



Relationship between Vitamin D Status, Dyslipaemia and Antioxidant Status in Children with Idiopathic Nephrotic Syndrome in South West, Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJOCS/2021/v10i419107

Editor(s):

(1) Dr. SungCheal Moon, Korea Institute of Materials Science, Republic of Korea.

Reviewers:

(1) Yavuz Ayar, Bursa City Hospital, Turkey.

(2) Shatha Hussain Ali, Al-Nahrain University, Iraq.

Complete Peer review History, details of the editor(s), Reviewers and additional Reviewers are available here:

<https://www.sdiarticle5.com/review-history/80376>

Original Research Article

Received 09 October 2021
Accepted 18 December 2021
Published 19 December 2021

ABSTRACT

Dysregulated lipid metabolism and oxidative stress are strong factors that are implicated in the development of proteinuria and glomerular injury in Nephrotic Syndrome (NS). Vitamin D seems to be a promising tool in influencing lipid metabolism and antioxidant status in NS.

Aim: This study aims at investigating the relationship between Vitamin D, dyslipaemia and oxidative stress in NS.

Study Design: This is a case-control study.

Place and Duration of Study: Children's Outpatient Clinic (CHOP) of University College Hospital (UCH) Ibadan, Nigeria between year 2019-2021.

Methods: This study involves fifty children aged 5 to 12 years, freshly diagnosed with Idiopathic NS and fifty apparently healthy children as control. Blood samples were taken from them and analytes quantified by standard laboratory methods. Students' t test and Pearson correlation were used to compare variables between the two groups respectively.

Results: Results showed significant decrease ($P < .001$) in Vit. D levels, GPX, SOD and CAT in NS. A significant decrease ($P < .001$) occurred in HDL, a significant increase ($P < .001$) in TG, TC and LDL levels in children with NS when compared with the control. There was a strong significant positive relationship between Catalase and Vit. D, SOD and Vit. D ($r = 0.896, 0.869$ respectively, $P < .001$) in NS. While a weak non significant positive relationship occurred between HDL and Vit. D, GPX and Vit D ($r = 0.0585, 0.0236$ respectively, $P > .001$). A weak negative relationship occurred between TG and Vit. D, TC and Vit. D, LDL and Vit. D ($r = -0.0432, -0.219, -0.231$ respectively, $P > .001$), in NS. Thus, vitamin D insufficiency influences serum lipid profiles and antioxidants in paediatric Idiopathic NS.

Keywords: Idiopathic nephrotic syndrome; antioxidants; glomerular injury; lipid profile; proteinuria.

1. INTRODUCTION

Nephrotic syndrome (NS) is a disorder of the kidneys that results from increased permeability of the glomerular filtration barrier. It is characterized by proteinuria, edema, hypoalbuminaemia, and hyperlipidaemia [1]. Nephrotic syndrome can affect children of any age, from infancy to adolescence, and is most commonly seen among school-aged children and adolescents [2]. The prevalence worldwide is approximately 16 cases per 100,000 children with an incidence of 2 to 7 per 100,000 children [3]. Idiopathic nephrotic syndrome (INS) is the most common form of this condition in children. Most children with INS have minimal glomerular lesions on histological examination of the renal biopsy. Less frequently, the other two characteristic lesions of INS are observed: hypercellularity or diffuse mesangial proliferation and focal and segmental glomerulosclerosis (FSGS). Approximately 80-90% of children with INS respond to treatment with corticosteroids [4]. Therefore, it is classified as steroid-sensitive INS [5]. Nephrotic range proteinuria is present if early morning urine protein is 3+/4+ (on dipstick test), spot protein/creatinine ratio $>2\text{mg/mg}$ or $>200\text{mg/mmol}$ urine albumin excretion $>40\text{mg/m}^2$ per hour [5]. The pathogenesis of idiopathic NS is thought to involve immune dysregulation, or inherited structural abnormalities of the podocyte [6]. NS is classified as idiopathic when it is due to primary glomerulopathies or may be secondary to various disorders. Precise quantitative measurement is done via 24 hour urine protein measurement [7]. Patients with nephrotic syndrome are at risk for the development of a variety of complications, which include thrombosis, infections, dyslipaemia and renal dysfunction.

Dysregulated lipid metabolism is an often under-recognized complication of persistent nephrotic syndrome. Although increased serum levels of

cholesterol and triglycerides have been noted since the early descriptions of nephrotic syndrome, information on the long-term consequences of prolonged dyslipaemia in nephrotic syndrome has not been established. However, hyperlipidaemia has been associated with an increased risk of both accelerated cardiovascular disease and progressive kidney disease, and persistent nephrotic syndrome is characteristically accompanied by moderate to severe hyperlipidaemia [8].

The extent of altered lipid metabolism in nephrotic syndrome correlates with the magnitude of proteinuria [9]. Proteinuria in nephrotic syndrome is associated with an increased risk of nephrotoxicity, which often result in progressive kidney disease [9]. The production of free radicals can cause renal injury and play an important role in the pathogenesis of idiopathic nephrotic syndrome [10]. Free radicals are extremely reactive compounds that interact with lipids, proteins, and nucleic acids. The kidney physiologically generates a small amount of reactive oxygen species (ROS) as part of oxidative metabolism, which is well tolerated. If generated in larger amounts locally, ROS may conceivably cause or contribute to the damage of glomerular structures, leading to altered glomerular permselectivity [11]. A study reported increased plasma levels of malonyldialdehyde and nitrite in acute nephrotic syndrome which resulted to increased lipid and protein peroxidation. Also, increased urinary excretion of urinary 8-hydroxydeoxyguanosine (8-OH-DG) as observed by [12] reflects the interaction of ROS with cellular DNA [12]. Hence, their finding nicely complements the concept of an imbalance of ROS induction and impaired antioxidant mechanisms in acute nephrotic syndrome [13, 14].

Vitamin D is a prohormone important for calcium and phosphate metabolism. It has been found

that vitamin D receptors exist in a variety of cells thus its biological effect exceed that of mineral metabolism. Recent reports have found that hypo 25-hydroxyvitamin D is associated with atherosclerosis [15], obesity [16], diabetes [17], hypertension [18], preeclampsia [19], myocardial infarction [20], and stroke [21] and might also be implicated in the pathogenesis of NS. Infact, Vitamin D has proved to be an important tool in the management and treatment of numerous disease condition. However, research are few and adequate information sparse on the role of Vitamin D in NS. Thus, this present study aim to investigate the relationship between vitamin D, antioxidant status, and lipid profile in children with Idiopathic Nephrotic syndrome.

2. MATERIALS AND METHODS

2.1 Subjects

Subjects were recruited from South East 2 children's ward and Children's Outpatient Clinic(CHOP) in University College Hospital (UCH) Ibadan, Nigeria. They were children between the ages of 5-12 years with freshly diagnosed Idiopathic Nephrotic Syndrome.

2.1.1 Study design

This is an observational case-control study. Participants considered to have Idiopathic Nephrotic Syndrome were subjects with heavy proteinuria, greater than 200mg/mmol in a 24 hour collection of urine, or dipstick result of 2+ or greater. Also they had hypoalbuminaemia of albumin levels less than 25g/l, with significant edema. Blood pressure, weight, height were measured and body mass index calculated in all groups.

2.1.2 Grouping

Hundred participants were recruited for this study, and grouped into;

Group A- 50 apparently normal children without Nephrotic Syndrome

Group B- 50 children with freshly diagnosed Idiopathic Nephrotic Syndrome

2.1.3 Sample collection

Blood samples were taken from each subjects after the informed consent forms were duly signed. Fifteen (15) milliliters of venous blood

was collected from each participants after issuing them the informed consent form. The blood was dispensed into EDTA bottle, centrifuged and plasma separated for analysis. Samples were stored at 4°C prior analysis.

2.2 Statistical Analysis

Data obtained from this study was subjected to statistical analysis using SPSS version 17.0. The results obtained were grouped and expressed as mean \pm Standard Error(SE). Students' t test was used to compare variables between the two groups. Pearson correlation was used to determine the relationship between the groups. Significant difference set at $P < 0.001$.

2.3 Biochemical Assessments

The biochemical assessments were analyzed using the following methods.

Vitamin D by Enzyme Linked Immunosorbent Assay as described by Holick [22].

Serum vitamin D status was defined as (in ng/ml): deficient (< 10 ng/ml), Insufficient (10ng/ml-30ng/ml), Sufficient(30ng/ml-100ng/ml), according to Calbiotech Inc.25(OH)Vitamin D Elisa kit used for this analysis.

Estimation of Plasma Cholesterol: Plasma Total cholesterol was analysed by the cholesterol CHOD-PAP method which is an enzymatic end point method [23].

Estimation of Serum HD-LC: HDL in the sample was quantified by enzymatic method [24].

Estimation of Serum Triglycerides: GPO-PAP method of Randox diagnostic kit [25].

Calculation of LDL-C in serum was obtained using Friedwald's formula [26], namely,

$$\text{LDL- cholesterol (mg/dl)} = \text{TC} - (\text{TG}/5 + \text{HDL})$$

Serum Glutathione activity was estimated by Colorimetric method as described by Wendel et al. [27].

Superoxide Dismutase (SOD) was evaluated by spectrophotometric method as described by Kuthan et al. [28].

Serum Catalase was assessed by using colorimetric method as described by Sinha et al. [29].

3. RESULTS AND DISCUSSION

($p < 0.001$) in TG, TC and LDL in children with NS when compared with the control.

The mean age, systolic blood pressure (SBP) and diastolic blood pressure (DBP) of the children with INS and Healthy Children without NS were not statistically different ($P > 0.001$), while the weight of children with NS when compared with the Children with INS was significantly higher ($P < 0.001$) than children without INS.

A statistically significant decrease ($P < 0.001$) occurred in Vit. D levels in children with NS when compared with the control. A statistically significant decrease ($P < 0.001$) occurred in HDL levels in children with NS when compared with the control, while there was a significant increase

There was a strong significant positive relationship between Catalase Vs Vit. D, SOD Vs Vit. D in NS. Also, a weak nonsignificant positive relationship occurred between HDL Vs Vit. D and also GPX Vs Vit. D. A weak non significant negative relationship occurred between TG Vs Vit. D, TC Vs Vit. D and LDL Vs Vit. D.

Table 1. Anthropometric Indices of Children with INS and Children without INS

Parameters	NS	Control	P-value
Age(yrs)	7.94±0.71	8.611±0.81	0.011
Weight(Kg)	27.61±0.45	24.42±0.66	.001***
SBP(mmHg)	112.9±0.78	110±0.92	0.034
DBP (mmHg)	86.3±3.24	90.2±1.22	0.006

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure

Table 2. Serum levels of vitamin d and lipids in children with INS and children without INS

Parameters	NS	Control	P-value
Vit. D (ng/ml)	26.44 ± 1.464	51.67 ± 1.76	.001***
TG (mg/dl)	230.3±11.43	77.81±8.3	.001***
TC (mg/dl)	386.29±18.5	156.36±5.3	.001***
LDL (mg/dl)	244.69±17.7	59.64±3.85	.001***
HDL (mg/dl)	36.90±4.4	61.34±2.9	.001***

TG: Triglyceride, TC: Total Cholesterol, LDL: Low Density Lipoproteins, HDL :High Density Lipoprotein

Table 3. Serum Levels of Antioxidants in children with INS and Children without INS

Parameters	NS	Control	P-value
CAT (µmol/ml)	69.75±6.09	172.79±3.2	.001***
SOD (µmol/ml)	43.43±1.58	103.44±1.5	.001***
GPX (IU/gHB)	74.04±1.89	126.89±0.25	.001***

CAT: Catalase, SOD: Superoxide Dismutase, GPX: Glutathione Peroxidase

Table 4. Pearson correlation between vitamin D, lipid profile and antioxidants in children with INS and children without INS

Parameters	r	P-value
Vit. D vs TG	-0.04328	.837
Vit. D vs TC	-0.219	.292
Vit. D vs HDL	0.0585	.781
Vit. D vs LDL	-0.2312	.266
Vit. D vs CAT	0.8961	.001***
Vit. D vs SOD	0.8693	.001***
Vit. D vs GPX	0.02365	.910

TG: Triglyceride, TC: Total Cholesterol, LDL: Low Density Lipoproteins, HDL :High Density Lipoprotein; CAT: Catalase, SOD: Superoxide Dismutase, GPX: Glutathione Peroxidase

3.1 Discussion

The results of this present study shows that the weight of INS children was higher than healthy control as seen in Table 1, which is in accordance with the work of [30,31]. The weight gain in INS children is often associated with characteristic dominant feature of NS : edema. Edema is a swelling that is caused by fluid trapped in the body's tissues, this happens most often in the feet, ankles, and legs, but can affect other parts of the body, such as the face, hands, and abdomen. Based on disease severity, patients may have edema that extends to the proximal lower extremities, lower abdomen, or genitalia [31,32]. There are proposed mechanisms related to the pathogenesis of nephrotic edema. The urinary loss of albumin due to increased glomerular permeability to albumin and other plasma proteins in NS leads to a decrease in plasma oncotic pressure which, with increased capillary ultrafiltration of sodium and water, leads to edema formation [30]. Therefore, the retention of sodium chloride in NS could be a consequence of the activation of the renin-angiotensin-aldosterone system (RAAS) secondary to plasma volume reduction. In contrast, that another mechanism states the primary intra-renal sodium and water retention caused by resistance to atrial natriuretic peptide (ANP) in NS and the activation of epithelial sodium channel (ENaC) in the inner medullary

collecting duct leads to an expansion of the intravascular compartment and subsequent edema [33].

Vitamin D insufficiency which is regarded as serum levels of 25(OH)D between 10ng/ml-30ng/ml was observed in the INS group as seen in Table 2, was also reported by Hussein and Selewski [34,35]. Vitamin D is an important hormone necessary for bone metabolism and regulation of calcium and phosphorous balance for bone mineralization and remodelling. Deficiency of this vitamin in early stages of life lead to rickets. However, abnormal vitamin D metabolism occurs in idiopathic NS, with contributions from losses of both vitamin D binding protein and 25(OH)D in the urine [36,37]. The urinary losses of vitamin D binding protein may be secondary to proteinuria, affecting the proximal tubule reabsorption via megalin and cubilin pathways [38]. Inadequate 25(OH)D may lead to hypocalcemia, hyperparathyroidism, and diminished bone mineral density/content which are common features seen in NS.

The present study also observed significant decrease in HDL levels and a significant increase in TG,TC and LDL in children with NS when compared with the control as seen in Table 2. This dyslipaemia observe red in the NS children was also supported by [39].

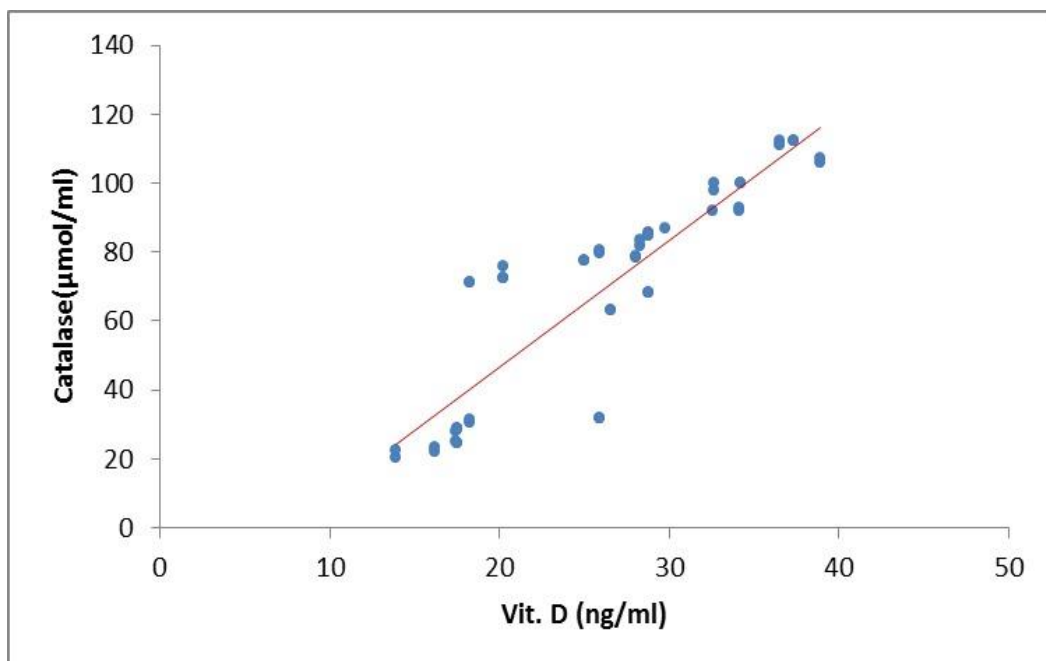


Fig. 1. Scatter plot showing correlation between vitamin D and Catalase in INS

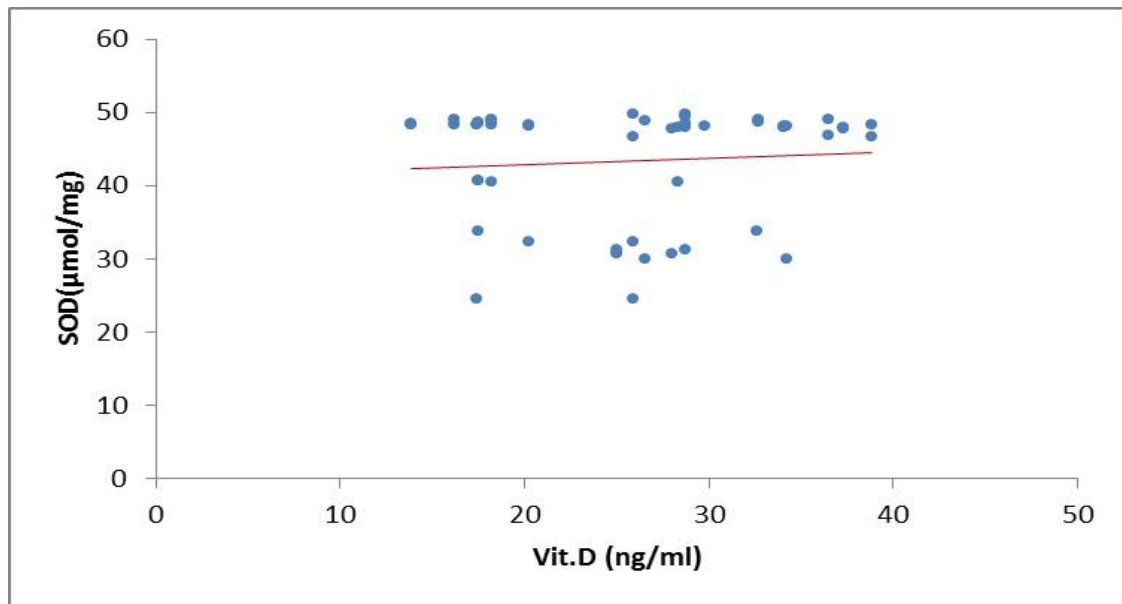


Fig. 2. Scatter Plot showing correlation between vitamin D and SOD in INS

Dyslipidaemia is a contributory factor in the progression of initial glomerular injury in NS [40]. Also, hyperlipidaemia has been associated with an increased risk of both accelerated cardiovascular disease and progressive kidney disease. The altered lipid metabolism in serum lipids and lipoproteins in patients with nephrotic syndrome are primarily a result of their impaired clearance and, to a lesser extent, their altered biosynthesis [41]. Impaired clearance of lipids is a result of decreased hepatic lipase activity and decreased lipoprotein lipase (LPL) activity in the endothelium and peripheral tissues [42]. Also, hepatic levels of proprotein convertase subtilisin/kexin type 9 (PCSK9) are elevated in patients with nephrotic syndrome; PCSK9 degrades the LDL receptor (LDLR), and is an important therapeutic target for lipid lowering. Hypercholesterolaemia and increased LDL levels occur in conjunction with upregulation of the expression and activity of liver acetyl CoA acetyltransferase 2 (ACAT2), which results in enhanced esterification of cholesterol and a reduction in the level of intracellular free cholesterol [42]. Cholesterol synthesis via 3-hydroxy 3-methylglutaryl CoA (HMG CoA) reductase is also increased in experimental models of nephrotic syndrome [42,43]. A statistically significant decrease occurred in GPX, SOD and CAT levels in children with NS when compared with the control as seen in Table 3, is similar to the work of Zachwieja et al. and J. Fydryk) Previous study on the total antioxidant status and mean antioxidant activity in 82

children with nephrotic syndrome of 4–16 years suggested that reduced antioxidant activity in nephrotic syndrome may be related to lipid abnormalities [44,45]. In a previous research by Diamond, he reported that an increase in lipid peroxidation and lipoproteins may cause the release of ROS, which are strong oxidants that are major causative factors of proteinuria and glomerular injury [39]. These ROS promote cell injury by lipid peroxidation, which disrupts the structural integrity of the tubular epithelial cells and increases the glomerular permeability to proteins together with an alteration in glomerular hemodynamics as seen in NS [46]. During oxidative stress, super-oxide mediated oxidative injury degrades the glomerular basement membrane and reduces de novo synthesis of proteoglycans that affects the glomerular permeability thereby leading to progression renal injury in NS [47,48].

A strong significant positive relationship exists between Catalase, SOD and Vit. D in children with NS as shown in Fig.1 and Fig. 2 respectively. This shows that the increased oxidative stress found in the pathogenesis of NS is related with Vitamin D insufficiency observed in paediatric NS. Emerging evidence supports the role of 25D administration in attenuating oxidative stress via increased nuclear factor-erythroid-2-related factor 2 (Nrf2) and up-regulation of the expression of genes encoding antioxidant enzymes, as well as modulating levels of ROS through control of cellular

antioxidants [49]. A study involving the supplementation of calcitriol in CKD subjects reduced the risk of morbidity and mortality [50]. The molecular mechanisms behind the actions of paricalcitol in the kidney may be from diminishing oxidative stress. The proposed mechanism may be that links oxidative stress to vitamin D insufficiency and deficiency is the Nrf2– Keap1 pathway [51]. Nuclear factor erythroid 2-related factor 2 (Nrf2) controls expression of ROS detoxifying and antioxidant agents via the antioxidant response element (ARE/EpRE). Nrf2 is sequestered in the cytoplasm by Kelch-like erythroid cell-derived protein with CNC homology (ECH)- associated protein 1 (Keap1), an actin binding repressor protein. Resulting in Keap1 contributing to augmented oxidative stress due to negative regulation of Nrf2 and ARE/EpRE activity [52]. Vit D3 could increase the expression of Nrf2 and reduce expression of Keap1 that decreases the development of nephropathy by inhibition of oxidative stress [51].

Another interesting result of this present study is that the dyslipidaemia found in the paediatric NS was weakly correlated with Vit. D insufficiency as seen in Table 4, is similar to a study done by [53]. This establishes the fact that Vitamin D is important in lipid metabolism. Studies on this relationship are few in paediatric NS. However, the possible mechanism for this relationship is that lack of vitamin D has a corresponding impact on beta-cell function, which leads to insulin resistance, disruption of lipoprotein metabolism, and ultimately, increased TG and decreased HDL cholesterol levels [54]. Specifically, some authors have proposed that increased calcium absorption may reduce the synthesis and secretion of TG in the liver [55]. Therefore, inadequate vitamin D levels may stimulate intestinal calcium uptake and consequently inhibit TG synthesis and secretion. In another theory, insoluble calcium–fatty acid complexes are formed as a result of inadequate vit. D to enhance absorption of calcium. Consequently, this brings about inhibition of intestinal absorption of fatty acids which further lowers levels of cholesterol in the serum [55].

4. CONCLUSION

Dyslipidaemia and oxidative stress are prominent features associated with the pathogenesis of NS. However, the results of this study suggests that vitamin D status influences serum lipid profiles and major antioxidants in Nephrotic syndrome. More longitudinal and laboratory-based

interventional studies on the effects of Vitamin D supplementation in paediatric Nephrotic Syndrome need to be carried out as evidence are few and research sparse. Also, Vitamin D supplements and diet rich in Vitamin D should be encouraged in NS patients.

CONSENT

Written informed consent was duly signed by all participants.

ETHICAL APPROVAL

Ethical clearance was issued by the Institute of Medical Research and Training (IMRAT) in the University College Hospital, Ibadan, Nigeria. All authors hereby declare that all experiments have been examined and approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

ACKNOWLEDGEMENTS

We acknowledge all the staff of Lead City University, Department of Biochemistry, and the staff of Chemical Pathology Department, University College Hospital (UCH) Ibadan for their support during the research work.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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