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Research Paper

Dexamethasone Promotes the Risk of Cardiovascular Disease in High Fructose-exposed Wistar Rats

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ABSTRACT

Background: Dyslipidemia constitutes a serious public health concern globally. It has been established that excessive fructose intake results in dyslipidemia; however, whether dexamethasone aggravates or alleviates fructose-induced dyslipidemia is unknown. Thus, we examined the effects of dexamethasone on dyslipidemia and hyperuricemia in high fructose-taking Wister rats.

Materials and Methods: Twenty male Wister rats were randomly grouped as control (distilled water), fructose (10% fructose w/v), dexamethasone (0.2 mg/kg, PO) and fructose+dexamethasone. After a 21-day exposure, the serum and heart samples were harvested, processed and analyzed for biochemical assays.

Results: Our findings reveal that exposure of rats to high fructose significantly increased blood glucose, elevated serum triglycerides and uric acid, activity of xanthine oxidase, and lowered high density lipoprotein cholesterol (HDL) level. However, dexamethasone administration had no significant effect on the blood glucose and did not alter the serum levels of triglycerides, uric acid and xanthine oxidase. Meanwhile, both fructose and dexamethasone treatments independently elevated the serum levels of total cholesterol (TC), low density lipoprotein cholesterol (LDL) and malondialdehyde. Further, the fructose treatment elevated the TG/HDL ratio, while both fructose and dexamethasone treatments individually and synergistically elevated TC/HDL ratio. Our study also showed that co-administration of fructose and dexamethasone aggravated the elevated serum levels of TC and LDL, while it impaired the enzymatic antioxidant systems.

Conclusion: Dexamethasone, though slightly reduced fructose-induced hyperglycemia, impaired the antioxidant enzymes and escalated dyslipidemia during fructose intake. Hence, our study suggests that dexamethasone administration may increase the risk of CVD in animals with excessive intake of fructose.

Keywords: Dexamethasone, Dyslipidemia, Fructose, Oxidative stress, Uric acid

Introduction

Dyslipidemia is a major factor that promotes the incidence of cardiovascular disease (CVD) [1]. It is characterized by impaired circulating level of lipids that include one or a combination of high total cholesterol (TC), increased low density lipoprotein (LDL) and decreased high-density lipoprotein (HDL) cholesterols, and elevated triglycerides (TG) levels. Specifically, the elevated levels of TC and LDL in the blood promote atherosclerosis, build up plaques in the arterial walls, and consequently increase the risk of CVD development [2]. Furthermore, about 10 mg/dL increase in TC results in 5% and 9% increases in mortality and death from cardiovascular disease, respectively [3].

Currently, dyslipidemia constitutes a public health challenge globally, as its prevalence and mortality rates keep rising [2]. In 2016 alone, approximately 4.4 million deaths and 93.8 million disability-adjusted life-years (DALYs) were attributed to hypercholesterolemia worldwide [4]. Further, high prevalence of dyslipidemia has been reported among adult population in Africa, with 23.6% and 25.7% of them having elevated TC and LDL, respectively; while the prevalence of hypertension, diabetes and HIV in patients is much higher [5]. Yet, the exact global prevalence of dyslipidemia cannot be ascertained as many individuals are oblivious to their blood lipid status, which translates into higher number of patients with untreated dyslipidemia [1]. Several factors such as changes in dietary and lifestyle, long-term sedentary work habits and hyperglycemia are major predictors of dyslipidemia [2].

Fructose is recognized as a major constituent of modern diet; with fruits and vegetables accounting for one-third of fructose sources [6]. For its taste and being less expensive, it is widely used as a sweetener in beverages, soft drinks, canned fruits, jams, paste candies, cakes, and others [7]. Fructose was initially considered to have lower glycemic index than glucose, thus was taken as the preferred sweetener by people with diabetes [8]. However, research evidence has shown that fructose consumption induces lipogenesis and aggravates blood lipids [9]. Further, excessive fructose consumption leads to adverse metabolic effects in humans [10, 11]; hence, contributing to increased incidence of dyslipidemia and CVD.

Glucocorticoids are well established treatment options for human inflammatory and immune system diseases [12, 13]. Despite their therapeutic efficacy, overdose or prolonged use of glucocorticoids has several adverse effects [14]. However, whether glucocorticoids can alleviate or aggravate fructose-induced dyslipidemia has not been examined.

Aim of the study: Considering the above facts, the present study was planned to examine the effects of dexamethasone alone and combined with fructose in Wister rats, as a first-step in vivo investigation of the two compounds on the incidence of CVD.

Materials and Methods

Twenty male Wister rats with an average weight of 109 g were obtained from the animal house of Ladoke Akintola University of Technology Ogbomosho, Oyo State, Nigeria. The rats were transported to the animal house of the Department of Zoology, University of Ilorin, at Ilorin, Nigeria, and maintained under standard environmental condition. The rats were allowed free access to standard rat food pellets and clean water ad libitum. Initially, they were left to acclimatize with the experimental environment for two weeks, before commencing the experiments. The rats were humanely handled based on the recommendations of the University of Ilorin's Ethics Committee, and in conformity with the guidelines of the U.S. National Institutes of Health required for the care and use of laboratory animals.

Treatment: Following acclimatization, the animals were randomly assigned to four groups; each consisting of five rats. The control rats were orally administered distilled water, the vehicle for fructose and dexamethasone. The fructose group was exposed to 10% fructose (w/v) dissolved in drinking water [15]. The dexamethasone group orally received 0.2 mg/kg body weight of the drug [16]. The combined treatment group received fructose (10%, w/v) and 0.2 mg/kg dexamethasone. All of the treatments were administered once daily for three consecutive weeks.

Fasting blood glucose and sample preparation: After three weeks of treatment, the rats were fasted for 12 hours and the fasting blood glucose was measured for each rat, using Accu-Chek® Active (Roche Diagnostics GmbH, Mannheim, Germany). Thereafter, the rats were sacrificed via cervical dislocation, while cardiac puncture was done to collect blood samples into plain test tubes. The blood samples were left to settle at room temperature and later centrifuged at 3000 rpm for 15 minutes to separate the sera from the whole blood samples. The sera were frozen prior to the biochemical assays. The heart was quickly removed from each animal, rinsed in normal saline to remove the at-

tached connective tissues and mechanically homogenized in cold 25 M sucrose solution. The resulting homogenates were further processed and analyzed for biomarkers of cardiac oxidative stress by a laboratory technician who was blinded to the animal grouping.

Biochemical assays

Estimation of uric acid and xanthine oxidase: A nonenzymatic colorimetric method was used to estimate the serum uric acid in rats, based on the instructions provided in the assay kit (Oxford Biomedical Research Inc., Oxford, USA). The activity of serum xanthine oxidase (XO) was measured by a standard enzymatic colorimetric method, using reagents obtained from Fortress Diagnostics Limited (Antrim, UK). The manufacturer's instructions were carefully followed to perform the assays.

Redox biomarkers: The activities of serum MDA, catalase and superoxide dismutase were determined by standard spectrophotometric methods, using the assay kits for each enzyme (Fortress Diagnostics Limited, Antrim, UK), while the manufacturer's instructions were followed for performing each assay.

Lipid profile and atherogenic indices: the concentrations of total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterols in the serum samples were assessed by standard colorimetric methods, based on the assay kits (Fortress Diagnostics Limited, Antrium, UK). The instructions from the manufacturer were followed to carry out the assays. TG/HDL and TC/HDL ratios were estimated and used as the atherogenic indices.

Statistical analyses: The data were statistically analyzed by one-way ANOVA and presented as the means±SEM of the triplicate samples, using GraphPad software, version 8.0 (GraphPad Software; CA, USA). The mean values were also compared among the groups by Tukey post-hoc test. The significant differences among the groups were determined at 95% confidence level, and $P<0.05$, $P<0.01$ and $P<0.001$ were considered as the significance levels.

Results

Effects of fructose and dexamethasone on lipid profile: Fructose or dexamethasone alone significantly elevated the serum TC and LDL, while fructose alone and the combined fructose and dexamethasone significantly decreased the serum HDL (Figure 1). There was an increased serum TG level in rats given fructose only. Whereas, the combined fructose and dexamethasone treatment increased TC and LDL. Compared with the controls, the serum lipid index, TG/HDL was significantly increased in rats taking either fructose alone or the combined fructose and dexamethasone. Similarly, fructose or dexamethasone alone elevated the serum TC/HDL ratio (Figure 2). The combined fructose and dexamethasone treatment further increased the TC/HDL ratio.

Effects of fructose and dexamethasone on serum and cardiac enzymes: As shown in Figure 3, exposure of the rats to fructose or dexamethasone alone, and co-administration of both fructose and dexamethasone significantly elevated both serum and cardiac levels of malondialdehyde (MDA), compared to those of the control rats. Meanwhile, fructose or dexamethasone alone significantly lowered the activities of catalase and superoxide dismutase (SOD) in the rats' sera and heart samples. Also, combined fructose and dexamethasone increased serum and cardiac activities of catalase but reduced the SOD activity in both sera and heart samples, as compared with those of the control.

Effect of fructose and dexamethasone on fasting blood sugar: As demonstrated in Figure 4, the fructose intake increased the fasting blood glucose (FBG) as compared to that of the control rats ($P<0.01$). Conversely, no significant changes in the FBG levels were noted in the group that received dexamethasone alone ($P>0.05$). Similarly, the administration of dexamethasone in fructose-exposed rats insignificantly reduced the fructose-induced hyperglycemia ($P>0.05$).

Effect of fructose and dexamethasone on serum uric acid and xanthine oxidase: fructose but not dexamethasone increased the serum levels of both uric acid (UA; $P<0.001$) and XO activities ($P<0.05$; Figure. 5). In contrast, the administration of dexamethasone to fructose-exposed rats insignificantly lowered the XO activity without affecting the serum UA levels ($P>0.05$).

Discussion

The present study examined the effects of dexamethasone alone and combined with fructose in Wistar rats, as a first-step toward more definitive in vivo research on the cardiovascular consequences of the combined administration of fructose and dexamethasone. Primarily, we demonstrated that fructose but not dexamethasone induced both hyperglycemia and hyperuricemia in this animal model. Further, exposure to either fructose or dexamethasone caused oxidative stress and resulted in dyslipidemia, while the combined treat-

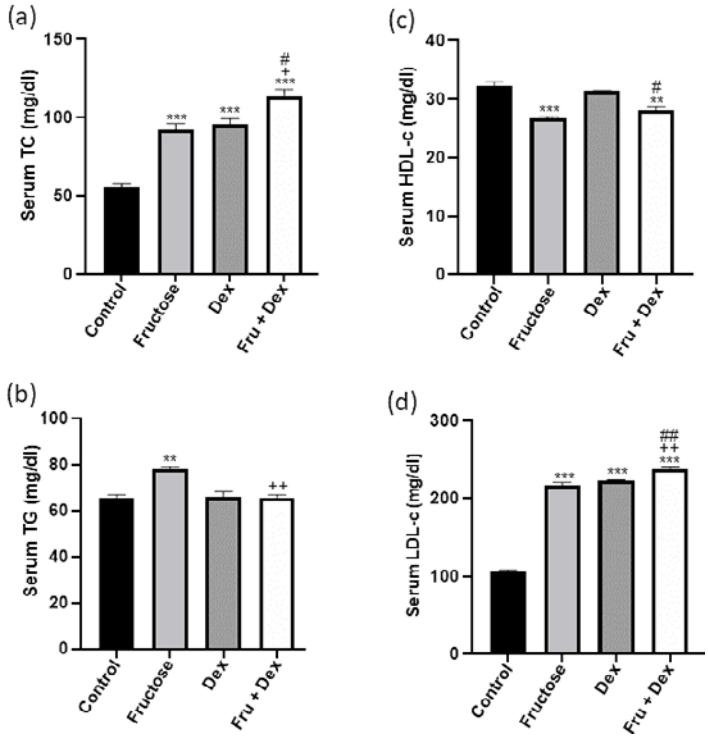

Figure 1. Effect of Fructose (10%) w/v, dexamethasone (Dex) (0.2 mg/kg body wt), and Fructose (10%) w/v+dexamethasone (Fru+Dex) (0.2 mg/kg) on serum parameters

(a) total cholesterol (TC); (b) triglycerides (TG); (c) high density lipoprotein cholesterol (HDL-c); and (d) low density lipoprotein cholesterol (LDL-c) in male Wistar rats. Mean values were compared among the groups by Tukey post hoc test.

**P<0.01 vs control; ***P<0.001 vs control; +P<0.05 vs fructose; ++P<0.01 vs fructose; #P<0.05 vs Dex; ##P<0.01 vs Dex

ment with fructose and dexamethasone increased lipid peroxidation, as evident by the increased MDA, which escalated the resultant dyslipidemia.

Effects on blood lipids: It has been reported in humans that a rise or decline in the total cholesterol level is associated with the elevation or reduction, respectively, of CVD risks in human adults [17]. In this context, the results of this study showed an increase in TG in rats that received fructose alone, and rises in the serum TC and LDL levels following the combined treatment with fructose and dexamethasone. Hence,

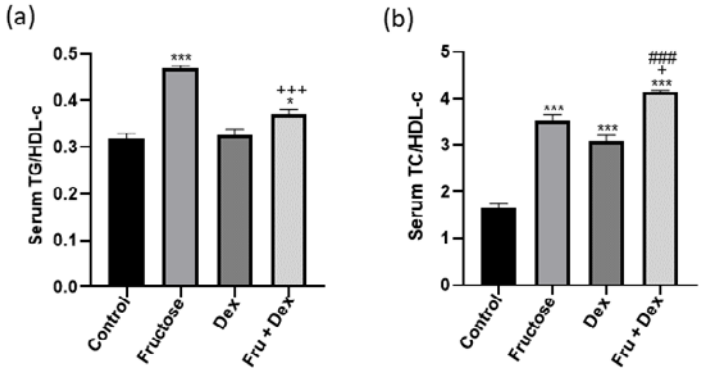

Figure 2. Effect of Fructose (10%) w/v, dexamethasone (Dex) (0.2 mg/kg body wt), and Fructose (10%) w/v+dexamethasone (Fru+Dex) (0.2 mg/kg) on serum lipid atherogenic indices

(a) TG/HDL-c, and (b) TC/HDL-c in male Wistar rats. Mean values were compared among the groups by Tukey post hoc test.

*P<0.05 vs control; *** P<0.001 vs control; +P<0.05 vs fructose; +++P<0.001 vs fructose; ###P<0.001 vs Dex

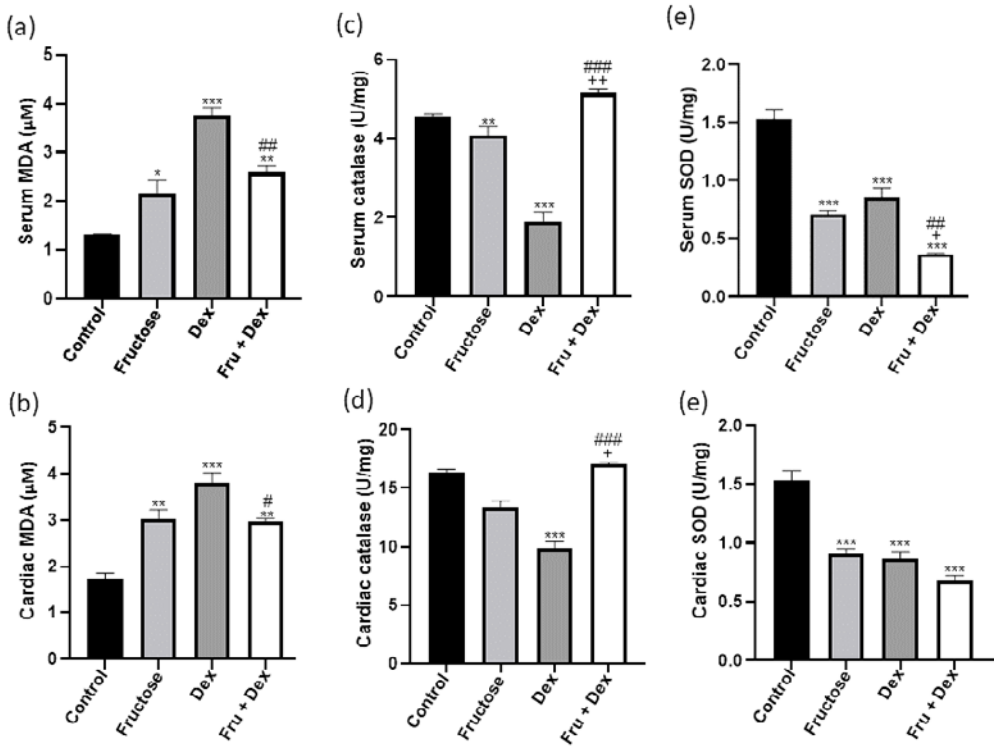

Figure 3. Effect of Fructose (10%) w/v, dexamethasone (Dex) (0.2 mg/kg body wt), and Fructose (10%) w/v+dexamethasone (Fru+Dex) (0.2 mg/kg) on serum and cardiac parameters

(a) serum malondialdehyde (MDA), (b) cardiac MDA, (c) serum catalase, (d) cardiac catalase, (e) serum superoxide dismutase (SOD), and (f) cardiac SOD in male Wistar rats. Mean values were compared among the groups by Tukey post hoc test.

*P<0.05 vs control; **P<0.01 vs control; ***P<0.001 vs control; +P<0.05 vs fructose; ++P<0.01 vs fructose; #P<0.05 vs Dex; ##P<0.01 vs Dex; ###P<0.001 vs Dex

these findings suggest that excessive intake of fructose and dexamethasone may promote CVD.

Our findings, which agree with earlier studies [10, 14] further imply that the combined fructose and dexamethasone treatment synergistically aggravated dyslipidemia in rats, promoting the heightened risk of CVD.

Effects on blood lipid ratios: To validate our observations, we assessed lipid atherogenic ratios (TG/HDL and

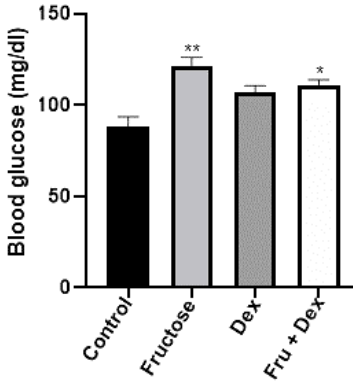

Figure 4. Effect of fructose (10%) w/v, dexamethasone (Dex) (0.2 mg/kg body wt), and fructose (10%) w/v+dexamethasone (Fru + Dex) (0.2 mg/kg) on fasting blood glucose in male Wistar rats

Mean values were compared among the groups by Tukey post hoc test.

*P<0.05 vs control; **P<0.01 vs control

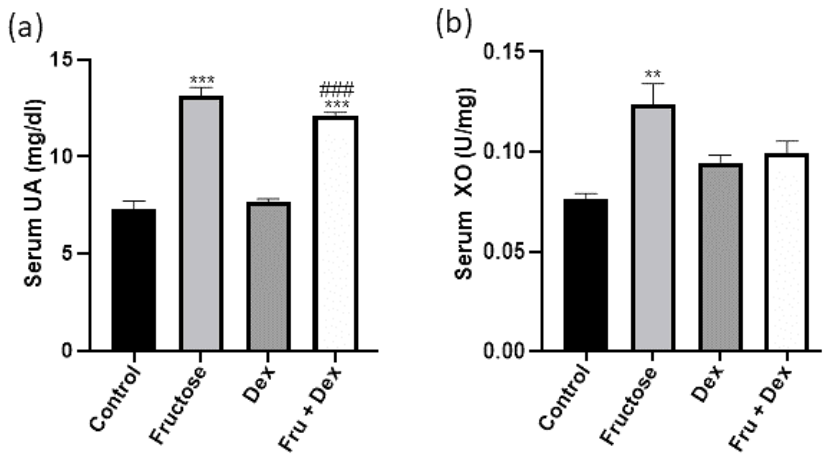

Figure 5. Effect of Fructose (10%) w/v, dexamethasone (Dex) (0.2 mg/kg body wt), and Fructose (10%) w/v + dexamethasone (Fru+Dex) (0.2 mg/kg) on serum parameters

(a) uric acid (UA), and (b) xanthine oxidase (XO) in male Wistar rats. Mean values were compared among the groups by Tukey post- hoc test.

$^{**}P<0.01$ vs control; $^{***}P<0.001$ vs control; $^{###}P<0.001$ vs Dex

TC/HDL) in all rat groups. Atherogenic ratios were formulated to better evaluate and predict the risk of CVD [18, 19]. Our data demonstrate that while only fructose increased the TG/HDL ratio, the administration of fructose and dexamethasone individually elevated the TC/HDL ratio. Further, the combined fructose and dexamethasone exacerbated the TC/HDL ratio. As a component marker of CVD, the TC/HDL ratio specifically predicts the risk of acute myocardial infarction [20]. Therefore, our findings reinstate that both fructose and dexamethasone treatments can independently promote the development of CVD. Further, our data suggest that the concurrent administration of dexamethasone and fructose can exacerbate dyslipidemia and raise the risk of CVD, especially myocardial infarction.

Effects on oxidative stressors: Oxidative stress is an important modulator of dyslipidemia and cardiometabolic disorders [21]. The rise in MDA level with concomitant decline in catalase and SOD levels, as observed in the rats treated with fructose or dexamethasone alone, may imply that either compound can induce lipid peroxidation and reduce the antioxidant activities, resulting in dyslipidemia. Similarly, the rise in the cardiac MDA level with the corresponding decline in the antioxidant activities may suggest impaired cardiac function due to the generation of reactive oxygen species (ROS), leading to contractile and structural damages [22].

Although the co-administration of fructose and dexamethasone increased the MDA but decreased the SOD activities, it elevated the catalase activity. Both catalase and SOD enzymes operate synergistically to protect against oxidative damages [23]. While SOD catalyzes the conversion of superoxide radicals into oxygen and H_2O_2, catalase converts H_2O_2 into harmless water and oxygen, leading to the elimination of ROS and the resultant tissue damages [24, 25]. Therefore, the low serum and cardiac SOD activities with the corresponding high catalase and MDA levels, as observed in rats exposed to combined fructose and dexamethasone, may suggest that dexamethasone generated a biochemical imbalance and impaired the antioxidant system concurrently with the fructose consumption.

Diabetogenic effects: Our results that showed a rise in blood glucose following fructose treatment confirms the previous studies which reported that high fructose-intake induces diabetes in rodents' models [26, 27]. However, in contrast with a previous study that showed elevated blood glucose in dexamethasone-treated rats [28], the present study did not find an increase in FBG level following dexamethasone administration. Instead, dexamethasone slightly lowered the hyperglycemia induced by fructose. This suggests a potential therapeutic role for this drug in the management of hyperglycemia in humans.

Effects on xanthine oxidase and uric acid: In agreement with previous studies [15, 29], the present research found elevations of serum XO and UA levels in rats following exposure to fructose but not to dexamethasone. This indicates that over consumption of fructose may induce excessive UA synthesis. Both hyperglycemia and hyperuricemia are associated with the generation of oxidative stress [30, 31]. Therefore, the overall findings of this study may suggest that exposure to excessive fructose increases blood glucose and elevates serum UA, consequently generating oxidative stress and dyslipidemia. However, dexamethasone-induced oxidative stress was not associated with any change in serum UA. This may suggest that dexamethasone-induced oxidative stress is not dependent upon hyperuricemia. Therefore, the cause of oxidative stress in dexamethasone-treated rats still remains unclear and requires further investigation.

Conclusions

This study reveals that dexamethasone, though slightly reduced the hyperglycemia and hyperuricemia induced by fructose, it impairs antioxidant enzymes and escalates dyslipidemia during fructose intake in rats. The findings of this study further suggest that the administration of dexamethasone may potentially increase the risk of CVD in individuals with excessive consumption of fructose. Therefore, dexamethasone should be recommended cautiously in patients who are at high risk of CVD.

Ethical Considerations

Compliance with ethical guidelines

All animals used in this study were handled and kept in conformity with the guidelines of the Ethics Committee, University of Ilorin, Ilorin, Nigeria (Code #: UERC/ASN/2016/513) and in line with the recommendations of the U.S. National Institutes of Health guidelines on the care and use of laboratory animals.

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Authors' contributions

All authors equally contributed to preparing this article. All authors reviewed and approved the final manuscript prior to submission to this journal.

Conflict of interest

The authors declare no conflict of interests.

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