MICROALBUMINURIA AS PREDICTOR OF EARLY GLOMERULAR INJURY IN CHILDREN AND ADOLESCENTS WITH SICKLE CELL ANAEMIA AT MUHIMBILI NATIONAL HOSPITAL DAR ES SALAAM, TANZANIA 2012

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MMed (Paediatrics and Child Health) Dissertation

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By

Richard Christopher, MD

A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Medicine (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences

Muhimbili University of Health and Allied Sciences

November 2012

CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by the Muhimbili University of Health and Allied Sciences a dissertation entitled: ***Microalbuminuria as predictor of early glomerular injury in children and adolescents with sickle cell anaemia at Muhimbili National Hospital, Dar es salaam,Tanzania,2012,*** in partial fulfillment of the requirements for the degree of Master of Medicine, (Paediatrics and Child Health) of the Muhimbili University of Health and Allied Sciences (MUHAS).

……

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(Supervisor)

Date: .....

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Date: …….

DECLARATION AND COPYRIGHT

I, Richard Christopher, declare that this **dissertation** is my own original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature …… **Date**.....

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DEDICATION

This work is dedicated to my both sibling brother (Bernard) and sister (Sarah) who are known patients with SCA.

My adorable little baby boy Randy Richards.

ABSTRACT

Background: Microalbuminuria (MA) is the earliest marker of various diseases affecting the renal system. Its relevance in children and adolescents with sickle cell anaemia (SCA), who are known to be prone to renal complications, has not been fully explored in our setting. Several studies have shown microalbuminuria to be prevalent among SCA children. It is now used extensively as a sensitive test of preclinical glomerular damage. Microalbuminuria in the early stages of sickle cell nephropathy is a hallmark of future deterioration of renal function. It is important to detect this early with routine surveillance. Intervention at this stage may prevent or at least delay the end stage renal disease.

Objectives: To determine the prevalence of microalbuminuria and its clinical correlates in children and adolescents with SCA attending sickle cell clinic at Muhimbili National Hospital.

Materials and Methods: This was a hospital based descriptive cross-sectional study. Children and adolescents aged 3 – 18 years attending sickle cell clinic were randomly selected. Urine sample of all eligible children and adolescent with SCA was screened for microalbuminuria by special Micral urine taste strips (Cliawaived Microlalbumin 2-1 Combo, USA),with sensitivity and specificity of 96.5% and 98.3 respectively. The resting blood pressure (BP) measurements, haemoglobin level, were obtained and clinical events associated with microalbuminuria were recorded. Data were analyzed using Statistical Package for Social Science (SPSS) version 17 statistical packages. Chi-square test was used for categorical variables, and student *t* test for independent sample means. Binary logistic regression was used to analyze potential effect modifiers of microalbuminuria.

Results: The study group was made up of 120 subjects aged 3 to 18 years (53% females). Microalbuminuria (MA) was found in 29/120 (24%). None of the clinical characteristics (painful crisis, blood transfusion, abnormal pressure) were significantly related with MA. Haemoglobin levels were significantly lower in subjects with MA than in those without MA (5.9±1.2 vs 7.4±1.0g/dL, respectively)p=0.001 . In multivariate logistic regression model of MA both Hb level and age remain in the final model as clinical correlates of MA. Higher Hb level showed a protective effect against MA (Odds ratio=0.55) p=0.001 while subjects with MA were more likely to have older age. (Odds ratio=1.7) p=0.001

Conclusion and Recommendations: MA is common among children and adolescents with SCA and directly related to age and inversely related to the haemoglobin levels. Urinary MA measurement is a simple and non-invasive screening biomarker which may be utilized as part of routine health care in children and adolescents with SCA. Screening for microalbuminuria seems prudent after age 6 to 7 years especially in those with severe anaemia. Longitudinal studies are essential to determine the significance of childhood microalbuminuria in the development of renal disease.

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LIST OF ABBREVIATIONS

ACEI	ANGIOTENSIN CONVERTING ENZYME INHIBITOR
ACR	ALBUMIN CREATININE RATIO
BP	BLOOD PRESSURE
BT	BLOOD TRANSFUSION
ESRD	END STAGE RENAL DISEASE
GFR	GLOMERULAR FILTRATION RATE
HB	HAEMOGLOBIN
HBAS	SICKLE CELL TRAIT
HBSS	HOMOZYGOUS HEMOGLOBIN S
MA	MICROALBUMINURIA
MNH	MUHIMBILI NATIONAL HOSPITAL
MPGN	MEMBRANOPROLIFERATIVE GLOMERURONEPHRITIS
MUHAS	MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES
RBC	RED BLOOD CELL
SCA	SICKLE CELL ANAEMIA
SCD	SICKLE CELL DISEASE
VOC	VASOOCCLUSIVE CRISES

CHAPTER ONE

1.0 INTRODUCTION AND LITERATURE REVIEW

1.1 Background.

Sickle cell disease (SCD) is a group of inherited sickling disorders. The most common form of SCD arises from the homozygous inheritance of the beta-haemoglobin S allele (HbS) resulting in sickle cell anemia (SCA). This is characterized with sequale of chronic haemolysis and repeated vaso occlusive episodes.

James B Herrick first described the disease in 1910 in a 20yr old West Indian dental student who had recurrent jaundice, fever and chronic ulceration of lower limbs. The patient was anaemic and striking morphologic abnormalities of the red blood cells were present. His circulating blood contained bizarre elongated cresent shaped cells that were fancifully compared to the blade of the sickle.[1, 2]

1.1.1Epidemiology

SCD is found frequently in Afro Caribbean population and sporadically throughout the Mediterranean region, India and Middle East. The highest gene concentration occurs in the equatorial Africa where up to 40% of West African people possess the HbS gene. The prevalence in the African regions away from equator both north and south is considerably low.

In Dar es salaam, Tanzania approximately 17% of children entering hospital for any reason are carrier of sickle cell gene, of these one in every four have homozygous form HbSS. In other areas like Karagwe, North West of Tanzania 13% of population are carriers and one in every thirty patients has the homozygous SCD.[3] Recently, prevalence of SCA in Tanzania is estimated to be 0.5% of all live births and prevalence of sickle cell trait up to 15% (Makani unpublished).

SCA can be diagnosed at birth but in 90% of the population clinical abnormalities do not occur before age of 3-6 months. This coincides with the replacement of much of fetal haemoglobin by HbS. Infants are largely protected by high level of fetal haemoglobin (HbF) in the first six months of life which represents about 80%of total haemoglobin. This provides protective effect as it inhibits the polymerization of HbS in vitro. Therefore HbF drops to about 10% and HbS expression and the clinical condition becomes evident.

Sickle cell nephropathy is a large group of renal abnormalities, which encompasses many structural and functional disorders. Various forms of renal abnormalities have been observed in SCA patients[4-9] study done by Dharnidharka *et al*, Mc Burney *et al*, Marsenic *et al*, Becton et al, Ibadin *et al* showed microalbuminuria is prevalent by26.5%, 19%, 25%, 16%, 20.3%[10-14] respectively. Microalbuminuria has been found to be an early manifestation of sickle cell nephropathy. [15]The incidence of microalbuminuria was found also to increase with advancing age.In the study done by Mc Burney *et al* they showed that Microalbuminuria is strongly and directly related to age and strongly and inversely related to hemoglobin levels.[11]

1.1.2 Pathophysiology and clinical manifestation of sickle cell nephropathy.

Many structural and functional abnormalities of the kidney are observed in patients with SCA [16]. These abnormalities are observed along the entire length of the nephron from the glomerulus to the papillary tip. Because the rate of oxygen consumption by the kidney is very high, a rate exceeded only by that of the heart, the kidney is especially sensitive to the vaso-oclusion-induced hypoxia that can result from red cell sickling and/or from sickle cell–endothelial cell adhesion. The environment of the renal medulla is characterized by acidosis, hyper tonicity, and hypoxia. These factors tend to promote hemoglobin S polymerization and red cell sickling, thereby making this area of the kidney particularly susceptible to changes in oxygen delivery.[17]

Chronic sickling underlies several mechanisms for kidney injury[18]. The arterial side of the renal microvasculature has a low oxygen tension. The hyper tonicity and low pH of the renal medulla promote the formation of haemoglobin polymers in the red cells with deformation of the sickled cells. This result in an increase in the blood viscosity, functional venous engorgement, and interstitial edema, predisposing the renal microcirculation to ischemia and infarction. [19] Obliteration of the medullary vasculature produces segmental scarring and interstitial fibrosis which result in the formation of dilated renal pelvic capillaries and veins. Heamaturia may result from rupture of vessels from the early venous engorgement or from the dilated vessels that result from scarring.

The development of collateral vessels and their abnormal orientation in the medulla interferes with the countercurrent exchange mechanism which culminates through the years, in irreversible loss of medullary tonicity. Renal cortical blood flow and GFR are increased perhaps by the secretion of medullary vasodilator prostaglandins. [20] Hyperfiltration, coupled with glomerular hypertrophy can lead to glomerulosclerosis. [21]. Glomerular enlargement has been described as part of SCA children. This finding has been reported more frequently beyond 3 year of age. This pattern is more obvious in the juxtamedullary glomeruli. A difference in size has been shown when glomeruli from SCA children are compared with healthy children. [22-24]

In older patients with renal involvement, progressive ischemia and fibrosis lead to obliteration of the glomeruli and observed perihilar focal segmental glomerulosclerosis. [25] The sclerotic segments were adherent to Bowman's capsule with areas of hyalinosis, lipid vacuolation, and foam cells. Adjacent to the glomeruli, focal interstitial fibrosis and tubular atrophy were noted. Immunofluorescence studies in one series of four young patients with Hb-SS and glomerular disease revealed MPGN-like lesions associated with immunoglobulins and complement deposition. Renal tubular epithelial antigen deposition in a granular pattern along the glomerular basement membrane was also

noted in the circulation of some patients, tubular epithelial antigens and cryoprecipitable renal tubular antigen-antibody complexes were detected as well.[24]

The composite picture of sickle cell glomerulopathy is one of glomerular hypertrophy and focal glomerulosclerosis with either an expansive or collapsing pattern. The basement membran and areas of apparent duplication present a variable non immune MPGN-like picture [14], without the lobular appearance of immune MPGN. In a few cases, an immune complex nephropathy has been reported although it is uncertain whether this is part of sickle nephropathy or an unusual appearance of an immune complex nephropathy modified by the presence of sickle cell disease. [26] Medullary lesions consist of edema, focal scarring, and interstitial fibrosis with consequent atrophy and mono nuclear infiltration. Renal papillary necrosis appears focally, with a few collecting ducts surrounded by an extensive area of fibrosis. Once progression of the glomerular damage is evident, GFR begins to decrease, likely with some contribution from the ingestion of analgesics eg NSAIDS that can independently induce interstitial nephropathy. [27, 28]., [10]

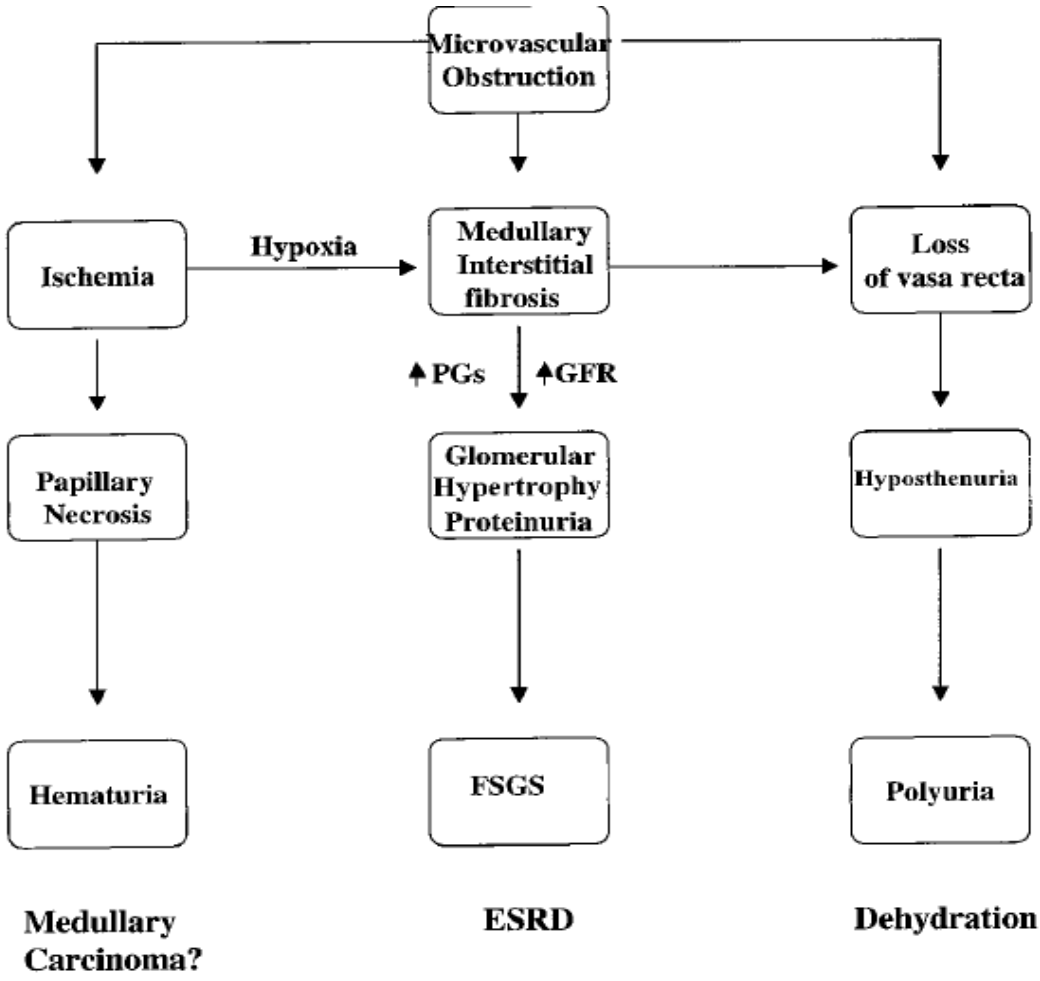


Figure 1. Etiologic algorithm for sickle cell nephropathy.

Adopted from department of Paediatrics Commonwealth University Medical college of Virginia Campus.

1.1.3 Microalbuminuria

In SCA, proteinuria appears to be associated with more rapid decline in renal function [(4).] Furthermore, 15–80% of patients with hemoglobin SS develop Albuminuria.Including microalbuminuria, and this percentage increases with age from mid-childhood to over 40 years of age.[(29)] Albuminuria is the earliest sign of glomerular damage, long before glomerular filtration rate (GFR) declines. Albuminuria is classified as microalbuminuria which is usually asymptomatic, and macroalbuminuria or glomerular proteinuria when

the albumin excretion is large, and is frequently associated with clinical symptoms, such as edema.

It is well known that conditions characterized by renal hyperfiltration and hyperperfusion (e.g. diabetes mellitus) are associated with renal damage. [30, 31] Microalbuminuria (MA) is defined as the urinary excretion of minutely elevated quantities of albumin prior to the development of proteinuria, as detectable by conventional methods, such as colorimetric quantization. It is now used extensively as a sensitive test of preclinical kidney dysfunction prior to the development of overt proteinuria. Screening for microalbuminuria in patients with these conditions can predict ultimate end organ disease such as renal failure. [32, 33] Because children with sickle cell anaemia experience hyperfiltration and hyperperfusion, a logical deduction is that microalbuminuria may well be an important early sign of renal disease in sickle cell anemia. [34] It has been suggested that a prolonged period of microalbuminuria precedes persistent proteinuria, which is subsequently followed by renal failure in sickle cell anemia.[35] Microalbuminuria is a frequent finding in SCA. Identification of risk factors for microalbuminuria may allow earlier intervention to prevent renal complications in patients with sickle cell anaemia. [25, 36-38].

Regarding the treatment for albuminuria in SCA, there are no long-term data to assess its merits. The benefit of angiotensin converting enzyme inhibitors on the albuminuria of sickle cell patients included small cohorts with extremely short follow-up, [39, 40] supporting the benefit of angiotensin receptor blockers or angiotensin converting enzyme inhibitors, alone or in combination, to decrease albuminuria and preserve renal function. [41, 42]

1.1.4 Hypertension

The incidence of hypertension in patients with SCA ranges between 2 and 6% [43] 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 SCA, although this would suggest chronic volume depletion. A defect in vascular tone has also been suggested.

Data from the Cooperative Study of Sickle Cell Disease demonstrated that individuals with SCA have blood pressure (BP) levels that are significantly lower than in the general population. Predictive variables of BP by a multiple regression analysis showed that in males under 18 years had a positive correlation between diastolic BP and blood urea nitrogen, and a negative correlation with the estimated creatinine clearance. Systolic BP correlated with blood urea nitrogen in females over 17 yr of age. Alarmingly, values that could be considered normal or that represent mild hypertension in healthy individuals should be considered a risk for important cardiovascular complications in patients with SCA. Also there was a positive association between BP, and increased level of MA. [44]

1.1.5 Haematuria

Haematuria is one of the most common renal abnormalities in the Sickle hemoglobinopathies, occurring not only in SCA patients, but also in individuals with trait. The bleeding appears to occur as a consequence of hemoglobin S polymerization and erythrocyte sickling within the renal medulla. In some cases, the haematuria is caused by papillary necrosis, a condition that can be diagnosed radiologically.[45, 46] The bleeding comes from the left kidney in about 80% of cases. It is bilateral in only a small minority of individuals. In rare instances, sickle cell haematuria may be quite massive with the passage of clots and severe anemia. The management of haematuria is usually conservative, with bedrest, maintenance of high urinary flow, alkalinization of the urine, and, when necessary, blood transfusion. Another cause of haematuria in sickle cell patients is renal medullary carcinoma. This is a rare and very aggressive malignancy which has been described in young individuals with both SCD and trait.[47, 48]

1.1.6 Renal failure

Renal failure occurs with either an acute or chronic presentation. Acute non oliguric renal failure is present in 10% of patients hospitalized with SCA. [48, 49] 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 SCA patients. Usually in sickle cell nephropathy the development

of ESRD occurs between the third and fifth decades of life. However, the renal abnormalities begin at earlier age with the presence of microalbuminuria. [50] Hyperfiltration is common in young patients with SCA , and is closely related to glomerular hypertrophy.[51] 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 SCA is a clinical marker for ESRD evolving from the progression of glomerulosclerosis.[31, 52] Patients with SCA develop renal failure at a significantly younger age than patients with HbSC disease. In a prospective study of SCD patients, the median age of onset of renal insufficiency was 23 years for HbSS patients, compared with a median age of 50 years for patients with HbSC disease. Hypertension, proteinuria, increasingly severe anaemia, and haematuria predict renal failure in SS patients.However the renal function tend to be normal at the early age before second decade of life.[53]

1.1.7 Papillary necrosis

Papillary necrosis is associated with all of the SCDs as well as with sickle cell trait. The propensity for these individuals to develop papillary necrosis is thought to be related to obstruction of the microvasculature in the vasa rectae with resulting medullary ischemia and infarction. Papillary necrosis is typically associated with haematuria. [7, 54]

1.1.8 Glomerular abnormalities

The alterations in glomerular structure and function that are found in sickle cell nephropathy may be similar to those found with the glomerular hypertension that appears in rodents following partial ablative nephrectomy.[55] At the time of autopsy, a pathological examination of the kidney remnants revealed perihilar focal and segmental glomerulosclerosis. These changes were observed to be ameliorated by ACE inhibitors, presumably through dilation of the efferent arterioles [56]. Brief course of enalapril was found to decrease urinary protein excretion in ten SCA patients with early manifestations of sickle cell nephropathy .While the exact pathogenesis of this

glomerular abnormality still remains to be defined, a number of potential etiologic factors exist.These include mesangial phagocytosis of sickled cells; immune complex glomerulonephritis , auto antigens released from ischemic tubules, glomerular injury caused by hyperfiltration and glomerular hypertrophy. [57] The most common clinical manifestation of glomerular injury in SCA is proteinuria which may progresses to the full-blown nephrotic syndrome. [24, 25] In a prospective study, 40% of SS patients with nephrotic syndrome eventually went on to develop end-stage renal disease. Incidence of multi-organ dysfunction insufficiency is reported to occur in 4–18% of SCA patients.[58]

1.1.9 Haemodynamic changes

Young children have supranormal renal hemodynamics. Their effective renal plasma flow (ERPF) is elevated, and their GFR is measured found to be increased. Furthermore, they have a decreased filtration fraction indicating that the increase in ERPF substantially exceeds the increase in GFR. Both GFR and ERPF decline toward normal during adolescence and fall to subnormal levels as SCA patients age.[59] Because of the increased rate of creatinine secretion by the proximal tubules, SCA patients may actually have a significant deterioration in renal function long before it is detected by traditional clinical measurements e.g. creatinine clearance.[60, 61] The pathophysiological factors which cause alterations in GFR appear to result from altered glomerular autoregulation, a change that affects the tone of both the afferent and efferent arterioles. Prostaglandins have been shown to be important mediators of altered glomerular function. This observation suggests that glomerular function in SCA patients is maintained, at least in part, by prostaglandin-mediated arteriolar vasodilation. This increase in prostaglandin synthesis thought to be related to ischemic damage to the renal medulla. [7, 37, 43]

1.1.10 Abnormalities of distal nephron function

Hyposthenuria, an inability to concentrate urine maximally, is the most frequent clinically recognized renal abnormality in SCA patients. [7] This urinary concentrating defect becomes apparent at an early age. The renal concentrating defect in sickle beta thalassemia may be as prominent as in SCA, although in this condition and in the other SCDs, as well as in sickle cell trait, the concentrating defect presents much later in life.
Red cell transfusion can often ameliorate the concentrating defect in SCA patients up to the age of 15, but it has little effect in older individuals.[62] However, anemia per se is not responsible for hyposthenuria since patients with anemia of other etiologies respond normally to water deprivation.[63] The ability to concentrate urine in a normal manner depends upon the structural integrity of the loops of Henle as they course through the hypertonic environment of the renal medulla. Hyposthenuria in SCA is primarily due to loss of deep juxtamedullary nephrons that are necessary for maximal urine concentration. Because the outer medulla is relatively spared, these patients are generally capable of concentrating their urine to the extent required under normal circumstances. However, under conditions of substantial water deprivation and/or volume loss, more rapid and severe volume contraction may ensue.[64, 65]

1.3 PROBLEM STATEMENT

More than 90% of those with SCD are born in Africa and the prevalence of the sickle cell trait ranges between 10 - 40% of the population in some parts of Africa. Rough estimates show that the prevalence of the trait in Tanzania ranges between 15 - 20%, which is among the highest in Africa. Approximately 17% of children attending hospital in Dar es salaam have homozygous Hbss diseases [66]The estimated birth incidence of children with SCA in Tanzania is between 6 to 7 per 1000 children.

As medical progress has permitted those with SCA to live well into adulthood, late complications of the disease are being seen more frequently than in the past. One of these complications is renal failure which is up to 18% of adult with SCA, attributed to interruption of renal blood flow by the abnormal, sickle-shaped blood cells**.**

The average age for kidney dysfunction in patients with SCD is 23 years. This in turn, is associated with increased morbidity and mortality. By the fifth decade of life, nearly one-half of the surviving patients develop some form of irreversible organ damage such as renal failure .[11]

Some studies in paediatric SCA patients reveal that renal damage starts during child-hood and continues throughout life. Prolonged glomerular hyperfiltration in SCA during childhood and early adult years leads to glomerular injury resulting in glomerular sclerosis, microalbuminuria, proteinuria and progressive renal failure.

Microalbuminuria (MA) is the earliest sign of glomerular damage, long before glomerular filtration rate declines, which is usually asymptomatic and appears to be associated with more rapid decline in renal function, patients with HbSS develop MA and this percentage increases with age. Screening for MA in patients with SCA at early age can predict ultimate end organ disease such as renal failure. Prompt attention to the warning signs of kidney failure in sickle cell patients might lead to opportunities for early intervention, and an increase in the lifespan of those sickle cell patients.

1.4 RATIONALE OF THE STUDY

SCA is common in Tanzania and prevalence of microalbuminuria in children with SCA in Tanzania is not well known. Microalbuminuria is common in patients with SCA as it starts early in the childhood and is a major risk factor for future development of renal failure [10-12, 14, 29]

This study will determine the prevalence and clinical correlates of microalbuminuria among stable children and adolescents with SCA attending sickle cell clinic at MNH. This will try to enlighten the prevalence of early marker of renal dysfunction in children and adolescent patients with SCA.

This study will help to identify at risk children who will require more specific renal evaluation and early intervention before they develop renal failure. Hence the study will give a better understanding of the problem and there by contributing improving management of patients with SCA who might have renal abnormalities.

1.5 STUDY HYPOTHESIS

Microalbuminuria is prevalent in children with sickle cell anemia

1.6. STUDY OBJECTIVES

1.6.1 Broad objective

To determine the prevalence of microalbuminuria and its clinical correlates in children and adolescents with sickle cell anaemia attending sickle cell clinic at Muhimbili National Hospital

1.6.2 Specific Objectives

1.6.3 To describe proportion of children and adolescents with sickle cell anaemia with microalbuminuria according to age and sex.

1.6.4 To determine the association of haemoglobin level with microalbuminuria in children and adolescent with sickle cell anaemia.

1.6.5 To describe clinical characteristics associated with microalbuminuria in children and adolescents with sickle cell anaemia.

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study design

This was a descriptive, hospital based cross-sectional study.

2.2 Study duration

The study was conducted in a period of six months, September-February, 2012

2.3 Study area

The study was carried out at sickle cell outpatient clinic Muhimbili National Hospital. MNH is the national hospital and the largest referral hospital in Tanzania. It receives referrals from three municipal hospitals namely Ilala, Temeke and Mwananyamala and other parts of the country. Children with SCA are referred from different hospitals to MNH where they are regularly followed up at least every three months.

2.4 Study Population

The patients were enrolled from the ongoing prospective SCD study. Active recruitment and follow up of this cohort was started in March 2004. A total of 1750 patients with sickle cell anemia (HbSS) have been enrolled in the main SCD cohort as of end of October 2009, aged from 8 months to 49 years with most individuals in age group 10-19 years (36%) with 30% of them aged between 6-9 years. In this study eligible participants were those with ages ranging from 3-18 yrs. Study participants are scheduled for routine outpatient visits every 3-6 months at which detailed clinical and laboratory data are recorded and plasma/serum samples stored. Similarly all admissions to MNH of SCD patients are documented and the cause of admission classified into the broad categories of pain, anemia, fever, and jaundice. The clinic offers free health services, and is the preferred health care provider for patients, and the principle source of referral for hospital admission. At each clinic attendance, patients are questioned about clinical complications and hospital admissions since last seen, and relevant hospital notes are

periodically reviewed. Clinic records are therefore believed to be reasonably complete and comprehensive.

2.5 Inclusion Criteria.

Children who were eligible for this study had the following criteria:

1. A confirmed diagnosis of SCA by Hb Electrophoresis or HPLC.
2. 3 to 18years old
3. Consent

2.6 Exclusion Criteria

Children was excluded from the study who had

1. Co existing renal disease such as nephrotic syndrome.
2. Clinical sign of acute infection at the time of investigation.
3. Parents or caretakers who will refuse to participate in the study.
4. Known patients with Diabetes Mellitus or Hypertension.
5. Known patients with Paediatrics AIDS.

2.7 **Definition of terms**

1. Albuminuria, was defined when the urine albumin is above 20mg/L or 0.02g/L
2. Microalbuminuria defined as Albumin to creatinine ratio(ACR) between (30-300)mg/g
3. Proteinuria (Macroalbuminuria) >300mg/g
4. Children < 10 years
5. Adolescents patients aged 10 to 18 years(3)

Anaemia was defined in the following categories (WHO)

6. Mild anaemia Haemoglobin 10-11g/dl
7. Moderate anaemia Haemoglobin 8-9g/dl
8. Severe anaemia Haemoglobin 5-7g/d

2.8 Sample size estimation

The sample size was determined by Epi info version six using the following assumption Microalbuminuria occur in 20 % of sickle cell anaemia patients[13] Significance level 5% The maximum likely error (E) =8%

The sample size was calculated from the following formulae

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

Where Z = Critical value 1.96 corresponding to 5% significance level

N = Estimated sample size

E = Margin of error (8%)

P = Prevalence of microalbuminuria in sickle cell disease patients 20%

Therefore, $N = (1.96)^2 \times 20 (100-20) / (8\%)^2 =$

N= 96

The minimum size was 96 plus 10% to allow non response, incomplete investigation, and other factors that will decrease the yield of response, therefore sample size was 106. This study enrolled 120 subjects.

2.9 Sampling procedures recruitment of study subjects

Once the study was started all eligible children and adolescent whose parents/care givers consented to participate were enrolled employing simple random sampling method. At the clinic recruitment was done by starting with provision of information regarding the study to the parent/guardian after which they were requested to sign the consent form for participation in the study. On every thursday and friday during sickle cell clinic the names of eligible subjects were written on the small piece of paper, folded and mixed thoroughly in a box and the author picked up ten pieces of paper randomly. These were the subjects then studied. Approximately ten subjects were recruited every week. To avoid re-recruitment patients file were coded with number.

2.9.1 Procedures and data collection

This study utilized existing and prospectively collected data from the ongoing SCD cohort. The database of the clinical cohort study was used to ascertain information regarding the SCD status Structured questionnaires were used to collect information from the children and adolescents, including social demographic data, clinical events, blood pressure, and laboratory results of hemoglobin status. Urine was collected in universal bottles and measurement of microalbuminuria was done within one hour by special Microalbumin 2-1 Combo strips(USA). The physical measurements were taken by the author and research assistance as described below.

2.9.2 Measurement of Microalbuminuria (MA)

All enrolled subjects were provided with the pre labeled universal bottle for the collection of the early morning urine, subjects were instructed to collect ten milliliters of the clear catch morning urine, and sample of each individual was measured by author at the clinic within an hour.

Urine sample was first tested for Macroalbuminuria (Proteinuria) using the normal Uro-dip-10 strips (German). This test cannot detect protein urine below the value of 300mg/L.

Sample negative for Proteinuria was subsequently tested for MA using Microalbumin 2-1 test strips and employing methods as described by manufacturer (Cliawaived Microlalbumin 2-1 Combo, USA). This test is capable of detecting very small amount of albumin in the urine as low as 20mg/L which cannot be detected by normal traditionally used dipstick such as Uro-dip-10.

Each strip was immersed in the fresh, well mixed urine sample and removed immediately while touched the side of the rim of the bottle to remove excess urine, further the blotting was done lengthwise by the edge of the strip on the absorbent paper towel to avoid running over (contamination from adjacent reagents pad).

Then it was compared with reagent area to its corresponding color blocks. Results were then obtained by direct reading on color chart comparison. Reading was done 30 seconds after removal of strip from the bottle.

Microalbuminuria (ACR) was defined by varying color blocks of pale green to aqua blue and Tan respectively in the test strips that correspond to the range of 30 to 300mg/g after computing the ratio. Each strip was used once and discarded and when result for microalbuminuria was not conclusive the test could be repeated for the second time following the same procedure.

2.9.2.1 Explanation of the test and Test principle.

Cliawaived Microalbumin 2-1 Combo strip (USA) is used for semi- quantitative determination of albumin and creatinine in urine samples. It measures two tests at the same time from a single void urine sample which allows determination of albumin to creatinine ratio (ACR) in urine. The Combo strips give a positive or negative result for albumin, with positive results classified at concentrations of 20, 30, or 80 or 150 mg/L. Any albumin present in the urine binds specifically with sulfonepthalein dye present on reagent areas on the strip to develop a visual color scale which was then be used to determine the result. The resulting color ranges from pale green to aqua blue.

Creatinine excretion into urine is usually constant. Though the concentration of urine varies throughout the day, the urinary creatinine level is relative stable, which allows its

measurement to be useful as a corrective factor in the random/spot urine sample. Creatinine reacts with a creatinine indicator in an alkaline condition to form a purplish-brown color complex (Tan). The classified concentration of creatinine is directly proportional to the color intensity of the test pad as 0.1, 0.5, 1.0, 2.0, 3.0g/L. Albumin to creatinine ratio (ACR) is a preferred test and recommended test for screening of microalbuminuria. According to the manufacturer these Combo strips are 96.5% sensitive and 98.3% specific for the detection of microalbuminuria.

2.9.3 Laboratory investigations (Full Blood Picture)

Blood samples were collected from all eligible study subjects. About three milliliters of venous blood was taken aseptically from the anterior cubital fossa of each subject, using a sterile disposable syringe and needle after a thorough cleaning of the venopuncture site with a swab soaked in 70% alcohol. Samples were then collected in vacutainers containing EDTA (Ethylenediaminetetra-acetic acid). Estimation of the haemoglobin, total and differential cell white counts was determined using an ABX Pentra (ABX France). A blood sample from an EDTA bottle was mixed up using a mixing machine, and a 1ml of blood was fed into machine to determine the above mentioned parameters automatically.

2.9.4 Clinical Events

The following clinical events were recorded over period of 12 months. These were sickle cell related clinical events that necessitated admission.Painful crisis, dactylitis, blood transfusion, convulsions, neurological deficit, acute chest illness, priapism, avascular necrosis and aplastic crisis. Episodes of clinical events were defined by the diagnosis recorded in the medical record.

2.9.5 Blood pressure

The resting blood pressure (BP) measurement was obtained from the right upper arm using DINAMAP PRO 400V2 (USA) electronic BP machine. An appropriate BP cuff size for children and adolescents was applied on the right mid upper arm with his/her

forearm relaxed on the examination table. The cuff used covered at least 75% of the upper arm without obscuring the anterior cubital fossa.

Blood pressure was measured three times at an interval of five minutes on the same day and at the same sitting. The mean of the three measurements was recorded.
Systolic BP Percentile Interpretation

- Percentile <90: normal systolic blood pressure
- Percentile >90 and <95: pre hypertensive systolic blood pressure
- Percentile >95: hypertensive systolic blood pressure

Diastolic BP Percentile Interpretation

- Percentile <90: normal diastolic blood pressure
- Percentile >90 and <95: pre hypertensive diastolic blood pressure
- Percentile >95: hypertensive diastolic blood pressure

Blood pressure was interpreted on the basis of sex, age and height (Appendix 4)

2.9.6 Anthropometry

The author and one research assistant performed anthropometric measurements including weight and height. These measurements were performed after the subjects have removed their shoes and upper garments. Weight of each subject was measured to the nearest 0.1 kg using weighing scale, TANITA UM 075, which was periodically checked for accuracy and calibrated as necessary.

The standing height was measured to the nearest 1 cm with a portable Leicester stadiometer; the subject was upright and the head in the Frankfurt plane.

BMI (kg/m^2) was computed using weight (in kilogram) divided by height (in meters squared).

Interpretation of BMI was as follows:

- Below 5^{th} percentile: Underweight

- Between 5th to 84th percentile: Healthy Weight
- Above 85th: Overweight

BMI for age percentiles for boys and girls respectively was used for interpretation (Appendix 5)

2.9.7 Variables

The dependent variable was percentage scores of microalbuminuria and independent variables were age, sex, clinical events, and hypertension and haemoglobin levels.

2.10 DATA PROCESSING AND ANALYSIS

2.10.1 Data entry Pre- testing

Pre- testing of the data collection tool was conducted at sickle cell clinic at MNH. Necessary amendments of the tool were done to obtain the required information**.**

All completed questionnaires was coded, and checked for consistency before double entry into the Epi Info Version 3.5.1 computer database. Data cleaning was done in terms of consistency checks for outliers and missing data. Data analysis was done using SPSS version 17. The prevalence of microalbuminuria was expressed in percentages for the entire study group and by age, sex.

With categorical variables (e.g. sex, age), χ^2 test was used to examine association between microalbuminuria and the variable. Test for two independent sample means was applied for numerical variables.

Two-sided test of significance was used where applicable; Chi-square test and Fisher exact test was used for categorical variables. Student *t* test was used to assess difference in continuous variables between groups. Logistic regression was used to analyse the dependence of abnormal level of MA on other variables. Correlation coefficient was used to determine the relationship of MA and independent variable. A P value < 0.05 was considered as evidence of a statistically significant association or difference.

2.11 ETHICAL CLEARANCE

Before conducting the study permission was obtained from Muhimbili University of Health and Allied Sciences (MUHAS)'s Senate for Research and Publications Committee.

2.12 ETHICAL CONSIDERATION

In every child an informed written consent was sought from the parent or guardian after a full explanation of the purpose and nature of the study done. Where appropriate assent from the children was sought and documented on the consent form.

In this study subjects were treated according to the usual sickle cell clinic protocols. At the end of study all subjects continued with the usual follow up in sickle cell clinic. Information about detected abnormal microalbuminuria findings were communicated to the patients and made available to the doctors attending the patients for close long-term follow up and management.

Parents/guardian who did not consent was assured that their children would receive same quality of care as any other child with SCA. Their decision not to participate in the study did not deny their children the right of being treated properly.

CHAPTER THREE

3.0 RESULTS

A total of 120 subjects at steady state made up the study group. Of these males were 56(47%) and 64(53%) females, giving a M: F ratio of 1 to 1.14. Their age ranged from 3 to 18 years .The mean age of study population was 10.6±4.5 years. Fifty-nine of 120 the subjects were more than 10 years of age (49.0%). The range of Haemoglobin was 3.6 – 10.6g/dl. Mean Haemoglobin of study group was 7.0±1.4g/dl. Twenty-nine subjects (24%) out of 120 tested positive for microalbuminuria.

The BP (systolic or diastolic) was above the 90^{th} percentile by age, sex and height in 25(20.4%) subjects and none of subject had 95^{th} percentile. Of those with elevated BP (above 90^{th} percentile) 7 (20.8%) had elevated systolic BP (SBP), 68% elevated diastolic BP (DBP).Of all clinical events associated with SCA only painful crisis (12.5%) and Blood transfusion (7.5%) were reported. The socio demographic and clinical characteristics of study participants are summarized in table 1.

Table 1: Social and demographic characteristics of the study participants (n = 120)

Characteristics	Mean ± SD	Frequency	
		N	%
Age	10.6 ± 4.5		
< 9 years		52	43.3
10 - 18 years		68	56.7
Sex			
Males		56	47.0
Females		64	53.0
Microalbuminuria (%)	31.8 ± 46.2		
< 30mg/g		91	76.0
>30 -300mg/g		29	24.0
Blood pressure level(mmHg)			
<90th percentile		95	79.2
90 - 95th percentile		25	20.8
BMI (Kg/m²)	15.7 ± 4.0		
≤ 4th percentile		18	15.0
4th - 84th percentile		99	82.5
≥85th percentile		3	2.5
Haemoglobin level	7.0±1.4		
Mild anaemia		1	1
Moderate anaemia		63	52
Severe anaemia		56	47
Clinical events in 12months			
Admissions		24	20.0
VOC		15	12.5
Blood transfusion		9	7.5

Table number 2 shows that most of the subjects had severe anaemia and moderate anaemia. Only one subject had mild anaemia. More children had moderate anaemia (56%) than adolescents (50%) and vice versa in case of severe anaemia; however those differences were not statistically significant.

Table 2: Distribution of anaemia category between adolescent and children.

Age category	Anaemia category			Total (%)
	Severe (%)	Moderate (%)	Mild (%)	
Children	22(42)	29(56)	1(2%)	52
Adolescents	34(50)	34(50)	0(0)	68
Total	56(47)	63(52)	1(1%)	120

Fishers exact test =0.39 P =value 0.87

3.1 Proportion of microalbuminuria in children and adolescents with SCA according to age and sex

The prevalence of MA was 24% (29/ 120). There was no child less than 7 years of age who had MA. The results show that MA prevalence was higher (52%) in older age category than the younger age category (17%). This was statistically significant.

Table 3: Distribution of subjects with and without microalbuminuria according to age group

Age group	Microalbuminuria		Total (%)
	Negative (%)	Positive (%)	
3-6	31(100)	0 (0)	31
7-10	25 (83)	5 (17)	30
11-14	20 (71)	8 (29)	28
15-18	15 (48)	16 (52)	31
Total	91(76)	29(24)	120

P = 0.01 Fisher test =23.83

When only children with microalbuminuria were analyzed, it was found that in the MA group the gender specific prevalence was in favor of male 18 (62%) than female11 (38%). It was further shown that male adolescents had higher percentages (68%) of MA than female children, and vice versa in female subjects. However this was not statistically significant.

Table 4: Sex distribution among children and adolescent with microalbuminuria

Age group	Male (%)	Female (%)	Total (%)
Children	1(25)	3 (75)	4
Adolescent	17 (68)	8(32)	25
Total	18(62)	11(38)	29

Fishers exact test =1.39 p = value 0.26

3.2 Association of haemoglobin level in relation to microalbuminuria in children and adolescent with sickle cell anaemia.

Table 5 shows that many subjects with microalbuminuria were found more in severe anaemia group (45%) compared to the moderate group (7%) and this was statistically significant, the opposite trend was noted in MA negative group.

Table 5:Anaemia category distribution in children and adolescents with and without Microalbuminuria.

Anaemia category	Microalbuminuria		Total (%)
	Positive (%)	Negative (%)	
Mild	0(0)	1 (100)	1
Moderate	4(7)	59 (93)	63
Severe	25 (45)	31 (55)	56
Total	29(24)	91(76)	120 (100)

Fisher's exact test = 25.0 P=value 0.01

3.3 Clinical characteristics associated with microalbuminuria

Table 6 shows the clinical characteristics of study population in relation to MA status. Haemoglobin differed significantly between those with and without MA. The mean Hb of subjects, with MA was 5.9± 1.2 g/dl in contrast to mean Hb of 7.4±1.0 years for children without MA (P<0.005).

Admissions, painful crises, blood transfusions (BT), BP level, were not significantly related to the presence of MA when entire group was considered. Out of 120 subjects only 25(21%) had abnormal BP and of these only 4 subjects had MA. Out of 120 subjects only 24(20%) had admission in the period of last 12months, in which only 29% (7/24) subjects were in MA group while71% (17/24) was in the non MA group.

When demographic characteristics of study population were analyzed in relation to MA status, age differed significantly between those with and without MA. The mean age of subjects, with MA was 14.0±3.5years in contrast to mean age of 9.6±0.5years for children without MA. (P<0.005), Gender, BMI, were not significantly related to the presence of MA when entire group was considered.

Table 6.Clinical and demographic characteristics of study population in relation to MA status

Variable	All subjects 120(100%)	SCA with MA 29(24%)	SCAwithout MA 91(76%)	p-value
Hb level(g/dl)	7.0±1.4	5.9±1.2	7.4±1.0	0.001
MCV(fl)	83.7±9.3	85.8±5.7	83.1±10.1	0.529
MCH(pg)	26.6±6.4	26.9±2.8	25.4±7.2	0.222
WBC(K/ul)	14.5±5.14	14.3±4.5	15.2±5.2	0.762
Age(years)	10.6±4.5	14.0±3.5	9.6±0.5	0.001
Gender (%)				
Male	56(47)	18(62)	38(42)	0.570
Female	64(53)	11(38)	53(58)	0.070
BMI	15.7±4.0	16.2±2.2	15.5±4.5	0.425
Admission in yr	24(20%)	7 (20.1%)	17 (19%)	0.436
Blood pressure				
Normotensive	95 (79%)	25 (12.5)	70(77%)	0.503
Pre hypertensive	25 (21%)	4 (25.0)	21(23%)	0.286
VOC episodes	15 (12.5)	3(10%)	12(13.2)	0.857
BT	9(7.5%)	4(12.1%)	5(24%)	0.123

Univariate logistic regression analysis showed that the presence of MA was significant related to age and Hb, with older children being more likely to have MA, sex was not significantly associated with MA, As shown in table 7, for univariate models older subjects were 1.4times more likely to have MA than younger subjects, Subjects with higher haemoglobin were less likely to have MA at odds ratio of 0.18.Male sex was not significantly associated with MA.

Similar results were found with multivariate logistic regression as shown in the table. Age and Haemoglobin were confirmed as statistically significant variables. Both Haemoglobin level and Age remain in the final model as clinical correlates of MA. Higher Hb level showed a protective effect against MA (Odds ratio=0.55) p=0.001 while subjects with MA were more likely to have older age. (Odds ratio=1.7) p=0.001

Table 7: Univariate and Multivariate logistic regression on the outcome of MA status

Variable	Odds ratio	95%CI	P value
Univariate model			
Male sex	0.59	0.18-1.99	0.451
Age in years	1.4	1.19-1.69	0.001
Haemoglobin level	0.18	0.83-0.39	0.001
Multivariate model			
Male sex	1.6	0.50-5.5	0.403
Age in years	1.7	0.59-0.84	0.001
Haemoglobin level	0.55	2.5-12.02	0.001
Final Multivariate Model			
Age in years	1.7	0.59-0.84	0.001
Haemoglobin level	0.55	2.5-12.02	0.001

Figure 2; shows linear relationship between the MA (mg/g) and the Haemoglobin (g/dl). This shows the association which is negative, r, is -0.148, which is negative (anticorelation) P = 0.001. Beta coefficient is -13. This means as Hb level decreases the chances of MA occurrence increases.

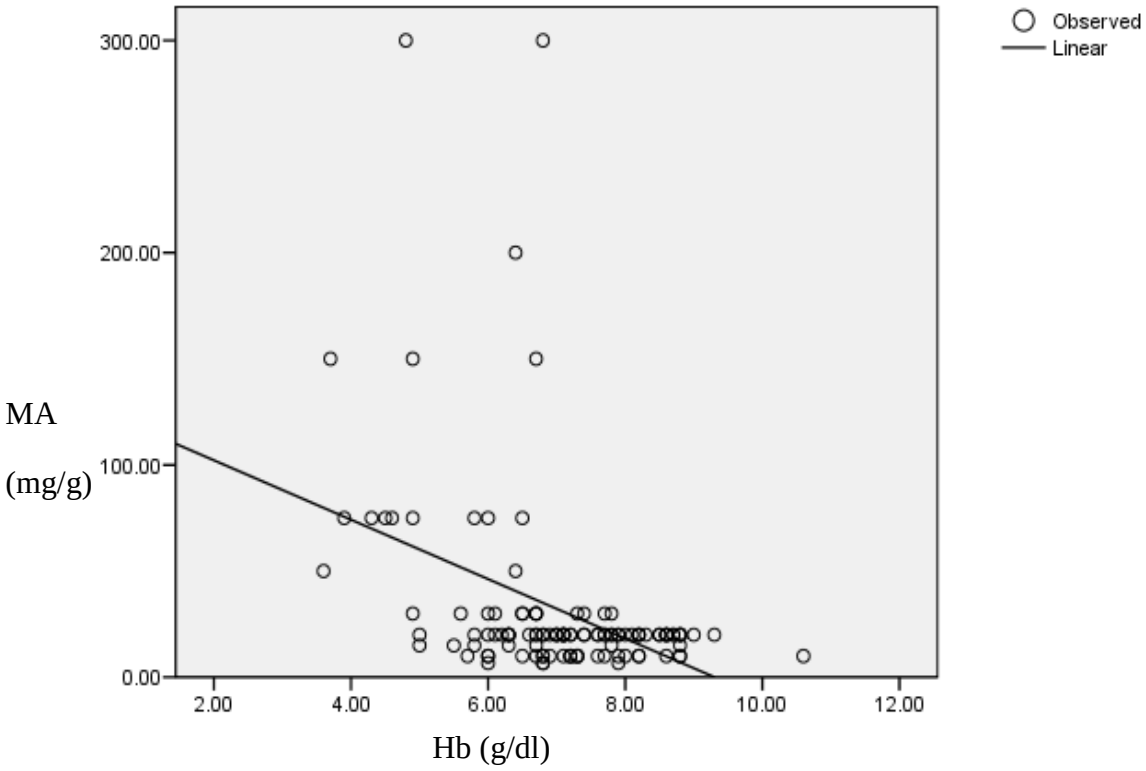
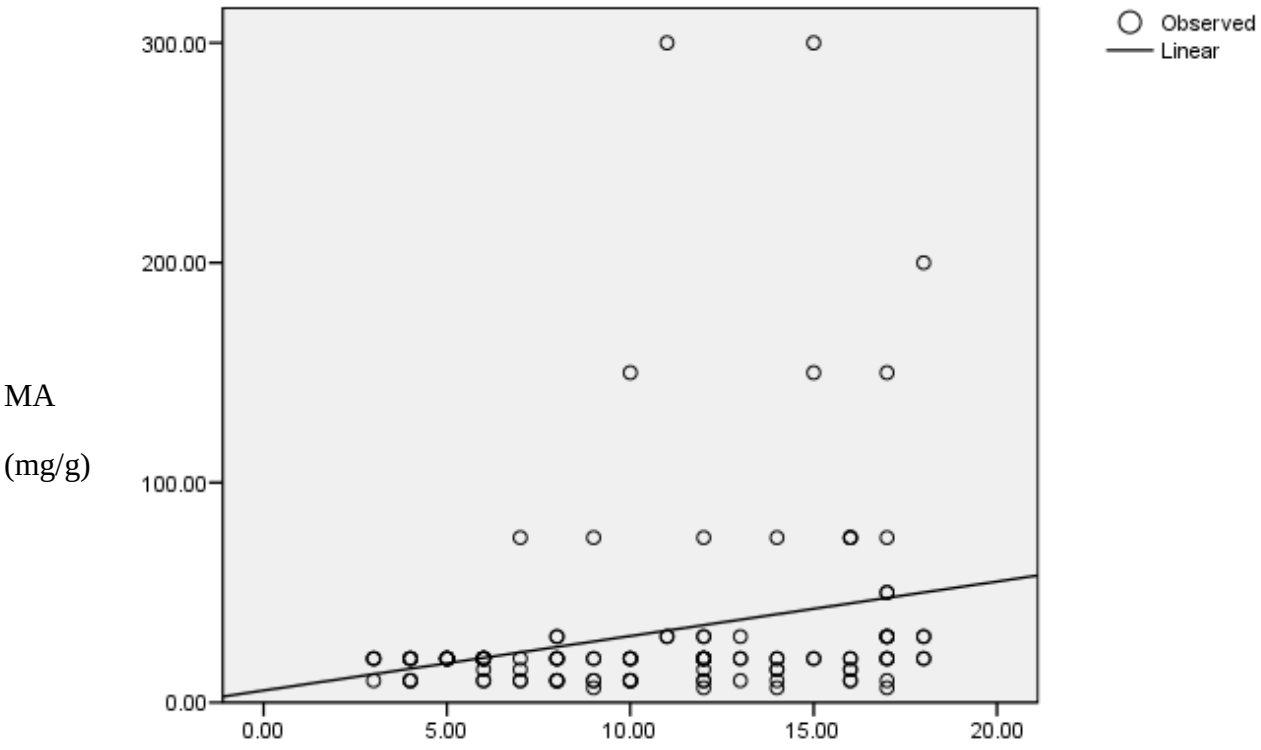


Figure 3.Shows positive linear correlation between the Microalbuminuria (mg/g) and the age (years) r = 0.06, which is positive P = 0.001, beta coefficient is 2.4

Which means that there positive relationship i.e. as the age increases the chances of having MA in urine increases.



CHAPTER FOUR

4.0 DISCUSSION

In this study, the prevalence of MA was found to be 24% which is consistent with what has been previously reported by other authors [10-12, 20, 67].The relationship of age and haemoglobin level to MA in children and adolescents was revealed. The relevance of this finding was highlighted by Wigfall *et al* [68] who reported the relationship between MA and haemoglobin in the paediatric sickle cell population.

Datta *et al* [67] in 2003 reported 19.2% prevalence of MA among Indian children.However in their study they included other forms of SCD. Similarly, Alvarez *et al*[29] in 2006 recorded a prevalence of 15.8%, the low prevalence could be explained by higher haemoglobin level of their study subjects.

In United States Mc Burney *et al*[11], in 2002 found the prevalence of MA in 142 subjects with SCA to be 19%. In yet another American study, Dharnidhaka *et al* [10]in 1998 reported on 102 subjects aged 2-18 years with SCA, to have a higher prevalence of 26.5% in their study subjects.

Like what was found by other studies [10, 11, 13] where MA was not seen in any child less than seven years, this is consistent with our finding. This could be explained by the fact that in their study they only involved subjects with the only HbSS like in the current study.

Further more in 1998 Sesso *et al* [8], recorded a prevalence of 30% in Brazil. Their subjects were both children and adults with SCA. The higher figures may therefore be ascribed to the fact that older subjects were more recruited for study than younger subjects.

In this study, it was found that MA was related to age, with positive linear correlation. The prevalence figures were low among children 8% and rose to 37% in those adolescents. The mean age of patients with microalbuminuria in this study was 14.0years, which is similar to the mean age of 13.44 years found by Dharnidharka *et al*.[10]

Prevalence in the older subjects (age 10 years and older) in the current study was 37% compared with finding of Dharnidharka *et al* [10]who reported a prevalence of 46% in patients ages 10 to 18 years old. A likely reason for the lower prevalence found in our study population compared with that of Dharnidharka *et al* is that we used (30 mg/g) as our lower limit for microalbuminuria, whereas those authors used (20 mg/g).

Consistent with the results of Dharnidharka *et al* [10],and Mc Burney *et al* [11]we found no children younger than 6 years old with MA. This similar finding can be explained by the fact that only used Hb genotype (HbSS) as inclusion criteria like in our study.

Foucan *et al* [35]defined MA as a microalbumin-to-creatinine ratio of at least 30 mg/g. They found a prevalence of MA of 19.4%, with increased age being positive correlates for MA. Alvarez *et al*[29] also found increased age to be a positive correlate with MA in their study of 120 patients with SCA.

Other studies [10, 67] have found similar prevalence rates and correlations with increased patient age, despite lowering the threshold for MA to a microalbumin-to-creatinine ratio to 20 mg/g. Michael Ibadin *et al* [13]also had shown the association of age and MA in which prevalence was higher in preschool age.

This study reported that more males were seen to have higher percentages of MA than females who had MA, despite the fact that there more females in the study population than male subjects. However the difference was not statistically significant.

No significant difference were found between the prevalence of MA in male patients versus female patients in other studies .Only study done by Mc Burney *et al*[11], reported that increasing age was a strong correlate of MA in male patients.

The fact that only those male patients in their study showed a statistically significant association between increased MA was interesting. This finding still remained debatable if at all that male patients have an increased severity of sickle cell nephropathy.

The finding of Mc Burney *et al* on preponderance of MA on sex was not supported with any study of MA in sickle cell patients. Even in our study it was found that although gender specific prevalence of MA was in favor of males however the difference was not statistically significant.

Nigerian study[13] showed the gender specific prevalence to be higher in female. This observation was similar to the study studies[10, 11].They hypothesized that this may be due to the factors known to confound MA such as UTI (Urinary Tract Infection) which is common in female subjects.

UTI alone could not suffice to describe the gender preponderance on MA because as much as possible like in our study measure were taken to exclude subjects with UTI, as perhaps was also done in other studies. In our study we enrolled outpatients subject who were in the steady state who had been well three-week prior recruitment.

Our study found the association of haemoglobin and MA to have to be inversely related.This was consistent with other studies which showed a similar trend. It was found the mean haemoglobin levels in our subjects with MA was 5.9g/dl versus 7.4g/dl in those without MA Decrease in haemoglobin level increased the likehood of having MA.

This could be explained with hypoxic environment that may prevail in the renal medulla. However Ibadin *et al* [13]did not report this finding.This may be because of small number of subjects in their study. Furthermore the oldest subject in their study was 16years as the study aimed to enroll subjects with SCA who were up to 18years.

Haemoglobin level was independently associated with MA in our study. In our multivariate regression analysis, a higher haemoglobin level was independently associated with not having MA (OR 0.55), which is consistent with data from previous studies. [10, 11, 29, 67].

Furthermore with regard to MA and Hb, Foucan *et al*[35] showed a significant association between hematocrit and urinary albumin excretion in young adults with SCA. They found that urinary albumin excretion was significantly higher in patients with haemoglobin less than 7g/dl than the patients with Hb exceeding 7g/dl.

Different from our study, other studies [14, 42] went further to show at least a theoretical protective benefit to treatment with hydroxyurea, which increases the expression of fetal Hb in patients with severe SCA hence reduction of MA occurrence. In our study none of our subject were on hydroxyurea.

In the current study several clinical factors were analyzed for an association with microalbuminuria (MA) .Among clinical correlates of MA in children with SCA examined, BP had not been shown to correlate with MA as it was seen many subjects with abnormal BP measurements had no MA, this however was not consistent with the study done by Becton *et al*[12] in which subjects with MA were more likely to have abnormal BP measurements.

Lower prevalence of abnormal BP in our study can be supported with mechanism explained by Ataga et al[17] that's patient with sickle cell anaemia have haemodymic changes which are due to cardiac dilation, decrease peripheral resistance which reduce afterload. However the exact trend was not clarified.

It was found that number of admission, pain episodes, blood transfusion was not associated with the microalbuminuria occurrence to any significant degree[10-12, 14] this sounded unexpected since it was thought the more the clinical events could be associated with MA. However this could be masked with treatement offered in these studies such as hydroxyurea.

However, only Alvez *et al*[29] showed episodes of acute chest syndrome (ACS) were found to be significantly related to MA. This could be explained with other genotype of Hb, but this still remain to be debatable because other studies had other genotype still no association was seen on clinical events.

In this study none of our subjects received the treatment to reduce microalbuminuria in urine, others studies [11, 12, 14, 29] have shown treatment with an ACEI or Hydroxyurea has a potentially renoprotective effect in the setting of MA. This could probably explain lower prevalence of MA in their studies compared to ours.

4.1 STUDY LIMITATION

The study was cross-sectional design which does not determine the full significance of pediatric MA in the development of kidney disease. The only way to determine the true predictive value of childhood MA is to follow up all 120 subjects into adulthood in cohort study.

Serology for HIV was not done so asymptomatic patients might be included in the study however medical records files were used to cross check the HIV status.

This was hospital based study hence prone to selection bias. However since all sickle cell patients in Dar es salaam were referred to this clinic it reduced the chances of high selection bias.

The lowest statistically acceptable sample size was used due to high investigation cost.

CHAPTER FIVE

5.0 CONCLUSION

With regard with this study it was found that the MA is also prevalent (24%) in our setting where the burden of SCA is high.

Occurrence of MA is directly proportional to age and inversely proportional to Haemoglobin level.

No association was found between MA and clinical events and abnormal blood pressure. Gender had no effect upon MA occurrence.

5.1 RECOMMENDATION

Measurement of urinary microalbumin is simple and non-invasive screening biomarkers, which may be utilized as part of routine health care maintenance in children with SCA. Screening for microalbuminuria seems prudent after age six to seven years of age.

Children with lower hemoglobin levels should be monitored closely because they appear to be at increased risk. Routine screening of microalbuminuria will likely be as helpful a predictor of end-renal damage particularly in those subjects with severe anaemia.

Longitudinal studies are essential to determine the significance of childhood microalbuminuria in the development of renal disease and then to devise a strategy to prevent sickle cell nephropathy.

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7.0 APPENDICES

Appendix I: Questionnaire

PROFORMA FOR SICKLE CELL DISEASE STUDY – MICROALBUMINURIA STUDY

SCD Study No.....…..|__|__|__|__|

SCD Recruitment Control No.....…..|__|__|__|__|

SCREENING *(registration station)*

1. Informed consent (**N/Y**) ……..|__|
2. Today's Date (DD-MM-YY) ……|__|__|-|__|__|-|__|__|**DATETOD**

DEMOGRAPHIC HISTORY *(registration station)*

3. Hospital ID number (HID) ……|__|__|__|__|__|__|**HID**
4. Name ……|_____|**NAME**
5. Date of birth (DD-MM-YY) ……|__|__|-|__|__|-|__|__|**DOB**
6. Age ……|_____|**AGE**
7. Sex (**M/F**) ……..|__|**SEX**

RESIDENCE INFORMATION *(registration station)*

8. Place ……|_____|**PLACE**
9. District ……|_____|**DISTR**
10. Division ……|_____|**DIVSN**
11. Contanct telphon no (**N/Y**) ……|__|-|__|__|__|__|__|__|__|__|__|__|__|**CONT**

GENERAL EXAMINATION *(anthropometry station)*

12. Temperature ……..|__|__|. |__|__|^{0}**CTEMP**
13. Weight ……..|__|__|__| bpm **PULSE**
14. Height ……..…|__|__|__|mmHg**SBP**
15. Diastolic blood pressure ……|__|__|__|mmHg**DBP**
16. Systolic blood pressure ……..|____||**BPLEV**

PERSONAL HISTORY *(clinical station)*

17. Age at diagnosis (years -months) ……|__|__| - |__|__|**AGED**

18. Have you been well for the last three weeks (**N/Y**) ……|__|**WE**L

19. Have you ever been admitted to hospital because of a sickle related event (**N/Y**)……..|__|**ADM**

20. If yes, please give history of number of admissions in lifetime and details of last admission the last 12 months and date of the most recent

Lifetime(#/<5/ 5-10/ 10+)	Number in last 12 months	Date (mm-yy) and Place	Cause of last admission
NUM ADMIT LIFE	**NUM ADMIT 12**	**DATE PLACE**	**PROBLEM**

21. Have you/your child ever had had any of these problems that necessitated either hospital admission or OPD attendance (in lifetime)

	N/Y	Number
Blood transfusion	|__|	|__|__|
Dactylitis	|__|	|__|__|
Painful crises	|__|	|__|__|
Acute Chest illness	|__|	|__|__|
Convulsion	|__|	|__|__|
Neurological deficit	|__|	|__|__|
Leg ulcers	|__|	|__|__|
Priapism	|__|	|__|__|

22. Have u ever been on medication for treating pain for long time (**N/Y**) …|__|**PMED**

23. If yes (**N**SAIDS/Others) ……|_____

TEST RESULT FOR MICROALBUMINURIA|

24. Albumin (**N**ormal/**A**bnormal -details) ...|__|-|_____|mg/l**ALB**

25. Creatinine (**N**ormal/**A**bnormal -details) ...|__|-|_____|g/l**CRE**

26. Albumin to creatinine ratio (**N**ormal/**A**bnormal -details).|__|-|_____|mg/g**ACR**

TEST RESULT FOR URINALYSIS *(clinical station)*

27. Leukocytes (**N**ormal/**A**bnormal -details) …|__|-|_____|LEU

28. Nitrites (**N**ormal/**A**bnormal -details) ……|__|-|_____|NITR

29. Blood (**N**ormal/**A**bnormal -details) ……..|__|-|_____|BLD

30. Specific gravity (**N**ormal/**A**bnormal -details) ….|__|-|_____|SGRV

HEAMOGRAM *(clinical station)*|

31. Red blood cells (**N**ormal/**A**bnormal -details)….|__|-|_____|RBC

32. Haemoglobin (**N**ormal/**A**bnormal -details) …….|__|-|_____|HB

33. Mean Corpuscular Haemoglobin (**N**ormal/**A**bnormal -details)…. |__|-|_____MCV

34. Mean Concentration Heamoglobin (**N**ormal/**A**bnormal -details)…|__|-|_____MCH

38. Red Cell Distribution Width (**N**ormal/**A**bnormal -details)….|__|-|_____|RDW

35. White blood cells (**N**ormal/**A**bnormal -details)……..|__|-|_____|WBC

36. Platelates (**N**ormal/**A**bnormal -details)……|__|-|_____|PLT

INITIALS OF CLINICAL INVESTIGATOR.....|__|__|__|

Appendix II: **Consent Form - English Version**

Consent to participate in the study of Microalbuminuria as predictor of early glomerular injury in sickle cell patients attending MNH.

Dear Sir/Madam,

Greetings!

My Name is Dr. Richard Christopher, a resident doctor in the Department of Paediatrics and Child Health at MUHAS. I am conducting a study regarding the prevalence of Microalbuminuria 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 Microalbuminuria 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.

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

We don't expect 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 risk of kidney problem in the future and the early interventional strategy to prevent further damage of your kidney

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. Richard Christopher

Principal Investigator

Muhimbili University of Health and Allied Sciences (MUHAS)

Department of Pediatrics and Child Health

P.O. Box 65001 Dar es Salaam.

Tel. 0713 439291

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 Richard Christopher na ni Daktari katika shahada ya Uzamili katika Chuo Kikuu Cha Sayansi Za Tiba cha Muhimbili. Nafanya utafiti kuhusu kiwango cha kiashiria cha mwanzo cha kuharibika kwa figo kwa watoto na vijana wenye Seli hai Mundu (Sickle cell) hapa Muhimbili hospitali.

Ninaomba ushirikiano wako.

Nia ya Utafiti;

Dhumuni ni kujua ni wagonjwa wangapi wako katika hatari au dalili za awali ya kupata uharibifu ya 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.

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 dalili za mwanzo hatarishi kwa figo.

Pia utafaidika kupata matibabu halisia kama itakavyokuwa inahitajika ili kuzuia uharibifu zaidi wa figo mbeleni.

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. Richard Christopher, Chuo kikuu Cha Afya Na Sayansi za Tiba Muhimbili; Idara ya Tiba; S.L.P 65001 Dar Es Salaam. Simu 0713439291.

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……..

APPENDIX IV

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

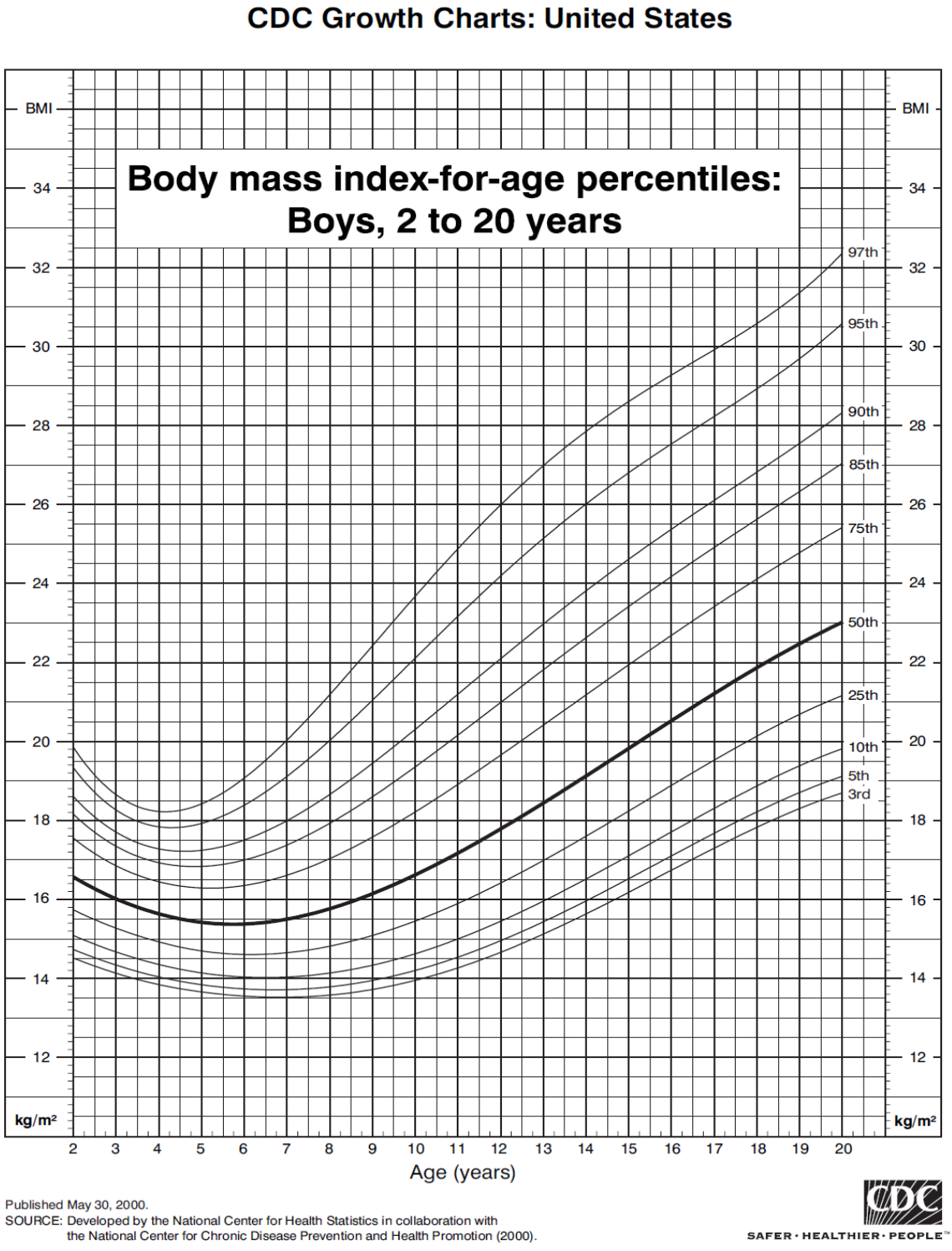
Source: Reprinted from National High Blood Pressure Education Program Working Group on Hypertension Control in Children and Adolescents. Blood pressure percentile determined by a single measurement.

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

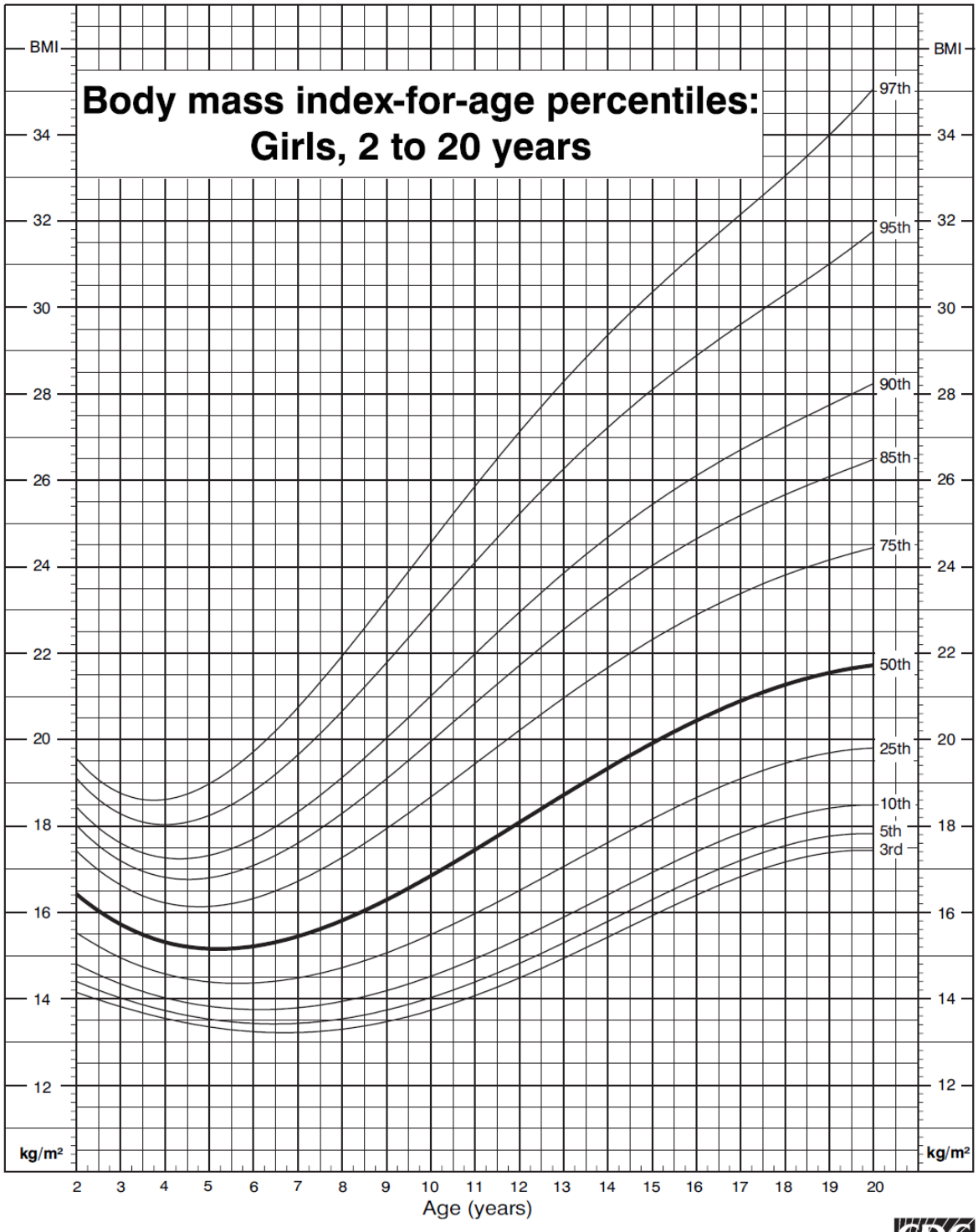
		Systolic BP (mm Hg), by Height Percentile from Standard Growth Curves							Diastolic BP (mm Hg), by Height Percentile from Standard Growth Curves						
Age	BP Percentile	5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	90TH	97	98	99	100	102	103	104	53	53	53	54	55	56	56
	95TH	101	102	103	104	105	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 V


CDC Growth Charts: United States
Body mass index-for-age percentiles:
Boys, 2 to 20 years
BMI
kg/m²
97th
95th
90th
85th
75th
50th
25th
10th
5th
3rd
2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (years)
Published May 30, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).
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CDC Growth Charts: United States



Published May 30, 2000.
SOURCE: Developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000).

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