A COMPARATIVE STUDY OF ESTIMATED GFR VERSUS MEASURED CREATINININE CLEARANCE IN REFERENCE POPULATION OF INDIAN ORIGIN

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ABSTRACT

Objective: The aim of this study was to compare the GFR (glomerular filtration rate) estimating equations with 24hrs creatinine clearance to predict renal function in healthy individuals and kidney donors.

Methods: A descriptive study was conducted at St. Johns Medical College Hospital, Bangalore during the period of December 2013-December 2014. 30 male and 30 female kidney donors/ volunteers aged between 20 – 30 years were enrolled and categorised into four groups based on serum creatinine. Serum creatinine (SCr), urine creatinine (Ucr) and 24hrs creatinine clearance (24 hr urine-CrCl) where measured. Estimated GFR (eGFR) was calculated using Cockcroft-Gault formula (CG/ eGFRCG), the Modification of Diet in Renal Disease equation (MDRD/ eGFRMDRD), and the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI/ eGFRCKD-EPI) equations, their performance was compared with 24 hr urine-CrCl (24 hr urine-CrCl).

Results: The eGFRCKD-EPI showed significant correlation with measured GFR in three groups. The Bias was 4.5, 15.16, and 16.66 ml/min/1.73m² for CKD-EPI eGFR for group I (SCr >0.9), group II (SCr </ =0.9), and group III (SCr >0.7) as seen in the Bland Altman plot.

Conclusion: The eGFRCKD-EPI showed higher correlation with measured GFR (24 hr urine-CrCl ) compared to eGFRMDRD and eGFRCG equations when serum creatinine levels were more than 0.7 mg/dl in females and 0.9 mg/dl in males.

KEYWORDS: 24hrs creatinine clearance (24 hr urine-CrCl) , Cockcroft-Gault (CG/ eGFRCG), eGFR estimated Glomerular filtration rate, GFR= Glomerular filtration rate, Modification of Diet in Renal Disease (MDRD/ eGFRMDRD) equation, The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI/ eGFRCKD-EPI) equation.
INTRODUCTION
Renal function is evaluated in clinical practice to check for kidney disease in chronic conditions like diabetes and hypertension, to calculate drug dosage for renal clearance as in chemotherapy, and to follow the evolution of known kidney disease into its various stages, for prognosis and dialysis.[1]

Glomerular filtration rate is a useful index to assess the kidney function.[2, 3] The GFR varies as per renal mass which corresponds to body mass. Thus GFR is conventionally corrected for body surface area (BSA), since renal mass is proportional to body size, which in healthy adults is approximately 1.73m² and represents an average value for normal young men and women. The normal corrected GFR is 80–120 ml/min/1.73m².[4]

The gold standard for measurement of GFR is clearance of exogenous substances such as inulin, iothalmate or iohexol and radiolabelled isotopes: Technetium- 99m diethyl triamine penta- acetic acid (Tc⁹⁹m DTPA) or chromium 51 Ethylenediaminetetraacetic acid (EDTA) (Cr⁵¹ EDTA).[4] These procedures are costly, time consuming and are not suitable for the routine detection of kidney disease.

Hence GFR is often estimated from the serum concentration of endogenous filtration marker creatinine. The most widely used measures of GFR in clinical practice are based on the 24 hr urine-CrCl considered the measured GFR (mGFR) or serum creatinine equations the eGFR.

GFR prediction equations such as eGFR(CG), eGFR(MDRD), eGFR(CKD-EPI) provide a rapid method of assessing GFR from SCr.[5,6&7] The eGFR(CG), eGFR(MDRD) formulas have their own limitations when used in healthy individuals or donors, since they were developed in patients with chronic kidney disease (CKD). The eGFR(CKD-EPI) formula had individuals of various GFR ranges including normal GFR and also included individuals belonging to various races in the study which derived it. Various studies have observed that the CKD-EPI formula studied in several populations has performed better compared to MDRD formula, more so in individuals with normal GFR.
MATERIALS AND METHODS
A total of 60 healthy Indian adults who underwent the kidney donor workup during the period of December 2013 - December 2014 were included in this study. The following data was collected from the subjects – age, sex, weight, height and medical history to rule out renal disease. The laboratory evaluation included Scr, Ucr and 24-hour urine CrCl. Scr and Ucr values were measured using a Modified Jaffe method traceable to Isotope Dilution Mass Spectrometry (IDMS) with standard reference material (SRM) 967 through the use of appropriate post-calibration correlation factors derived from an offline correlation to the Isotope Dilution- Gas Chromatography/ Mass Spectrometry (ID-GC/MS) reference method for creatinine. The Creatinine was measured on Siemens EXL Max instrument, Siemens, Bangalore, India.\(^8\)

The study subjects were grouped into 2 groups - male and female groups with 30 in each group and males where further grouped into two – group I and group II depending on their serum creatinine levels Males- >0.9 (group I) and ≤ 0.9 (group II )and Females with creatinine levels of >0.7 and ≤ 0.7 as group III and group IV respectively.

The study subjects were given the appropriate instructions for collection of 24hr urine sample and a plastic can was provided for the same.

The mGFR- 24 hr urine-CrCl was calculated as follows\(^4\)

\[
\text{Creatinine Clearance} = \frac{U \times V \times 1.73}{P \times A}
\]

\(U\) = Urine creatinine (mg/dl);
\(V\) = Urine volume / minute i.e., **Total volume**
\(24 \times 60\)
\(P\) = Plasma, Serum creatinine (mg/dl), 1.73=Average body weight and
\(A\) = Body surface area can be calculated either using Duboi’s formula
\(A=\text{height}^{0.73} \times \text{weight}^{0.425} \times 7.1 \times 10^{-3}\)

The eGFR was calculated using eGFR\(_{\text{CG}},\) eGFR\(_{\text{MDRD}},\) and eGFR\(_{\text{CKD-EPI}}\) equations.

Cockcroft-Gault Equation (eGFR\(_{\text{CG}}\))\(^5\)
\(C_{\text{Cr}}= (140-\text{age}) \times \text{weight} \times (0.85 \text{ if female})
\(72 \times S_{\text{Cr}}\)
Where creatinine clearance \((C_{Cr})\) is expressed in milliliters per minute, age in years, weight in kilograms, and serum creatinine \((S_{Cr})\) in milligrams per deciliter.\[^5\]

Modification of Diet in Renal Disease formula, 4-variable MDRD\[^2,6,9,10\]

\[
eGFR_{MDRD} \text{ (IDMS aligned)} = 175 \times (S_{Cr})^{-1.154} \times \text{Age}^{-0.203} \times [0.742 \text{ if female}] \times [1.212 \text{ if black}]
\]

\(S_{Cr}\) is expressed in milligrams per decilitre (mg/dl), eGFR expressed in ml/min/1.73m\(^2\).

The Chronic Kidney Disease Epidemiology Collaboration equation\[^2,7,11\]

\[
eGFR_{CKD-EPI} \text{ equation}
\]

For ‘non-black females’: If Serum creatinine \(\leq 0.7\) mg/dl
\[
eGFR = 144 \times (S_{Cr}/0.7)^{-0.329} \times 0.993^{\text{Age}}
\]

If Serum creatinine > 0.7 mg/dl
\[
eGFR = 144 \times (S_{Cr}/0.7)^{-1.209} \times 0.993^{\text{Age}}
\]

For ‘non-black males’: If Serum creatinine \(\leq 0.9\) mg/dl
\[
eGFR = 141 \times (S_{Cr}/0.9)^{-0.411} \times 0.993^{\text{Age}}
\]

If Serum creatinine > 0.9 mg/dl
\[
eGFR = 141 \times (S_{Cr}/0.9)^{-1.209} \times 0.993^{\text{Age}}
\]

This study was approved by the Institutional Ethical committee.

**Statistical Analysis**

Descriptive statistics was carried out in the present study. The results on continuous variables were presented using Mean (x) and Standard Deviation (SD), Mean \(\pm\) Standard deviation. Paired T test was used to compare the mean of 24 hour creatinine clearance with mean of CG, MDRD, and CKD-EPI. Pearson’s co-relation was used to assess the relationship between 24 hour creatinine clearance with mean of CG, MDRD, and CKD-EPI. Blant-Altman plot was done to compare the different measures using Graph pad. All the analyses were performed by gender stratification and creatinine level stratification P-value less than 5\% was considered statistically significant.
RESULTS AND DISCUSSION

Baseline Characteristics of Patient Population

In the study group the 30 men had mean SCr of 0.945 ± 0.06 mg/dl, the mean height of 167.8 ± 6.22 cm, mean weight of 65.06±6.61 kg and mean BSA of 1.75±0.10m² and the 30 women had mean SCr of 0.80 ± 0.05 mg/dl, mean height of 157.1 ± 6.47 cm, mean weight of 54.06 ±8.34 kg and mean BSA of 1.54±0.12m².

The mean mGFR and eGFR in men; 24 hr urine-CrCl, eGFR<sub>CG</sub>, eGFR<sub>MDRD</sub>, and eGFR<sub>CKD-EPI</sub> were 120.73, 111.47, 99.06, and 110.90 ml/min/1.73 m^2 respectively. And in women the means were 116.69, 94.26, 91.30 and 107.42 ml/min/1.73 m^2 respectively.

In this study it was observed that the mean anthropometric measures of our study populations were lower compared to the western study population in whom these equations have been derived.<sup>[12, 13, 14]</sup> Since the GFR equations use anthropometric variables such as age, sex, body weight for calculation, lower anthropometric values would probably lead to low GFR.

The eGFR estimating equations were developed mainly in western populations and they do not include any correction factors or constants for Asian or Indian populations who have different BSA, height, weight, food habits and ethnicity compared to western population.<sup>[15,16,17]</sup> Significant number of studies have proposed for modification of these GFR equations based on populations characteristics it is being applied for.<sup>[18-27]</sup>

The mean 24 hr urine-CrCl in different Groups, GROUP I, II, III and IV was 110.12, 136.33, 112.87, and 130.11ml/min/1.73 m² respectively. The 95% Confidence Interval of 24 hr urine-CrCl ranged from 105.69 – 115.55 ml/min/1.73 m² in Group I, 132.49 - 140.18 ml/min/1.73 m² in Group II, 104.95 -120.78 ml/min/1.73 m² in Group III and 125.66 - 134.56 ml/min/1.73 m² in Group IV.

The mean eGFR<sub>CG</sub> in different Groups, GROUP I, II, III and IV was 105.02, 117.91, 86.42, and 102.86 ml/min/1.73 m² respectively. The 95% Confidence Interval of eGFR<sub>CG</sub> ranged from 96.95 – 113.09 ml/min/1.73 m² in Group I, 110.61 – 125.21 ml/min/1.73 m² in Group II, 78.93 - 93.91 ml/min/1.73 m² in Group III and 92.57 – 111.61 ml/min/1.73 m² in Group IV.
The Cockcroft Gault formula\[^6\] is not adjusted for body surface area. The eGFR\[^{CG}\][^5] was derived mostly from hospitalised CKD patients mainly men (with only 9 women in the study group).\[^{5,7}\]

The mean eGFR\[^{MDRD}\] in Different Groups, GROUP I , II, III and IV was 87.01, 111.09, 82.62, and 99.97 ml/min/1.73 m\(^2\) respectively. The 95% Confidence Interval of eGFR\[^{MDRD}\] ranged from 83.44 - 90.58 in Group I, 104.32 – 117.87 in Group II, 77.92 – 87.33 in Group III and 99.28 – 100.65 ml/min/1.73 m\(^2\) in Group IV.

The mean eGFR\[^{CKD-EPI}\] in different Groups I, II, III and IV was 100.62, 121.17, 96.21 and 118.62ml/min/1.73 m\(^2\) respectively. The 95% Confidence Interval of eGFR\[^{CKD-EPI}\] ranged from 97.51 – 103.72 in Group I, 118.51 – 123.84 in Group II, 89.85 – 102.56 in Group III and 117.85 – 119.40 ml/min/1.73 m\(^2\) in Group IV.

**Table 1: The Paired Sample t test Difference (Men)**

<table>
<thead>
<tr>
<th>Creatinine</th>
<th>Paired Differences</th>
<th>Mean</th>
<th>SD</th>
<th>Std. Error Mean</th>
<th>95% Confidence Interval of the Difference</th>
<th>t</th>
<th>df</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0.924 hr ur.CrCl - eGFR[^{CG}]</td>
<td>24 hr ur.CrCl - eGFR[^{CG}]</td>
<td>16.02</td>
<td>2.56</td>
<td>0.72</td>
<td>14.89</td>
<td>19.32</td>
<td>17.87</td>
<td>14</td>
</tr>
<tr>
<td>Paired 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paired 2</td>
<td>24 hr ur.CrCl - eGFR[^{MDRD}]</td>
<td>18.11</td>
<td>3.54</td>
<td>0.91</td>
<td>16.15</td>
<td>20.07</td>
<td>19.80</td>
<td>14</td>
</tr>
<tr>
<td>Paired 3</td>
<td>24 hr ur.CrCl - eGFR[^{CKD-EPI}]</td>
<td>4.50</td>
<td>1.45</td>
<td>0.37</td>
<td>3.70</td>
<td>5.31</td>
<td>12.02</td>
<td>14</td>
</tr>
<tr>
<td>&lt;=0.924 hr ur.CrCl - eGFR[^{CG}]</td>
<td>24 hr ur.CrCl - eGFR[^{CG}]</td>
<td>18.42</td>
<td>10.3</td>
<td>2.66</td>
<td>12.71</td>
<td>24.13</td>
<td>6.92</td>
<td>14</td>
</tr>
<tr>
<td>Paired 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paired 2</td>
<td>24 hr ur.CrCl - eGFR[^{MDRD}]</td>
<td>25.24</td>
<td>8.30</td>
<td>2.14</td>
<td>20.64</td>
<td>29.83</td>
<td>11.78</td>
<td>14</td>
</tr>
<tr>
<td>Paired 3</td>
<td>24 hr ur.CrCl - eGFR[^{CKD-EPI}]</td>
<td>15.16</td>
<td>4.55</td>
<td>1.18</td>
<td>12.64</td>
<td>17.68</td>
<td>12.89</td>
<td>14</td>
</tr>
</tbody>
</table>

Paired T Test: The means of eGFR\[^{CG}\], eGFR\[^{MDRD}\], and eGFR\[^{CKD-EPI}\] where compared with 24 hr urine-CrCl to analyse whether the means were same or different, if different was the difference statistically significant.

Paired sample t test for men, group I and group II have high t- value and p-value of 0.00 which shows that the means are statistically different (Table 1). Paired sample t test for women, group III and group IV have high t value and p-value of 0.00 which shows that the means are statistically different (Table 2).
In the present study in all the four groups the MDRD equation significantly under estimated the measured GFR compared to CG formula similar outcome was seen in a study by Piggio et al.\textsuperscript{[20, 21]} The MDRD equation has an constant for black Americans since their height and weight are higher than those of Caucasians but there is no such constant for Asians.\textsuperscript{[9,10,11]} The MDRD was also derived from CKD patients.\textsuperscript{[6,7]} The eGFR_{CKD-EPI} was developed from a population which included CKD patients as well as healthy individuals.\textsuperscript{[6,7,9,10]}

The MDRD Study equation was re-expressed for use with standardized creatinine Values, that is IDMS (isotope dilution Mass spectrometry) but the CKD-EPI equation was developed using standardized creatinine\textsuperscript{[10]}, whereas the CG equation was not re-expressed.

**Table 2: The Paired Sample t test Difference (Women)**

<table>
<thead>
<tr>
<th>Creatinine</th>
<th>Paired Differences</th>
<th>Mean</th>
<th>SD</th>
<th>Std. Error Mean</th>
<th>95% Confidence Interval of the Difference</th>
<th>t</th>
<th>df</th>
<th>Sig. (2-tailed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.7</td>
<td>Pair 1 - 24hr-'CrCl - eGFR_{CG}</td>
<td>26.45</td>
<td>13.81</td>
<td>3.57</td>
<td>18.80 to 34.10</td>
<td>7.41</td>
<td>14</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Pair 2 - 24hr-'CrCl - eGFR_{MDRD}</td>
<td>30.24</td>
<td>7.29</td>
<td>1.88</td>
<td>26.20 to 34.28</td>
<td>16.07</td>
<td>14</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Pair 3 - 24hr-'CrCl - eGFR_{CKD-EPI}</td>
<td>16.66</td>
<td>5.51</td>
<td>1.42</td>
<td>13.61 to 19.71</td>
<td>11.70</td>
<td>14</td>
<td>0.00</td>
</tr>
<tr>
<td>≤0.7</td>
<td>Pair 1 - 24hr-'CrCl - eGFR_{CG}</td>
<td>28.02</td>
<td>17.53</td>
<td>4.53</td>
<td>18.31 to 37.72</td>
<td>6.19</td>
<td>14</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Pair 2 - 24hr-'CrCl - eGFR_{MDRD}</td>
<td>30.14</td>
<td>7.79</td>
<td>2.01</td>
<td>25.82 to 34.45</td>
<td>14.98</td>
<td>14</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>Pair 3 - 24hr-'CrCl - eGFR_{CKD-EPI}</td>
<td>11.48</td>
<td>7.78</td>
<td>2.01</td>
<td>7.18 to 15.79</td>
<td>5.72</td>
<td>14</td>
<td>0.00</td>
</tr>
</tbody>
</table>

To measure the strength of linear relationship Pearson’s Correlation was used (Table 3). The r - value of .843 and .975 in group I (SCr>0.9), the r -value of .760 and .757 in group II (SCr≤0.9) and the r - value of .919 and .931 in group III (SCr>0.7) shows positive correlation for MDRD & CKD-EPI with 24hr CrCl and these are statistically significant with p-value of 0.00/0.01.

This study showed a higher positive correlation with CKD-EPI eGFR than MDRD eGFR with 24hr CrCl. In order to evaluate the agreement among two different measurements techniques that is CKD-EPI eGFR and 24hr creatinine clearance Bland and Altman plots
were used. Bland and Altman plots allowed us to investigate the existence of any systematic difference between the measurements (i.e., fixed bias) and to identify possible outliers.

In this study the GFR estimating equations CG, MDRD AND CKD-EPI under estimated GFR compared to 24hr CrCl but eGFR\textit{CKD-EPI} showed only minimal bias. The Bias was 4.5, 15.16, and 16.66 ml/min/1.73m² for CKD-EPI eGFR for group I (SCr >0.9), group II (SCr <\(=\)0.9), and group III (SCr >0.7) as seen in the Bland Altman plot. Various studies have shown the MDRD equation and CG equation to be less accurate in healthy population without kidney disease.[13, 23, 26]

**TABLE 3: PEARSON’S CORRELATION (r-value)**

<table>
<thead>
<tr>
<th>Creatinine</th>
<th>24Hr-'CrCl mGFR</th>
<th>COCKCROFT eGFR</th>
<th>MDRD eGFR</th>
<th>CKD-EPI eGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;0.9</td>
<td>Pearson Correlation</td>
<td>1</td>
<td>-.300</td>
<td>.843**</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.278</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>&lt;=0.9</td>
<td>Pearson Correlation</td>
<td>1</td>
<td>.632*</td>
<td>.760**</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.011</td>
<td>.001</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>&gt;0.7</td>
<td>Pearson Correlation</td>
<td>1</td>
<td>.508</td>
<td>.919**</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.053</td>
<td>.000</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>&lt;=0.7</td>
<td>Pearson Correlation</td>
<td>1</td>
<td>.191</td>
<td>.271</td>
</tr>
<tr>
<td></td>
<td>Sig. (2-tailed)</td>
<td></td>
<td>.494</td>
<td>.328</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>

**Correlation is significant at the 0.01 level (2-tailed)**

The estimated bias by Bland – Altman Plot for Group I, II and III between 24Hr CrCl \& CKD- EPI was within the 95% limits of agreement indicating the two methods can be interchangeably (Fig 1,2 and 3).
Fig 1: BLAND-ALTMAN SCr >0.9 24Hr CrCl & CKD- EPI
Bias 4.504 ml/min/1.73 m², SD of bias 1.453 ml/min/1.73 m²
95% Limits of Agreement from 1.656 to 7.352 ml/min/1.73 m².

Fig 2: BLAND-ALTMAN SCr </=0.9 24Hr CrCl & CKD- EPI
Bias 15.16 ml/min/1.73 m², SD of bias 4.553 ml/min/1.73 m²
95% Limits of Agreement from 6.234 to 24.08 ml/min/1.73 m²

Fig 3: BLAND-ALTMAN SCr >0.7 24Hr CrCl & CKD- EPI
Bias 16.66 ml/min/1.73 m², SD of bias 5.513 ml/min/1.73 m²
95% Limits of Agreement from 5.853 to 27.47 ml/min/1.73 m²
The present study does have its own limitations. A gold standard like inulin clearance could not be used for measuring true GFR. This descriptive study only included healthy adults between the age of 20 to 30 yrs and only 30 male and 30 female subjects. The 24hr urine collection used for creatinine clearance against which the eGFR equations were compared may have its own errors.[23] This study does have its positive side that it used standard methods to measure Scr and Ucr that is creatinine standardisation traceable to isotope dilution mass spectrometry (IDMS).

CONCLUSION

The present study result from healthy Indian population suggests that the equations, MDRD and CKD-EPI are more accurate than CG and that the CKD-EPI eGFR is the least biased in comparison to 24 hr CrCl. This study results indicate good performance of CKD-EPI equation in evaluation of renal function among healthy adult population.

CONFLICTS OF INTERESTS

All authors have none to declare

REFERENCES


