PREVALENCE OF RENAL FAILURE IN SICKLE CELL DISEASE PATIENTS ATTENDING MUHIMBILI NATIONAL HOSPITAL IN DAR ES SALAAM, TANZANIA.

By

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A dissertation in (partial) Fulfilment of the Requirements for the Degree of Masters of Medicine (Internal Medicine) of Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences

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CERTIFICATION

The undersigned certify that he has read and hereby recommend for examination of a dissertation entitled **'Prevalence of renal failure among sickle cell disease patients attending Muhimbili National Hospital, Dar es Salaam'** in the fulfilment of the requirements for the degree of Master of Medicine (Internal Medicine) of the Muhimbili University of Health and Allied sciences (MUHAS)

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DECLARATION AND COPYRIGHT

I, Dr. Primus Felician Saidia, declare that this dissertation work is my own original work and that it has not been presented and will not be presented to any other university for similar or any other dgree award

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DEDICATION

To my Mother for her educational belief and support

To my wife Lucia and our sons, Mwolisa, Jose and Ngashase

ABSTRACT

Background: Sickle-cell disease, is an inheritable hemoglobinopathy where red cells assume an abnormal, rigid, sickle shape leading to several complications, one of them, chronic renal failure. The disease is common among blacks. Renal failure in SCD patients ranges from 5 to 18 percent and contributes to 18% of the overall mortality in SCD patients. Despite its remarkable contribution in mortality, no data from Africa and especially Tanzania is available to address the extent of renal failure in SCD patients.

Objective: This study aimed to determine the prevalence of renal failure and associated factors among sickle cell disease patients attending Muhimbili National Hospital in Dar es Salaam, Tanzania.

Methods: A descriptive cross sectional study was done for a period of seven months, September 2010 through March 2011. During this period, patients attending the outpatient SCD clinic were enrolled and screened for features suggestive of renal failure. The data included demographic data, anthropometric measurements and clinical information. Blood for CBC, serum creatinine, urea and electrolytes was obtained, urinalysis inclusive. Renal ultrasound was performed for those with established renal failure. The end point of this study was renal failure defined by eGFR less than 60ml/min/1.73m^2. The collected data was recorded cleaned, validated and finally analysed using SPSS version 15.0. Various associations between the outcome and risk factors were assessed and p-value less than 0.05 was taken as statistically significant

Results: A total of 313 sickle cell disease patients were enrolled into the study. Of these 14.7% had established renal failure (i.e. with eGFR<60ml/min/1.73m^2). Children under 10 years of age were predominantly affected with renal failure (P=0.01). There was no gender predilection (P=0.2).There was statistically significant association between severe anaemia and renal failure. Proteinuria and hypertension were 16.9% and 14.4% respectively however; both had no significant association with renal failure. Proteinuria was associated with advanced age. Anaemia was more severe in those with low eGFR (P 0.001). Blood urea level was significantly associated with renal failure (P<0.0001).There was established renal parenchymal disease ultrasonogarphyically in 44.4% of renal failure patients who underwent renal ultrasound.

Conclusion: This study has revealed that renal failure exists in SCD patients (14.7%), as other studies have documented it to be 5 to 18 percent. The age predilection has changed from advanced age to children less than 10 years of age. Other parameters like proteinuria being common in advanced age, low incidence of hypertension (14.4%), severe anaemia in patients with renal failure, and renal parenchyma changes have remained similar. However, proteinuria and hypertension were not associated with renal

failure (P>0.5). Conclusively, early diagnosis and treatment of renal failure in sickle cell disease patients may retard progression to end stage renal disease.

DEFINITION OF TERMS

Anaemia severity : For the purpose of the study severity of anaemia was defined and classified as follows{<5gm/dl = severe anaemia ; 5-7gm/dl = moderate anaemia ; 7.1-12gm/dl =mild anaemia

eGFR is defined as estimated Glomerular Filtration Rate measured in mL/min/1.73m^2 as calculated from Cockcroft-Gault formula.(ref no.7)

Established Renal Failure was defined as eGFR less than 60 mL/min/1.73m^2

Classification of Hypertension for adults was done in accordance to the European Society of Hypertension classification 2007 whereby hypertension is defined as SBP and DBP ≥ 140/90 mmHg. (Annex **1).** Blood pressure above or equal to the 95th percentiles in children below 18 years, by gender, height and age, were recorded as hypertension according to the American National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents tables 2004(Annex 2)

ABBREVIATIONS

ARF = Acute Renal Failure
BP = Blood Pressure
CBC = Complete Blood Count
CKD = Chronic Kidney Disease
CRF = Chronic Renal Failure
CRD = Chronic Renal Disease
DBP = Diastolic Blood Pressure
eCcr = Estimated Creatinine Clearance
EDTA = Ethylenedeamine-acetic acid
ESRD = End Stage Renal Disease
eGFR = estimated Glomerular Filtration Rate
GFR = Glomerular Filtration Rate
Hb = Haemoglobin
HbSS = Homozygous hemoglobin S
MD = Medical Doctor
M.MED = Masters of Medicine
MPGN = Membranoproliferative Glomerulonephritis
MSc = Masters of Science
MUHAS = Muhimbili University of Health and Allied Sciences
MNH = Muhimbili National Hospital
NOS = Nitric Oxide Synthetase
SBP = Systolic Blood Pressure
SCD = Sickle Cell Disease
SCN = Sickle Cell Nephropathy

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CHAPTER ONE

1.1 INTRODUCTION AND LITERATURE REVIEW

1.1.1 Overview

Sickle-cell disease (or drepanocytosis) is a life-long blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and results in a risk of various complications. The sickling occurs because of a mutation in the hemoglobin gene. (1)

Mutations occur in the ß chain of Hb whereby the hydrophobic amino acid valine takes the place of hydrophilic glutamic acid at the sixth amino acid position of the polypeptide chain. This substitution creates a hydrophobic spot on the outside of the protein structure that sticks to the hydrophobic region of an adjacent haemoglobin molecule's beta chain. This clumping together (polymerization) of Hb S molecules into rigid fibers causes the "sickling" of red blood cells. (2)

SCD has several complications, including chronic renal failure, manifesting with hypertension (high blood pressure) proteinuria (protein loss in the urine), hematuria (red blood cells in urine) and worsened anemia. Progression to end-stage renal failure confers poor prognosis (3).

Over the past 20 years, early medical treatment has significantly increased the life expectancy of children with sickle cell disease. More than 90% of patients now reach the age of 20, and the median life expectancy of sickle cell patients is at least 50 years in countries with advanced healthcare systems. Gender wise, life expectancy averages to 42 and 48 years for males and females, respectively. (1, 4)

Renal failure manifests as acute or chronic in which acute renal failure (ARF) is a syndrome characterized by the rapid decline in glomerular filtration rate (hours to days), retention of nitrogenous waste products, and perturbation of extracellular fluid volume

and electrolyte and acid-base homeostasis. Chronic renal disease (CRD) is a more gradual pathophysiologic process with multiple etiologies, resulting in the inexorable attrition of nephron number and function and frequently leading to end-stage renal disease (ESRD) evident in a period of three months or more ((5).

1.1.2 Cockcroft – Gault equation/formula

This formula is a commonly used surrogate marker for actual creatinine clearance, which may be used to calculate an Estimated Creatinine Clearance, which in turn estimates GFR.

It is named after it's founders and it uses creatinine measurements and a patient's weight to predict the creatinine clearance. (6)

The formula, as originally published for creatinine in µmol/L, is:

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times Constant}{\text{Serum Creatinine (in } \mu\text{mol/L)}}$$

Where *Constant* is *1.23* for men and *1.04* for women.

1.1.3 Stages of Chronic Kidney Disease (7)

Stage	Description	Glomerular Filtration Rate (GFR)
At increased risk	Risk factors for kidney disease (e.g., diabetes, high blood pressure, family history, older age, ethnic group)	More than 90
1	Kidney damage (protein in the urine) and normal GFR	More than 90
2	Kidney damage and mild decrease in GFR	60 to 89
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	Kidney failure (dialysis or kidney transplant needed)	Less than 15

1.1.4 Prevalence and mortality

In the US, sickle cell anemia usually occurs in black people, but sometimes occurs in Hispanic people. In the United States, about one in five hundred black births, and about one in 36,000 Hispanic births, have sickle cell anemia. (8)

The prevalence of sickle cell disease is extremely high in Africa, where 150,000 to 300,000 homozygous individuals are born every year. Africans were well aware of the disease before its first description in America (9). In a newborn screening study in Nigeria, the prevalence of HbSS was 2.8%. (10).

In Tanzania, a study done to evaluate prevalence of sickle cell haemoglobin, HbSS in highlands and lowland revealed that lowlands had higher prevalence of high HbSS than highlands (HbS = 16.04% (98/611) versus 6.32% (36/570), P = 0.0001)(11). It has been estimated that birth incidence of SCD is 6-7 per 1000 children (12).

Also, it is roughly estimated that the prevalence of the trait in Tanzania ranges between 15 - 20%, which is among the highest in Africa (12) In Kenya prevalence of HbSS was found to be 0.8% in one of the coastal regions and constituted to 1.6% of all paediatric admissions. (13)

Despite the fact that more than 70% of sufferers live in Africa, expenditure on the related care and research in the continent is negligible and most advances in the understanding and management of this condition have been based on research conducted in the North. (14)

The prevalence of renal failure in sickle cell disease ranges from 5 to 18% of the total population of SCD patients (15). In a prospective, case-control study of patients with SCD compared with sickle cell hemoglobin C patients, 31 (4.2%) patients were affected by renal failure. The median age at the time of renal failure was 23.1 years. Survival time was 4 years with a median age of death of 27 years after the diagnosis of end-stage renal disease (ESRD) in spite of dialysis treatment. Proteinuria, hypertension, severe anaemia, and hematuria were reliable predictors of chronic renal failure (16). In this series, the presence of the inherited Central African Republic $ß^{s}$-gene cluster haplotype in a patient with SCD increased significantly the risk of chronic renal failure (16). In a prospective survival analysis of 964 patients with sickle cell anaemia in adults, it was found that an 18% overall mortality in adult SCD patients with 40% of these (7.6% of the total) manifesting overt renal failure. None received a kidney transplant. By multivariate regression analysis, renal failure was identified as the major risk factor for early mortality in adult patients with SCD (17, 18, 19)

In a population study of 368 patients, documented chronic renal insufficiency was found in 4.6% of SCD patients and was significantly associated with proteinuria and increased age (20, 4). In patients with SCD, priapism episodes, especially those with postpubertal presentation and tricorporal disease (corpora cavernosa and corpus spongiosa involvement), were associated with increased risk of multiorgan failure, including kidney failure, which has shown to be one of the causes of increased hospital admissions in SCD patients (21, 22).

There is no gender predilection for renal failure in most series. The U.S Renal Data System database shows a marked male predominance of sickle cell nephropathy (SCN), in which few patients were offered transplantation (23).

1.1.5 Pathophysiology

Chronic sickling underlies several mechanisms for kidney injury. The arterial side of the renal microvasculature has a low O_2 tension. The hypertonicity and low pH of the renal medulla promote the formation of hemoglobin polymers in the red cells with deformation of the sickled cells, resulting in an increase in the blood viscosity, functional venous engorgement, and interstitial edema, predisposing the renal microcirculation to ischemia and infarction. Obliteration of the medullary vasculature produces segmental scarring and interstitial fibrosis (structural papillectomy), with formation of dilated renal pelvic capillaries and veins. Hematuria results 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 medulla interferes with the countercurrent exchange mechanism, culminating through the years in irreversible loss of medullary tonicity. It has been postulated that renal cortical blood flow and eGFR are increased by the secretion of medullary vasodilator prostaglandins. (24)

Hyperfiltration coupled with glomerular hypertrophy can lead to glomerulosclerosis (15,24,25). Once progression of the glomerular damage is evident, eGFR begins to decrease, worsened by the ingestion of analgesics that can independently induce interstitial nephropathy (15). There is a documented pattern of increased dextran

permeability in the glomerular basement membrane of SCD patients, with an incremental increase in the pore radius. These changes could cause a nonselective proteinuria rather than the microalbuminuria associated with hyperfiltration (26).

Another study using a transgenic sickle cell mouse model showed that there is an induction of nitric oxide synthase II (NOS II) in the glomeruli and distal nephron. This enzyme may increase the synthesis of nitric oxide leading to vasodilation and contribute subsequently to hyperfiltration (27).

1.1.6 Clinical features

The clinical manifestations of these pathophysiologic processes in SCD are well defined Hyposthenuria is the first clinical evidence of defective medullary tonicity. In SCD patients older than 10 years, the maximal urinary concentration is often reduced to 400 mosmol/kg H_2O. This urine concentrating capacity can be restored with multiple transfusions of normal erythrocytes, showing the reversible nature of the defect. However, in patients older than 15 years, the process is often irreversible. Both vasopressin generation and urinary diluting capacity in SCD renal failure patients remain unchanged (15). Hyposthenuria can produce a higher than usual obligatory urine output, thereby increasing the risk of dehydration.

Hematuria

Asymptomatic hematuria is one of the most prevalent features of the disease (15, 24) and occurs either in heterozygous or homozygous patients at any age. Gross hematuria may also be observed in patients with sickle cell trait, either alone or in combination with von Willebrand disease, even in the absence of extrarenal bleeding (15,24). The hematuria is usually unilateral with the left kidney four times more frequently involved than the right. This may be explained by increased venous pressure due to the greater length of the left renal vein (24). Most of the episodes are self-limited, although dramatic and prolonged periods of gross hematuria may be seen (15).

Renal Tubular Acidosis

In sickle cell trait, renal acidification is normal (15 ,24). The distal tubule of homozygous hemoglobin S (Hb-SS) patients requires a greater acidic stimulus to reach a maximum urine-to-blood hydrogen ion gradient. The acidification defect is consistent with less than maximal generation of titratable acid (24). Usually this defect does not cause systemic metabolic acidosis (15). There is no proximal loss of bicarbonate.

Proteinuria

Proteinuria is a frequent finding in SCD and is present in 30% of patients during long-term follow-up (24). Both proteinuria and renal insufficiency increase with age in a parallel pattern (15, 24, 28). Nephrotic syndrome is found in approximately 40% of the patients with sickle cell nephropathy (SCN) (15,42, 29, 30). In a summarized series it was suggested that the nephrotic syndrome in SCD is a predictor of progression to chronic renal failure.

It is believed that glomerular capillary hypertension, thought to be present in sickle cell nephropathy, mediates proteinuria. This concept is supported by the decrease in protein excretion that is observed with the administration of angiotensin-converting enzyme inhibitors (16, 31, 32 and 33).

Renal failure

Renal failure occurs with either an acute or chronic presentation. Acute nonoliguric renal failure is present in 10% of patients hospitalized with SCD (34). Frequently, a concomitant infection or rhabdomyolysis is detected with the renal failure. Less often, renal vein thrombosis and intravascular hemolysis have been reported as causes of acute renal insufficiency in SCD patients (34). Despite the sparse literature, the prognosis appears to be favorable (34). In a retrospective case-control study of 12 SCD patients with acute renal failure, it was reported that 83% of patients survived with recovery of renal function in all patients who survived, without progression to ESRD (34).

Usually, in sickle cell nephropathy the development of ESRD occurs between the third and fifth decades of life (15, 28). However, the renal abnormalities begin at earlier ages (35).

Hyperfiltration is common in young patients with SCD (35) and is closely related to glomerular hypertrophy. Proteinuria in sickle cell nephropathy is associated with glomerulosclerosis on renal biopsy, which often progresses to renal failure. The presence of the nephrotic syndrome in patients with SCN is a clinical marker for ESRD, evolving from the progression of glomerulosclerosis. It is reasonable to argue that chronic renal failure is almost always the consequence of the progression of this mechanism of renal injury in SCN, clinically manifested by proteinuria and pathologically represented by glomerular hypertrophy and focal segmental glomerulosclerosis.

Hypertension

The incidence of hypertension in patients with Hb-SS ranges between 2 and 6% (24) compared with the published incidence for the black population in the United States of 28%. A renal salt-losing state has been suggested to explain the rather low incidence of hypertension in patients with SCD (24), although this would suggest chronic volume depletion. A defect in vascular tone has also been suggested (36). Recent data from the Cooperative Study of Sickle Cell Disease demonstrated that individuals with SCD have blood pressure levels that are significantly lower than in the general population. Predictive variables of blood pressure by multiple regression analysis showed that in males under 18 years, there was a positive correlation between diastolic blood pressure and blood urea nitrogen and a negative correlation with the estimated creatinine clearance. Systolic blood pressure correlated with blood urea nitrogen in females over 17 years of age. Alarmingly, values that could be considered normal or that represent mild hypertension in healthy individuals should be considered a risk factor for important cardiovascular complications in patients with SCD. Also, there is a positive association between blood pressure, stroke, and increased mortality in SCD. (37)

1.1.7 Diagnosis

Proteinuria

Once proteinuria is detected by dipstick, it should be quantified, and renal function should be assessed (15). Diseases other than sickle cell nephropathy should be considered.

Sudden oedema or massive proteinuria (>3 g/24 h) may initially suggest idiopathic nephrotic syndrome, although renal vein thrombosis should always be considered, due to the predisposition of patients with Hb-SS to experience venous thrombosis (15, 24).

Hematuria

Exclusion of other causes of hematuria is important before considering the diagnosis of sickle cell nephropathy. Renal and bladder ultrasound can identify bleeding from a stone or tumor. Increased echogenicity of the renal pyramids or calyceal clubbing by urography, in the absence of hypercalciuria or nephrocalcinosis, may suggest sickle cell disease (15). In gross hematuria, the use of cystoscopy may identify the source of bleeding. Coagulation tests are useful to rule out the concomitant appearance of von Willebrand disease in sickle trait patients.

Hyperfiltration

The upper limit for a normal eGFR is not certain even with inulin clearance (15). Simplified methods for nonisotopic iothalamate and *para*-aminohippurate measurement are now available, although for most clinical purposes an accurate measure of eGFR is not necessary (38). A decrease in eGFR over time in a patient with sickle cell disease, especially when accompanied by proteinuria, requires careful follow-up (15).

1.1.8 Histopathology

Glomerular enlargement was described as part of SCD in 1960 (38). In children, the finding has been reported more frequently beyond 2 years of age (39). This pattern is more obvious in the juxtamedullary glomeruli. A difference in size has been shown when glomeruli from SCD children are compared with healthy children (39). In adults with Hb-SS, the average diameter of the glomeruli (186 ± 14.5 μm) has been found to be greater than that in glomeruli from control biopsies (137.9 ± 19.3 μm) (32). In older patients with

renal involvement, progressive ischemia and fibrosis lead to obliteration of the glomeruli (15).

One histological study, observed perihilar focal and segmental glomerulosclerosis in eight of 10 biopsy specimens (32). The sclerotic segments were adherent to Bowman's capsule with areas of hyalinosis, lipid vacuolation, and foam cells (32). Adjacent to the glomeruli, focal interstitial fibrosis and tubular atrophy were noted. Immunofluorescence microscopy revealed only irregular staining for IgM, C3, and C1q in sclerotic areas. No electron-dense immune complex-type deposits were seen. Some areas of subendothelial rarefaction had the appearance of basement membrane duplication (32).

In an analysis of kidney biopsies from six nephrotic patients with Hb-SS, both collapse of the capillaries and mesangial atrophy and expansion of the obliterated tuft segment by mesangial matrix in maximally hypertrophied glomeruli in focal segmental glomerulosclerosis were described. The mean glomerular diameter was enlarged in nephrotic Hb-SS (233.6 ± 25.3 µm) and non-SCD nephrotic patients (243.0 ± 12.5 µm) compared with control subjects (158.0 ± 12.7 µm). Some peripheral capillary loops had the appearance of duplication, others a wrinkling appearance (40).

In analysing 240 patients with SCD, twelve had nephrotic syndrome. In nine, the glomerular lesion consisted of mesangial expansion and basement membrane duplication (nonimmune membranoproliferative glomerulonephritis [MPGN]-like lesion) and global or focal segmental glomerulosclerosis (32).

Immunofluorescence studies in one series of four young patients with Hb-SS and glomerular disease revealed MPGN like lesions associated with Ig and complement deposition (four patients), and renal tubular epithelial antigen deposition (two patients) in a granular pattern along the glomerular basement membrane (38). In the circulation of some patients, tubular epithelial antigens and cryoprecipitable renal tubular antigen-antibody complexes have been detected (38). It is uncertain whether these were attributable to SCD.

The composite picture of sickle cell glomerulopathy is one of glomerular hypertrophy and focal glomerulosclerosis (32), with either an expansive or collapsing pattern (40). The basement membrane lucencies and areas of apparent duplication present a variable nonimmune MPGN-like picture (17), without the lobular appearance of immune MPGN. In a few cases, an immune complex nephropathy has been reported (38, 41), although it is uncertain whether this is part of sickle cell nephropathy or an unusual appearance of an immune complex nephropathy modified by the presence of sickle cell disease.

Medullary lesions consist of oedema, focal scarring, and interstitial fibrosis with consequent atrophy and mononuclear infiltration. Renal papillary necrosis appears focally, with a few collecting ducts surrounded by an extensive area of fibrosis (15, 24).
Tubular hemosiderin deposits observed in biopsy specimens may play a role in the progression of the nephropathy. Magnetic resonance imaging in SCD patients shows a decrease in the renal cortical spin echo signal, suggesting defective renal cortical iron metabolism (42). In experimental models using rabbits, saccharated-iron complexes can produce the nephrotic syndrome (43).

1.1.9 Management of SCD Renal Failure

Prevention

Treatment aims at preventing vaso-occlusive crises and control of infections which can worsen renal function, in addition to proper identification and management of renal complications. Early neonatal screening for SCD improves survival. (44)
Altitudes above 2500 m without the use of supplementary oxygen should be avoided by SCD patients (24). Heavy exercise may be dangerous to these patients because of the risk of lactic acidosis. Sudden death has rarely been reported, but occurs even in sickle trait patients. Before elective surgery, it is recommended that transfusions with filtered normal red blood cells be performed.

Fluids

Close monitoring of fluid intake and output should be performed. Fluid deprivation, excessive fluid loss, and inability to ingest fluids can induce dehydration in Hb-SS more

rapidly than in a normal population, thus exposing the patient to the additional risk of a potential sickle-cell crisis (24, 28). Urine output usually should be maintained above 2000 ml/day in adults and in children in proportion to their size (24) to ensure adequate hydration. In states of circulatory overload in critically ill patients due to multiple transfusions, the use of furosemide is recommended (15).

Hematuria

Most episodes of gross hematuria in patients with SCD subside spontaneously. However, in a few patients hematuria may be massive. Bed rest is recommended to avoid dislodging clots. The use of hypotonic solutions (4 L/1.73 m^2 per day) in conjunction with diuretics (furosemide or thiazide) can efficiently eliminate clots from the bladder and concomitantly alleviate sickling and possibly prevent renal papillary necrosis (15). Transfusions may be necessary for excessive blood loss. The use of epsilon-aminocaproic acid for fibrinolysis may be necessary. To control hematuria, low doses may be adequate, starting from 1 g per 1.73 m^2 body surface area orally 3 times daily with a subsequent incremental increase until bleeding subsides (15).

Arteriographic localization and local embolization of the affected renal segment are indicated in patients with uncontrolled bleeding (15). Rarely, nephrectomy is required.

Proteinuria

The avoidance of a high protein intake (greater than the recommended dietary allowance) may prevent further deterioration of the nephropathy. However, protein restriction is not recommended due to pre-existent growth failure and the low energy state of many Hb-SS patients (45).

The use of angiotensin-converting enzyme inhibitors potentially can diminish the degree proteinuria in SCD patients with nephropathy. A 2 week trial with enalapril therapy involving 10 patients with mild nephropathy showed that proteinuria decreased by 57%, but returned to high levels after treatment withdrawal. Blood pressure, GFR, and effective renal plasma flow did not change significantly (32)

Renal Transplant

Renal transplantation in SCD patients is as well useful in SCD patients with ESRD. However, little is offered by physicians by assuming there is a poor chance for successful therapy. A study by Ojo and colleagues reported similar short-term survival of renal allografts in recipients with end-stage SCN with non sicklers with ESRD. However, long term benefits were comparatively low in SCD patients with ESRD. (46)

Furthermore, renal transplant conferred better patient survival compared to dialysis in patients with ESRD. Similar results hold true for adolescent patients (47).

Preparation prior to transplantation includes transfusion of lymphocyte-depleted packed cells (often required due to inherent erythropoietin resistance). A rise in the hematocrit and plasma viscosity may precipitate a plasma cell crisis, which is especially common in the first year after transplantation. The concurrent use of hydroxyurea to increase hemoglobin F production while decreasing the hematocrit may reduce the frequency of crises, thereby improving graft survival (48, 49).

In summary, sickle cell nephropathy is an important cause of mortality in SCD patients, with specific genetic and clinical markers that can indicate further progression to ESRD. Chronic sickling promotes different mechanisms of kidney injury: structural papillectomy, urine concentration defects, hyperfiltration, and glomerular enlargement and sclerosis. Clinical detection of the manifestations of these processes, as well as detection of risk factors for medullary carcinoma, can permit the clinician to offer a rational treatment to the SCD patient.

Chronic dialysis and transplantation represent reasonable options for those patients who develop ESRD.

1.2 PROBLEM STATEMENT

Sickle cell disease is common in Africa with 150,000 to 300,000 homozygous individuals born every year (8).). It has been estimated that birth incidence of SCD is 6-7 per 1000 children.

In addition, it is roughly estimated that the prevalence of the trait in Tanzania ranges between 15 - 20%, which is among the highest in Africa (12)

The World Health Organization has recently recognized that Sickle cell disease (SCD) as a problem of major public health significance. Despite the fact that more >70% of sufferers live in Africa, expenditure on the related care and research in the continent is negligible, and most advances in the understanding and management of this condition have been based on research conducted in the North (14).

From previous published reports, the presence of renal failure in sickle cell disease (SCD) ranges between 5 - 18% of the total population of SCD patients (1)

Chronic sickling underlies several mechanisms for kidney injury. The arterial side of the renal microvasculature has a low O_2 tension. The hypertonicity and low pH of the renal medulla promote the formation of hemoglobin polymers in the red cells with deformation of the sickled cells, resulting in an increase in the blood viscosity, functional venous engorgement, and interstitial edema, predisposing the renal microcirculation to ischemia and infarction. This results into glomerular damage and therefore real failure (15).

Despite such a high prevalence of renal failure among sickle cell patients, no other study has been done in Tanzania to evaluate the extent of this condition for betterment of SCD patient management and improved outcomes.

1.3 RATIONALE

Tanzania is currently establishing specialized renal unit at Muhimbili National Hospital and other centers in order to improve health care for people with renal problems. However, little is known on the extent of renal failure in high-risk groups such as sickle cell disease patients.

This study determined the prevalence of renal failure among sickle cell disease patients attending sickle cell clinic at Muhimbili National Hospital.

This study identified sickle cell disease patients with renal failure at different stages and the indicators for the disease.

The information obtained will help in the management of SCD patients and therefore improve quality of life and reduce mortality.

1.4 OBJECTIVES

Broad objective

To determine the prevalence of renal failure and associated factors among SCD patients attending sickle cell disease clinic at Muhimbili National Hospital.

Specific Objectives

1. To determine the prevalence of renal failure in SCD patients according to age and sex.

2. To describe the severity of renal failure in SCD patients by age and sex.

3. To determine the relationship between renal failure and past clinical illness within six months

4. To determine the relationship between renal failure in SCD patients and laboratory findings.

CHAPTER TWO
2.0 METHODOLOGY

2.1 Study Area

Muhimbili National Hospital, Dare es Salaam, Tanzania.

2.2 Study Design

A descriptive cross sectional study was done to determine the prevalence of renal failure among SCD patients attending sickle cell disease clinics.

2.3 Study Population

The study participants were sampled from the sickle cell disease adult and paediatric clinics at Muhimbili National Hospital

2.4 Inclusion Criteria

All sickle cell disease patients aged 5 years and above were considered for enrolment. Only those consenting and assenting for the study were studied.

2.5 Sample size:

The sample size will be calculated from the following formula

$$N= Z^2 P (100- P)/ E^2$$

Where: Z= critical value 1.96

N = Estimated sample size

E = Margin of error

P = Prevalence of renal failure in SCD

$$N = (1.96)^2 \times 18(100-18)/(4.2)^2$$

$$=308.$$

2.6 Sampling procedure

Convenience sampling procedure was used whereby all SCD patients with the above criteria were consecutively enrolled into the study after patients/parents/guardians provided written consent. For children above ten years, verbal assent to participate was obtained and the written consent was signed by the accompanying parent or guardian until the sample size was reached.

Patients were enrolled into the study during clinic visits whereby the first 20 to 30 patients were enrolled per each clinic visit.

2.7 Data collection

Data were collected using structured questionnaires designed for the purpose of the study. Data collected included demographic data, age, sex and past clinical illness/crisis as well as laboratory investigations. To minimize recall bias, the information about the past clinical events was taken within six months period.

2.8 Patients' management

Routine clinical procedures in patient management were followed and, in addition, patient's body weight was measured using a bathroom weighing scale. Blood pressure was measured using an electronic blood pressure machine type Omron(M6), where appropriate paediatric cuff was used for children. Blood pressure reading was taken three times and the average was recorded as the patient's blood pressure.

Systolic blood pressure of 140mmHg and above and diastolic blood pressure of 90mmHg above were recorded as hypertension for adults aged 18 years according to the European Society of hypertension classification 2007. Blood pressure above or equal to the 95^{th} percentiles in children below 18 years, by gender, height and age, were recorded as hypertension according to the American National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents tables 2004. Specific investigations were performed including complete blood count, urinalysis,

renal function tests (creatinine and urea) and serum electrolytes. Results were communicated to the attending doctor and the patient to aid in the general care for the patient.

2.9 Specimens and Investigations

Blood samples for RFT and electrolytes were collected aseptically in 5 ml red top vacutainers.(BD, NJ, USA). Samples for CBC were collected in vacutainers containing EDTA (Ethylenediaminetetra-acetic acid). Approximately 3 ml was collected.
About 10 ml of mid-stream urine was collected in universal sterile clear bottles for urinalysis. Young children were assisted by their accompanying parents/guardians on collecting the midstream urine, where they were instructed to wait a few seconds as the child starts voiding, then collect the urine .

RFT and electrolytes were performed in the laboratory using Architect Chemistry Analyser (Make: Abbot). Serum creatinine and urea were recorded for analysis. Complete blood count (CBC) was done using Cell-dyn 3500R analyser. Urinalysis was done macroscopically using urine dipstick and microscopy using microscope.
Estimated Glomerular Filtration Rate (eGFR) was calculated using the Cockroft- Gault equation/formula. eGFR of less than 60mL/min/1.73m^2 was described as established renal failure. Proteinuria in patients with eGFR >90 defined stage one renal failure.

Renal ultrasonography was done to patients with eGFR less than 60mL/min/1.73m^2 described as established renal failure to ascertain features of SCD involvement and to exclude other causes of renal failure including renal or bladder stones.

2.10 Data management and Statistical analysis

Data was entered, cleaned, validated and analyzed using SPSS version 15.0. The prevalence of renal failure was expressed in percentages for the entire study group and by age and sex.

χ^2 test was used to examine the association between renal failure and categorical variables and Fisher's exact test was used when the expected count was less than five. Student t-test was used to determine the association between two continuous variables. P values < 0.05 were taken as statistically significant.

2.11 Ethical issues

A written consent was obtained from the adult patients/parent/ guardian prior to enrolment and in addition, a verbal assent was obtained from older children (10-17 years). The following information was given during patient/parent/guardian education to ensure that they have the information needed to make an informed choice: a complete description of the aims of the study, investigations that were to be performed, potential benefits and risks, specimen collection procedures, and assurance of confidentiality of any information given as well as test results. Any other requested additional information was provided to patients/parents/guardian by study personnel. Patients found with renal failure were referred to the hospital renal unit. Patient's information and results were dealt with confidentially

2.13 Ethical clearance

Ethical clearance was obtained from the MUHAS high degree ethical committee of research and publication.

CHAPTER THREE

3.0 RESULTS

3.1Demographic characteristics and prevalence of renal failure.

During the study, a total number of 313 known sickle cell disease patients were enrolled, out of which 173 (55.3%) were females. The majority of the patients 160(51.1%) were between 10-19 years of age.

All the patients were anaemic with haemoglobin range between 3.1-12g/dl (7.7±1.4, median , 7.6g/dl) (Table 1.)

The study revealed that 14.7% of the study participants had established renal failure (eGFR<60mL/min/1.73m^2). Of those with renal failure, a significant number (45.2%, P=0.01) were children under 10 years. Thirty-one female patients (17.9%) had established renal failure; however, there was no gender predilection. (P = 0.2) (Table 2). The mean age at established renal failure was found to 10.6 years. There were no patients with eGFR less than 30mL/min/1.73m^2, hence no stage four and five renal failure in the study population.

Table1: Demographic,and laboratory characteristics in the study population (N = 313)

Category	Min value	Max value	Median	Frequency	Mean±std
Sex					
Male				140(44.7%)	
Female				173(55.3%)	
Age (yrs)	5	44	16		16±7
Pulse rate (bpm)	59	147	88		90±14
SBP (mmHg)	90	153	111		113±15
DBP (mmHg)	41	108	72		72±12
Serum Creatinine (umol/L)	26.4	176.7	50.2		53.7±16.4
BUN (mmol/L)	1.0	10.0	2.2		2.4±1.2
GFR (mL/min/1.73m^2)	33.0	183.0	93		92.9±29.3
Calcium level (mmol/L)	2.0	2.7	2.3		2.3±0.2
Phosphate Level (mmol/L)	0.7	2.1	1.4		1.4±0.2
Potassium Level (mmol/L)	3.1	10.0	4.2		4.4±0.9
Sodium Level(mmol/L)	123.0	157.0	137		138.8±5.4
Chlorine level (mmol/L)	96.0	124.0	107		107.9±4.6
Urine Protein	0	+2			
RBC Casts (present)				9(2.9%)	
SG	1.00	1.03			1.02±0.0
RBC (M/uL)	1.22	5.75	2.8		2.94±0.75
Hemoglobin level (g/dl)	3.1	12.0	7.6		7.7±1.4
MCV(fL)	54	128	88		86.9±10.3
MCHC(g/dl)	23.1	33.2	30.8		30.5±1.2
MCH(pg)	14.9	41.0	27.2		26.7±3.7
WBC (K/uL)	3.6	33.8	13.4		14.12±5.0

Table 2: The Stages of Kidney function according to age and sex (N=313)

GFR(ml/min/1.73m²) Characteristic	Normal (≥90)	Stage II (60-89)	Stage III (30-59)	Total	P-value
Age(Years)					<0.01
5-9	7 (9.6%)	33 (45.2%)	33 (45.2%)	73 (100%)	
10-19	101 (63.1%)	52 (32.5%)	7 (4.4%)	160 100	
20-44	58 (72.5%)	16 (20.0%)	6 (7.5%)	80 100%	
Total	166 (53.0%)	101 (32.3%)	46 (14.7%)	313 100%	
Sex					
Male	78 (55.70%)	47 (33.6%)	15 (10.7%)	140 (100%)	
Female	88 (50.9%)	54 (31.2%)	31 (17.9%)	173 (100%)	0.20
Total	166 (53.0%)	101 (32.3%)	46 (14.7%)	313 100%	

3.2 Proteinuria and Renal Failure

The prevalence of proteinuria in this study has been shown to be 16.9% (53 patients). However, there is no significant association between proteinuria and different stages of renal failure (P=0.144)

By definition of stage one renal failure, that is eGFR more than 90 with protein in urine, 33 out of 313 patients (10.6%) have stage I renal failure, while 42.5% had normal renal function. (Table 3). Further analysis revealed statistically significant association between proteinuria and advanced age, P= 0.04

Table 3: Proteinuria and the level of kidney function (eGFR in mL/min/1.73m^2)

N=313

		Levels of GFR			Total
		90+	60-89.9	30-59.9	
Protein in urine	absent	133	90	37	260
		80.1%	89.1%	80.4%	83.1%
	present	33	11	9	53
		19.9%	10.9%	19.6%	16.9%
	Total	166	101	46	313
		100.0%	100.0%	100.0%	100.0%

P = 0.144

3.3 Renal function in relation to past clinical events/crisis, anaemia severity, hypertension and blood urea levels

The presence or absence of clinical events which included painful crisis, severe anaemia necessitating blood transfusion, acute chest syndrome, malaria or other infections within a six months period had no significant association with renal failure, p = 0.84 (table 4) Furthermore, the study has shown that anaemia was significantly more severe in patients with low eGFR, P<0.001 (table 4.)

Using the European Society of hypertension classification 2007 for adults (18 years and above) and blood pressure percentiles in children below 18 years, by gender, height and age, the overall prevalence of hypertension among SCD patients was found to be 14.4%. When analysed separately 4.2% and 4.5% had isolated systolic hypertension and diastolic hypertension respectively. Five point eight percent had both SBP and DBP elevated. Further analysis revealed no association between renal failure and hypertension (pvalue = 0.16) (Table 4)

Five patients (1.6%) were found to have asymptomatic uraemia. Further analysis has shown a statistically significant association between the severity of uraemia (urea above 7.2mmol/L) and renal failure. P= 0.0001. (Table 4)

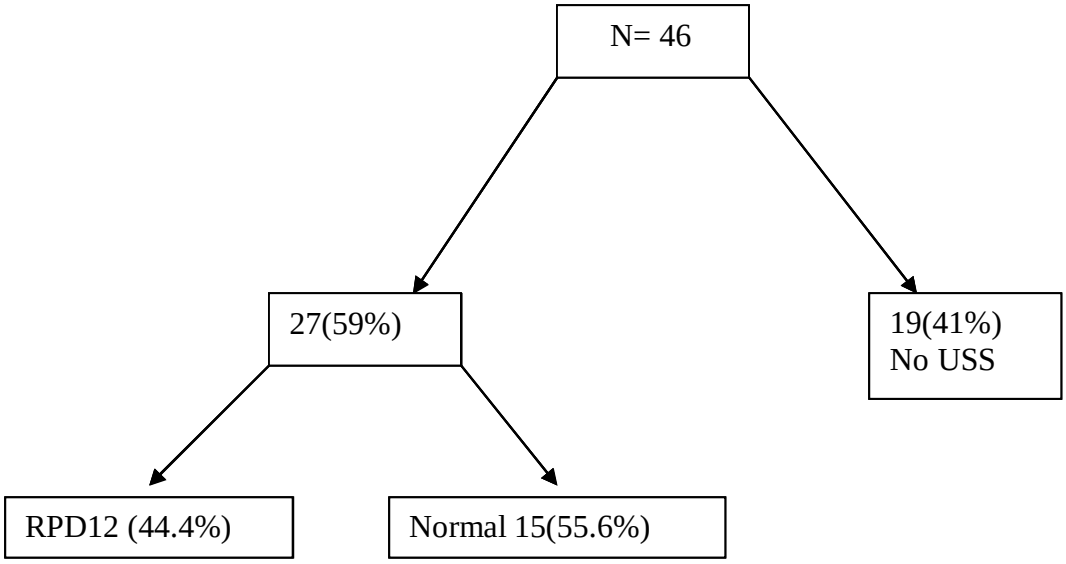
Table 4. Renal function in relation to past clinical events/crisis, anaemia severity, hypertension and blood urea and nitrogen levels

		Level of eGFR		Total	Pvalue
		<60	≥60		
Clinical event/crisis	Present	34(14.5%)	201(85.5%)	235(100%)	0.84
	Absent	12(15.4%)	66(84.6%)	78(100%)	
Anaemia severity	severe (Hb <5g/dl)	7(77.8%)	2(22.2%)	9(100%)	0.001
	Moderate (Hb 5-7g/dl)	18(22.5%)	62(77.5%)	80(100%)	
	Mild(HB 7.1-12g/dl)	21(9.4%)	203(90.6%)	224(100%)	
Hypertension	YES	3(7.0%)	42(93.0%)	45(100%)	0.16
	NO	43(16.0%)	267(85.3%)	268(100%)	
Urea Levels	Low	3(17.6%)	14(82.4%)	17(100%)	0.0001
	Normal	38(13.1%)	253(86.9%)	291(100%)	
	High	5(100%)	0(0%)	5(100%)	

3.4 Renal Ultrasonography findings in patients with established renal failure

From Figure 1 below, 59% of patient with established renal failure by GFR (less than 60 mL/min/1.73m^2) appeared for renal ultrasound. Based on echogenicity and corticomedullary differentiation, 44.4% had established renal parenchyma disease.(fig 1)

Fig 1.Renal Ultrasound Findings



RPD= renal parenchyma disease

CHAPTER FOUR

4.0 DISCUSSION

4.1 Major findings

The major findings in this study are, firstly the prevalence of renal failure among sickle cell disease patients attending SCD clinics at MNH is relatively high. Secondly, the younger patients are more affected by renal failure with no gender predilection. Thirdly, severity of anaemia was statistically significant with the level of kidney function by eGFR, indicating that those with low eGFR have worsening anaemia. Fourthly, proteinuria and hypertension were relatively high with no association to renal failure. Lastly, there was evidence of renal parenchymal disease in patients with established renal failure by renal ultrasonography.

4.2 Prevalence of renal failure by age and sex

The prevalence of renal failure in this study was found to be 14.7%, (with eGFR less than 60.) This is within ranges found by other studies where renal failure was estimated to be between 5 to 18 %.(15).

In this study, it has been shown that renal insufficiency (i.e., those with eGFR of 60-89) is approximately 32.3%. This is higher than results from previous studies where chronic renal insufficient has been documented to be 4.6% in sickle cell disease patients (4, 20).

This can be explained by the fact the Cockroft-Gault equation used to calculate the eGFR in this study, overestimates the eGFR by 5-23% when compared with other classical modalities such as inulin clearance (6) Therefore some of the patients classified as CKD stage two, may be in higher stages of renal failure.

The study has also shown age predilection whereby renal failure affects younger patients between 5 to 9 years (P =0.01). The mean age at established renal failure was 10.6 years This is contrary to other study findings where increased age was a risk factor for renal failure. Studies have shown age predilection, revealing that manifestation of CKD start

around 10 years of age with hyposthenuria as the first clinical indicator. The median age at ESRD is 23.1 years (15,16).

This can be explained by the fact that most of other studies to determine renal failure in sickle cell disease patients were done in developed countries where quality of life and health care is optimal, hence slow progression to organ damage in sickle cell disease patients. Early diagnosis, regular clinic follow-up and management of sickle cell patients retards chronic kidney damage (44). These services are rarely available in underdeveloped countries like Tanzania where the study has been conducted. Studies done in West Africa have demonstrated vey high prevalence of chronic renal failure, others recording as high as 31.8% (53)

It has as well been documented that presence of the inherited Central African Republic bs-gene cluster haplotype in a patient with SCD increased significantly the risk of chronic renal failure even at young age (3). This study being done in Africa, there may be some inherited gene cluster haplotypes which may worsen and fasten the establishment of renal failure in young patients with sickle cell disease.

The study has shown no gender predilection (p =0.2), thereby concurring with other studies. However, the US database system shows a marked male predominance (23).

4.3 Proteinuria and renal function

In this study, prevalence of proteinuria was 16.9%. Moreover, there was no statistically significant association between proteinuria and renal failure(P = 0.14). Other studies have documented that with many other predictors such as hypertension, severe anaemia and hematuria, proteinuria predicted renal failure (16). This can be explained by the fact that in this study only dipstick urine protein was performed which cannot detect very low levels of protein in urine.

The study has also shown proteinuria to increase significantly with age (P=0.04). This has been documented by other studies which have shown proteinuria and renal failure increasing parallel with age(15,24,28)

Proteinuria is a useful in staging renal failure or chronic kidney disease (CKD) in those patients with GFR more than 90, as the presence of protein in urine distinguishes between stage 1 and normal kidney function (7). In this study patients with protein in urine but with normal GFR were 33 out of 313 patients (10.6%) hence stage I renal failure, while 42.5% had normal renal function.

4.4 Hematuria in SCD patients

The prevalence of hematuria was 2.9%. Its association with renal failure was not assessed because of its very low prevalence. Other studies have shown that asymptomatic hematuria is one of the most prevalent features of the sickle cell disease independent of age (15, 24), this can either be gross or microscopic. However, the hematuria so observed in this study was purely microscopic. Gross hematuria may also be observed in patients with sickle cell disease either alone or in combination with von Willebrand disease, even in the absence of extrarenal bleeding (15,24).

It has been proved by studies that hematuria is usually unilateral frequently from the left kidney four times than the right. This may be explained by increased venous pressure due to the greater length of the left renal vein. Most of the episodes are self-limited, although dramatic and prolonged periods of gross hematuria may be seen (15,24). The study did not asses the laterality of the hematuria so observe. Therefore, exclusion of other causes of hematuria such as renal or bladder stones by ultra sound or other investigations are important before considering diagnosis of SCD nephropathy.

4.5 Hypertension in SCD patients with renal failure

The overall prevalence of hypertension among SCD patients was found to be 14.4%. When analysed separately 4.2% and 4.5% had isolated systolic hypertension and diastolic hypertension respectively. Five point eight percent had both SBP and DBP elevated.

Further analysis revealed no association between renal failure and hypertension (p = 0.16). Other studies have documented the prevalence of hypertension in SCD patients to range between 2 to 6% (24). Therefore, the study findings show slightly high prevalence as compared to other studies.

However, this is still low concurring with the fact that the prevalence of hypertension in sickle cell disease is notably low as compared to the incidence in black population in the United States which is 28%. Renal salt loosing state, defect in vascular tone have been suggested to be the cause of low incidence of hypertension in sickle cell disease.(24,36)

Studies have shown that blood pressure values that could be considered normal or mild hypertension in normal individuals are important risks for major cardiovascular events such as stroke and increased mortality in sickle cell disease patients (37)

4.6 Clinical illness in SCD patients with renal failure

In this study reported sickle cell crisis or clinical event/illness in the past six months which included painful crisis, acute chest syndrome, severe anaemia with blood transfusion, malaria and other infections did not predict increased risk of renal failure.(p = 0.84). In other studies, recurrent clinical events or sickle cell crisis have been shown to be associated with increased risk of multiple organ failure, including renal failure (21,22).However, other studies have documented occurrence of organ damage irrespective of the rate of clinical illness such as painful crisis concurring with the above findings(50). This study based on self reported clinical events or crisis in the past six months. Recall bias may have accounted for the above.

4.7 Uraemia and renal function.

Asymptomatic uraemia was present in 5% of all patients. Concurrently all patients with uraemia had established renal failure with eGFR less than 60 (P = 00001). This correlates with uraemia as defining finding in renal failure. In CKD, the level of serum urea increases with decreasing eGFR. However, symptomatic uraemia usually develops only after the creatinine clearance falls to less than 10 mL/min, although some patients may be

symptomatic at higher clearance levels, especially if renal failure acutely develops. The syndrome may be heralded by the clinical onset of nausea, vomiting, fatigue, anorexia, weight loss, muscle cramps, pruritus, and change in mental status (51). However, in this study the lowest eGFR was 33mL/min/1.73m². Moreover, dehydration may have been a confounder.

4.8 Anaemia and renal failure

There was a very strong significant association between renal failure and severity of anaemia (P=0.000). Therefore increasing severity of anaemia predicted advanced stage of renal failure. This comply with other studies which have show that worsening anaemia predicts renal failure (15,24,28). Anaemia commonly worsens in patients with established renal failure due to erythropoietin deficiency , increased erythrocyte destruction due to uraemia, and bone marrow suppression. Moreover, studies have shown that anemia begins early in the course of chronic renal insufficiency therefore highly associated with established renal failure (52). Hence in the presence of sickle cell anaemia, the condition is worsened by presence of renal failure

4.9 Renal ultrasonography in SCD nephropathy

The study has revealed established renal parenchymal disease in 12 patients (44.4%) out of 27 patients with established renal failure who underwent renal-pelvic ultrasound. Established renal parenchyma disease was based on loss of corticomedullary differentiation and increased echogenicity. Other studies have shown that, with ultrasonography, there is increased echogenicity of the inner medulla, and in more advanced cases, a filling defect in the area of the medullary tip in patients with sickle cell disease nephropathy.(15) Therefore, the ultrasonographic findings have show presence of renal parenchymal disease in those with renal failure. However early parenchymal changes may have not been evident in the renal ultrasonography.

CHAPTER FIVE

5.0, CONCLUSION AND RECOMMENDATIONS, STUDY LIMITATIONS

5.1 Conclusion

- This study has estimated the presence renal failure (14.7%)among SCD patients attending the hospital clinic
- Severe anaemia (Hb <5g/dl) in sickle cell patients was found to be strongly associated with renal failure
- Younger patients have increased prevalence of renal failure, therefore contrasting the previous knowledge that renal failure is a disease of advanced age in SCD patients.
- Protein in urine increases with increased age. However, proteinuria and hypertention do not correlate with eGFR reduction.

5.2 Recommendations

- Patients with SCD should regularly within three to six months period be screened for renal function using eGFR and or other simple investigations such as urine analysis which are readily available.
- Further follow-up studies should be conducted in our setting to further evaluate the extent and outcome of patients with SCD when screening tests are abnormal
- Evaluation with prompt treatment of those with features of declining renal function should be done as treatment with ACE inhibitors for those with proteinuria slows the progress to ESRD.

5.3 Study Limitations:

- This study is a single centre cross-sectional study therefore its findings may not be generalizable.
- Recall bias/error in self-reported responses about past illnesses
- Other causes of renal failure such as HIV/AIDS, diabetes were not assessed.
- Lack of a comparison group in those who did the ultrasound.

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Annex 1

Classification of Hypertension according to the European Society of Hypertension Classification 2007

Category	Systolic		Diastolic
Optimal	<120	and	<80
Normal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1 hypertension	140–159	and/or	90–99
Grade 2 hypertension	160–179	and/or	100–109
Grade 3 hypertension	≥180	and/or	≥110
Isolated systolic hypertension	≥140	and	<90

Isolated systolic hypertension should be graded (1,2,3) according to systolic blood pressure values in the ranges indicated, provided that diastolic values are <90 mmHg.

Annex II: American National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004. Tables for estimating Blood pressure in children and adolescents

TABLE 3. BP Levels for Boys by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	80	81	83	85	87	88	89	34	35	36	37	38	39	39
	90th	94	95	97	99	100	102	103	49	50	51	52	53	53	54
	95th	98	99	101	103	104	106	106	54	54	55	56	57	58	58
	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	50th	84	85	87	88	90	92	92	39	40	41	42	43	44	44
	90th	97	99	100	102	104	105	106	54	55	56	57	58	58	59
	95th	101	102	104	106	108	109	110	59	59	60	61	62	63	63
	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	50th	86	87	89	91	93	94	95	44	44	45	46	47	48	48
	90th	100	101	103	105	107	108	109	59	59	60	61	62	63	63
	95th	104	105	107	109	110	112	113	63	63	64	65	66	67	67
	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	50th	88	89	91	93	95	96	97	47	48	49	50	51	51	52
	90th	102	103	105	107	109	110	111	62	63	64	65	66	66	67
	95th	106	107	109	111	112	114	115	66	67	68	69	70	71	71
	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	50th	90	91	93	95	96	98	98	50	51	52	53	54	55	55
	90th	104	105	106	108	110	111	112	65	66	67	68	69	69	70
	95th	108	109	110	112	114	115	116	69	70	71	72	73	74	74
	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	50th	91	92	94	96	98	99	100	53	53	54	55	56	57	57
	90th	105	106	108	110	111	113	113	68	68	69	70	71	72	72
	95th	109	110	112	114	115	117	117	72	72	73	74	75	76	76
	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	50th	92	94	95	97	99	100	101	55	55	56	57	58	59	59
	90th	106	107	109	111	113	114	115	70	70	71	72	73	74	74
	95th	110	111	113	115	117	118	119	74	74	75	76	77	78	78
	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	50th	94	95	97	99	100	102	102	56	57	58	59	60	60	61
	90th	107	109	110	112	114	115	116	71	72	72	73	74	75	76
	95th	111	112	114	116	118	119	120	75	76	77	78	79	79	80
	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	50th	95	96	98	100	102	103	104	57	58	59	60	61	61	62
	90th	109	110	112	114	115	117	118	72	73	74	75	76	76	77
	95th	113	114	116	118	119	121	121	76	77	78	79	80	81	81
	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	50th	97	98	100	102	103	105	106	58	59	60	61	61	62	63
	90th	111	112	114	115	117	119	119	73	73	74	75	76	77	78
	95th	115	116	117	119	121	122	123	77	78	79	80	81	81	82
	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	50th	99	100	102	104	105	107	107	59	59	60	61	62	63	63
	90th	113	114	115	117	119	120	121	74	74	75	76	77	78	78
	95th	117	118	119	121	123	124	125	78	78	79	80	81	82	82
	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	50th	101	102	104	106	108	109	110	59	60	61	62	63	63	64
	90th	115	116	118	120	121	123	123	74	75	75	76	77	78	79
	95th	119	120	122	123	125	127	127	78	79	80	81	82	82	83
	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	50th	104	105	106	108	110	111	112	60	60	61	62	63	64	64
	90th	117	118	120	122	124	125	126	75	75	76	77	78	79	79
	95th	121	122	124	126	128	129	130	79	79	80	81	82	83	83
	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	50th	106	107	109	111	113	114	115	60	61	62	63	64	65	65
	90th	120	121	123	125	126	128	128	75	76	77	78	79	79	80
	95th	124	125	127	128	130	132	132	80	80	81	82	83	84	84
	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	50th	109	110	112	113	115	117	117	61	62	63	64	65	66	66
	90th	122	124	125	127	129	130	131	76	77	78	79	80	80	81
	95th	126	127	129	131	133	134	135	81	81	82	83	84	85	85
	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	50th	111	112	114	116	118	119	120	63	63	64	65	66	67	67
	90th	125	126	128	130	131	133	134	78	78	79	80	81	82	82
	95th	129	130	132	134	135	137	137	82	83	83	84	85	86	87
	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
17	50th	114	115	116	118	120	121	122	65	66	66	67	68	69	70
	90th	127	128	130	132	134	135	136	80	80	81	82	83	84	84
	95th	131	132	134	136	138	139	140	84	85	86	87	87	88	89
	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
For research purposes, the SDs in Table B1 allow one to compute BP Z scores and percentiles for boys with height percentiles given in Table 3 (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z scores given by: 5% = −1.645; 10% = −1.28; 25% = −0.68; 50% = 0; 75% = 0.68; 90% = 1.28; and 95% = 1.645, and then computed according to the methodology in steps 2 through 4 described in Appendix B. For children with height percentiles other than these, follow steps 1 through 4 as described in Appendix B.

TABLE 4. BP Levels for Girls by Age and Height Percentile

Age, y	BP Percentile	SBP, mm Hg							DBP, mm Hg						
		Percentile of Height							Percentile of Height						
		5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	50th	83	84	85	86	88	89	90	38	39	39	40	41	41	42
	90th	97	97	98	100	101	102	103	52	53	53	54	55	55	56
	95th	100	101	102	104	105	106	107	56	57	57	58	59	59	60
	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	50th	85	85	87	88	89	91	91	43	44	44	45	46	46	47
	90th	98	99	100	101	103	104	105	57	58	58	59	60	61	61
	95th	102	103	104	105	107	108	109	61	62	62	63	64	65	65
	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	50th	86	87	88	89	91	92	93	47	48	48	49	50	50	51
	90th	100	100	102	103	104	106	106	61	62	62	63	64	64	65
	95th	104	104	105	107	108	109	110	65	66	66	67	68	68	69
	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	50th	88	88	90	91	92	94	94	50	50	51	52	52	53	54
	90th	101	102	103	104	106	107	108	64	64	65	66	67	67	68
	95th	105	106	107	108	110	111	112	68	68	69	70	71	71	72
	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	50th	89	90	91	93	94	95	96	52	53	53	54	55	55	56
	90th	103	103	105	106	107	109	109	66	67	67	68	69	69	70
	95th	107	107	108	110	111	112	113	70	71	71	72	73	73	74
	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	50th	91	92	93	94	96	97	98	54	54	55	56	56	57	58
	90th	104	105	106	108	109	110	111	68	68	69	70	70	71	72
	95th	108	109	110	111	113	114	115	72	72	73	74	74	75	76
	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	50th	93	93	95	96	97	99	99	55	56	56	57	58	58	59
	90th	106	107	108	109	111	112	113	69	70	70	71	72	72	73
	95th	110	111	112	113	115	116	116	73	74	74	75	76	76	77
	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	50th	95	95	96	98	99	100	101	57	57	57	58	59	60	60
	90th	108	109	110	111	113	114	114	71	71	71	72	73	74	74
	95th	112	112	114	115	116	118	118	75	75	75	76	77	78	78
	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	50th	96	97	98	100	101	102	103	58	58	58	59	60	61	61
	90th	110	110	112	113	114	116	116	72	72	72	73	74	75	75
	95th	114	114	115	117	118	119	120	76	76	76	77	78	79	79
	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	50th	98	99	100	102	103	104	105	59	59	59	60	61	62	62
	90th	112	112	114	115	116	118	118	73	73	73	74	75	76	76
	95th	116	116	117	119	120	121	122	77	77	77	78	79	80	80
	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	50th	100	101	102	103	105	106	107	60	60	60	61	62	63	63
	90th	114	114	116	117	118	119	120	74	74	74	75	76	77	77
	95th	118	118	119	121	122	123	124	78	78	78	79	80	81	81
	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	50th	102	103	104	105	107	108	109	61	61	61	62	63	64	64
	90th	116	116	117	119	120	121	122	75	75	75	76	77	78	78
	95th	119	120	121	123	124	125	126	79	79	79	80	81	82	82
	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	50th	104	105	106	107	109	110	110	62	62	62	63	64	65	65
	90th	117	118	119	121	122	123	124	76	76	76	77	78	79	79
	95th	121	122	123	124	126	127	128	80	80	80	81	82	83	83
	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	50th	106	106	107	109	110	111	112	63	63	63	64	65	66	66
	90th	119	120	121	122	124	125	125	77	77	77	78	79	80	80
	95th	123	123	125	126	127	129	129	81	81	81	82	83	84	84
	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	50th	107	108	109	110	111	113	113	64	64	64	65	66	67	67
	90th	120	121	122	123	125	126	127	78	78	78	79	80	81	81
	95th	124	125	126	127	129	130	131	82	82	82	83	84	85	85
	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	50th	108	108	110	111	112	114	114	64	64	65	66	66	67	68
	90th	121	122	123	124	126	127	128	78	78	79	80	81	81	82
	95th	125	126	127	128	130	131	132	82	82	83	84	85	85	86
	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
17	50th	108	109	110	111	113	114	115	64	65	65	66	67	67	68
	90th	122	122	123	125	126	127	128	78	79	79	80	81	81	82
	95th	125	126	127	129	130	131	132	82	83	83	84	85	85	86
	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

* The 90th percentile is 1.28 SD, the 95th percentile is 1.645 SD, and the 99th percentile is 2.326 SD over the mean.
For research purposes, the SDs in Table B1 allow one to compute BP Z scores and percentiles for girls with height percentiles given in Table 4 (ie, the 5th, 10th, 25th, 50th, 75th, 90th, and 95th percentiles). These height percentiles must be converted to height Z scores given by: 5% = −1.645; 10% = −1.28; 25% = −0.68; 50% = 0; 75% = 0.68; 90% = 1.28; and 95% = 1.645 and then computed according to the methodology in steps 2 through 4 described in Appendix B. For children with height percentiles other than these, follow steps 1 through 4 as described in Appendix B.

APPENDICES

Appendix I : Questionnaire **QIN [SN]** ☐

PREVALENCE OF RENAL FAILURE AMONG SICKLE CELL DISEASE PATIENTS ATTENDING MNH

1.0 PATIENT'S BACKGROUND INFORMATION.

File No_____[FN]

SCD No_____[SCDN]

Name _____ [NAME]

Phone number_____

Date of enrolment_____ [DOE]

Sex: 1. Male 2. Female ---------- [SEX] ☐

Date of birth_____[DOB]

Age (years)_____[AGE]

2.0 Anthropometry:

Temperature (oC)…… [TEMP]

Pulse rate (bpm)…… [PULSE]

Systolic Blood Pressure (mmHg)…… [SBP]

Diastolic Blood Pressure (mmHg)…… [DBP]

Oxygen saturation (%)…… [OXYGEN]

Height (cm)…… [HEIGHT]

Weight (kg)…… [WEIGHT]

3.0 Clinical events in the past 6 months

1. Have you ever had a sickle cell crisis in the past 6 months? [CRISIS]
   1) Yes ☐
   2) No

If Yes, How many times …….. [CRISFREQ]

2. If yes what type of crisis/illness:…….[CRISTYPE]

1. Pain/ painful crisis
2. Acute chest syndrome
3. Severe anaemia necessitating blood transfusion
4. Malaria/infections
5. Others ……..
6. N/A

3. How were you treated?..... [TREAT]

1. Outpatient
2. Admitted
3. N/A

4. Have you been on medication for treating pain for a long time?..[TREATPAIN]

1. Yes
2. No

5. If yes, what type of medication?.....[MEDTYPE]

1. NSAIDS
2. Others
3. N/A

4.0 Laboratory Results

1. Renal Function tests:a) Creatinine(umol/L.)_____CREAT]

b) BUN(mmol/L)_____[UREA]

c) GFR_____[GFR]

3. Electrolytes:

Ca (mmol/L)……..[Ca].

Phosp(mmol/L)……[PHOSPH]

K(mmol/L)……[K]

Na (mmol/L).....[Na]

Cl(mmol/L)……[CL]

4. Urinalysis: i) Urine Protein_____ [URIPOT]

ii) RBC casts_____ [RBCcast]

iii) Others: S.G_____ [SG]

Pus Cells _____ [PUScells]

Sugar _____ [SUGAR]

5. Hemogram:

a) RBC_____ [RBC]

b) HB_____ [HB]

c) HCT_____ [HCT]

d) MCV_____ [MCV]

e)MCHC_____ [MCHC]

f)MCH _____[MCH]

g)RDW_____[RDW]

h) WBC_____ [WBC]

5.0 Ultrasound

results.....

.....

.....

.....

.....

.....

Appendix II: CONSENT FORM

Consent to participate in the study of Prevalence of renal failure in sickle cell patients attending MNH.

Dear Sir/Madam,

Greetings!

My Name is Dr. Primus Saidia, a resident doctor in the Department of Internal Medicine at MUHAS. I am conducting a study regarding the Prevalence of Renal Failure among Sickle Cell Disease Patients attending MNH. I am requesting your participation.

PURPOSE OF THE STUDY:

The aim of this study is to determine the prevalence of renal failure among sickle cell patients.

HOW TO PARTICIPATE:

Patients who will be ready to participate will sign a consent form to approve his/her willingness.

Short interview will be done and sample for investigation such as blood and urine will be taken. For those with serious problems, ultrasound may be required.

CONFIDENTIALITY:

Information obtained from you will be confidential and will be of help in this study and better care for patients with sickle cell disease in the future.

COSTS:

You will not be required to pay anything for your participation.

VOLUNTARY PARTICIPATION & RIGHTS TO WITHDRAW:

Your participation is voluntary and you have the right to withdraw from participating in our study at any time. Whatever your decision may be, it will not affect in any way your rights to care and treatment.

RISKS

There’s no risk by drawing blood although you will feel some pain when the needle pierces your skin for drawing this blood.

BENEFITS:

Your participation in this study will help you know about the status of your kidney functions.

You will as well get the benefit of getting appropriate treatment as per need.

We hope that the information from this research will be useful in contributing to improve the quality of care in Sickle Cell Disease patients.

CONTACT PERSONS:

If you have any inquiries about this study, please do not hesitate to contact:

Dr. Primus Saidia
Principal Investigator
Muhimbili University of Health and Allied Sciences (MUHAS)
Department of Internal Medicine
P.O. Box 65001 Dar es Salaam.
Tel. 0754 809742

OR in case of any information about your rights as a participant in this study please contact:

Professor E.F. Lyamuya.
The Director
Research and Publication Committee Research and Publication Committee
Muhimbili University of Health and Allied Sciences (MUHAS)
P.O. Box 65001 Dar es Salaam
Tel. 2151489

I will be grateful if you willingly agree to participate in this study

I _____

Have understood the above information and my questions have been answered by the investigator to my satisfaction. I willingly agree to take part in this research.

Name of the participant: _____

Signature of the participant: _____Date _____

Signature of Investigator _____ Date: _____

Appendix III: ***CONSENT FORM - SWAHILI VERSION***

FOMU YA MAKUBALIANO YA KUSHIRIKI KATIKA UTAFITI

Habari! Mimi ni Dk Primus Saidia na ni Daktari katika shahada ya Uzamili katika Chuo Kikuu Cha Sayansi Za Tiba cha Muhimbili. Nafanya utafiti kuhusu kiwango cha kuharibika kwa figo kwa wagonjwa wa Sickle Cell hapa Muhimbili hospitali. Ninaomba ushirikiano wako.

Nia ya Utafiti;

Dhumuni ni kujua ni wagonjwa wangapi wana uharibifu wa figo miongoni mwa wagonjwa wa sickle cell wanaotibiwa hapa Muhimbili.

Jinsi ya Kushiriki:

Mgonjwa ambaye yuko tayari kushiriki ataweka sahihi yake , ili kuonyesha utayari. Yatafuata maswali machache ya Utangulizi, kisha vipimo vya damu, na mkojo vitachukuliwa. Kwa wale wenye shida kubwa ya figo, watatakiwa kufanya kipimo cha ultra sound ya tumbo.

Usiri:

Taarifa ya magonjwa yako hazitatangazwa kwa yoyote zaidi ya mtafiti. Matokeo ya utafiti kwa ujumla yatasaidia kuboresha huduma ya tiba kwa kwa wagonjwa wa sickle cell.

Gharama:

Hutatakiwa kulipa gharama yoyote kwa kushiriki kwako.

Utayari wakushiriki au kujitoa:

Kushiriki kwako ni hiyari na waweza kujitoa. Lakini haitakunyima haki ya kupata tiba zingine.

Faida:

Kushiriki kwako katika utafiti huu, kutakusaidia kujua hali ya figo zako.

Pia utafaidika kupata matibabu halisia kama itakavyokuwa inahitajika.

Ni tumaini letu kuwa utafiti huu utasidia kuboresha huduma kwa wagonjwa wa sickle cell hapa kwetu na penginepo.

Nitakushukuru kwa kushiriki kwako utafiti huu. Aksante.

Iwapo utakuwa na swali lolote kuhusu utafiti huu wasiliana na Dr. Primus Saidia, Chuo kikuu Cha Afya Na Sayansi za Tiba Muhimbili; Idara ya Tiba; S.L.P 65001 Dar Es Salaam. Simu 0754 809742.

AU endapo utakuwa na swali lolote kuhusu haki zako kama mshiriki katika utafiti huu wasiliana na:

Prof E.F Lyamuya; Mkurugenzi wa kamati ya tafiti na matoleo chuoni. Chuo Kikuu Cha Afya na Sayansi za Tiba Muhimbili; S.L.P 65001 Dar Es Salaam; S.L.P 65001 Dar Es Salaam . Simu 2151489.

Mimi……nimeelezwa/ nimesoma yaliyomo katika fomu hii na nimeelewa maana yake. Nakubali kushiriki katika utafiti huu.

Sahihi……..(Mshiriki) Tarehe……..

Sahihi…….. (Mtafiti) Tarehe……..