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Short Communication

Evaluation of CKD-EPI and MDRD Prediction Equations for Estimation of GFR in Lean and Obese Bangladeshi Subjects

M. Saiedullah[1*], S. Begum[1], M. R. Rahman[2], M. A. H. Khan[3], S. Hayat[1], S. M. Kamaluddin[1], M. A. H. Shaheen[4]

[1]Department of Biochemistry, Bangladesh Institute of Health Sciences & Hospital, Mirpur, Dhaka, Bangladesh

[2]Department of Biochemistry, Delta Medical College, Mirpur, Dhaka, Bangladesh

[3]Department of Biochemistry, Enam Medical College, Savar, Dhaka, Bangladesh

[4]Department of Internal Medicine, Bangladesh Institute of Health Sciences & Hospital, Mirpur, Dhaka, Bangladesh

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Abstract

Glomerular filtration rate (GFR) is the filtrate produced by the kidneys in each minute. Chronic kidney disease epidemiology (CKD-EPI) and standardized modification of diet in renal disease (MDRD) equations are the commonly used equations to estimate GFR. Evaluation of GFR prediction equations regarding body mass index is not available in Bangladeshi population. In this study we compared estimated GFR (eGFR) with GFR measured by creatinine clearance rate (CCR) in lean and obese Bangladeshi subjects. Measured GFR were 40±21 and 45±22 ml/min/1.73m^2 in lean and obese groups, respectively. Compared to measured GFR, estimated GFRs were 7.5 (p<0.0001), 5.2 (p<0.0001) ml/min/1.73m^2 higher for CKD-EPI and MDRD four variables (MDRD4) equations in lean group and 6.9 (p<0.0001), 3.2 (p>0.05) ml/min/1.73 m^2 higher for CKD-EPI and MDRD4 equations in obese group. The precision (r^2) was 0.6461 for CKD-EPI, 0.6508 for MDRD4 equations in lean group and 0.6337 for CKD-EPI and 0.6021 for MDRD4 equations in obese group. The percentages of eGFR falling within 15% measured GFR were 37 for CKD-EPI, 52 for MDRD4 in lean group; 41 for CKD-EPI, 39 for MDRD4 in obese group. CKD-EPI equation overestimates GFR in both lean and obese, but MDRD4 equation overestimates GFR only in lean Bangladeshi subjects.

Keywords: eGFR; Estimated GFR; Lean, Obese; CKD-EPI; MDRD4; CCR; Bangladeshi population.

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1. Introduction

Glomerular filtration rate (GFR) is an established marker of kidney function. The GFR can be precisely measured by using the filtration markers inulin, [^{125}I]iothalamate, ^{51}Cr-

* *Corresponding author*: md.saiedullah@gmail.com

ethylenediaminetetraacetic acid, ^{99m}Tc-diethylenetriaminepentaacetic acid and iohexol [1]. These exogenous markers are expensive and cumbersome to use and may involve radioactivity, which requires special handling and disposal. Moreover, measurement of GFR by these standard methods requires hospitalization of the patient, injection and a complex collection protocol, and it is time consuming, labor-intensive procedure and so not suitable for the detection of chronic kidney disease (CKD) in clinical practice. In clinical practice, GFR is estimated by measuring serum creatinine and twenty four hours creatinine excretion since it gives measures similar to inulin clearance rate. The inconvenience of a timed urine collection, inappropriate specimen collection, wider intra-individual variability and tubular secretion of creatinine limit the usefulness of this procedure. Alternatively, GFR can be estimated using prediction equations that incorporate serum creatinine concentration with demographic and clinical variables such as age, gender, race, and body size [2-11]. Of these, probably the most frequently used formulas are the Cockcroft and Gault equation [2] and the Modification of Diet in Renal Disease (MDRD) study equation [3-5]. The original MDRD study equation [3] was developed by using 1628 patients with predominantly nondiabetic kidney disease. It was based on six variables (age, sex, ethnicity and serum creatinine, urea and albumin concentrations). Subsequent simplification [4] and standardization of serum creatinine measurement (traceable to isotope-dilution mass spectroscopy, IDMS), MDRD four variables equation was reexpressed [5]. Previously, serum creatinine concentrations were measured by alkaline picrate kinetic method in the original MDRD study (1988 – 1994) with the Beckman Synchron CX3, which were reassayed in 2004 with the same instrument by enzymatic kinetic technique traceable to IDMS. Due to imprecision and systematic underestimation of measured GFR at higher levels (GFR>90 ml/min/1.73m^2) of the standardized four variables equation [12], a more accurate prediction equation, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [6] was developed and validated in the US population using data of 12,150 subjects. The CKD-EPI equation was developed using log transformed measured GFR, log transformed serum creatinine concentrations (modeled as a two-slope linear spline with sex-specific knots at 0.7 mg/dl in women and 0.9 mg/dl in men) with sex, race and age on the natural scale. The CKD-EPI equation was shown to be as accurate as standardized four variables MDRD (MDRD4) equation at GFR<60 ml/min/1.73m^2 and substantially more accurate at GFR>60 ml/min/1.73m^2. Compared to MDRD4 equation, concordance of estimated and measured GFR stages was significantly higher for the CKD-EPI equation (69% vs 64%) [6].

Evaluation of the performance of CKD-EPI and standardized MDRD4 equations in African lean population showed that both CKD-EPI and MDRD4 equations overestimate GFR compared to GFR measured by creatinine clearance rate [13]. In Indian [14] and Pakistani [15] populations estimated GFR are significantly higher than measured GFR, whereas both equations underestimate GFR in Thai population [16]. Significant differences between estimated GFR and measured GFR were also observed in Japanese [17] and Korean populations [18]. On the other hand, study on multiethnic Asian

population [19] demonstrated better performance of CKD-EPI equation than MDRD equation without ethnic adjustment. CKD-EPI equation was also shown to be accurate enough for the prediction of GFR in Chinese population without ethnic coefficient adjustment [20].

CKD-EPI and MDRD4 equations are independent of body mass index (BMI) or muscle mass and errors of prediction equations vary with ethnicity [6,10, 16-18], and BMI [21]. To improve the performance of prediction equations, Asian investigators subsequently have derived coefficient for their populations [10, 16-18, 22]. Evaluation of the performance of CKD-EPI and standardized 4 variables MDRD prediction equations in lean or obese Bangladeshi human subjects is not found. In this study we aimed to compare estimated GFR with GFR measured by creatinine clearance rate in lean and obese Bangladeshi subjects.

2. Materials and Methods

This cross-sectional study was carried out in the Department of Biochemistry, Bangladesh Institute of Health Sciences (BIHS) & Hospital, Dhaka, Bangladesh during the period of September 2009 to August 2011. We included 278 Bangladeshi subjects referred for the estimation of GFR from the department of Internal Medicine, BIHS. Verbal consent was taken from the patients before collection of anthropometric data and specimens. Subjects were requested to collect 24 hours urine in the supplied container. At the end of urine collection, three milliliters of venous blood specimens were collected in fasting state and serum was separated for the estimation of serum creatinine. Serum creatinine and 24-hours urinary creatinine were measured on the same day by an enzymatic kinetic technique using VITROS CREA Slides (calibration is traceable to isotope-dilution mass spectroscopy) with Vitros-250 Chemistry System (Ortho-Clinical Diagnostics, Inc., USA). GFR was measured from serum creatinine and 24-hours urinary creatinine excretion according to Eq. 1 and adjusted for body surface area according to Eq. 2 [24]. GFR was also estimated by standardized Chronic Kidney Disease Epidemiology study (CKD-EPI) (Eq. 3, [6]) and Modification of the Modified Diet and Renal Disease study (MDRD) four variables standardized prediction equation for non-black (Eq. 4, [5]). Results were expressed as mean±SD and compared by two-tailed paired *t* test, precision (r^2), area under the receiver-operating characteristic (ROC) curve and accuracy within 15%, 30% and 50% of the measured GFR. For statistical analysis, GraphPad Prism version 5.04 for Windows and MedCalc® version 11.4 for Windows were used. The equations used to determine CCR, BSA and eGFR are as follows:

$$\text{CCR} = \frac{\text{UC (mg/dl)}}{\text{SC (mg/dl)}} \times \frac{\text{24h urine volume (ml)}}{1440} \times \frac{1.73\,\text{m}^2}{\text{BSA}} \quad (1)$$

where UC= concentration of urine creatinine, SC = concentration of serum creatinine.

$$\text{BSA} = (\text{Height in cm})^{0.725} \times (\text{Weight in kg})^{0.425} \times 0.007184 \quad (2)$$

$$GFR_{CKD\text{-}EPI} = 141\times\min(Scr/k,1)^{\alpha}\times\max(Scr/k,1)^{-1.209}\times 0.993^{Age}\times 1.018 \text{ (if female)} \quad (3)$$

where k = 0.7 for females and 0.9 for males, α = -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or 1, max indicates the maximum of Scr/k or 1.

$$GFR_{MDRD4} = 175\times \text{standardized } Scr^{-1.154}\times Age^{-0.203}\times 0.742 \text{ (if female)} \quad (4)$$

3. Results

The mean age of the study subjects was 57±10.9 years (range: 28–87 years). Of the total patients, 133 (48%) subjects were male and 145 (52%) subjects were female. The mean±SD of serum creatinine and measured GFR were 1.64±0.88 mg/dl (range: 0.54–9.73 mg/dl) and 43±23 ml/min/1.73m^2 (range: 4–109 ml/min/1.73m^2). Among the study subjects, 220 (79%) had CKD (GFR<60 ml/min/1.73m^2). The mean±SD of BMI was 26.35±4.50 (range: 13.99 – 42.15) kg/m^2 and 116 (42%) had BMI<25 kg/m^2 (lean) and 54 (19%) had BMI>30 kg/m^2 (obese).

In the total study subjects (n=278), GFR estimated by CKD-EPI and standardized MDRD4 equations were 50±25, 47±23 ml/min/1.73m^2, respectively. The correlation coefficients of measured GFR with the estimated GFR were 0.8308 (p<0.0001), 0.8200 (p<0.0001), respectively.

Table 1. Comparison of estimated GFR with measured GFR in lean and obese groups.

	Lean (n=116)		Obese (n=54)	
Measured GFR (ml/min/1.73m^2)	40±21		45±22	
Equations	$GFR_{CKD\text{-}EPI}$	GFR_{MDRD4}	$GFR_{CKD\text{-}EPI}$	GFR_{MDRD4}
eGFR (Mean±SD, ml/min/1.73m^2)	48±22*	45±20*	52±27*	48±25^{ns}
Mean difference (ml/min/1.73m^2)	-7.5	-5.2	-6.9	-3.2
Precision, r^2	0.6461	0.6508	0.6337	0.6021
AUC	0.945	0.940	0.863	0.877
Accuracy				
Within 15% of measured GFR	43(37%)	60(52%)	22(41%)	21(39%)
Within 30% of measured GFR	76(65%)	84(73%)	36(67%)	39(73%)
Within 50% of measured GFR	96(83%)	95(83%)	45(84%)	48(90%)

Table 1 shows the descriptive statistics of estimated GFR with measured GFR in lean and obese groups. The mean value of measured GFR was 40±21, 45±22 ml/min/1.73 m^2 in lean and obese groups respectively. The correlation coefficient of CKD-EPI and MDRD4 eGFR with measured GFR were 0.8067 (p<0.0001), 0.8038 (p<0.0001) in lean group and 0.8007 (p<0.0001), 0.7794 (p<0.0001) in obese group respectively. Comparison of receiver-operating characteristic curves at GFR cut-off value of 60

ml/min/1.73m^2 between CKD-EPI and MDRD4 equations in lean and obese groups is presented in Fig. 1. Differences between areas under ROC curves of CKD-EPI and MDRD4 equations were not significant in both groups (Fig. 1).

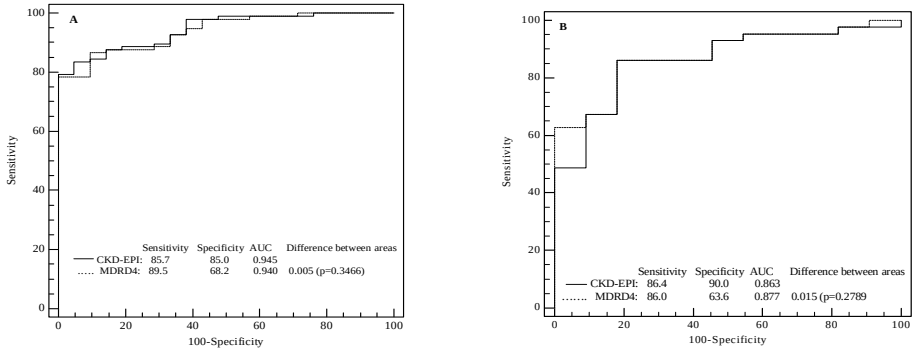

Fig. 1. Receiver-operating characteristic curves for CKD-EPI and MDRD4 equations in lean (A) and obese (B) groups.

At the cut-off value GFR= 60 ml/min/1.73 m^2, the area under the ROC curve (AUC) was 0.945 (p<0.0001), sensitivity was 85.7% and specificity was 85.0% for CKD-EPI equation and the AUC was 0.940 (p<0.0001), sensitivity was 89.5% and specificity was 68.2% for MDRD4 equation in lean group. In obese group, AUC was 0.863 (p<0.0001), sensitivity was 86.4% and specificity was 90.0% for CKD-EPI and the AUC was 0.877 (p<0.0001), sensitivity was 86.0% and specificity was 63.6% for MDRD4 equation. In lean group, the predictive value of positive test (PV^+) was 96.6% for CKD-EPI and 92.3% for MDRD4 equation, and the negative predictive value (PV^-) was 54.8% for CKD-EPI equation and 57.7% for MDRD4 equation. In obese group, PV^+ was 97.4% for CKD-EPI and 90.2% for MDRD4, and PV^- was 60% for CKD-EPI and 53.8% for MDRD4 equation.

4. Discussion

The CKD-EPI and MDRD equations for the estimation of GFR have been developed using data of Caucasian and African-American populations [5,6]. Recent studies have shown that the calculation of eGFR derived from non-Asian populations for Asian population without prior validation could result inaccurate estimation of GFR [14-18]. The inaccuracy may be due to the diversity of anthropometry, socioeconomic status and dietary intake. In this context, the current study was undertaken to evaluate the performance of CKD-EPI and standardized four variables MDRD equations in lean and obese Bangladeshi subjects.

In this study, both CKD-EPI and MDRD4 eGFR showed statistically significant correlation with measured GFR in the total, lean and obese subjects (p<0.0001). In lean group, compared to measured GFR, estimated GFR were 7.5 and 5.2 ml/min/1.73m^2 higher for CKD-EPI and MDRD4 prediction equations respectively and these are

statistically significant (p<0.0001, Table 1). In obese group, eGFR was significantly higher for CKD-EPI (6.9 ml/min/1.73m^2, p<0.0001) but no significant difference between eGFR and measured GFR was observed for MDRD4 equation (p>0.05, Table 1). In lean group, precision (r^2) is better, area under the receiver-operating characteristic curve is similar and accuracy within 15% of measured GFR is better for MDRD4 than CKD-EPI equation (Table 1). In the obese group, precision (r^2) is better for CKD-EPI than MDRD4 but AUC is similar and accuracy within 15%, 30% and 50% of measured GFR is better for MDRD4 than CKD-EPI equation (Table 1). Regarding mean difference and accuracy, performance of MDRD4 equation is better than CKD-EPI equation in both lean and obese subjects, whereas regarding sensitivity and specificity, positive and negative predictive values CKD-EPI equation is better than MDRD4 equation in both groups. Since GFR is a quantitative measure of kidney function rather than qualitative, MDRD4 appears to give GFR values closer to measured GFR compared to CKD-EPI equation in lean or obese Bangladeshi subjects.

As in the study of Eastwood *et al.* [13], our data showed that CKD-EPI and MDRD4 variables standardized equations overestimated GFR compared to adjusted creatinine clearance rate in lean Bangladeshi subjects. It is also consistent with the study of Srinivas *et al.* [14] in which the study subjects were healthy kidney donors with low body surface area (also low BMI). Moreover, 18% of study subjects were Bangladeshi in the study of Srinivas *et al.* [14]. Jafar *et al.* [15] also reported the overestimation of GFR in Pakistani population. Low muscle mass, dietary protein intake, nutritional status, method of creatinine estimation or lack of standard method for the estimation of GFR may be related to the differences between measured GFR and estimated GFR in our study population. Though serum and urinary creatinine concentrations were measured by an enzymatic kinetic method (calibration is traceable to IDMS), the GFR was measured by creatinine clearance rate. Moreover, compared to inulin clearance rate, overestimation of GFR by creatinine clearance rate is common in CKD patients with low GFR [23]. Hence, the true GFR in our study subjects may be lower than that estimated by creatinine clearance rate and the mean differences between measured GFR and estimated GFR may be higher than the values obtained in this study.

So the overestimation of GFR by CKD-EPI and MDRD4 equations requires to be considered for the assessment of kidney function in lean or obese Bangladeshi population. Validation of these prediction equations using gold standard methods is required before use in clinical practice.

5. Conclusion

The performance of MDRD4 equation is better than the performance of CKD-EPI equation in both lean and obese subjects. In lean subjects, both equations overestimate GFR whereas only CKD-EPI equation overestimates GFR in obese Bangladeshi subjects.

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