

Associations of Hyper-filtration and Proteinuria with Clinical Severity Score among Adult Sudanese Sickle anemia patients

Mohamed Abdelazim Osman

Department of Physiology Faculty of Medicine Alneelain University

Nazeer Hassan Suliman

Department of Physiology Faculty of Medicine Alneelain University Khartoum Sudan

Lamis AbdelGadir Kaddam (✉ lamiskaddam@hotmail.com)

Alneelain University Faculty of Medicine <https://orcid.org/0000-0002-1083-4514>

Research article

Keywords: Sickle cell anemia, glomerular hyper-filtration, proteinuria, hyper-uricemia

Posted Date: April 1st, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-19681/v1>

License:  This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: Sickle Cell Anemia (SCA) is an autosomal recessive haemoglobinopathy with high morbidity and mortality. Global survival of sickle patients is increased and subsequently, prevalence of chronic complications including renal manifestations due to advances in management. Therefore, early detection and management of these complications become mandatory. This study aimed to investigate the estimated Glomerular Filtration Rate (eGFR), proteinuria and serum uric acid as markers of renal involvement in Sudanese sickle adults and association between these parameters and clinical severity score of sickle cell disease.

Methods: Cross-sectional hospital-based study included thirty-two adult Sudanese patients diagnosed with SCA and twenty-three controls. Written informed consent was obtained. Blood and urine samples were collected. Severity score was calculated using Bios online calculator and eGFR was calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula without adjustment for ethnicity.

Results: Protein/Creatinine Ratio (PCR) was significantly higher (p -value < 0.001) in sickle cell anaemia group compared to controls. Hyper-filtration and Hyperuricemia were manifested in 75% and 6.3% of SCA group respectively. There was no association between the severity score and renal manifestations in the SCA group.

Conclusions: Hyperfiltration and proteinuria were the most prevalent renal manifestations in SCA group. Further studies are recommended to determine the predictors of renal complications and early management of them.

Introduction:

Sickle cell anemia (SCA) is an autosomal recessive disease resulting from substitution of amino acid glutamate by valine in position 6 of beta-globin chain(1). Sickle Cell Disease is the most inherited blood disorder worldwide(2). In USA approximately one in every thirteen African American have sickle cell trait and in some African regions the prevalence of SCA may reach up to 30%(3). In Sudan, SCA is one of the most prevalent genetic diseases mainly in Western Sudan; in some tribes prevalence may reach 30% due to high consanguinity rates (4). Sickle cell anemia is a severely morbid condition with high mortality rates even in developed countries where the average survival age is 40 to 50 years(5). In Africa an accurate data is inadequate, but the median survival is far lower and most of the children die before completing their first decade(5).

Sickling of the RBCs, hemolysis, increase viscosity, vaso-occlusion, hypoxia, and ischemia-reperfusion injury are the hallmarks of the SCD(6). Survival age increases in patients with SCA due to advances in management leading to widespread tissue necrosis and end organ damage (5). Renal impairment predominates organs' failure and it was documented among 40% of SCA patients who died(5). Previous study revealed that the median age of diagnosis of renal failure in SCD patients is 23.1 years and median

survival after diagnosis of End Stage Renal Disease (ESRD) in SCD was only 4 years despite hemodialysis(7).

This study aimed to measure proteinuria, uric acid level, and estimated GFR as markers of renal function in steady state SCA adult patients, and to identify the associations between these parameters and the clinical severity score of SCA. Steady state refers to a point of time where SCA patient does not experience acute infection, crisis or needs hospital admission or blood transfusion in the previous three months preceding data collection(8). Studying renal parameters in SCA enables early detection and management of renal complications to decrease morbidity, mortality and improve quality of life (QOL). Best to our knowledge this first study investigated renal parameters and their association with the severity score among sickle cell anemia patients.

Methods:

This study is a cross sectional hospital-based study held in Omdurman Military Hospital, which is the one of the biggest tertiary hospitals in the Sudan. A total sample of 32 SCA adult patients (13 males, 19 females) in a steady state, who attended the hematology referred clinic in the hospital from October to December 2017. Control group (11 males, 12 females) were healthy students recruited from Faculty of Medicine, Al Neelain University. Diabetics, Chronic Kidney Disease (CKD) patients due to other causes, patients with acute illness and pregnant women were excluded.

Blood pressure (BP) measured for all participants using mercury sphygmomanometer and stethoscope. Participants were classified according to the last American Heart Association classification of hypertension in to: normal BP, elevated BP, stage 1 and stage 2 hypertension; if their BP \leq 120/80, 120–129/80, 130–140 /80–90 and $>$ 140/90 respectively (9). Weight was measured in Kilogram using digital weight scale. Height was measured by meter using wall mounted scale. BMI was calculated from the height and weight using this equation: $BMI = \frac{\text{Weight in Kg}}{(\text{height in meter})^2}$

Patients were classified according to the WHO classification of BMI available at (<http://apps.who.int/bmi/index>) to underweight, obese, overweight and normal weight when their BMI: < 18.5, \geq 30, 24.9–30, 18.5–25 Kg/m² respectively.

Venous blood sample (5 ml) was obtained from each participant in to plain, EDTA and heparin containers. Then the collected samples sent to the laboratory for CBC, RFT, UA, bilirubin and reticulocyte count using Automated Hematology Analyzer (BC-2800 Mindary, Nanshan, China). Random spot urine collected in clean, dry, closed, wide neck urine container and sent to the laboratory for PCR using colorimetric method. Study population classified according to their PCR using NICE Guidelines to group with significant proteinuria if PCR \geq 50 mg/mmol and another with non-significant proteinuria when PCR \leq 50 mg/mmol (10).

GFR calculated using CKD-EPI formula without adjustment for ethnicity which is the best GFR formula for SCD (11). This formula was proved by France prospective observational cohort study conducted in Sub-

Saharan and French West Indies native populations; after the comparison between measured GFR using Iohexol plasma clearance method with estimated GFR by using formulas (MDRD, Cockcroft-Gault, CKD-EPI, CKD-EPI and MDRD without adjustment for ethnicity)(11). GFR < 60 ml/min/1.73 m² regarded as CKD. Despite there is no consensus about the cut-off point of hyper-filtration; more than 130 ml/min/1.73 m² in females and > 140 in males is regarded as glomerular hyper-filtration based on previous reported literature(12).

CKD-EPI without adjustment of ethnicity formula:

GFR (ml/min/1.73 m²) = 141 min (Scr/k, 1) ^a × max (Scr/k, 1)^{-1.209} × 0.993^{age} × 1.018 (if female). Whereas: SCr is Serum Creatinine, k is 0.7 for females and 0.9 for males, a is -0.329 for females and -0.411 for males, min: indicates the minimum of SCr/k or 1, and max indicates the maximum of S. Cr/k or 1.

Severity score is estimation of risk of death among SCD was calculated using a validated online clinical severity score calculator based on study made by Sebastian et al(13) and developed by Bioinformatics group called Bios in the University of Granada in Spain and made it available freely online at <http://bios.ugr.es/dss-calculator>. Severity score includes clinical and laboratory characteristics to estimate 5-year-risk of death among sickle cell anaemia patients. The range of the score is from zero to one; where zero means 0% and one means 100% risk of death in the next five years. Fifteen out of sixteen clinical and laboratory characteristics were entered to the online calculator. Severity Score Variables include: Stroke, blood transfusion times, pain, priapism, acute coronary syndrome, avascular necrosis, systolic blood pressure, Hemoglobin, Hb genotype, MCV, TWBCs, Reticulocyte count, and Serum bilirubin beside age and gender. Patients were classified in to high, moderate and low risk of death if they score > 0.72, (0.55–0.72) and < 0.55 respectively according to Guilheme et al study(14).

Data were summarized and analysed using (SPSS) version 23. We used frequency tables, means and standard deviation (SD) to describe the values. One-sample Kolmogorov-Smirnov Test was used to test the distributions of variables. Unpaired T. Test was used for normally distributed variables and Mann Whitney U test for non-normally distributed ones. A correlation analysis was applied to investigate the relation between study variables. p- value ≤ 0.05 was considered as statistically significant cut off point.

Study was ethically approved from Institutional Review Board (IRB) of Al Neelain University. Informed written consents were obtained from participants after explaining the purpose, procedures and measurement needed for the study.

Results:

Characteristics of study population:

Most of our participants were < 25 years. According to WHO classification 71.9% of SCA group were underweight and only 3.1% were overweight. In control group 21.7% were underweight and 56.6% had normal BMI (Table 1).

Table 1
Basic Characteristics of study population:

Variable	SCA group	Control	P. Value
Gender			
Male	13 (40.6%)	11 (47.8%)	
Female	19 (59.4%)	12 (52.2%)	
Age (years)	(23.9 ± 6.1)	(22.1 ± 4.1)	0.34
BMI (Kg/m ²)	(17.6 ± 2.6)	(23 ± 4.8)	< 0.001*
*p-value is significant; BMI: Body mass index			

Table 2
Severity Score Laboratory
characteristics of SCA group

Variables	Mean ± SD
Hb mg/dl	(7.6 ± 1.6)
MCV (fl)	88.9 ± 11.6
Retics %	2.5 ± 0.6
TWBC (× 10 ⁹ / l)	(13.2 ± 3.4)
D. bilirubin (mg/dl)	0.7 ± 0.8
I. bilirubin (mg/dl)	1.3 ± 1.6

Renal Parameters Among SCA Patients:

Hyper-filtration was observed in 75% and significant proteinuria was reported in 12.5% while hyperuricemia reported in 6.3% of SCA patients. (Table 3) Illustrates renal parameters among SCA patients and the control group. According to the guidelines, 84.4% of SCD group have normal BP, 12.5% have elevated BP and 3.1% have stage II systolic HTN, while 87% of the control have normal systolic BP, 13% have an elevated BP. 6.3% of SCD group have stage I diastolic HTN and none of the control group have diastolic HTN.

Table 3
Renal Parameters comparison among SCA and control groups:

Variable	SCD	Control	P-value
	Mean ± SD	Mean ± SD	
Urea (mg/dl)	21.6 ± 8.4	33.8 ± 5.9	< 0.001*
Creatinine (mg/dl)	0.65 ± 0.18	0.7 ± 0.03	0.386
eGFR (ml/min)	149.7 ± 29.6	127.5 ± 5.1	< 0.001*
PCR (mg/mmol)	30.9 ± 25.2	17.3 ± 3.4	< 0.001*
UA (mg/dl)	5.3 ± 3.3	4.1 ± 1	0.086
Systolic BP (mmHg)	112 ± 14	114 ± 10	0.45
Diastolic BP (mmHg)	67 ± 11	72 ± 6	0.02*
MAP	82.2 ± 10.2	86.7 ± 6.5	0.06

*: Statistically significant; GFR: glomerular filtration rate; PCR: protein creatinine ratio; UA: uric acid; MAP: mean arterial pressure

Severity score

The mean severity score of SCA group was 0.69. SCA patients were stratified according to their severity score into: Mild, moderate and severe according to Guilheme et al study (14). (Table 4) shows severity score grading of SCA group.

Table 4
Severity Score grading of SCA group:

MORTALITY	N	%
HIGH (> 0.72)	17	53.1
MODERATE (0.55–0.72)	11	34.4
LOW (< 0.55)	4	12.5

N: number of SCA patients; % percentage among SCA group

There is no correlation observed between the severity score and renal parameters in this study, but there is positive correlation between PCR, age and systolic BP. (Table 5) shows the correlation between renal parameters, age, BP and severity score.

Table 5
Correlation of Renal Parameters, BP, Age and severity score among SCA:

		AGE	SBP	DBP	Uric acid	eGFR	PCR	S. SCORE
AGE	R	1	.573	.378*	0.324	-0.315	0.273	0.239
	P- value		0.001	0.033	0.071	0.079	0.13	0.187
SBP	R	.573	1	0.347	0.147	-0.155	.436*	0.316
	P- value	0.001		0.052	0.421	0.396	0.013	0.078
DBP	R	.378*	0.347	1	-0.026	0.029	-0.092	-0.036
	P- value	0.033	0.052		0.886	0.876	0.615	0.846
Uric acid	R	0.324	0.147	-0.026	1	-0.303	-0.031	0.153
	P- value	0.071	0.421	0.886		0.092	0.865	0.403
eGFR	R	-0.315	-0.155	0.029	-0.303	1	-0.055	-0.123
	P- value	0.079	0.396	0.876	0.092		0.766	0.501
PCR	R	0.273	.436*	-0.092	-0.031	-0.055	1	0.142
	P- value	0.13	0.013	0.615	0.865	0.766		0.437
S. SCORE	R	0.239	0.316	-0.036	0.153	-0.123	0.142	1
	P- value	0.187	0.078	0.846	0.403	0.501	0.437	

* Correlation is significant at the 0.05 level (2-tailed).

Discussion:

This study proposed to investigate renal characteristics (proteinuria, eGFR and uric acid level) among sickle cell anemia patients and their association with severity score. Hyper-filtration and glomerular hypertrophy dominate early onset renal involvement in Sickle Cell Anemia ; as the disease progress with time, eGFR decreases due to increased fibrosis and glomerulosclerosis(15). Low eGFR was not reported in this study among SCA patients unlike other studies (15–17); this may be due to the low BMI and younger age of the patients. In contrast, all control group had normal eGFR (Table 3).

Significant proteinuria was detected in 12.5% of SCA patients while none of the control group had significant proteinuria; this might have resulted from tubular damage, increase glomerular permeability related to repeated vaso-occlusive crisis and poor management of SCA(6). A retrospective study conducted in inpatients adult Sudanese with SCD, reported proteinuria in 81.8% of patients(18); this may indicate a higher levels of proteinuria in SCA patients during crisis. Proteinuria is a prevalent complication of SCD, it was detected in variable proportions in many previous studies for example: Jamaican's (65.3%)

(16), North American's (42.8%)(17) and 65.6%)(15) and Nigerian's(51%)(19), this variation may result from specific nucleotide polymorphism(20). Further studies are necessary in this area to identify if there are specific genetic polymorphisms in Sudanese SCA patients related to proteinuria. In this study, proteinuria grade was determined through a spot urine PCR as an acceptable alternative for ACR(21).

More than 50% of SCA patients in this study scored a high risk of death (severity score > 0.72) (Table 4). Using the same calculator a previous investigation conducted in referral center of hemoglobinopathies in St George's hospital in London found that only 12% of SCA had severe risk of death(22). This high severity score among Sudanese study population requires early preventive measures to decrease morbidity and mortality among adults Sudanese SCA patients.

Significant reduction in diastolic Blood Pressure (BP) was noted (p value 0.02) in SCA group compared to the control group. Other studies also showed similar observations (15, 23, 24). This may be due to loss of sodium and water related to medullary tonicity defects(25). In addition to, high levels prostaglandin, decrease vascular reactivity and systemic vaso-dilatation response to micro-vascular dysfunction(6) or might be due to chronic activation of Nitric Oxide system (NO)(15, 25).

Positive correlation was observed in the current study between SBP and PCR among SCA patients (P value = 0.013) (Table 3). This correlation was documented previously among hypertensive patients which also stated that both proteinuria and hypertension can increase cardiovascular and renal risks independently(26). There was also positive correlation between SBP and age which can be explained by aging process and chronic depletion of nitric oxide due to its consumption in SCA patients(27).

Uric acid was used as a marker of renal function(28). In SCA high uric acid level may result from increased haemolysis and rapid turnover of the RBCs and decreased uric acid clearance by the kidneys(29). No significant difference regarding UA between sickle and control group (Table 3), this finding is similar to former study among Sudanese population(24). In this study hyperuricemia is reported only in 6.3% of SCA group; this likely due to the compensation of the high GFR (high UA clearance) among those young group; as age increases, GFR decreases and they may develop higher rates of hyperuricemia(30). Hyper-filtration, proteinuria, high UA levels and lower BP were also reported in similar study conducted in Congo SCD pediatrics populations(31); which indicated the early onset of renal pathophysiological processes in SCD patients.

This report demonstrated that patients with SCA in spite having normal urea, creatinine, UA levels and lower diastolic BP in compare to control group, but they suffered from hyper-filtration and proteinuria. Eventually they may end up with CKD, hypertension and hyperuricemia. Therefore, caring physician of SCA patients must consider those early signs of SCN and manage them appropriately to prevent further complications. In spite of lack of association of severity score with each individual renal parameter but we observed that both impaired renal parameters and severity score were high among our SCA group; so we may need modified severity score to address these renal manifestations among sickle cell anemia patients .

In conclusion, Proteinuria and hyper-filtration were the most prevalent renal manifestation in SCA patients. SCA patient had higher UA, levels and lower BP compared to control group. There was lack of association between the clinical severity score and renal manifestations of SCA.

Abbreviations

BP: Blood Pressure, CKD: Chronic kidney Disease, eGFR:Estimated Glomerular Filtration Rate ,GFR: Glomerular Filtration Rate, PCR: Protein to Creatinine Ratio, SCA: Sickle Cell Anemia ,UA: Uric Acid, SCD: Sickle Cell Disease ,SCN: Sickle Cell Nephropathy, WBC: White Blood Count

Declarations

Ethics approval and consent to participate:

Central Institutional Review Board at Al -Neelain University, approved the study. Written informed consent was obtained from each participant prior to enrollment.

Consent for publication:

Principal investigator obtained informed consent from each participant to publish the data without breaching confidentiality.

Availability of data and material:

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

We declare no conflict of interest

Funding:

No fund was obtained

Authors' contribution:

MS, and LK participated in study design. MS and LK were involved in all aspects of the study conduct. MS and AH collected data. MS and AH analyzed data. MS, LK and AH participated in writing and review of the manuscript. All authors approved final version of manuscript

Acknowledgement:

We acknowledge Al Neelain University administration for supporting this research. Special thanks to our colleagues: Awab Omer for his participation in data collection,

References

1. D.L. Kasper F, Haucer, Longo, Jameson, Loscalso. Harrison's principles of internal medicine 19th ed. New Yourk City: McGraw-Hill Education; 2015.
2. Adewoyin AS. Management of Sickle Cell Disease: A Review for Physician Education in Nigeria (Sub-Saharan Africa). Anemia. 2015.
3. Sickle Cell Anemia [Internet]. Medscape. 2017 [cited 25 May 2018].
4. Daak AAE, E.Ali, E. H. Mohamed, F. A. Abdel-Rahman, M. E. Elderdery, A. Y. Talbot, O. Kraft, P.Ghebremeskel, K. Elbashir, M. I. Fawzi, W. Sickle cell disease in western Sudan: genetic epidemiology and predictors of knowledge attitude and practices. Tropical medicine & international health : TM & IH. 2016;21(5):642-53.
5. Ebah LM. Renal involvement in sickle cell disease: an African perspective for an African condition. Clin Kidney J [Internet]. 2013 2013; 6:[6–7 pp.].
6. Renal manifestation of sickle cell disease [Internet]. Medscape. 2017.
7. SCHEINMAN PSaJI. Sickle Cell Nephropathy. J Am Soc Nephrol. 1999;10:187-92.
8. Omoti CE. HAEMATOLOGICAL VALUES IN SICKLE CELL ANAEMIA IN STEADY STATE AND DURING VASO-OCCLUSIVE CRISIS IN BENIN CITY, NIGERIA Annals of African Medicine. 2005;4(2):62 – 7.
9. guidlines AcocAhatfocp. 2017 Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults. A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2017;Sep 2017, 23976; DOI: 10.1016/j.jacc.2017.07.745:1 - 28.
10. Chronic Kidney Disease in Adults: Assessment and Management (2014).
11. Jean-Benoît Arlet J-AR, Gilles Chatellier, Dominique Eladari, Sophie De Seigneux, Jean-Claude Souberbielle, Gérard Friedlander, Marianne de Montalembert, Jacques Pouchot, Dominique Prié, and Marie Courbebaisse. Determination of the best method to estimate glomerular filtration rate from serum creatinine in adult patients with sickle cell disease: a prospective observational cohort study. BMC Nephrology 2012. 2012;13.
12. Francois Cachat CC, † Michel Cauderay,‡ Eric Girardin,§ and Hassib Chehade*. A Systematic Review of Glomerular Hyperfiltration Assessment and Definition in the Medical Literature. Clinical Jornal of American Society of Nephrology. 2015;10.
13. Paola Sebastiani VGN, Clinton T. Baldwin, Maria M. Abad-Grau, Ling Wang, Adeboye H. Adewoye, Lillian C. McMahon, Lindsay A. Farrer, James G. Taylor IV, Gregory J. Kato, Mark T. Gladwin, and Martin H. Steinberg. network model to predict the risk of death in sickle cell disease. Blood. 2007;110.
14. Guilherme Henrique Hencklain Fonseca LIVdG, Rogerio Souza, Liliana Mitie Suganuma, Vanderson Rocha and Sandra Fatima Gualandro. NIH Bayesian Score As a Stratification Tool in Sickle Cell Disease - Results from a Single Center Cohort in Brazil. Blood. 2017;130(2254).
15. Richard Kobina Dadzie Ephraim DNMO, Obed Cudjoe, Enos Amoako Oduro, Lyudmila Asante-Asamani, Juliana Mitchell, Hope Agbodzakey and Prince Adoba. Chronic kidney disease is common

- in sickle cell disease: a cross-sectional study in the Tema Metropolis, Ghana. *BMC Nephrology*. 2015;17(75):1 - 7.
16. Reid MRA. Renal function in adult Jamaicans with homozygous sickle cell disease. *Hematology*. 2015;20(7):422 - 8.
 17. Elvira O. Gosmanova F, Sahar Zaidi Jim Y. Wan and Patricia E. Adams-Graves. Prevalence and Progression of Chronic Kidney Disease in Adult Patients With Sickle Cell Disease. *Journal of Investigative Medicine* 2014;62(5):804 - 7.
 18. Amin S. Banaga1 HIE, Khalifa Elmusharaf. Renal Manifestations among Adult Sickle Cell Disease Patients: A Single Center Study in Khartoum, Sudan. *Open Journal of Nephrology*. 2016;6:157-60.
 19. R. A. Bolarinwa KSA, M. A. O. Kuti, O. O. Olawale, N. O. Akinola. Renal Disease in Adult Nigerians with Sickle Cell Anemia: A Report of Prevalence, Clinical Features and Risk Factors *Saudi J Kidney Dis Transpl* 2012;23:171-5.
 20. Allison E. Ashley-Koch ECO, Melanie E. Garrett, Karen Soldano, Laura M. De Castro, Jude C. Jonassaint, Eugene P. Orringer, James R. Eckman, and Marilyn J. Telen. MYH9 and APOL1 are both associated with sickle cell disease nephropathy. *British journal of haematology*. 2011;155:386–94.
 21. nephrology iSo. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Diseases. *Kidney International Supplements*. 2013;3(1):1 - 163.
 22. Anoop P. usefulness and limitations of Bayesian network model as a mortality risk assessment tool in sickle cell anemia. *American journal of Hematology*. 2009.
 23. Paul Drawz SA, Mehdi Nouraie, Santosh Saraf, Victor Gordeuk, Thomas Hostetter, Mark T. Gladwin, and Jane Little. Kidney Disease among Patients with Sickle Cell Disease, Hemoglobin SS and SC. *Clin J Am Soc Nephrol* 11. 2015;11.
 24. Babiker AO, Kaddam LA. Risk factors of metabolic syndrome among adult Sudanese sickle cell anemia patients. *BMC hematology*. 2018;18(1):38.
 25. Maria Pikilidou MY, MariaAntoniou, Eleftherios Papakonstantinou, Despoina Pantelidou, Panagiota, Chalkia, Peter Nilsson, John Yovos, Pantelis Zebekakis. Arterial Stiffness and Peripheral and Central Blood Pressure in Patients with Sickle Cell Disease. *The journal of Clinical Hypertension*. 2015;17(9):726 - 31.
 26. Ausilia Maione LA, Giovanni Strippoli. Proteinuria and Clinical Outcomes in Hypertensive Patients. *American Journal of Hypertension*. 2009;22(11):1137 - 47.
 27. Sharpe CC, Thein SL. Sickle cell nephropathy—a practical approach. *British journal of haematology*. 2011;155(3):287-97.
 28. Ching-Wei Tsai S-YL, Chin-Chi Kuo, Chiu-Ching Huang. Serum Uric Acid and Progression of Kidney Disease: A Longitudinal Analysis and MiniReview. *PLOS ONE* 2017;12(1):1 - 16.
 29. K DE CEULAER AGM, E CHOO-KANG, W A WILLSON, G R SERJEANT. Serum urate concentration in homozygous sickle cell disease *J of clinical pathology*. 1981.

30. Christin Giordano OK, Kelli King-Morris and Abdo Asmar. Uric Acid as a Marker of Kidney Disease: Review of the Current Literature. Hindawi Publishing Corporation Disease Markers. 2015:1 - 6.
31. Michel Ntetani Aloni¹ RMN, Jean-Lambert Gini-Ehungu, Ce 'lestine Ndosimao Nsibu, Mathilde Bothale Ekila, Francis Bompeka Lepira, Nazaire Mangani Nseka⁴. Renal Function in Children Suffering from Sickle Cell Disease: Challenge of Early Detection in Highly ResourceScarce Settings PLOS ONE. 2014;9(5).