ORGINAL ARTICLE

Effect of 4-weeks Endurance Training and Berberine on Glycemic Index and Inflammation in Diabetic Rats

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Abstract

Objective: Exercise and herbal medicine Berberine are known as anti-inflammatory agents. This study aimed to evaluate the effect of 4-weeks of endurance training and Berberine Chloride (BC) consumption on inflammatory factors and glycemic index in male wistar diabetic rats.

Materials and Methods: In an experimental trial, 36 male wistar rats divided into 6 groups of 6 rats including 1) control, 2) 15 mg/kg BC, 3) 30 mg/kg BC, 4) endurance training, 5) endurance training with 15 mg/kg BC and 6) endurance training with 30 mg/kg of BC. During 4 weeks, rats in groups 2, 3, 5, and 6 received BC by gavage at specified doses, and rats in groups 4- 6 also ran on the treadmill at speeds of 10-15 m/min for 10-30 minutes. For statistical analysis of data-independent sample T-test, two-way ANOVA were used (*P*-value= 0.05).

Results: Training and BC significantly increased function of pancreatic beta cells and reduced FBS, TNF-α, and IL- 6 (*P*-value= 0.001); Training significantly increased VO_{2max} and insulin; interaction of training and BC on an increase of VO_{2max} and reduction of TNF-α were significant (*P*-value= 0.001) and 30 mg/kg BC reduced TNF-α and FBS much more than 15 mg/kg BC (*P*-value= 0.001).

Conclusion: It appears that Endurance training and BC can decrease glycemic index and inflammatory markers of diabetes and the effects of BC is dose-dependent, so that the 30 mg/kg BC is more effective rather than the 15 mg/kg BC.

Keywords: Training, Berberine chloride, Glycemic index, Inflammation, Diabetes

Introduction

Diabetes mellitus (DM) has been one of the major health-threatening problems of the present century, which its main structure being impaired insulin production or its receptors in the peripheral tissues (1). According to statistics from the World Health Organization (WHO), people with diabetes will reach over 360 million by 2030 (2). For this reason, there is a great desire to prevent and treat diabetes worldwide. Diabetes is a

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very complex disease that is primarily caused by the interaction of several factors. These factors include genetics, nutrition style, physical activity levels, psychological stress, etc. (3). Dietary modification, physical activity, and medication are the main strategies to control diabetes and reduce its adverse effects. Regular physical activity has beneficial effects on controlling diabetes-related disorders in a way that can improve immune-inflammatory responses (4) and improve glycemic status (5). Since the development of inflammation is one of the major mechanisms justifying the onset of diabetes disorders, the role of physical activity in the treatment of diabetes is very important, as it not only controls glycemic status by reducing blood glucose but also by reduction of inflammation mediators reduces the deleterious effects of diabetes on body tissues (6, 7). Another way to treat diabetes is to use phytochemicals. Many active ingredients in medicinal plants have been reported to be used directly and indirectly in the preparation of more than 50% of synthetic drugs after extraction and isolation (8). Ethnobotanical knowledge has shown that more than 800 plants have anti-diabetic properties (9). One of these herbs is Berberis aristata, which its anti-diabetic effects have been proven due to the active ingredient berberine chloride (BC) (10, 11). Berberine is an isoquinoline alkaloid that has anti-cancer, anti-hyperglycemic, anti-hyperlipidemia, antimicrobial, anti-inflammatory, and antioxidant activities (12-14). In one study, the simultaneous effects of 6-weeks of Aerobic training and Berberine chloride hydrate on plasma glucose, interleukin-6, and tumor necrosis factor alpha (TNF-α) were studied, and the results are very significant. In this study, plasma glucose and TNF-α levels were significantly reduced (15). Since the length of the intervention period may affect the results, it is therefore questionable whether the combination of aerobic training and supplementation of BC in a shorter time of time can enhance each other's effects on glycemic indices and inflammatory markers. So that this study aimed to determine the short-term effects of endurance training and BC on glycemic indices, TNF- α and IL-6 concentrations in streptozotocin (STZ)-induced diabetic rats.

Materials and Methods

Animals

In an experimental trial, 36 rats weighing 240-280 g were purchased from the Pasteur Institute and transferred to the animal home of Yazd Shahid Sadoughi University of Medical Sciences. The rats were kept in standard conditions for one week (to adapt to the laboratory environment). After that 36 diabetic rats divided in 6 groups of 6 rats including 1) control, 2) 15 mg / kg BC, 3) 30 mg / kg BC, 4) endurance training, 5) endurance training with 15 mg / kg BC and 6) endurance training with 30 mg / kg of BC. Also, BMI measured using the Lee index, and the food intake and water intake of rat rats were calculated in the last week.

Diabetes induction

To diabetes induction, all rats were injected intraperitoneally with 60 mg/kg STZ (Sigma, S0130). Then, 4 days after injection, the rats were blood sampled by a punching method to measure fasting blood glucose (FBS) using a blood glucometer. Rats with FBS more than 300 mg/kg selected as a statistical sample.

BC consumption

During 4 weeks, rats in groups 2, 3, 5, and 6 received BC (made by Sigma American Company in the form of 5 g yellow powder, code B3251) by gavage at specified doses.

Training program

The standardized incremental test of Bedford et al. (1979) was used to measure maximum oxygen consumption (VO_{2max}) (16). The test consisted of 10 three- minute steps. The velocity was 0.3 km / h in the first step and the velocity was added 0.3 km / h later, while at all stages the slope was zero. At each stage of the test where the animal was no longer able to

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run, the speed at that stage was considered equivalent to the animal's velocity at VO_{2max} or maximum velocity. Rats in groups 4– 6 also ran on the treadmill at speeds of 10- 15 m / min for 10- 30 minutes. In fact, in the present study, the endurance training protocol was performed with an average intensity of 50-55% of VO_{2max}. In each training session, rats were warmed up and cooled down for 5 minutes with a speed of 4-5 m/min. The speed and duration of main training (running on the treadmill) gradually increased so that the main training in the first week consisted of 10 minutes running at speed of 10 m/min in the first week, 20 min running at speed of 10 m/min in the second week, 20 min running at speed of 14-15 m/min in the third week and 30 min running at speed of 14-15 m/min in the fourth week. (Table 1)

Rat sacrificing and biochemical measurement

Forty-eight hours after the last training session and BC gavage, rats were anesthetized with ketamine (30-50 mg/kg/BW) and xylazine (3-5 mg/kg/BW), and then blood samples collected directly from the heart. Insulin (mercodia kit; Sweden), IL-6 (ZellBio GmbH kit; 0.05 ng / L sensitivity and Cat. No ZB-1035S-R9648; Germany) and TNF-α (Diaclone French Made Kit; 15 pg/mL sensitivity and Cat. No 865,000.096) measured in serum by ELISA method. The function of pancreatic beta cells was calculated using the HOMA-B formula (20 × fasting insulin (μIU/ml)/ FBS (mmol/ml) – 3.5) (17).

Statistical analysis

All data on mean and standard deviation. To determine the effect of diabetes on FBS, insulin, TNF-α, IL-6 concentration, beta-cell function, VO_{2max}, weight, and BMI in healthy control and diabetic control groups were compared using independent sample t-test. Two-way analysis of variance was used to determine the effect of endurance training, BC, and interaction of endurance training and BC on the outcome. If a significant difference was observed, the Bonferroni post hoc test was used to find the origin of the difference (*P*-value= 0.05). All statistical calculations were performed using SPSS version 22 software.

Ethical considerations

The study was approved by Gachsaran Branch, Islamic Azad University, Iran (Ethic code: IR.IAU.IAUG.REC.1399.016).

Results

Diabetes induction significantly increases FBS (*P*-value= 0.001), TNF-α (*P*-value= 0.001) and IL- 6 (*P*-value= 0.001) nevertheless significantly decrease weight (*P*-value=0.001), BMI (*P*-value= 0.002), VO_{2max} (*P*-value= 0.007), insulin (*P*-value= 0.001) and function of pancreatic beta cells (*P*-value= 0.001).

Endurance Training (F= 66.38, *P*-value= 0.001,η= 0.689) and BC (F= 34.73, *P*-value= 0.001,η= 0.698) significantly reduced FBS nevertheless the effect of BC on FBS was dose dependent, so that 30 mg/kg BC reduced FBS much more than 15 mg/kg BC (*P*-value= 0.002) but interaction of training and BC on FBS was not significant (F= 1.07, *P*-value= 0.356, η= 0.067).

Endurance Training significantly increased VO_{2max} (F= 176.89, *P*-value= 0.001, η= 0.855) but BC had no significant effect (F= 0.379, *P*-value=0.688, η=0.025) nevertheless interaction of training and BC significantly increased VO_{2max} (F= 5.57, *P*-value= 0.009, η= 0.271).

Endurance Training significantly increased insulin (F=33.15, *P*-value= 0.001, η= 0.525) but BC had not significant effect (F= 1.61, *P*-value= 0.216, η= 0.0.097) also interaction of training and BC was not significant (F= 0.756, *P*-value= 0.478, η= 0.048).

endurance training (F= 67.72, *P*-value= 0.001,

Table 1. The Endurance training program

Practice variable	Week 1	Week 2	Week 3	Week 4
Speed (m/min)	10	10	14–15	14–15
Duration (min)	10	20	20	30

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η=0.693) and BC (F=137.45, *P*-value= 0.001, η=0.902) significantly reduced TNF-α as well as interaction of training and BC was significant (F=13.89, *P*-value= 0.001, η=0.481). The effects of BC on TNF-α was dose-dependent so that 30 mg/kg BC reduced TNF-α much more than 15 mg/kg BC (*P*-value= 0. 001).

Endurance Training (F=32.47, *P*-value= 0.001, η= 0.520) and BC (F=4.76, *P*-value= 0.016, η= 0.241) reduced IL-6 but reduction just observed in dose of 30 mg/kg (*P*-value= 0.001) nevertheless interaction of training and BC on IL- 6 was not significant (F=2.21, *P*-value =0.126, η=0.129).

Endurance Training significantly increased the function of pancreatic beta cells (F=52.75, *P*-value= 0.001, η=0.637) although BC significantly increased the function of these cells (F=17.31, *P*-value= 0.001, η=0.536) only in the 30 mg/kg dose the beta-cell function increased (*P*-value= 0.001) as well as the interaction of training and BC on the function of pancreatic beta-cells was significant (F=5.69, *P*-value= 0.008, η=0.275) (Table 2).

Discussion

In this study, TNF-α and IL-6 levels were significantly increased by diabetes induction nevertheless training and BC were able to decrease this increase. Diabetes is essentially an inflammatory disease and as a result, inflammatory mediators increase dramatically (38). Therefore, physical exercise, especially aerobic training, can reduce inflammatory mediators and increase anti-inflammatory mediators. In the present study, BC was able to decrease the levels of TNF- α and IL-6. The anti-inflammatory effects of BC have been reported in both animal and human models and it has been reported that BC can decrease IL-6 and TNF-α mRNA levels in adipose cells. In this study, VO_{2max} was significantly reduced by diabetes induction. Endurance training was able to significantly increase the VO_{2max} in diabetic rats, whereas BC alone had no significant effect on VO_{2max}. For the first time in the 1980s, the negative effects of diabetes on functional capacity were identified and reported (18). At that time, it was reported that the training performance in maximal and submaximal intensity in people with diabetes significantly reduce so that is (noted weakness) without clinical signs (19,20). Diabetes seems to impair the functioning of the lung, heart, muscles, and arteries, weakening the body's ability to absorb and move oxygen. Mitochondrial dysfunction in heart and muscle tissue is very common in diabetes (21,22). Cardiac and skeletal muscle perfusion is crucial for physiological function during physical activity, on the other hand, in diabetes, the heart and skeletal muscle perfusion are severely impaired, which may contribute to VO_{2max} reduction (23). There is evidence that aerobic training as a multifaceted intervention can increase the components involved in oxygen uptake, transporting, and consuming oxygen. Aerobic training through nitric oxide synthase and SIRT-1 activates mitochondrial biogenesis and angiogenesis in muscle tissue (24).

In the present study, the glucose concentration was significantly increased in diabetic rats, indicates the effect of diabetes induction and

Table 2. Comparison levels of FBS, TNF-α, IL-6, Weight, BMI, Vo_{2max}' and Homa-β in the study groups after experiment

Variable	Training-BC-15 Mean (±SD)	Training-BC-30 Mean (±SD)	Training Mean (±SD)	BC-15 Mean (±SD)	BC-30 Mean (±SD)	Control Mean (±SD)
FBS (mg/dl)	353.16 (±52.76)	187.66 (±24.57)	410.50 (±24.57)	500.33 (±68.25)	382.66 (±92.46)	538.16 (±58)
TNF-α (pg/ml)	17.01 (±0.49)	14.14 (±0.74)	23.57 (±1.36)	21.36 (±0.83)	18.55 (±0.75)	23.86 (±1.81)
IL-6 (ng/L)	1.99 (±0.11)	1.89 (±0.08)	2.03 (±2.88)	2.46 (±0.36)	2.30 (±0.05)	2.92 (±0.29)
Weight (gr)	244.48 (±22.84)	236.44 (±22.84)	254.33 (±30.56)	233.56 (±32.64)	243.14 (±23.91)	238.62 (±25.58)
BMI (gr/cm^2)	0.49 (±0.4)	0.43 (±0.20)	0.50 (±0.4)	0.46 (±0.04)	0.33 (±0.26)	0.46 (±0.03)
Vo_{2max} (mg.min-1.kg-1)	27.5 (±3.44)	26.33 (±2.16)	29.33 (±2.94)	16.33 (±1.03)	19.16 (±2.71)	15.66 (±1.03)
Insulin (μIU/L)	0.23(0.14)	0.24(0.06)	0.22(0.8)	0.05(0.03)	0.14(0.04)	0.06(0.02)
Homa-β	7.86 (±6.04)	18.16 (±5.02)	5.96 (±2.46)	1.07 (±0.7)	4.34 (±1.96)	1.29 (±0.68)

BC: Berberine Chloride

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beta-cell damage by STZ injection. But training and BC reduced glucose concentration, and also glucose-lowering effect of BC was dose-dependent. Various mechanisms have been proposed to justify the effect of training on the reduction of blood glucose in diabetic conditions. One of these mechanisms is the positive effect of exercise on gene expression (26) and GLUT-4 translocation (27) in skeletal muscle tissue. Increased GLUT-4 increases the amount of glucose uptake by the muscles, which reduces blood glucose. Another mechanism to reduce blood glucose by exercise is decreased hepatic glucose production. Even a single session of prolonged endurance exercise has been reported to decrease hepatic glucose production by decreasing the expression of hepatic gluconeogenesis genes such as PEPCK and G6Pase (28). It is worth to note that the contribution of the liver to elevated blood glucose levels is important, and clinical studies have suggested that hepatic glucose production by regulating hepatic gluconeogenesis is one of the most important processes in balancing blood glucose levels. On the other hand, in the present study, BC reduced glucose.

There is some evidence that BC can inhibit gluconeogenesis as one of the major mechanisms of hepatic glucose production by regulating beta-cell function. BC can also increase glucose utilization by increasing glycolysis (29). Berberine can also reduce abnormal levels of plasma hormones such as glucagon-like peptides- 1 and 2, insulin-stimulating polypeptides, and pancreatic polypeptides (30). Berberine can stimulate glucagon and prohormone inverses synthesis by stimulating L-cell proliferation and increases GLP-1 secretion in diabetic rats (31). Accordingly, berberine can regulate glucose by stimulating GLP-1 secretion in the intestine. Based on the proposed mechanisms, it is possible to justify the reduction of glucose in the present study.

In the present study, training increased both insulin concentration and beta-cell function, which was reduced by STZ injection. Exercise has been reported to improve beta-cell function in diabetic conditions (32). New evidence suggests that despite the importance of glycemic indices for determining diabetes status, insulin secretion may be a better predictor of exercise effectiveness on glycemic control than insulin sensitivity (33). Following regular exercise in healthy people with normal pancreas, they have less insulin secretion, which is a sign of insulin sensitivity in peripheral tissues. But in conditions of pancreatic abnormalities, when the beta-cell function is impaired, exercise simultaneously increases insulin production from beta cells along with increased insulin sensitivity (34, 35). The reason for the improvement of beta-cell function through exercise can be justified by lowering blood glucose. However, increased secretion of anti-inflammatory mediators from muscle and adipose tissue during exercise may also be one of the important mechanisms to improve beta cell function. In this study, TNF-α and IL-6 levels were significantly increased by diabetes induction nevertheless training and BC were able to decrease this increase. Diabetes is essentially an inflammatory disease and as a result, inflammatory mediators increase dramatically. Therefore, physical exercise, especially aerobic trainings, can reduce inflammatory mediators and increase anti-inflammatory mediators. This is why exercise can reduce many of the systemic and tissue complications of diabetes. As a result of exercise and muscle contraction, the production of inflammatory mediators such as TNF- α is reduced and anti-inflammatory mediators such as adiponectin are markedly increased.

Conclusions

According to the protective effects of training and BC on glycemic and inflammatory status, it is recommended to use these two interventions in diabetes situations; however, further studies are needed to better understand the effect of these interventions.

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Conflict of Interest

Authors declare that they have no competing interests.

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