Nigerian Journal of Paediatrics 2009; 36 (1&2): 1-8

Comparative usefulness of Serum Creatinine and Microalbuminuria in detecting early Renal Changes in Children with Sickle Cell Anaemia in Benin City

IB Abhulimhen-Iyoha, OM Ibadin+, EG Ofovwe***

Abstract

Abhulimhen-Iyoha IB, Ibadin OM, Ofovwe EG. Comparative usefulness of Serum Creatinine and Microalbuminuria in detecting early Renal Changes in Children with Sickle Cell Anaemia in Benin City. *Nigerian Journal of Paediatrics* 2009; 36:1.

Background: Microalbuminuria as an early marker of certain diseases including those affecting the renal system is widely acknowledged. Its performance in this regard vis a vis routine use of serum creatinine in sickle cell anaemia (SCA) patients known to be prone to renal complications has however not been fully explored, particularly in the study locale.

Objective: To compare the usefulness of serum creatinine and microalbuminuria in the early detection of renal changes in children with SCA in Benin City.

Methods: A cohort of 69 children with SCA aged 1-16 years were consecutively enrolled into this cross sectional and descriptive study which was conducted between November 2006 and February 2007. Using the Micral Test strips, microalbuminuria in early morning urine specimen (spot) was determined in each subject. Also determined were serum creatinine, urea, electrolytes and creatinine clearance.

Results: The prevalence of microalbuminuria in the study subjects was 20.3 percent. Serum creatinine values in all subjects were normal but increased with increasing age. Similarly, serum urea, creatinine clearance and electrolytes in the subjects were within normal limits. Apart from the negative predictive value of 79.7 percent, other indices such as sensitivity (0.0 percent), specificity (0.0 percent) and positive predictive value (0.0 percent) of serum creatinine were low as a gold standard in the early detection of renal changes when compared with microalbuminuria.

Conclusion and recommendation: Microalbuminuria is common enough in children with SCA to warrant routine screening for it. Reliance on serum creatinine for the detection of early renal changes would be misplaced. Measures that could assist in the early detection of ensuing renal diseases and improve case management of the child with SCA, who is particularly prone to renal complications, are warranted and these could be partially determined by using the presence of microalbuminuria. Interventional measures known to retard the rate of deterioration of kidney function following prolonged proteinuria could thus be instituted.

Key Words: Serum creatinine, Predictive value, Microalbuminuria, Sickle Cell Anaemia, Children.

Introduction

THE role of dipstick urinalysis in screening for urinary abnormalities is widely acknowledged, as it detects proteinuria, haematuria, urinary specific gravity, and leukocyturia, among others.[1-3] Its limitation however is its inability to detect early renal changes that are heralded by proteinuria below a value of 30mg/dl. Microalbuminuria (MA) is the excretion in urine of very small amounts of albumin, slightly in excess of 20ðg/minute, in the range of 30-300mg/24 hours[4] – levels that require sensitive radioimmunoassay for detection. Detection of microalbuminuria could be achieved using the Micral-test strip (Commercial test strips that detect microalbuminuria in spot urine). The role of microalbuminuria in a variety of renal and non-renal diseases, including diabetes mellitus,[5] hypertension[6] and sickle cell disease,[7,8] have been

University of Benin Teaching Hospital, Benin City

Department of Child Health
* Lecturer I
\+ Professor
** Senior Lecturer

Correspondence: Professor OM Ibadin
E-mail: mikobadin@yahoo.com

evaluated. Microalbuminuria has also been found to be an important prognostic indicator in meningitis,[9] malignancies[10] and hypertension.[11] Furthermore, it has been found to be an important marker of glomerular injury, particularly in patients with sickle cell anaemia.

The term, sickle cell nephropathy, encompasses structural and functional abnormalities of the kidneys seen in sickle cell disease.[12] These defects are more pronounced in homozygous sickle cell patients.[13] Early detection of impaired renal function is desirable as it could assist in forestalling the development of daunting complications, as interventional measures aimed at retarding the rate of excretion of proteinuria could be instituted. The role of microalbuminuria in this regard is acknowledged. However, its exact predictive value in the early detection of renal abnormalities in comparison with routine serum urea, electrolyte and creatinine, is rather uncertain. This study, therefore aimed to evaluate microalbuminuria in children with sickle cell anaemia (SCA) as a marker of renal impairment in comparison with serum electrolytes, urea and creatinine. This is against the backdrop of the facts that serum creatinine is mainly of value in established cases,[14] i.e. shortly after the onset of acute renal failure and cessation of urine output, and that creatinine level may be normal even though there is compromised renal function. Micral-test strips have sensitivity greater than 95 percent (range 90-99 percent) and specificity in the range of 70-90 percent for impaired renal functions.[15]

Patients and Methods

The studywas a prospective and cross-sectional study carried out at the Consultant Out-Patient Clinic (COPC) of the University of Benin Teaching Hospital (UBTH) and the Sickle Cell Centre (SCC), both in Benin City. The duration of the study was November 2006 to February 2007. Sample size was determined using a prevalence rate[16] of 0.028 and the formula $n = Z^2pq/d^2$.

The subjects consisted of 69 children aged one to 16 years, with sickle cell anaemia (confirmed by electrophoresis using cellulose acetate paper) in their steady state. Steady state refers to a state when children with SCA are free of infection, crises or any acute problem and had been well for at least, four weeks after the last crisis.[17-19] Excluded from the study were children involved in competitive sport/exercise in the 12 hours preceding sample collection, children with fever at presentation or a history of febrile illness within the preceding week and children with ongoing menstruation or vaginal/penile discharge. Also excluded were children with symptoms and signs suggestive of urinary tract infection or a pre-existing renal disease and history of use of drugs such as oxytetracycline known to cause proteinuria. The protocol did not specifically exclude patients with Human Immunodeficiency Virus (HIV) infection.

Patients were recruited consecutively into the study. Evaluation entailed a minimum of two clinical contacts; the second contact being a week after the first. Detailed history obtained in respect of each child included patient's age, gender and relevant medical history of recurrent admissions, blood transfusions, cigarette smoking, family history of hypertension and drug use within 72 hours antedating sample collection. This was followed by a thorough physical examination checking among others, for peripheral oedema and determining the blood pressure. Heights of the subjects were measured by means of a stadiometer, using the technique described by Paynter and Parkins[20] with values obtained expressed in centimetres. The lower of two blood pressure (BP) readings taken on arrival and on departure was recorded with the patient in sitting position and using the Accoson Mercury Sphygmomanometer. Values obtained were compared to established standards for age, to determine those that were hypertensive. Findings were recorded in a proforma designed for the study. Informed consent was obtained from the parents or caregivers of subjects. Ethical approval was obtained from the Ethical Committees of UBTH and the SCC.

All recruited subjects were provided with pre-labeled universal bottles for the collection of early morning urine. Subjects or their parents or guardians were instructed on how to collect early morning mid-stream/clean catch urine and to return same as early as possible after collection, but preferably between 7.00am and 8.00am. Using aseptic procedure, five millilitres of venous blood was collected from each patient by venepuncture on the second visit and one ml of the sample placed in an EDTA bottle for determination/confirmation of the patient's haemoglobin genotype. The remaining 4ml of blood was used for the determination of creatinine, urea and electrolytes using standard methods. Jaffe's method[21] was used for serum creatinine estimation while creatinine clearance was calculated using a simple and reliable formula (modified Schwartz formula)[22] for quick approximation of creatinine clearance (C_{Cr}). It incorporated the use of the serum creatinine (S_{Cr}) and the child's height expressed in centimetres.

$$C_{Cr}\ (ml/min/1.73m^2) = \frac{K \times Height\ (cm)}{S_{Cr}\ (mg/dl)}$$

where K = 0.55 for children 1 to 12 years old.

K = 0.55 for girls 13 to 21 years old.
K = 0.70 for boys 13 to 21 years old.

The value obtained was corrected thus:

$$\text{"Corrected" } C_{Cr} = \frac{\text{Patient's } C_{Cr} \times 1.73m^2}{\text{Patient's body surface area}}$$

Only urine samples negative for albuminuria using the Combi-10 multi-strips were further tested for MA using the Micral-test strips and employing the methods described by the manufacturers (*Roche Diagnostics, Quebec, Canada*). Microalbuminuria was defined by varying shades of pink in the test strip that corresponded to a range of 20 – 250mg/l of urinary albumin. All patients that had microalbuminuria were referred to the paediatric nephrology clinic for further evaluation.

The data collected were entered into Microsoft Excel 2003 programme of a computer and further crosschecked for accuracy and then sorted. Means and standard deviations were calculated for continuous variables. Where appropriate, data were uploaded into Statistical Package for Social Sciences (SPSS) 11.0 for the calculation of frequencies and association between variables. The specificity, sensitivity, positive predictive value and negative predictive value of serum creatinine as against MA were calculated. Student's t-test, and chi-square analysis were used where appropriate. Values of $p < 0.05$ were interpreted as significant.

Results

Of the 69 subjects recruited into the study, 42 (60.9 percent) were males while 27 (39.1 percent) were females (M: F ratio of 1.6: 1). The distribution of subjects in the various age cohorts for both males and females is shown in Table I. The mean age of the study population was 8.8 ± 4.7 years. The mean age for males was 8.7 ± 4.8 years compared to 9.0 ± 4.7 years for females; there was no significant difference between the mean ages ($p = 0.799$). The mean weight of the study subjects was 28.0 ± 5.8 kg. Males had a mean weight of 27.4 ± 6.1 kg and females 28.6 ± 5.4 kg. The mean height for all subjects was 131.5 ± 10.1 cm; the males had a mean height of 130.3 ± 11.4 cm as against 132.6 ± 8.7 cm for the females. The mean body surface area for all subjects was 1.00 ± 0.2 m^2 while it was 0.99 ± 0.2 and 1.01 ± 0.1 m^2 for the males and females, respectively. Generally, the females had comparable anthropometry with their male counterparts (Table II).

Fourteen (20.3 percent) of the 69 subjects had MA. Although not statistically significant, the gender specific prevalence revealed more female involvement (25.9 percent vs 16.7 percent). In the age group ≥9 years involving 34 subjects, the prevalence of MA was 22.9 percent as against 17.6 percent in those <9 years. The mean age of subjects with MA of 10.9 ± 4.9 years did not differ significantly from that obtained in those without MA (8.3 ± 4.6 years). Blood pressure was normal in all subjects. No differences were observed in systolic and diastolic blood pressures between the groups with and without MA.

The serum urea and electrolytes were essentially normal in all subjects. The mean electrolyte values were 137.6 ± 2.1 mmol/L, 3.8 ± 0.4 mmo/L, 24.7 ± 2.4 mmol/L and 101.9 ± 4.8 mmol/L for sodium, potassium, bicarbonate and chloride, respectively. The mean serum urea was 28.2 ± 5.7 mg/dl (Table III). The mean urea for subjects with MA of 29.6 ± 5.0 mg/dl was not significantly different ($p = 0.305$) from that obtained in those without MA of 27.8 ± 6.0 mg/dl (Table V).

Serum creatinine varied between 0.8 and 1.1 mg/dl (mean 0.923 ± 0.093 mg/dl). The mean creatinine clearance, corrected for age, was 148.96 ± 23.3 ml/min/1.73m^2, while the range was 96 – 203 ml/min/1.73m^2 (Table IV). The table reveals that serum creatinine increased with age. The patients who were

Table I

Demographic Characteristics of the Study Population

Age (years)	*Male (%)*	*Female (%)*	*Total (%)*
≤5	14 (66.7)	7 (33.3)	21 (100)
6 – 8	7 (53.8)	6 (46.2)	13 (100)
9 – 11	6 (54.5)	5 (45.5)	11 (100)
12 – 14	9 (69.2)	4 (30.8)	13 (100)
≥15	6 (54.5)	5 (45.5)	11 (100)
Total	42 (60.9)	27 (39.1)	69 (100)

Table II

Anthropometric Characteristics of the Subjects

Age (years)	Weight (kg) (Mean ± SD)		Height (cm) (Mean ± SD)		Body Surface Area (m^2) (Mean ± SD)	
	Male	Female	Male	Female	Male	Female
≤5	16.1 ± 7.1	14.9 ± 2.6	100.4 ± 13.9	99.9 ± 8.0	0.67 ± 0.2	0.64 ± 0.1
6 – 8	22.6 ± 3.7	20.3 ± 3.2	122.5 ± 6.6	117.8 ± 8.3	0.88 ± 0.1	0.81 ± 0.1
9 – 11	27.7 ± 4.6	27.6 ± 3.8	131.4 ± 5.2	136.0 ± 5.7	1.00 ± 0.4	1.00 ± 0.1
12 – 14	33.1 ± 5.8	40.3 ± 6.1	145.4 ± 7.7	150.3 ± 12.0	1.15 ± 0.2	1.28 ± 0.3
≥15	37.5 ± 9.1	40.1 ± 11.4	152.0 ± 13.8	159.0 ± 9.4	1.26 ± 0.2	1.33 ± 0.1
Mean Total	27.4 ± 6.1	28.6 ± 5.4	130.3 ± 11.4	132.6 ± 8.7	0.99 ± 0.2	1.01 ± 0.1
Mean for all subjects	28.0 ± 5.8		131.5 ± 10.1		1.00 ± 0.2	

Table III

Mean Serum Electrolytes and Urea Profile in Various Age Groups

Age (years)	Mean Values				
	Sodium	Potassium	Bicarbonate	Chloride	Urea
≤5	138.1 ± 1.6	3.7 ± 0.3	24.9 ± 2.4	102.5 ± 5.4	28.5 ± 6.4
6 – 8	138.1 ± 1.7	3.9 ± 0.5	25.3 ± 2.1	102.9 ± 4.7	29.4 ± 5.7
9 – 11	137.0 ± 2.3	3.6 ± 0.3	23.4 ± 1.8	100.5 ± 5.2	29.2 ±4.0
12 – 14	137.5 ± 2.8	3.9 ± 0.5	23.0 ± 2.5	102.5 ± 4.8	26.5 ± 6.3
≥15	137.3 ± 1.9	3.8 ± 0.2	27.0 ± 3.4	100.9 ± 3.8	27.2 ± 6.2
Mean	137.6 ± 2.1	3.8 ± 0.4	24.7 ± 2.4	101.9 ± 4.8	28.2 ± 5.7

MA negative (n = 55), had a mean creatinine clearance of 153.4 ± 24.5 ml/min/1.73m^2 (range 96 – 203) compared to those that were MA positive (n = 14), who had a mean creatinine clearance of 140.4 ± 19.9 ml/min/1.73^2 (range 115 – 194 ml/min/1.73m^2). The difference in creatinine clearance between the two groups was however, not statistically significant (Table V). All the subjects had normal serum creatinine and creatinine clearance. No significant relationships existed between MA and serum electrolytes, urea, creatinine, of subjects as shown in Table V.

The sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of creatinine were 0.0 percent, 100 percent, 0.0 percent and 79.7 percent, respectively. Thus, besides the NPV of serum creatinine, its performance vis-à-vis MA in predicting early renal changes was poor.

Discussion

Nephropathy is a common complication of sickle cell anaemia as it develops in at least one-third of adolescent and adult patients.[23-25] The pathophysiology of sickle nephropathy is not completely understood, but involves both glomerular and tubular injury and dysfunction.[26] Renal damage in SCA begins in childhood, presumably as a consequence of chronic anaemia, resulting in increased circulating blood volume, and increased renal blood flow and repeated intraparenchymal sickling. Among children with SCA, the first clinical sign of glomerular injury is often asymptomatic proteinuria.[24,27]

In the present study, serum creatinine as against MA as indicator of early renal changes had low positive predictive value, specificity and sensitivity suggesting its limited use as an indicator of early renal

Table IV

Serum Creatinine Levels and Creatinine Clearance in Subjects according to Age Groups

Age (Years)	*Serum Creatinine (Mean ± SD)*	*Creatinine Clearance (Mean ± SD)*
≤5	0.914 ± 0.101	161.2 ± 21.1[a]
6-8	0.915 ± 0.099	149.4 ± 16.7[b]
9-11	0.918 ± 0.098	139.1 ± 21.3[c]
12-14	0.939 ± 0.077	150.9 ± 29.2[d]
≥15	0.972 ± 0.091	144.2 ± 27.8[e]
	F = 0.1729	F = 1.942
	P = 0.952	P = 0.114
Mean ± SD	0.923 ± 0.093 mg/dl	148.96 ± 23.2 ml/min/1.73m^2

Footnote to Table IV

Comparison	*Mean ± SD*		*Mean Difference*	*t*	*p-value*
a vs e	161.2 ± 21.1	144.2 ± 27.8	16.9	1.933	0.063
a vs b	161.2 ± 21.1	149.4 ± 16.7	11.7	1.706	0.098
a vs c	161.2 ± 21.1	139 ± 21.3	22.1	2.806	0.009*
a vs d	161.2 ± 21.1	150.9 ± 29.8	10.3	1.181	0.247
b vs c	149.4 ± 16.7	139 ± 21.3	10.3	1.332	0.196
b vs d	149.4 ± 16.7	150.9 ± 29.8	-1.5	-0.154	0.879
c vs e	139 ± 21.3	144.2 ± 27.8	-5.2	-0.489	0.630

**Statistically significant*

Table V

Relationship between Microalbuminuria and Serum Electrolytes, Urea, Creatinine and Creatinine Clearance in the Subjects

Parameter	*MA Positive (n = 14) (Mean ± SD)*	*MA Negative (n = 55) (Mean ± SD)*	*t*	*p-value*
Sodium (mmol/L)	137.9 ± 1.8	137.7 ± 2.1	1.470	0.146
Potassium (mmol/L)	3.8 ± 0.2	3.8 ± 0.4	0.000	1.000
Bicarbonate (mmol/L)	25.6 ± 3.2	24.5 ± 2.9	1.241	0.219
Chloride (mmol/L)	101.4 ± 4.4	102.2 ± 5.0	0.547	0.587
Urea (mg/dl)	29.6 ± 5.0	27.8 ± 6.0	1.033	0.305
Serum creatinine (mg/dl)	0.93 ± 0.08	0.92 ± 0.10	0.346	0.730
Creatinine clearance	140.4 ± 19.9	153.4 ± 24.5	-1.834	0.071

Table VI

Performance of Serum Creatinine as against Microalbuminuria in the Detection of Renal Impairment

Serum Creatinine	*Microalbuminuria*		
	Yes (%)	*No (%)*	*Total (%)*
Elevated	0 (0.0)	0 (0.0)	0 (0)
Normal	14 (20.3)	55 (79.7)	69 (100)
Total	14 (20.3)	55 (79.7)	69 (100)

compromise. Serum creatinine as a poor indicator of early changes in renal diseases has been acknowledged in such conditions as diabetes mellitus and hypertension.[14] Thus, serum creatinine cannot be relied upon for the detection of early renal changes. In other words, serum creatinine, though reliable as a marker of established renal diseases, may not be too relevant in the screening for early renal changes particularly in sicklers. This is borne out of the fact that by its unique metabolism, serum creatinine will only be persistently deranged following substantial decline in renal function.[14] The obvious implication of this is the superiority of MA over serum creatinine as an index of early renal changes even in children with SCA. Our observation is in tandem with the findings by Guasch *et al*[28] who observed that routine screening using either serum creatinine or creatinine clearance would be very insensitive in detecting early renal failure in the sickle cell patient population and that MA might be required to detect those with early glomerular damage.

Once end-stage renal disease (ESRD) occurs, the prognosis is very poor despite intervention measures.[23] Unfortunately, there are no national data regarding the prevalence of sickle cell nephropathy in Nigeria. However, among 375,152 patients with ESRD reported in the United States Renal Data System, 397 (0.11 percent) had SCD. The mean age at presentation was 40.68 ± 14 years, with overall increased risk of mortality as compared to other patients with ESRD.[29] Powars *et al*[23] also demonstrated increased risk of mortality in comparison with non-SCD patients with CRF/ESRD. Conditions culminating in ESRD in these patients could have started in childhood given the mean age at presentation of such patients. Early detection of the renal changes coupled with specific interventions could have decelerated or retarded the progression of the renal assault. As previously described, MA or the preclinical increased excretion in urinary albumin is an early sign of glomerular damage.[7,8] Generally, a prolonged period of MA may precede persistent proteinuria.[30] Given the high prevalence of sickle cell disease in Nigeria, a substantial number of persons are at risk of ESRD from complications inherent in SCA. Viewed against this background, early detection of renal changes as could be achieved through the use of MA become invaluable.

In this study, serum sodium levels were normal, a finding that was in keeping with that of Bayazit *et al*[31] who also noted normal sodium values in children with SCA. However, Aluoch[32] in a study carried out in the Netherlands, recorded low sodium levels in his cohort of children with SCA. The difference in sodium levels observed between our study and those reported by Aluoch could be ascribed to differences in the characteristics of the study population. Whereas our study involved children aged one to 16 years, Aluoch's subjects were not categorized to allow for comparison. Contrary to the normal serum potassium levels noted in our subjects, Aluoch[32] and Bayazit *et al*[31] documented higher levels of serum potassium in patients with SCA. Aluoch[32] found hyperkalaemia of greater than 5 mmol/L in 50 percent of SCA cases. However, he ascribed some high potassium levels to probable *in-vitro* haemolysis. In consonance with the findings in this study, Falk *et al*[33] in 1992 and Bayazit *et al*[31] in 2002 recorded normal serum creatinine in children with SCD. Levels of serum creatinine would be normal in such patients unless they had profound renal function compromise.

The children with MA did not vary in their height, serum electrolyte, urea, creatinine, and creatinine clearance when compared to their counterparts without MA. Other workers also did not find any association specifically between creatinine clearance and MA.[7,34]

In conclusion, the serum urea and electrolyte profile of children with SCA in Benin City were normal for age. The same applied to serum creatinine of all the

children although it increased with age. Performance of serum creatinine as a predictor of early renal impairment as against MA in children with SCA was poor.

Acknowledgements

We wish to express our profound gratitude to the children recruited for the study and their families for their co-operation. The contributions of resident doctors in the Department of Child Health to the success of the study are also acknowledged.

References

1. Adedoyin OT, Akindele JA, Ajayi OA, Okesina AB. Urinalysis in clinically stable Nigerian newborns. *Nig J Paediatr* 2000; 27: 1-5.
2. Oviasu E, Oviasu SV. Urinary abnormalities in asymptomatic adolescents Nigerians. *West Afr J Med* 1994; 13: 152-5.
3. Ajasin MA. The prevalence of isolated proteinuria in asymptomatic school children in Mushin, Lagos. *West Afr J Med* 1986; 5: 215-8.
4. Pinto-Sietsma SJ, Mulder J, Janssen WM, Hillege HL, de ZeeUw D, de Jong PE. Smoking is related to albuminuria and abnormal renal function in nondiabetic persons. *Ann Intern Med* 2000;133:585-91.
5. Gatling W, Mullee MA, Knight C, Hill RD. Microalbuminuria in diabetes: relationships between urinary albumin excretion and diabetes related variables. *Diabet Med* 1988; 5:348-51.
6. Mimran A, Ribstein J, DuCailar G. Microalbuminuria in essential hypertension. *Curr Opin Nephrol Hypertens* 1999; 8:359-63.
7. Dharnidharka VR, Dabbagh S, Atiyeh B, Simpson P, Sarnaik S. Prevalence of microalbuminuria in children with sickle cell disease. *Pediatr Nephrol* 1998;12:475-8.
8. Sesso R, Almeida MA, Figueiredo MS, Bordin JO. Renal dysfunction in patients with sickle cell anemia or sickle cell trait. *Braz J Med Biol Res* 1998; 31:1257-62.
9. Roine I. Microalbuminuria: an index of severity in childhood meningitis. *Pediatr Infect Dis J* 1993; 12:584-8.
10. Sawyer N, Wadsworth J, Wijnen M, Gabriel R. Prevalence, concentration and prognostic importance of proteinuria in patients with malignancies. *Br Med J (Clin Res Ed)* 1988; 296: 1295-8.
11. Viberti G. Prognostic significance of microalbuminuria. *Am J Hypertens* 1994; 7:69S-72S.
12. Allon M. Renal abnormalities in sickle cell disease. *Arch Intern Med* 1990; 150:501-4.
13. Serjeant GR. Sickle cell Disease. London: Oxford University Press, 1985: 1-222.
14. Bergestein JM. Structure and Function of the Kidney. In: Behrman RE, Kliegman RM, Jenson HB, eds. Nelson Textbook of Pediatrics. Philadelphia: WB Saunders Co, 2000: 1590-1.
15. Evaluation Report Micral-Test, an ACCU-CHEK product: Roche Diagnostics Manual. 2001.
16. Adewuyi JO, Akintunde EA. Survey of haemoglobin genotypes in children at Ilorin. *Nig J Paediatr* 1990; 17:23-6.
17. Buchanan GR, Glader BE. Leucoyte counts in children with sickle cell disease. Comparative values in the steady state, vaso-occlusive crisis, and bacterial infection. *Am J Dis Child* 1978; 132:396-8.
18. Olanrewaju DM, Adekile AD. Anthropometric status of sickle cell anaemia patients in Ile-Ife, Nigeria. *Nig Med Pract* 1989; 18:63-6.
19. Ojuawo A, Adedoyin MA, Fagbule D. Hepatic function tests in children with sickle cell anaemia during vasoocclusive crisis. *Cent Afr J Med* 1994; 40:342-5.
20. Paynter AS, Parkin M. Growth in Childhood. In: Stanfield P, Brueton M, Chan M, *et al*, eds. Diseases of Children in the Subtropics and Tropics. ELST with Arnold 1991: 268-9.
21. Cheesbrough M. Clinical Chemistry Test. In: District Laboratory Practice in Tropical Countries. Cambridge University Press, United Kingdom, 1998: 333-7.
22. Schwartz GJ, Brion LP, Spitzer A. The use of plasma creatinine concentration for estimating glomerular filtration rate in infants, children, and adolescents. *Pediatr Clin North Am* 1987; 34:571-90.
23. Powars DR, Elliott-Mills DD, Chan L, Niland J, Hiti AL, Opas LM, Johnson C. Chronic renal failure in sickle cell disease: risk factors, clinical course, and mortality. *Ann Intern Med* 1991; 115:614-20.
24. Falk RJ, Jennette JC. Sickle cell nephropathy. *Adv Nephrol* 1994; 23:133–47.
25. Pham PT, Pham PC, Wilkinson AH, Lew SQ. Renal abnormalities in sickle cell disease. *Kidney Int* 2000; 57:1–8.
26. Wesson DE. The initiation and progression of sickle cell nephropathy. *Kidney Int* 2002; 61:2277–86.
27. Wigfall DR, Ware RE, Burchinal MR, Kinney TR, Foreman JW. Prevalence and clinical correlates of glomerulopathy in children with sickle cell disease. *J Pediatr* 2000; 136:749–53.
28. Guasch A, Cua M, You W, Mitch WE. Sickle cell anemia causes a distinct pattern of glomerular dysfunction. *Kidney Int* 1997; 51:826-33.

29. Abbott KC, Hypolite IO, Agodoa LY. Sickle cell nephropathy at end-stage renal disease in the United States: patient characteristics and survival. *Clin Nephrol* 2002; 58:9-15.
30. Remuzzi G, Bertani T. Pathophysiology of progressive nephropathies. *N Eng J* Med 1998; 339: 1448-56.
31. Bayazit AK, Noyan A, Aldudak B, Ozel A, Anarat A, Kilinc Y, Sasmaz, Gali E, Anarat R, Dikmen N. Renal function in children with sickle cell anaemia. *Clin Nephrol* 2002; 57:127-30.
32. Aluoch JR. Renal and electrolyte profile in steady state sickle cell disease: observations in patients with sickle cell disease in The Netherlands. *Trop Geogr Med* 1989; 41:128-32.
33. Falk RJ, Scheinman J, Phillips G, Orringer E, Johnson A, Jeanette JC. Prevalence and pathologic features of sickle cell nephropathy and response to inhibition of angiotensin-converting enzyme. *N Engl J Med* 1992; 326:910-5.
34. Alvarez O, Montane B, Lopez G, Wilkinson J, Miller T. Early blood transfusions protect against microalbuminuria in children with sickle cell disease. *Pediatr Blood Cancer* 2006; 47: 71-6.