Comparison of serum creatinine-based estimating equations with gates protocol for predicting glomerular filtration rate in indian population

A. V. Mulay[1,2], S. M. Gokhale[3]

[1]Department of Nephrology, Dialysis Unit, Inlaks and Budhrani Hospital, [2]Kidney Research and Support Network Trust, [3]Department of Nuclear Medicine, Inlaks and Budhrani Hospital, Pune, Maharashtra, India

ABSTRACT

In clinical practice, serum creatinine-based predicting equations and Gates protocol based on gamma camera imaging of kidneys after injection of Tc99m-diethylenetriaminepentaacetic acid (DTPA) are commonly used to assess glomerular filtration rate (GFR). Comparison of these methods, especially the chronic kidney disease-epidemiology collaboration (CKD-EPI) equation with gold standard method of assessment of GFR by plasma clearance of Tc-99mDTPA is not well-studied in Indian population. We conducted this study to compare GFR estimation by gamma camera-based Gates protocol and serum creatinine-based predicting equations with GFR measured by plasma clearance of Tc-99mDTPA. One hundred and five patients (65 male and 40 female) underwent Tc-99m DTPA renal scan followed by withdrawal of venous blood samples at 2, 3, and 4 h as per predefined protocol. Gates method GFR (GFR_s) was assessed using standard protocol. GFR by plasma sampling (GFR_p) was calculated by slope-intercept method with provision for corrections. Estimated GFR was calculated by Cockroft-Gault formula, four variable modification of diet in renal disease (MDRD) equation, and CKD-EPI equation (GFR_{CG}, GFR_{MDRD}, $GFR_{CKD-EPI}$, respectively). GFR measured by gold standard method (GFR_p) was compared with that estimated by other methods by calculating correlation coefficient, bias, precision, and accuracy. GFR estimated by all three estimating equations correlated better than GFR_s with GFR_p. For estimating GFR_p, $GFR_{CKD-EPI}$ had highest correlation with GFR_p with least bias and highest precision. Gamma camera-based Gates protocol was the least precise and least accurate method for estimating GFR_p. To conclude, all three estimating equations based on serum creatinine are superior to Tc-99m DTPA scintigraphy for estimating GFR; CKD-EPI equation being the most accurate and precise.

Key words: Chronic kidney disease-epidemiology collaboration equation, diethylenetriaminepentaacetic acid renogram, estimated glomerular filtration rate, measured glomerular filtration rate

Introduction

Glomerular filtration rate (GFR) is the most important measure of overall kidney function. Accurate estimation of GFR is necessary in a number of clinical situations such as renal donor evaluation, monitoring patients of chronic kidney disease (CKD) for disease progression, monitoring of patients with single kidney or renal transplant recipients, and calculating doses of drugs with narrow therapeutic window such as chemotherapeutic agents.

Inulin clearance is considered the gold standard procedure for the measurement of GFR,[1,2] but procurement of inulin and the cumbersome procedure pose a challenge for its routine clinical use. GFR can be measured using tracers that are cleared exclusively by glomerular

Address for correspondence:
Dr. A. V. Mulay,
Dialysis Unit, Inlaks and Budhrani Hospital, Koregaon Park,
Lane No. 1, Pune, Maharashtra, India.
E-mail: atulmul@yahoo.com

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filtration without significant tubular secretion or reabsorption. Ethylenediaminetetraaceticacid (EDTA) and diethylenetriaminepentaaceticacid (DTPA) are such chemicals that are exclusively handled by glomerular filtration. Plasma clearance of radio-labeled EDTA (Cr-51EDTA) and DTPA (Tc-99m DTPA) emerged in the 1960's and 1970's as a reliable method of estimation of GFR. This technique of GFR estimation involved a single injection of radio-labeled EDTA or DTPA followed by multiple sampling of blood and measuring the clearance by calculating the area under the curve.[3,4] However, it was found to be labor intensive and was further simplified by restricting the blood sampling to the second of the two exponential components of clearance.[5] This is known as slope-intercept method. This simplification introduced systematic errors in the values of GFR, and various methods of correction have been applied.[5-7] There could be systematic differences in the values of GFR estimated depending on the substance being used, whether urinary or plasma clearance is used and whether arterial or venous samples are used. It is recommended that clearance of EDTA from venous samples be taken as standard measure of GFR. Small systematic differences have been observed between GFR measurements obtained from EDTA and DTPA clearance.[8] However, they are sufficiently small and plasma clearance of radio-labeled DTPA can be recommended as suitable alternative radiopharmaceutical to EDTA.

There are three methods of estimating the plasma clearance of DTPA - area under curve method, slope-intercept method, and single-sample method. The "area under curve" method is too cumbersome and the "single-sample method" is not precise. The "slope-intercept method" is not only accurate and precise but also provides scope for quality control checks by means of various correlations e.g., Chantler technique.[5-7]

To avoid repeated blood sampling, kidneys can be imaged sequentially using a gamma camera after injection of Tc-99m DTPA and Gates protocol can be used to estimate GFR from the images obtained. Studies have shown that GFR estimated using Gates protocol correlates with GFR measured using plasma sampling method.[9] Gates protocol is commonly used in clinical setting since it is easily available and it does not require multiple blood sampling thus making it more convenient.

In day-to-day clinical practice, serum creatinine is used as a marker of kidney function, though this method may be fraught with errors depending on laboratory method of measurement of serum creatinine.[10] A number of serum creatinine-based estimating equations have been developed over last four decades to predict GFR. The most commonly used equations are Cockroft-Gault equation normalized for body surface area, four-variable modification of diet in renal disease (MDRD) equation, and the recently described CKD-epidemiology collaboration (CKD-EPI) equation. The MDRD study equation and the CKD-EPI equation both include variable for age, gender, and race. The CKD-EPI equation uses a two-slope "Spline" for the relationship between GFR and age, sex, race, and serum creatinine.[11] When estimated GFR (eGFR) value is <60 ml/min, both the equations were equally accurate. However, at eGFR values of 60–120 ml/min, the CKD-EPI equation performed better.[11] However, these equations have been validated in the Caucasian population, and Caucasian patients with CKD. There are very limited data on the performance of the newer CKD-EPI equation in Indian population.

We undertook the current study to determine performance of the CKD-EPI equation for predicting gold standard GFR as measured by plasma clearance of Tc-99m DTPA and comparing it with GFR estimated using Cockroft-Gault equation, 4-variable MDRD formula, and Tc-99mDTPA imaging using Gates protocol.

Materials and Methods

Adult persons of either gender (>12 years of age) who had undergone clinical examination and investigations and were advised GFR estimation by plasma clearance of DTPA at the discretion of treating physicians were included in the study. They included healthy subjects who were being evaluated as renal donors as well as patients with stable CKD.

Tc-99m-diethylenetriaminepentaacetic acid glomerular filtration rate by plasma sampling and by Gates method

We made sure that the subjects were well-hydrated before the study. They were advised to avoid high-protein diet. The patients were not on any nephrotoxic medications. The height and weight of the patients were noted, for calculation of body surface area. A dose of 10mCi Tc-99m DTPA was measured by the "activity method."[12] A standard solution was prepared as described in the GFR protocol of the nuclear medicine procedure manual of The Ottawa Hospital, Ottawa, Canada.[13] A DTPA renal scan was performed on a dual head gamma camera GEHawkeye4 and the GFRs was calculated by Gates method using vendor provided software. Heparinized blood samples of 7ml each were withdrawn from opposite arm at 2, 3, and 4 h post injection, and the time was recorded. Each of the blood samples was centrifuged for 10 min at 4000 rpm and 100 microliter (μl) of serum was collected in counting tubes with a pipette. An equal amount of standard was pipetted in a counting tube. All the samples plus background were counted for two cycles of 10 min each.[12]

The slope-intercept method with required corrections was integrated in to an Excel program to calculate GFR corrected to body surface area.[13] The GFR thus measured (GFR_p) was considered as the gold standard GFR.

Estimated glomerular filtration rate using serum creatinine

Serum creatinine was measured by modified Jaffe's reaction on an EM360 Transasia machine using manufacturer provided reagent.

We calculated GFR by using the following formulae:

- Cockroft-Gault formula corrected for body surface area (GFR_{CG})[2]
- 4-variable MDRD equation (GFR_{MDRD})[2]
- CKD-EPI equation ($GFR_{CKD-EPI}$).[11]

Statistical analysis

We calculated Pearson and Spearman correlation coefficients between GFR_p and other methods of estimating GFR, namely Cockroft-Gault formula (GFR_{CG}), four-variable MDRD equation (GFR_{MDRD}), CKD-EPI equation ($GFR_{CKD-EPI}$), and renal scan with Gates method (GFR_s). We also calculated the bias as mean difference between GFR_p and GFR estimated by each of the other methods. Precision was calculated as standard deviation (SD) of the difference. We calculated the accuracy of each equation as proportion (%) of patients with estimated GFR within 30% of measured gold standard GFR.[2] Bias expresses systematic deviation from the gold standard. Precision expresses the variability (or dispersion) around the bias. Accuracy combines precision and bias. Achieving a high level of accuracy requires low bias and high precision.

We performed Bland-Altman analysis and examined whether bias of each method of estimating GFR correlated with the level of true GFR by using Pearson correlation coefficient and linear regression. This provided information whether bias increased significantly at either lower or higher GFR.

In addition, we also examined the subgroup of patients with GFR <60 ml/min to determine the best method of estimating GFR in this subgroup, since this subgroup is more relevant to monitor patients with CKD and for adjusting doses of drugs.

Results

A total of 105 patients were studied, of which 65 were male and 40 were female. The mean ± SD age was 49.9 ± 16.6 years.

The mean ± SD GFR measured by plasma clearance of Tc-99m DTPA was 82.8 ± 29.2 ml/min/1.73 m^2, and it ranged from 12 ml/min/1.73 m^2 to 151 ml/min/1.73 m^2. Twenty subjects (19%) had measured GFR ≤60 ml/min/1.73 m^2.

Performance of estimated glomerular filtration rate in the entire group

Table 1 shows the correlation of GFR_p with other methods of predicting GFR. All three serum creatinine-based predicting equations correlated better with GFR_p than gamma camera-based method. The correlation was greatest with CKD-EPI equation (Pearson correlation coefficient 0.7). Bias was least with $GFR_{CKD-EPI}$ equation, which also had the best precision among all methods of predicting GFR. MDRD equation had higher bias but better precision as compared to Cockroft-Gault equation.

Figure 1 shows scatter plot of GFRs and $GFR_{CKD-EPI}$ against GFR_p. Figure 2 shows scatter plot of bias of GFRs and $GFR_{CKD-EPI}$ against GFR_p.

CKD-EPI equation had the highest accuracy (proportion of patients with estimated GFR within 30% of measured gold standard GFR), (73/105, 69.5%) followed closely by that of MDRD equation (65.7%) and Cockroft-Gault equation (64.8%). Gamma camera scan-based Gates method (GFRs) had much lower accuracy (54.9%).

Table 1: Correlation, bias, and precision of Gates method (GFR_s), Cockroft-Gault equation (GFR_{CG}), MDRD equation (GFR_{MDRD}), and CKD-EPI equation ($GFR_{CKD-EPI}$) for predicting GFR measured using plasma clearance of Tc-99m-diethylenetriaminepentaacetic acid by multiple plasma sampling (GFR_p)

Method of estimating GFR	Pearson correlation coefficient (r_p)	Spearman correlation coefficient (r_s)	Bias (ml/min)	Precision (ml/min)
GFR_s	0.57	0.59	6.7	33.3
GFR_{CG}	0.63	0.68	3.1	32.7
GFR_{MDRD}	0.64	0.67	7.6	28.9
$GFR_{CKD-EPI}$	0.70	0.69	1.4	26.6

CKD-EPI: Chronic kidney disease-epidemiology collaboration, GFR: Glomerular filtration rate, MDRD: Modification of diet in renal disease, CG: Cockroft-Gault

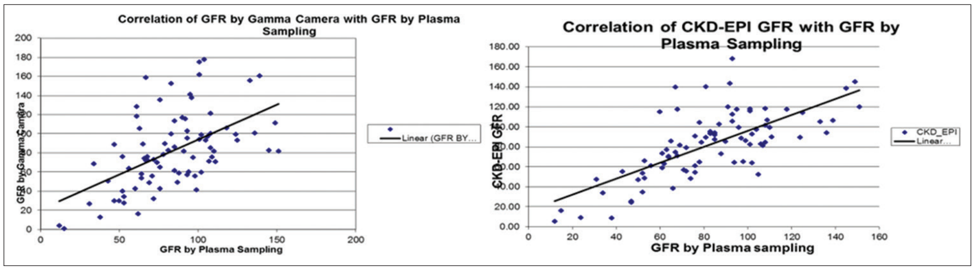

Figure 1: Scatter plot of estimated glomerular filtration rate by Gates method and by chronic kidney disease-epidemiology collaboration equation against measured glomerular filtration rate (GFR_p)

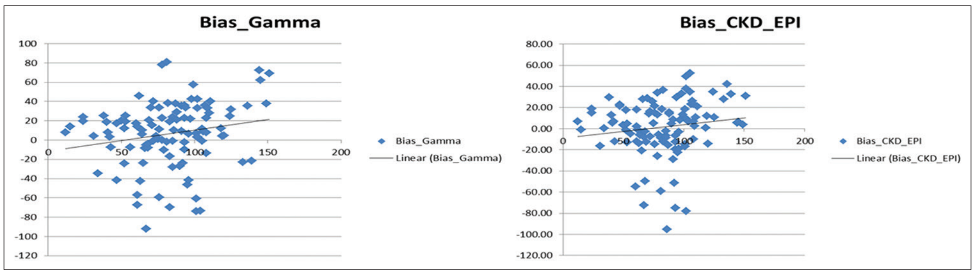

Figure 2: Scatter plots of bias for Gates method and chronic kidney disease-epidemiology collaboration equation

Performance of estimated glomerular filtration rate in subgroup of chronic kidney disease 3–5

We examined subgroup of patients with GFR ≤60 ml/min by plasma sampling, since this subgroup is clinically more relevant for estimating GFR in patients of CKD. In this subgroup also, bias was least with CKD-EPI equation, though precision was highest with Cockroft-Gault equation. Gamma camera-based estimated GFR performed worst with highest bias and least precision even in this subgroup. In the subgroup of patients with GFR >60 ml/min, bias and precision was best for CKD-EPI equation, whereas MDRD equation had highest bias and gamma camera GFR had the least precision.

Association of bias with measured glomerular filtration rate

Bias with GFR_{CG} had the least slope followed by $GFR_{CKD-EPI}$, both of which were not significant. Thus, bias associated with GFR_{CG} and $GFR_{CKD-EPI}$ equations did not depend on true GFR. As against this, bias associated with both GFRs and GFR_{MDRD} had a significant positive correlation with the level of true GFR.

Discussion

This is the first study to the best of our knowledge to examine the performance of CKD-EPI equation in Indian population by comparing it with gold standard measure of GFR, namely plasma clearance of DTPA using multiple plasma sampling. In addition, we also compared Cockroft-Gault equation, 4-variable MDRD equation, and Gates protocol with the gold standard to determine the most accurate method of estimating GFR. We found that CKD-EPI equation was the most accurate with both least bias and highest precision. Even in patients with Stage 3 to Stage 5 CKD, CKD-EPI equation had the least bias. Gates protocol was the least accurate both in the entire group as well as the subgroup of patients with Stage 3 to Stage 5 CKD.

Performance of CKD-EPI equation has previously been studied in Asian population. Jeong *et al*. measured GFR by Cr-EDTA method in 607 Korean patients and compared the performance of CKD-EPI equation with that of MDRD equation.[14] They found that bias was significantly lower with CKD-EPI equation, and accuracy of CKD-EPI equation was significantly better in patients with GFR >60 ml/min. A study from Pakistan involving 581 participants of age greater than 40 years, also showed that CKD-EPI equation had greater accuracy and precision than MDRD equation.[15] Our study confirms better accuracy of CKD-EPI equation in Indian population compared to MDRD equation.

Conflicting data exist regarding accuracy of Gates method of estimating GFR. Prasad *et al*.[9] studied 897 subjects of all levels of GFR and compared MDRD equation and Gates method with two-sample plasma clearance of Tc-99m DTPA. They found that Gates method had better correlation with measured GFR than MDRD equation at all levels of GFR. Hephzibah *et al*.[16] found that in voluntary kidney donors, Gates method had poor correlation with GFR measured by two-sample plasma clearance method (r = 0.27), whereas Cockroft-Gault formula had somewhat better correlation ($r = 0.36$). We used three-sample plasma clearance method, which may be more accurate than two-sample method for measuring GFR by plasma clearance. Our data using three-sample method suggests that creatinine based estimating equations, especially the newer CKD-EPI equation is superior to Gates method for estimating GFR.

Our study has several limitations. Number of patients with GFR <60 ml/min/1.73 m^2 was limited. Thus, caution is warranted while applying these findings in advanced kidney disease. We did not include special populations such as patients with liver disease, advanced heart failure, or advanced malignancy; thus applicability of our finding in these groups will need further study.

Conclusion

CKD-EPI equation is the best predictor of GFR in Indian population. MDRD equation and Cockroft-Gault equation also performed better than Gates method based on renal scintigraphy. Gates method may not be suitable for estimating GFR in potential kidney donors and patients with CKD.

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Conflicts of interest
There are no conflicts of interest.

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