

Ameliorative Effects of Vitamin C and E on Serum Lipid Profiles and Liver Enzymes on Fructose induced hyperglycaemia in Wistar Rats

¹Tanko Y., ¹Eze E. D., ¹Daja H. S., Jimoh A., ¹Mohammed K. A. and ²K.Y. Musa

¹Department of Human Physiology, Faculty of Medicine, Ahmadu Bello University, Zaria, Nigeria.

²Department of Pharmacognosy and Drug development, Ahmadu Bello University, Zaria, Nigeria.

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ABSTRACT

The aim of this study is to determine the effect of vitamin C and E administration on serum lipid profiles and liver enzymes on fructose-induced diabetes on Wistar rats. Diabetes was induced by administration of 20% (20g/100ml) of fructose dissolved in distilled water for a period of six (6) weeks to the animals. After which the animals were randomly assigned into 4 groups of 6 rats each. Group 1 (control) administered distilled water, Group 2 administered vitamin C (100mg/kg b w), Group 3 administered vitamin E (100mg/kg b w) and Group 4 administered Metformin (250 mg/kg b w). The results obtained showed a statistical significant reduction ($p < 0.05$) in the level of serum total cholesterol and triglyceride in all groups administered vitamin C (100 mg/kg b w) and E (100 mg/kg b w) when compared to diabetic control group. However, the serum level of high density lipoprotein was significant increase in the group treated with vitamin E (100 mg/kg b w) when compared to diabetic control group. There was a significant decrease ($p < 0.05$) levels of all serum liver enzymes (AST, ALT and ALP) in the groups treated with Vitamin C and Metformin. However, serum AST there was no significant change in the group treated with vitamin E (100 mg/kg b w).

INTRODUCTION

Fructose a naturally found sugar in many fruit is now commonly used as industrial sweetener and is excessively consumed in western diets. High fructose intake is increasingly recognized as causative in development of pre-diabetes and metabolic syndrome (Bray *et al.*, 2004). The metabolic syndrome is a constellation of pathologies including obesity, insulin resistance, dislipidemia, and hypertension (Elliott *et al.*, 2002). In animal studies, consumption of diets high in fructose produces obesity, insulin resistance and dyslipidemia (Elliott *et al.*, 2002; Havel, 2005). Fructose induced dislipidemia also contributes to insulin resistance and glucose intolerance (Faeh *et al.*, 2005). Dyslipidemia is common in both insulin deficiency and insulin resistance which affects enzymes and pathways of lipid metabolism. It is a well recognized risk factor for cardiovascular diseases which is currently a leading cause of morbidity and mortality worldwide (Yach *et al.*, 2004). Abnormalities of lipids metabolism include elevated levels of triacylglycerols (TG),

total cholesterol, decreased high density lipoprotein cholesterol (HDL-C) and increased low density lipoprotein-cholesterol (LDLC), which are documented as risk factors for atherogenesis (Beckman *et al.*, 1980).

The liver plays a major role in the regulation of carbohydrate, lipids and protein metabolism, it also has the capability to store glucose as glycogen and synthesize glucose from non carbohydrate sources through the use of it hepatocellular enzymes (Lewis *et al.*, 1984). Increased activities of liver enzymes such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline Phosphatase (ALP) are indicators of hepatocellular injury, associated with insulin resistance (Marchesini *et al.*, 2001), metabolic syndrome, and type 2 diabetes (Nakanishi *et al.*, 2005; Wannamethee *et al.*, 2005). Vitamin C is a water-soluble vitamin that is found intra- and extracellularly as ascorbate (Chihuilaf *et al.*, 2002). It is a natural antioxidant that prevents the increased production of FRs induced by oxidative damage to lipids and lipoproteins in various cellular compartments and tissues (Sies *et al.*, 1992). It has been shown to react directly with superoxide (Hemila *et al.*, 1985), hydroxyl radicals (Bielski, 1982) and singlet oxygen (Bodannes and Chan, 1999).

* Corresponding Author

Department of Human Physiology, Faculty of Medicine,
Ahmadu Bello University, Zaria Nigeria.

Tel: +23437054274

It is generally regarded as a primary first-line protective agent that repairs or nullifies FRs by donating a single electron, followed by a proton to yield a chemically reduced non-radical product and ascorbyl radical. The ascorbyl radical dismutates to ascorbate and dehydroascorbic acid (Halliwell, 2001). Vitamin E, the principal lipid-soluble antioxidant (Chow, 2001). Vitamin E includes 8 naturally occurring forms, which can be divided into two families of compounds, the tocopherols and the tocotrienols; collectively known as tocopherols (Shekelle *et al.*, 2003). Specifically, vitamin E is able to extinguish single oxygen species as well as to terminate free radical chain reactions (Giugliano, 2000). Alpha-tocopherol acts as an antioxidant either by donating a hydrogen radical to remove the free lipid radical, reacting with it to form non-radical products, or simply trapping the lipid radical (Upston *et al.*, 1999). This protective activity of vitamin E depends on vitamin C to recycle oxidized vitamin E (Gey, 1998). The present study is aimed at investigating the ameliorative effect of vitamin C and E on serum lipid profile and liver enzymes in fructose-induced hyperglycaemic Wistar rats.

MATERIALS AND METHODS

Drugs used

Vitamin C and E were obtained from was obtained from a pharmaceutical store in Zaria. Each tablet of ascorbic acid (100 mg; Med Vit C® ,Dol-Med Laboratories Limited, Lagos, Nigeria was reconstituted to 100 mg/mL suspension, just prior to its daily administration while Vitamin E (100 mg/capsule) each capsule was aspirated into a syringe and then reconstituted with soya oil to 100% v/v prior to daily administration.

Animals

Twenty (24) healthy Wistar albino rats of both sexes between the ages of 10-12 weeks old and weighed between 150-200 g were used for the study. The animals were kept in well aerated laboratory cages in the Department of Human Physiology and were allowed to acclimatize to the laboratory environment for a period of one week before the study commenced. They were maintained on standard animal feeds and drinking water *ad libitum*. The Principle of laboratory animal care “ (NIH publication No 85- 23)” guideline and procedures were followed in this study (NIH publication reserved 1985).

Experimental induction of diabetes mellitus

D-Fructose (BDH, Poole, England) with a molecular weight of 180.16g was used for the study. Each rat, regardless of their weight was made diabetic by feeding them with 20% (20g/100ml) of fructose dissolved in distilled water for a period of six (6) weeks (Comte, *et al.*, 2004). Diabetes mellitus was confirmed by collecting fasting blood samples from the tail vein of the rats by using glucose oxidase method (Beach and Turner, 1958) using a digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany). Rats having fasting blood glucose level greater than 130 mg/dl were considered as diabetic.

Group 1: Diabetic control and received 1ml of distilled water

Group 2: Received 100mg/kg b w of Vitamin E

Group 3: Received 100mg/kg b w of Vitamin C

Group 4: Received 250mg/kg b w of Metformin

The administration was by oral gavage spanning for a period of two weeks.

Preparation of serum samples

After the last day of administration the animals were euthanized and blood samples were drawn from the heart of each by cardiac puncture into plain tubes and were allowed to clot and the serum separated by centrifugation using Denley BS400 centrifuge (England) at 3000 r p m for 15minutes and the serum collected and then subjected to biochemical assays.

Estimation of lipid profiles

Determination of serum total cholesterol

The serum level of total cholesterol was quantified after enzymatic hydrolysis and oxidation of the sample as described by method of Stein (1987). 1000µl of the reagent was added to each of the sample and standard. This was incubated for 10 minutes at 20-25 °C after mixing and the absorbance of the sample (A_{sample}) and standard (A_{standard}) was measured against the reagent blank within 30 minutes at 546nm. The value of TC present in serum was expressed in the unit of mg/dl.

Determination of serum triglyceride

The serum triglyceride level was determined after enzymatic hydrolysis of the sample with lipases as described by method of Tietz (1990). 1000µl of the reagent was added to each of the sample and standard. This was incubated for 10 minutes at 20-25 °C after mixing and the absorbance of the sample (A_{sample}) and standard (A_{standard}) was measured against the reagent blank within 30 minutes at 546nm. The value of triglyceride present in the serum was expressed in the unit of mg/dl.

Determination of serum high-density lipoprotein cholesterol

The serum level of HDL-C was measured by the method of Wacnic and Albers (1978). Low-density lipoproteins (LDL and VLDL) and chylomicron fractions in the sample were precipitated quantitatively by addition of phosphotungstic acid in the presence of magnesium ions. The mixture was allowed to stand for 10 minutes at room temperature and centrifuged for 10 minutes at 4000 rpm. The supernatant represented the HDL-C fraction. The cholesterol concentration in the HDL fraction, which remained in the supernatant, was determined. The value of HDL-C was expressed in the unit of mg/dl.

Determination of serum low-density lipoprotein cholesterol

The serum level of (LDL-C) was measured according to protocol of Friedewald *et al.*, (1972) using the relationship below:

$$\text{LDL-C} = \text{TC} - \text{TGL}/5 + \text{HDL-C}$$

The value was expressed in the unit of mg/dl.

Evaluation of serum liver enzymes

The serum enzymes Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), Alkaline phosphatase (ALP) were determined spectrophotometrically, using enzymatic colometric assay kits according to the laboratory procedures of Randox Laboratories Limited kits, United Kingdom, using Reitman and Frankel method (1957).

Statistical analysis

All the data are expressed as mean \pm SEM. Statistical comparisons were performed by one way analysis of variance (ANOVA) followed by Duncan's multiple range tests (Duncan *et al.*, 1977). The results were considered statistically significant if the *p* values were 0.05 or less. The data were analyzed using Sigma Stat v2.0 (Jandel Scientific, Palo Aho, CA, USA).

RESULTS

Effect of Vitamin C and E on mean \pm SEM serum liver enzymes on fructose-induced hyperglycemic wistar rats

Result obtained showed a statistical significant reduction ($p < 0.05$) in the level of serum total cholesterol and triglyceride in all groups administered with vitamin C (100 mg/kg b w) and E (100 mg/kg b w) when compared to diabetic control group. However, the serum level of high density lipoprotein was significantly elevated especially in vitamin E (100 mg/kg b w) treated group when compared to diabetic control group as shown in table 1.

Table 1: Effect of Vitamin C and E on mean \pm SEM serum lipid profile in fructose-induced hyperglycemic wistar rats.

Treatment Given	Serum total cholesterol (mmol/L)	Serum triglyceride (mmol/L)	Serum high density lipoprotein (mmol/L)
Diabetic control + distilled water	2.90 \pm 0.13	1.14 \pm 0.08	0.52 \pm 0.09
Vitamin C (100 mg/kg b w)	2.08 \pm 0.12 ^a	0.50 \pm 0.73 ^a	0.68 \pm 0.04 ^{ns}
Vitamin E (100mg/kg b w)	2.14 \pm 0.50 ^a	0.46 \pm 0.18 ^a	0.82 \pm 0.04 ^a
Metformin (250 mg/kg b w)	1.94 \pm 0.07 ^a	0.42 \pm 0.04 ^a	1.00 \pm 0.03 ^a

$P < 0.05$ is statistically significant when compared to the control group while ns= significant and ns = non significant.

Table 2: Effect of Vitamin C and E on mean \pm SEM serum liver enzymes in fructose-induced hyperglycemic wistar rats.

Treatment Given	Serum AST (U/L)	Serum ALT (U/L)	Serum ALP (U/L)
Diabetic control + distilled water	25.60 \pm 0.51	74.06 \pm 2.18	34.60 \pm 1.40
Vitamin C (100 mg/kg b w)	20.60 \pm 0.41 ^a	51.80 \pm 2.0 ^a	21.40 \pm 0.52 ^a
Vitamin E (100mg/kg b w)	22.20 \pm 0.58 ^{ns}	48.60 \pm 1.02 ^a	20.20 \pm 0.37 ^a
Metformin (250 mg/kg b w)	20.60 \pm 0.51 ^a	42.60 \pm 1.02 ^a	20.20 \pm 0.37 ^a

$P < 0.05$ is statistically significant when compared to the control group while ns= significant and ns = non significant.

Effect of Vitamin C and E on mean \pm SEM serum liver enzymes in fructose-induced hyperglycemic wistar rats

There was a significantly decreased ($p < 0.05$) levels of all serum liver enzymes (AST, ALT and ALP) in all groups administered with vitamin C and E. However, serum AST was not significant in the group administered with vitamin E (100 mg/kg b w) as shown in table 2.

DISCUSSION

The present study demonstrated the effects of vitamin C and E lipid profiles and liver enzymes in fructose-induced hyperglycemic rats. The present study sustained hyperglycemia was achieved in animals regardless of their weight by feeding them with 20% (20g/100ml) of fructose dissolved in distilled water for a period of six weeks (Comte, *et al.*, 2004). This finding in our current work agrees with the report of Ostos *et al.*, (2002) who demonstrated persistent hyperglycemia in rats with features similar those seen in patients with type 2 diabetes mellitus (DM) following ingestion of high doses of fructose over a prolonged period, hence its use in type 2- like DM induction in animals. In patients with diabetes, alteration in distribution of lipid increased risk of atherosclerosis. Specifically, insulin resistance and insulin deficiency have been identified as phenotype of dyslipidemia in diabetes mellitus (Taskinen, 2003; Krauss and Siri, 2004; Chahil and Ginsberg, 2006). This is usually characterized by high plasma triglyceride level, low HDL cholesterol level and increased level of small dense LDL-cholesterol (Mooradian, 2008). Our present study showed significant increased serum concentration of total cholesterol, triglyceride and decreased serum level of high density lipoprotein in animals fed with high doses of fructose when compared. The observations from the present study agree with those of Miller *et al.*, (1999) and Mohammed *et al.*, (2011) who reported that the fructose-fed rat model develops an insulin-resistance syndrome with a very similar metabolic profile to the human condition, including hypertriglyceridemia, and decreased HDL cholesterol. Plasma triglycerides (TG) have been reported to increase both in humans (Bantle *et al.*, 2000) and rodents (Huang *et al.*, 1997), following the ingestion of high doses of fructose. This may be due to stimulation of hepatic de novo lipogenesis (DNL) and increased secretion of triglyceride-rich particles by the liver or to decreased extra-hepatic clearance of triglyceride particles (Parks and Hellerstein, 2000; Pagliassotti and Horton, 2004). In addition low HDL cholesterol and increased triglyceride levels may contribute to the increased risk of cardiovascular disease (Salwa, 2010). How administration of vitamin C (100 mg/kg b w) and E (100 mg/kg b w) to fructose-induced animals resulted to a significantly decreased serum levels of these serum lipids. The liver plays an important role in many metabolic processes such as glycemic control, detoxification of xenobiotics, synthesis of lipoproteins, hormones and enzymes (Klip and Vranic, 2006). Liver enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase AST, and alkaline phosphatase

(ALP) are known marker enzymes for the assessment of the functional integrity of the liver cells (Adaramoye *et al.*, 2008). In diabetes mellitus, the liver is associated with abnormalities such as elevations in serum aspartate aminotransferase, alkaline phosphatase and alanine aminotransferase (Leeds *et al.*, 2009). The present research work recorded a significantly elevated level of serum liver enzymes in the fructose-induced untreated animals. Increase in the levels of these enzymes in diabetes may be as a result of leaking out of these enzymes from the tissue into the blood stream.

This is also coupled with the fact that liver tissues are grossly damaged during diabetes mellitus, Liver-alkaline phosphatase is usually mobilized most rapidly into blood and its levels in plasma may increase at early periods of liver damage (Eze *et al.*, 2012). In our present work there was a significantly decreased levels of serum liver enzymes (ALT and ALP) at all tested doses of vitamin C (100 mg/kg b w) and E (100 mg/kg b w). However, serum AST was not significantly changed in the group administered with vitamin E (100 mg/kg b w) when compared to control group. Available evidence suggests that the liver is susceptible to oxidative stress and damage; and the beneficial effect of antioxidants such as vitamin C and E on hepatic oxidative stress has been documented (Dias *et al.*, 2005; Gumieniczek, 2005). The findings from the present study agree with those of Ayo *et al.*, (2006), Chen *et al.* (2000), Frei (2004), and Ambali *et al.* (2007), who reported that vitamin C is an effective antioxidant in various biological systems. According to Odigie *et al.* (2007) and Idogun and Ajala (2005), both animal and human studies have shown that ascorbic acid is a potent antioxidant that mediates its antioxidant effect by scavenging reactive oxygen species. The foregoing indicates that, as an antioxidant agent, vitamin C may have inhibited the chain reactions of chemical agent-generated free radicals or scavenged the reactive free radicals. According to Maritz and Van Wyk (1997), vitamin E is known to be an effective antioxidant; it converts superoxide radicals, lipid peroxy radicals to less reactive form. This result suggests that vitamin C and E offer protection by preserving the structural integrity of hepatocellulars membrane against fructose-induced hepatic damage and also by scavenging reactive oxygen species.

CONCLUSION

It can be concluded that the observed significant reduced serum total cholesterol and triglyceride and elevated high density lipoprotein and also decreased serum liver enzymes recorded in fructose-induced insulin resistance in animals suggests that vitamin C and E ameliorated hyperlipidemia and hepatocellular damage associated with type 2 diabetes mellitus.

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