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Research Article

Cardiac and Renal Protective Effect of Vitamin E in Dexamethasone-Induced Oxidative Stressed Wistar Rats

Okon I.A.[1], Ufot U.F.[2], Beshel J.A.[1] and *Owu D.U.[1]

[1]Department of Physiology, College of Medical Sciences, University of Calabar, Calabar, Nigeria
[2]Department of Biological Sciences, Faculty of Natural and Applied Sciences, Akwa Ibom State University, Ikot Akpaden, Mkpat Enin L.G.A., Akwa Ibom State, Nigeria.

Summary: Vitamin E is a potent antioxidant used in the management of various ailments arising from oxidative stress. The cardiac and renal protective effect of vitamin E in dexamethasone (Dex)-induced oxidative stress was studied. Twenty four Wistar rats were randomly assigned to four groups of 6 rats each. Group 1 was the control that was administered normal saline placebo. Group 2 was the Dex-induced oxidative stress group (DEX; 30µg/kg b.w i.p). Group 3 was vitamin E group (300 IU/kg administered orally), and group 4 was the Dex (30µg/kg b.w i.p) + vitamin E (300 IU/kg administered orally) group. Administration lasted for 14 days. All animals were fed *ad libitum* with normal rat chow and drinking water. Blood samples were obtained by cardiac puncture and the serum concentrations of nitric oxide, bilirubin, superoxide dismutase, angiotensin converting enzyme and lactate dehydrogenase enzyme activities were analyzed. The heart and kidney were processed for hematoxylin and eosin histological staining. The results show a significant ($p<0.05$) decrease in serum nitric oxide, bilirubin and superoxide dismutase concentration in DEX-only group compared to the control, and were elevated following vitamin E treatment. The angiotensin converting enzyme and lactate dehydrogenase enzyme activities were significantly ($p<0.01$) reduced in DEX+Vit E group. Cardiac and renal histology in DEX-only group showed cardiac hypertrophy and renal injury compared to the control, which were ameliorated following vitamin E treatment. The results of this study suggest that vitamin E may exert ameliorative effects on oxidative stress-induced cardiac and renal impairment in Wistar rats.

Keywords*: Oxidative stress, Vitamin E, Antioxidant, Heart, Kidney.*

**Address for correspondence*: *danielowu@unical.edu.ng, Tel: +234 (0) 8093243446*

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INTRODUCTION

Oxidative stress is an abnormal condition characterized by transient increases in the concentration of reactive oxygen species leading to a disturbance in cellular metabolism, regulation and damage to cellular constituent (Dalle-Donne *et al*., 2016). Reactive oxygen species (ROS) are free radicals produced as a result of cellular metabolism and examples include the hydroxyl radical (OH), superoxide anion (O_2^-) and non-radical molecules such as hydrogen peroxide (H_2O_2) and singlet oxygen ($O_2^{\cdot}$). Proper regulation of ROS has a great impact on many physiological and pathological conditions. ROS level is seen to increase greatly during cell stress and its highly reactive nature can lead to changes in other oxygen species, lipids or proteins, a condition often known as oxidative stress (Bayr, 2005). Increased production or decreased scavenging of reactive oxygen species has been the major cause of diverse diseases such as atherosclerosis, myocardial infarction, hypertension, diabetes and cancer (Wiseman and Halliwell, 1996). Thus, maintaining a normal cellular concentration of ROS is important for proper physiological functions of different cell types in the body (Krötz *et al*., 2004). The various antioxidants present in the body are responsible for this function of reducing ROS in the living system such as vitamins A, C and E.

Evidence abound that abnormal production of ROS results in a cascade of cardiovascular disorders like hypertension, coronary heart disease, neurological disorders, and physiological ageing (Pacher and Szabo, 2008; Vassalle *et al*., 2008). ROS and free radicals also cause damage to biological membranes, modification of proteins, and deactivation of enzymes (Niki, 2010). Endothelial dysfunction is a principal concept of cardiovascular disease pathogenesis mediated by free radicals. It is responsible for the vascular tone regulation, inflammation, thrombosis, platelet activity, and atherosclerosis. The endothelial tone of the vasculature is a responsibility of substances like the endothelins, nitric oxide, endothelium-derived relaxation factor, and prostacyclins (Zorio *et al*., 2008) and is an underlying cause of rise in blood pressure.

Studies have also shown that in renovascular hypertension, essential hypertension, pre-eclampsia and malignant hypertension, there is increased ROS production (Higashi *et al*., 2002; Lip *et al*., 2002). Reactive oxygen species activities result in a direct cardiac injury due to oxidation of cellular constituents, diminishing nitric oxide bioactivity, and disruption of proteins critical for excitation-contraction coupling (Lubos *et al*., 2008).

A precursor of intracellular NOS, L-arginine, improves on the vascular endothelium and causes dilatation of blood vessels in patients with cardiac risk factors (Guoyao and Meininger, 2000). Superoxide dismutase supplementation improves on the endothelium and causes vasodilatation of coronary arteries. Calorie restrictions of superoxide dismutase for 3–12 months enhance cGMP formation and eNOS expression in mice (Nisoli *et al*., 2005).

Vitamin E is the term given to a group of tocotrienols and tocopherols which include alpha (α), delta (δ) and gamma (ϒ) tocopherols that is the most abundant and potent radical-scavenging in vivo antioxidant (Traber and Atkinson, 2007). Vitamin E is the major lipid-soluble component in the cell antioxidant defense system (Comitato *et al*., 2017). It has a role in antioxidant activity and it is derived from dietary component. The antioxidant property of Vitamin E is due to its ability to impede oxidative chain reactions and to scavenge lipid radicals thus, protecting the cardiovascular system from oxidative stress damage (Alshiek *et al*., 2017). Studies have shown that individuals who consume high amounts of vitamin E have decreased rates of chronic diseases like cardiovascular diseases (Rimm *et al*., 1993; Stamfer *et al*., 1993). The antioxidant property of Vitamin E is due to its ability to impede oxidative chain reactions and scavenge lipid radicals thus, protecting the cardiovascular system from oxidative stress damage (Alshiek *et al*., 2017).

Dexamethasone (DEX) is a member of glucocorticoid class of hormones that is strictly controlled for use due to its serious side effects that includes oxidative stress (You *et al*, 2009). Although used to treat inflammatory and autoimmune conditions, study conducted by Hasona *et al*, (2017) revealed that long-term use of dexamethasone reduced the antioxidant capacity of renal tissue and thereby leads to the formation of ROS. DEX suppresses endothelium-dependent vasodilatation of resistance arterioles by inhibiting endothelium nitric oxide synthethase (eNOS), a potent enzyme that helps in vasodilatation (Schafer *et al*, 2005). When eNOS is inhibited, there is vasoconstriction resulting in an increase in blood pressure. This study was designed to investigate cardiac and renal protective effects of vitamin E on dexamethasone-induced oxidative stress using rats as experimental model.

MATERIALS AND METHODS

Drugs and chemicals: Dexamethasone, vitamin E, chloroform and formalin were purchased from Sigma Aldrich (St. Louis, MO, USA). The angiotensin converting enzyme, nitric oxide, lactate dehydrogenase enzyme and bilirubin (ELISA) kits were purchased from Cayman Chemical Company, USA.

Experimental animal: Approval for the animal study was obtained from the Faculty of Basic Medical Sciences Animal Research Ethics Committee, University of Calabar (Approval No: 019PY20317). Twenty-four (24) healthy Wistar rats of both sexes weighing 180-250g were randomly assigned to four (4) groups of six rats each namely; group 1 - Normal Control (NC), group 2 - dexamethasone (DEX) only, group 3 - Vitamin E (Vit E) only and group 4 dexamethasone + Vitamin E (DEX+ Vit E), respectively. The rats were acclimatized for seven (7) days and housed in plastic cages in the animal room of the Faculty of Basic Medical Sciences, University of Calabar. The animals were kept at room temperature of 28±2ºC with a 12-hour light/dark cycle and were fed with normal rat chow and tap water *ad libitum.*

Induction of oxidative stress: Oxidative stress was induced following the method of Safaeian *et al* (2014) using dexamethasone (30µg/kg body weight). The drug was administered intraperitoneally daily for two (2) weeks.

Administration of vitamin E: Vitamin E was dissolved in 1 ml olive oil and administered orally using orogastric tube at a dose of 300 IU/kg body weight for two (2) weeks following the method of Safaeian *et al* (2014). It was administered concurrently with dexamethasone.

Collection of blood sample: All animals were euthanized under chloroform anaesthesia. The rats were then quickly dissected and blood was collected via cardiac puncture into plain sample bottles. The blood samples were allowed to stand for two hours and then centrifuged at 3000 g for ten minutes to obtain the serum. The serum was then collected and stored at - 20ºC for subsequent use for biochemical analysis.

Determination of cardiac and hypertension biomarkers: Biomarkers of hypertension namely nitric oxide (NO), bilirubin, angiotensin converting enzymes (ACE) and lactate dehydrogenase were determined as follows using appropriate methods. Measurement of nitric oxide was carried out by the method of Asl *et al.*, (2008) while serum bilirubin was determined using the method of Powel (1944). Angiotensin converting Enzyme (ACE) was

determined using ELISA kit following the method described by Syed *et al*., (2016) while lactate dehydrogenase was determined following the method of Sobel and Shell (1972).

Histopathological analysis: The hearts and the kidneys were rapidly dissected and fixed in 10% buffered formalin. The tissues were processed following the method of Mohammed and Ismail (2017). Briefly, the tissues were embedded in paraffin, sectioned at 5µm and stained with Haematoxylin and Eosin (H&E). The sections were examined under the light microscope (Zeiss, Germany) and the photomicrographs were captured using digital camera (Sony, Japan) attached to the microscope and connected to a personal computer (iCore 5, 4,00 MB RAM) at x400 magnification.

Determination of body weight

Total body weight of all the rats in each group was measured using a digital weighing balance each day before and after the experimental period with recordings taken as initial and final body weight respectively. The mean body weight was measured for each group from the total body weight and analyzed appropriately.

Statistical Analysis

Results were expressed as mean ± standard error of mean (SEM). Data obtained were analysed using one-way analysis of Variance (ANOVA) followed by Tukey's post hoc test using Graphpad prism software version 5.5 for Windows (Graphpad Software, San Diego, California, USA). For all statistical analysis, results were considered significant at $p<0.05$.

RESULTS

Serum nitric oxide concentration

The result for the normal control group (NC) was 133±1.3 nmol/L. It was 122±0.9 nmol/L in DEX only group and 138±0.4 nmol/L in Vit E group (Table 1). Administration of Vit E significantly ($P<0.01$) increased serum nitric oxide concentration from 122±0.9 nmol/L in dexamethasone-induced oxidative stress group to 134±0.5 nmol/L in DEX+Vit E group. However, serum level of NO in normal rats administered Vit E (138±0.4 nmol/L) was significantly ($p<0.01$) raised when compared to normal control (133±1.3 nmol/L) (Table 1). There was no significant difference between the control compared with DEX+Vit E group.

Serum angiotensin converting enzymes (ACE) activity: The result for serum angiotensin converting enzyme activity in the control group was 17.5±0.5 ng/ml, 24.3±0.1 ng/ml in DEX only group and 18.6±0.6 ng/ml in Vit E only group (Table 1). Administration of Vit E to DEX-induced oxidative stress rats significantly ($P<0.01$) reduced serum ACE activity to 21.0±0.4 ng/ml when compared with DEX only group, reversing the values towards the normal control group. The ACE activity in DEX+Vit E group was significantly ($p<0.05$) compared with control.

Serum total bilirubin level: The serum total bilirubin concentration in the control, Dex only, Vitamin E only, and Dex + Vitamin E groups was 3.20 ± 0.2µmol/L, 2.58 ± 0.1µmol/L,7.35 ± 0.1µmol/L, and 4.40 ± 0.1 µmol/L respectively. The result showed a significant ($p<0.01$) decrease concentration of bilirubin in the Dex only group compared to the control. The concentration was however significantly ($p<0.01$) increased after treatment with vitamin E. Vitamin E only group resulted in a significant ($p<0.01$) increase bilirubin concentration compared to both the control and Dex + vitamin E groups. This is presented in Table 1.

Serum level of lactate dehydrogenase enzyme (LDH): Administration of DEX to rats resulted in a significant ($P<0.01$) elevation (1315 ± 2.9IU/L) of LDH activity compared with control (347 ± 8.2IU/L) and Vitamin E only (397 ± 3.8IU/L) groups. In the Dex + Vitamin E group, LDH activity was significantly ($p<0.01$) decreased (846 ± 1.89IU/L) compared with the Dex only group, but still higher than the control and Vitamin E only groups (Table 1).

Table 1:
Serum levels of biomarkers of cardiac function and oxidative stress in dexamethasone-induced oxidative stressed rats treated with vitamin E

Parameter	Control	DEX only	Vit E only	DEX+Vit E
NO (nmol/L)	133±1.3	122±0.9**	138±0.4^{*a}	134±0.5^{b}
ACE (ng/ml)	17.5±0.5	24.3±0.4**	18.6±0.6	21.0±0.4^{a,c}
Bilirubin (µmol/L)	3.20±0.2	2.58±0.1	7.35±0.1**	4.40±0.1^{a}
LDH (IU/L)	347±8.2	1315±2.9**	397±3.8a	846±1.89^{*b}
SOD (U/ml)	4.7±0.6	0.91±0.7**	8.8±0.8^{a}	5.7±0.7^{ab}
MDA(nmol/L)	0.27±0.01	0.59±0.02**	0.32±0.01	0.42±0.02^{ab}

*** = P< 0.01 compared with control; a = p<0.01 compared with DEX only; b= p<0.01 compared with vitamin E; c=p<0.05 compared with control group; n = 6.*

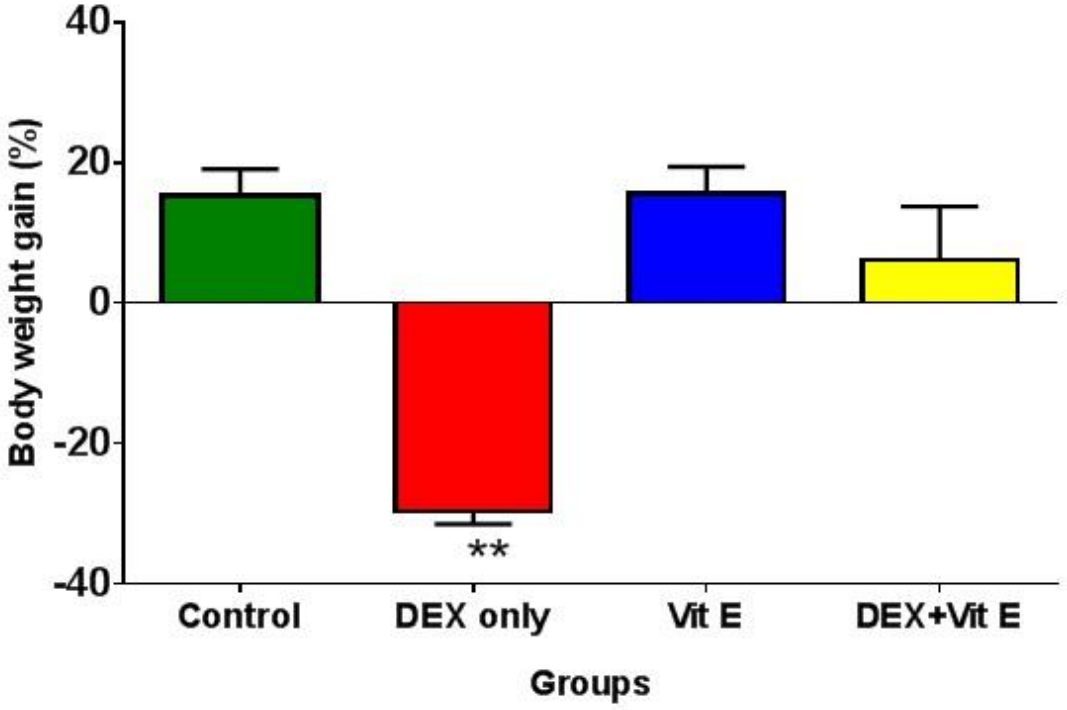

Figure 1:
Body weight gain in dexamethasone-induced oxidative rats treated with vitamin E.
*** = p<0.01 compared with other groups. N=6*

Serum superoxide dismutase (SOD) activity: A significant (p<0.01) reduction of SOD activity in DEX only group was observed compared with the normal control group. Administration of Vit E to DEX-induced oxidative stress rats significantly (P<0.01) increased serum superoxide dismutase activity compared with DEX only group and normal control group. Vitamin E administration also resulted in a significant (p<0.05) increase in SOD activity when compared with DEX only and control groups (Table 1).

Serum malondialdehyde (MDA) level: MDA level is a biomarker of oxidative stress. The result for normal control group as presented in table 1 was 0.27±0.01nmol/L. It was 0.59±0.02nmol/L in DEX only group and 0.32±0.01nmol/L in Vit E only group. Administration of Vit E to DEX-induced oxidative stress rats significantly (P<0.05) reduced serum MDA level to 0.42±0.02nmol/L. No significant difference was observed in Vit E only group (0.32±0.01nmol/L) when compared to the normal control group (0.27±0.01nmol/L). However, serum MDA level increased significantly (P<0.01) in DEX only group (0.59±0.02 nmol/L) when compared with other groups.

Body weight changes: The body weights of the experimental animals were similar at the start of the experiment. At the end of experiment, the body weight in the DEX-induced group (102±6 g) was significantly (P<0.01) reduced when compared with the control group (180±15 g). The body weights in Vit E (180±9 g) group increased significantly (P<0.01) when compared to the DEX-induced group. There was no significant difference in body weight between control and Vit E only groups. Treatment of DEX-induced oxidative groups with vitamin E (163±1 g) led to a significant (p<0.01) increase in body weight when compared with DEX only group.

The result for body weight gain within each group is presented in figure 1. There was a weight gain of 15.3±3.8% in the normal control and 15.5±3.9% in Vit E only group. There was weight loss of 29.7± 1.9% in DEX-induced oxidative group while Vit E treatment in resulted in body weight gain of 6.08±7.7%. The results showed a significant (p<0.01) decrease in body weight gain in the DEX-induced oxidative stressed rats compared to all other groups.

Histological analysis of cardiac muscles: Section of cardiac muscle from the control group showed intersecting bundles of striated muscle fibres running parallel with interdigitation. The individual cardiac myocytes had prominent nuclei with moderate amount of cytoplasm. The separating fibrocollagenous stroma is sparse and contains thin walled blood vessels. The photomicrograph for the normal control group is shown in Fig. 2A.

Section of cardiac muscle in DEX-induced oxidative stress rats showed intersecting bundles of striated muscle fibres running parallel with interdigitation with hypertrophied and widely separated cardiac cells. The cells were plumped with abundant cytoplasm and enlarged nuclei with clumped chromatin pattern. The separating fibrocollagenous stroma showed scanty and thin walled dilated blood vessels (Fig. 2B).

Section of cardiac muscle from Vit E only group showed intersecting bundles of striated muscle fibres running parallel with interdigitation. The individual muscle fibres were stretched out with moderate amounts of cytoplasm and abundant fibrocollagenous stroma within which were congested blood vessels. The cells had enlarged nuclei and clumped chromatin pattern (Fig. 2C).

In DEX +Vit E treated group (figure 2D), section of cardiac muscle showed intersecting bundles of striated muscle fibres running parallel with interdigitation. The fibres showed moderate cardiac hypertrophy with separated thinned fibrocollagenous stroma within which were congested blood vessels. The cells were plumped with abundant cytoplasm and enlarged nuclei having clumped chromatin pattern. The separating fibrocollagenous stroma were scanty and contained thin walled dilated blood vessels

Histological analysis of the kidney: Section of the kidney in control group showed prominent glomeruli and renal tubules. The glomeruli consisted of empty Bowman space surrounding the cellular mesangium comprising of the mesangial cells and arterioles. The renal tubules were lined by tall cuboidal to columnar cells. The intervening interstitium was scanty and contained thin walled blood vessels (figure 3A).

In DEX-induced oxidative stressed group, the section of the kidney showed glomeruli and renal tubules that had empty Bowman spaces surrounding the hypocellular mesangium. The mesangial cells were sparsely populated and atrophic and characterized by arteriolar haemorrhage. The intervening interstitium was scanty and with congested blood vessels suggesting glomerular injury (figure 3B).

In the Vit E only group, the section of the kidney shows glomeruli and renal tubules that were mildly swollen and had empty Bowman spaces surrounding a cellular mesangium. The mesangial cells were also sparsely populated. The renal tubules were preserved but closely packed with empty lumen and their lining epithelium were cuboidal to columnar. The photomicrograph for vitamin E only group is shown in figure 3C.

In the DEX+Vit E group, section of the kidney showed glomeruli and renal tubules. The Glomeruli consisted of an empty Bowman's space surrounding the cellular mesangium. The mesangial cells were prominent. The renal tubules were also preserved but closely packed with empty lumen. The intervening interstitium was scanty and contained thin walled congested blood vessels. The photomicrograph for DEX+ Vit E group is shown in figure 3D.

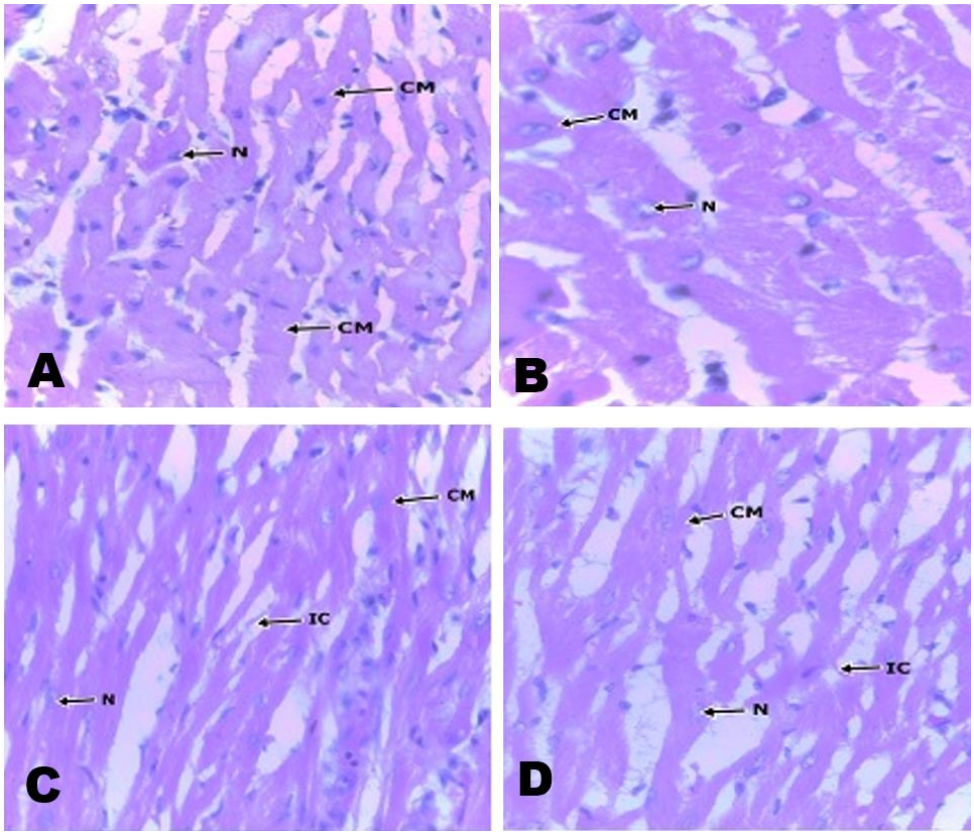

Figure 2: Representative photomicrograph of the cardiac muscles in control and dexamethasone-induced oxidative stress rats in rats treated with vitamin E.
A= Control;
B= DEX only;
C= VIT E group;
D= DEX +Vit E;
CM = cardiac muscle; N = nucleus; IC = intracellular capsule;
H & E stain (X400)

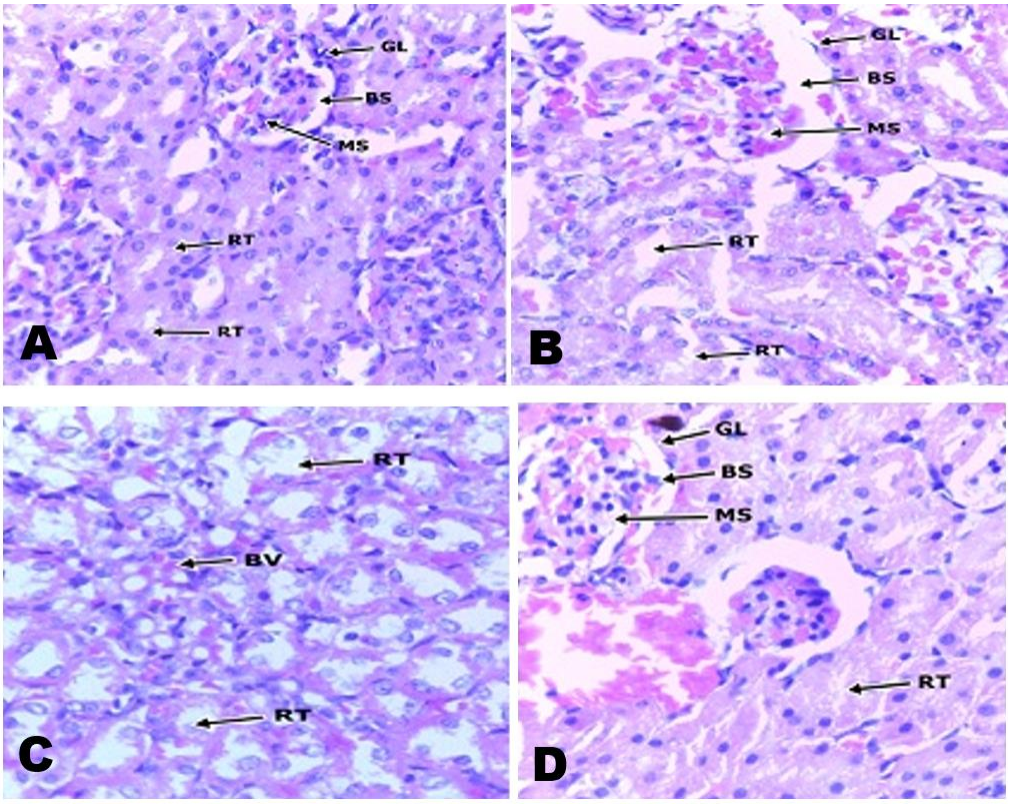

Figure 3: Representative photomicrograph of the kidney in control and dexamethasone-induced oxidative stress rats in rats treated with vitamin E.
A= control;
B= DEX only;
C= VIT E group;
D= DEX +Vit E;
BS= Bowman's space;
RT= Renal tubule;
BV= Blood vessel;
GL= Glomerulus;
MS= Mesengium
H & E stain (X400)

DISCUSSION

This study was aimed at investigating the cardiac and renal protective effects of Vitamin E in dexamethasone-induced oxidative stressed rats. Dexamethasone resulted in oxidative stress and lipid peroxidation of tissues. This is evident in the reduction of the serum concentration of superoxide dismutase (SOD) and elevation in the concentration of malondialdehyde (MDA). The result agrees with previous studies where dexamethasone was used to induce oxidative stress (Bjelavonic *et al*., 2007; Feng and Tang, 2014). The oxidative stress caused by dexamethasone resulted in a reduction in the serum concentrations of nitric oxide and bilirubin, and caused increase in the concentrations of angiotensin converting enzyme and lactate dehydrogenase. However, treatment with vitamin E reversed the effects of dexamethasone tending towards normal.

Increased reactive oxygen species (ROS) production has been reported to reduce the bioavailability of nitric oxide (NO) in addition to the formation of peroxynitrite (Montezano, and Touyz, 2012). Peroxynitrite uncouples the endothelial nitric oxide (NO) synthase to form a harmful superoxide generating enzymes which in turn contributes to vascular damage. Nitric oxide is a vasodilator produced by an enzyme, endothelium nitric oxide synthetase (ENOS) in the endothelium and in the brain by inducible nitric oxide synthatase (INOS) (Alp and Channon, 2004). Inactivation or reduction in NO synthesis is one of the risk factors for cardiovascular diseases including hypertension (Forsterman, 2010). The group treated with vitamin E showed a significant increase in NO concentration when compared to oxidative stress-induced group. This suppression of free radicals by vitamin E could possibly act to reduce the adverse effect of ROS that has vasoconstrictive effects due to a decrease in NO concentration (Tsao, 2010). Vitamin E probably caused a reduction in oxidative stress via its antioxidant activity.

Angiotensin converting enzymes (ACE) is present as a membrane-bound enzyme in endothelial cells other cells of the body. It catalyzes the conversion of Angiotensin I to angiotensin II, a potent vasoconstrictor that raises blood pressure (Skidgel and Erdos, 1993). Activation and increased level of angiotensin converting enzymes (ACE) occurs during stress conditions such as hypertension and myocardial infarction (Barreto-Chaves *et al*., 2000). The results from this study show that there was a significant increase in the ACE activity of rats induced with oxidative stress. Vitamin E administration to oxidative stress group led to a significant decrease in ACE activity. The observed decrease in ACE level suggests the beneficial action of vitamin E in reducing or inhibiting the angiotensin system (RAS) pathway thus reducing the adverse effect of oxidative stress. A study has shown that inhibition of ACE enhances vascular health (Bakris, 2001).

In humans and other mammals, increased serum total bilirubin levels have been reported to decrease the risk of coronary artery disease and atherosclerosis (Montezano and Touyz, 2014). As a risk factor in

arterial hypertension, bilirubin has an inverse relation in hypertension since high level of serum bilirubin decreases blood pressure (Huang *et al*, 2016; Xu *et al* 2017). Bilirubin is also one of the non-enzymatic antioxidant, and function as a chain breaking antioxidant (Stocker *et al*., 1987).

The results showed increased level of serum total bilirubin in rats that were given vitamin E only and in rats treated with vitamin E after inducing oxidative stress. Increased bilirubin level in Vitamin E administration could possibly be attributed to the enhanced activity of haeme oxygenase, a rate limiting enzyme that aids in converting biliverdin to bilirubin. Degradation of heme may mediate beneficial effect such as anti- inflammatory and antioxidant properties. Heme oxygenase mediates antioxidant and anti-inflammatory beneficial effects and has been reported to reduce blood pressure (Biyani *et al*., 2016). Thus, increase bilirubin level reflect an increase in antioxidant activity of vitamin E.

Lactate dehydrogenase is an enzyme found in almost all living cells and it is produced mostly by cardiac and skeletal muscles (Vettor *et al*., 1997). LDH is a marker of myocardial infarction and hypertension (Hu *et al*., 2015). Lipid peroxidation during oxidative stress disrupts cell integrity leading to an increase level of LDH activity (Jovanovic *et al*., 2010). The observed decrease in LDH activity due to vitamin E administration could be due to reduction in oxidative damage. Vitamin E has been shown to reduce LDH activity in oxidative stress induced by various conditions (Ilavazhagan *et al.,* 2001; Pashkow, 2011).

Superoxide dismutase (SOD) is an important endogenous enzyme that exists in several forms and act as a first line of defense system against ROS (Fukai and Ushio-Fukai, 2011). Several studies have revealed a reduction in the activity of SOD in hypertensive patients and in experimental models of oxidative stress (Lassègue and Griendling, 2004; Sousa *et al*., 2008). The significant increase in SOD activity in oxidative stress group treated with vitamin E and vitamin E-only group shows the protective effect of vitamin E against oxidative injury. It has been reported that vitamin E protects cellular membrane from lipid peroxidation and thus reduces oxidative stress caused by ROS (Urso and Clarkson, 2003). Dietary supplementation with antioxidant vitamins such as vitamin C and E has been reported to increase antioxidant enzymes activity (Day and Lal, 2012).

Malondialdehyde (MDA) is one of the end products of oxidative reactions in biological tissues and fluids and is used as a biomarker of oxidative stress (Todorova *et al*, 2005). Increased MDA levels indicates a high rate of lipid peroxidation (Huszar and Vigue, 1994). The significant increase in MDA level in dexamethasone treated rats reflects oxidative stress induced by dexamethasone. Vitamin E administration resulted in a low level of MDA in DEX+VitE suggesting a decrease in lipid peroxidation. A study has shown that vitamin E administration reduces lipid peroxidation by inhibiting various steps in lipid peroxidation (Krajčovičová-Kudláčková *et al*., 2004).

There was a decrease in body weight caused by dexamethasone administration. This finding is in agreement with a previous study that reported body weight loss in rats due to dexamethasone treatment (Amar *et al*, 2013). This body weight loss could be attributed to its inhibitory effect on the appetite centre. It has been reported that dexamethasone down-regulates the hypothalamic appetite centre through the release of neurotransmitters, insulin signaling and neuropeptides leading to a reduction in food intake and ultimate body weight loss (Chruvattil *et al*., 2016). An increased body weight was observed in the groups of animals treated with vitamin E showing the beneficial effect of vitamin E in improving body weight. Studies have reported that vitamin E enhances body weight due to its protective role on the cell membrane and slowing down body metabolism and lipolysis (Azman *et al*., 2001; Shvedova *et al.,* 2007).

Histological analysis on the structural integrity of the cardiac muscle in dexamethasone-induced oxidative stress group showed cardiac injury and hypertrophy. An earlier study has shown that administration of graded doses of dexamethasone causes lesions in the kidney and marked necrosis of the cardiac fibers and cytoplasmic fatty vacuolation (Ahmed and Masoud, 2014). In the vitamin E treated group, there was minimal hypertrophy revealing the cardio-protective property of vitamin E. The hypertrophied cardiac muscle in dexamethasone-induced oxidative stress group may be due to stress, pressure load and damage of the blood vessels caused by increased ROS. Prolonged used of dexamethasone causes cardiac hypertrophy and remodeling (de Vries *et al.,* 2002). Vitamin E reversed the damage of cardiac muscle as evidenced by minimal myocyte loss and mild glomerular injury seen in DEX+Vit E group. This result shows the ability of vitamin E in reducing ROS that may cause oxidative damage to tissues.

In summary, the results of this study have shown that dexamethasone adversely altered biomarkers of hypertension and caused cardiac and renal injury. Vitamin E significantly reduced angiotensin converting enzymes, lactate dehydrogenase and total serum bilirubin level in oxidative stress model, while it increased nitric oxide concentration significantly. Oxidative stress markers such as superoxide dismutase level increased significantly in vitamin E treated groups, while malondialdehyde concentration was reduced significantly in the treated group. In conclusion, vitamin E ameliorates dexamethasone-induced oxidative stress and protects the cardiac and renal tissues against oxidative injury.

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