RENAL DIMENSION AND RENAL ARTERY RESISTIVE INDEX IN CHILDREN WITH SICKLE CELL DISEASE IN KANO NIGERIA-
A COMPARATIVE ULTRASONOGRAPHIC EVALUATION

BY

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This is to certify that the research proposal titled renal dimension and renal artery resistive index in children with sickle cell disease in Kano Nigeria- A comparative ultrasonographic evaluation. Submitted to the National Postgraduate Medical College of Nigeria, was reviewed by us and we have also agreed to supervise the conduct of the study.

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## SUMMARY
Introduction: Sickle cell disease (SCD) is an autosomal recessive disorder causing red blood cell sickling, vasoocclusion and haemolysis. Doppler ultrasonography of the renal vessels provides a non-invasive method of investigating renal diseases which includes sickle cell nephropathy.

Aims and objective: To compare the renal dimensions and renal artery resistive index (RI) in children with sickle cell disease with those of healthy children.

Methodology: This prospective study was conducted from May, 2013 to December, 2013. 50 patients with SCD and 50 apparently healthy children matched for age were recruited for this study. Ultrasound assessment of the kidney including the renal dimension and Doppler scan of the interlobar artery of the kidneys was performed.

Results: The mean renal length (RL) in children with SCD is 8.5±1.29 cm on the right side (RT) and 8.5±1.34 cm on the left side (LT). The mean RL in the control is 7.8±1.2 cm on the RT and 8.0±1.26 cm on the LT. The cortical thickness (CT) in children with SCD is 1.0±0.24cm on the RT and 1.1±0.20cm on the LT. The CT in the control is 0.9±0.24cm on the RT and 0.9±0.28cm on the LT. The RI in children with SCD is 0.7±0.06 on the RT and 0.8±0.05 on the LT. The RI in the control group is 0.6±0.05 on RT and 0.6±0.06 on the LT. The PSV is children with SCD is 77.5±22.3 on the RT and 83.0±20.53 on the LT. The PSV in the control group is 67.2±18.78 on the RT and 74.4±19.58 on the LT. The RL, CT, RI and PSV were found to be higher in SCD patient when compared with the control.

Conclusion: The mean renal length, cortical thickness, RI and PSV was found to be higher in children with SCD than the control group.

KEY WORDS: SICKLE CELL DISEASE, RENAL DIMENSION, RENAL ARTERY RI

INTRODUCTION
Sickle cell disease (SCD) is an autosomal recessive disorder caused by alteration in the molecular structure of haemoglobin; a single pair DNA mutation encoding the β-globins molecules resulting in substitution of valine for glutamic acid at sixth position of β-globin chain\(^1\). This causes red blood cell sickling, vaso-occlusion and haemolysis\(^2\). SCD may occur as homozygous inheritance of haemoglobin S (HbSS), compound heterogeneous inheritance; HbS with other β-globin mutation such as haemoglobin C or quantitative mutation that result in decrease or absent β-globin synthesis (haemoglobin β\(^+\) and β\(^0\) thalassemia respectively). HbSS and HbSβ\(^0\) are clinically identical disorders that are associated with severe anaemia and disease complication whereas HbSC and HbSβ\(^+\) thalassemia tend to have fewer and less severe acute complication. Chronic organ damage including renal damage is a feature of all forms of SCD\(^2\)\(^3\)\(^4\).

Sonography is often used as the initial imaging procedure to evaluation a patient with renal disease. However only basic anatomic information is obtained with this modality; renal length, cortical thickness and degree of collecting system dilatation are assessed\(^5\)\(^6\). Previous studies show that the use of resistive index (RI) which measures the resistance of renal arterial flow to the kidney and pulsatility index (PI) which is a measure of the variability of blood velocity in a vessel can serve as an early predictor of renovascular abnormalities in SCD at an early stage when renal changes are reversible using blood transfusion\(^1\). It is therefore important to detect these early changes with routine surveillance; intervention at this stage may prevent or at least delay the renal damage. This is particularly relevant because patient with SCD do not do well with dialysis or renal transplantation because of vasoocclusive crises and other complications\(^7\)\(^6\)\(^8\).

To recognise abnormal renal Doppler findings in sickle cell nephropathy, the range of normal values of intrarenal Doppler parameters such as resistive index should be established. This
study therefore will determine and compare the renal dimension and resistive index in both normal children and those sickle cell disease.

AIMS AND OBJECTIVES
GENERAL

To determine the renal dimension and renal artery resistive index (RI) in both healthy and children with sickle cell disease.

SPECIFIC

1. To determine the renal length and cortical thickness in healthy children and children with SCD using ultrasound. The healthy children are the control group.
2. To measure the RI and peak PSV in both sets of children using Doppler ultrasound.
3. To compare the parameters in normal and SCD children.

WORKING HYPOTHESIS
HYPOTHESIS

There is no statistically significant difference in the renal dimension and renal artery resistive index between sickle cell disease patients and control (normal).
JUSTIFICATION

According to the WHO report 2006 on sickle cell anaemia (SCA) Nigeria is regarded as the capital of SCA in the world. From the report, the total figure ascribed to Africa is 200,000 on annual bases with Nigeria taking 150,000 of the number. Advance in medical care results in observation of the disease complication including sickle cell nephropathy. Irreversible renal damage occurs in at least a third of patient and is a frequent cause of death beyond early adulthood1. Considering the high prevalence of the disease in Nigeria, it is required that renovascular changes are detected at an early stage before irreversible organ damage occurs due to chronic vasculopathy.

A series of articles published during the past decade indicated the potential of Doppler sonography for improving the sonographic assessment of the renal dysfunction. Changes in intrarenal waveform were shown to be associated with several types of intrinsic renal disorder and renal vascular diseases5. Detection of renal changes with Doppler ultrasound in SCD can therefore guide clinicians in the use of intensive monitoring of other laboratory values and initiating adequate treatment at early stage when the consequence of the disease are reversible by transfusing the patient with blood1.
ANATOMY OF THE KIDNEYS

EMBRYOLOGY: The kidney develops from metanephros, pronephros and mesonephros. Only the duct of mesonephros persists. Thus the nephrons arise from the metanephros. Parts of the nephron formed are Bowman’s capsule, proximal convoluted tubule, loop of Henle and distal convoluted tubule. The collecting part of the kidney develops from ureteric bud, which is an outgrowth of the mesonephric duct. The ureteric bud which is the precursor of the ureter gets capped by the metanephric tissue. The ureteric bud forms the ureter. Soon it dilates to form the renal pelvis and divides and subdivides to form major and minor calyces and 1-3 million collecting tubules. The kidney starts developing in the sacral region and assumes its adult position by the differential growth of the ureters relative to the trunk. It is supplied first by branches of the iliac artery and subsequently by series of vessels from the abdominal aorta, each of which disappears as the kidney develops a new supply\textsuperscript{9}.

GROSS ANATOMY: The kidneys are bean shaped, convex on the lateral and concave on the medial border. They are enclosed by an adipose capsule the thickness of which varies depending on the general constitution of the patient. They are located retroperitoneally in the paravertebral gutters of the posterior abdominal wall and slide on the quadratus lumborum and psoas muscles during inspiration and expiration\textsuperscript{10}. The kidneys lie obliquely with their upper poles more medial and more posterior than their lower poles\textsuperscript{9}.

On coronal cross-section each kidney have a peripheral cortex and an inner medulla. Extensions of the cortex centrally as columns (of Bertin) separate the medulla into pyramids whose apices, jutting into the calyces, are called the papillae\textsuperscript{9}.

The kidneys are supplied by renal arteries which originate from the abdominal aorta just below the level of the superior mesenteric artery. The renal veins follow a course parallel to the renal arteries\textsuperscript{11}. The lymphatics system of the kidney drain into lateral aortic nodes.
located at the level of origin of the renal arteries. The nerve supply of the kidney is from the renal plexus which is a branch of the coeliac plexus.

**SONOGRAPHIC ANATOMY:**

The normal renal cortex is usually less echogenic than the liver or spleen, but in the young infant is iso or hyperechoic with respect to these organs. The cortex is distinguishable from the relatively hypoechoic renal pyramids - a difference that is more marked in infant. The renal sinus is highly echogenic because of the multiple tissue interfaces. It contains fat, calyces, infundibulae and vessels. The renal pelvis may be intrarenal or extrarenal. When extrarenal, it may appear dilated. Visualization of the collecting system is variable. It is best seen when the subject is well hydrated and/or in a state of diuresis.

The left kidney sometimes has a very wide parenchyma in the medial portion, a so called splenic notch or dromedary hump. This is a normal finding and should not be confused with renal mass. The echogenicity in the area of the hump will be the same as in the surrounding parenchyma and medullary pyramids will still be present and the vessels architecture will be unaffected. The renal artery is seen to turn posteriorly and laterally. In slim patients it is occasionally possible to follow the renal artery and vein into the hilum of the kidney by applying compression with the transducer and slightly oblique angulation. Scanning from the right flank and angling the probe anteriorly to align the sonographic plane with the coronal plane of the kidney allows the vessels at the renal hilum and within the kidney to be sampled. These can be observed with colour Doppler radiating from the hilum.

The right lobe of the liver acts as an acoustic window to the right renal artery. On the left there is no such acoustic window and visualisation of the left renal artery from origin to
hilum is difficult this may be facilitated by compression, or by using the coronal approach to the kidney and follow the course of the renal artery in retrograde fashion towards its origin. In addition much of the left renal vein is demonstrated with the patient in supine position; it’s more anterior and superior location, together with larger diameter, allowing visualisation using left lobe of the liver as an acoustic window\textsuperscript{11}.

Demonstration of the anatomical location and course of the intrarenal vessels is almost exclusively restricted to the colour Doppler\textsuperscript{11}, although pulsations can be seen on real time at the site of the interlobar vessels, and occasionally at bright reflectors at the corticomedullary margin which represent the arcuate vessels. The arteries are each accompanied by veins.
Fig 1: A longitudinal sonogram of the right kidney in a child showing the hypoechoic cortex (straight arrow) and echogenic central sinus (curve arrow) echoes.
Fig 2: A sketch of longitudinal sonogram showing the liver (longitudinal arrow) and right kidney (transverse arrow).
Fig 3: Sonogram showing the Doppler spectra of the interlobar artery of a child.
LITERATURE REVIEW

Sickle cell anaemia (also known as sickle cell disorder or sickle cell disease) is a common genetic condition due to haemoglobin disorder-inheritance of mutant haemoglobin genes from both parents. Such haemoglobinopathies, mainly thalassemias and sickle cell anaemia are globally widespread; about 5% of the world population carries the genes responsible for haemoglobinopathies. Each year about 300,000 infants are born with major haemoglobin disorders-including more than 200,000 cases of sickle cell anaemia in Africa\textsuperscript{12}.

In broad terms, the prevalence of the sickle cell trait (healthy carriers who have inherited the mutant gene from only one parent) ranges between 10\% and 40\% across the equatorial Africa and decreases to between 1\% and 2\% on the north African coast and <1\% in south Africa. This distribution reflect the fact that sickle cell trait confers a survival advantage against malaria and that selection pressure due to malaria has resulted in high frequencies of the mutant gene especially in areas of high malarial transmission\textsuperscript{12}.

The greatest burden of SCD is in sub-Saharan Africa where 75\% of the 300,000 global birth affected children live\textsuperscript{13}. The World Health Organisation (WHO) estimated 70\% of sickle cell anaemia (SCA) deaths in Africa which is preventable with simple cost effective intervention such as early identification of SCA patients by new born screening and subsequent provision of comprehensive health care. WHO estimated the prevalence of SCA to be about 20 in 1000 live birth annually which translate into about 150,000 children born annually with SCA in Nigeria making it the country with the highest burden of SCA in the world\textsuperscript{13}. Recent progress in medical care of SCA patient has increased their life span; this has resulted in more frequent observation of various chronic complications of SCA, particularly end-organ failure\textsuperscript{14,15}. 

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In West African countries such as Ghana and Nigeria the frequency of the trait is 15% to 30% whereas in Uganda it shows marked tribal variation, reaching 45% among the Baamba tribe in the west of the Uganda. Frequencies of the carrier state determine the prevalence of sickle cell anaemia at birth. For example, in Nigeria by far the most populous country in the sub region 24% of the population are carriers of the mutant genes and the prevalence of sickle cell anaemia is about 20 per 1000 births. This means that in Nigeria alone, about 150,000 children are born annually with sickle cell anaemia.

The pathophysiology of nephropathy in sickle cell disease is complex and still not fully understood. Development of transgenic mice has provided useful information in understanding the pathophysiology of renal disease in SCD. Sickle cell nephropathy results from recurrent renal vasooclusion, ischaemic injury and loss of nephric mass. Chronic sickling underlies several mechanisms for kidney injury. The arterial side of the microvasculature has a low oxygen tension. The hypertonicity and low PH of the renal medulla promote the formation of haemoglobin polymers in the red cells with deformation of sickle cells resulting in an increase in the blood viscosity, functional venous engorgement and interstitial oedema predisposing the renal microvasculature to ischaemia and infarction. Obliteration of the medullary vasculature produces segmental scarring and interstitial fibrosis (structural papillectomy), resulting in the formation of dilated renal pelvic capillaries and veins. Haematuria may result from rupture of vessels from the early venous engorgement or from the dilated vessels that result from scarring. The development of collateral vessels and their abnormal orientation in the medullar interferes with the counter current exchange mechanism, culminating through years in irreversible loss of medullary tonicity. Renal cortical flow and GFR are increased perhaps by the secretion of the medullary vasodilator prostaglandins (hyperfiltration). Prolong hyperfiltration due to sickle cell disease during
childhood lead to glomerular damage resulting in glomerular sclerosis, protunuria and progressive renal failure\textsuperscript{7,19}.

Renal abnormalities in SCD start in childhood with haematuria being the most common manifestation\textsuperscript{2,3}. Sickle cell nephropathy results from recurrent renal vasoocclusion, ischemic injury and loss of nephric mass leading to several pathological and physiological defects in the kidney\textsuperscript{20-21}. Reduction of urine concentrating ability and decrease excretion of titrable acid are common. These are attributed to disruption of medullary vasculature with loss of vasa recta resulting from the sickling of the red blood cell in the hypertonic environment surrounding the vessels\textsuperscript{22-24}.

Diagnostic value of the Doppler ultrasonography of the renal vessels has proven its utility in different clinical situations\textsuperscript{25,26}. The analysis of intrarenal arterial Doppler flow profile provides a non-invasive method of investigating renal medical diseases including sickle cell nephropathy\textsuperscript{27,28}. Colour and power Doppler ultrasound easily demonstrate the general increase or decrease of renal parenchymal blood flow and hemodynamic changes of the renal blood flow can be assessed by Doppler spectral analysis.

Ultrasound scan, computed tomography (CT) and magnetic resonance imaging (MRI) are the imaging modalities that evaluate the anatomical structure of the kidneys, while the intravenous urography (IVU) and nuclear medicine are used primarily for physiology of the kidney\textsuperscript{9}.

Ultrasound is usually the initial imaging study of the kidney because it is readily available cheap and free from ionizing radiation. It is a reliable technique for renal dimension assessment. The length of both kidneys in adults is considered to be normal when it is between 9-13 cm and renal parenchymal thickness between 1-1.5 cm avoiding renal pyramids\textsuperscript{29}. The ultrasound findings of renal parenchymal diseases are often non specific but
Doppler ultrasound has expanded the role of ultrasound in the evaluation of renal parenchymal disease. Doppler blood flow velocity waveform recorded sonographically is known to give a non invasive evaluation of impedance to blood flow distal to the site of measurement.\textsuperscript{30}

On Computed tomography (CT) the renal substance is of homogenous density on non contrast CT images. The use of CT in renal parenchymal disease is very limited. Non contrast CT scan is useful in detecting renal parenchymal calcification. Contrast enhanced CT scan may reveal the pattern of contrast enhancement and excretion in patient with impaired renal function. Early dynamic scan following a bolus injection of contrast medium can give further hemodynamic information. Delayed scan without further injection of contrast media can sometimes provide valuable information by demonstrating the pattern of washout and delayed contrast enhancement\textsuperscript{9}.

On MRI, the intrinsic contrast between cortex and medulla is seen on T1 and T2 weighted images. On T1 weighted images the renal cortex has a slightly higher signal than the medulla. On T2 weighted images the renal cortex is slightly lower in signal than the medulla. On both CT and MRI three phases of enhancement can be appreciated: an arterial corticomedullary phase, where the cortex enhances strongly and contrast between cortex and medulla is greatest; a venous nephrographic phase, where the contrast is homogenous throughout the kidney; and delayed excretory phase, where contrast is seen from the base to tip at the hilum on axial images and are cut at various degrees of obliquity in other slices\textsuperscript{9}.

Kadioglu et al\textsuperscript{29} established that renal length increase with age and between the ages of 10 and 16 years the graph of renal length versus patient age had a zig zag pattern. A study conducted by Adedeji et al\textsuperscript{31} show that the renal size decrease with age in hypertensive adult and female hypertensive patient have smaller kidneys than male. They also show that the
renal size on the left is larger than the right side. Another study from South-Eastern Nigeria by Okoye et al\textsuperscript{32} showed no significant difference in renal length between the right and left sides. In another study by Okoye et al\textsuperscript{33} there were no variations in renal size between the left and right sides. In patient with sickle cell disease glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) are increased in childhood and are associated with glomerular hypertrophy but falls as individual ages\textsuperscript{34}. Aikimbaev et al\textsuperscript{35} found that children with sickle cell disease have significantly larger size of both kidneys when compared with healthy control. This has been related to hyperfiltration which is common in sickle cell disease patients (mean renal length is SCD patient is 14.8±2.6cm while that in control group is 10.5±7cm).

Duplex Doppler ultrasound has the potential to provide the physiologic information regarding the hemodynamic state of the kidney which is normally highly vascular. Assessment of renal vascular resistance is obtained by Doppler waveform analysis. The Increased sensitivity of colour Doppler and power Doppler provided by latest digital ultrasound equipment allows depiction and interrogation of renal parenchymal vessels up to interlobular arteries\textsuperscript{30}.

The resistive and pulsatility indices are different indices calculated from the blood flow during cardiac cycle. PI and RI are used as pulse wave Doppler measurement of downstream resistance in arteries. The RI declines from the segmental artery in the hilar region to the interlobular arteries in the peripheral part of the kidney, of all these vessels interlobar arteries provide the best site for obtaining Doppler spectrum for the evaluation of renal parenchymal disease\textsuperscript{29}. The normal renal vascular bed has a low resistance and Doppler spectra obtained from intrarenal arteries have continuous prominent forward flow during diastole. RI of the normal kidney is usually below 0.65 and seldom exceeds 0.70.\textsuperscript{36} Certain factors such as age, systemic blood pressure, and heart rate may affect RI\textsuperscript{36}. 

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Platt et al\textsuperscript{37} observed that RI values less than 0.70 can be used as an indicator of normal renal vascular resistance in adults. RI greater than 0.70 can be interpreted as a sign of elevated renal vascular resistance and can be found in several renal parenchymal diseases\textsuperscript{37}. Renal parenchymal disease primarily involving tubule-interstitial or vascular compartment generally results in an elevated RI whereas diseases limited to the glomeruli do not. Platt et al\textsuperscript{38} conducted a study that correlates RI values with biopsy findings in various renal parenchymal disease which revealed that kidneys with active disease in tubulointerstitial or vascular compartment present elevated RI (>0.80) whereas kidneys with glomerular disease present more often normal RI values.

The RI of renal arteries in values as measured in healthy children show significant dependence on age. The overall trend shows decline with increasing age. This has been related to the decrease in both active plasma rennin and aldosterone with increasing age. Sagirci et al\textsuperscript{39} indicate that intrarenal RI in healthy children older than 54 month is always under 0.70 a value that is reasonable upper limits for intrarenal RI. Similar study conducted by Ronald et al\textsuperscript{40} shows that there is greater tendency for children younger than 7 years to have RI greater than 0.70 than older children. In addition the study revealed that none of the children 4 years and older have RI >0.70 and they concluded that mean adult RI criteria should be applicable to children aged 4 years and older. Khalil et al\textsuperscript{41} revealed that Doppler ultrasound indices excluding the PI do not vary between the right and left kidney in healthy adults.

Although many factors influence the vascular state in sickle cell disease it has been shown that haematological abnormalities are associated with elevated renal vascular resistance. Renal vascular resistance assessed by Doppler sonography is raised in sickle cell disease when compared with age matched healthy subjects. These changes are more pronounced in
those with more severe manifestations of the disease and correlated with haematological and clinical features of sickle cell disease\textsuperscript{35}.

The Turkish Study by Aikimbaev et al\textsuperscript{35} revealed that the RI and PI are much higher in patients with sickle cell disease than in healthy subject. It shows that patient with higher values of RI had more severe haematological disorder. Similar study was carried out in India by Kishor et al\textsuperscript{1} and revealed a significant increase in the RI in patient with sickle cell disease compared with control group and this may be as a result of increase in renal vascular tone due to various vascular occlusive mechanisms occurring in sickle affected kidneys.
METHODOLOGY

This prospective study was conducted from May, 2013 to December, 2013 at the Department of Radiology, Aminu Kano Teaching Hospital (AKTH), Kano Nigeria.

The sickle cell patients used in this study were recruited from sickle cell clinic of Aminu Kano Teaching Hospital based on the inclusion criteria itemised below using systemic random sampling until the sample size of 50 patients was reached. Fifty apparently healthy children matched for age between 1-16 years and referred to the department for abdomino-pelvic to the department of Radiology, AKTH served as the control group. Informed consent was obtained from parents or guardians.

Sample size determination

Sample size was determined using formula for sample size determination for comparative studies:\textsuperscript{42}

\[ N = \left( \sigma_1^2 + \sigma_2^2 \right) \left( Z_{\alpha} + Z_{\beta} \right) \left( M_1^2 - M_2^2 \right) \]

- \( N \) = Minimum sample size for each of the comparison group.
- \( \sigma_1 \) = Standard deviation of the outcome variable in group 1.
- \( \sigma_2 \) = Standard deviation of the outcome variable in group 2.
- \( Z_{\alpha} \) = Standard normal deviate set at 95% confidence level= 1.96
- \( Z_{\beta} \) = Standard normal deviate for power of test to detect difference between sickle cell disease patient and control (normal) set as 80% corresponding to 0.84.
- \( M_1 \) = Mean of the outcome variable in group 1.
- \( M_2 \) = Mean of the outcome variable in group 2.
Based on the study by Aikimbaev et al\textsuperscript{35} the mean renal length in sickle cell disease patient is $14.8 \pm 2.6$ cm and mean renal length in control (normal) is $10.5 \pm 7.0$ cm.

Therefore:

- Standard deviation of the outcome variable in group 1 ($O_1$) = 2.6
- Standard deviation of the outcome variable in group 2 ($O_2$) = 7.0
- Mean of the outcome variable in group 1 ($M_1$) = 14.8
- Mean of the outcome variable in group 2 ($M_2$) = 10.5

Substituting the values gives:

$$N = \frac{(2.6^2 + 7.0^2) \times (1.96 + 0.84)^2}{(14.8 - 10.5)^2}$$

$$= (6.76 + 49.0) \times \frac{(2.8)^2}{(4.3)^2}$$

$$= 55.76 \times \frac{7.84}{18.49}$$

$$= 55.76 \times 0.4240$$

$$= 23.64 \sim 24.0$$

Therefore the minimum sample size in each group is 24 Subject.

For purpose of this research 50 SCD patients and 50 controls Subject was enrolled.

**Inclusion criteria**

1- Children with SCD from sickle cell clinic of Aminu Kano Teaching Hospital.

2- Apparently healthy children matched for age coming for other investigations in the department.

3- Age range of both sets of children was between 1-16 years.
Exclusion criteria

1- Clinical or morphologic signs of end-stage renal disease.
2- High blood pressure.
3- Tachycardia.
4- Technically inadequate pulsed Doppler tracings.

Data collection

Data was collected using structured data collection sheet (see the appendix-II). The age, gender, genotype and vital signs such as blood pressure and pulse rate were included.

Methodology

A real time Colour coded scanner [Mindray D-C 6 Schenzen China] was used by the same examiner with the imaging and Doppler system generated using a 3.5 MHz curvilinear transducer. The patient was examined using lateral or posterolateral approach and position optimised to obtain renal images and Doppler tracing. Water soluble coupling gel was applied liberally on the area of interest to permit sound conduction. A global examination of the kidneys was performed, the echogenicity first assessed to establish it normality (relative to the liver and spleen). The renal length measurements were performed in the sagittal view, with patients in the supine position or in prone position. The maximum length of each kidney was measured in cm between the uppermost edge of the upper pole and the lowest edge of the lower pole (Fig 1). Sagittal plane images were obtained either from the long-axis view, using a subcostal approach with the patient in the supine position, or from the prone position view, using a posterior approach with the patient in prone position. Three readings were obtained and the average taken to minimise the inter-observer variations. The
cortical thickness is measured from the base of the medullary pyramid to the outer cortex (Fig 2).

Colour mapping was then performed to image blood flow in the kidney. Three Doppler waveforms was obtained from each kidney by sampling the interlobar artery (along the border of medullary pyramids) of the superior, middle and inferior portion of the kidney and average value calculated manually(Fig 3). The flow velocity waveform was obtained at an optimal insonating angle of 60°. The Doppler tracing was obtained and recorded by placing a gate of 2.5 mm (adjusted when necessary) over the artery, lowest possible filter was utilised and selecting smallest scale that displayed the flow without aliasing was selected. The height of the Doppler waveforms was maximised to facilitate measurement. A trend of at least three similar sequential Doppler waveforms was obtained during suspended respiration. Then the measurement of resistive index was determined using the internal callipers and analytical software of the sonography unit. The resistive index was calculated using the formula [\((\text{peak systolic frequency shift} - \text{peak diastolic frequency shift})/\text{peak systolic frequency shift}\)]. The PSV were recorded from the Doppler traces as the fastest velocity recorded from the spectral traces.

**Ethical considerations**

Approval/permission was sought from the ethics and research committee of Aminu Kano Teaching Hospital. In addition, informed oral or written consent was obtained from the caregivers of the subject in the study. The researcher will bore the cost of ultrasound scan.
METHOD OF DATA ANALYSIS

The generated data was analysed with the statistical package for social sciences (SPSS) version 17.0 software. The measured renal length, cortical thickness, resistive index, peak systolic velocity was summarized as means, standard deviation, median and range. In addition to these descriptive statistics, possible correlation between the measured renal length, cortical thickness, resistive index, peak systolic velocity, age, sex and subject’s sides (right or left) was examined with analysis of variance (ANOVA) and correlation co-efficient. Chi square was used for comparison of proportion and t-test for comparing means. A probability of $\leq 0.05$ was considered as significant for all statistical calculations.

Findings are presented in the form of summarizing indices (numerically in tabular form and graphically in the form of histogram, pie chart and scatter diagrams).
RESULTS

One hundred (100) subjects were involved in the study, Fifty (50) had normal haemoglobin genotype (AA) and the remaining fifty (50) abnormal haemoglobin genotype (SS) (Table 1).

As shown on figure 1 they comprised of 56 males (56%) and 44 females (44%). Among those with normal haemoglobin genotype 32 were males (64%) and 18 were Females (36%) as shown on table 2, those with abnormal haemoglobin genotype consists of 24 males (48%) and 26 females (52%)(Table 2).

The mean age of the entire study subjects was 7.5 ± 4.94 years. The mean age of those with normal haemoglobin genotype and those with abnormal haemoglobin genotype was 6.6±4.65 years and 8.4±5.09 years respectively (Table 3). The difference between the two groups is however not statistically significant (p-value 0.07). As shown on table 1 the study subjects within the age of 1-5 years constitute the majority (n = 44 or 44%) of the study population, followed by those within the age group of 6-10 years (n = 26 or 26%).

The mean renal length for those with normal haemoglobin genotype was 7.8±1.2 cm on the right and 8.0±1.26 cm on the left. On the other hand, the mean renal length in those with abnormal haemoglobin genotype was 8.5±1.29 cm on the right side and 8.5±1.34 cm on the left side. The mean renal length was therefore higher in those with SS haemoglobin genotype than those with AA haemoglobin genotype. These differences were statistically significant (p-value = 0.01 on the right and 0.03 on the left) (Table 4).
The cortical thickness for the subjects with SS haemoglobin genotype was 1.0±0.24cm on the right side and 1.1±0.20cm on the left. The mean cortical thickness for the subject with AA haemoglobin genotype was 0.9±0.24cm on the right and 0.9±0.28cm on the left. This showed higher cortical thickness was found to be higher in those with SS genotype haemoglobin genotype than those with AA haemoglobin genotype. This difference was statistically significant (p-value 0.02 and 0.01 on the right and left side respectively)(Table 4)

The renal arteries of subjects with SS genotype show mean resistive indices of 0.7±0.06 on the right side and 0.8±0.05 on the left. Whereas the control showed resistive indices of 0.6±0.05 and 0.6±0.06 on the right and left side respectively. This implied higher resistive index in subjects with SS haemoglobin genotype than those with normal haemoglobin genotype. This difference was statistically significant (p-value <0.01 on each side)(Table 4)

The average of the peak systolic velocity of the interlobar artery in the subjects with SS haemoglobin genotype was found to be 77.5±22.3 on the right side and 83.0±20.53 on the left side. The peak systolic velocity in subjects with AA haemoglobin genotype was found to be 67.2±18.78 on the right side and 74.4±19.58 on the left side. The peak systolic velocity was higher in the subjects with SS haemoglobin genotype than those with AA haemoglobin genotype. This difference was statistically significant (p-value 0.01 on the right and 0.03 on the left side)(Table 4)
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<thead>
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<td>6-10</td>
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<td>11-15</td>
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<table>
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<tr>
<td><strong>Total</strong></td>
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<table>
<thead>
<tr>
<th>Genotype</th>
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<th>%</th>
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</thead>
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<tr>
<td>Abnormal (SS)</td>
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<td>50</td>
</tr>
<tr>
<td>Normal (AA)</td>
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<td><strong>100</strong></td>
<td><strong>100</strong></td>
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Table 2: Comparison of age of participants with their corresponding genotype.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Females</th>
<th>Males</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>SS</td>
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<td>52</td>
<td>24</td>
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<tr>
<td>AA</td>
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<td>36</td>
<td>32</td>
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</table>

$\chi^2 = 2.597$  df=1  p-value=0.11
Table 3: Comparison of age of the study participants based on genotype

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Mean</th>
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<th>t</th>
<th>p-value</th>
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</thead>
<tbody>
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<tr>
<td>AA</td>
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<td>Mean</td>
<td>Standard deviation</td>
<td>t-statistics</td>
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<td>-------------------------</td>
<td>----------</td>
<td>------</td>
<td>--------------------</td>
<td>--------------</td>
</tr>
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</tr>
<tr>
<td>Left renal length</td>
<td>AA</td>
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<td>1.26</td>
<td>-2.15</td>
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<tr>
<td></td>
<td>SS</td>
<td>8.5</td>
<td>1.34</td>
<td></td>
</tr>
<tr>
<td>Right cortical thickness</td>
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<td>1.0</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
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</tr>
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<td>0.05</td>
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</tr>
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<tr>
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<td>0.05</td>
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<tr>
<td>Velocity</td>
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<td>22.33</td>
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</tr>
<tr>
<td>Left Peak Systolic</td>
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<td>19.58</td>
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</tr>
<tr>
<td>Velocity</td>
<td>SS</td>
<td>83.0</td>
<td>20.53</td>
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Table 5: Association between demographic factors and indices

<table>
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<th>Renal dimensions</th>
<th>Sex</th>
<th>n</th>
<th>Mean</th>
<th>Std. Deviation</th>
<th>t-statistic</th>
<th>p-value</th>
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</thead>
<tbody>
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<td>1.23</td>
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<tr>
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<td>1.33</td>
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<td></td>
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<td>1.22</td>
<td>0.04</td>
<td>0.97</td>
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<td>0.26</td>
<td>0.12</td>
<td>0.91</td>
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<td>1.0</td>
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<td>0.09</td>
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<td>56</td>
<td>0.7</td>
<td>0.07</td>
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<tr>
<td>Left Resistive Index</td>
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<td>1.30</td>
<td>0.20</td>
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<td>0.7</td>
<td>0.09</td>
<td></td>
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<tr>
<td>Right Peak Systolic Velocity</td>
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<td>71.8</td>
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<td>21.78</td>
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<td>Left Peak Systolic Velocity</td>
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<td>79.3</td>
<td>21.55</td>
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</table>

*significant
Fig 4: A pie chart showing gender distribution of the study participants.
Fig 5: A histogram showing the age distribution of the study participants.
RLRt = Right renal length

Fig 6: A scatter diagram showing a linear relationship between age and right renal length.
RLLt = Left renal length

Fig 7: A scatter diagram showing a linear relationship between age and left renal length.
DISCUSSION

Sickle cell disease is a group of genetic disorder of haemoglobin that causes multisystem morbidity and increased risk of early death. The survival of young children with sickle cell disease has improved dramatically over the past decade due to improvement in patient care.\textsuperscript{43, 44}

Renal Doppler sonography was first introduced in the mid 1980 for screening of renovascular disease.\textsuperscript{1} Since then many studies have been published indicating the potential of Doppler assessment of various renal diseases. The colour Doppler sonography enables non invasive visualisation of the blood flow, resistive index, and measurement of velocity of flow in intrarenal arteries.

This study comprises of 100 subjects. Among the study participants 56 subjects were males (56%) while 44 were females (44%). The fact that there are more males than females may probably be a coincidence of statistical probability since the sample for this study was drawn using randomised sampling technique with no sex or age preference. Studies by other researchers\textsuperscript{1, 29} also show no specific frequency bias in the sex of the subjects studied.

The age group 1-5 years represent almost half of the study population. The reason for this could be proffered from the fact that the bulk of the subjects used in this study was drawn from paediatric clinic where most of them were 5 years and below.

SCA is associated with many structural and functional complications of the kidney, which may progress to chronic renal failure and end-stage renal disease. Several studies have reported medullary or diffuse increase in reflectivity on renal ultrasonography in patients with SCA.\textsuperscript{7} The cause and significance of this entity is unknown; However, renal papillary necrosis, high concentrations of iron deposits within tubular epithelial cells, focal scaring and
interstitial fibrosis in the vasa recta system, glomerular hypertrophy, and renal sclerosis have been suggested as factors that may cause increased renal echogenicity.

The study showed no statistically significant difference of the renal length between males and females (Table 5). Gender does not affect kidney dimensions in the pediatric age group. This has been discussed in the literature. The results of this study also show that renal length gradually increased with age. Fluctuating relationship was noticed between the age and renal length in those patient aged 10 to 16 years (Figs 6 and 7). This pattern was also observed by Kadioglu et al as well. The mean renal length was found to be higher in sickle cell disease patients as against the healthy control children in this study (Table 4). This is in agreement with the studies reported previously by various authors. The mechanism of renal enlargement is unknown although enlargement of sickle cell kidneys has been attributed to vascular dilatation, engorgement of vessels believed to be as a result of increased renal blood volume from the anemia, glomerular hypertrophy, increased blood volume, and interstitial edema.

The mean cortical thickness is found to be significantly higher in sickle cell patients than the control population (Table 4). This may be attributed to glomerula hypertrophy and increase blood flow commonly seen in sickle cell disease patients.

The RI provides information about arterial impedance. The pressure differential between the systole and diastole was shown to be a major factor influencing RI, along with the vascular compliance and the cross-sectional area of the downstream vascular bed. The renal RI values as measured in healthy children show a significant dependence on age. This age dependency of the renal RI is also seen in this study, those with younger age group having a higher RI (Fig
The age dependency of the renal RI and renal vascular resistance was connected to change in active plasma renin level which is higher in younger age group\textsuperscript{40}. One explanation may be related to renal volume. It increases with age, causing an increase in vascular diameter, cross-sectional area, and then leading to decrease of RI. Hanefi et al\textsuperscript{49} speculated that the arterial afterload may be smaller in a big kidney than in a small one. Other explanations may be the low or absent diastolic flow associated with low glomerular filtration rate (GFR) caused by the large number of immature glomeruli in younger children.

This study revealed a significant increase in the RI in patients with SCD compared with the control group (Table 4). This is in agreement with the previous studies\textsuperscript{1,35}. Kairgueldy et al\textsuperscript{50} also found the renal vascular resistance to be raised in SCD patients as compared with age-matched, apparently healthy persons. They revealed that these changes are more pronounced in those with more severe manifestations of disease and correlated with hematological and clinical features of sickle cell disease. This phenomenon of increase RI may be a result of the increased renal vascular tone due to various vascular occlusive mechanisms occurring in sickle-affected kidneys. These mechanisms include vascular intimal hyperplasia, thrombosis, altered vascular reactivity, and frank vasospasm. These various mechanisms identify the multi-factorial nature of the disease other than just micro-vascular occlusion by sickled red blood cells (RBC). The mechanisms of vascular intimal hyperplasia and thrombosis in turn are related to the abnormal adhesive and pro-coagulant properties of sickled RBC. The PSV was also found to be significantly higher in sickle cell disease patients than in the control population.
CONCLUSION

The data from this study showed that the renal length and cortical thickness in SCD patients are larger when compared with age matched healthy subjects. The RI and PSV were also higher in SCD patients when compared with age matched healthy subjects. The data generated from this study can help draw attention of the utility of renal Doppler sonography indices as early predictors of renovascular changes in SCD. Doppler sonography can therefore guide the clinicians in the use of more intensive monitoring of other laboratory values thus initiating adequate treatment at an early stage when the consequences of the disease are still reversible using blood transfusion.
RECOMMENDATION

1. Renal Doppler sonography should be part of routine screening work up for patients with sickle cell disease.

2. All patients that are found to have abnormal Doppler findings should be referred to the paediatrician for assessment of the renal function and treatment to prevent further renal damage.

3. Further studies are required to correlate the Doppler sonographic findings with the laboratory parameters suggesting renal diseases in SCD patient as well as the clinical features of renal diseases.
Study limitations

1  Intraobserver variability in the measurement of renal dimension and resistive index; however, it was reduced to the minimum by taking the average of three measurements.

2  Difficulty in terms of cooperation by the child. This is overcome with the mother holding the child during the examinations.

3  Non measurement of renal function in the study population. This can be overcome in subsequent studies by determining biochemical parameters of renal function.
REFERENCES


