Evaluation of the Performance of Predictive Formulae in the Assessment of Glomerular Filteration Rate in Patients with Sickle Cell Disease

*Adegoke AO[1], Aneke JC[2], Oyekunle AA[2], Nouraie SM[3], Sanusi AA[4], Akinola NO[2] and Durosinmi MA[2]

[1.]Department of Chemical Pathology, Obafemi Awolowo University, Ile-Ife, Nigeria.
[2.]Department of Heamatology, Obafemi Awolowo University, Ile-Ife, Nigeria.
[3.]Department of Medicine and Centre for Sickle Cell Disease, Howard University, Washington DC, USA.
[4.]Department of Medicine, Obafemi Awolowo University, Ile-Ife, Nigeria

Abstract

Background: *The magnitude of sickle cell nephropathy is high. Creatinine clearance is perhaps the best means to determine the severity of renal impairment in resource limited economies. With the various sources of errors inherent in the process of collecting timed urine for clearance studies, it is imperative to find alternative means of assessing the status of renal function. Predictive formulae have not been studied in Nigerians with sickle cell disease (SCD).*

Objective: *To evaluate five commonly used predictive formulae to estimate glomerular filtration rate (GFR) in patients with sickle cell disease in the out-patient setting. Also to determine if any predictive formulae can be used in place of the measured value.*

Methods: *Consecutive SCD patients, who attended the haematology outpatient clinic of the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), were recruited into the study over a seven-month period. Those on medications that can interfere with renal function were excluded. Demographic details were collected and recorded. Blood and 24-hour urine samples were analyzed for serum and urinary creatinine, and creatinine clearance. The latter was compared with glomerular filtration rates estimated from five predictive formulae.*

Results: *One hundred SCD patients (including 79 HbSS and 21 HbSC patients) were studied. The mean age was 26.2 ± 7.4 years and 54% were females. The highest agreement was between measured GFR and Cockcroft-Gault (CG) estimates (k = 0.50), followed by Mawer (k = 0.49), Hull (k = 0.26), Gates (k = 0.21) and MDRD (k = 0.02). Using the Bland-Altman technique, the Hull (mean = -15 ± 55) and MDRD (mean = -48 ± 61) formulae significantly underestimated GFR while the Mawer (mean = 8 ± 39) and CG (mean = -10 ± 39) formulae overestimated GFR. The Gates formula (mean = 0.6 ± 54) showed no difference with measured GFR.*

Conclusion: *If we rely on the serum creatinine and the predictive formulae that are commonly in use, the status of renal function many patients with sickle cell disease will be inappropriately classified. However the CG formula may be used with the understanding of its limitation.*

Keywords: *Creatinine clearance, sickle cell disease, predictive formulae.*

No conflicts of interest have been declared by the authors

Introduction

Many patients with sickle cell disease (SCD) develop organ damage and any organ may be affected including the kidneys[1,2]. The disease may result in both renal functional disturbances as well as anatomical alterations. Therefore, monitoring of renal function parameters is key to prevention of end-stage renal disease[3]. In a group of patients studied in South-West Nigeria, it was noted that 50% had albuminuria while 31% had glomerular hyperfilteration[4]. Among the latter, 25%, 42% and 3% had stages 1, 2 and 3 chronic kidney disease, respectively. Similarly, Arogundade et al., while alluding to the magnitude of renal dysfunction in SCD, noted that 37% of a population of cohorts studied had significant renal impairement[5].

The most common method for assessing glomerular filteration rate (GFR) is performing a timed urine collection for evaluation of creatinine clearance (CC). This test is cumbersome and inconvenient and prone to errors due mainly to inaccuracy in the urine collection. Recently, calculation of estimated GFR using mathematical derivations has been advocated as a simple and reliable means of assessing kidney function. Many GFR prediction equations that take into account the serum creatinine, age, gender and body weight have shown sufficient precision[6,7]. There are no fewer than 46 different equations currently available, although the two most commonly used are the Cockroft-Gault (CG) and the modification of diet in renal disease (MDRD) formulae[8]. The objective of this study is to evaluate and compare five predictive formulae for GFR with measured value in Nigerian patients with sickle cell disease (SCD).

Patients and Methods

All consecutive patients with SCD, aged 15 years and above, in steady state condition, were recruited from the haematology outpatient clinic of the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC), Ile-Ife. The study was approved by the research and ethics committee of the hospital and participation was voluntary. Each participant was physically examined, and height and weight were determined. The body surface area (BSA) was calculated using the Mosteller formular[9], while body mass index (BMI) was calculated using the standard formula,

$$\frac{\text{Weight(kg)}}{\text{Height}^2\text{(m)}}$$

Exclusion Criteria

Patients on dialysis, those with massive oedema and patients on medications that may interfer with renal function such as cimetidine and probenecid were excluded.

Sample collection and preparation

Venous blood samples were collected after an overnight fast (12 – 14 hours) into plain bottle, and allowed to clot. It was centrifuged at 500g for 15 minutes. The serum was separated and stored at – 200C until laboratory analysis. Serum and urinary creatinine measurements were performed by the Jaffe alkaline picrate method10. In the Jaffe reaction, creatinine in the test sample reacts directly with picric acid, in an alkaline medium to form a deep yellow complex. The working reagent consists of an equal mix of sodium Hydroxide (NaOH) and picric acid, 1ml of which is added to 100µl of standard/sample and mixed. The absorbance at 500nm wavelength of both test sample and standard was read off a spectrophotometer at 30 seconds and then at 120 seconds. The concentration of creatinine is obtained from the equation:

$$\frac{\text{Absorbance of sample x Concentration of standard}}{\text{Absorbance of standard}}$$

Statistical Analysis

SPSS version 9 was used for the inferential statistics. Values are given as mean ± standard deviation. We used a paired sample t-test to compare the calculated creatinine clearance with the measured values.

Twenty-four-hour urine creatinine clearance was used as the reference method for GFR calculation. Renal function categories were in 3 groups: group 1: GFR > 90 ml/min; group 2: GFR 60-90 ml/min and group 3 : GFR < 60 ml/min. The estimated GFR was calculated according to the following five formulae: Cockroft-Gault, Hull, Mawer, Gates and the MDRD; and subsequently adjusted for the BSA. According to this classification, Kappa (k) statistics was applied to measure the agreement between the five GFR estimates and measured GFR. We also used the Bland-Altman method[11] to assess the agreement between the GFR estimates and measured GFR.

Results

A total of one hundred sickle cell patients (40 men, 60 women) were studied. The median age was 26 (range, 15-56) years (Table 1). Pairwise comparison showed a statistically significant difference between the calculated parameters and the measured GFR, except that from the Gates formula (Table 2). Based on measured GFR, 17% had GFR > 90 ml/min, 37% had GFR 60-90 ml/min, 42% had GFR 30-59 ml/min and 4% had 15-29 ml/min. No patients had a GFR below 15 ml/min. The highest agreement was between measured GFR and Cockcroft-Gault estimates (k = 0.50) followed by Mawer (0.49), Hull (k = 0.26), Gates (k = 0.21) and MDRD (k = 0.02). The difference between each estimated and measured GFR was increased in lower GFR values (figure 1). Two formulae including the

Table 1. Demographic and clinic characteristics of study

Parameter	SCD (n = 100)	HbSS (n = 79)	HbSC (n = 21)
Age (years)	26.2 ± 7.4	25.3 ± 6.7	29.3 ± 8.9
Wt (kg)	51.9 ± 10.47	49.4 ± 9.0	61.2 ± 11.7
BMI (kg/m2)	19.5 ± 3.9	18.3 ± 2.5	23.7 ± 5.1
Serum creatinine (μmol/ml)	83.0 ± 22.1	82.0 ± 20.4	88.7 ± 27.8
Urine creatinine (μmol/ml)	3949 ± 2190	3813 ± 2120	4457 ± 2422

Table 2. Comparison of GFR methods in study population (n = 100)

Methods	Mean	SD	p*
Measured Creatinine clearance (ml/min)	66.80	26.36	
Gates (ml/min/m2)	66.24	28.31	<0.9
Cockroft-Gault (ml/min/m2)	56.40	16.68	<0.001
Mawer (ml/min/m2)	58.38	17.47	<0.007
Hull (ml/min/m2)	81.98	27.48	<0.001
MDRD (ml/min/m2)	115.15	39.84	<0.001

**From paired sample t-test for comparing the methods mean.*

Fig. 1: The difference of measured GFR and estimated GFR by using the Hull, MDRD, Cockroft-Gault (CG), Mawer, and Gates formulae. The horizontal lines indicate the mean difference in each graph.

Hull (mean = -15 ± 55) and MDRD (mean = -48 ± 61) underestimated the GFR. The Mawer (mean = 8 ± 39) and the Cockcroft-Gault (mean = -10 ± 39) formulae on the other hand overestimated the GFR, while the Gates (mean = 0.6 ± 54) showed no difference between the estimated and the measured GFR (figure 1).

Discussion

Many scientists have recommended the use of equations that estimate the GFR to facilitate the detection, evaluation, and management of chronic kidney disease[12]. Indeed, many clinical laboratories already report estimated GRF values whenever the serum creatinine level is measured.

The estimation of GFR is ideally performed using inulin or 125 I-iothalamate clearance methods. However these methods are expensive, time-consuming, technically complicated and impractical in the clinical setting. Cystatin-C, a low-molecular-weight plasma protein, has been proposed as the substitute for creatinine for the estimation of GFR. Although some researchers have found cystatin-C to be a more accurate marker of GFR, others have suggested that it does not show clear advantages over creatinine, necessitating further studies[13]. Errors in creatinine measurement itself might be due to laboratory variabilities,[14] prompting some nephrologists to advocate for population-specific adjustments of the GFR equations[15].

Creatinine clearance measurement through a 24-hour urine collection, despite its many disadvantages (i.e. improper urine collection and overestimation of GFR due to kidney tubular secretion of creatinine), is the closest measurement one can get to the real GFR in the clinical setting. This method is considered by several experts to be the preferred clinically-relevant method of GFR estimation[16]. On many occasions in clinical practice, a fast and reliable estimate of the GFR is required. We observe that the CG equation approximates well to the measured GFR in our cohorts.

While some studies[17,18] confirmed that the MDRD equation is better than the CG, we are unable to demonstrate this. One of the most important practical uses of a GFR predictive formula is for early diagnosis of renal malfunction. Levey *et al*,[19] demonstrated that the four-variable (4v)-MDRD formula is better than the CG formula, as it does not include body weight in its derivation. This is in contrast to our study which shows that the CG has an edge over the other four formulae. Our findings are similar to the independent works of Owiredu, Sanusi and Abefe *et al* [20, 21,22] whose cohorts were patients with chronic kidney disease.

Recommendations for evaluating people at increased risk of kidney disease are to measure urine albumin and to estimate the GFR with an equation, based on the level of serum creatinine and estimating equation for GFR have been developed chiefly in study populations consisting predominantly of patients with chronic kidney disease[23]. Both the MDRD study and the CG equations have been reported to be less accurate in populations without chronic kidney disease[24]. Among healthy Ghanaians, Eastwood et al demonstrated that muscle mass caused a considerable difference between the values of creatinine clearance obtained from using a 24-hour urine collection and that estimated, most especially with the 4v-MDRD and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[25]. In this wise, they advocated an equation appropriate for the lean population of Africa. Of all the formulae, the CG formula is that which gives the value closest to the measured value in our cohort of SCD patients.

Late referral to nephrologists before the initiation of dialysis is associated with increased rates of morbidity and mortality[26]. It is therefore important to refer early any patient with impaired renal function to nephrologists for co-management. The guidelines of the National kidney foundation recommend that the prediction equations are useful estimates of GFR[27].

This study is limited by the use of creatinine clearance rather than inulin

clearance. Radioisotopic methods provide acceptable alternatives, but are time-consuming, expensive and largely unavailable in Nigerian hospitals. We also did not apply measurement at different age groups and levels of renal function.

Conclusion

We have demonstrated that a good estimation of renal function in patients with SCD can be assessed using the Cockroft-Gault formula. Among other formulae, it provides a fast means of estimating the GFR.

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