Comparison of Different Equations with GFR Measured by Scintigraphy in Kidney Donors

Abstract

Background: Technetium-99[m] diethylene-triamine-pentaacetate (99[m]Tc-DTPA)-based scintigraphy is a convenient way to assess measured glomerular filtration rate (mGFR) in kidney donors. Equations have been developed to calculate GFR in the general population. This study aims to identify the best among commonly employed equations to better predict GFR when compared with scintigraphy-based mGFR. Also, the trends in mGFR values were studied over 1 year post-donation. **Materials and Methods:** Thirty-four kidney donors were recruited for this study from November 2017 to November 2018 and followed-up for a year. Estimated GFR (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) Equation, Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation, and Nankivell formula; the values were compared to that obtained using 99[m]Tc-DTPA both pre-and post-donation. Correlation and agreement between the eGFR and mGFR were studied using Statistical Package for the Social Sciences (SPSS) version 23.0 and Microsoft Excel. **Results:** mGFR was augmented by 32.3 ± 27.8% in the remnant kidney post-donation. The baseline mGFR, post-donation mGFR, and the quantum of its increase post-donation did not differ between overweight donors and donors with normal body mass index (BMI). mGFR correlated poorly with all the eGFR equations both pre- and post-donation. Bland-Altman analysis showed weak agreement with significant bias and variance between mGFR and all eGFR equations. **Conclusion:** In Indian kidney donors, mGFR by 99[m]Tc-DTPA scintigraphy shows poor correlation and agreement with the commonly used eGFR equations. An individualized approach is needed to assess the kidney function of live donors to minimize harm to both the recipient and the donor.

Keywords: mGFR, eGFR, DTPA, Donor nephrectomy, CKD-EPI

Gerard Vinodh[1], Prashant C Dheerendra[2] , Aleya Anitha[2], Deepashree Goravigere Anandkumar[2], Deepesh Vellakampadi[2], Gokulnath[2]

[1]Department of Nephrology, Karpagam Faculty of Medical Sciences and Research, Coimbatore, Tamil Nadu, [2]Department of Nephrology, Apollo Hospitals, Bangalore, Karnataka, India.

Corresponding author: *Prashant C Dheerendra, Department of Nephrology, Apollo Hospitals, Bangalore, Karnataka, India. E-mail: cdprash@gmail.com*

Introduction

Kidney donation is a safe procedure in the short term but confers an elevated risk for kidney failure, cardiovascular mortality, and all-cause mortality over the long term.[1] Hence, a comprehensive evaluation of the donor kidney function assumes heightened significance, keeping in mind the medical dictum of "primum non nocere" (first, do no harm).

The preferred method for assessing total renal function is the measurement of glomerular filtration rate (GFR). Creatinine clearance, requiring a 24-h urine collection, is commonly used for donor evaluation but has errors associated with timed collection and tubular secretion of creatinine. Inulin clearance is the gold standard to measure GFR but is cumbersome and impractical in daily clinical practice. Technetium-99[m] diethylene-triamine-pentaacetate (99[m]Tc-DTPA) is a radionuclide that is useful to get a value of measured GFR (mGFR). Two methods are generally used to obtain mGFR using 99[m]Tc-DTPA—a scintigraphy-based method and a plasma sampling method. The plasma sampling method involves repeated blood sampling though it is more accurate compared to the scintigraphy-based method.[2] It also needs measurement of activity in the syringe before and after injection of the radionuclide and hence is a time-consuming process.[3] The scintigraphy-based method is easier and quicker to perform.[4,5]

Various estimated GFR (eGFR) equations have been formulated based on patient characteristics like age, gender, race, serum

creatinine, etc. While the equations are easy to use and inexpensive, they have not been validated in Indian kidney donors. The commonly used equations are the Modification of Diet in Renal Disease (MDRD) equation, Chronic Kidney Disease Epidemiology (CKD-EPI) Collaboration equation, and the Nankivell equation.[6–8] The MDRD equation was derived from patients with kidney disease and underestimates GFR in people with good renal function.[9] The CKD-EPI equation is the recommended equation for GFR estimation in people with normal renal function.[10] Three variants of the equation are used incorporating serum creatinine or serum cystatin or both.[6,11] The CKD-EPI creatinine is the most commonly used. The Nankivell formula is the only one derived from patients with a single functioning kidney after receiving a kidney transplant.[8]

Despite the availability of these equations, none of them has been validated among Indian renal donors. In this study, we aimed to evaluate which equation accurately estimated GFR pre- and post-donor nephrectomy when compared to 99^{m}Tc-DTPA-based scintigraphy measured GFR (mGFR). Also, we studied the trends in mGFR over a period of 1 year after donation.

Materials and Methods

Study participants

In this prospective observational study, a total of 34 live kidney donors who were evaluated at the Department of Nephrology at our hospital from November 2017 to November 2018 were included. The study was initiated after receiving approval from the Institutional Ethics Committee of the Scientific Review Board, number AplBlr/SRB/ DNB/0023/2017, dated 15/9/2017. Written informed consent was obtained from all participants.

Laboratory study

Donors were evaluated based on clinical history, physical examination, and laboratory investigation. Serum creatinine was measured using Jaffe's uncompensated photometric method with a Beckman Coulter AU 680 pre-donation and 1 year post-donation. Other routine blood tests were done as part of donor work-up and follow-up.

A dynamic renal study (Gates' method) was conducted utilizing 99^{m}Tc-DTPA as a radiotracer to determine the GFR level pre-donation and at 1 year post-donation. An intravenous injection of 99^{m}Tc-DTPA (3-5 millicurie) was administered prior to the scan. Dynamic imaging, with the participant in the supine position, was carried out using a gamma camera at an acquisition rate of 1 frame/3 seconds for 1 min and subsequently 1 frame/19 seconds for 19 min. GFR was calculated using the algorithm from Gates' software. The eGFR was calculated based on serum creatinine level using the four variable MDRD equation, CKD-EPI creatinine equation, and Nankivell formula.

Statistical analysis

Categorical variables were represented as numbers or percentage. Continuous variables were represented as mean ± standard deviation. Spearman correlation was used to determine the correlation between mGFR and eGFR values.

Bland-Altman analysis was performed to study the agreement between mGFR and eGFR by various equations. The analysis plots the mean of the GFR obtained by the two methods along X axis against the difference between them along the Y axis. The plot was used to calculate bias and variance of eGFR compared to mGFR.

A p-value <0.05 was considered significant. Microsoft Excel and the Statistical Package for the Social Sciences (SPSS) version 23 software were used for all statistical analyses.

Results

Description of the study population

Thirty-four participants were evaluated in this study. The donors evaluated in the study were predominantly female (n = 28) as compared to males (n = 6). Age and BMI were not significantly different across the genders. Of the 34 donors, 22 were overweight and had a BMI of more than 25 kg/m².

Twenty-four (70.5%) participants completed the 1-year follow-up. Lack of follow-up was mainly due to financial or logistical reasons. Table 1 depicts the important baseline characteristics of the participants.

Changes in GFR by 99^{m}Tc-DTPA pre- and 1 year post-donation

Mean GFR measured by 99^{m}Tc-DTPA pre-donation was 104.49 ± 10.38 mL/min/1.73m². The mean pre-donation mGFR of the remnant kidney was 51.41 ± 6.36 mL/min/1.73m². Mean mGFR 1 year after donation was 67.30 ± 12.33 mL/min/1.73m². The mGFR of the remnant kidney increased by an average of 32.3 ± 27.8%.

When mGFR values were compared in patients with BMI less than 25 kg/m² (normal BMI) and more than 25 kg/m²

Table 1: Baseline characteristics of the study population

Parameter	Values
Age, Years (n = 34)	47.5 (11.9)
Gender—Number of Females (%)	28 (82.4%)
Pre-Diabetes—Number (%)	9 (26.5%)
Hypertension—Number (%)	4 (11.8%)
Overweight—Number (%)	22 (64.7%)
Body Mass Index	27.3 (4.7)
Pre-surgery Creatinine in Males, mg/dL (n = 6)	0.98 (0.09)
Pre-Surgery Creatinine in Females, mg/dL (n = 28)	0.74 (0.10)

Frequency has been represented as number (%) while age, BMI, and serum creatinine values have been represented as mean ± standard deviation.

(overweight), no difference was found in the pre-donation values (102.33 ± 11.91 mL/min/1.73m^2 vs 105 ± 10.02 mL/min/1.73m^2, p = 0.56), post-donation values (67.88 ± 16.41 mL/min/1.73m^2 vs 67.07 ± 11.00 mL/min/1.73m^2, p = 0.89), and the quantum of increase of mGFR in the remnant kidney after donation (17.71 ± 15.14 mL/min/1.73m^2 vs 15.17 ± 12.01 mL/min/1.73m^2, p = 0.68).

Correlation and agreement between mGFR and eGFR

mGFR using 99^{m}Tc-DTPA was compared with eGFR obtained from the equations in donors both pre- and post-surgery. Although the estimated GFR results across formulas correlated strongly with each other, mGFR values correlated poorly with eGFR values as estimated by MDRD (p-value = 0.628) and CKD-EPI (p-value = 0.573) equations pre-surgery. Similarly, mGFR 1 year post-surgery correlated poorly with eGFR by MDRD (p-value = 0.300), CKD EPI (p-value = 0.368), or Nankivell (p-value = 0.301) equations. The correlation coefficients of the various methods are depicted as a correlation matrix in Figure 1.

Accuracy of estimation, defined as proportion of eGFR values within 10% of the mGFR values, was low across all formulas. Pre-donation, 74% values of eGFR by MDRD and 56% values by CKD-EPI differed from the 99^{m}Tc-DTPA based mGFR by a margin of more than 10%. Post-donation the proportions were 58%, 62.5%, and 67% for MDRD, CKD-EPI, and Nankivell formulas respectively.

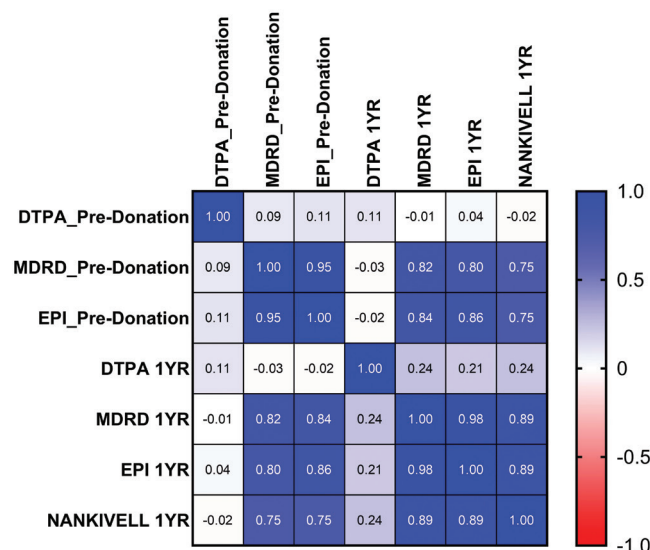Bland-Altman analysis evaluates the differences between two methods across the range of measurement.

Figure 1: Correlation matrix of GFR measurements by various methods pre- and 1 year post-donation. There was poor correlation of mGFR with the commonly used eGFR equations. Generally, there was a strong correlation between the equations. The strongest correlation was between MDRD and CKD-EPI equations at both time points. DTPA= Technetium-99^m diethylene-triamine-pentaacetate (99^{m}Tc-DTPA) GFR, MDRD = Modification of Diet in Renal Disease equation, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation, mGFR: measured glomerular filtration rate

Comparison of methods by Bland-Altman analysis demonstrated high variability across mGFR and eGFR methods [Table 2]. mGFR demonstrated a positive bias pre-surgery when compared to both MDRD and CKD-EPI equations. This means that, on an average, mGFR values were higher than the eGFR values pre-surgery. Interestingly, post-surgery mGFR showed a negative bias compared to all the equations.

Figures 2 and 3 depict the Bland-Altman analysis as a scatterplot. Both the figures show a few common characteristics. Data points clustered close to the zero line suggest strong agreement in Bland-Altman plots, but in this study, a sizeable number of points are distant from the zero line. Data points close to the bias line (dotted black line) suggest a strong correlation between the methods. But in our study a majority of the data points are away from the bias line. The range of limits of agreement (dotted red lines) is noted to be wide.

Discussion

Evaluation of renal function in live kidney donors is an important part of pre-donation assessment. While many formulas are used, their validity in renal donors as a unique subpopulation is not well established in the Indian context. It is a common practice to perform tests to assess measured GFR for kidney donors.

Donors with BMI higher than 25 kg/m^2 formed a substantial proportion (22 out of 34 donors) of donors in our study. There was no difference in pre- and post-donation mGFR between overweight and normal donors. In contrast, the study by Gozdowska *et al.* (n = 25) found a significant negative correlation between BMI and mGFR using methods similar to our study.[12] A much larger retrospective study (n = 1878) also found a negative correlation between BMI and mGFR in obese women, though it used clearance of Cr-51-EDTA as the method to measure GFR.[13]
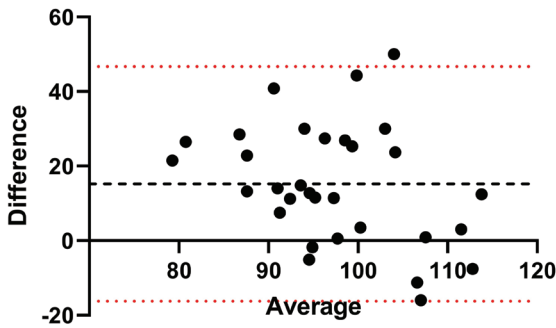
Our study confirmed a lack of accuracy of the eGFR equations compared to mGFR by 99^{m}Tc-DTPA scintigraphy

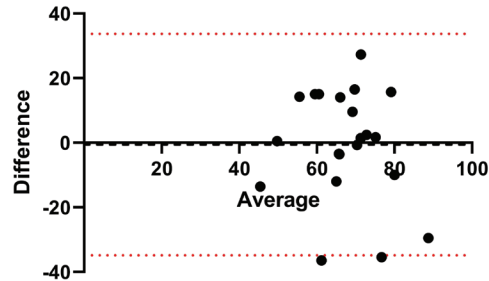**Table 2: Summary of Bland-Altman analysis comparing Tc99-DTPA measured GFR against estimated GFR**

Measured GFR	Estimated GFR	Bias	SD of Bias	95% Limits of Agreement
Tc99-DTPA (Pre-Surgery)	MDRD	15.25	16.05	(-16.21 to 46.72)
	CKD-EPI	11.78	15.35	(-18.3 to 41.86)
Tc99-DTPA (Post-Surgery)	MDRD	-0.5352	17.48	(-34.8 to 33.73)
	CKD-EPI	-4.226	19.14	(-41.73 to 33.28)
	Nankivell	-10.62	19.21	(-48.28 to 27.04)

GFR: Glomerular filtration rate, DTPA: Diethylenetriamine pentaacetate, CKD-EPI: Chronic kidney disease-Epidemiology collaboration, MDRD: Modification of diet in renal disease
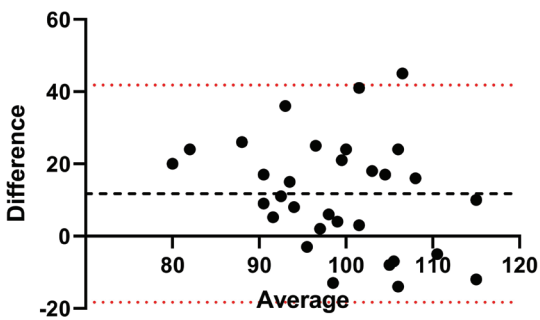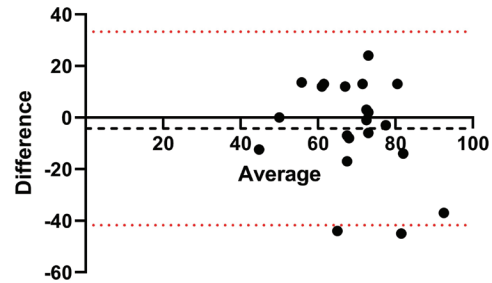
Bland-Altman: DTPA vs. MDRD (Pre-Surgery)

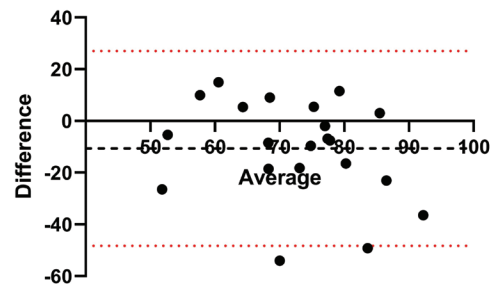## Bland-Altman: DTPA vs CKD-EPI (Pre-Surgery)

Figure 2: Comparison of methods by Bland-Altman analysis demonstrated high variability, poor agreement, and positive bias across mGFR and eGFR methods pre-donation. DTPA = Technetium-99m diethylene-triamine-pentaacetate (99mTc-DTPA) GFR, MDRD = Modification of Diet in Renal Disease equation, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation.

Bland-Altman: DTPA vs. MDRD (1 yr Post-Surgery)

Bland-Altman: DTPA vs. CKD-EPI (1 Yr Post-Surgery)

Bland-Altman: DTPA vs. Nankivell (1 Yr Post-Surgery)

Figure 3: Post-donation analysis of mGFR and the eGFR equations continued to show high variability and poor agreement but the bias was now negative. DTPA = Technetium-99m diethylene-triamine-pentaacetate (99mTc-DTPA) GFR, MDRD = Modification of Diet in Renal Disease equation, CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration equation, mGFR: measured glomerular filtration rate, eGFR: estimated GFR.

noted previously in renal donors. Mahajan studied 122 renal donors from India and observed that median percentage absolute difference between the estimated GFR by MDRD and measured GFR was 20.8%.[14] In Polish kidney donors, 73% of eGFR values estimated by MDRD and 67% by CKD-EPI differed by a margin of more than 10% from the scintigraphy-based mGFR using 99mTc-DTPA—findings similar to our study.[15] Interestingly, the same study found that of 11 equations, mGFR by 99mTc-DTPA correlated best with the Nankivell formula with a correlation coefficient of 0.47 and p = 0.009.

Bland-Altman analysis is used to assess agreement between two methods of measurement. While correlation analysis looks at the strength of linear relationship between variables, Bland-Altman analysis looks at the differences and constructs limits of agreement within which 95% of the observed values occur. Most studies confirm the lack of agreement between mGFR by 99mTc-DTPA and eGFR.[12,14–17] Specifically, the limits of agreement on Bland-Altman analysis need to be evaluated in a clinical context. In the present study, the limits of agreement are too wide to be clinically acceptable.

Ours is one of the few studies which have performed a follow-up mGFR estimation after donor nephrectomy. The GFR in the remnant kidney increased substantially (mean 32.3%) as previously reported in Indian kidney donors by Bahirani *et al.* and Chavan *et al.* with the mean increase after 3 months being 16.7 % and 21.2%, respectively.[18,19] More importantly, as noted in the present study, overweight and obese donors had a similar augmentation in mGFR compared to donors with normal BMI.[19] A study by Chen *et al.* measured GFR by 99mTc-DTPA at 1 month and 12 months after donor nephrectomy and concluded that a bulk increase in GFR occurred within the first month.[20] The correlation and agreement between mGFR and eGFR continued to be weak post-donation.

Using plasma sampling of a radionuclide-like 99mTc-DTPA is more accurate than the Gates method to assess

mGFR, even though the method is more cumbersome.[21,22] Simplification of the plasma sampling method by limiting to a single blood draw or applying a correction factor based on large numbers of measurements in the population has been described.[2,23] Their utility in clinical practice requires further study.

However, there are certain limitations to this study. The study had a relatively small sample size, and the follow-up period was short. In addition, there were more dropouts during the follow-up study than initially anticipated because of financial and logistical reasons. Instead of utilizing inulin clearance, which is considered the gold standard for measuring GFR, the study relied on scintigraphic measurement of GFR by Tc-99m DTPA, a more convenient method.

Conclusion

Kidney donation for transplantation carries some risk, particularly for those with preexisting medical issues. Reassuringly, overweight and obese donors have an increase in mGFR that is comparable to donors with normal BMI at the end of 1 year post-donation. Accurate evaluation of kidney function in donors is made more challenging by poor correlation and agreement between mGFR by Tc-99m DTPA scintigraphy and eGFR by the commonly used equations. mGFR obtained by plasma sampling after injection of Tc-99m DTPA is more accurate compared to the Gates' method based on scintigraphy. The agreement of the plasma sampling method with scintigraphy-derived mGFR and the eGFR equations needs to be looked at in larger studies. It may be possible to calculate a correction factor based on a large population study comparing mGFR by scintigraphy and plasma sampling. This may allow clinicians to get a more accurate estimate of GFR while retaining the convenience of the scintigraphic method.

Acknowledgement

Conflicts of interest
There are no conflicts of interest.

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