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Correlation of Serum Creatinine Based Calculation of Glomerular Filtration Rate with Measured Radio Isotope Glomerular Filtration Rate in Healthy Individuals and Chronic Kidney Disease Patients

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ABSTRACT

INTRODUCTION: GFR is best index of kidney function in health and disease and accurate values are needed for optimal decision making in clinical settings. Estimated GFR (eGFR) based on serum creatinine is "first line" test of kidney function. CG formula is creatinine based equation and widely applied. Tc^{99m}-DTPA (Diethylene Triamine Penta Acetic acid) is the most commonly used radiopharmaceutical for GFR studies. The Gate method has been most common in the routine setting. **AIM AND OBJECTIVES:** To study correlation of serum creatinine based calculation of GFR with measured ratio isotope GFR in healthy individuals & CKD patients. To assess the accuracy of GFR as calculated by CG GFR formulae using serum creatinine against measured RI-GFR (Tc-99m- DTPA). **METHODS:** This study observational study, which is done in department of medicine and department of nuclear medicine at Army Hospital R&R, Delhi Cantt in CKD and healthy individuals. Our study includes a total of 100 subjects with varying renal functions which includes 50 healthy individual & 50 CKD patients. **RESULTS:** In this study it has been observed that in healthy group CG GFR has weak correlation with DTPA GFR (r = 0.104 with p: 0.471). In study it has been observed that in CKD patients CG GFR significantly correlate with DTPA. (r = 0.614 with a p: < 0.001). In category 79 subjects was selected with creatinine value between 0.7 to 3.7 mg/dl. In this group it has been observed that CG GFR significantly correlate with DTPA. (r = 0.815 with P: < 0.001). In healthy subjects mean eGFR by CGGFR is 104.26 ± 31.09 (range 65.4-176.2) ml/min/1.73m^2, whereas mean mGFR by DTPA is 92.15 ± 17.85 (range 49.9-131.8) ml/min/1.73m^2. In healthy subjects eGFR by CGGFR overestimate the mGFR by DTPA GFR. On the other hand there is poor correlation between eGFR by formula with mGFR. In CKD subjects mean eGFR by CG GFR is 31.10 ± 14.51 (range 4.74 to 57.9) ml/min/1.73m^2, whereas mean mGFR by DTPA is 40.06 ± 13.64 (range 10.4 to 84.19) ml/min/1.73 m^2. In these subjects eGFR by GCGFR underestimate the mGFR by DTPA. On the other hand there is positive significant correlation (p : <0.001) between eGFR by both formula with mGFR. We have also observed that subjects with creatinine value between 0.7 to 3.5 mg/dl, irrespective of their disease status (Healthy & CKD subjects) has significant positive correlation between eGFR (CG GFR with mGFR (DPTA) (p value <0.001). It signifies that with extremes of creatinine (either very low or very high) value eGFR doesn't correlate with mGFR. **CONCLUSION AND RECOOMANDATIONS:** In conclusion, the modified Gate's method is undoubtedly an important method in unilateral renal function measurement. But our results implied that its performance in total GFR estimation was not better than the CG equations.

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INTRODUCTION

GFR is widely accepted as the best index of kidney function in health and disease and accurate values are needed for optimal decision making in clinical settings. Estimated GFR (eGFR) based on serum creatinine is "first line" test of kidney function. This is followed by more accurate confirmatory tests. Measured GFR (mGFR) using urinary or plasma clearance of exogenous filtration markers is considered the gold standard for evaluation of kidney function but is not routinely available because of the complexity of measurement protocols. Instead clinicians usually rely on endogenous creatinine clearance.

Cockcroft-Gault equation (CG):
GFR (mL/min) = (140-age) x weight x 1.228/S Cr (0.85, if female)

CG formula is creatinine based equation. Since this prediction formula has been evolved using western population they are not applicable as such to the entire

ethnic population group. These formulas have not been validated in Indian population group. So there is a need of validation of these formulae in our setting.

Radio-Nuclide Evaluation of GFR:
Tc^{99m}-DTPA (Diethylene Triamine Penta Acetic acid) is the most commonly used radiopharmaceutical for GFR studies, although up to 10% of the preparation may be bound to protein, therefore slightly underestimating the GFR. The Gate method introduced by Gates has been most common in the routine setting. Although the diagnostic accuracy of the gamma camera methods is debated, the program is provided as a software package by manufacturers in commercially available computer systems dedicated for nuclear medicine.

AIM AND OBJECTIVES:
AIM: To study correlation of serum creatinine based calculation of GFR with measured ratio isotope GFR in healthy individuals & CKD patients.

OBJECTIVE: To assess the accuracy of GFR as calculated by CG GFR formulae using serum creatinine against measured RI- GFR (Tc-99m- DTPA) in healthy individuals & CKD patients.

PATIENTS / SUBJECTS / MATERIALS AND METHODS INCLUDING PLAN OF STATISTICAL EVALUATION
This study was conducted in the Department of Medicine, Army Hospital (Research and Referral) Delhi during the period October 2009 to January 2011. 50 Chronic kidney disease patients and 50 healthy individuals were included in the study.

INCLUSION CRITERIA
1. Chronic kidney disease patients. Individuals having serum creatinine more than 1.5 mg/dl persisting for more than three months in the absence of reversible factor.
2. Healthy individuals who do not have any history of renal disease. Individuals having serum creatinine less than 1.2 mg/dL. Most of these are prospective renal donors. Normal range of creatinine in our lab is < 1.4 mg/dl.
3. Patients who have given informed consent.

EXCLUSION CRITERIA
1. Patients with obstructive uropathy.
2. Patient with Acute kidney injury.
3. Patient who has not given informed consent.
4. Gross edema
5. CKD patients those are on any type of maintenance dialysis (hemo /peritoneal)
6. Significant pleural or abdominal effusion.

Each subject, after formal consent for the study was subjected to detail clinical history and through physical examination, including weight and height. Serum creatinine was done in each subject on same day.

Measurement of GFR using the ^{99m}Tc-DTPA renal dynamic imaging method:
Measuring of GFR in our center, gamma camera based method has been used. It requires no blood sampling and only few minutes of imaging time. A small dose of ^{99m}Tc DTPA is counted a set distance from the camera face to determine the count rate before injecting it into the patient. The actual administrated dose is than corrected for the post injection residual in the syringe and serves as a standard.

After injection images are acquired for 6 minutes Region of Interest (ROI) are drawn around the kidney and the counts in the background subtracted. Attenuation of photons caused by varying renal depth is corrected using formulae based on patient weight and height.

GFR by modified Gate's method was calculated with the following formula [27]:

$$\text{Total renal uptake percent (\%)} = \frac{[(R - RB)/e^{-\mu \chi R} + (L - LB)/e^{-\mu \chi L}]}{(Pre - Post)}$$

$$\text{Global GFR} = \text{Total percent renal uptake (\%)} \times 100 \times 9.81270 - 6.82519$$

Where Pre: pre-count, Post: post-count, R: right kidney counts, RB: right kidney background counts, L: left kidney counts, LB: left kidney background counts, χR: right kidney depth, χL: left kidney depth, μ: attenuation coefficient of ^{99m}Tc in soft tissue (0.153/cm), e: constant

DOSE:
Adults – 3-5mCi (185 MBq)

Children – 200 micro Ci/kg (1mCiminimum, 3mCi maximum)

INSTRUMENTATION:
Camera: Large field view of gamma.

Collimator: Low energy parallel hole.

Photo peak: 15-20% window centered over 140 keV

COMPUTER ACQUISITION-
Blood flow 1-2 second frames for 60 second. Dynamic- 30 second frames for 25 minute.

Pre-void image 500 k count. Post-void image.

PROCESSING-
Computer region of interest around kidneys and background area is drawn.

Generated time: Activity curves for 60 second flow phase and for 25 minute dynamic study

Estimation of GFR from Cockcroft-Gault equation
Cockcroft-Gault formula: GFR (mL/min) = (140-age) x weight x 1.228/S Cr x (0.85, if female)

$$\text{CG-GFR} = \text{CG-CrCl} \times \frac{\text{BSA}}{1.73} = \text{GFR ml/min/1.73m}^2$$

BSA is calculated by Dubois & Dubois formula [1]

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

Where Serum Creatinine was in unit of mg/dl, age was in years. Creatinine levels were measured in a single laboratory (Department Pathology, Army Hospital Research and Referral), normal reference range up to 1.4 mg/dl on a Hitachi 7600 analyser using the Jaffe's kinetic method .

Where Serum Creatinine was in unit of mg/dl; age was in years, weight was in kilogram. The CG-CrCl is then adjusted to be comparable to an average sized person with a BSA of 1.73m^2. This is done by;

Statistical Analysis:
The data was presented in terms of Descriptive statistics (Range, Mean, Standard deviation) for quantitative variables and frequency, percentage for category variables was presented in each group. For determining the statistical significance, the statistical method for quantitative variables were used as 2 sample student 't' test for normally

distributed variables in case when quantities variables do not follow a normal distribution, non parametric Mann' Whitney statistical test was applied . For categorical variables, the statically test were used as Chi square / Fischer exact. The level of statistical significance has taken as p < than or = 0.05.

Data was analyzed by using SPSS 16.

OBSERVATIONS AND RESULTS

This study includes a total of 100 subjects, which includes 50 healthy individual & 50 CKD patients. There are total 100 males (66.7%) and 50 females (33.3%). In healthy group there are 25 male (50%) and 25 female (50%), whereas in CKD group there are 13 female (26%) and 37 male (74%). Proportion of males was higher in each group. Age of the subjects ranged from (overall) 3 to 85 years with a mean age of 41.87 ± 14.94 years. In healthy group age ranged from 20 to 70 years with a mean age of 44.16 ± 12.048 years. In CKD group age ranged from 3 to 85 years with a mean age 47.76 ± 17.28 years. Overall maximum subjects were from 41 to 50 years age group that is 35 individual (23.3%) In healthy group maximum subjects were from 40 to 50 years age group that is 18 individual (36%). In CKD individual equally distributed in more than 30 years of age.

Height of the individuals (overall) ranged from 110 to 183 cm. Mean height is 162.04 ± 11.78 cm. In healthy group height ranged 127 to179 cm with a mean height 160.26 ± 9.71 cm. In CKD group height ranged 110 to176 cm with a mean height 161.70 ± 14.11 cm. Weight of the individuals (overall) ranged from 14 to 82 kg. Mean weight is 56.93 ± 12.53 kg. In healthy group weight ranged 35 to 82 kg with a mean weight 58.19 ± 10.18 kg. In CKD group weight ranged 14 to 80 kg with a mean weight 59.03 ± 10.18 kg. BSA of the individuals (overall) ranged from 0.65 to 2 m^2. Mean BSA is 1.59 ± 0.21 m^2. In healthy group BSA ranged from 1.22 to 1.91 m^2 with a mean BSA 1.59 ± 0.16 m^2 .In CKD group BSA ranged from 0.65 to 1.96 m^2 with a mean BSA 1.61 m^2 ± 0.26 m^2.

Creatinine values of the individuals (overall) ranged from 0.4 to 10.4 mg/dl. Mean creatinine is 1.57 ± 1.28 mg/dl. In healthy group creatinine ranged 0.4 to 1.1 mg/dl with a mean creatinine 0.78 ± 0.18 mg/dl. In CKD group creatinine ranged 1.6 to 10.8 mg/dl with a mean creatinine 2.65 ± 0.46 mg/dl.

eGFR by CG GFR formula of all subjects (overall) ranged from 4.74 to 176.2 ml/min. Mean eGFR is 67.64 ± 38.28 ml/min. In healthy group eGFR ranged from 65.4 to 176.2 ml/min with a mean eGFR 104.26 ± 31.09 ml/min. In CKD group eGFR ranged from 4.74 to 57.9 ml/min with a mean eGFR 31.10 ± 14.51 ml/min. GFR by DTPA of all subjects (overall) ranged from 10.7 to 131.8 ml/min. Mean GFR is 58.97 ± 29.19 ml/min. In healthy group GFR ranged 49.9 to 131.8 ml/min with a mean GFR 92.15 ± 17.85 ml/min. In CKD group GFR ranged 10.4 to 84.19 ml/min with a mean GFR of 40.06 ± 13.64 ml/min.

Correlation of GFR by CG-GFR and DTPA GFR in Healthy Group: In this study it has been observed that in healthy group CG GFR has weak correlation with DTPA GFR (r = 0.104 with p: 0.471).

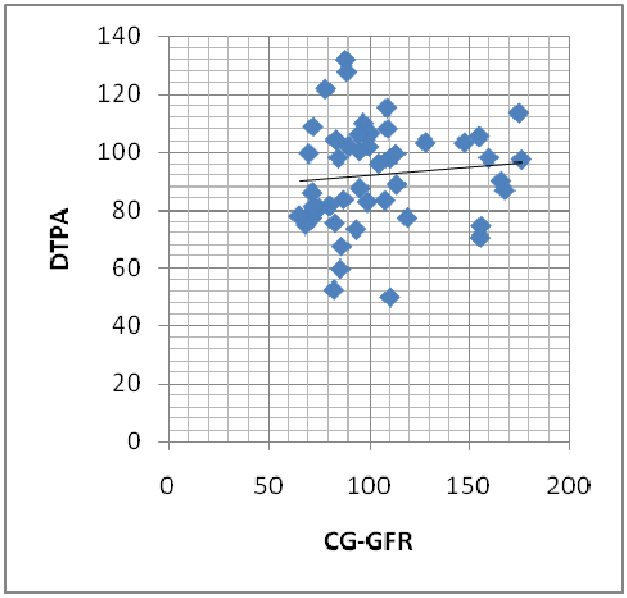

Figure 1 Scatter plot of GFRs determined by DTPA (modified Gates' method) against that by CG GFR formula method in healthy study group

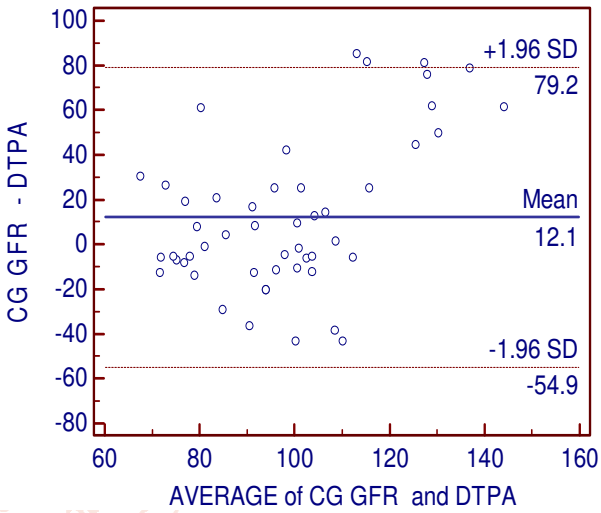

Figure 2 Bland Altman plot of difference between the GFR by CGGFR and DTPA. Solid line represents the mean difference between two methods and dashed line represents the 95% limits of agreement

Correlation of GFR by CG- GFR and DTPA GFR in CKD Group: In study it has been observed that in CKD patients CG GFR significantly correlate with DTPA. (r = 0.614 with a p: < 0.001).

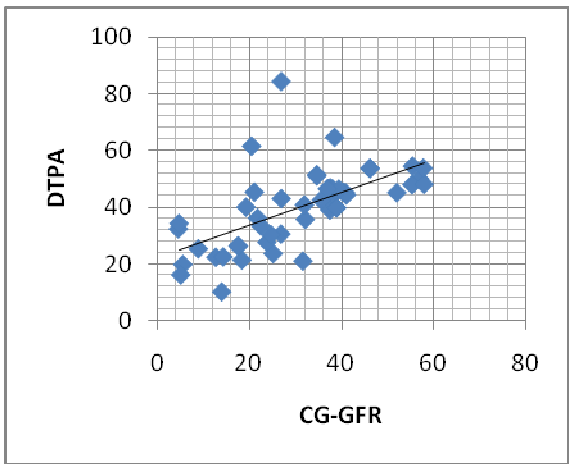

Figure 3 . Scatter plot of GFRs determined by DTPA (modified Gates'method) against that by CG GFR formule in CKD study group.

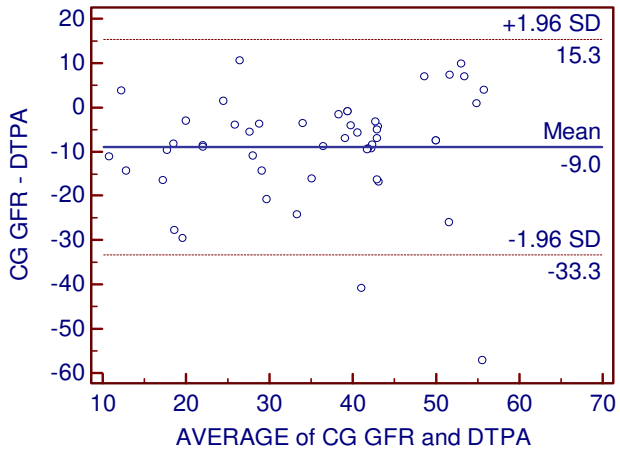

Figure 4 Bland Altman plot of differences between the GFR by CGGFR and DTPA in CKD group. Solid line represents the mean difference between two methods and dashed line represents the 95% limits of agreement

CORRELATION IN GFR (HEATHY & CKD SUBJECTS) WHEN CREATININE VALUE IS BETWEEN 0.7 TO 3.7 mg/dl: In these category 79 subjects was selected with creatinine value between 0.7 to 3.7 mg/dl.

Correlation of GFR by CG GFR and DTPA: In this study it has been observed that CG GFR significantly correlate with DTPA. (r = 0.815 with P: < 0.001).

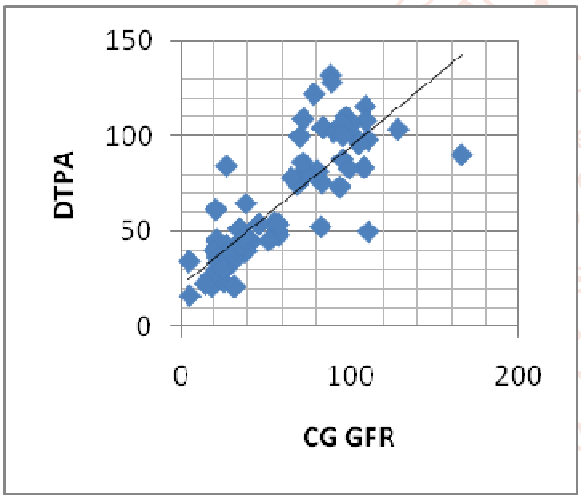

Figure 5. Scatter plot of GFRs determined by DTPA against that by CG GFR formule in healthy study group.

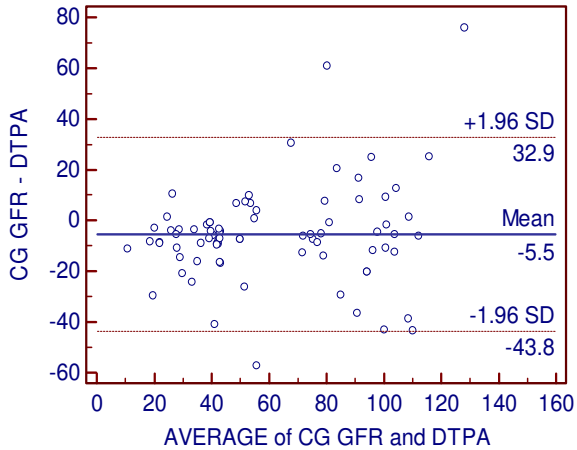

Figure 6. Bland Altman plot of difference between the GFR by CGGFR and DTPA. Solid line represent the mean difference between two methods and dashed line represent the 95% limits of agreement

DISCUSSION: Since K/DOQI CKD has classified CKD into 5 groups, therefore an accurate estimation of GFR is essential for proper staging of the disease, understanding its implications and its appropriate management. There is a lack of an easily available, cheap, reliable and reproducible GFR marker, which has been validated in our population as the prediction equations best perform in the population where they were developed. With this background this study was carried out in the Department of Medicine at Army Hospital (R&R) to correlate serum creatinine based estimation of GFR (eGFR) with measured radio isotope GFR (mGFR) in healthy individuals and chronic kidney disease patients.

Demographic and clinical characteristics of study population

Study includes 100 individuals. Classification was on the bases of their creatinine level and past history of renal disease. Our study has comparatively less number of female (33.3%). This is much less than the prevalent sex ratio in our country (M/F:50/45.7) [2]. Mean age of our subjects was 41.48 ± 14.92 years (range 3 to 85 years). Mean height of our subjects was 162.04 ± 11.74 cm (range 110 to 183 cm). Mean weight of our subjects was 56.93 ± 12.53 kg (range 14 to 82 kg). Mean BSA of our subjects was 1.59 ± 0.21 m^2 (range 0.65 to 2 m^2).

In our study lower mean age and male predominance because of the fact that our hospital is military hospital and most of the patients are serving as defense personnel. In our study the demographic profile is similar to other Indian studies such as Agarwal et al [3], which was also hospital based study on the spectrum of renal disease in Indian adults. Observed, mean age of their patients was 38.69 ± 15.5 years with male predominance (60%).

Correlation of eGFR with mGFR:

We estimated GFR with CG-GFR formula in all cases and compared with mGFR (^{99m}Tc DTPA by Gates method). In healthy subjects mean eGFR by CGGFR is 104.26 ± 31.09 (range 65.4-176.2) ml/min/1.73m^2, whereas mean mGFR by DTPA is 92.15 ± 17.85 (range 49.9-131.8) ml/min/1.73m^2. In healthy subjects eGFR by CGGFR overestimate the mGFR by DTPA GFR. On the other hand there is poor correlation between eGFR by formula with mGFR.

Vervoot [4], Rigalleau [5], Poggio [6], Froissart [7] and Lin [8] et al were amongst the investigators who had also showed that the CG formula persistently overestimated the measured GFR in healthy.

Poggio et al [6] and Froissart et al [7] have also reported that the CG GFR was accurate but not precise in the population without CKD. Lin et al [8] had verified that correcting the original CG formula to estimate GFR does not improve the predictive ability of the CG equation. They also noticed a high bias and poor accuracy compared to DTPA.

Indian studies such as Mahajan et al. [9] has also observed poor agreement of eGFR with mGFR in healthy Indian transplant donors. Similar study was done by Shrinivas et al. [10], in South Asian healthy renal donors and they also observed higher bias and low accuracy in stage 1 CKD.

In our study CKD subjects mean eGFR by CG GFR is 31.10 ± 14.51 (range 4.74 to 57.9) ml/min/1.73m^2, whereas mean mGFR by DTPA is 40.06 ± 13.64 (range 10.4 to 84.19) ml/min/1.73 m^2. In these subjects eGFR by GCGFR underestimate the mGFR by DTPA. On the other hand there

is positive significant correlation (p : <0.001) between eGFR by both formula with mGFR.

Kim DH et al. [11] also reported that CG-GFR and GFR by ^{99m}Tc-DTPA renal scan correlated significantly with MDRD-GFR in all CKD stages and all age groups (p<0.001).

We have also observed that subjects with creatinine value between 0.7 to 3.5 mg/dl, irrespective of their disease status (Healthy & CKD subjects) has significant positive correlation between eGFR (CG GFR with mGFR (DPTA) (p value <0.001). It signifies that with extremes of creatinine (either very low or very high) value eGFR doesn't correlate with mGFR.

We cannot consider DTPA Gate's method as gold standard because there are varieties of sources of errors in the estimation of GFR using the modified Gate's method. The most important, in our opinion, was that the modified Gate's method was derived from an empirical equation obtained using the measured creatinine clearance as reference GFR, to yield total and separate kidneys clearance, because of the well-known pitfalls of CrCl, the Gate's method inherited inevitable shortcomings of CrCl. The Gate's method can be improved if a more proper reference GFR method is used instead of CrCl in prediction of total GFR.

Many studies have been conducted to test the accuracy of the modified Gate's method in estimation of GFR. John et al. [12] compared the ^{99m}Tc-DTPA renal dynamic imaging method with ^{99m}Tc-DTPA plasma clearance as the reference GFR (rGFR), and found significant difference between the modified Gate's method and rGFR. Using inulin clearance as the reference standard, Natale et al. [13] indicated that the Gate's method tended to overestimate GFR at low levels, and underestimate GFR at high levels of GFR. Kazuo Itoh et al. [14] also found that Gates was proved to be inaccurate and less precise than the CG for predicting the GFR. In addition, Gates tended to overestimate the GFR. The renal dynamic imaging method that measured GFR was far from satisfactory, and even less valuable than CrCl [15]. Serum Cr-based GFR equations take into account age, gender and race, and allow a more reliable GFR estimation compared with renal dynamic method.

With the improvement of Creatinine based GFR estimation, the renal dynamic imaging would become more unreliable when compared with the Creatinine based equation. In this study the performances of the CG GFR and the modified Gate's method in GFR estimation were compared. The modified Gate's method showed higher difference and absolute difference, than the modified abbreviated CG GFR.

The one of the limitation of our study lies in the day-to-day variations that are known to occur in serum creatinine (15.5%–19.6%) [16]. Furthermore, we did not pay special attention to the calibration of serum creatinine measurements, which has been shown to be of critical importance in individuals with normal or near-normal serum creatinine values, and to influence the accuracy of MDRD equations. The accuracy of the creatinine based formula could be improved by calibrating serum creatinine measurement.

A Cockcroft–Gault equation is essentially rescaled serum creatinine levels with the same pitfalls as using the serum creatinine level itself. This is based on statistical models predicting averages, and our patient was not average. Therefore, clinical judgment is always required with eGFR, and the clinician has the advantage of being able to consider dietary history and physical examination. These factors are not considered in these equations. eGFR may be inaccurate in patients whose body size and muscle mass or dietary intake (e.g. high protein diets and creatinine supplements) at the extremes of normal range.

CONCLUSION AND RECOOMANDATIONS

In conclusion, the modified Gate's method is undoubtedly an important method in unilateral renal function measurement. We presume that the dynamic renal imaging method for measuring of GFR can be improved by using proper reference GFR, as well as more adequate background subtraction and soft-tissue attenuation correction. However, our results suggest that GFR estimation by Gate's Method was not better than the CG equations. In advance terminal CKD patients précised GFR it not important. It is enough to know whether GFR is getting better or worse. Best way is to determine GFR periodically is by the equations based on Cr (Cockroft Gold) since it is less expensive and less time consuming test. The equation based results are accurate and they do not need to be precise as in clinical trials. Clinical judgment is always required with eGFR, and the clinician has the advantage of being able to consider dietary history and physical examination factors not considered in these equations.

Conflict of interest: None

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