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EGFR EQUATIONS: EVALUATION AGAINST REFERENCE GFR IN INDIAN POPULATION

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ABSTRACT

Glomerular filtration rate (GFR) is the best overall index to measure and monitor kidney function. Older method to measure GFR by using Inulin was cumbersome and cannot be used in clinical practice. Serum creatinine based equations are the choice of GFR estimation in present clinical setting. In this study, we have compared the creatinine based equations with DTPA scan GFR (Reference GFR) measurements and found that serum creatinine based equations either underestimated or overestimated GFR. We found that Cockcroft –Gault equation was found to have least negative bias with reference GFR after adjustment for body surface area, followed by MDRD (6-Variable) equation.

KEY WORDS: **Reference GFR, Serum creatinine, Cockcroft-Gault equation, MDRD-equations**

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INTRODUCTION

Clinical assessment of kidney function is part of routine medical practice for adults and is essential for assessing overall health, interpreting signs and symptoms, selecting the correct dosage for drugs that are excreted by the kidneys, preparing for invasive diagnostic or therapeutic procedures, and detecting, evaluating, and monitoring acute and chronic kidney diseases. The glomerular filtration rate (GFR) is considered the best overall index of kidney function in health and disease. The GFR cannot be measured easily in clinical practice. The "gold standard" for determining GFR is to measure the clearance of exogenous substances such as inulin, iohexol, 51Cr EDTA, 99mTc-labeled diethylenetriamine pentaacetic acid (DTPA), or 125I-labeled iothalamate[1], there are practical difficulties in using these methods to measure GFR. Therefore serum creatinine level is used to calculate GFR. But serum creatinine is influenced by a multitude of factors other than renal function like muscle mass, age, gender, weight, and race. [2] Therefore the equations used to estimate GFR based on serum creatinine level have also included age, race, sex, and body size in it. The validity of various eGFR equations was not widely assessed in Indian subjects before with reference to standard GFR measured by Radio-isotope scan.

AIMS & OBJECTIVES

The aim of this study is to compare the eGFRs based on 4 different equations based on serum creatinine like Cockcroft–Gault formula, MDRD (6-variable), MDRD (4-variable),CKD-EPI GFR equations with the gold standard GFR obtained by ^{99m}Tc-DTPA method and to identify the eGFR equation that best matches with DTPA scan GFR (Reference GFR).

MATERIALS & METHODS

Sixty one consecutive patients referred to Nuclear Medicine department for DTPA renal scan were selected into the study. Serum creatinine was estimated by kinetic Jaffe's method on Siemens Dade Dimension analyzer. Reference GFR was measured with ^{99m}Tc-DTPA and eGFR calculated using the serum creatinine by 4 different equations. All the GFR values were adjusted to standard body surface area of 1.73 m^2.

The equations which are used to calculate eGFR are[3]

Cockcroft–Gault formula: GFR (mL/min) = (140 − age) X weight X 1.228/S.Cr X (0.85, if female)

MDRD (6-variable): GFR (mL/min/1.73 m^2) = 170 X $(S.Cr / 88.4)^{-0.999}$ X $age^{-0.176}$ X $(SU\ X\ 2.78)^{-0.17}$ X $albumin^{0.318}$ X (0.762,if F) (1.18, if African American)

MDRD (4-variable): GFR (mL/min/1.73 m^2) = 186X$(S.Cr/88.4)^{-1.154}$X $age^{-0.203}$X (0.742, if female) X (1.210, if African American)

CKD-EPI GFR: 141 x min $(S.cr/ḱ,1)^{ά}$x max(S.cr/ ḱ,$1^{)-1.209}$x0.993^{Age}x1.018 [if female] x1.159[if black],

ḱ is 0.7 for females and 0.9 for males, ά is-0.329 for females and -0.411 for males, min indicates the minimum of S.cr/ ḱ or 1, and max indicates the maximum of S.cr/ ḱ or 1.

STATISTICAL ANALYSIS

Linear regression analysis was done to model the relationship between DTPA GFR and creatinine based eGFR. ANOVA was done to find out significance among variables.

RESULTS

Sixty one patients coming to nuclear medicine department for evaluation of kidney function were selected. Blood samples collected, and serum creatinine, Urea and Liver function tests were performed in all of them. These creatinine values were used to estimate the GFR by using above mentioned equations along with the age, sex, urea and albumin.

DEMOGRAPHIC DATA AND RESULTS

Demographic data and laboratory parameters and various GFR measurements were shown in Table.1.

Table 1
Depiction of various parameters

Variables	Mean + SD
Age (yrs)	37.9 + 14.8
Sex (N %)	M:39 (64%) F:22 (36%)
BSA (m^2)	1.57 + 0.21
Urea (mg/dl)	23.6 + 14.1
Creatinine (mg/dl)	1.1 + 0.6
DTPA-GFR ml/min/1.73m^2	80.9 + 27
Cockcroft- Gault GFR ml/min/1.73m^2	79.2 + 33.6
4- MDRD GFR ml/min/1.73m^2	85.6 + 31.1
6 – MDRD GFR ml/min/1.73m^2	84.5 + 29.8
CKD- EPI GFR ml/min/1.73m^2	97.2 + 36.3
Urine Protein creatinine ratio	0.87 + 0.6

BSA: Body surface area, 4-MDRD: MDRD-4-variable GFR, MDRD-6: MDRD-6- variable GFR, CKD-EPI: Chronic kidney disease- Epidemiology GFR.

The mean (± SD) DTPA-GFR was 80.9 + 27) ml/min/1.73m^2 and there is good correlation of various eGFRs with DTPA-GFR ('r' = 0.63, 0.62, 0.60 and 0.48 for Cockcroft-Gault, MDRD (4-variable), MDRD (6- variable) and CKD-EPI respectively) (Fig2-5). The various equations either underestimated or overestimated the GFR: 79.2 + 33.6 ml/min/1.73m^2 (Cockcroft-Gault), 85.6 + 31.1 ml/min/1.73m^2 MDRD (4-variable), 84.5 + 29.8 ml/min/1.73m^2 MDRD (6-variable) and 97.2 + 36.3 ml/min/1.73m^2 (CKD EPI)(Fig.1). These differences were statistically significant by ANOVA (p= 0.018). Post hoc analysis showed that CKD-EPI was significantly differing from reference GFR (p= 0.017). The negative bias was found to be the least with the Cockcroft-Gault equation (1.7 ml/min/1.73m^2) followed by 6-MDRD equation (3.6 ml/min/1.73m^2).

Table 2
Correlation of Reference GFR with Creatinine based GFRs.

		C.G GFR	MDRD (4-variable) GFR	MDRD (6-variable) GFR	CKD-EPI GFR
DTPA GFR	**r –value**	0.6303	0.6195	0.5985	0.4821
	p-value*	<0.0001	<0.0001	<0.0001	<0.0001

DTPA-GFR: Reference GFR, C.G GFR: Cockcroft-Gault GFR, 4-MDRD: MDRD-4-variable GFR, MDRD-6: MDRD-6- variable GFR, CKD-EPI: Chronic kidney disease- Epidemiology GFR. *p-value <0.05 is taken as significant.

Figure 1
Comparison of means of various types of GFR

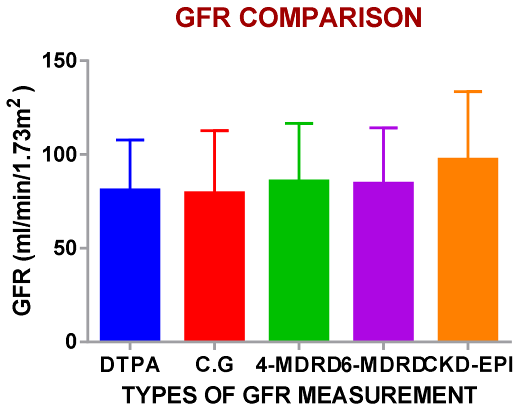


Figure 2
Correlation of Reference GFR with Cockcroft- Gault GFR.

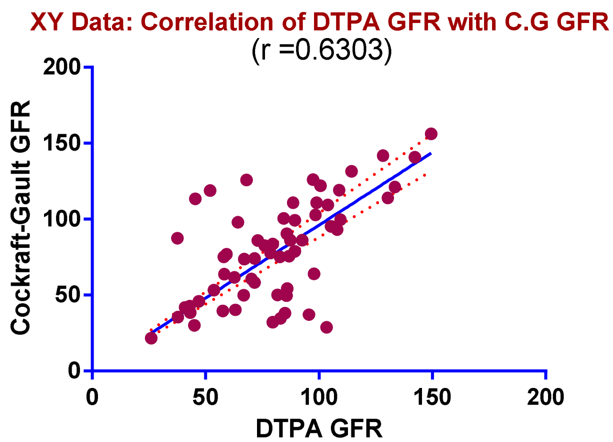


Figure 3
Correlation of Reference GFR with MDRD(4-Variable) GFR.

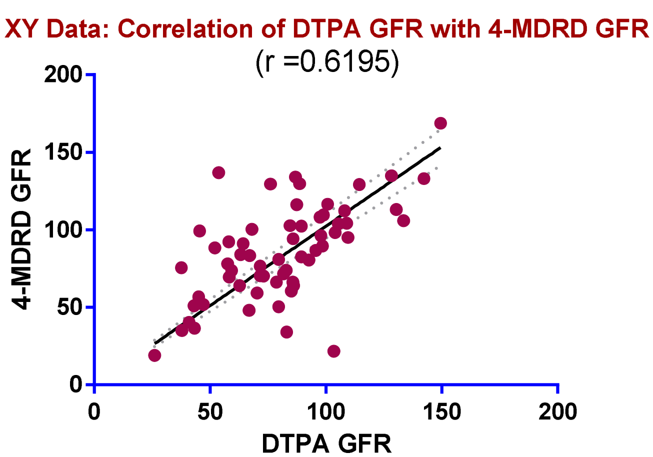


Figure 4
Correlation of Reference GFR with MDRD(6-Variable) GFR.

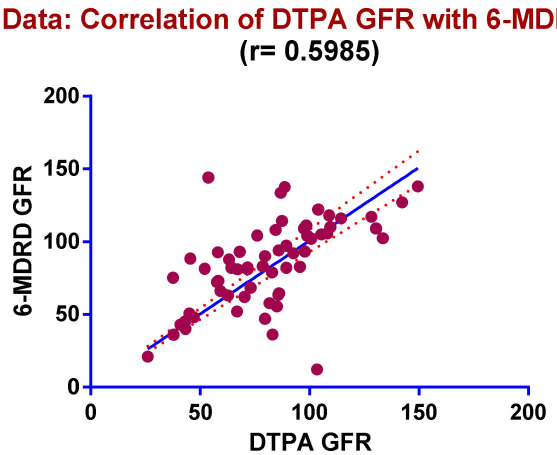
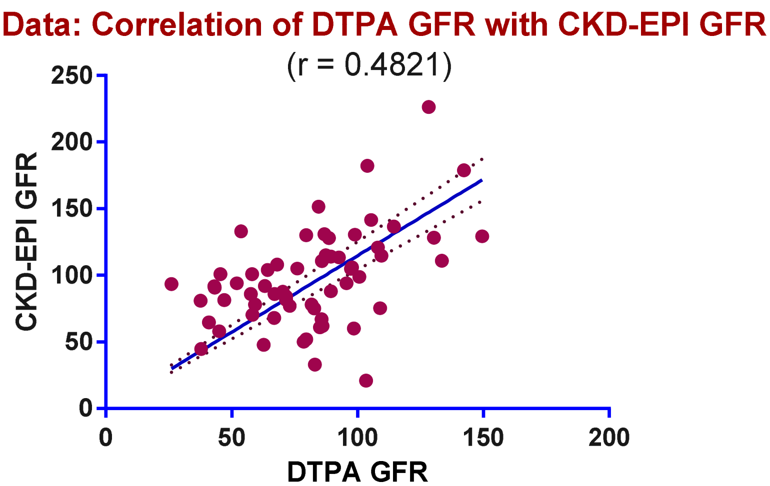


Figure 5
Correlation of Reference GFR with CKD-EPI GFR.



DISCUSSION

In our study eGFR using various equations is either low or high compared to DTPA GFR. Most of these equations have been derived from Caucasians and African Americans suffering from varying degrees of chronic kidney disease. The Cockcroft-Gault formula was developed in 1973 using data from 249 men with creatinine clearance from approximately 30 to 130 mL/min. It is not adjusted for body surface area, and is not appropriate in marked obesity[4]. The 4-variable MDRD Study equation was developed in 1999 using data from 1628 patients with CKD with GFR from approximately 5 to 90 milliliters per minute per 1.73 m^2. It estimates GFR adjusted for body surface area and is more accurate than measured creatinine clearance from 24-hour urine collections or estimated by the Cockcroft-Gault formula[5]. The equation was re-expressed in 2005 for use with a standardized serum creatinine assay, which yields 5% lower values for serum creatinine concentration. MDRD equation was derived from American patients with moderate to severe kidney disease in the MDRD study[6]. It is less accurate at GFR estimates >60 mL/min/1.73 m^2. The

CKD-EPI equation was developed in 2009 to estimate GFR from serum creatinine, age, sex, and race. The CKD-EPI equation is as accurate as the MDRD Study equation in the subgroup with eGFR less than 60 mL/min/1.73 $m^2$and substantially more accurate in the subgroup with eGFR greater than 60 mL/min/1.73 m^2. CKD-EPI equation developed based on serum creatinine, age, sex, and race, and is useful in people with and without kidney disease, diabetes, and solid organ transplants who had a wide range of GFR (2 to 198 mL/min/1.73 m^2)[7]. Modifications of the CKD-EPI and MDRD Study equations have been developed for Japanese and Chinese people. They have not yet been validated in children (age <18 years), pregnant women, the elderly (age >85 years), or in some racial or ethnic subgroups, such as Hispanics. Therefore, there is a need to validate EGFR equations in Indian population. Though the various eGFRs correlated with the reference GFR, they are not accurate. The different EGFR equations either underestimated or overestimated the GFR with a negative bias, ranging from -0.3 to 18 ml/min/1.73m^2. The least bias was found with Cockcroft –Gault equation after adjustment for body surface area followed by MDRD (6-variable) equation. The highest bias was found with CKD-EPI equation.

CONCLUSION

Though the various eGFRs correlated with the reference GFR, they are not accurate. The different eGFR equations which are used clinically to assess kidney function are not in concordance with reference GFR. The Cockcroft-Gault equation is having least negative bias with reference GFR after adjusting for body surface area, followed by 6-MDRD equation. Our results point towards the need for developing our own equations suitable for Indian subjects for more accurate estimation of GFR. They need to be validated in different stages of CKD and in different clinical contexts like diabetes, renal transplantation, pregnant women, the elderly (age >85 years), or in some racial or ethnic subgroups, such as Hispanics.

LIMITATION: Small sample size.

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