Comparison of Gates' Method and CKD-EPI Equation with Plasma Sample Method for Estimation of GFR

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ABSTRACT

Objectives: **Glomerular Filtration Rate (GFR) is an important parameter of kidney function. Many methods are used to measure GFR namely: inulin clearance, double plasma sample method (DPSM), Gates' method, and equation based method. DPSM has become the gold standard in clinical research. Gates' method is routinely practiced at National Institute of Nuclear Medicine and Allied Sciences. Chronic kidney disease epidemi-ology collaboration (CKD-EPI) equation is encouraged as it is simple and reliable. The aim of the study was assesment of agreement between Gates' method and CKD-EPI equation with plasma sample method for estima-tion of GFR.**

Patients and methods: **This cross sectional observational study was carried out at NINMAS, during July 2017 to June 2018. A total of 70 subjects referred for $_{99m}$TC-DTPA renography along with GFR estimation, were included in this study.**

Result: **The mean GFR value evaluated by DPSM, Gates' and CKD-EPI equation were, 81.86 ± 22.42, 86.13 ± 26.70 and 78.48 ± 23.87 mL/min/1.73 m_2 respectively. A strong positive correlation (r = 0.922) was found between DPSM and Gates' method and also between DPSM and CKD-EPI equation (r= 0.930). The Gates' and CKD-EPI equation also showed strong positive correlation (r = 0.872). The mean difference between DPSM and Gates', between DPSM and CKD-EPI equation, between Gates' and CKD-EPI equation were 4.26 ± 10.45, 3.38 ± 8.78 and 7.64 ± 13.09 mL/min/1.73 m_2 respectively.**

Conclusion: **Strong positive correlation and excellent agreement were observed between DPSM and Gates' and also between DPSM and CKD-EPI equation. Strong correlation was also found in between Gates' and CKD-EPI equation. So, DPSM, Gates' method and CKD-EPI equation can reflect GFR almost equally and used interchangeably.**

Key words: **GRF estimation, Gates' method, DPSM, CKD-EPI equation**

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INTRODUCTION

Kidneys are the vital organs, maintaining the homeostasis of human body. The kidneys are responsible for excreting waste from blood, regulation of water and electrolyte balance, secreting hormone and activating vitamin D (1). Glomerular Filtration Rate (GFR) is the most important parameter of overall kidney function (2). GFR is the volume of fluid filtered from the renal glomerular capillaries into the Bowman's capsule per unit time (3). The filtration speed of the primary urine is the GFR and is approximately 120 ml/min (4). Many methods have been established for measurement of GFR such as; inulin clearance, single or multiple plasma sample method, $_{99m}$Tc-DTPA renogram (Gates' method), serum creatinine and serum cystatin – C based equations, and twenty-four hours endogenous creatinine clearance. Inulin clearance is considered as gold standard for the measurement of GFR but procurement of inulin and the cumbersome procedure pose a challenge for its routine clinical use (2).

GFR can be measured by Nuclear Medicine techniques using different radiopharmaceuticals like Diethylene-triamine- penta- acetic acid (DTPA) and Ethylene-diamine-tetra-acetic acid (EDTA) (2). Plasma clearance of $_{99m}$Tc- DTPA correlates better with inulin clearance. In view of relative simplicity and satisfactory accuracy, the $_{99m}$Tc-DTPA dual plasma sample method was taken as the reference approach in determining GFR by the Nephrology Committee of Society of Nuclear Medicine (5). To avoid repeated blood sampling Gates' proposed gamma camera-based estimation of GFR after administration of radio-labelled DTPA. Gamma camera-based $_{99m}$Tc-DTPA renogram is a simple and easy method for estimation of GFR and the evaluation of renal function in comparison to the standard method of GFR determination i.e. inulin clearance (6). As serum creatinine is an important marker of kidney function, several serum creatinine based estimating equations have been developed over last four decades. Among them, 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 are mentionable. The CKD-EPI equations includes variables for age, race and gender and shows better performance when e-GFR measures about 60-120 mL/min/1.73 m^2, however this method is validated only for the Caucasian population with CKD (2).

Patients & Method

A total of 70 subjects (35 male and 35 female) undergoing ^{99m}TC-DTPA renography with GFR estimation were included in this study. Patients less than18 years of age, severely ill patient, pregnant and lactating mothers were excluded. GFR was estimated by gamma camera based Gates' method, CKD-EPI equation based method and also by double plasma sample method (DPSM), which is considered as the reference method for GFR estimation. Written informed consents were obtained from the patients and ensured proper state of hydration. After a bolus injection of 3-5 mCi of ^{99m}Tc DTPA in patient's forearm, the residual radioactivity was calculated. After DTPA injection, venous blood sample (5 ml) is collected in a syringe from the contralateral arm at 60th and 180th min. The blood sample is centrifuged and one ml of plasma is pipetted meticulously by taking care to avoid interface between red blood cell and plasma. The collected plasma and the standard were counted in an automatic gamma counter for one minute. Decay correction was ensured and timing of sample collection was recorded. ^{99m}Tc- DTPA plasma clearance by Double plasma sampling method (t-GFR) was calculated according to the following Russell's equation :

$$\text{Russell's DPSM: } \frac{D \ln (P_1 / P_2)}{T_2 - T_1 \exp^{(T_1 \ln P_2) - (T_2 \ln P_1) / T_2 - T_1}} \qquad (1)$$

Where D = total injected dose counts (cpm)

P_1 = activity (cpm/ml) at the time of T_1

P_2 = activity (cpm/ml) at the time of T_2

T_1 = 60 min

T_2 = 180 min

The measured GFR is corrected with body surface area (BSA) value of 1.73 m^2. The standard BSA equation is $GFR_{corr} = GFR \times (1.73/BSA\ m^2)$, where BSA values were estimated from the height and weight of the patients using Haycock formula

BSA (m^2) = $0.024265 \times wt^{0.5378} \times Ht^{0.3964}$ (Weight in kilograms, Height in centimeters)

The BSA corrected GFR is distinguished by referring to it in units of ml/min/1.73 m^2(7).

In case of Gates' method kidney can be imaged sequentially using a gamma camera after injection of ^{99m}Tc-DTPA. Region of interest (ROI) was drawn manually to generate a background corrected time activity curve (5). The fractionated uptake (FU) of each kidney is predicted according to Tonnesen's equation; FU = (renal count/e^{-uy}) / total injected dose count x 100. Here the renal count was background subtracted and the counts were expressed in counts per minute (cpm). u = attenuation coefficient of ^{99m}Tc- DTPA and y =kidney depth in cm. In vivo GFR was automatically calculated by commercially available computer software according to the Gates' algorithm after proper input of patient's height and weight (7). The CKD-EPI equation expressed for specified race, gender and serum creatinine level for estimation of GFR and the equation summary is as follows:

a) Female:

If the serum creatinine level ≤ 62 µ mol /L or ≤ 0.7 mg/dl

$GFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$

If the serum creatinine level ≥ 62 µ mol /L or ≥0.7 mg/dl

$GFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$

b) Male:

If the serum creatinine level ≤ 80 µ mol /L or ≤ 0.9 mg/dl

$GFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{Age}$

If the serum creatinine level ≥ 80 µ mol /L or ≥ 0.9 mg/dl

$GFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{Age}$ (8).

RESULT

This cross sectional observational study included 70 subjects (M=35, F=35) of 18 to 75 years of age (40.50 ± 13.67), 137 to 172 cm height (159.4 ± 6.63) and 34 to 87 kilograms of weight (59.28 ± 11.2). Majority (45) of the patients had unilateral hydronephrosis (57%) and four subjects (5.7%) had bilateral hydronephrosis, 13 (18.6%) patients had chronic kidney disease and eight (11.4%) of other clinical diagnosis. Serum creatinine level was within the reference range in 77.1% subjects and serum higher than the reference range in 22.9% subjects.

Obtained GFR (mean) by double plasma sample method was 81.46 ± 22.42 ml/min/1.73 m_2 (range: 29.67 - 159.70), by Gates' method 86.13 ± 26.70 ml/min/1.73 m_2 (range: 22.10 - 158.50) and by CKD-EPI equation 78.48 ± 23.87 ml/min/1.73 m_2 (range: 24 -139) (Table 1).

Table 1. Mean GFRs of studied subjects by different methods (n=70)

Method	GFR Mean ± SD (mL/min/1.73 m^2)	GFR Range (mL/min/1.73 m^2)
Plasma sample method	81.46 ± 22.42	29.67-159.70
Gates' method	86.13 = 26.70	22.10-158.50
CKD-EPI equation	78.48 ± 23.87	24-139

Table 2 and Figure 1, 2 and 3 shows strong positive correlation between the three methods using Pearson's correlation coefficient test.

Table 2: Pearson's correlation between different methods

DPSM and Gates' method	0.922	0.000
DPSM and CKD-EPI equation	0.930	0.000
Gates' and CKD-EPI equation	0.872	0.000

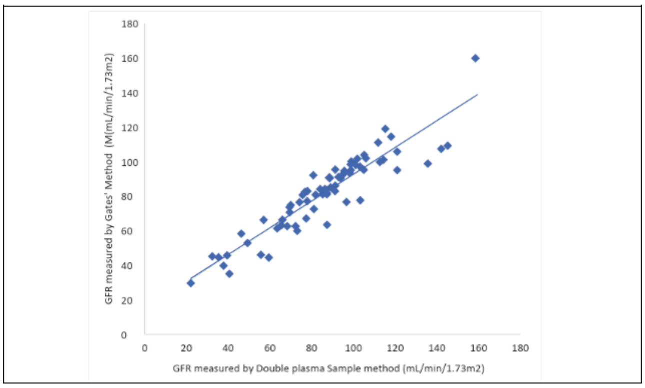

Figure 1: Scatter diagram showing Pearson correlation (r = 0.922; *p* = 0.000) between the GFR measured by DPSM and Gates' method

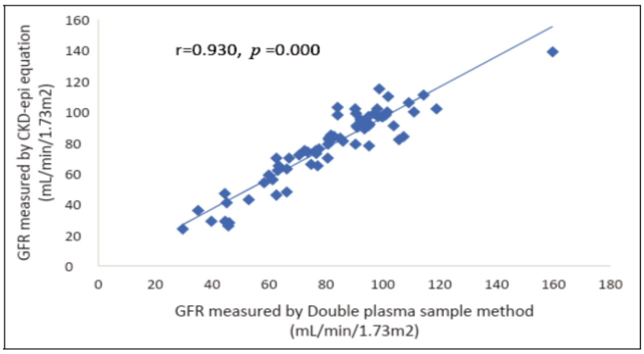

Figure 2: Scatter diagram showing Pearson correlation (r = 0.930, *p* = 0.000) between the GFR measured by DPSM and CKD-EPI equation method

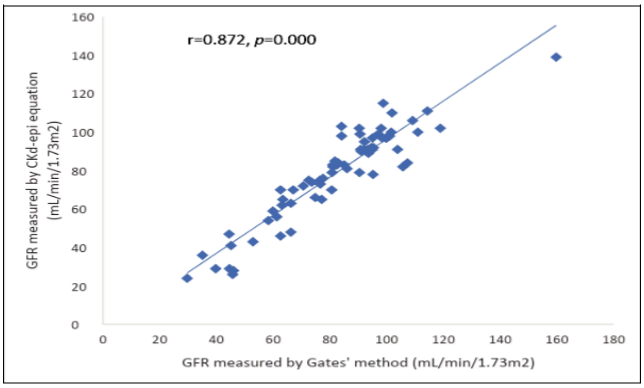

Figure 3: Scatter diagram showing Pearson correlation (r = 0.872 , *p* = 0.000) between the GFR measured by Gates' method and CKD-EPI

The Bland-Altman analysis shows excellent agreement between DPSM and Gates' method, between DPSM and CKD-EPI equation method and also in between Gates' and CKD -EPI equation method (Figure 4, 5, 6). The mean difference between DPSM and Gates', DPSM and CKD-EPI equation method and in between Gates' and CKD-EPI equation were -4.266 ± 10.454 mL/min/m_2, 3.38 ± 8.78 mL/min/1.73 m_2 and 7.6 ± 13.09 mL/min/m_2 respectively. Overall, confidence interval (CI) was 95% .

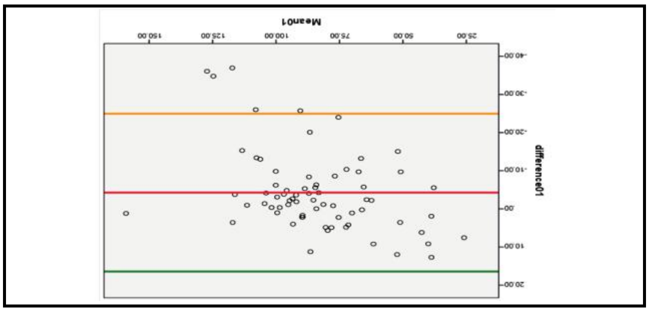

Figure 4: Scatter diagram showing agreement between the GFR measured by DPSM and and Gates' method.

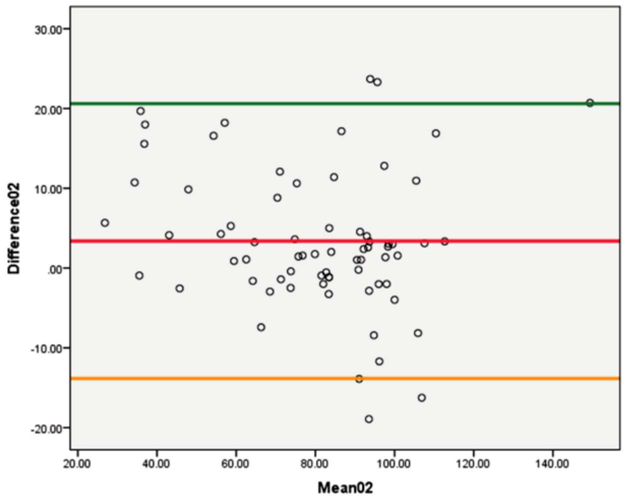

Figure 5: Scatter diagram showing agreement between the GFR measured by DPSM and CKD-EPI equation.

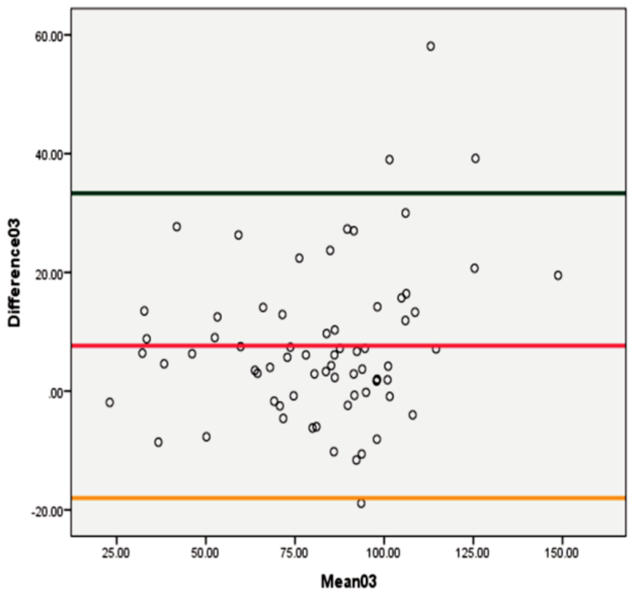

Figure 6: Scatter diagram showing agreement between the GFR measured by Gates' and CKD-EPI equation.

DISCUSSION

Jackson, Blue and Ghaed showed that the Gates' method tended to overestimate GFR in comparison to the DPSM method (9). Itoh also found that Gates' method tended to overestimate GFR in comparison to the method (10). In this study it was observed that, in DPSM, mean GFR was 81.86 ± 22.42 ml/min/m$_2$, ranging from 29.67 to 159.70 ml/min/1.73 m$_2$. Mulay et al. and Kumar et al. reported similar mean GFR measured by DPSM (2 &11). In current study, mean GFR measured by Gates' method, was found 86.13 ± 26.70 ml/min/1.73 m$_2$ ranging from 22.10 to 158.50 ml/min/1.73 m$_2$. It was found that mean GFR measured by Gates' method is slightly higher than mean GFR measured by DPSM.

Ayan et al. found a strong positive correlation between DPSM and Gates' method, where Pearson correlation coefficient (r=0.76) and p=0.0001(12). Similarly, Mutsuddy, et al. found a strong positive correlation (r= 0.833 and p=0.00010) (13). Whereas, studies conducted by Mulay et al.

, Younis et al. and Kumar, et al. showed moderate significant correlation between the DPSM and Gates' method, while correlation was performed by Pearson's correlation coefficient (r=0.57, r=0.68, r=0.685, respectively**)** (2,5 &11).

Mean GFR measured by CKD-EPI equation was 78.48 ± 23.87 mL/ min/ 1.73 m$_{-2}$, ranging from 24 - 139 mL/ min/ 1.73 m$_{-2}$. Younis et al. found slightly higher mean GFR (85.2 ± 22.4 mL/ min/ 1.73 m$_{-2}$), ranging from 45.0 to 124.0 mL/ min/ 1.73 m$_2$ in CKD-EPI equation in patients with obstructive uropathy (5). However, present study showed strong positive correlation (r = 0.930; *p* = 0.000) between DPSM with CKD-EPI equation. Mulay and Gokhale, also found a strong positive correlation (r = 0.7) between DPSM and CKD-EPI equation, which is comparable with the recent studies (2). But Younis et al. showed that moderate significant correlation between DPSM and CKD-EPI equation in both control and patients group (where r=0.37 and 0.46 respectively) (5).

It was found that GFR measured by Gates' method (mean Gates' GFR was 86.13±26.70, ranging from 22.10 to 158.50. mL/ min/ 1.73 m$_2$) is higher than GFR measured by CKD-EPI equation (mean GFR 78.48 ± 23.87 mL/ min/ 1.73 m-2, ranging from 24 - 139 mL/ min/ 1.73 m$_2$). Strong positive correlation (r=0.872; *p*=0.000) was found between Gates method and CKD-EPI equation for measurement GFR. Chen et al. showed CKD-EPI equation based on serum creatinine (CKD-EPI $_{cr}$**)** showed moderate significant correlation with Gates' GFR (r = 0.606) (14). It was observed that the mean difference of GFR measured by DPSM and Gates' method was -4.266 ± 10.454 mL/min/1.73m$_2$, the limit of agreement being -24.95 to 16.22 mL/min/1.73m$_2$. The bias between the methods was considered as not significant. The differences between mean ± 1.96 SD are not clinically significant. The Bland-Altman analysis, showed the *p* value = 0.000 which is <0.05, so, agreement between DPSM and Gates' method is excellent. Kumar et al. showed that the mean difference of

GFR measured by DPSM and Gates' method was -3.17 (95% confidence interval was -7 to 1. 46). The limit of agreement ranged from – 54.3 to 49.7 mL/min/1.73m2 which is comparable with recent study (11). Ayan et al. observed that the mean difference of GFR measured by DPSM and Gates' method was -11.2 ± 10.71 mL/min/1.73m2. The limit of agreement ranged from -32.3 to 9.8 mL/min/1.73m2 which is close to the recent series (12). It was found that the mean difference of GFR measured by DPSM and CKD-EPI equation method was 3.38 ± 8.78 mL/min/m2. The limit of agreement ranged from -13.84 mL/min/1.73m2 to 20.60 mL/min/1.73m2. The bias between the methods was considered as not significant. The differences within mean ± 1.96 SD are not clinically significant. The Bland-Altman analysis, showed the *p* value = 0.000 which is <0.05, so, agreement between DPSM and CKD-EPI equation method was excellent. In this study, it was found that the mean difference of GFR measured by Gates' and CKD-EPI equation method was 7.648 ± 13.09 mL/min/1.73m2. Mean difference between the methods was small. The limit of agreement ranged from -18.01 to 33.31 mL/min/1.73m2. The bias between the methods was considered as not significant. The differences within mean ± 1.96 SD are not clinically significant. The Bland-Altman analysis, showed the *p* value = 0.000 which is <0.05, so, agreement between DPSM and CKD-EPI equation method is excellent.

Conclusion: There were a strong positive correlation between DPSM and Gates' method and also DPSM and CKD-EPI equation method. Strong correlation was also found in between Gates' and CKD-EPI equation method. In case of agreement analysis the mean difference between two methods was small. The differences within mean ± 1.96 are not clinically important. So double plasma sample method (DPSM), Gates' method and CKD-EPI equation methods can reflect GFR almost equally and can be used interchangeably.

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