ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 11, Issue 10, 2018

Online - 2455-3891
Print - 0974-2441

Research Article

EFFECTS OF CHROMIUM PICOLINATE ON OXIDATIVE STRESS AND HYPERGLYCEMIA IN EXPERIMENTAL TYPE 2 DIABETIC RATS

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Received: 19 July 2018, Revised and Accepted: 04 Sep 2018

ABSTRACT

Objective: In this study, we aimed to determine the effects of chromium picolinate (CrPic) on diabetes, one of the most common and fatal diseases in the world, and its associated oxidative damages.

Methods: CrPic (100 µg/kg) and metformin (1000 mg/kg) were orally administered for 21 days in rats with nicotinamide + streptozotocin-induced Type 2 diabetes.

Results: Significant decreases in fasting blood glucose levels were observed 14 days after initial administration in both CrPic ($p<0.01$) and metformin ($p<0.001$) groups compared with a diabetic control group (DC). Malondialdehyde (MDA) levels of all tissues were significantly higher in the DC group than in a normoglycemic control group ($p<0.001$). MDA levels of the CrPic group significantly decreased in heart ($p<0.05$) and liver ($p<0.01$) tissues. Glutathione (GSH) and catalase (CAT) levels in heart, kidney, and liver tissues increased in CrPic group (GSH $p<0.001$, $p<0.05$, and $p<0.01$; CAT $p<0.001$, $p<0.001$, and $p<0.05$, respectively). Superoxide dismutase enzyme levels significantly increased in CrPic group in the liver tissue ($p>0.001$), but no such changes were observed in heart and kidney tissues ($p>0.05$).

Conclusion: The results obtained from this study indicate that CrPic may be effective in alleviating hyperglycemia and its consequent oxidative damage in experimental Type 2 diabetes.

Keywords: Type 2 diabetes, Hyperglycemia, Oxidative stress, Chromium picolinate.

 DOI: http://dx.doi.org/10.22159/ajpcr.2018.v11i10.28608

INTRODUCTION

Diabetes mellitus is a metabolic disease characterized by hyperglycemia resulting from deficiency of insulin secretion, insulin effect, or both [1,2]. Chronic hyperglycemia can cause dysfunction and failure of various organs including the eyes, kidneys, nerves, heart, and blood vessels [3-6]. According to the International Diabetes Federation 2018 report, the number of people affected by diabetes today is estimated to be 425 million, while it is estimated to reach 629 million by 2045 [7]. There is no definitive treatment for Type 2 diabetes today. On the other hand, it is stated that the worldwide cost of treating and preventing this disease is US$ 1 trillion in annually [5]. For this reason, the tendency toward the use of natural antioxidant compounds and essential minerals (such as chromium [Cr], vanadium, selenium, and manganese) for the treatment of diabetes and its complications have increased, and studies have focused on this issue. Many researchers suggest that oxidative stress plays a significant role in the pathogenesis of diabetes mellitus and its complications [8-10]. Levels of reactive oxygen species are tightly controlled by the protective actions of antioxidant enzymes and non-enzymatic antioxidants in healthy individuals [11]. In contrast, antioxidant mechanisms are reduced in diabetic patients, which may, therefore, increase oxidative stress [12,13]. Cr is a trace element that plays a significant role in controlling blood glucose and lipid levels [14,15]. It is a ubiquitous metal, occurring in water, soil, and biological systems. The three forms of Cr occurring in the environment are metallic (Cr^0), trivalent (Cr^3), and hexavalent (Cr^6). Cr^3 is considered to be an essential element, both in animal and human nutrition [15,16]. Cr deficiency is associated with diabetes mellitus, insulin resistance, and glucose sensitivity [17,18]. It has also been reported that Cr deficiency may be seen in patients with Type 2 diabetes [19]. Moreover, it has been indicated that plasma [20] and serum [21,22] Cr levels are lower in diabetic patients than in non-diabetic control (DC) patients.

In this study, we aimed to determine the protective effects of Cr^3 against hyperglycemia and hyperglycemia-induced oxidative damage in liver, kidney, and heart tissues.

METHODS

Experimental design

This study was conducted under the approval (2016–106) of Kafkas University, Animal Experiments Local Ethics Committee. A total of 40 female Sprague-Dawley rats were divided into four groups of 10 individuals as follows.

Normoglycemic control group (NC)

This group was fed *ad libitum* throughout the study. Physiological saline was administered by oral gavage throughout the study to provide the same conditions as those for the experimental groups.

Diabetic control group (DC)

This group received 110 mg/kg intraperitoneal (i.p.) nicotinamide (NAD) + 65 mg/kg intravenous (i.v.) streptozotocin (STZ). In addition, physiological saline was administered by oral gavage, during the study to ensure the same conditions as those for the experimental groups.

Diabetic + chromium picolinate (D + CrPic)

This group was orally administered 110 mg/kg i.p. NAD + 65 mg/kg i.v. STZ + 100 µg/kg orally CrPic.

Diabetic + metformin (D + M)

This group was orally administered 110 mg/kg i.p. NAD + 65 mg/kg i.v. STZ + 1000 mg/kg orally metformin.

NAD (Sigma) was administered i.p. 15 min before STZ (Sigma) injection [23]. Rats with fasting blood glucose levels of ≥ 200 mg/dL 7 days after NAD + STZ administration were defined as Type 2 diabetics. The experimental groups were administered CrPic (GNC) and metformin for 21 days in accordance with the above procedure.

Preparation of study materials

At the end of the study period, animals were sacrificed by decapitation under 0.4 mL/kg pentobarbital sodium anesthesia, and tissue samples (kidney, heart, and liver) were obtained. Tissues were homogenized in phosphate buffer saline (1:9 dilution) using a homogenizer (Wigen Hauser). The homogenates were then centrifuged at 10,000 g for 5 min at 4°C to separate the supernatants.

Biochemical analysis

Blood glucose levels were periodically determined (days 0, 7, 14, 21, and 28) using a glucometer after 8 h of fasting. Malondialdehyde (MDA) and glutathione (GSH) levels were measured using the methods of Placer *et al*. [24] and Sedlak and Lindsay [25], respectively. The levels of superoxide dismutase (SOD) (Sigma-Aldrich) and catalase (CAT) (Cayman) were determined using spectrophotometric test kits.

Statistical analysis

The SPSS 18 package program was used for statistical analysis of the data. One-way analysis of variance and Tukey's test were used to analyze among group differences. Statistical significance was accepted at p<0.05 (*, #: p<0.05, **, ##: p<0.01, and ***, ###: p<0.001).

RESULTS

At the beginning of the study, blood glucose levels of the animals ranged from 71 to 98 mg/dL (mean±standard deviation, n=40). 7 days after injecting NAD + STZ, blood glucose levels were significantly increased (p<0.001). No significant differences were detected between the DC and experimental groups on days 7 and 14 of the study period (p>0.05). However, on days 21 and 28 of the study, blood glucose levels significantly decreased as a result of CrPic (p<0.01) and metformin (p<0.001) administration, respectively (Fig. 1).

MDA levels in the heart tissue significantly decreased in the DC group (p<0.001). However, MDA level in the heart tissue significantly decreased in the D + CrPic (p<0.05) and D + M (p<0.001) groups. GSH and CAT levels significantly decreased in the DC group (p<0.05 and p<0.01, respectively). As a result of CrPic and metformin administration, GSH and CAT levels significantly increased (p<0.001). No change was observed in SOD antioxidant enzyme levels (p>0.05) (Fig. 2).

MDA levels significantly increased in the kidney tissue of the DC group (p<0.001), whereas it decreased in the D + M group (p<0.01). In addition, GSH and CAT levels significantly decreased in the DC group (p<0.05 and p<0.001, respectively) but increased in the D + CrPic

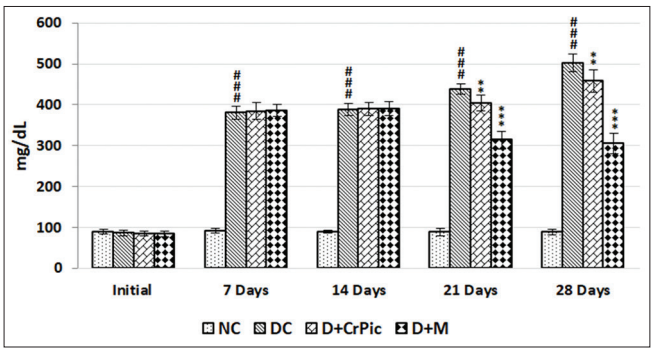

Fig. 1: Effect of chromium picolinate on fasting blood glucose levels (mean±standard deviation, n=10). **p<0.01, ***p<0.001 as compared with diabetic control group, ### p<0.001 as compared with normoglycemic control group

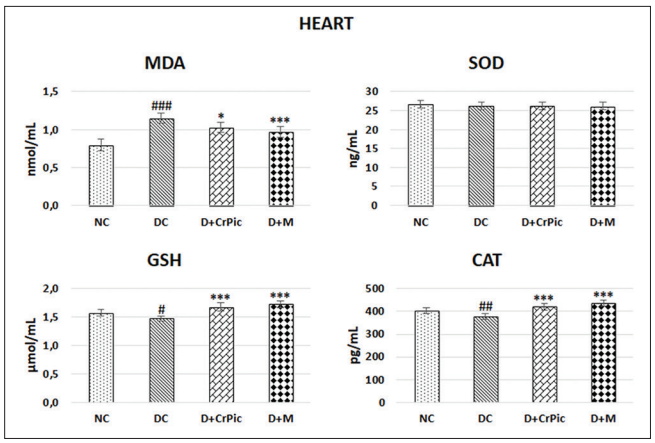

Fig. 2: Effect of chromium picolinate on oxidative stress parameters in heart tissue (mean±standard deviation, n=10). *p<0.05, ***p<0.001 as compared with diabetic control group, # p<0.05, ## p<0.01, ### p<0.001 as compared with normoglycemic control group

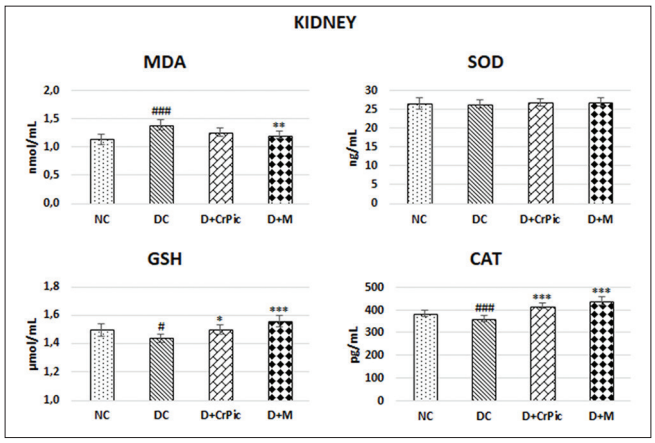

Fig. 3: Effect of chromium picolinate on oxidative stress parameters in kidney tissue (mean±standard deviation, n=10). *p<0.05, **p<0.01, ***p<0.001 as compared with diabetic control group, # p<0.05, ### p<0.001 as compared with normoglycemic control group

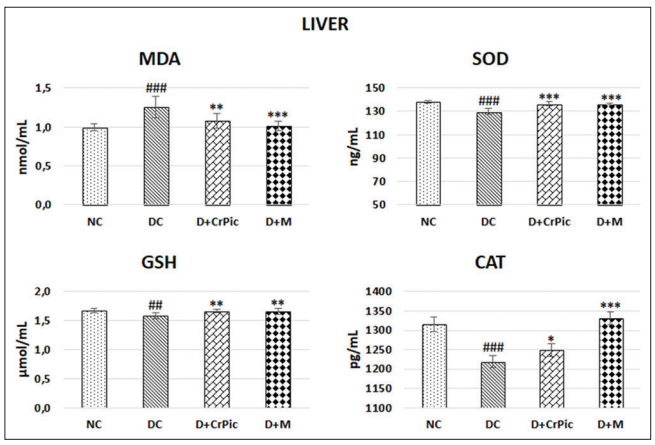

Fig. 4: Effect of chromium picolinate on oxidative stress parameters in liver tissue (mean±standard deviation, n=10). *p<0.05, **p<0.01, ***p<0.001 as compared with diabetic control group, ##p<0.05, ###p<0.001 as compared with normoglycemic control group

($p<0.05$ and $p<0.001$, respectively) and D + M ($p<0.001$) groups. No significant differences were detected between SOD levels in the groups ($p>0.05$) (Fig. 3).

MDA levels in the liver tissue of the DC group were found to be significantly higher than in that of the NC group ($p<0.001$). MDA levels in liver tissues of the D + CrPic and D + M groups significantly decreased ($p<0.01$ and $p<0.001$, respectively). SOD, GSH, and CAT antioxidant enzyme levels significantly decreased in the DC group ($p<0.001$, $p<0.01$, and $p<0.001$, respectively) but increased in the D + CrPic ($p<0.001$, $p<0.01$, and $p<0.05$, respectively) and D + M ($p<0.001$, $p<0.01$, and $p<0.001$, respectively) groups (Fig. 4).

DISCUSSION

Insulin resistance is an important cause of diabetes, metabolic syndrome, obesity, hypertension, dyslipidemia, and cardiovascular diseases [26,27]. In Type 2 diabetes, treatment aims to increase insulin sensitivity. This study demonstrated that CrPic can increase insulin sensitivity and reduce hyperglycemia in diabetic rats (Fig. 1). Many other studies have previously demonstrated that CrPic can lower blood glucose levels in animals and diabetic patients [11,28-30]. Doddigarla *et al*. stated that CrPic and melatonin each alone and in combination decreased blood glucose levels in high carbohydrate diet-fed male rats [31]. Refaie *et al*. also reported that CrPic did not alter blood glucose in non-diabetic rats but significantly reduced in alloxan-induced diabetes. They stated that CrPic has also linked this mode of action to the glucose tolerance in the host [32]. Another study indicated that CrPic reduced plasma glucose levels and improved unbalanced carbohydrate metabolism in diabetic rats [33]. CrPic exerts its antihyperglycemic and insulin-sensitizing actions through two mechanisms. The first is through increased GLUT4 expression [34] and the second through the regulation of lipid and carbohydrate metabolism [35].

Hyperglycemia can lead to decreased antioxidant enzyme levels despite increases in free radical levels in diabetes mellitus [11,36]. Increase in lipid peroxidation and activation of the hexosamine pathway, polyol pathway, and protein kinase C increase the production of free oxygen radicals [37,38]. Nowadays, researchers have stated that antioxidants obtained from natural sources as well as some trace elements such as CrPic can help prevent diabetes and its complications [14,15]. Another study stated that Cr supplementation decreased plasma glucose, TBARS, and HbA1c levels, while it increased levels of TAS in Type 2 diabetes patients [39]. Refaie *et al*. found that diabetic rats have significant reductions in SOD, GPx, and CAT activities in liver tissues. They stated that this reduction may be related to overproduction of ROS and disrupting the activity of these enzymes. In the same study, researchers were determined that CrPic reduced liver MDA levels, whereas increased SOD, CAT, and GPx levels [32]. In the present study, MDA levels in heart, kidney, and liver tissues significantly increased in the DC group compared with the NC group (Figs. 2-4). There were no differences in SOD antioxidant enzyme levels in heart and kidney tissues between groups (Figs. 2 and 3). However, SOD levels in the liver tissue significantly increased in the D + CrPic group compared with those in the DC group (Fig. 4). Moreover, GSH and CAT enzyme levels in all tissues significantly increased in the D + CrPic group (Figs. 2-4). Previous studies have demonstrated that CrPic supplementation inhibits the increase in lipid peroxidation seen in diabetic patients [40,41]. Sundaram *et al.* found that CrPic significantly increased liver GSH, GSH reductase, CAT, and SOD enzyme levels in rats with Type 1 diabetes [37]. Al-Rasheed *et al*. reported the modulating effect of CrPic in myocardial infarction-induced oxidative stress [42]. However, the mechanism by which CrPic reduces oxidative stress is not fully understood. We hypothesize that CrPic may reduce oxidative damage by reducing fasting glucose levels.

CONCLUSION

In this study, CrPic was found to be effective in reducing hyperglycemia in Type 2 diabetes and in suppressing lipid peroxidation by enhancing antioxidant mechanisms.

AUTHORS' CONTRIBUTION

All authors participated equally in the design, analysis, and writing of the research.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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