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Protective effects of calcitriol against fructose-induced hyperglycemia and dyslipidemia in male albino Wistar rats

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ABSTRACT

Background: Hyperglycemia and lipidemia have been found to produceadverse metabolic alterations in glucose and lipid metabolism. The current study was designed to investigate the preventive role of calcitriol (CTR) supplementation on fructose-induced hyperglycemia and dyslipidemia in fructose drinking albino Wistar rats.

Methods: Twenty-five male albino rats were used in this research work. The rats were divided into five groups of five animals each. Group I: control; received normal rat feed + distilled water, Group II: received normal rat feed + 125 µg/kg of CTR, Group III: received normal rat feed + 10% fructose drinking rats (FDR), Group IV: received normal rat feed + 10% fructose solution (FDR) + 0.3 mg/kg of glibenclamide (GLIB), and Group V: received normal rat feed + 10% fructose solution (FDR) + 125 µg/kg of CTR. For the induction of hyperglycemia and lipidemia, rats were given 10% fructose solution as drinking water for 8 weeks. The levels of fasting sugar and glycated hemoglobin (HbA1c) were measured. Changes in body weights and lipid profile of rats were determined.

Results: CTR group exhibited no significant ($P < 0.05$) change in plasma glucose levels, HbA1c, and body weights when compared to the control (5.09 ± 0.45 mmol/l *vs*. 5.20 ± 0.15 mmol/l, 4.57% ± 0.24% *vs*. 4.29% ± 0.31%, and 193.0 ± 12.25 g *vs*. 189.2 ± 6.37 g, respectively). In FDR group, fasting sugar levels, HbA1c, and weights were found to be significantly ($P < 0.05$) increased when compared to group I (6.49 ± 0.16 mmol/l *vs*. 5.20 ± 0.15 mmol/l, 5.23% ± 0.17% *vs*. 4.29% ± 0.31%, and 219.1 ± 17.36 g *vs*. 189.2 ± 6.37 g, respectively). Glibenclamide administration in GLIB + FDR group effectively abolished the fructose-induced hyperglycemia and HbA1c in rats when compared to FDR group (5.53 ± 1.92 mmol/l *vs*. 6.49 ± 0.28 mmol/l and 4.10% ± 0.54% *vs*. 5.23% ± 0.17%, respectively). In FDR + CTR group, CTR supplementation successfully blocked and prevented the fructose-induced increase in fasting sugar, HbA1c levels, and weight in rats when compared with FDR group (5.12 ± 0.39 mmol/l *vs*. 6.49 ± 0.28 mmol/l, 4.43% ± 0.24% *vs*. 5.23% ± 0.17%, and 192.2 ± 11.23 g *vs*. 219.1 ± 17.36 g, respectively). CTR group exhibited no significant ($P > 0.05$) changes in lipid profile parameters when compared to control (3.88 ± 0.19 mmol/l *vs*. 3.89 ± 0.38 mmol/l, 1.20 ± 0.16 mmol/l *vs*. 1.12 ± 0.11 mmol/l, 2.16 ± 0.17 mmol/l *vs*. 2.20 ± 0.22 mmol/l, and 1.32 ± 0.22 mmol/l *vs*. 1.30 ± 0.16 mmol/l) for total cholesterol (TC), triglyceride (TG), low density lipoprotein (LDL), and high density lipoprotein (HDL), respectively. FDR exhibited a significant ($P < 0.01$) increase in serum TC (4.90 ± 0.23 mmol/l) when compared to control group (3.88 ± 0.19 mmol/l). Similarly, fructose feeding resulted in a significant elevation ($P < 0.01$) in TGs levels (1.90 ± 0.27 mmol/l *vs*. 1.20 ± 0.16 mmol/l) in comparison to the corresponding control rats. In addition, FDR group rats had elevated levels of LDL-cholesterol (LDL-C) which was significant ($P < 0.05$) when compared with the corresponding control group (2.80 ± 0.26 mmol/l *vs*. 2.16 ± 0.17 mmol/l). Although, HDL-C was increased in FDR group, the increase was not significant ($P > 0.05$) and the result was comparable to that of the control (1.22 ± 0.07 mmol/l

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vs. 1.32 ± 0.22 mmol/l). In FDR + CTR group, oral CTR supplementation potentially prevented fructose in inducing alterations in serum lipid profiles when compared to FDR group.
Conclusion: The result showed that CTR supplemention in fructose drinking rats protects against hyperglycemia and dyslipidemia.

Introduction

Disturbances in glucose metabolism and changes in lipid profiles are important biochemical findings in fructose-fed rats [1–3]. These metabolic alterations are attributed to disturbances in glucose uptake pathways and glucose metabolism and changes in the expression of several enzymes involved in hepatic lipid production and hydrolytic pathways [4,5]. Fructose-rich diet induced impaired glucose tolerance accompanied by insulin resistance and hyperinsulinemia [5]. In addition, high levels of glucose and free fatty acids have been shown to promote oxidative cellular damage and exert detrimental effects by inducing the generation of free radicals as well as reducing antioxidant defenses [6–8]. Consequently, hyperglycemia and lipidemia produced adverse metabolic alterations in glucose and lipid metabolism [2,3,9]. The mechanism underlying fructose-induced metabolic syndrome is complex but may be related to fructose induced increases in gluconeogenesis and lipogenesis since it by-passes the major regulatory steps of glycolysis [6].

Calcitriol (CTR) is the physiologically active form of vitamin D. It is formed primarily in the kidney by enzymatic hydroxylation of 25-hydroxycholecalciferol. Vitamin D receptors (VDRs) and the 1α-hydroxylase enzyme, which catalyzes the conversion of calcidiol to cholesterolare found in most human tissues [10,11], indicating its potential role in the regulation of numerous metabolic processes in the body. This nutrient might exert its biological activities through increase insulin action by enhancing insulin synthesis and release [12,13]. Insulin receptor is a macromolecule, its expression on the cell surface is essential for cell sensitivity to insulin [14–16]. The present study was designed to investigate the preventive role of CTR supplementation on fructose-induced hyperglycemia and dyslipidemia in fructose drinking rats.

Materials and Methods

Animals

Twenty-five adult male Wistar rats weighing between 190 and 200 g were obtained from the animal house of the Department of Human Physiology, College of Medical Sciences, Gombe State University, Gombe, Nigeria. The animals were cared for in accordance with guidelines for the care and use of experimental animals. They were fed with growers and starter mash vital feed (Vital feed Company Kaduna, Nigeria) and allowed free access to water ad-libitum except when fasting was required in the course of the experiment.

Drugs and chemicals

CTR, Glibenclamide (GLIB), and D-fructose were obtained from Toteil Nigeria Limited Kano, Nigeria. All other chemicals used were of analytical grade.

Preparation and administration of calcitriol

A dose of 125 µg/kg body weight of CTR used was based on a previous study [17]. CTR has wide range of doses to produce toxic effect i.e., the 125 µg/kg body weight of CTR used in the experiment was proved to be non toxic to the rats. CTR was dissolved in 10 g/l of carboxymethyl cellulose in 10 ml and supplemented orally as described by Hamden et al. [16].

Induction of hyperglycemia and lipidemia in albino rats

For the induction of hyperglycemia and lipidemia, rats were given 10% fructose solution as drinking water for 8 weeks according to the method of Neeharika et al. [17].

Experimental design and treatment schedule

Male albino Wistar rats were randomly divided into five groups, five for each as follows:

Group I: control; received normal rat feed + distilled water

Group II: received normal rat feed + 125 µg/kg of CTR

Group III: received normal rat feed + 10% fructose solution fructose drinking rats (FDR)

Group IV: received normal rat feed + 10% fructose solution (FDR) + 0.3 mg/kg of GLIB

Group V: received normal rat feed + 10% fructose solution (FDR) + 125 µg/kg of CTR

Measurement of fasting sugar levels

Blood samples were collected from the tail vein by the tail tip method [18]. Fasting sugar levels of test animals were measured at the beginning and at the end of the study using Accu-check glucometer and Accu-check active 50 test strips (Roche Diagnostic GmbH Mannheim, Germany). Results were expressed in mmol/l. Glycated hemoglobin (HbA1c) was determined according to the methods of Susheela et al. [19] and Veerapur et al. [20].

Collection of blood samples for biochemical analysis

Eight weeks after the commencement of the treatment, over night fasted rats were sacrificed and blood samples were collected by cardiac puncture in centrifuge tubes as described by Susheela et al. [19]. The serum was separated by centrifugation using BS400 centrifuge at 3,000 × g for 15 minutes (Denley BS400; England). Plasma was collected into bottles using a Pasteur pipette to be used for biochemical analysis of lipid profiles.

Determination of body weights of the albino Wistar rats

Weights of the experimental animals were determined at the end of the study period using Adam weighing scale and body weights were recorded in grams (g).

Determination of serum lipid profiles of albino Wistar rats

The lipid profiles; total cholesterol (TC), TGs, low density lipoproteins (LDL-C), and high density lipoproteins (HDLs) levels in plasma were determined using commercial diagnostic kits according to the instruction of the manufacturer (Asan Pharmaceutical, Seoul, Korea). Results were expressed in millimols per liter (mmol/l).

Statistical analysis

Data were expressed as mean ± standard error of mean (SEM). Data were analyzed using one way analysis of variance followed by Turkey-Kramer multiple comparison post-hoc tests to show multiple comparisons *versus* control. Data analysis was performed using SPSS version 20.0. $P \leq 0.05$ was considered significant.

Results

CTR group exhibited no significant ($P < 0.05$) change in plasma glucose levels, HbA1c, and body weights when compared to the control (5.09 ± 0.45 mmol/l *vs*. 5.20 ± 0.15 mmol/l and 4.57% ± 0.24% *vs*. 4.29% ± 0.31%, 193.0 ± 12.25 g *vs*. 189.2 ± 6.37 g). In FDR group, fasting sugar levels, HbA1c, and weights were found to be significantly ($P < 0.05$) increased compared to the control (6.49 ± 0.16 mmol/l *vs*. 5.20 ± 0.15 mmol/l and 5.23% ± 0.17% *vs*. 4.29% ± 0.31%, 219.1 ± 17.36 g *vs*. 189.2 ± 6.37 g) respectively. Glibenclamide administration in GLIB + FDR group effectively abolished the fructose-induced hyperglycemia and HbA1c in rats when compared to FDR group (5.53 ± 1.92 mmol/l *vs*. 6.49 ± 0.28 mmol/l and 4.10% ± 0.54% *vs*. 5.23% ± 0.17%). In FDR + CTR group, CTR supplementation successfully blocked and prevented the fructose-induced increase in fasting sugar, HbA1c levels, and weights in rats when compared with FDR group (5.12 ± 0.39 mmol/l *vs*. 6.49 ± 0.28 mmol/l, 4.43% ± 0.24% *vs*. 5.23% ± 0.17%, and 192.2 ± 11.23 g *vs*. 219.1 ± 17.36 g) respectively as shown in Figures 1–3.

CTR group when compared with the control exhibited no significant ($P > 0.05$) changes in lipid profile parameters (3.88 ± 0.19 mmol/l *vs*. 3.89 ± 0.38 mmol/l, 1.20 ± 0.16 mmol/l *vs*. 1.12 ± 0.11 mmol/l, 2.16 ± 0.17 mmol/l *vs*. 2.20 ± 0.22 mmol/l, and 1.32 ± 0.22 mmol/l *vs*. 1.30 ± 0.16 mmol/l) for TC, TG, LDL, and HDL, respectively. CTR treatment has little or no effects on lipid profiles of normal rats. FDR group exhibited a significant ($P < 0.01$) increase in serum TC (4.90 ± 0.23 mmol/l) when compared to control group (3.88 ± 0.19 mmol/l). Similarly, fructose feeding resulted in a significant elevation ($P < 0.01$) in TGs levels (1.90 ± 0.27 mmol/l *vs*. 1.20 ± 0.16 mmol/l) in comparison to the corresponding control rats. In addition, fructose drinking rats had elevated levels of LDL-C which was significant ($P < 0.05$) when compared with the corresponding control group (2.80 ± 0.26 mmol/l *vs*. 2.16 ± 0.17 mmol/l). Although, HDL-cholesterol (C) was increased in fructose drinking rats, the increased was not significant ($P > 0.05$) and the result was comparable to that of the control (1.22 ± 0.07 mmol/l *vs*. 1.32 ± 0.22 mmol/l). Thus, fructose feeding produced significant alterations in lipid profiles in FDR group rats. In FDR + CTR group, oral CTR supplementation potentially prevented fructose in inducing alterations in serum lipid profiles when compared to FDR group and the results were comparable to their corresponding controls except for HDL-C as shown on Table 1.

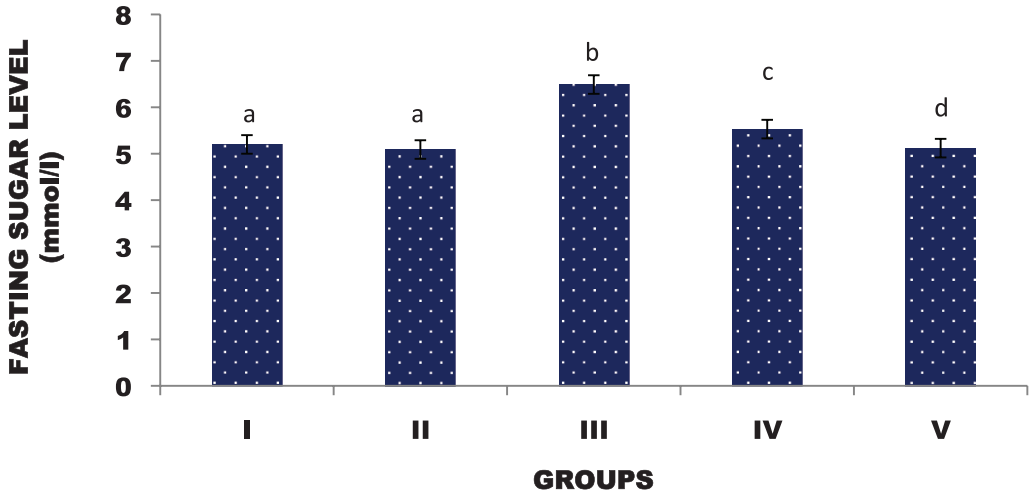

Figure 1. The effects of CTR (125 µg/l) supplementation in fructose drinking albino Wistar rats on fasting sugar levels.

Data is presented as mean ± SEM; $n = 5$. Values with different superscript letters are statistically significant at $P < 0.05$.

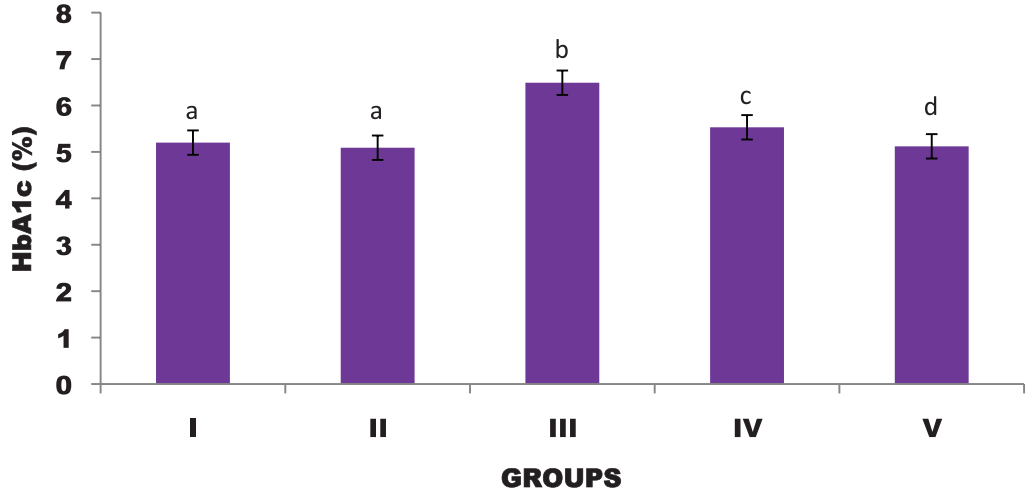

Figure 2. The effects of CTR (125 µg/l) supplementation in fructose drinking albino Wistar rats on HbA1c.

Data is presented as mean ± SEM; $n = 5$. Values with different superscript letters are statistically significant at $P < 0.05$.

Discussion

In this study, the effect of CTR was investigated using a model of fructose drinking rats. Consistent with the findings of previous studies [8,21,22], the results of the present study revealed that fructose drinking rats had significant hyperglycemia, higher levels of HbA1c, increased in body weights, and dyslipidemia. This observation suggests that metabolic disturbances have been developed in these animals. In the co-administered group, CTR treatment effectively prevented and blocked the diabetogenic effects of high fructose feeding by preventing the development of hyperglycemia, higher HbA1c, increased body weights, and dyslipidemia in the albino Wistar rats. Thus, oral CTR administration prevented metabolic disturbances in fructose drinking rats. Similar to our findings, improved CTR level was reported to protect against type 2 diabetes mellitus [22], in addition the prevention of cardiometabolic disturbances in fructose drinking rats by oral CTR supplementation could be attributed to improve insulin secretion and sensitivity [12,13], the protective effects of CTR may be ascribed to its anti-oxidant and anti-inflammatory properties as well as its effects on calcium

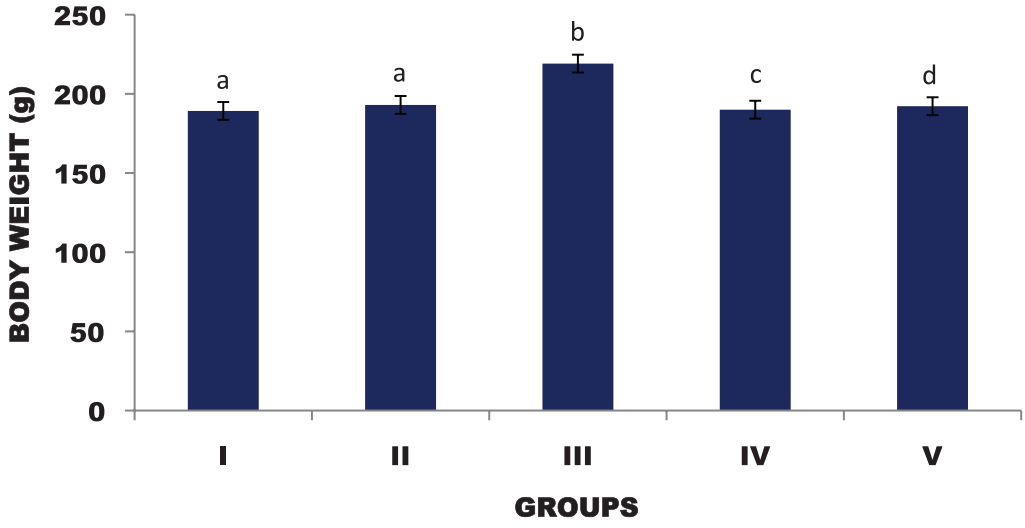

Figure 3. The effects of CTR (125 µg/l) supplementation in fructose drinking albino Wistar rats on body weight.

Data is presented as mean ± SEM; n = 5. Values with different superscript letters are statistically significant at $P < 0.05$.

Table 1. Effects of CTR supplementation in fructose drinking albino Wistar rats on lipid profile.

Group	TC (mmol/l)	TG (mmol/l)	LDL-C (mmol/l)	HDL (mmol/l)
I	3.88 ± 0.19	1.20 ± 0.16	2.16 ± 0.17	1.32 ± 0.22
II	3.89 ± 0.38$^{\#}$	1.12 ± 0.11$^{\#}$	2.20 ± 0.22$^{\#}$	1.30 ± 0.16
III	4.90 ± 0.23*	1.90 ± 0.27*	2.80 ± 0.26*	1.22 ± 0.07
IV	3.93 ± 0.16	1.24 ± 0.22	2.30 ± 0.22	1.36 ± 0.24
V	3.86 ± 0.16	1.18 ± 0.19	2.10 ± 0.13	1.35 ± 0.17

Data is presented as mean ± SEM; n = 5. *$P \leq 0.05$, **$P \leq 0.01$, $P \leq 0.001$ *vs*. group I, $^{\#}P \leq 0.05$, $^{\#\#}P \leq 0.01$ *vs*. group III.

and phosphorus metabolism [23–25]. Other possible mechanisms could be attributed to increased proliferative activities of VDRs, enhanced expression of calbindin-D28k [14], and regulation of human peroxisome proliferator activated receptor gamma-δa receptor that play an important role in insulin sensitivity through the regulation of fatty acids metabolism in skeletal muscle and adipose tissue [26].

Regarding the effects of CTR on lipid profiles, findings from our study showed significant reduction in serum TC, TG, and LDL with concomitant increase in HDL which attends no statistical significance. This reduction might be due to increased clearance and decreased production of the major transporters of endogenously synthesised cholesterol and TGs [27]. It has been shown that the liver participates in the uptake, oxidation, and metabolic conversion of fatty acids, the synthesis of cholesterol and phospholipids and the secretion of specific classes of lipoproteins [28]. In agreement with these findings, observational studies have shown an inverse relationship between serum vitamin D and lipid profiles [29,30]. The absence of dyslipidemia in fructose drinking rats by CTR administration could be assigned to calcium-regulating function of CTR, whereby increased calcium levels are proposed to reduce hepatic TG formation and secretion [29,30]. It has also been suggested that CTR administration improve lipid metabolism by preventing cholesterol synthesis and uptake and enhance cholesterol clearance in the plasma [13]. There was no significant changes in the levels of HDL between FDR group *versus* FDR + CTR group in this study. This could be as a result of transports of excess cholesterol from walls of arteries to the liver for processing and removal. Similar to our findings [13], showed that CTR promote HDL particle formation by regulating serum apolipoprotein A-1 levels which enhanced cholesterol transport resulting into overall improvement in lipid profiles. It may also affect the concentration of circulating lipids by increasing adiponectin levels which inhibits lipogenesis through its regulation of adipocyte activity

[31]. The protective effects of CTR in this study is in line with evidences suggesting that CTR administration decreases the risk of many chronic diseases including type 2 diabetes, metabolic syndrome [31], and cardiovascular diseases [32].

Conclusion

The result suggests the beneficial effects of the CTR in improving the imbalance in glucose and lipid metabolism in fructose drinking rats. Thus, adequate CTR levels could be useful in the treatment of dietary-induced glucose and lipid cardiometabolic abnormalities. The present study is limited to biochemical analysis in the serum, further investigations on histopathological and immunohistochemical examination would be conducted to proffer additional imputation on the benefit of CTR in the prevention of dietary metabolic abnormalities in fructose drinking albino Wistar rats.

Conflict of Interest

The authors have declared that ther is no conflict of interest.

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