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Effects of Cinnamon Extract Consumption and Swimming Exercise on the Expression of ATGL and CGI-58 in the Visceral Adipose Tissue of Streptozotocin-induced Diabetic Rats

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ABSTRACT

Introduction: Diabetes is a widespread disease, and various techniques are used for its prevention, control, and treatment, including physical exercises and medicinal herbs. Natural medicines and exercise are comparatively inexpensive and cause fewer complications compared to chemical drugs. The present study aimed to evaluate the effects of a swimming course and cinnamon extract consumption on the expression of adipose triglyceride lipase and CGI-58 in the visceral adipose tissue of streptozotocin-induced diabetic rats.

Methods: This experimental study was conducted on 28 diabetic rats, which were randomly divided into four groups of seven, including 1) control (C),2) cinnamon use (Ci),3) swimming course(S), and 4) cinnamon extract with swimming (S+Ci). The animals received the intended treatment for six weeks in packs of three and four and five classes per week, while the rats in groups two and four received 200mg/kg of cinnamon orally every day for six weeks. Data analysis was performed using the one-way analysis of variance (ANOVA) and Tukey's post-hoc test at the significance level of $P \leq 0.050$.

Results: The results of ANOVA indicated that *ATGL* gene expression in the S (P=0.04) and S+Ci groups (P=0.0001) was significantly higher than the control group. In addition, *ATGL* gene expression in the S group (P=0.0006) was higher compared to the Ci group, while it was significantly higher in the S+Ci group (P=0.0001) compared to the Ci and S groups. *CGI-58* gene expression in the S+Ci group (P=0.0001) was also significantly higher than the control, S, and Ci groups, while it was significantly higher in the S group (P=0.036) compared to the Ci group.

Conclusion: According to the results, swimming exercise and cinnamon extract consumption increased the expression of CGI-58 and ATGL protein in the diabetic rats. Therefore, it seems that CGI-58 plays a key role in the activation of lipolysis by ATGL, and higher CGI-58 could increase ATGL, which ultimately accelerates the lipolysis process, reduces fat, and improves insulin resistance in the visceral adipose tissue.

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Introduction

Diabetes is a common metabolic disorder characterized by high blood sugar levels due to insufficient insulin secretion, insulin resistance, or a combination of both. Insulin resistance plays a pivotal role in the pathogenesis of type II diabetes (1). The chronic complications of diabetes are directly correlated with high blood glucose levels (2).Hyperglycemia leads to the non-enzymatic binding of glucose to the proteins inside and outside the cell, and patients with long-term diabetes often experience kidney failure, eye damage, cardiovascular failure, and central nervous system deficiency.

Type II diabetes is often associated with the disorders of lipid metabolism, and plasma fatty acids play a key role in increasing insulin resistance. As such, plasma fatty acids cause dyslipidemia in diabetic patients through increasing the very-low-density lipoprotein center in the liver and cholesterol-transporting proteins, thereby increasing low-density lipoprotein (LDL) and decreasing high-density lipoprotein (HDL).This atherogenic function of lipoproteins (i.e., increased triglycerides, increased LDL, and decreased HDL) causes atherosclerosis and increases the risk of cardiovascular events, which is the most common cause of death in type II diabetic patients (3). Therefore, extensive research is required on the factors that could reduce the pathogens in this patient population.

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Comparative gene identification-58 (CGI-58) is an extremely small protein that controls intracellular triglyceride levels by activating adipose triglyceride lipase (ATGL). Recent studies have emphasized the importance of CGI-58 as a regulator of intracellular energy homeostasis by modeling the hydrolysis of triacylglycerol (TAG) using ATGL. Correspondingly, the rats and humans lacking CGI-58 accumulate TAG in various tissues (4). Not only the presence of CGI-58 will increase ATGL activity, but it also expands its specific substrate, which highlights the significance of this protein in fat metabolism and energy (4). In the absence of ATGL, CGI-58 cannot increase lipolysis activity through any other pathways (5). Therefore, the interaction between ATGL and CGI-58 plays a pivotal role in the lipolysis and hydrolysis of TAG by lipases (6-8). If CGI-58 is combined with ATGL, lipolytic activity increases significantly compared to ATGL alone (9).

Physical exercise could effectively improve obesity through the activation of lipolysis (10). Evidence suggests that the visceral fat mass increases after detraining, and exercise without calorie restriction increases the level of fat-dependent proteins in the adipose tissue of obese rats, thereby reducing the volume of visceral fat and the size of fat droplets. Visceral fat is considered to be a stronger cause of metabolic diseases compared to subcutaneous fat. Moreover, it has been proposed that exercise after 15 weeks of high-fat diet could increase CGI-58 and ATGL by activating the catecholamine pathway and increasing cAMP and perilipin-1 levels, which in turn has a positive effect on increased lipolysis and decreased fat mass, while non-training has an opposite effect (11).

Research indicates that ATGL activity may be regulated by phosphorylation in response to hormonal stimulation during exercise (12). Therefore, high-intensity exercise training increases ATGL levels by increasing beta-adrenergic stimulation, which could increase the lipolysis process. In this regard, Hashimut et al. (2013) investigated obese rats and reported that six weeks of moderate aerobic training causeda significant decrease in epidermal fat and a significant increase in ATGL and CGI-58 (13).Furthermore, the findings of Jo Yang B et al. (2017) indicated that eight weeks of training could increase CGI-58 and ATGL (11).

Given the importance of the intracellular mechanisms of IMTG lipolysis in reducing or increasing the inflammatory processes caused by diabetes and other metabolic disorders, the storage and release of the regulatory factors of IMTG (e.g., exercise) must be investigated. Several studies have shown that exercise could further reduce the fat mass by activating the AMPK, PPARγ, and PPARG pathways as the important activators of cAMP, thereby increasing the levels of perilipin-1, ATGL, and CGI-58 (14-16).

Today, the traditional treatment of diabetes by using medicinal plants and herbal extracts is widely practiced across the world (17).Cinnamon (*Cinnamomum zeylanicum*) is a plant belonging to the Lauraceae family, which is has long proven effective in the treatment of diabetes (18).Recent finding son cinnamon have confirmed its ability to lower blood sugar (19). Different parts of the cinnamon plant (including its skin) are reported to have multiple the rapeutic properties, and the consumption of cinnamon is known to strengthen the heart, stomach, and intestines. Moreover, cinnamon could improve kidney function and increase sexual potency (20).High levels of antioxidants in cinnamon cause the plant to act as a cell protector against chemical damage (e.g., environmental toxins), reduce lipid peroxides, and protect the liver against stress. Therefore, cinnamon may play a key role in improving the antioxidant state of obese diabetic patients, as well as patients with cardiovascular diseases and metabolic syndrome (21). Studies have also shown that cinnamon is more effective in the regulation of glucose metabolism compared to other herbal products, such as green tea, olive oil, garlic, and onion (22,23).

According to the literature, daily consumption of one gram of cinnamon for 30 days could reduce the blood glucose and lipid levels of diabetic patients (22). Today, experts believe that diet and medication alone are not sufficient in the treatment and control of the glucose and fat metabolism of diabetic patients, and physical activity and exercise should be incorporated into the daily routine of this patient population.

Given the beneficial effects of cinnamon consumption and sports activities on diabetic patients and considering that no research has been focused on the effects of these factors on these patients, the present study aimed to evaluate the correlation between exercise training and cinnamon extract consumption on the expression of adipose glyceride lipase and CGI-58 in the visceral adipose tissue of streptozotocin-induced diabetic rats.

Materials and Methods

Subjects

This experimental, applied research was conducted on 28 rats aged 8-10 weeks, which were purchased from the Center for the Breeding and Reproduction of Laboratory Animals affiliated to Islamic Azad University of Marvdasht Branch, Iran. The animals were kept in the Animal Sports Physiology Laboratory of the university for one week to be subjected to the adaptation course. Notably, the animals were kept in standard conditions within a 12-hour light/dark cycle with 55% humidity at the temperature of 22-24° C inside transparent polycarbonate cages, which were equipped with autoclave functionality and free meals. After one week, 28 rats received a peritoneal injection of streptozotocin (Sigma, USA) at the concentration of55 mg/kg of the body weight. After four days, the blood glucose range of the rats was measured using the tail punching method.

To homogenize the study groups, the diabetic rats were divided into four groups of seven based on their fasting blood glucose, including 1) control, 2) cinnamon consumption(Ci), 3) swimming course (S), and 4)swimming course plus cinnamon consumption(S+Ci). The rats in the training groups completed the intended course for six weeks (five sessions per week), and each session was implemented in line with the specific protocol of the current research. The rats in the cinnamon consumption groups were administered with an aqueous extract of cinnamon orally at the concentration of 200 mg/kg of the body weight.

After six weeks of the intervention and 48 hours after the final training session, the rats in all the study groups were anesthetized via the peritoneal injection of ketamine and xylazine (3:1) following 16 hours of fasting. After confirming full anesthesia by ache reflex tests through squeezing the tail and ensuring that analgesia by laboratory specialists, blood samples were collected directly from the target tissues using a 5 cc syringe, and biopsies were extracted by the lab specialists. The blood samples were immediately frozen at the temperature of -80°C.

Swimming Exercise Protocol

To evaluate the ability of the rats to perform the swimming training, they swam in a special rats' swimming pool at a moderate temperature. Afterwards, their activities were meticulously observed for two minutes, and the process was repeated three times a week to familiarize the rats with the training conditions. Subsequently, swimming training was performed for two minutes five days a week in the first week in accordance with the study by Lubkaska et al. (2019). Moreover, 30 seconds was added to the training time in each training session until the training duration reached four minutes. Following that, the rats trained for four minutes until the end of the sixth week. The rats' swimming pool was composed of a special swimming tank for rats with the length of 100 centimeters, width of 50 centimeters, and depth of 50 centimeters (24).

Cinnamon Supplementation

Initially, 200 grams of cinnamon powder was dissolved in 1000 milliliters of pure water and boiled for 10 minutes. After cooling, the solution was filtered through paper filter No. 1. The prepared solution contained 20% cinnamon extract, with each milliliter containing 200 milligrams of cinnamon extract. For the daily consumption of each rat in a cage (equivalent to approximately one kilogram), 0.2 cc of the solution was added to their drinking water (25).

Measurement of the Research Variables

A molecular research was conducted at a gene expression level. For this purpose, RNA was initially extracted from the visceral fat tissues, and the process was performed in accordance with the manufacture's protocol in Iran. A mild absorption at the wavelength of 260 nanometers was used to quantitatively acquire the concentration and purity of the RNA samples. To this end, we used the following formula:

$C\ (\mu g/\mu l) = A260 \times \varepsilon \times d/1000$

After extracting extremely high purity and RNA concentration from the samples, the guidelines for cDNA synthesis in the fermentas kit (K1621) were applied, and the synthesized cDNA was processed for a reverse transcription reaction. Initially, the designed primer-related genes were examined, and the expression of the genes was assessed using the quantitative q-RT-PCR method. In addition, their relative expression was determined using the 2-ΔΔCt formula.

Statistical Analysis

Data analysis was performed in SPSS version 24 using descriptive statistics (mean and standard deviation [SD]) to obtain the data. Moreover, the Shapiro-Wilk test was used to assess the normality of data distribution, and one-way analysis of variance (ANOVA) and Tukey's post-hoc test were employed to compare the performance of the animals. All the statistical analyses were carried out at the significance level of P<0.05.

Results

According to the results of one-way ANOVA, eight weeks of swimming and cinnamon consumption significantly increased the *ATGL* gene expression in the visceral adipose tissue of the diabetic rats(P=0.001). Furthermore, the results of Tukey's post-hoc demonstrated that the *ATGL* gene expression in the S group (P=0.04) and S+Ci group (P=0.0001) was significantly higher compared to the control group. *ATGL* gene expression was also significantly higher in the S group (P=0.0006) compared to the Ci group, while it was significantly higher in the S+Ci group (P=0.0001) compared to the Ci and S groups (Figure 1).

The findings of one-way ANOVA confirmed that eight weeks of a swimming course along with cinnamon consumption could significantly increase*CGI-58* gene expression in the adipose tissue of the diabetic rats(P=0.001). Furthermore, the results of Tukey's post-hoc test indicated that *CGI-58* gene expression in the S+Ci group was significantly higher than the control, S, and Ci groups (P=0.0001). *CGI-58* gene expression in the S group was also significantly higher compared to the Ci group (P=0.036) (Figure 2).

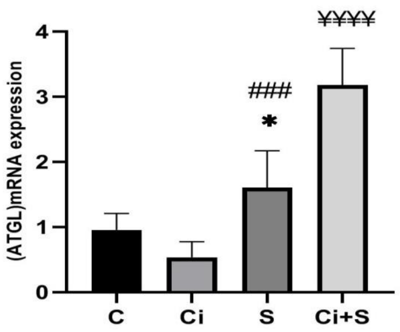

Figure1. ATGL gene expression levels in the visceral adipose tissue of diabetic rats in the four study groups
* (P= 0.01): significantly increase compared to the C groups;
(P = 0.001): significant increase compared to the Ci group;
¥¥¥¥ (P = 0.0001): significant increase compared to the Ci, C, and S groups.

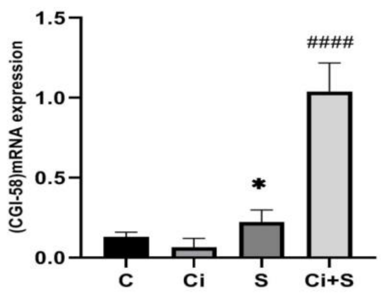

Figure 2: CGI-58 gene expression levels in the visceral adipose tissue of diabetic rats in the four study groups
*(P= 0.01): significant increase compared to the Ci group;
####(P = 0.0001): significant increase compared to the Ci, C, and S groups.

Discussion

The present study aimed to investigate the effects of swimming training with cinnamon extract consumption on the expression of adipose triglyceride lipase (*ATGL* and *CGI-58* genes) in the visceral adipose tissue of streptozotocin-induced diabetic rats. The results of the first hypothesis showed a significant difference in the gene expression of adipose triglyceride lipase (i.e., ATGL) in the visceral adipose tissue after the training intervention with cinnamon supplementation. It seems that a significant increase in the ATGL of the trained diabetic rats could regulate the mobilization and fat consumption of IMTGs through intracellular and hormonal metabolites. Unlike adipose tissue lipolysis, which is stimulated over time by the depletion of the body's energy, lipolysis in the skeletal muscles responds specifically to local muscle demands. The results of research by Tronbol et al. (2016) also indicated that eight weeks of endurance training increased the ATGL protein in all the training skeletal muscles of rats (26), and the increased ATGL expression could probably maintain the low metabolic concentration of muscle fatty acids, thereby improving insulin sensitivity in strenuous training.

In another study, Yao Brongaser et al. reported that the increased rate of IMGT breakdown was associated with increased insulin sensitivity following exercise training. The increased expression or activity of lipolytic enzyme (i.e., ATGL) by endurance training facilitates the breakdown of IMGT, thereby providing the adequate substrate to the muscles. Due to the intensity and duration of training and the level of access to the substrate, the amount of FA used for oxidation metabolism during endurance training reaches its maximum (27), while at higher intensities, plasma free fatty acid levels do not change despite increased adipose tissue lipolysis, and the higher ATGL expression ultimately in diabetic rat's increases lipolysis. As a result, the release of fatty acids will increase, leading to cell requirements in the absence of energy glucose. Other proven factors (e.g., insulin depletion and alpha-adrenergic pathways) have also been reported to increase lipolysis in diabetic patients (28).

According to the findings of Morville et al. (2017), the repetition of long-term training could reduce fat oxidation in elderly men and significantly increase the expression of HKII, GLUT4, and ATGL proteins, which in turn increases the glucose transport capacity and muscle lipolysis capacity, contributing to higher external glucose and intracellular fat during training (29).In the current research, the consumption of cinnamon caused ATGL expression in the diabetic rats compared to the control group. In contrast, Belvin et al. conducted a study in the United States, reporting that consuming one gram of cinnamon per day for three months had no effects on the fat, triglyceride, cholesterol, LDL, and HDL profiles of the subjects, and no significant reduction was denoted in these markers (22).

A meta-analysis performed by Baker et al. indicated that cinnamon could not affect blood lipid levels compared to placebo (30).In another study conducted by Mirfeiz et al. in Karaj (Iran), consuming 500-milligram cinnamon capsules twice a day for 90 days caused no significant difference in blood lipid profiles compared to the control group(31). Furthermore, the results of a clinical trial conducted by Zahmatkesh et al. in Yazd (Iran) demonstrated that receiving two grams of cinnamon per day for eight weeks had no effects on the required indicators compared to the placebo group, and no significant differences were observed between the two groups in this regard (32).Previous findings in this regard are not consistent with the present study, which could be due to differences in the amount of prescribed cinnamon, duration of cinnamon consumption, and the sample populations.

Cinnamon could lower blood glucose and lipids due to its cinnamaldehyde content. Cinnamaldehyde is responsible for increasing insulin release, increasing insulin sensitivity, and regulating the activity of the tyrosine phosphatase enzyme (33). In the current research, the results of the second hypothesis test indicated a significant difference in the gene expression of *CGI-58* in the visceral adipose tissue after the training intervention combined with cinnamon supplementation. Moreover, a significant difference was observed in CGI-58 protein expression between the intervention and the control groups. Therefore, a tendency to increase was observed in CGI-58 with exercise training.

Since CGI-58 is associated with ATGL and the interaction between CGI-58 and ATGL increases AGTL regulatory activity from baseline to active, increasing lipolysis by ATGL could also be attributed to higher CGI-58. According to the study by Nagy et al. (2014), ATGL is required for the effective mobilization of triglycerides in the adipose and non-adipose tissues, and ATGL is essential to the availability of fatty acids for metabolic reactions. ATGL is regulated by a complex network of lipolytic and anti-lipolytic hormones. In addition, signals by controlling enzymatic expression and ATGL interaction with the regulatory protein CGI-58 in the ATGL regulatory function indicate the key role of this protein particularly in fat metabolism and muscle energy (34). On the other hand, the up-regulation of CGI-58 expression in primary human myotome accelerates TAG depletion, while increasing lipolysis and FA oxidation (35). In contrast, degenerated GCI-58 decreases lipolysis and increases TAG accumulation, indicating thatCGI-58 plays a pivotal role in the regulation of skeletal muscle ATGL activity and TAG dynamics, especially during training(36).

Recent findings have confirmed the key role of CGI-58 in the activation of lipolysis by ATGL, as well as its effects on the adipose tissue metabolism. Therefore, the increase in CGI-58 through ATGL could be justified in the present study. On the other hand, cinnamon consumption caused the expression of CGI-58 in the diabetic rats compared to the diabetic control group. Due to the presence of hydroxyl groups in its molecular structure, the polyphenolic compounds of cinnamon affect the lipid and phospholipid membranes of cells and integrate with lipid layers, thereby increasing intracellular dynamics and biological activity. In addition, they stimulate the sympathetic system and increase basal metabolism, exerting a greater impact on the fat stores through oxidation and heat production in the body, followed by an increase in energy consumption 24 hours a day (21). According to the findings of Brodhurst et al., the compounds in cinnamon could increase the action of insulin three fold and decrease the insulin resistance of the epidermal fat cells in rats (37).

Conclusion

According to the results regarding the effects of combined exercise training and cinnamon extract as an antioxidant supplement, these two factors could increase the expression of ATGL protein and decrease serum insulin and glucose levels in diabetic rats. Moreover, increased levels of ATGL lead to higher insulin sensitivity and improved insulin resistance in diabetic rats. Therefore, it seems that CGI-58 plays a pivotal role in the activation of lipolysis by ATGL, and increased CGI-58 leads to ATGL, which ultimately accelerates the lipolysis process, reduces fat, and improves insulin resistance in the visceral adipose tissue.

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