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**Effects of Physical Exercise and Cinnamon Extract on Blood Chemistry of Type 1 Diabetic Rats**

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##### ABSTRACT

**Moura LP,Chiyoda A, Teixeira CVL, Sponton CHG, Coelho FGM, Lima MCS, Hernandez SSS, Vital TM, Fernandes RA, Mello MAR**. Effects of Exercise and Cinnamon Extract on Blood Chemistry of Type 1 Diabetic Rats. ***JEP***2010;13(4):17-28. The present study was designed to analyze the effects of the association between cinnamon extract and aerobic exercise on the glycemic control and serum lipid profile of diabetic rats. Fifty Wistar male rats divided into five groups: control (C), sedentary nondiabetic rats; diabetic (D), sedentary diabetic rats; diabetic cinnamon (DC), sedentary diabetic rats that received cinnamon extract; diabetic exercise (DE), sedentary diabetic rats subjected to physical training; and diabetic cinnamon exercise (DCE), diabetic rats that received cinnamon extract and were subjected to physical training. For the induction of diabetes, the rats received alloxan. The cinnamon was administered to once a day for four weeks. The groups performed swimming exercises for one hour each day with lead overloads (3% - 5% of b.w) for five days a week for four weeks. Body weight loss was lower in the DE group compared to the other diabetic groups. The basal serum glucose of all the diabetic groups was higher compared to the control group. Group D had higher serum cholesterol concentrations compared to the DE and DCE groups. The resting blood lactate in group D was higher than the resting blood lactate in the DC and DE groups. Aerobic exercise partially counteracted the diabetic effects on body weight, serum cholesterol and blood lactate concentrations. No additional beneficial effects of cinnamon extract and aerobic exercise were observed on the parameters studied.

**Key Words**: Herbal Extracts, Glucose Intolerance, Physical Activity and Blood Lipids

**INTRODUCTION**

Diabetes mellitus is characterized by hyperglycemia and the impairment of protein and lipid metabolism resulting from reduced insulin secretion and/or action (41). According to the World Health Organization (WHO), there are 180 million diabetics worldwide, and it is predicted that this number may rise to over 330 million people by the year 2025 (46).

Failure in insulin production by the body is diagnosed as type 1 diabetes mellitus (T1DM) that results from an autoimmune process directed against pancreatic beta-cells, and is mediated by the T lymphocytes (12) and influenced by a combination of genetic and environmental factors (35). The high blood glucose concentrations may lead to various complications, such as blindness, end stage renal disease, atherosclerotic macrovascular disease and a variety of debilitating neuropathies reducing the patients’ quality of life and life expectancy (10,17).

There is a great interest in medicinal herbs due to the collateral effects caused by therapeutic agents used for diabetes treatment, such as oral antidiabetics and insulin (11,30,38). Many traditional and popular herbal extracts have been used for the treatment of diabetes. However, most of them have demonstrated little or no effect on glycemic control even though several herbs have glycemia-lowering properties (4,40).

Cinnamon, *Cinnamomi cassiae* (Lauraceae), is a popular herb used in Korea, China and Russia for the treatment of diabetes mellitus (4,6). Cinnamic aldehyde (45), tannin (13) and methylhydroxychalcone polymer (MHCP) (15) are among the active components of cinnamon with the cinnamic aldehyde thought to be a potential antidiabetic agent (40,31). The MHCP has an important role mimicking insulin action that causes the peripheral tissues of individuals with T1DM to take up glucose independent of insulin action. Studies have demonstrated that the cinnamon extract decreased serum glucose in euglycemic Wistar rats (31,42) and diabetic mice (19). Similar results were observed in diabetic patients (18,26,36).

On the other hand, regular physical activity has been considered fundamental in the control and treatment of T1DM. The main benefit of physical activity is the improvement of glucose tolerance (14) because muscle contraction activates the insulin signaling pathway (7,22). This activation induces glucose uptake in individuals with T1DM even in the absence of insulin, which helps glycemic homeostasis. The effects of the association between cinnamon intake and regular physical exercise on the glycemic control in diabetes are unknown. Therefore, the purpose of this study was to investigate the effects of the association between aerobic physical exercise and cinnamon extract intake on glycemic control, serum lipid profile and blood lactate response to exercise in alloxan diabetic rats.

METHODS

Animals

Fifty 60-day-old male Wistar rats (Central Biotherium of UNESP, São Paulo State University, Botucatu Campus) were used in this study. The animals were kept in the Nutrition, Metabolism and Exercise Laboratory of UNESP (São Paulo State University, Rio Claro Campus). The rats were fed with balanced rat chow (Purina, Paulínia/SP, Brazil) and water “ad libitum” and were kept in collective plastic cages (4 animals per cage) in a room with a temperature set at 25ºC with a 12 h of light/dark photo period. This experiment was approved by the Ethics Committee in Research of the College of Sciences (São Paulo State University, UNESP, Bauru, SP, Brazil; Protocol number: 1501/46/01/08).

Experimental Groups

The animals were randomly distributed into five experimental groups as follows: control (C), nondiabetic sedentary rats; diabetic (D), diabetic sedentary rats; diabetic cinnamon (DC), diabetic sedentary rats that received cinnamon extract; diabetic exercise (DE), diabetic sedentary rats subjected to physical training; and diabetic cinnamon exercise (DCE), diabetic rats that received cinnamon extract and were subjected to physical training.

Experimental Diabetes

The rats received alloxan monohydrate (Sigma-Aldrich Inc., St. Louis, MO, USA) dissolved in 0.01 M citrate buffer (pH 4.5 and 30 mg/kg of body weight (b.w.)) intravenously after a 15 h fasting (23). Control rats of the same age were injected with a vehicle (citrate buffer). The animals were considered diabetic when their fasting serum glucose was 126 mg.dL-1 or higher after two weeks of alloxan administration (2). Blood glucose concentrations were determined by a glucose-oxidase method (Laborlab Kit, Guarulhos, SP, Brazil).

**Adaptation to Water**

The water adaptation lasted two weeks and involved keeping the animals in shallow water at 30°C ± 2°C during the first week. During the second week, the animals performed swimming exercises with increasing time periods without overloads. This adaptation procedure aimed to reduce the stress of the animals subjected to the swimming tests (43).

**Physical exercise**

The training consisted of one hour/day of swimming exercises, five days a week, during four weeks, in collective tanks (100 cm x 80 cm x 80 cm) filled with water at 30°C ± 2ºC, with the animals carrying a lead overload of 3% - 5% of the body weight attached to the chest. This protocol was selected because it represents aerobic exercise for alloxanic rats (29).

Cinnamon Extract Treatment

The cinnamon extract (Federal Laboratories, USA) was given daily in a water solution (300 mg.kg-1 BW) by gavage once per day for four weeks.

General Evaluation

All animals had their body weights, food intake and water intake recorded once a week. The data were analyzed by the total area under the curve of body weight, food intake and water intake during the four weeks of the experiment using the trapezoidal method (27) with the aid of the ORIGIN 6.0 software (Microcal Software Inc®, Northampton, MA).

**Oral Glucose Tolerance Test (OGTT)**

The OGTT was performed on the animals in the last week of the experiment after 15 h of fasting. The first blood sample was collected from a small cut to the tip of tail (Time 0). Immediately after, a 20% glucose solution (2 g.kg-1 of the b.w.) was given to the rats by gavage. The blood samples were collected after 30, 60 and 120 min with heparinized capillary tubes calibrated for 25 µL for the determination of glucose concentrations by the glucose-oxidase method (Laborlab Kit, Guarulhos, SP, Brazil). The glucose responses during the OGTT were analyzed by the total area under the serum glucose curves using the trapezoidal method (27) with aid of the ORIGIN 6.0 software.

**Insulin Tolerance Test (ITT)**

Insulin sensitivity was evaluated by the ITT. The test was performed on the animals 48 h after the OGTT. The first blood samples were collected from a small cut to the tip of tail (Time 0). Immediately after, a solution of crystal insulin (30 mU/100 g BW; LILLY U 41, Mexico City, Mexico) was administrated subcutaneously. The blood samples were collected after 30, 60 and 120 min with heparinized capillary tubes calibrated for 25 µL for the determination of glucose concentrations (Laborlab Kit, Guarulhos, SP, Brazil). A glucose disappearance rate (KITT) was calculated by the following formula: KITT = 0.0693/t/2. The serum glucose (t1/2) was calculated using the ORIGIN 6.0 software from the slope of the least square analysis of the serum glucose concentration from 0 min - 30 min after insulin injection when the serum glucose concentration linearly decreased (25).

**Effort Test**

Forty eight hours after the ITT, all the animals were subjected to a 20 min swimming session holding a 3.5% body weight lead overload attached to the chest. Blood collections (25 µL) were taken every 5 min from a small cut to the tip of the tail for lactate analysis. The blood lactate concentrations were determined by a lactate analyzer (Model YSI 1500 Sport, Yellow Springs, OH, USA).

**Biological Material Collection**

At the end of the experiment, which was 48 h after the last *in vivo* evaluation, the animals were anesthetized with carbon dioxide (CO2) and blood samples were collected to determine the concentrations of serum glucose, triglycerides and total cholesterol by calorimetric methods using commercial kits (Laborlab Kit, Guarulhos, SP, Brazil). The concentrations of free fatty acids (FFAs) were also determined as described by Nogueira et al. (28).

**Statistics Analyses**

The Komolgorov-Smirnov test analyzed the normality of the data. In the cases where the normality was rejected, the logarithmic adjustment was adopted. The values of the means and standard deviations were adopted as measurements of central tendency and dispersion, respectively. The *one-way* ANOVA established comparisons between different groups in the conditions where there was no dependence between analyses. ANOVA for repeated measurements was used for the latter cases. In the situations where ANOVA confirmed the existence of differences, the *Tukey post hoc* testwas applied. The software used for the analyses was SPSS, version 13.0 (IBM Company).

**RESULTS**

In Table 1, the results are shown for the areas under the curve for water intake ((ml.100g-1 BW) x 4 weeks), food intake ((g.100g-1 BW) x 4 weeks) and body weight (g x 4 weeks) during the experiment. The diabetic groups had higher water and food intake and smaller body weights when compared to the control group. Group D had higher water intake than the other diabetic groups. The DE group demonstrated lower food intake when compared to the other diabetic groups. The physical exercise maintained the body weight values of the exercised diabetic animals (groups DE and DCE) closer to the values of group C when compared to the other diabetic groups (D and DC).

**Table 1. Areas under the curves of water intake, food intake and body weight during the experiment.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | ***C*** | ***D*** | ***DC*** | ***DE*** | ***DCE*** |
| ***Water Intake***  | 6063.8 ± 358.9a | 24191.8 ± 3190.1b | 26337.5 ± 14082.0 | 20371.8 ± 5590.7 | 27905.5 ± 4964.6 |
| ***Food* Intake** | 178 ± 1.5 | 439.2 ± 19.8 | 403.33 ± 18.09 | 338.8 ± 6.4c | 411.7 ± 16.4 |
| ***Body Mass*** | 13663.3 ± 1758.0a | 9865.2 ± 2353.0 | 10263.9 ± 2002 | 11035.2 ± 1798.7d | 9973.1 ± 1834.2d |

Results expressed as means ± SD (n=10/group). Water Intake; (ml100g-1) x four weeks), Food Intake; (g.100g-1) x four weeks), Body Mass: (g x four weeks). Abbreviations: C; control, D; diabetic, DC; diabetic with cinnamon supplementation, DE; diabetic and exercise, DCE; diabetic with cinnamon supplementation and exercise. Statistical differences (ANOVA p < 0.05) are as follows: a; different from diabetics groups, b; different from C, DC, DE and DCE groups, c; different from C, D, DC and DCE groups, and d; different from C, D and DC groups.

Figure 1a shows the serum glucose concentrations (mg.dL-1) and Figure 1b shows the areas under the serum glucose curve during the OGTT ((mg.dL-1) x 120 min) for the different groups. The control group had a lower value for the area under the serum glucose curve compared to the diabetic groups, which did not show any differences among them.

**Figure 1a. Serum glucose concentrations during the OGTT. Results expressed as means ± SD (n=10/group). See Table 1 for abbreviations.**

Figure 2a shows the serum glucose concentrations (mg.dL-1) and Figure 2b shows the glucose disappearance rates (KITT; %/min) during the ITT for the different groups. The control group had lower serum glucose concentrations when compared to the diabetic groups. The variance analysis did not detect differences in the KITT values among the groups.

Blood lactate concentrations (mmol/L) during the effort test for the different groups is shown in Figure 3. Differences among the groups were only found at the initial moment of the test (Time 0). Group D had higher values when compared to group DC. All groups demonstrated higher lactate concentrations in the last blood collection after 20 min of exercise (Time 20) when compared to the first blood samples (Time 0).

**Figure 1b. Area under the glucose curve during the OGTT during the OGTT. Results expressed as mean ± SD (n=10/group). See Table 1 for abbreviations.**

Table 2 is the comparisons among the different groups concerning serum glucose concentrations and lipid profiles at the end of the experiment. The variance analysis indicated that the diabetic groups had higher serum glucose concentrations when compared to the control group. However, no difference was found among the diabetic groups. However, group D had higher total serum cholesterol concentrations when compared to groups DE and DCE. The DCE group had higher serum triglycerides than the D and DC groups.

**DISCUSSION**

Appropriate glycemic control is important for the treatment of diabetes because it decreases the risk of long term complications of the disease. The conventional treatment consists of the use of insulin or oral hypoglycemics depending on the type of diabetes, diet and physical exercise. Several herbs, such as cinnamon, have been studied in the treatment of diabetes because they have been shown to have hypoglycemic effects in animal models (18,19,41) and in human patients (24,26,36). The effect of the association between exercise and the use of cinnamon for glycemic control is unknown. Therefore, the aim of this study was to investigate the effects of the association between aerobic physical exercise and cinnamon extract intake on the glucose homeostasis of diabetic rats.

**Figure 2a. Serum glucose concentrations during the ITT. Results expressed as means ± SD (n=10/group). See Table 1 for abbreviations.**

**Figure 2b. Glucose disappearance rates during the ITT. Results expressed as means ± SD (n=10/group). See Table 1 for abbreviations.**

**Effects of Alloxan Administration**

Alloxan has been proved to be a suitable compound for inducing experimental diabetes in animals. Alloxan induced diabetes is similar to diabetes mellitus found in humans with typical symptoms, such as body weight loss, polydipsia and hyperphagia (21). These symptoms were reproduced in the rats in this study.

The body weight loss of the diabetic rats of the present study may be attributed to the major effects of the lack of insulin on glucose, lipid and protein metabolism in untreated diabetes.

The markedly increased mobilization of fat from storage areas and the protein depletion in the tissues of the body is associated with the excessive loss of body fluids, which contributes to body weight loss.

Our diabetic rats presented increased food and water intake when compared to controls. Hyperphagia occurs due to insulin deficiency because insulin together with leptin play important roles in the inhibition of arcuate nucleus neurons coexpressing neuropeptide Y and Agouti related polypeptides, which are peptides that stimulate food ingestion. The high food intake of the diabetic rats may also be explained by the action of ghrelin. It was demonstrated that the ghrelin hormone increases the expression of neuropeptide Y and reduces the expression of α-MSH in streptozotocin diabetic rats (9). Furthermore, in ghrelinknockout rats, the induction of diabetes does not increase neuropeptide Y expression**.** In addition, the low glucose metabolism in the neurons of the hypothalamus ventromedial nucleus also contributes to the diabetic hyperphagia. When glucose utilization by the hypothalamus ventromedial nucleus is low, its activity is reduced leading to a sensation of hunger (9). Another consequence of untreated diabetes is polydipsia, which a result of hyperglycemia. The decreased glucose utilization leads to glycosuria, osmotic diuresis and polyuria. The overall effect of excessive fluid loss in urine causes dehydration and thirst (2). In summary, alloxan administration successfully induced T1DM in the animals.

**Figure 3. Serum lactate during the effort test. Results expressed as means ± SD (n=10/group). See Table 1 for abbreviations.**

**Effects of Exercise Training on Blood Lactate During Effort Test**

The results of effort tests indicated that the swimming exercise protocol led to a reduction of resting blood lactate suggesting an improvement in lactate metabolism in these animals. Physical training typically reduces the accumulation of lactate during and after exercise for the same submaximal effort due to the higher ability of substrate removal from the blood stream (31). However, during the exercise session, no difference was observed between trained and sedentary diabetic rats. The relatively short training period (4 weeks), the intensity of the exercise or a lack of training periodization, which leads to monotonous training without a specific time for recovery and supercompensation, (8,44), may be among the factors contributing to the absence of improvement in the lactate kinetics during the effort test of the diabetic animals.

**Table 2. Serum glucose, total cholesterol and triglycerides at the end of the experiment.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | ***C*** | ***D*** | ***DC*** | ***DE*** | ***DCE*** |
| ***Glucose(mg.dL-1)*** | 89.0 ± 7.0 | 413.0 ± 149.0a | 371.0 ± 46.0 a | 408.0 ± 96.0a | 446.0 ± 129.0a |
| ***Total Cholesterol (g.L-1)*** | 102.0 ± 22.0 | 123.0 ± 15.0 d,e | 102.0 ±15.0 | 97.0 ±16.0 | 93.0 ± 17.0 |
| ***Triglycerides (g.L-1)*** | 232.0 ± 23.0 | 220.0 ± 9.0e | 199.0 ± 36.0e | 247.0 ± 20.0 | 272.0 ± 31.0 |

Results expressed as means ± SD (n=10/group). See Table 1 for abbreviations

**Effects of Exercise Training and Cinnamon Treatment on Diabetic Outcome**

The best known effects of cinnamon on glucose metabolism are due to MHCP. This substance phosphorylates the insulin receptor and other proteins in the insulin pathway leading to an increase in glucose utilization by the cells (3,15,31). Muscle contraction also promotes improvement in the glycemic homeostasis through the phosphorylation of the insulin receptor (7,22). Because individuals with T1DM lack insulin to regulate glucose metabolism, these factors may play an important role in disease management.

In the present study, exercise training and cinnamon extract treatment, alone or in combination, reduced water intake in diabetic rats. Exercise training alone decreased food intake in diabetic rats, but cinnamon treatment alone did not alter this variable. Furthermore, the trained diabetic groups (DE and DCE) had significantly higher body weights than the sedentary diabetic groups (D and DC). Diabetic patients have body weight loss, in part, due to muscle mass loss originated by hypoinsulinemia, which impairs protein synthesis and facilitates protein catabolism (20). Accelerated proteolysis via the ubiquitin-proteasome pathway is the principal cause of muscle atrophy induced by diabetes and othe catabolic diseases (33).Regular physical activity may improve protein synthesis and reduce protein degradation helping the patients to better preserve muscle mass (24). Therefore, exercise training attenuated the general effects of the lack of insulin in type 1 diabetic rats whereas cinnamon treatment interfered with only water intake.

During the OGTT, the higher values of the area under the curve of serum glucose in the diabetic groups compared to the control group indicated glucose intolerance. The cinnamon treatment did not alter the glucose tolerance in the diabetic groups, which agrees with previous results (1). Physical activity activates the insulin signaling pathway allowing glucose uptake without the requirement for insulin (7,22) and has been prescribed to diabetic patients to improve glucose homeostasis (2). Nevertheless, in the present study, an improvement in blood glucose was not reported. This result may be a consequence of the training period, intensity of the training, or other characteristics of the exercise protocol (8,44). These observations indicate the requirement for additional studies on exercise protocols for animal models of diabetes.

We did not observe insulin resistance in the diabetic rats as the glucose disappearance rates during the ITT was similar in control and diabetic groups. The present study evaluated type 1 (alloxanic) diabetic rats in which the glucose intolerance may be explained by the reduction in insulin secretion and not by the resistance to its peripheral action. In summary, cinnamon extract failed to improve glycemic control in this study. Similar results were previously reported in type 1 diabetic teenagers (1).

Despite the absence of improvement in the lactate kinetics during exercise, the exercise training improved blood cholesterol concentrations in diabetic rats because total cholesterol values of group D were higher than the concentrations of groups DE and DCE. These results are in agreement with previous studies performed in human patients (34,39) in which exercise decreased blood cholesterol. However, similar to several other study (16), no alterations in blood cholesterol were observed after the ingestion of cinnamon extract.

On the other hand, the DCE group had higher serum triglyceride concentrations than groups D and DE. Although there are studies demonstrating the benefits of exercise (37)and cinnamon extract (16) administered separately on serum triglycerides, this study demonstrated that the combination of both treatments increased serum triglycerides in alloxanic diabetic rats. In a meta-analysis study, Baker (2008) demonstrated that cinnamon extract treatment does not improve the serum triglyceride concentrations because the author did not observe improvements in serum triglyceride concentrations in patients with type 1 diabetes who were treated with different doses of cinnamon. Our study demonstrates that the combination of cinnamon and exercise was not an effective treatment for diabetes. Therefore, more research needs to be completed to further test the effectiveness of this combination.

**CONCLUSION**

The aerobic exercise partially counteracted the effects of diabetes on food intake, water intake, body weight, serum cholesterol concentrations and blood lactate concentrations. No additional beneficial effects were observed with the simultaneous administration of cinnamon extract with the parameters studied. Further studies, using alternative exercise protocols, are required to understand the effects of the combination of exercise training and cinnamon intake on glycemic control, serum lipid concentrations and aerobic performance.

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