

ASSESSMENT OF RENAL FUNCTION IN PATIENTS WITH
SICKLE CELL ANAEMIA AND SICKLE CELL TRAIT AT
THE KENYATTA NATIONAL HOSPITAL

A dissertation submitted in part fulfilment for the
Degree of Master of Medicine (Medicine) in the
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DR. MARY MBITHE KIKO, M.B.Ch.B. (Nairobi)

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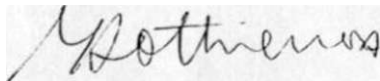
DR. KIKO M. M. M.D.Ch.B (Nairobi)

This dissertation has been submitted for M. Med. (Medicine) examination with our approval as University Supervisors.



Signed:

PROF. L.S. OTIENO, M.R.C.P. (UK),
F.R.C.P. (E)
PROFESSOR IN MEDICINE,
DEPARTMENT OF MEDICINE,
UNIVERSITY OF NAIROBI.



Signed:

DR. N.A.O. ABINYA, MB.Ch.B (Nairobi)
M. MED. (Nairobi)
LECTURER,
DEPARTMENT OF MEDICINE,
UNIVERSITY OF NAIROBI.

<u>TABLE OF CONTENTS</u>	<u>PAGE</u>
TITLE	(i)
DECLARATION	(ii)
TABLE OF CONTENTS	(iii)
LIST OF TABLES	(iv)
LIST OF ABBREVIATIONS	(v)
SUMMARY	(vi)
INTRODUCTION AND LITERATURE REVIEW	1
AIMS	7
MATERIALS AND METHODS	8
RESULTS	13
DISCUSSION	25
CONCLUSIONS	32
RECOMMENDATIONS	32
ACKNOWLEDGEMENTS	33
REFERENCES	34
APPENDIX	41

LIST OF TABLES

TABLE 1
Haematological Indices

TABLE 2
Clinical Presentation

TABLE 3
Urinary Findings

TABLE 4
Causes of Urinary Tract Infection
Patients with Sickle Cell Anaemia

TABLE 5
Sensitivity Test Results

LIST OF ABBREVIATIONS

1.	SCD	-	Sickle Cell Disease
2.	SCA	-	Sickle Cell Anaemia
3.	SCT	-	Sickle Cell Trait
4.	1*	-	Beta
5.	IlbS	-	Sickle Cell haemoglobin
6.	ERBF	-	Effective Renal Blood Flow
7.	ERPF	-	Effective Renal Plasma Flow
8.	GFR	-	Glomerular Filtration Rate
9.	ADU	-	Anti-diuretic Hormone
10.	BUN	-	Blood Urea Nitrogen
11.	W. H. O	-	World Health Organization
12.	mmol/l	-	Millimols per litre
13.	umol/l	-	Micromols per litre
14.	rbc	-	Red Blood Cell
15.	HPF	-	High Power Field
16.	S	-	Sensitive
17.	R	-	Resistant
18.	Retic	-	Reticulocyte
19.	%	-	Percent
20.	K. N. H.	-	Kenyatta National Hospital
21.	Hb	-	Haemoglobin
22.	PCV	-	Packed Cell Volume
23.	WBC (T)	-	White Blood Cell Total Counts
24.	S.D	-	Standard Deviation

SUMMARY

This study was conducted over a period of ten months from April, 1989 to February, 1990.

The study included a total of 160 cases. Of these, 58 were sickle cell anaemia patients of whom 32 were females, 50 were sickle cell trait cases of whom 32 were females, and 52 were controls of whom 32 were females.

The ages of the patients with sickle cell anaemia ranged between 2 years and 36 years with a mean of 15 ± 7.2 (S.D.) years, the ages of the sickle cell trait cases from 4 years to 44 years with a mean of 18.5 ± 10.3 (S.D.) years, and the ages of the controls between 4 years and 35 years with a mean of 16.5 ± 8.4 (S.D.) years. The age and sex variation between the three groups were not significant ($P > 0.05$).

Clinical features and some biochemical indices of renal function, together with the prevalence of urinary tract infection in patients with sickle cell anaemia, sickle cell traits and controls were studied.

Polyuria, nocturia, polydypsia and enuresis were noted more frequently in sickle cell anaemia patients and sickle cell trait cases than in controls, and this was statistically significant ($P < 0.05$) in both cases. There was no statistical difference in these clinical parameters between sickle cell anaemia patients and sickle cell trait cases. Enuresis was more common among the younger age group in both groups, with 54% of all the sickle cell anaemia patients with enuresis and all the sickle cell trait cases with enuresis being in the age group 5 - 10 years.

A urine concentrating defect was observed in sickle cell anaemia patients and sickle cell trait cases. The mean urine specific gravity was significantly lower in both sickle cell anaemia patients and sickle cell trait cases than in controls ($P < 0.05$). There was no statistical difference in the mean urine specific gravity between the former two groups.

Significant bacteriuria was demonstrated in 14% of the patients with sickle cell anaemia. No patient among the sickle cell trait cases or the control cases had significant bacteriuria. Statistically, the sickle cell anaemia patients had significantly higher cases with significant bacteriuria than the latter two groups.

Haematuria was observed more commonly in sickle cell anaemia patients than in sickle cell trait cases and controls. History of overt haematuria was more common than the finding of microscopic haematuria. 14% of sickle cell anaemia patients gave a history of overt haematuria previously. Only 4% of sickle cell trait cases and no patient in the control group had history of overt haematuria.

Mean urine pH was significantly lower in the control group compared to the sickle cell trait cases and sickle cell anaemia patients.

Serum biochemistry showed significant elevation in uric acid, creatinine, potassium and calcium in patients with sickle cell anaemia as compared with the control group although the levels were still within normal limits.

INTRODUCTION AND LITERATURE REVIEW

Sickle cell disease is a hereditary disorder of haemoglobin synthesis and is due to the presence of sickle cell haemoglobin in the red blood cell (rbc), (1-3).

The basic defect in the haemoglobin molecule is the substitution of valine for glutamic acid in position 6 of the β -globin chain. The mode of inheritance is either autosomal recessive or autosomal dominant with variable penetrance and expressivity (1, 2). The disease is usually manifested in the homozygous state (HbSS) but in some situations, disease manifestations may be observed in the heterozygous state if HbS is 40% or more.

Sickle cell anaemia was first described as a distinct disease entity by Herrick in 1910 (2). Following that discovery, many other manifestations of the disorder involving such other organs and systems as the cardiovascular, the pulmonary, the kidneys and the eyes have been described (3, 4, 5). Anaemia is the main feature of the disease (1, 2, 6-9). Sickle cell haemoglobin is known to undergo gelation in conditions of hypoxia, low pH (acidosis), increased levels of erythrocyte 2, 3 - diphosphoglycerate, or hypertonicity. This is due to the polymerization of the haemoglobin molecules in this state. It is not absolutely clear how this causes sickling phenomenon. It appears to be due to the unusual solubility characteristics of the Hbs which undergoes liquid crystal (tactoid) formation as it becomes deoxygenated. In the latter state, aggregates of sickled haemoglobin molecules arrange themselves in parallel, rod-like structures with a diameter of approximately 11.6nm. The molecules of these strands are in a helical configuration. It seems likely that there is a tendency for normal haemoglobin molecules to become lined in a similar way when the haemoglobin is in de-oxyconfiguration, and in sickle cells, the β valine substitution somehow stabilizes these molecular stacks (1, 9-11).

During their passage through the circulation, red blood cells containing Hbs at high concentrations go through a series of cycles of sickling and desickling and finally, owing to loss of membrane and changes in membrane permeability, the cells become irreversibly sickled. Aggregates of sickled erythrocytes form, particularly in the microvasculature, and this leads to increased viscosity of the blood which is accompanied by vascular stasis, local hypoxia, further sickling and in extreme cases, to complete blockage of small vessels and tissue infarction.

The renal manifestations of sickle cell anaemia have been summarized by Behrman (12) and include gross hematuria, papillary necrosis, the nephrotic syndrome, renal infarction, urinary concentrating defect and pyelonephritis. These features have been confirmed and documented in another study (13).

The kidney in sickle cell disease is affected by both the haemodynamic changes of a chronic anaemia and by the consequences of vaso-occlusion which are marked within the renal medulla. In children and young adults, there are increases in effective renal blood flow (ERBF), effective renal plasma flow (ERPF) and glomerular filtration rate (GFR), although the filtration fraction is decreased. With age, there is a progressive decline in ERBF, ERPF, and GFR (14 -16) and in patients over the age of 40 years, a marked reduction in GFR is common (17) and progressive renal failure is a major cause of morbidity and mortality.

The increased GFR and ERPF in sickle cell disease has been postulated to be due to increased synthesis of prostaglandins (18). Renal prostaglandin synthesis is believed to take place in the renal medullary interstitial cells. Hence medullary ischaemia might stimulate prostaglandin synthesis leading to increased tubular sodium loss and increased renin activity (18-19).

Cortical scarring has been observed in the intravenous urographic studies in patients with sickle cell anaemia, the degree increasing with age (20 - 23).

Radiological evidence of renal papillary necrosis was reported in 26% of adult patients in a Jamaican study (23). Such high prevalence have been noted in other studies (22, 24). The frequency has been noted to be low in children (22, 24, 25), although renal papillary necrosis has been observed as early as in year olds (26).

Conditions in the renal medulla are uniquely conducive to sickling. These conditions include, low oxygen tension, the high acid pH and hypertonicity. The sickling will encourage vaso-occlusion within the vasa rectae system, leading to an almost complete obliteration of the fine vessel system which have been observed in micro-radio-angiographic studies. The vascular disorganization in the medulla are more marked in sickle cell anaemia than in the sickle cell trait. Such vascular disorganization result in tubular changes with atrophy, dilatation and proteinaceous casts. These produce the so-called "thyroidization" in the renal medulla.

Hyposthenuria (passage of urine of low specific gravity as a result of defective concentrating power of the kidneys) has been noted both in sickle cell anaemia and in sickle cell trait. It occurs in children as young as 6 months (2, 15, 26 - 28) and progresses with age. It is less marked in subjects with sickle cell trait.

Both low urinary specific gravity and inability to concentrate urine normally on fluid deprivation have been noted in earlier studies (1, 28 - 30).

The maximum urine osmolality is reduced in the sickle cell trait and this reduction is more marked in the sickle cell disease. Values in the latter usually being less than 600 mosm/Kgl⁰ and often less than 450 mosm/Kgl⁰ (31). Transfusion to normal haemoglobin levels corrected the defective urinary concentrating capacity in children under 2 years (30) but this reversibility declined with age and was negligible after the age of 10 years. The normal diurnal variation in fluid and electrolyte excretion is lost probably because of the sustained high urinary volumes (32 - 35).

Water balance is precarious, children and adults barely balancing intake and output (27) and restricted fluid intake is poorly tolerated with loss of weight, rapid dehydration and a tendency to develop painful crisis. Diuresis induced by cold may further aggravate this situation and possibly precipitate painful crisis.

Early work on hyposthenuria indicated that the defect was not due to lack of ADH since it was not corrected by large doses of exogenous vasopressin (30, 31). Anaemia per se cannot be responsible since the defect occurs in the presence of normal haemoglobin in the sickle cell trait and does not occur in chronic anaemia unassociated with libs. The reversibility following transfusion with normal blood suggests that it may be related to libs containing cells and a specific tubular defect secondary to sickling within the renal vessels was postulated (30).

Haematuria, in the absence of any obvious organic cause, occurs in the sickle cell trait and in sickle cell disease (36, 37). The prevalence is unknown, but since it is presumed to result from micro-infarction of the renal pyramids by intravascular sickling, it might be expected to occur more commonly in sickle cell disease than in the sickle cell trait.

(5)

Pathological examination in cases with haematuria revealed lesions of the renal pelvis including minute ulcerations, areas of medullary oedema and fibrosis together with renal papillary necrosis (25, 37, 38).

Glomerular size (on autopsy or biopsy) increases with age in sickle cell anaemia, whereas little relationship with age has been noted in normal people. This increase in glomerular size occur both in juxtaglomerular area and within the renal cortex. Electron microscopy of glomeruli in sickle cell anaemia without renal involvement revealed occasional effacement of foot processes and local thickening of the basement membrane, changes which have been more marked in cases of sickle cell anaemia associated with the nephrotic syndrome (15, 39).

Acute glomerulonephritis in sickle cell anaemia is thought to be probably post-streptococcal, or due to deposition of other immune complexes within the glomeruli. These complexes are composed of renal tubular epithelial antigen and specific antibodies released by ischaemic damage in the medulla.

Proteinuria occurring in sickle cell anaemia usually does not reach the range in nephrotic syndrome, and its pathological basis is not clear. Nephrotic syndrome per se does occur in sickle cell disease, and its manifestations are similar to those of the nephrotic syndrome from other causes, although hypercholesterolemia is less common (35).

Although the cause of this nephrotic syndrome is not clear, it may be secondary to the glomerulonephritis, or related to protein-iron complexes released from the broken down sickled cells that have been partially phagocytosed by glomerular mesangial cells (39).

Chronic renal failure is an important cause of morbidity and mortality especially in patients with sickle cell anaemia aged over 40 years (1, 17, 21) and regular monitoring of renal function should be performed in this age group. Renal failure is usually insidious in onset and clinically manifests only by a falling haemoglobin level and symptoms of worsening anaemia. At this stage, there is often gross reduction in creatinine clearance. Excretory urography indicates a poorly functioning scarred shrunken kidney and renal biopsy reveals a grossly damaged 'end stage' kidney disease.

The aetiology of renal failure in sickle cell anaemia is probably multifactorial, with contributions from progressive glomerular sclerosis, tubular damage, cortical and medullary infarction, and infection, or a sequele of many years of hyperfunction of the few remaining nephrons, with their subsequent loss.

Mwangemi in 1977 (9), studying causes of morbidity and mortality among sickle cell anaemia patients aged 13 - 33 years at the Kenyatta National Hospital (KNH), Nairobi, confirmed skeletal and cardiovascular complications as being prominent. An earlier study by Njai, Bwibo and Ogada (40) emphasized the importance of haematological problems. Mboloi in 1983 showed hyperuricaemia in sickle cell anaemia (4). Amolo in 1981 (5) mainly studied GFR and urine flow rates in paediatric patients with sickle cell disease in painful (vaso-occlusive) crisis. No clear renal manifestations were recorded in any of these studies.

At KNH, patients with sickle cell anaemia attend the Haematology Clinic. There are, however, no baseline data about renal function in patients with sickle cell anaemia in this hospital.

It was with the present state of knowledge of sickle cell anaemia at KNH together with lack of renal function baseline data that the study was launched.

AIMS

1. To evaluate some clinical features and biochemical indices of renal function in patients with sickle cell anaemia at steady state, sickle cell trait and controls.

2. To study the prevalence of urinary tract infection in patients with sickle cell anaemia, sickle cell trait and controls.

MATERIALS AND METHODSSTUDY PERIOD AND DURATION

The study was conducted over a period of ten months from April, 1989 to February, 1990.

Patients attending the Haematology Clinic with a diagnosis of sickle cell anaemia or sickle cell trait based on cellulose acetate paper electrophoresis (C.A.P.E.) (41) were included in the study. Consecutive patients were taken until the required number was reached.

The controls were selected concurrently from the general out patient clinics and from the eye clinic. They were otherwise well, and did not have sickle cell anaemia or sickle cell trait on cellulose acetate paper electrophoresis (C.A.P.E.). The controls, sickle cell traits and sickle cell anaemia patients were matched for age and sex.

People who were excluded from the study included patients in sickle cell crisis and those who were pregnant, had hypertension or diabetes, heart disease, pyelonephritis, severe urinary tract infection or any non-specific renal disease. Also excluded were female patients who had their menstrual periods at the time.

The following were then obtained:-

a) A thorough history and physical examination.

Important among these were:-

Age, sex, weight, height, Hb electrophoresis, any current treatment, and the number of hospital admissions in the preceding one year.

Weight was taken with the subject sitting on a chair of the spring balance type. Height was taken with the subject standing against a wall without shoes. Blood pressure was taken with the subject lying supine, using standard mercury sphygmomanometer with cuff size covering 2/3 of the patients upper arm.

b) 9 nils, of blood was drawn from the anterior cubital veins. 2 mis. of this blood was drawn into each of 2 sequestrene bottles, and another 5 mis. into a biochemistry bottle.

The following laboratory tests were then carried out:-

Complete haemogram, to include haemoglobin levels, white blood cells - total and differential counts, packed cell volume and platelet count - by the Coulter Counter Model S (42).

Reticulocyte count - Supravital staining with brilliant cresyl blue. Counts were done among 1000 mature erythrocytes and then this was expressed as a percentage (43).

Peripheral blood film - was prepared from anticoagulated blood on the same day the blood was taken.

Haemoglobin electrophoresis - was done through cellulose acetate paper electrophoresis (C.A.P.E.) method (41).

Serum sodium and potassium - were done through flame photometer as used conventionally (44).

BUN was analysed using the modified method of Marsh, Fingerhut and Miller (45).

Uric acid was estimated using a modified method of Sibrinho (46).

Creatinine was analysed using a modified Chasson et al method (47) This method is based on the reaction of saturated picric acid with creatinine in the presence of an alkali.

Calcium was estimated by a modified Barnett et al method (48). This method is based on the principle that in alkaline buffer solution, calcium forms with 0-cresolphthaleine, a violet dye, which is measured photometrically.

Inorganic phosphate was estimated by a modified Henry Colorimetric method (49).

Midstream early morning specimen of urine (after an overnight, 12 hour fluid deprivation) was collected into urine bottles and the following observations were made within 2 hours of collection.

The appearance of the urine was noted including blood staining.

A dipstick analysis for protein, sugar, blood and PII were obtained using combur 9 strips.

Microscopic examination of sediment for cells, casts and pus cells were done using ordinary light microscopy.

Urine specific gravity using a urinometer was performed and the result noted.

Urine Culture:

Urine was put on culture plates using the standard wire loop delivering a volume of 0.01 ml. onto a plate containing Citrate-Lactose-Electrolyte-Deficient (CLED) medium. The medium was then incubated at 37°C for 24 hours before counts were obtained. Bacterial growths were regarded as significant if there was a pure culture colony count of more than 10⁵/ml.

Drug sensitivity for those which were culture positive was done using Mastrings-S sensitivity discs KGL 3/4. The sensitivity of the organisms was compared with sensitivity to W.H.O. Standard organisms which is staph-aureus standard for gram positive organisms and E-coli standard for gram negative organisms. The organism was regarded as sensitive to a particular drug if its zone of inhibition was equal to or greater than that of the standard organism.

STATISTICAL CONSIDERATIONS

The patients and controls were statistically comparable in both age and sex. Data about patients in both the study groups and the controls were obtained and entered into a data (Appendix II). Data was analysed using a computer.

For categorical data, the chi-squared test was used (Mantel-Haenszel Technique). For continuous measurements, T-normal distribution was used. Non-parametric methods were used for analysis of skewed distribution. Analysis of covariance methods were used to investigate the differences in trends between the cases and controls.

ETHICAL CONSIDERATIONS

Informed consent was obtained before patients were included in the study.

RESULTS

A total of 160 cases were evaluated. This number included 58 patients with sickle cell anaemia of whom 32 were females, 50 sickle cell trait cases of whom 32 were females, and 52 controls of whom 32 were females. The sex distribution between the groups was comparable.

The ages of the patients with sickle cell anaemia ranged between 2 years and 36 years with a mean of 15 ± 7.2 (S.D.) years, the ages of the sickle cell trait cases from 4 years to 44 years with mean of 18.5 ± 10.3 (S.D.) years, and the ages of the controls between 4 years and 35 years with a mean of 16.5 ± 8.4 (S.D.) years. The age variation between the three groups was comparable.

Table 1 shows the haematological indices in patients with sickle cell anaemia, sickle cell trait and controls. The mean haemoglobin (Hb) level was 8.38 g/dl in sickle cell anaemia patients, 12.40 g/dl in sickle cell trait cases and 13.47 g/dl in controls. Statistically, the mean Hb was significantly lower in the sickle cell anaemia patients than in sickle cell trait cases and controls ($P < 0.001$ when sickle cell anaemia group was compared to each of the latter groups), the difference between the latter two groups not being significant.

The mean packed cell volume (PCV%) paralleled the mean haemoglobin levels in the three groups, and was significant lower in patients with sickle cell anaemia than in either sickle cell trait cases or controls ($P < 0.05$).

The mean red blood cell total counts (RBC(T)) were also noted to be significantly lower in the sickle cell anaemia patients' group than in sickle cell trait cases and controls ($P < 0.05$). There was no statistical differences in the mean RBC(T) counts between the latter two groups.

Sickle cell anaemia patients had a mean white blood cell total counts (WBC(T)) of $16.67 \times 10^9/l$, sickle cell trait cases $7.89 \times 10^9/l$ and controls $6.86 \times 10^9/l$. The sickle cell anaemia patients had significantly higher WBC(T) counts than each of the latter two groups ($P < 0.01$ when the former group was compared with each of the latter groups), the difference in the WBC(T) counts between the sickle cell trait cases and the controls not being significant.

Mean reticulocyte counts were significantly higher in sickle cell anaemia patients' group compared to the sickle cell traits and controls ($P < 0.05$ when the sickle cell anaemia patients' group was compared to each of the latter groups), with the sickle cell anaemia patients having mean reticulocyte count of $11.15\% \pm 9.00$ (S.D.), sickle cell trait cases mean of $1.57\% \pm 2.43$ (S.D.), and controls $1.00\% \pm 1.97$ (S.D.).

TABLE 1

Haematological data in 58 sickle cell anaemia patients, 50 sickle cell trait cases and 52 controls showing mean Hb, PCV, RBC(T), WBC(T) and Retic counts.

.PATIENTS , CONTROLS,! AND GENOTYPES IIAEMATOLOGICAL ^ DATA \	CONTROLS (HbAA)	SICKLE CELL TRAIT (HbAS)	SICKLE CELL ANAEMIA (HbSS)
1. Mean Haemoglobin (g/dl)	13.47	12.40	8.38
2. PCV %	41.58	39.60	28.00
3. RBC (T) X 10 ⁹ /1	4.94	5.00	3.06
4. WBC (T) X 10 ⁹ /1	6.87	7.89	16.67
5. Retic %	1.00	1.57	11.15

Significance

P < 0.05

The symptoms in patients with sickle cell anaemia, sickle cell trait and controls is as shown in Table 2. The urinary findings in Table 3.

Polyuria, nocturia, polydypsia and enuresis occurred more frequently in patients with sickle cell anaemia and sickle cell trait than among the controls ($P < 0.05$ for each of the former as compared with the controls). There was no statistically significant difference in the occurrence of these symptoms between the sickle cell anaemia and sickle cell trait groups themselves, $P > 0.05$. Enuresis was, however, more common among the sickle cell anaemia patients than the sickle cell trait cases, this not being statistically significant. It was further observed that, among the patients with sickle cell anaemia, enuresis occurred more frequently in the age group < 15 years, with 10 out of the 13 patients with enuresis occurring in this age group ($P < 0.05$). Polyuria, nocturia and polydypsia did not show a similar predilection. All sickle cell trait cases with enuresis were below the age of 10 years.

Patients with sickle cell anaemia and sickle cell trait cases gave history of gross haematuria. No patient in the control group had history of gross haematuria. This symptom occurred more frequently among the patients with sickle cell anaemia than sickle cell trait and controls cases and this was statistically significant ($P < 0.05$ when the former was compared with each of the latter groups).

Sickle cell anaemia patients complained of backache more commonly than the sickle cell trait cases and the controls, and this was statistically significant, $P < 0.01$ for each. Loin pain and loin tenderness were noted in sickle cell anaemia patients mainly, but this was of no statistical significance when compared with sickle cell trait cases and controls ($P > 0.05$).

Dysuria occurred more commonly among the sickle cell anaemia patients than either sickle cell trait cases and controls, and this was statistically significant when the former was compared with each of the latter groups ($P < 0.05$). It was further noted that the controls had significantly more cases with dysuria than sickle cell trait cases ($P < 0.05$).

Proteinuria was detected in sickle cell anaemia patients and sickle cell trait cases more frequently than in controls, but this was not statistically significant. Microscopic haematuria was observed more frequently in sickle cell anaemia patients than among sickle cell trait cases and controls. 4 (7%) sickle cell anaemia patients had microscopic haematuria. Of these 4 patients, 1 (25%) had proteinuria, and 1 (25%) gave history of passing gross haematuria previously.

In patients with sickle cell anaemia, the range of urine specific gravity was from 1.005 to 1.025 with a mean \pm S.D. of 1.0135 ± 0.0058 . For sickle cell trait cases, the range was from 1.005 to 1.030 with a mean \pm S.D. of 1.0153 ± 0.0068 and for controls, the range was from 1.010 to 1.030 with a mean \pm S.D. of 1.0229 ± 0.0053 . The difference in the mean specific gravity was statistically significant ($P < 0.05$) between patients with sickle cell anaemia and controls as well as sickle cell trait cases and controls. There was no statistical difference in the mean specific gravity between the sickle cell anaemia and the sickle cell trait group.

Mean urine pH was significantly lower in the control group than in the sickle cell trait and the sickle cell anaemia groups ($P < 0.05$ between the former and each of the latter groups), the difference in the mean urine pH between the latter two groups not being significant ($P > 0.05$).

TABLE 2

Symptoms in 58 patients with sickle cell anaemia,
50 sickle cell trait cases and 52 controls.

PATIENTS, CONTROLS, AND GENOTYPES (CLINICAL BINDINGS \ \	CONTROLS (HbAA)	SICKLE CELL TRAIT (HbAS)	SICKLE CELL ANAEMIA (HbSS)
Nocturia	9 (17%)	39 (81%)	42 (72%)
Polyuria	10 (19%)	32 (67%)	37 (64%)
Polydypsia	3 (6%)	23 (48%)	35 (60%)
Enuresis	2 (4%)	7 (15%)	13 (23%)
Dysuria	4 (8%)	0 (0%)	12 (21%)
Gross Hematuria	0 (0%)	2 (4%)	8 (14%)

Significance

P < 0.05

Oliguria was absent in all the groups.

TABLE 3

Urinary findings in 58 sickle cell anaemia patients,
50 sickle cell trait cases and 52 controls.

^PATIENTS, CONTROLS, \ AND GENOTYPES URINE FINDINGS	CONTROLS (HbAA)	SICKLE CELL TRAIT (HbAS)	SICKLE CELL ANAEMIA (HbSS)
Mean Urine specific gravity SD	1.02288 0.00527	1.01532 0.00679	1.01345 0.00577
Mean pH SD	5.08 0.44	5.28 0.45	5.32 0.52
Proteinuria	0 (0%)	3 (6%)	2 (3%)
Microscopic hematuria	1 (2%)	1 (2%)	4 (7%)

Significance P < 0.05

Glycosuria was absent in all the groups.

Serum uric acid levels ranged from 145 - 731 $\mu\text{mol/l}$ in patients with sickle cell anaemia with mean \pm S.D. of $350.96 \pm 131.94 \mu\text{mol/l}$, 148 - 478 $\mu\text{mol/l}$ with mean \pm S.D. of $262.89 \pm 96.47 \mu\text{mol/l}$ in sickle cell trait cases and 149 - 475 $\mu\text{mol/l}$ with mean \pm S.D. of $301.48 \pm 81.75 \mu\text{mol/l}$ in the controls. These mean values were within normal limits although the serum uric acid was significantly lower in sickle cell trait group than in controls and in sickle cell anaemia cases ($P < 0.05$ in both). 12 (18.9%) of the patients with sickle cell anaemia had hyperuricaemia (normal uric acid 120 - 420 $\mu\text{mol/l}$), compared to 3 (6.7%) in the sickle cell trait group and 3 (6.3%) in the controls. Uric acid showed some increase with age, more so among the sickle cell anaemia patients who had a uric acid/age correlation coefficient of 0.4625. The three control cases with hyperuricaemia were 2 males and 1 female who had no evidence of its cause clinically.

The serum BUN range was from 2.0 - 9.0 mmol/l with mean \pm S.D. of $4.21 \pm 1.63 \text{mmol/l}$ in patients with sickle cell anaemia, 1.6 - 8.0 mmol/l with mean \pm S.D. of $4.97 \pm 1.76 \text{mmol/l}$ in sickle cell trait group and 2.2 - 7.3 mmol/l with mean \pm S.D. of $4.34 \pm 1.47 \text{mmol/l}$ in the control group. All these mean values were within the normal range (2.5 - 6.7 mmol/l) and there was no statistical difference between the three groups ($P = 0.05$).

Serum creatinine levels ranged from 56 - 184 $\mu\text{mol/l}$ with mean \pm S.D. of $99.45 \pm 27.70 \mu\text{mol/l}$ in patients with sickle cell anaemia, 56 - 144 $\mu\text{mol/l}$ with mean \pm S.D. of $89.35 \pm 21.12 \mu\text{mol/l}$ in sickle cell trait cases and 49 - 117 $\mu\text{mol/l}$ with mean \pm S.D. of $87.22 \pm 17.39 \mu\text{mol/l}$ in the control group. The mean serum

creatinine was significantly higher in the sickle cell anaemia group than in the sickle cell trait group and the controls ($P < 0.05$) the difference in the latter two groups not being significant. 17.9% of patients with sickle cell anaemia had elevated serum creatinine (normal 62 - 120 $\mu\text{mol/l}$), compared to 2.0% in the sickle cell trait group and none in the controls.

The range in serum sodium levels was from 120 - 145 mmol/l in patients with sickle cell anaemia with mean \pm S.D. of 139.71 ± 5.88 mmol/l , 130 - 148 mmol/l with mean \pm S.I), of 139.0 ± 4.76 mmol/l in sickle cell trait cases and 132 - 145 mmol/l with mean \pm S.D. of 138.60 ± 3.65 mmol/l in the controls (normal 135 - 145 mmol/l). There was no statistical difference in the mean sodium levels between the three groups ($P > 0.05$).

The serum potassium levels ranged from 4.0 - 5.6 mmol/l with mean + S.D. of 4.69 ± 0.44 mmol/l in the sickle cell anaemia group, 4.0 - 5.2 mmol/l with mean \pm S.D. of 4.52 ± 0.44 mmol/l in the sickle cell trait group and 3.6 - 5.3 mmol/l with mean \pm S.D. of 4.43 ± 0.47 mmol/l in the control group. Sickle cell anaemia patients had significantly higher mean serum potassium levels compared to the sickle cell trait and control groups $P < 0.05$, although all these mean levels are within normal limits (3.5 - 5.0 mmol/l).

Urine culture yielded significant bacterial growth only in the sickle cell anaemia patients group. This was statistically significant ($P = 0.0008$) compared to the sickle cell trait cases and controls. 8 (14%) of the sickle cell anaemia patients had significant bacterial growth.

Table 4 shows the causes of urinary tract infection in eight patients with sickle cell anaemia. 5 (62.5%) were caused by *Escherichia coli*, 1 (12.5%) by *Klebsiella* species, 1 (12.5%) by a non-lactose fermenting coliform and 1 (12.5%) by *Streptococcus faecalis*. From this, it is evident that the major cause of urinary tract infection in sickle cell anaemia patients is *Escherichia coli*.

Table 5 shows the sensitivity pattern for the cultures done. The percentage sensitivity for each drug tested is as shown. Nitrofurantoin had 100% sensitivity, showing sensitivity to both gram positive and gram negative organisms.

TABLE 4

Microscopic findings and causes of urinary tract infection in eight patients with sickle cell anaemia.

Patients identity	Age/ years	Sex	Microscopy findings	Organisms cultured
1	2	M	Pus cells 8 - 10 IIPF No rbc's	Escherichia coli
2	6	M	Pus cells 10 - 15 HPF No rbc's	Escherichia coli
3	7	F	Pus cells 8 - 14 IIPF No rbc's	Escherichia coli
4	10	M	Pus cells 2 - 4 HPF No rbc's	Klebsiella species
5	14	F	Pus cells 2 - 4 HPF Epithelial cells - many rbc's - many	Streptococcus faecalis
6	15	F	Pus cells 1 - 2 HPF No rbc's	Escherichia coli
7	16	M	Normal	Non-Lactose fermenting coliform
8	21	F	Normal	Escherichia coli

TABLE 5

Sensitivity test results for eight patients with sickle anaemia and urinary tract infection at Kenyatta National Hospital.

Patient's identity	1	2	3	4	5	6	7	8	Percentage sensitivity
Organisms cultured	Escheri- chia coli	Escheri- chia coli	Escheri- chia coli	Klebsi- ella species	Strept. faecalis	Escheri- chia coli	Non-lactose fermenting coloform	Escheri- chia coli	
Drug tested: Ampicilin	R	R	R	R	R	R	R	R	0%
Tetracycline	R	S	S	R	S	R	S	R	50%
Nitrofurantoin	S	S	S	S	S	S	S	S	100%
Nalidixic Acid	S	S	S	S	R	S	S	S	87.5%
Streptomycin	R	S	R	R	R	R	R	R	12.5%
Gentamycin	R	S	S	R	R	S	S	S	62.5%
Sulphatriad	R	R	R	R	R	R	R	R	0%
Cotrimoxazole	S	R	R	R	R	R	R	S	25%

Legend:

R = Resistant
S - Sensitive

Nitrofurantoin is probably the drug of choice for sicklers with urinary tract infection.

DISCUSSION

This study lays down some baseline renal function data for patients with sickle cell anaemia in steady state and sickle cell trait.

The haematological parameters are in keeping with a chronic haemolytic anaemia in patients with sickle cell anaemia with reduced mean hb, PCV and RBC (T) counts while the mean reticulocyte count is markedly elevated - 11.15 ± 9.00 (S.D.)%. Sergeant et al (1) observed similar parameters in sickle cell anaemia. The sickle cell trait and controls groups showed normal haematological indices.

The main clinical presentations relating to renal function in patients with sickle cell anaemia include polyuria, polydypsia, nocturia and enuresis. Similar findings were seen in sickle cell trait cases except enuresis which occurred at a lower frequency in sickle cell traits than in the sickle cell anaemia patients. Noll et al (50) studying enuresis in patients with sickle cell anaemia aged 5 - 18 years noted a history of enuresis in 29% of the patients. In the present study, enuresis was noted in 23% of all the sickle cell anaemia patients. It was further noted that 10 (77%) were below the age of 15 years and 7 (54%) were between ages 5 - 10 years.) 2 (15%) of these patients with enuresis were > 18 years. All sickle cell trait cases with enuresis were below the age of 10 years.

Patients with sickle cell haemoglobin (Hbs) are known to produce urine of low specific gravity resulting from a defect in the renal tubular reabsorption of water. This is probably due to reduced responsiveness to ADII since large doses of vasopressin did not correct the disorder in a study (31). Hyposthenuria leads to large losses of body water leading to polyuria accompanied by nocturia and enuresis. Polydypsia is then in an attempt to replenish the fluid loss.

Urine specific gravity was lower in patients with sickle cell anaemia and sickle cell trait cases as compared to controls, and this was statistically significant ($P < 0.001$). The mean urine specific gravity for patients with sickle cell anaemia was 1.01345 ± 0.00577 (S.D.) Sickle cell trait cases had slightly higher urine mean specific gravity of 1.01532 ± 0.00679 (S.D.). Similar findings have been reported before (1). The control patients had a mean specific gravity of 1.02288 ± 0.00527 (S.D.). There was no statistical difference between the specific gravity of urine in sickle cell anaemia and sickle cell trait groups, but the difference between each of the latter two groups and the controls was statistically significant ($P < 0.001$).

Kietel et al (31) found a urine concentrating defect with maximum specific gravity of 1.010 - 1.020 in adult patients with sickle cell anaemia. Mboloi in his work on adult sicklers had similar findings, with a mean urine specific gravity of 1.014 ± 0.0013 (4).

The low specific gravity of urine in patients with sickle cell anaemia and sickle cell trait is related to the presence of sickle cell haemoglobin (HbS) in the red blood cells since it did not occur in the cases with normal haemoglobin only (HbA). A tubular defect secondary to recurrent sickling within the renal vessels is probably responsible for the hyposthenuria.

Structural changes have been demonstrated in the renal medulla on histology with the main finding as diminished number of vasa recti. This is a direct result of recurrent sickling, vascular occlusion and ischaemia which is followed by fibrosis with obliteration or distortion of vasa recti. The hypertonic environment in the renal medulla most likely promotes sickling (28).

The dilute urine produced in these patients reflects lack of function of the juxtamedullary nephrons whose loops dip into the renal medulla and papillae to produce concentrated urine by countercurrent multiplication phenomenon. This gives urine of low osmolality in the range of 400 - 450 mosmol/Kg, which is equivalent to specific gravity of 1.015. Urine osmolality was not done in this study.

History of gross haematuria was more common in patients with sickle cell anaemia than in sickle cell traits. A history of gross haematuria was obtained in 14% of all patients with sickle cell anaemia and microscopic haematuria in 7%. Similar findings were noted in other studies (51, 52). 4% of the sickle cell trait cases had history of gross haematuria, and 2% had microscopic haematuria. Only one patient with sickle cell anaemia and history of gross haematuria was found to have microscopic haematuria. This patient did not have bacteriuria, but one of the sickle cell anaemia patients with microscopic haematuria had bacteriuria. No patient in the control population had history of gross haematuria, but one had microscopic haematuria with no other abnormal urinary findings. Amolo in his study of sickle cell anaemia patients in crisis had 2 (9%) patients with overt haematuria. None of the patients in this study had overt haematuria at the time of this study.

Frank haematuria is significant and is probably the most conspicuous and the most dramatic renal manifestations of sickle cell anaemia and sickle cell trait. It has been noted that the bleeding is generally painless, spontaneous and tends to be unilateral, occurring more frequently from the left kidney (36, 37, 53). The frequency of haematuria in these groups is not known for certain, although only 1% of 119 people with sickle cell trait developed this complication during 10 years of follow up in a community based Jamaican study (1). Crone and Associates (36) reported 8 cases of sickle cell trait haematuria, 3 of whom were associated with proven urinary tract infection, and in one in whom bleeding ceased after the infection was eradicated. In this

study the one case with sickle cell trait who had microscopic haematuria did not have clinical or laboratory diagnosis of urinary tract infection. Perrile and Epstein (28) found increased degrees of sickling in patients with sickle cell trait and sickle cell anaemia in the presence of hypertonic medium. They postulated, therefore, that the hypertonicity at the tips of the renal papillae led to increased sickling and stasis, resulting in ischaemic necrosis of the papillae, and haematuria.

Proteinuria was noted in 2 (3%) of patients with sickle cell anaemia and 3 (6%) sickle cell trait cases. Nobody in the control group had proteinuria. Statistically, there was no difference in the incidence of proteinuria in the three groups. Of the patients who had proteinuria, none had proteinuria in the nephrotic range. The latter was noted in previous studies (2, 5).

In this study the mean urinary pH was significantly lower in the controls than in the patients with sickle cell trait and sickle cell anaemia. It was further noted that sickle cell trait cases had lower mean urinary pH than sickle cell anaemia patients although not statistically significant ($P > 0.05$). Hong Ping Kong et al (54) found that sickle cell anaemia patients have a mild defect in ability to lower urinary pH. They also noted that the ability to acidify urine following ammonium chloride ingestion is decreased in these patients. There is, however, no systematic acidosis, and it is postulated that this impaired renal acidification of urine is an incomplete type of renal tubular acidosis.

Fourteen percent (8 patients) of the sickle cell anaemia group in this study had significant bacteriuria. An earlier study done here by Amolo (5) showed the incidence to be 9% in children with sickle cell anaemia studied. In the present study 87.5% of all the patients with laboratory features of urinary tract infection were < 16 years of age. Three (37.5%) of the patients with significant bacteriuria gave history of dysuria. Few studies are available on urinary tract infections in sickle cell anaemia and sickle cell trait. Asymptomatic

bacteriuria was noted more frequently in pregnant women with sickle cell trait than in controls (1). It is unknown whether men, children and non-pregnant women with sickle cell trait are more prone to asymptomatic bacteriuria. In the present study, sickle cell trait cases were noted not to have significant bacteriuria compared with controls.

High incidences of urinary tract infection in association with sickle cell anaemia and sickle cell trait have been reported in various studies (51, 55-57). The pathophysiologic basis for the increased susceptibility to urinary tract infection in sickle cell anaemia is probably the same as for the known proneness to infection with streptococcus pneumonia (58, 59) and haemophilus influenza (60) organisms. These patients have been found to be deficient in the opsonic adherence that enhances phagocytosis of pneumococci (61) due to a defect in the alternative pathway of the complement system.

The main bacteria cultured in urine in this study is Escherichia coli, with 5 (65%) patients having this organism, others cultured were Klebsiella species 1 (12.5%), Streptococcus faecalis 1 (12.5%) and a non-lactose fermenting coliform 1 (12.5%). It is evident from this that Escherichia coli is a major cause of urinary tract infection in sickle cell anaemia patients in this small group studied. Urine culture sensitivity results on all organisms cultured gave Nitrofurantoin 100% sensitivity, Nalidixic acid 87.5%, Gentamycin 62.5%, Tetracycline 50%, Cotrimoxazole 25%, Streptomycin 12.5%, and both Sulphatriad and Ampicillin showed 0% sensitivity. Nitrofurantoin having 100% sensitivity to organisms causing urinary tract infection in this small study of sickle cell anaemia patients at KNH may help to cut costs and improve on simplicity of treatment of these patients.

Uric acid is liberated when the purines adenine and guanine, structural units in nucleic acids are broken down. Conditions associated with increased cell turnover will be associated with increased uric acid production from the degradation of nuclear material (62) and this has been reported in sickle cell anaemia (4, 6, 63). The mean serum uric acid level was significantly higher in the sickle cell anaemia group than in the sickle cell trait group and controls, with sickle cell anaemia patients having mean uric acid of 350.86 ± 132 (S.D.) $\mu\text{mol/l}$ with a range from 145 - 731 $\mu\text{mol/l}$, sickle cell trait 262.89 ± 96.47 (S.D.) $\mu\text{mol/l}$ with a range from 148 - 478 $\mu\text{mol/l}$, and controls 301.48 ± 81.70 (S.D.) $\mu\text{mol/l}$ with a range from 149 - 475 $\mu\text{mol/l}$ ($P < 0.05$). These mean uric acid levels were within the normal range (120 - 420 $\mu\text{mol/l}$).

Chronic haemolytic anaemias are associated with hyperuricaemia which result from uric acid overproduction. The haematological parameters in sickle cell anaemia patients in this study are consistent with persistent haemolysis with mean reticulocyte count of 11.2 ± 9.00 (S.D.)%. White blood cell counts are also very high and the rapid white blood cell turnover may be contributing to the hyperuricaemia as well. Walker et al (63) reported studies that suggested uric acid excretion is reduced in some patients with sickle cell anaemia, and the resulting hyperuricaemia probably plays a role in the nephropathy of sickle cell anaemia.

17.9% of all the patients with sickle cell anaemia had elevated serum creatinine. The highest recorded was 184 $\mu\text{mol/l}$ (normal 60 - 120 $\mu\text{mol/l}$). 2% in the sickle cell trait group had elevated levels, but none in the controls. Statistically, there was a significant difference between the mean levels of creatinine in sickle cell anaemia patients as compared with controls and traits ($P < 0.05$). There was no statistical difference in the serum creatinine between the latter two groups.

BUN levels were consistently normal in patients with sickle cell anaemia, sickle cell trait cases and controls, with only a few exceptional patients who had mild elevations above normal. The highest recorded was BUN of 9.0 mmol/l in a sickle cell anaemia patient. All the mean BUN levels for the three groups were within the normal range (2.5 - 6.7 mmol/l).

Walker et al (64) observed that the renal function tests did not reflect glomerular lesions in sickle cell anaemia as shown on histology. Other workers have observed that glomerular function is intact or even supranormal during the earlier years of life, then progressively deteriorates after the age of 30 years (13, 31, 65).

Mean serum potassium level was significantly higher in patients with sickle cell anaemia as compared with sickle cell trait cases and controls ($P < 0.05$). There was no statistical difference between the latter two groups.

Sickle cell anaemia patients are in a state of chronic haemolysis. This leads to release of intracellular potassium into plasma, and therefore, contributes to the findings noted above. Similar findings were noted previously (6).

CONCLUSIONS

1. Hyposthenuria was demonstrated in sickle cell anaemia patients and sickle cell trait cases.
2. Haematuria occurs more commonly in sickle cell anaemia patients than in sickle cell traits and is a rare finding in people with normal haemoglobin (HbAA) .
3. Most patients with sickle cell anaemia and bacteriuria are asymptomatic.
4. Escherichia coli is the commonest cause of urinary tract infection in patients with sickle cell anaemia studied.
5. Nitrofurantoin is a useful drug in managing sickle cell anaemia patients with urinary tract infection.

RECOMMENDATIONS

1. Patients with sickle cell anaemia should be screened for asymptomatic bacteriuria.
2. Patients with sickle cell anaemia should have baseline renal function tests.
3. Where it is possible sickle cell anaemia patients and sickle cell trait cases should have urine osmolality and specific gravity checked regularly .
4. Further studies are recommended on patients with sickle cell anaemia and sickle cell trait cases, including renal ultrasound and creatinine clearance.

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APPENDIX 1

CONSENT FORM

I

agree to participate/for my child to participate in this renal functions in sickle cell disease research project.

I fully understand the purpose of this study and its implications as explained to me.

(i) Signature/L⁺ thumb print of patient/guardian

(ii) Signature of investigator/witness

APPENDIX II

DATA SHEET

NAME

CODE NO.

AGE

SEX

WEIGHT

HEIGHT

OCCUPATION

Haemoglobin Electrophoresis report by C.A.P.E.
method.

Symptoms/signs and any other current illness/
Treatment

Specify.

Malaria Prophylaxis. Yes/No - which drug.

Hospital admissions during the past 1 year. Yes/No

Specify.

Admission in sickle cell crisis during the past

1 year. Yes/No

Specify number of times.

History of blood transfusions in the past. Yes/No

Specify number and reason for each.

History of:

Poor weight gain Yes/No

Recurrent respiratory infections Yes/No

Recurrent leg ulcers Yes/No

Weakness Yes/No

Yellow eyes	Yes/No
Polydypsia	Yes/No
Polyuria	Yes/No
Oliguria	Yes/No
Ilaeinaturia	Yes/No
Smoky urine	Yes/No
Dysuria	Yes/No
Enuresis	Yes/No
Nocturia	Yes/No
Backache	Yes/No
Loin pain	Yes/No
Poor vision	Yes/No
Headache	Yes/No

OTHERS

5. Physical Findings:

-small for age	Yes/No
-pallor	Yes/No
-jaundice	Yes/No

If yes, specify.

PA:

Tenderness. Yes/No. If Yes, where.

Lt Loin tenderness Yes/No

Rt Loin tenderness Yes/No

Ilepatomegally Yes/No. Liver span _____ cm.

Spleen palpable/Not palpable. If palpable _____ size

Kidneys palpable (Lt) Yes/No

(Rt) Yes/No

CVS

Pulse rate

Blood pressure systolic Diastolic

Heart sounds

Murmurs

its

Specify findings.

CNS

Specify findings.

Laboratory data

a) Haemogram - **lib**

PCV

RBC

WBC- Total count

- Differential - N

M

E

B

- Reticulocyte count

Peripheral Blood Film Report

b) Blood urea nitrogen

Uric acid

Serum creatinine

Inorganic phosphates

Sodium

Potassium

Calcium

c) Urine

- Conibur 9 urinalysis

- Specific Gravity

- Culture

- Microscopy

Any other comment/finding not noted above.