with a separate mechanism of action can improve lipid profile in diabetic rats. In line with present study, Fayaz *et al.,* (2019) reported that high-intensity interval training (HIIT) with 100 mg/kg body weight C supplementation for 12 weeks significantly decreased LDL and insulin resistance as well as increased HDL (7) in ovariectomized Wistar rats as well as Badalzadeh *et al.,* (2014) showed that eight weeks of ET along with C consumption enhances lipid profile in healthy rats (34). Regards to the lipid lowering effects of exercise, it has been shown that free fatty acids produced from adipose tissue by accumulating in muscle cells, disrupt the transport of glucose transporter (GLUT4) to the surface of these cells; so that exercises prevent from their accumulation in muscle cells, by increase in oxidation of fatty acids (22). Also regards to C administration, it has been reported that C enhances blood glucose and insulin resistance in diabetic rats via increasing insulin activity by up to 20 times and increasing glucose metabolism by several times in fat cells. Methyl hydroxychalcone polymer in C, activates the insulin receptor kinase (IRK) in fat cells; As a result, the sensitivity of these cells to insulin increases and insulin resistance decreases (35).

One of the limitations of the present study was the lack of healthy control groups in investigating the effects of diabetes induction on lipid profile and comparing the interactive effects of ET and C administration in healthy and diabetic rats. Therefore, it is suggested in future studies, healthy control groups should also be investigated alongside diabetic rats. Another limitation of the present study was the lack of measurement of lipid profile in tissue and also the failure to measure glycemic indices such as insulin and glucose. Therefore, it is suggested that future studies investigate the simultaneous effects of ET and C administration on lipid profile levels and glycemic indices in important tissues of diabetic rats such as the heart, liver, and muscle.

## Conclusion

Although ET and C have lipid lowering effect in diabetic rats, nevertheless it seems that ET simultaneously with C administration has better effect on improving lipid profile compare to ET alone.

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This study is supported by the personal expenses of the researchers.

## Conflicts of Interest

The authors have declared that no conflict of interest exists.

## Authors Involvement

Study concept and design: Seyed Ali Hosseini, acquisition of data: Seyed Ali Hosseini; analysis and interpretation of data: Seyed Ali Hosseini, Rokhsare Rostami; drafting of the manuscript: Sepideh Dolati; critical revision of the manuscript: Sepideh Dolati, Rokhsare Rostami, Seyed Ali Hosseini, Alemeh Hariri Far, Abdossaleh Zar, statistical analysis: Seyed Ali Hosseini, Rokhsare Rostami, administrative, technical, or material support: Rokhsare Rostami, Seyed Ali Hosseini; and study supervision: Seyed Ali Hosseini, Sepideh Dolati, Alemeh Hariri Far

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