# SICKLE CELL NEPHROPATHY AMONG CHILDREN AND ADOLESCENTS WITH SICKLE CELL DISEASE AT BUNGOMA COUNTY REFERRAL HOSPITAL

**BY**

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# DECLARATION

**Student's declaration**

This research is the author's original work being submitted in partial fulfilment of the requirement for the award of the degree of Master of Medicine in Child Health and Pediatrics of Moi University and has not been submitted for an award of any academic credit in research institutions or Universities.

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**Supervisors' declaration**

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## DEDICATION

I would like to dedicate this thesis to God without whom it would not have been possible. To my husband Victor for his unconditional support. To my sons Ethan and Elon whose innocent smiles keep me going.

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## ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| **ACEI** | Angiotensin Converting Enzyme Inhibitors |
| **ACR** | Albumin Creatinine Ratio |
| **BCRH** | Bungoma County Referral Hospital |
| **BMI** | Body Mass Index |
| **ESRD** | End Stage Renal Disease |
| **FSGS** | Focal Segmental Glomerulosclerosis |
| **GFR** | Glomerular Filtration Rate |
| **Hb** | Hemoglobin |
| **MOPC** | Medical Outpatient Clinic |
| **MTRH** | Moi Teaching and Referral Hospital |
| **NKF** | National Kidney Foundation |
| **POPC** | Pediatric Outpatient Clinic |
| **RBC** | Red Blood Cell |
| **SCD** | Sickle Cell Disease |
| **SCN** | Sickle Cell Nephropathy |
| **USA** | United States of America |

## OPERATIONAL DEFINITIONS

| | |
|---|---|
| **Sickle cell nephropathy** | persistent albuminuria (albumin: creatinine ratio) on two occasions, one month apart. |
| **Children** | persons less than 14 years. |
| **Adolescents** | persons aged 14 to less than 19 years. |

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## ABSTRACT

**Background:** Sickle cell nephropathy (SCN) is one of the complications of sickle cell disease (SCD) in which albuminuria is one of the manifestations. Eighteen percent of those with sickle cell nephropathy progress to end stage renal disease. There is paucity of data on SCN in Bungoma County Referral Hospital which has a high burden of sickle cell disease. This study sought to determine the burden of sickle cell nephropathy among children and adolescents with SCD to advice policy on screening and management.

**Objectives:** To determine proportion of children and adolescents with SCN among those with SCD and their associated clinical-demographic characteristics.

**Methods:** A cross-sectional study was conducted at Bungoma County Referral Hospital pediatric and medical outpatient clinics between January and September 2019. Sample size was determined using Fisher's formula in which 127 eligible children and adolescents below 19 years of age with sickle cell disease were recruited. Age, gender, anthropometric measurements, number of transfusions, hospitalizations and use of hydroxyurea were recorded in a structured questionnaire. Spot urine sample was collected for urinalysis and albumin to creatinine ratio. Those positive for albuminuria had a repeat urinalysis and albumin to creatinine ratio after one month. Data analysis was done using STATA version 15. Categorical variables were summarized using frequencies and percentages. Continuous variables were summarized using mean and median. Significance of association between albuminuria and categorical variables was tested using Pearson Chi Square test and Fisher's exact test. Continuous variables were compared using the independent T-test. P-value of $<0.05$ was considered significant at 95% confidence interval.

**Results:** The proportion of those with SCN was 15.8%. The median age was 7.00(IQR: 1.42,18) years with 65(50.4%) being female. One hundred and eight (85%) were children among whom 14(12.96%) had SCN while among adolescents, 6(31.58%) had SCN. Among the characteristics of those with SCN, 14(21.5%) were female, 9(21.4%) had been transfused, 17(16.2%) had been hospitalized within one year prior to recruitment and 19(17.1%) were not using hydroxyurea. Age was significantly associated with SCN ($p=0.047$) while gender ($p=0.067$), number of hospitalizations ($p=0.989$), number of transfusions ($p=0.217$) and hydroxyurea use ($p=0.228$) was not significantly associated with SCN.

**Conclusion:** One in eight children and one in three adolescents had SCN. Older age was significantly associated with SCN but no clinical characteristics were significantly associated with SCN.

**Recommendation:** Screening for sickle cell nephropathy should be done in routine care of children with sickle cell disease during follow up at the clinics and continued throughout adolescence.

# CHAPTER ONE: INTRODUCTION

## 1.1 Background

Sickle Cell Disease is one of the most common hereditary hematologic disease in the world ( da Silva Junior, Libório, & Daher, 2011). It is a chronic hemolytic disease characterized by the presence of the mutated β-globin gene at the sixth position of the beta globulin chain in which glutamic acid is replaced by valine ( Audard, Bartolucci, & Stehlé, 2017). Sickle cell disease (SCD) is a generic term for a group of disorders that includes homozygous sickle cell anemia (HbSS), sickle cell hemoglobin C disease (HbSC), sickle cell thalassemia disease (S/thal) and other compound heterozygous conditions. In populations of African origin, sickle cell anemia represents 70% of people with sickle cell disease ( Rees, Williams & Gladwin, 2010). Other forms of sickle cell disease like HbSC and beta thalassemia are mostly found in North Africa and limited parts of Western Africa.

Sickle cell anemia is the most common and severe form of the disease and can present with many severe complications, including sickle cell nephropathy (Olaniran, Eneanya, Nigwekar, Vela-Parada, Achebe, Sharma & Thadhani, 2019) .The red blood cells assume a rigid sickle shape when exposed to low oxygen concentrations thus become ineffective in their oxygen carrying capacity to tissues ( Malowany & Butany, 2012).

In the renal medulla, sickled RBCs causes ischemia, micro-infarction and papillary necrosis due to decreased blood flow. This causes tubular and glomerular dysfunction thus affecting the function of the kidney (Alhwiesh, 2014).

Each year over 300,000 babies are born with sickle cell disease worldwide (WHO 2016). It is estimated that >70% of SCD is in Africa distributed mainly in Western, Central and Eastern Africa with trait prevalence of between 5 and 40% ( Williams, 2016).

In Kenya, the sickle cell gene is found mostly in Western, Nyanza and Coastal regions which are the malaria endemic areas, the main genotypes being HbSS and HbAS (sickle cell trait), the later having less severe phenotype ( Sadarangani, Makani, Komba, Ajala-Agbo, Newton, Marsh, & Williams, 2009). In Western Kenya, 4.5% of children are born with SCD ( Wanjiku, Njuguna, Chite, Mbunya, Githinji, Roberson, & Greist, 2019). Those with sickle cell anemia were predominantly from the Luo and the Luhya ethnic communities with the former having 58.4% and the later having 23.9% of those having sickle cell disease ( Aluoch, & Aluoch, 1993). Bungoma County Hospital is in Western Kenya region where there is a high burden of sickle cell disease and where the above communities are predominant.

Although mortality in Africa is still higher than that in developed countries like the United Kingdom and United States of America, recent estimates show a decline in mortality ( Makani, Ofori-Acquah, Nnodu, Wonkam, & Ohene-Frempong, 2013). A study in Tanzania of a clinic-based cohort showed a survival of 85% suggesting that sickle cell patients in Africa are surviving beyond childhood (Makani, Cox, Soka, Komba, Oruo, Mwamtemi, & Newton, 2011).

With better healthcare and management of this condition, burden of SCD is expected to increase thus need to focus on complications. The aim of this study is therefore to understand the burden of renal disease in children with SCD as it is one of the complications of the disease.

## 1.2 Problem Statement

Sickle cell nephropathy is one of the complications of sickle cell disease which can progress to chronic kidney disease and end stage renal disease (Olaniran et al., 2019; Thompson, Reid, Hambleton, & Serjeant, 2007).

Regionally, high prevalence of sickle cell nephropathy in children has been reported in Uganda at 28% (Mawanda, Ssenkusu, Odiit, Kiguli, Muyingo, & Ndugwa, 2011) and Kenyatta National Hospital at 39.1% (Muthiga, 2014).

Bungoma County Referral Hospital is in an area of high SCD burden yet there is paucity of data. Over 90% of patients seen at the pediatric outpatient clinic from the hospital records have sickle cell disease. Most of these patients are on folic acid, analgesics and proguanil for malaria prophylaxis with very few being on hydroxyurea.

Routine screening for SCN is not done at BCRH pediatric and medical outpatient clinics yet anecdotal information showed that there were three adolescents with SCD who had chronic kidney disease seen at the MOPC in 2018 (BCRH Hospital records).

Since screening is not routinely done at BCRH, renal changes which may start in childhood are not detected thus missing out on the chance to intervene early and prevent progression of the disease thus the need for this study.

### 1.3 Justification

SCN is one of the complications of SCD yet it is not routinely screened in Bungoma which is a region with high SCD burden and may progress to chronic kidney disease and end stage renal disease.

Renal changes are initially asymptomatic therefore screening can be useful, thus allow for intervention like hydroxyurea which slows down the progression of renal damage. This will furthermore save up on the otherwise scarce resources that could have been used in dialysis and other costs incurred when there is advanced renal damage. It will also improve the quality of life of these patients.

If SCN progresses to end stage kidney disease, the only option for management is renal replacement therapy which includes dialysis or renal transplant. These modalities are very expensive and out of reach of many in our country. If this study is not done, massive resources that would otherwise be saved will be used in renal replacement therapy. There will be an increase in disability adjusted life years for the patients living with chronic kidney disease and an increase in mortality once the patients get to end stage renal disease. Knowledge on SCN will also help to inform strategies and policies to prevent complications.

Findings from this study will be communicated to BCRH management, parents, guardians and the patients themselves and this will enable them to be aware of renal effects of SCD and that it can be slowed down if detected early thus improve their health seeking behavior and follow up.

## 1.4 Research Question

What is the proportion and associated clinical-demographic characteristics of children and adolescents with sickle cell nephropathy among those with sickle cell disease at Bungoma County Referral Hospital?

## 1.5 Objectives

### 1.5.1 Broad objective

To determine the proportion and associated clinical-demographic characteristics of children and adolescents with sickle cell nephropathy among those with sickle cell disease at Bungoma County Referral Hospital.

### 1.5.2 Specific objectives

1. To determine the proportion of children and adolescents with sickle cell nephropathy among those with sickle cell disease at Bungoma County Referral Hospital.
2. To describe the associated clinical-demographic characteristics of children and adolescents with sickle cell nephropathy among those with sickle cell disease at Bungoma County Referral Hospital.

# CHAPTER TWO: LITERATURE REVIEW

## 2.1 Pathogenesis of Sickle Cell Nephropathy

SCD pathology occurs when the sickle Hb polymerizes when deoxygenated. This causes sickling in vascular beds causing obstruction and subsequent ischemia and necrosis ( Malowany, & Butany, 2012).

This polymerization depends on intracellular sickle hemoglobin (HbS) and fetal hemoglobin (HbF) concentrations, degree of cell deoxygenation, acidosis or change in temperature ( Scheinman, 2009). Relative hypoxia caused by cyclical episodes of ischemia and ischemia-reperfusion cause damage to various organs including the lungs, spleen and kidneys (Audard et al., 2017).

In the renal medulla, the hypoxic, acidotic and hyperosmolar state promote polymerization and sickling of the erythrocytes (Scheinman, 2009). This causes slow blood flow in the vasa recta and thus prolonging the transit time of the RBCs through the medulla. This also promotes adhesion of the RBCs to the endothelium thus inducing ischemia and infarction ( Nath, & Hebbel, 2015).

There are several manifestations of sickle cell nephropathy: gross hematuria, papillary necrosis, nephrotic syndrome, renal infarction, hyposthenuria and renal medullary carcinoma. These can present as; hematuria, proteinuria, renal insufficiency and hyposthenuria ( Bayazit, Noyan, Aldudak, Özel, Anarat, Kilinç, & Dikmen, 2002).

### 2.1.1 Vasculopathy

Sickle cell nephropathy involves kidney vasculopathy marked by sickled cells in the renal medulla leading to decreased blood flow, increased stress induced vasoconstrictive response, thus causing ischemia and infarcts in the kidney (Nath & Hebbel, 2015).

Several mechanisms are responsible for the sickling of the RBCs causing renal injury. Low oxygen tension, hyper tonicity and low renal medullary pH promote the formation of hemoglobin polymers and deformation of the RBCs resulting in an increase in the blood viscosity, functional venous engorgement, and interstitial edema thus promote the renal microcirculation to ischemia and infarction (Alhwiesh, 2014). This affects the circulation causing gradual obliteration of the medullary vasculature eventually causing scarring and interstitial fibrosis (Audard et al, 2017). This causes development of collateral vessels and because their abnormal orientation in the medulla the counter current exchange mechanism is interfered with, and eventually there is irreversible loss of medullary tonicity over time ( McPherson Yee, Jabbar, Osunkwo, Clement, Lane, Eckman, & Guasch, 2011).

### 2.1.2 Hyposthenuria

This early renal damage is manifested clinically as loss in the ability to concentrate urine and results in polyuria in affected patients (da Silva Junior et al., 2011). This process may contribute to further episodes of sickling by causing dehydration thus worsening the disease process (Scheinman, 2009). At around 10-15 years of age, this may be reversible by repeated blood transfusion. However, this state becomes permanent due to medullary fibrosis causing damage to the collecting ducts especially after 15 years of age (Alhwiesh, 2014).

### 2.1.3 Tubular dysfunction

Due to distal tubular dysfunction, there is a compensatory mechanism by the proximal tubules where there is hyper-function (Scheinman, 2009). This is characterized by increased creatinine secretion and uric acid and phosphate reabsorption. There is also increased reabsorption of sodium and oxygen consumption (Nath & Hebbel, 2015).

This causes a hypermetabolic state that predisposes the nephron to oxidative stress thus causing tubulointerstitial injury.

This manifests clinically as an overestimation of glomerular filtration rate (GFR) thus overestimation of renal function. In addition, the greater oxygen consumption in the hypermetabolic state leads to more hypoxia in the kidney ( Lopez Revuelta, & Ricard Andres, 2011).

### 2.1.4 Glomerulopathy

The glomerular changes begin as early as the first decade of life in otherwise asymptomatic SCD patients ( Dharnidharka, Dabbagh, Atiyeh, Simpson, & Sarnaik, 1998 ; Imuetinyan, Okoeguale, & Egberue, 2011 ). The earliest glomerular changes are seen as high renal blood flow causing hyper filtration and glomerular hypertrophy. Initially thought to be secondary to immune complex deposition, evidence was found lacking and the pathogenesis is now known to be a combination of processes. Medullary ischemia causes production of prostaglandins which cause vasodilation thus increased intra glomerular pressure and glomerular hypertrophy (Nath & Hebbel, 2015). Efferent obstruction also contributes to this increased pressure leading to hyper filtration with gradual loss of glomerular permselectivity to both size and charge. Larger molecules, such as albumin, abnormally permeate the restrictive pores of the glomerular wall. This albumin excretion can be detected and has been shown to be an

early sensitive clinical marker of glomerulopathy ( Marsenic, Couloures, & Wiley, 2008).

There are four types of glomerular lesions seen in sickle cell disease; focal segmental glomerulosclerosis, membranoproliferative glomerulonephritis, glomerulopathy specific to sickle cell disease and thrombotic microangiopathy.

In sickle cell disease the most common lesion is focal segmental glomerulosclerosis (FSGS) (Alhwiesh, 2014).

Development of these lesions is caused directly by the proteinuria as well as endothelial damage induced by the occluding sickled cells, growth hormones and cytokines whose production is induced by proteins in the capsular space.

With loss of nephrons, pressure is transmitted to the remaining units, thus secondary damage due to compensatory hyper filtration even in initially unaffected units. This process is progressive leading to chronic renal insufficiency and end stage renal disease (ESRD) (Nath & Hebbel, 2015).

**2.2 Albuminuria**

Children with sickle cell disease can present with albuminuria as an early sign of kidney damage ( Osei-Yeboah, & Rodrigues, 2011). Persistent albuminuria is the initial marker for glomerulopathy (Alhwiesh, 2014; McBurney, Hanevold, Hernandez, Waller, & McKie, 2002). Albuminuria occurs due to the widening of the inter-podocyte pore radius and reduction of total podocyte pores due to blockage by sickled red bold cells therefore causing endothelial inflammation (Olaniran, 2019). Hemoglobin dimers formed due to hemolysis inhibit albumin re-uptake in the proximal tubule thus worsening the albuminuria (Audard, 2017). Albuminuria ranges from micro albuminuria to nephrotic range levels and can progress to end stage renal

disease (Belisário, da Silva, Silva, de Souza, Wakabayashi, Araújo & Simoes, 2019). Measurement of albumin in urine thus has an important role in secondary prevention, to decide treatment and monitor response to treatment ( Fitzhugh, Wigfall, & Ware, 2005).

There are various methods of measuring albumin in urine. The amount of albumin excreted over a 24-hour period is the gold standard ( Levey, Coresh, Balk, Kausz, Levin, Steffes & Eknoyan, 2003).

However 24-hour urine collections may be associated with significant collection errors, either due to improper timing and poor storage, in addition to causing inconvenience to the patients (Johnson, Jones, Mathew, Ludlow, Chadban, Usherwood, & Martin, 2012). Other practical and easier alternatives are collection of either first morning void or a spot (random) urine sample.

First morning void is preferred over a spot urine sample, because it is less influenced by factors such as hydration status and physical activity thus reducing the variability that can be caused by these factors (Johnson et al., 2012). Practically however, this might be a challenge to collect thus spot urine samples are preferred because they can be collected at the same time during consultation and therefore pose the least inconvenience for patients. According to the National Kidney Foundation (NKF) clinical practice guidelines, under most circumstances, untimed spot urine samples can be used to detect and monitor proteinuria (Levey et al., 2003). It is therefore not usually necessary to obtain an overnight or 24- hour urine sample for these evaluations in either children or adults (Johnson et al., 2012).

### 2.2.1 Prevalence of albuminuria

Several studies across various regions have shown the prevalence of albuminuria to be between 6% and 33% ( Wigfall, Ware, Burchinal, Kinney, & Foreman, 2000 ; Ranque, Menet, Diop, Thiam, Diallo, Diop & Jouven, 2014).

**Table 1: Prevalence of proteinuria among children and adolescents in various studies**

| Author/ country | Duration | Participants | Prevalence and clinical correlates |
|---|---|---|---|
| Becton et al<br>Medical university of South Carolina children's hospital | 6 months | N=90<br>Mean age 11.4 years+/_5.2 years. | Prevalence-15.5%<br>Significant-lower Hb |
| Wigfall et al<br>Duke University medical center USA<br>Prospective study | 10 years | N=442 | Prevalence of proteinuria 6.2%<br>Association-low Hb, increased leucocyte count |
| Dhanidharka et al<br>Children's hospital in Michigan and Wayne state University, USA | 6 months | N=102<br>2-18 years | Prevalence-26.5%<br>Significant-age<br>Non-significant-transfusion, pain frequency |
| McPherson et al<br>Emory School of Medicine, Atlanta Georgia. | 10 years | N=410<br>2-21 years | Prevalence-20.7%<br>Significant-age, lower hematocrit levels |
| Alvarez et al<br>Pediatric Hematology, University of Miami<br>Prospective study | 6 months | N=120<br>4-20 years | Prevalence-15.8%<br>Significant- increasing age , acute chest syndrome |
| King et al<br>Jamaica/Sickle Cell Unit, University of West Indies<br>Cross-sectional study | 6 months | N=244<br>2-14 years | Prevalence-18.4%<br>Increased eGFR, Hb related to micro-albuminuria. |
| Niss et al. longitudinal, multicenter study in 11 centers across USA and Jamaica | 8 years | N=303<br>2-64 years | Prevalence 32%,<br>Albuminuria increased with age by 3.5mg/g per year |
| Ranque et al: multinational study in Cameroon, Cote d'voire, Mali, Senagal<br>Prospective study | On-going | N=2582<br>Age above 3 years | Prevalence-33.7%<br>Significant-age, female, low Hb, high LDH levels |
| Imuetinyan University of Benin Hospital, Sickle Cell Centre, Nigeria<br>Cross-sectional study | 3 months | N=75<br>Average-16.8 years | Prevalence-17.3%<br>Significant-lower GFR, anemia<br>Non-significant-age, BMI, duration of disease |
| Ocheke et al.<br>Jos teaching hospital, Nigeria.<br>Cross-sectional comparative study | 6 months | N= 323<br>6 months to 18 years | Prevalence-26%.<br>Anemia, GFR associated with microalbuminuria. |

**Table 2: Prevalence of proteinuria among children and adolescents in various studies continued**

| Author/ country | Duration | Participants | Prevalence and clinical correlates |
|---|---|---|---|
| Eke et al. University of Nigeria Teaching Hospital. | 9 months | N= 200<br>4-17 years | Prevalence- 18.5% for subjects and 2.5% for controls.<br>Significant- increasing age, low Hb and increased number of hospitalizations. |
| Aloni et al. Cross-sectional study across 4 hospitals in Congo. | 8 months | N=150<br>2-18 years | Prevalence- 18%<br>Significant- age. |
| Mawanda et al<br>Mulago National Referral Hospital, Uganda<br>Cross-sectional study | 6 months | N=305<br>2-18 years | prevalence -28.2%<br>significant-increasing age, higher number of transfusions |
| Muthiga et al<br>Kenyatta National Hospital<br>Cross sectional study | 9 months | N=110<br>2-18 years | Prevalence-39.1%<br>Significant- hyperfiltration<br>Non-significant-Hb level, age, no of admissions |

There are many studies that observed that albuminuria was age dependent (Dharnidharka et al., 1998; Aloni et al., 2017) with most studies suggesting that albuminuria was associated with increase in age (Alvarez et al., 2006; Mawanda et al., 2011). Niss et al, 2020 in a multinational study showed increase in the level of albuminuria with increase in age in those with sickle cell anemia. However, a study by Marsenic et al in USA and Al-Musawa et al in Yemen showed a weak co-relation between age and albuminuria (Marsenic et al., 2008), (Al-Musawa, & Al-Saqladi, 2019).

Most studies did not find any statistical significance between male and female children in regards to albuminuria (Eke, Okafor, & Ibe, 2012).

Imuetinyan et al in Nigeria found statistical significance between weight and albuminuria. In contrast, Al-Musawa et al did not find any significant difference between weight or body mass index (Al-Musawa et al, 2019; Imuetinyan et al 2011).

Studies done by Becton et al and Imuetinyan et al found that there was an increase in the level of albuminuria in those who were hypertensive compared to those with normal blood pressure (Becton et al, 2010; Imuetinyan et al, 2011).

Low hemoglobin levels are also thought to be associated with albuminuria ( McKie, Hanevold, Hernandez, Waller, Ortiz, & McKie, 2007; Lebensburger, Johnson, Askenazi, Rozario, Howard, & Hilliard, 2011; Wigfall et al., 2000). A study by Alvarez et al showed that early start of chronic blood transfusions was associated with lower levels of albuminuria (Alvarez et al., 2006).

A study done in Uganda showed that increase in the number of blood transfusions is associated with higher levels of albuminuria ($P < 0.001$) especially those done sporadically due to severe anemia or acute chest syndrome (Mawanda et al., 2011).

A study by Eke et al showed significance of increased number of hospitalizations and albuminuria (Eke et al, 2012).

Interventional studies have shown significant benefit of hydroxyurea and angiotensin converting enzyme inhibitors. Falk et al in a six-year study to determine the prevalence and pathologic features of sickle cell nephropathy in children and adults showed 26% prevalence and FSGS as the typical pathologic lesion. Enalapril was administered for two weeks resulting in a 57% decline in protein excretion that was maintained two weeks after stoppage of medication (Falk et al., 1992).

A study by Fitzhugh et al in which children with sickle cell nephropathy were put on enalapril for three years showed normalization of serum albumin and decreased urinary protein excretion. Addition of hydroxyurea for three and a half years was associated with near normal urine protein to creatinine ratio in addition to increased fetal hemoglobin ( Fitzhugh, Wigfall, & Ware, 2005).

McKie et al in Georgia also studied the prevalence, prevention and treatment of micro albuminuria among HbSS patients aged 3-20yrs old. This study found a prevalence of 19.4%, with a positive test associated with higher mean age and lower Hb.

The average age of patients testing positive for micro albuminuria in the study was 14.95yrs and average age of onset of micro albuminuria to be 11.8 +3.93yrs on follow up of those who had initially tested negative. Further hydroxyurea was started in those with frequent vaso-occlusive episodes, acute chest syndrome and those positive for micro albuminuria/proteinuria. ACEI were instituted for persistent proteinuria and those who developed proteinuria while on hydroxyurea that had been started based on vaso-occlusive crises or acute chest syndrome. Results showed decline in micro albuminuria in 44% of those started on hydroxyurea. Eighty eight percent of those on both hydroxyurea and ACEI had reduction in micro albuminuria (McKie et al., 2007).

Hydroxyurea is associated with lower prevalence of albuminuria in patients with sickle cell disease ( Laurin, Nachman, Desai, Ataga, & Derebail, 2014). Hydroxyurea works by increasing the total fetal hemoglobin in children with sickle cell disease (Agrawal, Patel, Shah, Nainiwal, & Trivedi, 2014). Fetal hemoglobin cells have more affinity for oxygen and are more deformable than the sickled RBCS (Laurin et al, 2014). If there are more fetal hemoglobin cells, there is less tendency to have sickling of the RBCs. Hydroxyurea also reduces the levels of circulating leucocytes (Agrawal, 2014). This in turn reduces the adherence of neutrophils to the circulating

endothelium and therefore reduces the amount of painful crises leading to decreased incidences of sickle cell nephropathy (Alzahrani et al., 2021). Furthermore, recommendations were made by a panel of experts in 2014 on the use of these therapies in patients with albuminuria (Yawn, Buchanan, Afenyi-Annan, Ballas, Hassell, James, John-Sowah, 2014).

# CHAPTER THREE: METHODOLOGY

## 3.1 Study Site

The study was carried out in Bungoma County Hospital, located in Bungoma County. Bungoma is a county in western Kenya which lies within a malaria endemic zone in the tropics and hence high sickle cell disease prevalence. Bungoma County Referral Hospital is one of the two county hospitals that serves a catchment population of around 80,000 patients from all around the county and surrounding counties like Kakamega and Busia. Children and adolescents are followed up on Thursdays at pediatric and medical outpatient clinics respectively, mostly for chronic conditions. From the hospital records, 293 patients with sickle cell disease were seen in 2015 while in 2016, 219 patients were seen in the clinics. Patients who are seen in these clinics are those who have been discharged after in-patient care, those referred from outpatient or from lower level hospitals. Care for these patients involves administration of folic acid, proguanil for malaria prophylaxis and analgesics which are mostly NSAIDS and acetaminophen. There is no additional special vaccination for children with sickle cell disease apart from the national vaccination schedule neither is there a chronic transfusion program. Hydroxyurea is given to those with cerebral vascular accidents, acute chest syndrome or those with more than three admissions per year.

Those with new symptoms affecting other systems are reviewed accordingly and relevant investigations done and referred to sub-specialists in MTRH if need arises.

## 3.2 Study Design

Cross sectional study design

### 3.3 Study population

Children and adolescents with sickle cell disease attending pediatric and medical outpatient clinics in Bungoma County Referral Hospital.

### 3.4 Eligibility

#### 3.4.1 Inclusion Criteria

Children and adolescents less than 19 years with SCD attending pediatric and medical outpatient clinics in steady state i.e. afebrile, at least two weeks since last crisis.

Children and adolescents with SCD diagnosed by Hb electrophoresis.

#### 3.4.2 Exclusion Criteria

Children with other known renal disease secondary to other conditions like diabetes, HIV.

Those with physical signs of cardiac or renal disease like edema which could cause albuminuria and those with dehydration which could cause transient albuminuria.

Those with urinary tract infections as demonstrated by the presence of leucocytes or nitrites on urine dipstick.

### 3.5 Sample Size

This was arrived at using the Fisher's formula. A study in Congo showed a prevalence of 20.6% for both micro and macroalbuminuria (Aloni et al., 2017). Thus in order to be 95% sure that we report the proportion of children and adolescents within albuminuria within plus or minus 5% of 20.6% we determine the sufficient sample size using the following formula:

$$n = \left(\frac{Z_{1-\alpha/2}}{d}\right)^2 \times P \times (1-P)$$

$$= \left(\frac{1.96}{0.05}\right)^2 \times 0.206 \times (1-0.206)$$

$$= 252$$

Where

$Z_c$ is the quantile of the standard normal distribution corresponding to c x 100% percentile, c = (1-a/2), a = type I error rate equal to 5%,

d is the margin of error equal to 5%,

P is the proportion of the children and adolescents with micro-and macroalbuminuria among those with sickle cell disease.

Under infinite population we would need to sample 252 children and adolescents. However, we are sampling from a finite population with an average size of 256 per year. Records from the POPC of Bungoma County hospital show that 293 and 219 children and adolescents were seen in 2015, and 2016 respectively. This give us an average of 256. Hence we correct our sample size for this finite population size. This gives us $n\dfrac{n}{1+n/N} = \dfrac{252}{1+252/256} = 127$.

The study was carried out for a duration of nine months (January to September 2019).

### 3.6 Sampling procedure

The average number of patients with SCD seen per year is 256.

256/127=2.01, thus K=2

Systematic sampling approach was done where the first participant was selected at random on the first day of recruitment and thereafter, every second participant was recruited into the study.

### 3.7 Data Collection

Data on anthropometric measurements and clinical characteristics was collected using structured questionnaires.

Spot urine sample was taken for urinalysis and determination of urine albumin to creatinine ratio.

### 3.8 Study Procedure

Four research assistants were recruited: two clinical officers and two laboratory technicians based on commitment and reliability. Professional and research ethics was explained to the research assistants.

They were trained on the purpose of the study, recruitment procedure of study participants and procedure of data collection. The principal investigator and the two clinical officers took history and examined the eligible children at the clinic while the two laboratory technicians took spot urine samples and carried out dipstick and albuminuria tests.

Staff at the pediatric outpatient clinic and the medical outpatient clinic of Bungoma County Referral Hospital were sensitized about the study.

Patients were recruited at the pediatric and medical outpatient clinics, both of which run on Thursdays.

Consent was sought from parents and guardians of the children and assent was sought for children who were seven years or older by the principal investigator or the research assistants. Structured questionnaires were administered by the principal investigator and/or the research assistant and was used to collect data including demographics and history which included number of hospitalizations, number of transfusions, history of chronic illnesses like diabetes, use of Hydroxyurea, history of medications.

Physical examination was done including weight, height and blood pressure measurements. The participants were also examined for any signs of dehydration which could increase the urine specific gravity and thus give a false positive result for albuminuria. Edema, including facial and peripheral was checked as this this could be an indication of cardiac or renal disease. However we did not find any study participant with these signs.

The weight of the children, wearing light clothes only, was done using infant weighing scale (Kinlee 20 kg weighing scale) for those less than fifteen kilograms with precision of up to 50 grams. For older children digital weighing scale whose maximum weight is 150 kilograms with precision of up to 0.1 kilograms was used.

At the start of the weighing process, the child's clothing was removed and the weighing scale balanced to zero (i.e. the arrow should be on the zero mark). The child was placed lightly on the weighing scale, making sure that the child did not hold to anything. The child's weight was read and recorded to the nearest 100 grams.

Height was measured by use of a stadiometer (ADE stadiometer) whose maximum height is 150 cm and length by use of a measuring board.

The child stood upright against the middle of the measuring board. The child's head, shoulders, buttocks and knees were held against the board by the assistant. The

investigator then positioned the head and the cursor and the height was read to the nearest 0.1 cm. The measurements were recorded in a data collection form.

For reading of the length, the measuring board was placed on the ground, then the child was placed lying down on the middle of the board. The assistant then held the sides of the child's head and positioned the head until it firmly touched the fixed headboard with the hair compressed, the investigator then placed her hands on the child's legs, and gently stretched the child and then kept one hand on the thighs to prevent flexion.

While positioning the child's legs, the sliding foot-plate was pushed firmly on the child's bottom of the child's feet. For reading of the length the foot-plate must be perpendicular to the axis of the board, the height was read to the nearest 0.1 cm and recorded in the data collection form.

Weight and height were used to compute Z-scores. Different WHO charts were used to compute Z-score for those less than 5 years according to age and sex (Appendix 13& 14). For those above 5 years BMI ($kg/m^{2)}$ was computed using weight (Kilograms) divided by height (meters squared) charts and interpreted against age percentiles for boys and girls respectively. (Appendix 15).

Blood pressure was taken using Elite sphygmomanometer certified number 50112654. It was taken at least thirty minutes after the patients had been seated and relaxed. For the children who were not relaxed or were irritable the reading was repeated after 30 minutes.

Patients were seated upright and the arm on the table so that the cuff is on the same level of the heart. The right size cuff was used for different age of children (cuff covered two thirds of the arm). The cuff was wrapped on the right arm such that the bottom of the cuff is 1 cm above the elbow. The start button on the machine was

pressed and the cuff inflated automatically as the machine takes the reading. The blood pressure and pulse reading were displayed on the screen. If an error occurred, the process was repeated. The blood pressure categories were categorized as normal, hypotension or hypertension according to age and sex specific percentiles (appendix 11 and 12). Blood pressure machines were calibrated daily.

Spot urine samples were collected in a sterile bottle and taken for urinalysis and measurement of the urine albumin to creatinine ratio within one hour of collection. A mid-stream urine sample was to be collected using a 'clean-catch' technique where for girls, the labia had to be cleaned from front to back whiles for the boys, the tip of the penis had to be wiped before urination. Sterile urine sample containers were used which had to be filled by at least half of the urine sample container. (Appendix 6 for urinalysis procedure)

Urinalysis was done by urinalysis sticks whereby urinary tract infection was ruled out by presence of leucocytes and/or nitrites (suggestive of UTI) and those with glucose and ketones (suggestive of diabetes) were excluded.

Urine albumin: Creatinine Ratio was done using Siemens machine for albumin creatinine ratio (appendix 6).

Levels of albuminuria recorded as follows:

**Table 3: Various levels of albuminuria**

| Levels (independent of gender) | Urinary albumin excretion (mg/l) for spot sample | Urine albumin: creatinine ratio (mg/g)for spot sample |
|---|---|---|
| Normoalbuminuria | <20 | <30 |
| Microalbuminuria | 20 to 200 | 30 to 300 |
| Macroalbuminuria | >200 | >300 |

Those with albuminuria had a repeat urinalysis and albumin to creatinine ratio after one month to check for persistent albuminuria. Those with persistent albuminuria were classified as sickle cell nephropathy.

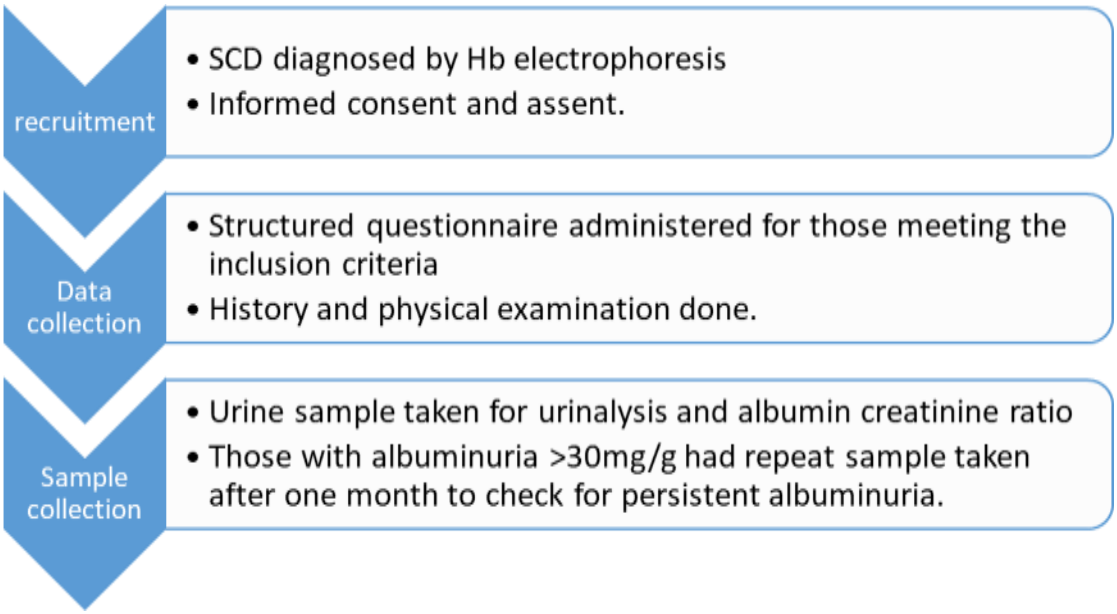


**Figure 1: Study procedure flow chart**

A total of 132 participants were enrolled. Of these, one was HIV positive, two had been ill the past two weeks prior to recruitment and two had urinary tract infection thus a total of five participants were excluded. The total number analyzed was 127.

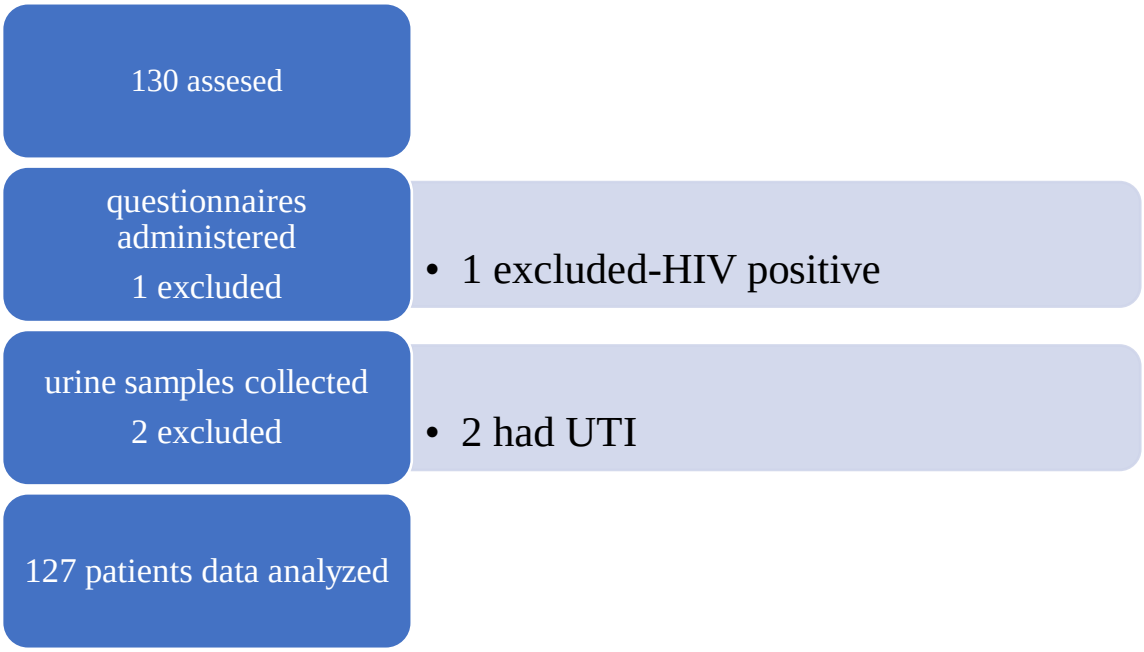


**Figure 2: Study profile**

### 3.9 Data Management

Data collected using questionnaires was de-identified and entered into an electronic database for safe storage and preparation for analysis. The database created using Microsoft excel was encrypted to ensure that confidentiality of the participants' information is maintained. Back-up of the data was done to safeguard against data loss and the principal investigator had the passwords to all the databases. The questionnaires were kept in a safe cabinet under a lock and key kept by the principal investigator.

Consistencies and completeness was checked regularly whenever data was added to the database.

### 3.10 Data Analysis

Data analysis was done using R: (R Core Team, 2017). Categorical variables such as gender, number of times hospitalized, were summarized using frequencies and the corresponding percentages. Continuous variables such as age, weight, height, body mass index, blood pressure were assessed for Gaussian assumptions using Shapiro-Wilk test. If the Gaussian assumptions held, they were summarized using mean and the corresponding assumptions, otherwise median and the corresponding inter quartile range (IQR) was used.

Albuminuria was determined by use of a cut-off value of albumin to creatinine ratio > 30 mg/g. The proportion with albuminuria was determined and the corresponding 95% confidence limits reported.

Association between albuminuria and categorical variables such gender was assessed using Pearson's Chi Square test. Continuous variables such as body mass index, age, systolic blood pressure, diastolic blood pressure were compared between participants with and without albuminuria using independent samples t-test if Gaussian assumptions held, if not, two-sample Wilcoxon rank-sum test was used.

Variables that were significantly associated with the outcome (albuminuria) were included in a multivariable logistic regression model. The odds ratios (OR) and the corresponding 95% confidence limits were reported.

Results were presented using graphs and tables.

### 3.11 Ethical Considerations

Approval was sought from the Institutional Research and Ethics Committee (IREC) and the hospital management of Bungoma County Referral Hospital.

Parents or guardians to the study participants were informed about the study before giving informed consent. For children older than seven years old assent was sought from them. No incentives were used to convince the guardians to consent to participate in the study. The data collection tool did not contain the names of the participants. Confidentiality was maintained throughout the study. Medical attention was given as necessary irrespective of their consent to participate in the study. Those whose urinalysis was suggestive for UTI were referred to the clinicians for treatment and those with persistent albuminuria were referred to the nephrologist for specialized care in MTRH.

The raw data collected was stored in a locked cabinet throughout the study period while the data in the computer was stored in a password protected file. The results will be presented in the university thesis defense and shall also be availed for publication in a reputable journal. The results of this study will also be availed to Bungoma County Referral Hospital staff and management.

# CHAPTER FOUR: RESULTS

## 4.1 Demographics

One hundred and twenty seven (127) participants were studied. Out of these, 65 were female and 62 were male.

The age range of our study participants was between one year five months to eighteen years old. Their median age was 7.00 (1.42,18.0) years. The median age was 11 years for those with albuminuria and 7 years for those without albuminuria.

108 (85%) of the participants were children while 19 (15%) were adolescents as shown in table 4.

**Table 4: Demographics**

N=127

| | | Percentage |
|---|---|---|
| Gender | Male | 62[49.6%] |
| | Female | 65[50.4%] |
| Age | Children | 108[85%] |
| | Adolescents | 19[15%] |

Median age: 7.00 [1.42, 18.0]

Among the under 5 year olds, 1 (2.4%) with a weight category of -1SD had albuminuria whereas 5 (11.9%) of the same weight category had no albuminuria.

Among the over 5 year olds, 1 (1.2%) with a weight category of underweight had albuminuria whereas 9 (10.6%) of the same weight category had no albuminuria as shown in table 5.

**Table 5: Demographics-weight categories**

| Characteristics N=127 | Albuminuria | No albuminuria | P-value |
|---|---|---|---|
| Z –score [<5 years] n= 42 | | | |
| Normal | 2 [4.8%] | 29 [69.0%] | |
| -1 SD | 1 [2.4%] | 5 [11.9%] | 0.813 |
| -2SD | 0 | 5 [11.9%] | |
| BMI [>5 years] n= 85 | | | |
| Normal | 16 [ 18.8%] | 59 [69.4%] | 0.718 |
| Underweight | 1 [ 1.2%] | 9 [10.6%] | |

Fisher's exact test

### 4.2 Proportion of cell nephropathy

The proportion of those with albuminuria with the first urine sample was (27/127) 21.2%. The proportion of those with sickle cell nephropathy which was defined as persistent albuminuria one month apart was (20/127) 15.8% as shown in figure 3.

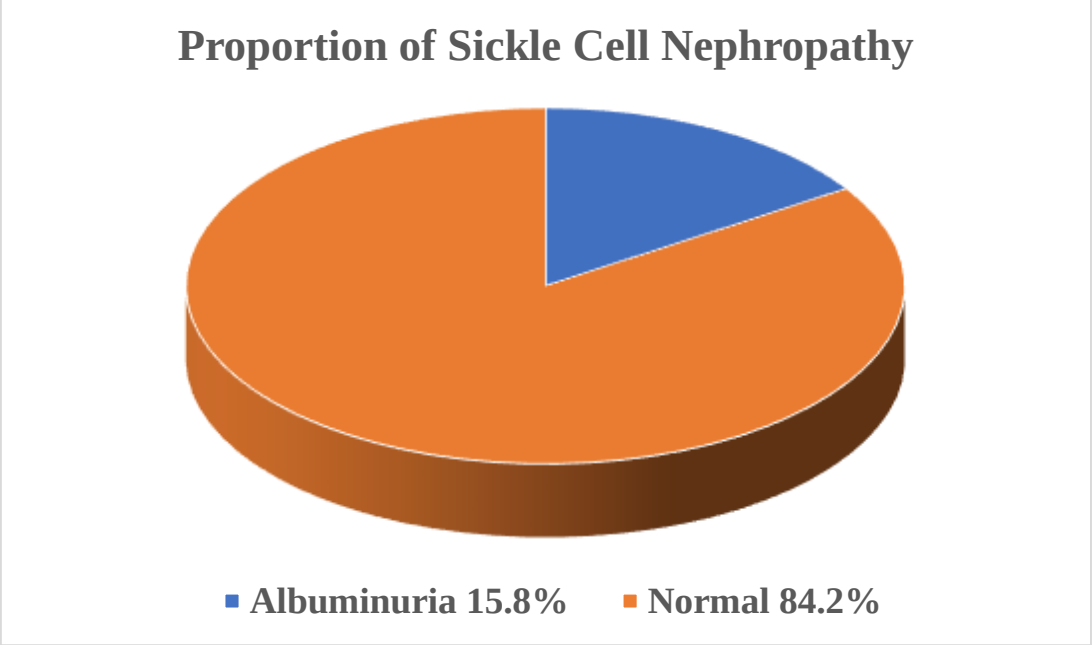


**Figure 3: Proportion of Sickle Cell Nephropathy**

The proportion of children with SCN was 14/108 (12.96%) while that of adolescents was higher at 6/19 (31.58%) as shown in figure 4.

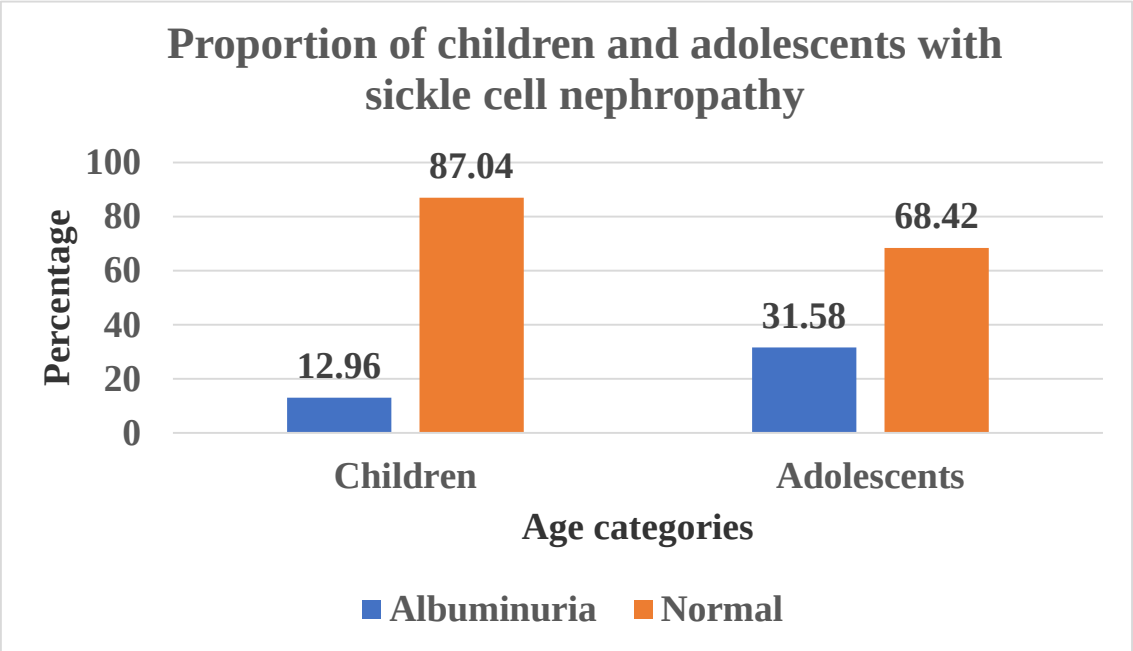


**Figure 4: Proportion of children and adolescents with sickle cell nephropathy**

A total of 19 (15%) had microalbuminuria 1 (0.8%) had macroalbuminuria as shown in table 5.

**Table 6: Results on levels of albuminuria**

| | Percentage N=127 |
|---|---|
| **Albumin Creatinine ratio** | |
| **>300mg/g [severely increased]** | **1 [0.8%]** |
| **30-300mg/g [moderately increased]** | **19 [15%]** |
| **< 30mg/g [normal to mildly increased]** | **107[84.2%]** |

Twenty-one percent of females had albuminuria as opposed to 9.7% of males who had albuminuria. Only one study participant had elevated blood pressure and did not have albuminuria.

Twenty-one percent of those who had been transfused in the past one year had albuminuria. In regards to the number of hospitalizations, sixteen percent of those who had been hospitalized in the past one year had albuminuria as opposed to 13% who had not been hospitalized developed albuminuria.

Seventeen percent of those who were not on Hydroxyurea had albuminuria while only six percent of those who were on Hydroxyurea had albuminuria.

**Table 7: Clinical-demographic characteristics**

| Characteristics | | Albuminuria N=20 | No albuminuria n=107 |
|---|---|---|---|
| Gender | Males | 6(9.7%) | 56(90.3%) |
| | females | 14(21.5%) | 51(78.5%) |
| Systolic BP | Normal | 20(15.8%) | 106(83.4%) |
| | Elevated | 0 | 1(0.8%) |
| Diastolic BP | Normal | 20(15.8%) | 106(83.4%) |
| | Elevated | 0 | 1(0.8%) |
| Number of blood transfusions | none | 11(12.9%) | 74(87.1%) |
| | Ever transfused | 9(21.4%) | 33(78.6%) |
| Number of hospitalizations | none | 3(13.6%) | 19(86.4%) |
| | Ever hospitalized | 17(16.2%) | 88(83.8%) |
| Hydroxyurea use | Yes | 1(6.2%) | 15(93.8%) |
| | No | 19(17.1%) | 92(82.9%) |

**Bi-variate logistic regression**

Age was statistically significant while in the age categories, adolescents were

significantly associated with albuminuria with an unadjusted odds ratio of three as shown in table 8.

None of the other clinical characteristics was significantly associated with albuminuria.

**Table 8: Characteristics associated with SCN**

| Variable | | Odds ratio | P>z | 95%CI Upper | 95%CI Lower |
|---|---|---|---|---|---|
| Age categories | Children | 1 | | | |
| | Adolescents | 3.989 | 0.047 | 0.123 | 9.483 |
| Systolic BP | | 1.024 | 0.4 | 0.969 | 1.081 |
| Diastolic BP | | 1.005 | 0.88 | 0.944 | 1.070 |
| Number of blood transfusions | None | 1.552 | 0.429 | 0.522 | 4.169 |
| | Ever transfused | 2.883 | 0.165 | 0.065 | 12.837 |
| Number of hospitalizations | None | 1.333 | 0.729 | 0.262 | 6.781 |
| | Ever hospitalized | 1.193 | 0.798 | 0.031 | 4.623 |
| Hydroxyurea use | Yes | 0.323 | 0.288 | 0.040 | 2.593 |
| | No | 0.207 | 0 | 0.126 | 0.338 |

# CHAPTER FIVE: DISCUSSION

The proportion of sickle cell nephropathy (15.8%) in this study was determined by dividing the total number of children with albuminuria (20) over the total number of patients with sickle cell disease analyzed (127). Alvarez et al in USA had a proportion (prevalence) of 15% with a sample size of 120 while Becton et al had 16% (Alvarez et al., 2006; Becton et al., 2010). This is probably because of similar sample sizes and the fact that they also took their samples twice for determination of persistent albuminuria. Unlike our study they took their samples one week and six months apart (Alvarez et al., 2006; Becton et al, 2010). The result however differs from other studies (Aloni et al., 2017; Mawanda et al., 2011 & Ocheke et al., 2019) who had higher proportions of albuminuria. This could be attributed to the study design where spot urine samples were taken only once for albuminuria while in this study, those whose spot urine samples turned positive for albuminuria had a repeat sample taken to confirm persistent albuminuria.

Mawanda et al in Uganda had a prevalence of 28.2%. This is higher than that in this study and could be because of the higher sample size of 301 that was used in their study. Furthermore, the methods used in determination of albuminuria were different. Their study used Micral strips as opposed to this study which used quantitative methods of albumin: creatinine ratio (Mawanda et al., 2011). The micral strips have high sensitivity but not specificity with lower positive predictive value than the quantitative method. Mcpherson et al in the USA had a prevalence of 20.7% which was higher than this study (McPherson Yee et al., 2011). This could probably be explained by the fact that their study included those with other forms of sickle cell disease like thelassemias which could also be complicated with sickle cell nephropathy although not as much as the homozygous form HbSS. Mcpherson also

had a larger sample size and their study design was longitudinal done over a ten-year period unlike this study which was cross-sectional.

The median age was higher in those with albuminuria than in those without albumninuria. This further indicates that advancement in age may lead to renal damage. This is comparable to studies done in the USA and Nigeria (Niss et al., 2020; Imuetinyan et al., 2011).

In contrast, Al-Musawa et al in Yemen did not find a difference in the mean ages of children with and without albuminuria 7.1(4.2) versus7.5(3.2) respectively. This may be attributed to the fact that their study had fewer adolescents (14).

The proportion of sickle cell nephropathy was higher in adolescents than in children(31.5% versus 12.96%). This is in line with other study findings (Alvarez et al., 2006; Dharnidharka et al., 1998) and corroborates the fact that renal damage may advance with age thus higher prevalence of albuminuria in adolescents. This is because with more advanced age, those with sickle cell disease are likely to have more crises which indicates firther renal damage with increased number of crises. The proportion of adolescents with albuminuria in this study was slightly lower compared to that of Dharnidharka et al in the USA (46%) (Dharnidharka et al., 1998). This may be attributed to the reason that Dharnidharka et al used urinary albumin excretion with a lower microalbuminuria limit of 20mg/g whereas this study used urine albumin: creatinine ratio which has a cut-off of 30mg/g.

This study however contrasted with Ocheke et al in Nigeria whose findings suggested that the prevalence of albuminuria was higher in the first decade as compared to the second decade (Ocheke et al., 2019). This could be explained by the fact that those who had anemia were more in the first decade of life than in the second decade and

low hematocrit was significantly associated with albuminuria. In sickle cell disease low hemoglobin levels are associated with hemolysis which is associated with sickle cell nephropathy in that the Hb dimers released during hemolysis prevent the re-absorption of albumin thus causing albuminuria.

Age was significantly associated with sickle cell nephropathy. This was similar to other studies done in Africa (Aloni et al., 2017; Eke et al., 2012; Imuetinyan et al., 2011 & Mawanda et al., 2011)).

It is also is conformity with other studies carried out in the USA (Alvarez et al., 2006; Dharnidharka et al., 1998 & McPherson Yee et al., 2011). However, a study in Yemen did not find age to be significant (Al-Musawa & Al-Saqladi, 2019).

This could be attributed to low albuminuria among adolescents possibly due to variation in patient selection and genetic predisposition. The minimum age of albuminuria in this study was four years. This was comparable to Imuetinyan et al in Nigeria who also found albuminuria in pre-school children (Imuetinyan et al., 2011). In contrast however, Dharnidharka et al in USA did not find any albuminuria in a child less than seven years of age (Dharnidharka et al., 1998). This could be explained by the difference in amount of resources in our study settings whereby unlike our setup, the children with sickle cell anemia are better managed thus resulting in fewer and less severe crises.

In regards to gender, more females in our study had nephropathy compared to males (21% versus 9%), although this was not significant. This is in line with Imuetinyan et al and Dharnidharka et al who also found a slight predominance in females though not significant (Dharnidharka et al., 1998; Imuetinyan et al., 2011). In contrast, a study done in Yemen showed more males had albuminuria compared to females (Al-

Musawa & Al-Saqladi, 2019). This is possible due to higher anabolic androgenic steroids in males which can induce or aggravate kidney injury and glomerular toxicity. The effects are mediated through stimulating the renin angiotensin aldosterone system, enhancing the production of endothelin, producing reactive oxygen species as well as inflammatory cytokines.

Body mass index was not significantly associated with SCN. This was in agreement with a study done in Yemen (Al-Musawa et al., 2019). However, Imuetinyan in Nigeria found significance between SCN and those who were underweight (Imuetinyan et al., 2011). This could be attributed to the fewer participants who had albuminuria that were underweight in this study compared to that done in Nigeria.

Blood pressure was not significantly associated and sickle cell nephropathy. This was in agreement with a study by Imuetinyan et al in Nigeria (Imuetinyan et al., 2011). However Becton et al found a significance between abnormal blood pressure (pre-hypertensive and hypertensive) to be significant with albuminuria (Becton et al., 2010). This could be attributed to the more pre-hypertensive and hypertensive participants recruited by Becton who had renal damage which could result a rise in blood pressure.

The number of blood transfusions was not significantly associated with sickle cell nephropathy. This was similar to a study by Al-Musawa et al in Yemen (Al-Musawa & Al-Saqladi, 2019). In this study done at BCRH, there were few participants who had more than three blood transfusions in one year. In our set up many blood transfusions in a year could be an indicator of severe disease (severe anemia mostly due to severe malaria, acute chest syndrome, priapism and cerebral vascular accident) among those with SCD. A study in Nigeria found number of transfusions to be

significant. More than sixty percent of their study participants had been transfused more than 3 times in the two years prior to the recruitment of the study participants (Nnaji & Ogoke, 2020). This could be explained by the fact those who were transfused were done sporadically due reasons mentioned above and this indicates more severe disease that could predispose to sickle cell nephropathy. Early therapeutic transfusion programs are associated with decreased risk of sickle cell nephropathy (Alvarez et al., 2006). In our setting however, we do not have therapeutic transfusion programs. Transfusions are done due to the indications mentioned above.

The number of hospitalizations was also not significantly associated with with SCN. This is comparable to what Dharnidharka et al in USA and Al-Musawa et al in Yemen found (Dharnidharka et al., 1998; Al-Musawa & Al-Saqladi, 2019). However, a study done by Eke et al in Nigeria found significant association between increased number of hospitalizations to albuminuria (Eke et al., 2012). This be attributed to the fact that more study participants in that study had more than three hospitalizations in the year prior to recruitment. This may indicate that more hospitalizations indicate more severe disease and more crises which could contribute to albuminuria.

There was no statistical significance between those not on hydroxyurea and SCN, even though those who were not on hydroxyurea had higher percentage of SCN compared to those who were on hydroxyurea. This could be explained by the fact that at the time of the study, very few of study participants were on the medication. Only two of the study participants were on Hydroxyurea for more than one year prior to recruitment in the study. This is also similar to what was reported in the USA (Alvarez et al., 2006). However, hydroxyurea has been shown to reduce the progress of albuminuria and in some cases even reverse it (Fitzhugh et al., 2005; Laurin et al., 2014). Hydroxyurea is a myelosuppressive agent which reduces the number of painful

crises by increasing the levels of fetal hemoglobin (Agrawal, Patel, Shah, Nainiwal, & Trivedi, 2014). Fetal hemoglobin is increased by intermittent cytotoxic suppression of erythroid precussors and cell stress signaling which affects erthyropoiesis kinetics and physiology and leads to recruitment of erythroid progenitors with increased fetal hemoglobin levels (Lebensburger, 2011). Unlike Niss et al whose study participants that were on hydroxyurea were followed up for three years after which they had a decrease in albuminuria levels, our study did not follow up the patients on hydroxyurea (Niss et al., 2020).

## LIMITATIONS

1. This was a hospital based study and thus might not generalize the whole population**.**

# CHAPTER SIX: CONCLUSION AND RECOMMENDATION

## 6.1 Conclusion

1. One in eight children and one in three adolescents had SCN.
2. Older age was significantly associated with SCN but no clinical characteristics were significantly associated with SCN.

## 6.2 Recommendation

Screening for SCN should be done in routine care of children with SCD during follow up at the clinics and continued throughout adolescence.

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# APPENDICES

## Appendix 1: Time Frame

| ACTIVITY | START | COMPLETE |
|---|---|---|
| PROPOSAL DEVELOPMENT | JANUARY 2017 | APRIL 2017 |
| DEPARTMENT PRESENTATION | MAY 2017 | MAY 2017 |
| PROPOSAL WRITING | JUNE 2017 | JULY 2017 |
| IREC APPROVAL | AUGUST 2018 | SEPTEMBER 2018 |
| DATA COLLECTION | JANUARY 2019 | SEPTEMBER 2019 |
| DATA ANALYSIS | OCTOBER 2019 | NOVEMBER 2019 |
| THESIS WRITING | DECEMBER 2019 | MARCH 2020 |
| MOCK DEFENSE | SEPTEMBER 2021 | SEPTEMBER 2021 |
| SCHOOL DEFENSE | APRIL 2021 | MAY 2021 |

**Appendix 2: Estimated Project Budget**

The estimated budget for this project is as illustrated below. The financial resources required to fund this research project shall be the researcher's own.

| **ITEM** | **QUANTITY** | **UNIT COST(KSH)** | **TOTAL(KSH)** |
|---|---|---|---|
| PRINTER AND PHOTOCOPIER | 1 | 10,000 | 10,000 |
| STATIONERY | - | 10,000 | 10,000 |
| BIOSTASTICIAN | 1 | 20,000 | 20,000 |
| INTERNET AND COMMUCATION | - | 10,000 | 10,000 |
| TRANSPORT | - | 200 | 30,000 |
| PUBLICATION | - | 30,000 | 30,000 |
| RESEARCH ASSISTANT | 4 | 40,000 | 40,000 |
| LAB INVESTIGATIONS-<br>URINALYSIS<br>ACR | <br><br>200<br>200 | <br><br>100<br>1000 | <br><br>20,000<br>200,000 |
| MISCELLANEOUS | - | - | 20,000 |
| **GRAND TOTAL** | - | - | 410,000 |

**Appendix 3: Questionnaire**

1. Biodata: Study number: _____ Age: _____ Gender: M/F

2. Anthropometric measures: Weight: _____kg Height: _____cm

Blood pressure: SBP _____ mm Hg, DBP _____mm Hg

3. Clinical severity of disease

How many times have you been hospitalized in the past year?

□ 5 or more

□ 2 -4

□ 1

□ Nil

Have you ever been transfused?

If yes, how many times?

Once

Twice

Thrice

Four times

Five or more

Have you been ill in the past two weeks?

□ Yes

□ No

Specify_____

Have you been diagnosed with any of the following?

□ Yes

□ No

(tick where appropriate)

□ Cerebrovascular accident

□ Leg ulcer

□ Congestive cardiac failure

□ Renal disease

□ Avascular bone necrosis

□ Priapism

□ Retinopathy

4. Medication history: Are you taking hydroxyurea?

□ Yes

□ No

Do you have any other chronic illness?

Yes

No

If yes, which one…….

Are you on any other medication?

Yes

No

If yes, list the medications……

Do you have symptoms of excessive thirst or increased frequency of passing urine?

Yes

No

5. Family history

Do you have any relative with renal disease?

□ Yes

□ No

If yes, what is their relation to you? .....

Do you have any relatives with hypertension?

□ Yes

□ No

If yes, what is their relation to you? .....

Do you have any relative with diabetes?

Yes

No

If yes, what is their relationship to you?

6. Physical examination: General:

Hydration status

No dehydration

Some dehydration

Severe dehydration

Periorbital edema

 Yes

 No

Pedal edema

 Yes

 No

Leg ulcer(s)

 Yes

 No

Cardiovascular system

 Normal

 Abnormal

HIV status…….

7. Urinalysis:

leucocytes

nitrites

ketones

proteins

bilirubin

8. Lab results:

albumin: creatinine ratio _____mg/g.

9.

| Levels(independent of gender) | Urine albumin: creatinine ratio(mg/g) for spot sample | Tick where appropriate(from the result in no ‘8’ |
|---|---|---|
| Normoalbuminuria | <30 | |
| Microalbuminuria | 30-300 | |
| Macroalbuminuria | >300 | |

**Appendix 4: Consent Form**
**Study number……**

**SICKLE CELL NEPHROPATHY IN CHILDREN AND ADOLESCENTS AT BUNGOMA COUNTY HOSPITAL**

**Principal Investigator: Winfred Nding'uri, Postgraduate student; Department of Child Health and Pediatrics, Moi University.**

**Introduction**:

I am a postgraduate student pursuing a degree in Pediatrics and child health. As part of this degree I am carrying out a study investigating renal disease in children with and adolescents with sickle cell disease. I wish to request your child's participation in the study.

**What is the purpose of this research?**

Sickle cell disease is a chronic condition where the patient's blood cells tend to get deformed within blood vessels resulting in pain and early destruction of the cells. This process takes place in various organs including the kidneys, which is the subject of this study. I am asking you to participate in this study aimed at establishing how common kidney involvement is in children and adolescents with sickle cell disease in our setup.

This study will help us in the long term management of sickle cell patients by informing on need for screening and thus early detection of kidney involvement allowing for early intervention hence improving quality of life.

**Voluntary participation:**

Taking part in this research project is voluntary. You can agree or decline to participate and this will not interfere in any way with the ongoing care of your child.

What will be done to my child if I agree?

- If you agree to have your child in this study, we will request to:
- Take a brief history from you concerning the child
- Do a physical examination including height and weight
- Collect a urine sample as instructed

**Benefits from participating in the study:**

During the history taking and examination, any new information will be relayed to the clinic or doctor for any necessary action. Results from your child's tests that also need any further action will also be communicated appropriately.

**Cost:** I will incur all costs involved in the study thus the tests involved will be at no cost to you. However no monies will be paid for your participation.

**Risk:** The research will not involve any treatment that is not part of what the doctor will be giving.

**Confidentiality:** All the information that we will gather about your child will be kept highly secret. Your name or that of the child will not be used at any time in the report of this research.

**Sharing of the results:** The results, which will come from this research will be sent to medical journals and may be published.

**Right to refuse or withdraw:** You may refuse your child to participate at any time or even withdraw after agreeing to consent.

I have been explained for and understand about the study.

Name of investigator:……..Signature:……Date:……

I agree to be part of this study.

Name:……Signature/thumb print……Date…...

**MAELEZO KWENYE CHETI CHA RIDHAA**

**Kichwa cha habari**: kubaini idadi ya watoto chinimyamiaka kumi na tisa wanao ugua ugonjwa mundu kiini yaani sickle cell wanao patikana na protein katika kipimo cha mkojo.

**Utangulizi:**

Mimi ni mwanafunzi katika chuo kikuu cha Moi kule ambako nijifunza taluma ya matibabu ya watoto .Ninahitajika kufanya utafiti katika taluma hii.Ningependa kufanya utafiti kwa watoto walio na ugonjwa mundu kiini yani sickle cell.Lengo langu ni kubaini idadi ya wanopatikana na dalili ya ugonjwa wa figo katika kundi hii ya watoto.Ningependa kuomba kushiriki kwa mtoto wako kwa utafiti huu.Uko na uhuru wa kuuliza maswali yeyote yale yanoyoambatana na utafiti huu.

**Kusudi la utafiti huu:**

Utafiti huu utasaidia kufahamu idadi y watoto ambao figo zimeanza kupata madhara ya ugonjwa mundu kiini ili kuwezesha shida hii kupelelezwa mapema na madawa ya kusitisha kudhoofika kwa figo kuanzishwa mapema.

**Kujitolea kushiriki**:

Kukubali mtoto kushiriki kwa utafiti huu ni kwa hiari yake mtu mwenyewe.Hakutakwepo na kulazimishwa ama kushurutishwa.Ni haki ya kila mshiriki kujiodoa kwenye utafiti huu wakati wowote.kujiondoa kwa mshiriki kwenye utafiti huu hakutapelekea mtoto wako kunyimwa matibabu anayostahili.

**Yale ambayo mtoto atafanyiwa:**

Mtoto yeyote ambaye atashiriki kwenye utafiti huu atafanyiwa yafuatayo.

 Rekodi zitapitiwa  Kuulizwa maswali ili kufahamu ukali ya maradhi au dalili za ugonjwa huu  Kupimwa uzito  Kupimwa urefu.  Kupimwa kwa mkojo

**Je mtoto wangu atanufaidika vipi kwa kushiriki kwa utafiti huu?**

Katika ile hali ya kueleza shida za mtoto wako na pia pale nitakapo mpima mtoto wako kama kuna mambo mapya nitapata ,nitamfahamisha daktari wako ili mtoto afaidike.

Hapatakwepo na malipo yeyote kwa kushiriki kwa mtoto wako,lakini nitagharamia malipo yote ya kupimwa mkojo.

Je kuna uwezekano wa madhara yeyote kwa mtoto wangu?

Hapatakwepo na madhara yeyote kwa mtoto wako.

**Hakikisho la siri kwa mhusika:**

Yale yote ambayo yatanakiliwa kuhusu mtoto wako yatabaki kuwa siri na hakuna majina ambayo yatatumika ambayo yanaweza kukutambulisha wewe au mtoto wako.

**Utumizi wa matokeo ya utafiti huu:**

Matokeo ya utafiti huu yanaweza kuchapishwa kwa majarida ya kisayansi lakini siri ya mshiriki itadumishwa.

**Haki ya kujiondoa kwa utafiti huu**:

Una haki ya kujiondoa kwenye utafiti huu wakati wowote ule.

**Cheti cha ridhaa:**

Mimi kwa hiari yangu nimejitolea kutoa idhini kwa niaba ya mtoto wangu kushiriki katika utafiti huu.Nimeshaelezwa sheria na kanuni zote zinazohusika na utafiti huu.

Jina----------

Sahihi ya mzazi kwa niaba ya mtoto----------

Tarehe----------

Sahihi ya anayeuliza maswali.----------

**Tarehe----------**

**Appendix 5: Assent form (FOR THOSE OLDER THAN SEVEN YEARS) SICKLE CELL NEPHROPATHY IN CHILDREN AND ADOLESCENTS AT BUNGOMA COUNTY HOSPITAL**

**Principal Investigator: Winfred Nding'uri, Postgraduate student; Department of Child Health and Pediatrics, Moi University.**

**Introduction**:

I am a postgraduate student pursuing a degree in Pediatrics and child health. As part of this degree I am carrying out a study investigating renal disease in children with and adolescents with sickle cell disease. I wish to request your participation in the study.

**What is the purpose of this research?**

Sickle cell disease is a chronic condition where the patient's blood cells tend to get deformed within blood vessels resulting in pain and early destruction of the cells. This process takes place in various organs including the kidneys, which is the subject of this study. I am asking you to participate in this study aimed at establishing how common kidney involvement is in children and adolescents with sickle cell disease in our setup.

This study will help us in the long term management of sickle cell patients by informing on need for screening and thus early detection of kidney involvement allowing for early intervention hence improving quality of life.

**Voluntary participation:**

Taking part in this research project is voluntary. You can agree or decline to participate and this will not interfere in any way with the care given to you.

What will be done to me if I agree?

- If you agree to participate in this study, we will request to:
- Take a brief history from you

- Do a physical examination including height and weight
- Collect a urine sample as instructed

**Benefits from participating in the study:**

During the history taking and examination, any new information will be relayed to the clinic or doctor for any necessary action. Results from your tests that also need any further action will also be communicated appropriately.

**Risk:** The research will not involve any treatment that is not part of what the doctor will be giving.

**Confidentiality:** All the information that we will gather about you will be kept highly secret. Your name will not be used at any time in the report of this research.

**Sharing of the results:** The results, which will come from this research will be sent to the hospital staff and other relevant authorities, and the information used to help other children.

**Right to refuse or withdraw:** You may refuse to participate at any time or even withdraw after agreeing to assent.

I have been explained for and understand about the study.

Name of Investigator:……..Signature:……Date:……

I agree to be part of this study.

Name:……Signature/thumb print……Date…...

**MAELEZO KWENYE CHETI CHA RIDHAA (KWA WALE ZAIDI YA MIAKA SABA)**

**Kichwa cha habari**: kubaini idadi ya watoto chinimyamiaka kumi na tisa wanao ugua ugonjwa mundu kiini yaani sickle cell wanao patikana na protein katika kipimo cha mkojo.

**Utangulizi:**

Mimi ni mwanafunzi katika chuo kikuu cha Moi kule ambako nijifunza taluma ya matibabu ya watoto .Ninahitajika kufanya utafiti katika taluma hii.Ningependa kufanya utafiti kwa watoto walio na ugonjwa mundu kiini yani sickle cell.Lengo langu ni kubaini idadi ya wanopatikana na dalili ya ugonjwa wa figo katika kundi hii ya watoto.Ningependa kuomba kushiriki kwako kwa utafiti huu.Uko na uhuru wa kuuliza maswali yeyote yale yanoyoambatana na utafiti huu.

**Kusudi la utafiti huu:**

Utafiti huu utasaidia kufahamu idadi ya watoto ambao figo zimeanza kupata madhara ya ugonjwa  mundu kiini ili kuwezesha shida hii kupelelezwa mapema na madawa ya kusitisha kudhoofika kwa figo kuanzishwa mapema.

**Kujitolea kushiriki**:

Kukubali  kushiriki kwa utafiti huu ni kwa hiari yako mwenyewe.Hakutakwepo na kulazimishwa ama kushurutishwa.Ni haki ya kila mshiriki kujiodoa kwenye utafiti huu wakati wowote. Kujiondoa kwa mshiriki kwenye utafiti huu hakutapelekea wewe kunyimwa matibabu anayostahili.

**Yale ambayo utafanyiwa:**

Ukikubali kushiriki kwenye utafiti huu, utafanyiwa yafuatayo.

 Rekodi zitapitiwa  Kuulizwa maswali ili kufahamu ukali ya maradhi au dalili za ugonjwa huu  Kupimwa uzito  Kupimwa urefu.  Kupimwa kwa mkojo

**Je, utanufaika vipi kwa kushiriki kwa utafiti huu?**

Katika ile hali ya kueleza shida yako na pia pale nitakapo kupima, kama kuna mambo mapya nitapata ,nitamfahamisha daktari wako ili ufaidike.

**Je kuna uwezekano wa madhara yeyote kwangu?**

Hapatakwepo na madhara yeyote kwako.

**Hakikisho la siri kwa mhusika:**

Yale yote ambayo yatanakiliwa kukuhusu yatabaki kuwa siri na hakuna majina ambayo yatatumika ambayo yanaweza kukutambulisha wewe.

**Utumizi wa matokeo ya utafiti huu:**

Matokeo ya utafiti huu yanaweza kuchapishwa kwa majarida ya kisayansi lakini siri ya mshiriki itadumishwa.

**Haki ya kujiondoa kwa utafiti huu**:

Una haki ya kujiondoa kwenye utafiti huu wakati wowote ule.

**Cheti cha ridhaa:**

Mimi kwa hiari yangu nimejitolea kutoa idhini kwa niaba ya mtoto wangu kushiriki katika utafiti huu.Nimeshaelezwa sheria na kanuni zote zinazohusika na utafiti huu.

Jina----------

Sahihi ya mzazi kwa niaba ya mtoto----------

Tarehe----------

Sahihi ya anayeuliza maswali.----------

Tarehe----------

**Appendix 6: Urinalysis Procedure**

Fresh urine sample will be collected in a dry sterile bottle pre-labelled with the participants' study number. The procedure was explained to the parents or guardians and the older children by the principal investigator who explained to them how to get mid-stream urine.

Clinitek multistix urine test strips (Siemens healthcare diagnostics, 1717 Deerfield Road, Deerfield, IL 60015-0778, USA) were used for urinalysis.

Within one hour of sample collection, the urinalysis was done by immersing the strip in the urine sample covering all the reagent areas for around 30 seconds. The edge of the strip was run against the rim of the urine container to drain any excess urine.

The reactions were read visually after 60 seconds. These color changes were compared against the uristix color chart on the bottle. All the parameters were looked at and where there was a discrepancy in reading another person (lab technician research assistant) was able to look at it.

Albumin and creatinine concentrations were measured using dipsticks (Clinitek micro-albumin 2 reagent strips)

Albumin: the test is based on the dye binding using high affinity sulfonephthalein dye. The change to any blue color is due to the presence of albumin and these colors range from pale green to aqua blue. Intensity of the color change is measured by spectrometry and will give the albumin concentration.

Creatinine: the test is based on the activity of the copper creatinine complex that catalyzes the reaction of diisipropylbenzene dihydroperoxide and tetramethylbenzidine. The color changes from orange through green to blue.

The dipsticks were placed in the analyzer (Siemens Clinitek status plus analyzer-Siemens Healthcare Diagnostics) and were used to measure the albumin:creatinine concentrations.

Albumin: creatinine ratio was read in mg/g and microalbuminuria levels were between 30-299mg/g while macroalbuminuria were levels above 300mg/g.

Normal and abnormal controls were run daily to ensure validity of results.

**Appendix 7: Formal approval**

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET

Reference: IREC/2017/145
***Approval Number: 0002040***

15th February, 2018

Dr. Winfred Wangui Nding'uri,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
**ELDORET-KENYA.**

15 FEB 2018

Dear Dr. Nding'uri,

**RE: FORMAL APPROVAL**

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

***"Sickle Cell Nephropathy among Children and Adolescents with Sickle Cell Disease at Bungoma County Hospital".***

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 2040*** on 15th February, 2018. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 14th February, 2019. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

**DR. S. NYABERA**
**DEPUTY-CHAIRMAN**
**INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE**

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

## Appendix 8: Continuing approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471/2/3

MOI UNIVERSITY
COLLEGE OF HEALTH SCIENCES
P.O. BOX 4606
ELDORET
Tel: 33471/2/3

Reference: IREC/2017/145
***Approval Number: 0002040***

15th February, 2019

Dr. Winfred Wangui Nding'uri,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
**ELDORET-KENYA.**

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
15 FEB 2019
APPROVED
P.O. Box 4606-30100 ELDORET

Dear Dr. Nding'uri

**RE: CONTINUING APPROVAL**

The Institutional Research and Ethics Committee has reviewed your request for continuing approval to your study titled:-

***"Sickle Cell Nephropathy among Children and Adolescents with Sickle Cell Disease at Bungoma County Hospital".***

Your proposal has been granted a Continuing Approval with effect from 15th February, 2019. You are therefore permitted to continue with your study.

Note that this approval is for 1 year; it will thus expire on 14th February, 2020. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

**DR. S. NYABERA**
**DEPUTY-CHAIRMAN**
**INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE**

cc: CEO - MTRH
Principal - CHS
Dean - SOM
Dean - SPH
Dean - SOD

**Appendix 9: Hospital approval**

# REPUBLIC OF KENYA

## COUNTY GOVERNMENT OF BUNGOMA
## MINISTRY OF HEALTH
## OFFICE OF THE COUNTY DIRECTOR
## HEALTH

**Telegrams: "MEDICAL", BUNGOMA**
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**When replaying please quote**

COUNTY DIRECTOR OF HEALTH,
BUNGOMA COUNTY
P O BOX 18-50200
**BUNGOMA**

**Ref: CG/BGM/CDH/RESRC/VOL.1(73)**

**DATE 7TH NOVEMBER, 2018**

DR. WINFRED WANGUI NDING'URI
MOI UNIVERSITY
P.O BOX 4606
**ELDORET.**

**RE: RESEARCH AUTHORIZATION**

I am pleased to inform you that you have been authorized to undertake research in Bungoma Referral Hospital for the period of **nine (9) months** following your application for authority to carry out research on **'Sickle Cell Nephropathy in Children and Adolescents at Bungoma County Referral Hospital'**,
Kindly note that, as an applicant who has been licensed under the Institutional Research and Ethics Committee (IREC) of Moi Teaching and Referral Hospital to conduct research in Kenya, you shall deposit **a copy** of the final research report to the County Director of Health and the office of Medical Superintendent of Bungoma County Referral Hospital

The soft copy of the same should be submitted through the online Reasearch Information system.

Thank you.

COUNTY DIRECTOR OF HEALTH
BUNGOMA COUNTY
P. O. Box 18-50200
BUNGOMA

**ROBERT MOSE**
**FOR, COUNTY DIRECTOR OF HEALTH**
**BUNGOMA COUNTY**
CC: MEDICAL SUPERINTENDENT-BCRH

**Appendix 10: Equipment used**

1. Siemens Clinitek status plus urine analyzer
2. Blood Pressure Machine (Elite sphygmomanometer certified 50112654)
3. ADE weighing scale with telescopic height/ length measure
4. ADE Stadiometer
5. Kinlee 20kg weighing scale

**Picture of Siemens Clinitek status plus urine analyzer**

## Appendix 11: Blood Pressure chart for Boys

*Blood Pressure Levels for the 90th and 95th Percentiles for Male Children and Adolescents Ages 1 to 17*

| | | Systolic BP (mm Hg), by Height Percentile from Standard Growth Curves | | | | | | | Diastolic BP (mm Hg), by Height Percentile from Standard Growth Curves | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | BP Percentile | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 1 | 90TH | 94 | 95 | 97 | 98 | 100 | 102 | 102 | 50 | 51 | 52 | 53 | 54 | 54 | 55 |
| | 95TH | 98 | 99 | 101 | 102 | 104 | 106 | 106 | 55 | 55 | 56 | 57 | 58 | 59 | 59 |
| 2 | 90TH | 98 | 99 | 100 | 102 | 104 | 105 | 106 | 55 | 55 | 56 | 57 | 58 | 59 | 59 |
| | 95TH | 101 | 102 | 104 | 106 | 108 | 109 | 110 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| 3 | 90TH | 100 | 101 | 103 | 105 | 107 | 108 | 109 | 59 | 59 | 60 | 61 | 62 | 63 | 63 |
| | 95TH | 104 | 105 | 107 | 109 | 111 | 112 | 113 | 63 | 63 | 64 | 65 | 66 | 67 | 67 |
| 4 | 90TH | 102 | 103 | 105 | 107 | 109 | 110 | 111 | 62 | 62 | 63 | 64 | 65 | 66 | 66 |
| | 95TH | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 66 | 67 | 67 | 68 | 69 | 70 | 71 |
| 5 | 90TH | 104 | 105 | 106 | 108 | 110 | 112 | 112 | 65 | 65 | 66 | 67 | 68 | 69 | 69 |
| | 95TH | 108 | 109 | 110 | 112 | 114 | 115 | 116 | 69 | 70 | 70 | 71 | 72 | 73 | 74 |
| 6 | 90TH | 105 | 106 | 108 | 110 | 111 | 113 | 114 | 67 | 68 | 69 | 70 | 70 | 71 | 72 |
| | 95TH | 109 | 110 | 112 | 114 | 115 | 117 | 117 | 72 | 72 | 73 | 74 | 75 | 76 | 76 |
| 7 | 90TH | 106 | 107 | 109 | 111 | 113 | 114 | 115 | 69 | 70 | 71 | 72 | 72 | 73 | 74 |
| | 95TH | 110 | 111 | 113 | 115 | 116 | 118 | 119 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| 8 | 90TH | 107 | 108 | 110 | 112 | 114 | 115 | 116 | 71 | 71 | 72 | 73 | 74 | 75 | 75 |
| | 95TH | 111 | 112 | 114 | 116 | 118 | 119 | 120 | 75 | 76 | 76 | 77 | 78 | 79 | 80 |
| 9 | 90TH | 109 | 110 | 112 | 113 | 115 | 117 | 117 | 72 | 73 | 73 | 74 | 75 | 76 | 77 |
| | 95TH | 113 | 114 | 116 | 117 | 119 | 121 | 121 | 76 | 77 | 78 | 79 | 80 | 80 | 81 |
| 10 | 90TH | 110 | 112 | 113 | 115 | 117 | 118 | 119 | 73 | 74 | 74 | 75 | 76 | 77 | 78 |
| | 95TH | 114 | 115 | 117 | 119 | 121 | 122 | 123 | 77 | 78 | 79 | 80 | 80 | 81 | 82 |
| 11 | 90TH | 112 | 113 | 115 | 117 | 119 | 120 | 121 | 74 | 74 | 75 | 76 | 77 | 78 | 78 |
| | 95TH | 116 | 117 | 119 | 121 | 123 | 124 | 125 | 78 | 79 | 79 | 80 | 81 | 82 | 83 |
| 12 | 90TH | 115 | 116 | 117 | 119 | 121 | 123 | 123 | 75 | 75 | 76 | 77 | 78 | 78 | 79 |
| | 95TH | 119 | 120 | 121 | 123 | 125 | 126 | 127 | 79 | 79 | 80 | 81 | 82 | 83 | 83 |
| 13 | 90TH | 117 | 118 | 120 | 122 | 124 | 125 | 126 | 75 | 76 | 76 | 77 | 78 | 79 | 80 |
| | 95TH | 121 | 122 | 124 | 126 | 128 | 129 | 130 | 79 | 80 | 81 | 82 | 83 | 83 | 84 |
| 14 | 90TH | 120 | 121 | 123 | 125 | 126 | 128 | 128 | 76 | 76 | 77 | 78 | 79 | 80 | 80 |
| | 95TH | 124 | 125 | 127 | 128 | 130 | 132 | 132 | 80 | 81 | 81 | 82 | 83 | 84 | 85 |
| 15 | 90TH | 123 | 124 | 125 | 127 | 129 | 131 | 131 | 77 | 77 | 78 | 79 | 80 | 81 | 81 |
| | 95TH | 127 | 128 | 129 | 131 | 133 | 134 | 135 | 81 | 82 | 83 | 83 | 84 | 85 | 86 |
| 16 | 90TH | 125 | 126 | 128 | 130 | 132 | 133 | 134 | 79 | 79 | 80 | 81 | 82 | 82 | 83 |
| | 95TH | 129 | 130 | 132 | 134 | 136 | 137 | 138 | 83 | 83 | 84 | 85 | 86 | 87 | 87 |
| 17 | 90TH | 128 | 129 | 131 | 133 | 134 | 136 | 136 | 81 | 81 | 82 | 83 | 84 | 85 | 85 |
| | 95TH | 132 | 133 | 135 | 136 | 138 | 140 | 140 | 85 | 85 | 86 | 87 | 88 | 89 | 89 |

*Source:* Reprinted from National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Blood pressure percentile determined by a single measurement.

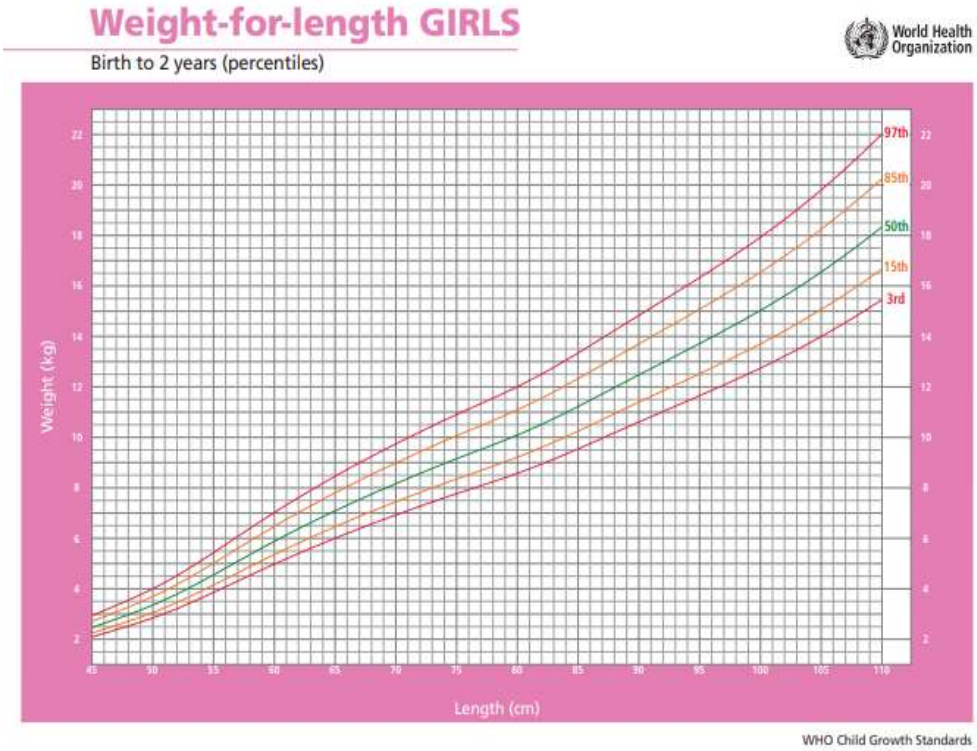
## Appendix 12: Blood pressure chart for girls

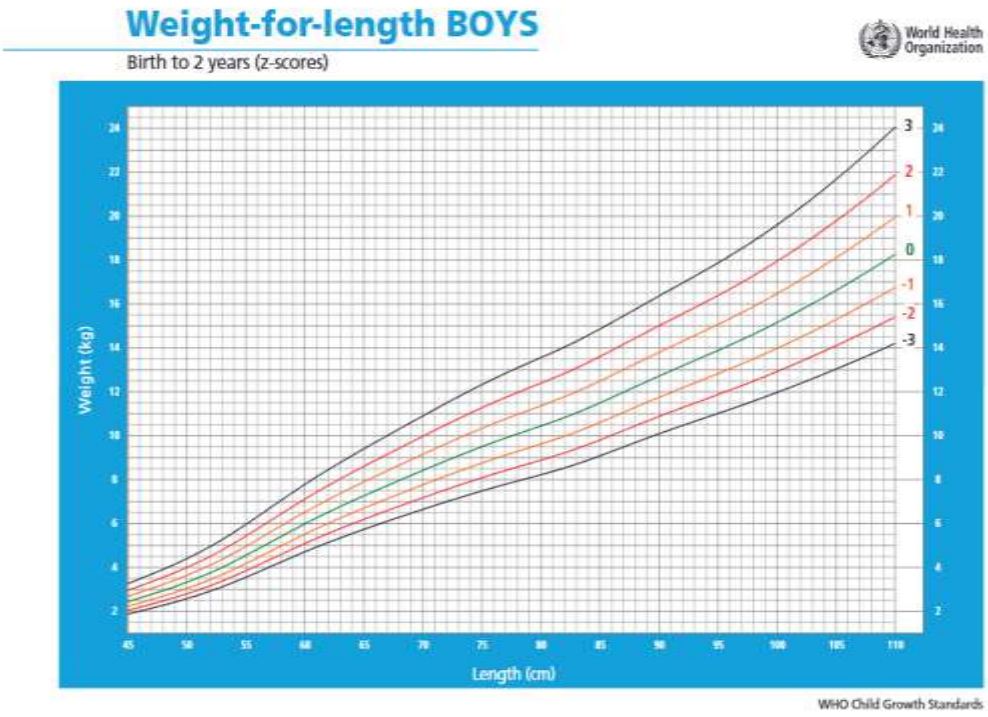
*Blood Pressure Levels for the 90th and 95th Percentiles for Female Children and Adolescents Ages 1 to 17*

| | | Systolic BP (mm Hg), by Height Percentile from Standard Growth Curves | | | | | | | Diastolic BP (mm Hg), by Height Percentile from Standard Growth Curves | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | BP Percentile | 5% | 10% | 25% | 50% | 75% | 90% | 95% | 5% | 10% | 25% | 50% | 75% | 90% | 95% |
| 1 | 90TH | 97 | 98 | 99 | 100 | 102 | 103 | 104 | 53 | 53 | 53 | 54 | 55 | 56 | 56 |
| | 95TH | 101 | 102 | 103 | 104 | 105 | 107 | 107 | 57 | 57 | 57 | 58 | 59 | 60 | 60 |
| 2 | 90TH | 99 | 99 | 100 | 102 | 103 | 104 | 105 | 57 | 57 | 58 | 58 | 59 | 60 | 61 |
| | 95TH | 102 | 103 | 104 | 105 | 107 | 108 | 109 | 61 | 61 | 62 | 62 | 63 | 64 | 65 |
| 3 | 90TH | 100 | 100 | 102 | 103 | 104 | 105 | 106 | 61 | 61 | 61 | 62 | 63 | 63 | 64 |
| | 95TH | 104 | 104 | 105 | 107 | 108 | 109 | 110 | 65 | 65 | 65 | 66 | 67 | 67 | 68 |
| 4 | 90TH | 101 | 102 | 103 | 104 | 106 | 107 | 108 | 63 | 63 | 64 | 65 | 65 | 66 | 67 |
| | 95TH | 105 | 106 | 107 | 108 | 109 | 111 | 111 | 67 | 67 | 68 | 69 | 69 | 70 | 71 |
| 5 | 90TH | 103 | 103 | 104 | 106 | 107 | 108 | 109 | 65 | 66 | 66 | 67 | 68 | 68 | 69 |
| | 95TH | 107 | 107 | 108 | 110 | 111 | 112 | 113 | 69 | 70 | 70 | 71 | 72 | 72 | 73 |
| 6 | 90TH | 104 | 105 | 106 | 107 | 109 | 110 | 111 | 67 | 67 | 68 | 69 | 69 | 70 | 71 |
| | 95TH | 108 | 109 | 110 | 111 | 112 | 114 | 114 | 71 | 71 | 72 | 73 | 73 | 74 | 75 |
| 7 | 90TH | 106 | 107 | 108 | 109 | 110 | 112 | 112 | 69 | 69 | 69 | 70 | 71 | 72 | 72 |
| | 95TH | 110 | 110 | 112 | 113 | 114 | 115 | 116 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| 8 | 90TH | 108 | 109 | 110 | 111 | 112 | 113 | 114 | 70 | 70 | 71 | 71 | 72 | 73 | 74 |
| | 95TH | 112 | 112 | 113 | 115 | 116 | 117 | 118 | 74 | 74 | 75 | 75 | 76 | 77 | 78 |
| 9 | 90TH | 110 | 110 | 112 | 113 | 114 | 115 | 116 | 71 | 72 | 72 | 73 | 74 | 74 | 75 |
| | 95TH | 114 | 114 | 115 | 117 | 118 | 119 | 120 | 15 | 76 | 76 | 77 | 78 | 78 | 79 |
| 10 | 90TH | 112 | 112 | 114 | 115 | 116 | 117 | 118 | 73 | 73 | 73 | 74 | 75 | 76 | 76 |
| | 95TH | 116 | 116 | 117 | 119 | 120 | 121 | 122 | 77 | 77 | 77 | 78 | 79 | 80 | 80 |
| 11 | 90TH | 114 | 114 | 116 | 117 | 118 | 119 | 120 | 74 | 74 | 75 | 75 | 76 | 77 | 77 |
| | 95TH | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 78 | 78 | 79 | 79 | 80 | 81 | 81 |
| 12 | 90TH | 116 | 116 | 118 | 119 | 120 | 121 | 122 | 75 | 75 | 76 | 76 | 77 | 78 | 78 |
| | 95TH | 120 | 120 | 121 | 123 | 124 | 125 | 126 | 79 | 79 | 80 | 80 | 81 | 82 | 82 |
| 13 | 90TH | 118 | 118 | 119 | 121 | 122 | 123 | 124 | 76 | 76 | 77 | 78 | 78 | 79 | 80 |
| | 95TH | 121 | 122 | 123 | 125 | 126 | 127 | 128 | 80 | 80 | 81 | 82 | 82 | 83 | 84 |
| 14 | 90TH | 119 | 120 | 121 | 122 | 124 | 125 | 126 | 77 | 77 | 78 | 79 | 79 | 80 | 81 |
| | 95TH | 123 | 124 | 125 | 126 | 128 | 129 | 130 | 81 | 81 | 82 | 83 | 83 | 84 | 85 |
| 15 | 90TH | 121 | 121 | 122 | 124 | 125 | 126 | 127 | 78 | 78 | 79 | 79 | 80 | 81 | 82 |
| | 95TH | 124 | 125 | 126 | 128 | 129 | 130 | 131 | 82 | 82 | 83 | 83 | 84 | 85 | 86 |
| 16 | 90TH | 122 | 122 | 123 | 125 | 126 | 127 | 128 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| | 95TH | 125 | 126 | 127 | 128 | 130 | 131 | 132 | 83 | 83 | 83 | 84 | 85 | 86 | 86 |
| 17 | 90TH | 122 | 123 | 124 | 125 | 126 | 128 | 128 | 79 | 79 | 79 | 80 | 81 | 82 | 82 |
| | 95TH | 126 | 126 | 127 | 129 | 130 | 131 | 132 | 83 | 83 | 83 | 84 | 85 | 86 | 86 |

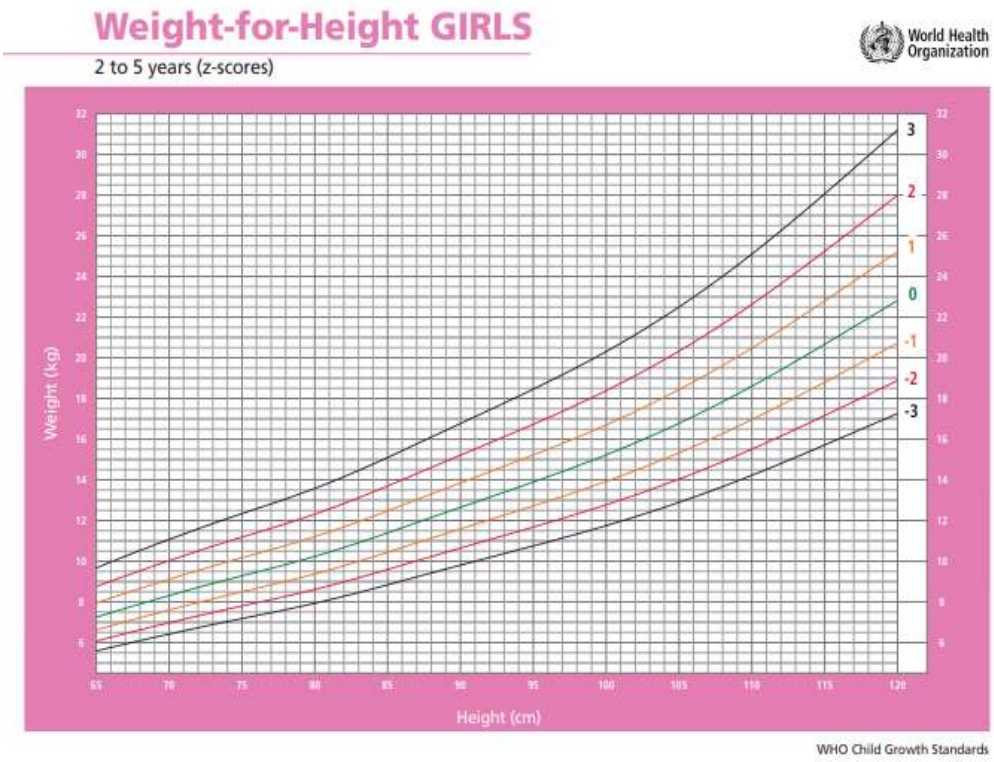
*Source:* Reprinted from National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents.
Blood pressure percentile determined by a single measurement.

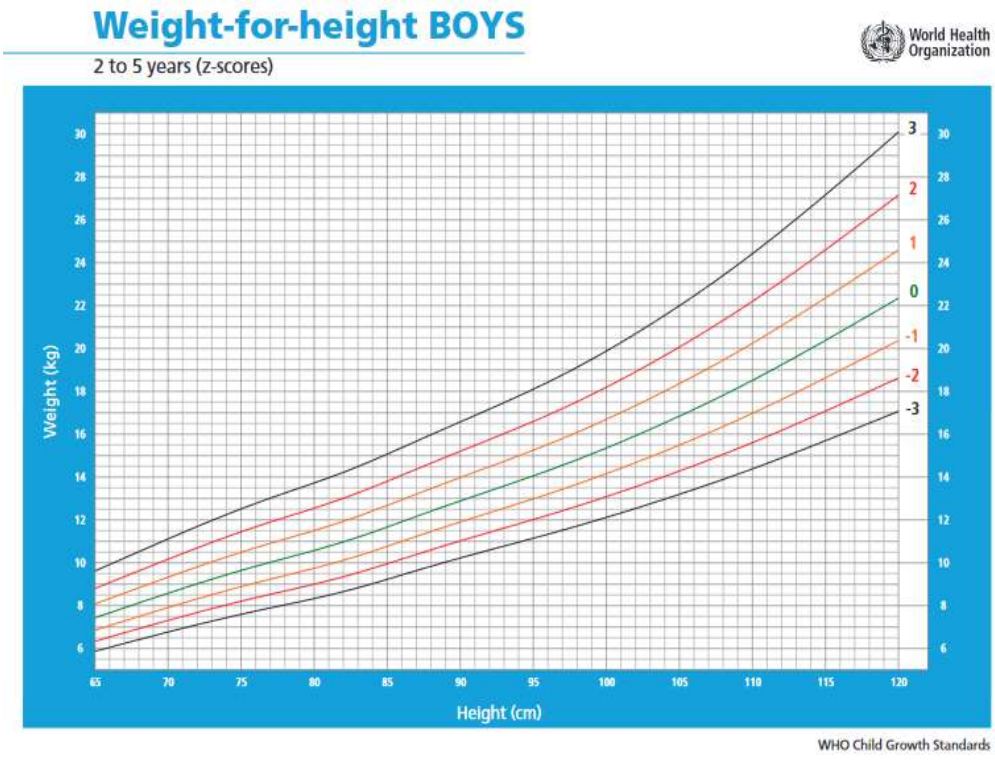
**Appendix 13: weight for length charts**



**Appendix 14: Weight for height charts**



**Appendix 15: BMI for age**