The utility of the CKD-EPI formula for determination of glomerular filtration rate in Nigerians with sickle cell disease

Aneke John C.[a], Oyekunle Anthony A.[b], Adegoke Adegbola O.[c], Sanusi Abubakr A.[d], Okocha Emmanuel C.[a], Akinola Norah O.[b], Durosinmi Muheez A.[b]

Background and objective Predictive formulae for the calculation of estimated glomerular filtration rate (eGFR) are increasingly being used in clinical practice for monitoring of renal function. We evaluated the usefulness of the CKD-EPI formula for eGFR in a population of Nigerian patients with sickle cell disease (SCD).

Patients and methods One hundred SCD patients were prospectively studied. Relevant information, including age, weight and sex, was obtained from the participants, whereas creatinine clearance was measured following a 24-h urine collection. The Cockcroft–Gault (C–G) and the CKD-EPI formulae were thereafter used to calculate the glomerular filtration rate (GFR) for all participants. SPSS (version 17) and Microsoft Excel 2007 computer software were used for all data collection and analyses. A *P*-value of less than 0.05 was considered significant.

Results The comparison of measured GFR versus eGFR by the C–G and CKD-EPI formulae in homozygous haemoglobin SS (HbSS) patients yielded correlation coefficients (*r* values) of 0.667 ($P < 0.001$) and 0.598 ($P < 0.001$), respectively. Correspondingly, among the heterozygous haemoglobin S + C (HbSC) patients, measured GFR versus eGFR resulted in *r* values of 0.819 ($P < 0.001$) and 0.848 ($P < 0.001$), respectively.

Conclusion The CKD-EPI formula is a good measure of eGFR in our population of SCD patients; however, it did not perform significantly better than the C–G formula. *Egyptian J Haematol* 40:185–189 © 2015 The Egyptian Society of Haematology.

Egyptian Journal of Haematology 2015, 40:185–189

Keywords: chronic kidney disease, CKD-EPI, estimated glomerular filtration rate, sickle cell disease

[a]Department of Haematology, Nnamdi Azikiwe University Teaching Hospital, Nnewi, Departments of [b]Haematology, [c]Chemical Pathology, [d]Medicine, Obafemi Awolowo University, Ile-Ife, Nigeria

Correspondence to Anthony A. Oyekunle, MBBS, MSc, FMCPath., Department of Haematology and Immunology, Obafemi Awolowo University, 234-220005 Ile-Ife, Osun State, Nigeria
Tel: +234 803 239 8360;
e-mail: oyekunleaa@yahoo.co.uk

Received 23 June 2015 **Accepted** 08 August 2015

Introduction

Assessment of renal function is an integral component of the comprehensive care of patients with sickle cell disease (SCD). This is made even more important by the finding that renal dysfunction is a major determinant of survival in SCD [1]. Kidney dysfunction, with potential for progression to end-stage kidney disease, is a major contributor to the morbidity and mortality of patients with SCD [2,3]. In fact, end-stage kidney disease has variously been documented in up to 11% of these patients [4,5]. In monitoring for sickle cell nephropathy, evaluation of proteinuria is important as it has been shown to indicate early glomerular dysfunction. This makes it an important marker of kidney pathology [2].

Glomerular filtration rate (GFR) is usually determined by measuring the creatinine clearance after a 24-h urine collection. This is time-consuming and laborious and cannot be easily measured in clinical practice. Consequently, predictive formulae have been developed to enable easier and faster calculation of GFR utilizing parameters such as serum creatinine, body size, age, race and sex [6,7]. A number of predictive formulae are currently available that enable the determination of estimated glomerular filtration rate (eGFR) in different disease states with reasonable degrees of accuracy and precision. The Cockcroft–Gault (C–G) [8] formula has gained widespread acceptance and has equally been variously validated in cardiac [9], renal [10] and recently in our population of SCD [11] patients.

Methods of GFR determination based on creatinine clearance are limited by the observation of renal tubular dysfunction in SCD, which leads to increased tubular secretion of creatinine and the consequent overestimation of GFR [12]. Indeed, Haymann *et al.* [13] reported some overestimation of true GFR when comparing the eGFR using the four-variable modification of diet in renal disease (MDRD) formula with ^{51}Cr-EDTA-based measured GFR, despite a good correlation. Moreover, Aparicio *et al.* [14] noted that a reduction in creatinine generation because of decreased muscle mass and changes in protein catabolism and hydration in SCD affects the results of creatinine clearance and also reported a poor correlation between measured

 DOI: 10.4103/1110-1067.170217

GFR using ^{51}Cr-EDTA and values using creatinine clearance. Similarly, studies in children with SCD have shown a poor correlation between measured GFR by the ^{99m}Tc-DTPA method and those utilizing urinary clearance of creatinine and cystatin C [15]. However, the use of radioisotopes for routine clinical assessment of GFR is yet to receive wide acceptance because they are largely labour intensive and hazardous [16].

The shortcomings of creatinine-based methods of GFR estimation notwithstanding, they are still used widely on account of their convenience and safety. A number of studies have alluded to the accuracy, precision and clinical adequacy of the predictive formulae derived from GFR measurements in different disease states [9–11]. The unique pathophysiologic changes associated with sickle cell nephropathy have made it necessary that a disease-specific formula be developed for patients with this condition [17,18]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) research group recently introduced a new equation [19], which has been validated independently by several research groups [20–22].

This study evaluated the performance of the CKD-EPI formula for eGFR in Nigerian patients with SCD.

Patients and methods

The study was prospective, carried out over a 7-month period from January to July 2010. Ethical approval was obtained from the Hospital Ethics Committee and all participants provided informed consent; consent was provided by the parent or the guardian for patients younger than 18 years old. Patients were between 15 and 56 years of age, and were regular attendees of the Hematology Outpatient Clinic of our hospital; there were 100 confirmed (by cellulose acetate electrophoresis, at alkaline pH) patients with SCD [79 homozygous sickle cell anaemia (HbSS) and 21 compound heterozygous sickle cell disease (HbSC) patients, mainly from south-west Nigeria] in stable clinical conditions at least 2 weeks before recruitment and had not received blood transfusion in the last 3 months. Exclusion criteria included oedema or ketosis (which may be indicative of congestive cardiac failure or complicated diabetes mellitus) and those currently on drugs such as co-trimoxazole, probenecid or cephalosporins, which are known to interfere with the tubular excretion of creatinine and alkaline picrate assay (Jaffé reaction) for serum creatinine [23].

Relevant clinical information was documented, and a 24-h urine collection was performed for each participant on an outpatient basis, using wide-bore 4-l containers to which boric acid had been added. On the morning of submission of the 24-h urine sample, 2.5 ml of venous blood was collected for serum creatinine estimation. Each participant was adequately and extensively counselled before commencement of urine collection to avoid errors. Both urinary and serum creatinine estimations were performed using Jaffe's reaction [24]. The eGFR calculations were performed using the following formulae: C–G [8]: [(140–age) × (weight, kg) × (0.85, if female)]/(72 × SCr) and CKD-EPI [19]: $141 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.209} \times 0.993^{age} \times 1.018$ (if female) × 1.159 (if Black), where SCr is the serum creatinine (mg/dl), κ is 0.7 (female) or 0.9 (male), *a* is −0.329 (female) or −0.411 (male), min is the minimum of SCr/κ and 1 and max is the maximum of SCr/κ and 1. The measured and eGFR were both adjusted for body surface area (1.73 m^2), calculated using the Mosteller formula [25]: [height (cm) × weight (kg)/3600]$^{0.5}$. SPSS (version 17; SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (2007) computer software were used for data collection and analysis. Pair-wise correlations were performed between measured and eGFR estimated using the two formulae. A *P*-value less than 0.05 was considered significant.

Results

The patients (HbSS, *n* = 79; HbSC, *n* = 21) included 40 males and 60 females. The mean age of the HbSS and HbSC patients was 25.34 ± 6.77 years (range, 15–56 years) and 29.33 ± 8.97 years (range, 17–50 years), respectively.

The means of measured GFR in HbSS and HbSC were 66.28 ± 27.52 and 97.04 ± 17.47 ml/min/1.73 m^2, respectively. Correspondingly, the mean eGFR were 56.26 ± 15.03 and 57.55 ± 17.46 ml/min/1.73 m^2 using the C–G formula and 115.44 ± 28.98 and 108.78 ± 30.78 ml/min/1.73 m^2 using the CKD-EPI formula in HbSS and HbSC, respectively (Table 1). Using the Kidney Disease: Improving Global Outcomes (KDIGO) classification [26], the majority of the patients (75 and 62% HbSS and HbSC, respectively) had 'normal or high' kidney function (Table 2).

Among the HbSS patients, measured GFR correlated significantly with the eGFR obtained by the C–G (r = 0.667, P < 0.001) and the CKD-EPI formulae (r = 0.598, P < 0.001). There was a better correlation between the measured GFR and the eGFR of the HbSC patients both by the C–G (r = 0.819, P < 0.001) and by the CKD-EPI formulae (r = 0.848, P < 0.001). shows the detailed comparisons between measured GFR and eGFR of the patients (Table 3).

Using a Bland–Altman analysis, there was a mean overestimation of GFR by 49.17 ± 25.36 and 35.03 ± 20.65 ml/min in the HbSS and HbSC patients, respectively, using the CKD-EPI formula, whereas correspondingly, the C–G was underestimated by a mean of 10.02 ± 21.17 and 11.83 ± 13.31 ml/min (Fig. 1).

Discussion

We had previously evaluated the utility of five predictive formulae for eGFR in our SCD patients, including the C–G, MDRD, Mawer, Gates and Hull. It was observed that eGFR by the C–G formula correlated best with measured GFR (using creatinine clearance) [11]. Similarly, several studies have also reported high correlations between the C–G formula and measured GFR in Nigerian patients with hypertension, congestive heart failure and chronic renal failure [9–10].

Following the introduction of the CKD-EPI formula, it has been shown to be a useful predictor of GFR in lean patients of sub-Saharan African descent [20]. It thus became imperative that this 'new' formula be tested in adult non-European, non-American SCD

Table 1: Means and standard deviations of measured and calculated GFR in HbSS and HbSC

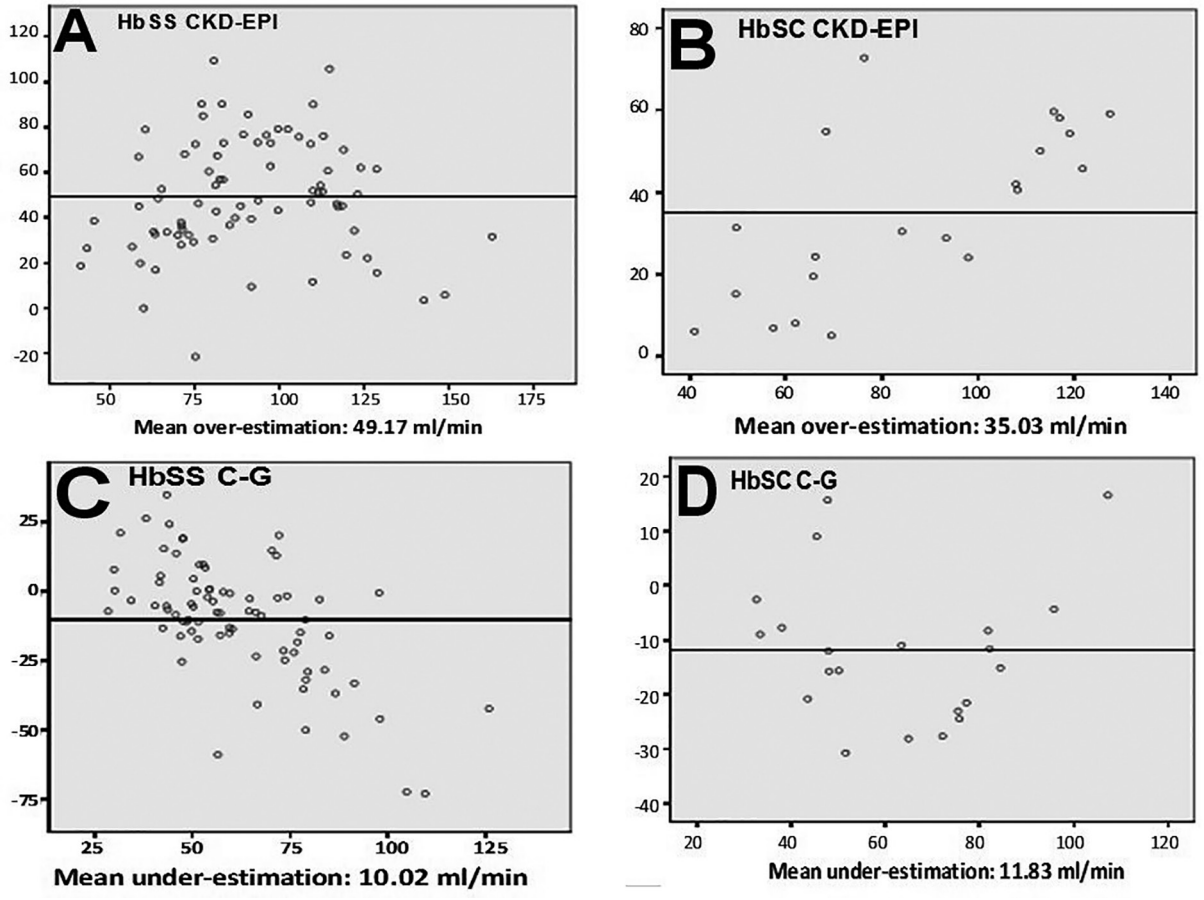
	HbSS (n = 79)	HbSC (n = 21)
	Means ± SD (ml/min/1.73m^2)	
Measured GFR	66.28 ± 27.52	97.04 ± 17.47
CKD-EPI GFR	115.44 ± 28.98	108.78 ± 30.76
C-G GFR	56.26 ± 15.03	57.55 ± 17.46

Table 2: The distribution of estimated GFR of subjects using the KDIGO 2012* nomenclature

KDIGO Class		eCrCl	HbSS	%	HbSC	%
G5	Kidney failure	<15	0	0.0	0	0.0
G4	Severely decreased	15–29	0	0.0	0	0.0
G3b	Moderately to severely decreased	30–44	0	0.0	1	4.8
G3a	Mildly to moderately decreased	45–59	3	3.8	1	4.8
G2	Mildly decreased	60–89	17	21.5	6	28.6
G1	Normal or high	≥90	59	74.7	13	61.9

*KDIGO, Kidney disease improving global outcomes. Kidney Int. Suppl. (2013) 3(1):136–150.

Fig. 1



Bland–Altman analysis of measured versus estimated glomerular filtration rate (eGFR) using CKD-EPI and Cockcroft–Gault (C–G) formulae. The Bland–Altman plots for heterozygous haemoglobin SC (b, d) and homozygous haemoglobin SS (a, c) show overestimation of the measured GFR by the CKD-EPI formula (a, b), whereas the C–G formula underestimates the measured GFR (c, d).

Table 3: Correlation of Measured and calculated GFR in HbSS and HbSC

Subjects		Measured GFR/CKD-EPI	Measured GFR/C-G
HbSS (*n* = 79)	R value	0.598	0.667
	P-value	<0.001	<0.001
HbSC (*n* = 21)	R value	0.848	0.819
	P-value	<0.001	<0.001

patients. Arlet *et al.* [21] reported eGFR by the CKD-EPI formula (in SCD patients aged between 18 and 67.5 years) as having the best correlation with measured GFR using the iohexol plasma clearance method, and thus recommended it be used for eGFR in SCD patients of non-Afro-American origin [21]. Similarly, Asnani *et al.* [22] compared eGFR derived from CKD-EPI, the C–G and the MDRD formulae with measured GFR using a ^{99m}Tc-DTPA nuclear renal scan in a cohort of Jamaican sickle cell anaemia patients. They observed that eGFR based on the CKD-EPI formula showed a better correlation with measured GFR.

Our study showed that the CKD-EPI formula consistently overestimated GFR in HbSS and HbSC patients by an average of 49.19 and 11.7 ml/min, respectively. Interestingly, GFR overestimation was less in HbSC than in HbSS patients. Asnani *et al.* [22] had similarly noted GFR overestimation in HbSS patients using the CKD-EPI formula by a mean of 41.2 ml/min. In our HbSS patients, both formulae correlated significantly with measured creatinine clearance, even though the C–G formula performed better (r = 0.667 vs. 0.598). Similarly, both formulae correlated significantly with measured creatinine clearance in our HbSC patients, although the CKD-EPI formula seemed to be better (r = 0.848 vs. 0.819).

Our finding in HbSS patients is in contrast with the reports of Arlet *et al.* [21] and Asnani *et al.* [22], both of which alluded to the superiority of the CKD-EPI formula in SCD patients. Although this discrepancy may reflect a true difference in patient populations as our patients were mainly from the Yoruba tribe of south-west Nigeria, the patients in the two studies alluded to above were mainly from the Caribbean. An increasing body of evidence has identified tribal (because of genetics) differences in GFR in health and disease [27–29]. In addition, it is important to note that different reference methods of GFR measurement were also used in these studies. Evaluation of tribal differences in GFR (and possibly its genetic determinants) among Nigerian patients could therefore be a subject of further research.

In conclusion, our study confirms that the CKD-EPI formula offers a good measure of GFR estimation in Nigerian SCD patients, although it slightly overestimates GFR measured by creatinine clearance. In addition, the CKD-EPI did not perform significantly better than the C–G formula in our cohort of patients. Some limitations of this study include the fact that reference markers such as inulin, ^{125}I-iothalamate, iohexol, technetium, diethylene triaminepentaacetic acid and chromium ethylene diaminetetraacetic acid, which are known to be superior to creatinine clearance, could not be used for GFR determination because of lack of facilities for them locally. Similarly, the diagnosis of SCD using haemoglobin electrophoresis alone could fail to detect patients with concurrent α-thalassaemia.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

References

1 Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, Klug PP. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994; **330**:1639–1644.

2 Abdu A, Emokpae MA, Uadia PO, Kuliya-Gwarzo A. Proteinuria among adult sickle cell anemia patients in Nigeria. Ann Afr Med 2011; **10**:34–37.

3 López Revuelta K, Ricard Andrés MP. Kidney abnormalities in sickle cell disease. *Nefrologia* 2011; **31**:591–601.

4 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**:614–620.

5 Serjeant GR, Higgs DR, Hambleton IR. Elderly survivors with homozygous sickle cell disease. *N Engl J Med* 2007; **356**:642–643.

6 Kopple JD. National kidney foundation K/DOQI clinical practice guidelines for nutrition in chronic renal failure. *Am J Kidney Dis* 2001; **37**:S66–S70.

7 Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function – measured and estimated glomerular filtration rate. *N Engl J Med* 2006; **354**:2473–2483.

8 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; **16**:31–41.

9 Ajayi AA. Estimation of creatinine clearance from serum creatinine: utility of the Cockroft and Gault equation in Nigerian patients. *Eur J Clin Pharmacol.* 1991; **40**:429–431.

10 Sanusi AA, Akinsola A, Ajayi AA. Creatinine clearance estimation from serum creatinine values: evaluation and comparison of five prediction formulae in Nigerian patients. *Afr J Med Med Sci* 2000; **29**:7-11.

11 Adegoke AO, Aneke JC, Oyekunle AA, Nouraie SM, Sanusu AA, Akinola NO, Durosinmi MA. Evaluation of the performance of predictive formulae in the assessment of glomerular filtration rate in patients with sickle cell disease. *Ann Trop Pathol.* 2012; **3**:9–15.

12 Thompson J, Reid M, Hambleton I, Serjeant GR. Albuminuria and renal function in homozygous sickle cell disease: observations from a cohort study. *Arch Intern Med* 2007; **167**:701–708.

13 Haymann JP, Stankovic K, Levy P, Avellino V, Tharaux PL, Letavernier E, *et al.* Glomerular hyperfiltration in adult sickle cell anemia: a frequent hemolysis associated feature. *Clin J Am Soc Nephrol* 2010; **5**:756–761.

14 Aparicio SA, Mojiminiyi S, Kay JD, Shepstone BJ, de Ceulaer K, Serjeant GR. Measurement of glomerular filtration rate in homozygous sickle cell disease: a comparison of ^{51}Cr-EDTA clearance, creatinine clearance, serum creatinine and beta 2 microglobulin. *J Clin Pathol* 1990; **43**:370–372.

15 Aygun B, Mortier NA, Smeltzer MP, Hankins JS, Ware RE. Glomerular hyperfiltration and albuminuria in children with sickle cell anemia. *Pediatr Nephrol* 2011; **26**:1285–1290.

16 Itoh K. Determination of glomerular filtration rate by means of newly developed plastic scintillation counter both with and without dilution procedures. *J Nucl Med* 2001; **42**:1484–1488.

17 Phuong-Thu TP, Phuong-Chi TP, Alan HW, Susie QL. Renal abnormalities in sickle cell disease. Kidney Int 2000; **57**:1–8.

18 Walker BR, Alexander F, Birdsall TR, Warren RL. Glomerular lesions in sickle cell nephropathy. *JAMA* 1971; **215**:437–440.

19 Levey AS, Coresh J, Balk E, Kausz AT, Levin A, Steffes MW, *et al.*, National Kidney Foundation National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Intern Med* 2003; **139**:137–147.

20 Eastwood JB, Kerry SM, Plange-Rhule J, Micah FB, Antwi S, Boa FG, *et al*. Assessment of GFR by four methods in adults in Ashanti, Ghana: the need for an eGFR equation for lean African populations. *Nephrol Dial Transplant* 2010; **25**:2178–2187.

21 Arlet JB, Ribeil JA, Chatellier G, Eladari D, De Seigneux S, Souberbielle JC, *et al.* 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 Nephrol* 2012; **13**:83.

22 Asnani MR, Lynch O, Reid ME. Determining glomerular filtration rate in homozygous sickle cell disease: utility of serum creatinine based estimating equations. *PLoS One* 2013; **8**:e69922.

23 Lascano ME, Poggio ED. Kidney function assessment by creatinine-based estimation equations. Kidney 2010;**2**:58.

24 Burtis CA, Ashwood ER. *Tietz fundamentals of clinical chemistry*. Philadelphia: W.B. Saunders Company; 2001.

25 Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med* 1987; **317**:1098.

26 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney inter., Suppl. 2013;**3**: 1–150.

27 Fox CS, Yang Q, Cupples LA, Guo CY, Larson MG, Leip EP, *et al*. Genomewide linkage analysis to serum creatinine, GFR, and creatinine clearance in a community-based population: the Framingham Heart Study. *J Am Soc Nephrol* 2004; **15**:2457–2461.

28. Hunter DJ, Lange Md, Snieder H, MacGregor AJ, Swaminathan R, Thakker RV, Spector TD Genetic contribution to renal function and electrolyte balance: a twin study. *Clin Sci (Lond)* 2002; **103**:259–265

29 Bathum L, Fagnani C, Christiansen L, Christensen K. Heritability of biochemical kidney markers and relation to survival in the elderly – results from a Danish population-based twin study. *Clin Chim Acta* 2004; **349**:143–150.