Assessment of Glomerular Filtration Rates by Cockcroft-Gault and Modification of Diet in Renal Disease Equations in a Cohort of Omani Patients

*Magdi E. Al-Osali,1 Salim S. Al-Qassabi,2 Saud M. Al-Harthi2*

**ABSTRACT:** Glomerular filtration rate (GFR) is the best index of renal function and is frequently assessed by corrected creatinine clearance (C(creat.)). The limitations of C(creat.) have inspired researchers to derive easy formulas to estimate GFR, with Cockcroft-Gault (C-G) and the modification of diet in renal disease (MDRD) being the most widely used. This study aimed to evaluate the validity of these equations by finding the relation between C(creat.) and estimated GFR (eGFR) (area under the curve was 0.846, 0.831, and 0.791; cut-off limits were 61.9, 58.3 and 59.5, respectively). A receiver operating characteristic curve analysis showed that the diagnostic accuracy of eGFRMDRD for diagnosing chronic kidney disease (CKD) was higher than that of eGFRc-G, which in turn was higher than that of eGFRMDRD (area under the curve was 0.846, 0.831, and 0.791; cut-off limits were 61.9, 58.3 and 59.5, respectively). **Conclusion:** C-G and MDRD equations can be an alternative to the C(creat) test for assessing GFR, thus avoiding the need for the cumbersome and expensive GFR test. The MDRD formula had greater validity than the C-G equation and the C-G equation validity was improved by an adjustment to BSA.

**Keywords:** Creatinine; Glomerular Filtration Rate; Diet Modification; Chronic Kidney Disease; Oman.

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glomerular filtration rate (GFR) is considered the best index of renal function as it assesses the progression of kidney dysfunction. The normal value is ~130 and 120 ml/min/1.73 m² for men and women, respectively, depending on age, sex and body size. GFR can be determined by measuring the clearance of exogenous (inulin, 125-iothalamate, 51 Cr-ethylene diamine tetra acetic acid [EDTA], 99mTc-diethylene triamine penta acetic acid [DTPA] and iohexol) or endogenous (creatinine) substances. Methods using exogenous substances are expensive, time-consuming, risky and cannot be easily implemented in clinical practice. Nevertheless, inulin clearance is the gold standard test for GFR as it is freely filtered and is not secreted, reabsorbed, synthesised or metabolised by the kidney. Creatine clearance (CL_{cr}) is an alternative to inulin clearance. Creatine is freely filtered and is not metabolised by the kidney; however, it is secreted by the renal tubules. If the effect of secretion is ignored, then all of the filtered creatinine will be excreted and this will reflect the GFR. Thus the GFR and CL_{cr} will be equal: \[ \text{UCr} \times V \div \text{SCr} \] where UCr is urine creatinine, V is the 24-hour urine volume and SCr is the serum creatinine. However, CL_{cr} tends to exceed the true GFR due to tubular secretion. It should therefore be adjusted to body surface area (BSA) so as to obtain the corrected creatinine clearance (CCL_{cr}) in ml/min/1.73 m² by the following equation:

\[
\text{CCL}_{\text{cr}} = \frac{(\text{CL}_{\text{cr}} \times 1.73)}{\text{BSA}}
\]

The normal value of CCL_{cr} is 95 ± 20 ml/min per 1.73 m² in women and 120 ± 25 ml/min per 1.73 m² in men.

SCr varies inversely with GFR and is used to assess stable kidney function, as a rise in SCr represents a reduction in GFR. However, in acute renal failure, GFR is markedly reduced and there is no time for creatinine to accumulate. The mean SCr values for men and women are 100 and 82 µmol/L, respectively. These values vary by race and differ according to its production, secretion, extrarenal excretion and assay.

In the C-G equation, CL_{cr} can be estimated by the following formula:

\[
\text{CL}_{\text{cr}} (\text{ml/min}) = \frac{(140 - \text{age in years} \times \text{weight in Kg}) \times 1.23}{\text{SCr in µmol/L}}
\]

This formula should be adjusted for BSA to increase its accuracy and compare normal values. It appears to be less accurate in the obese, those of different ethnicities, different age groups, children and pregnant women.

The original MDRD equation has six variables, including urea and albumin which was a limitation.
for the added cost and analytical variation. Recognising this, the MDRD-4 variable equation was developed based on SCr, age, gender and ethnicity by the following formula:

\[
eGFR_{\text{MDRD}} = \frac{175 \times \text{SCr}^{1.154} \times \text{age}^{0.203}}{\text{BSA}}
\]

where SCr equals the square root of SCr in µmol/L and age in years. None of our patients were African descent.

The eGFR \( \text{C-G} \) (ml/min) was then adjusted to BSA to obtain eGFR \( \text{mC-G} \), modified C-G \( \text{mC-G} \) and MDRD \( \text{mC-G} \) (eGFR \( \text{mC-G} \)) equations. Secondly, we sought to replace the CLcr test with eGFR for the assessment of kidney function in clinical practice, thereby avoiding the need for the time-consuming, cumbersome and expensive CLcr test.

Methods

This cross-sectional analytical study was carried out at Bowsher Polyclinic, Muscat, Oman, by auditing the files of subjects reporting to the Internal Medicine Clinic for a CLcr test to assess kidney function from 1 January 2007 to 30 April 2011. Ethical approval was received from the Regional Research & Ethics Committee of the Directorate General & Health Services of the Muscat Region.

The inclusion criteria included adult patients who reported to the Internal Medicine Clinic at Polyclinic for a CLcr test. However, patients who had incomplete data or dialysis therapy were excluded; thus 97 of the 255 files reviewed could not be considered, leaving a total of 158 subjects. Demographic data, such as age, gender, weight, height, body mass index (BMI) and BSA, were recorded.

All subjects were analysed for SCr and subjected to 24-hour urine collection to estimate urine volume (V) and urine creatinine (UCr). The CLcr was calculated by the following equation:

\[
\text{CLcr} \text{ (ml/min)} = \frac{(\text{UCr} \times V)}{\text{SCr}}
\]

The CLcr was then adjusted to BSA to get CCLcr in ml/min per 1.73 m² by the following formula, where BSA equals the square root of [height in cm x weight in Kg]/3600.

\[
\text{CCLcr} = \frac{(\text{CLcr} \times 1.73)}{\text{BSA}}
\]

Depending on a patient’s gender, age and SCr, C-G was used to obtain the predicted CLcr, which was abbreviated as eGFR\( \text{C-G} \), as in the following formula:

\[
eGFR_{\text{C-G}} \text{ (ml/min)} = (140 - \text{age in years}) \times \text{weight in Kg} \times 1.23 \text{ if male (1.04 if female)}/\text{SCr in µmol/L}
\]

The eGFR\( \text{C-G} \) (ml/min) was adjusted to BSA (modified C-G) to obtain eGFR\( \text{mC-G} \) (ml/min per 1.73 m²): eGFR\( \text{mC-G} = \text{eGFR}_{\text{C-G}} \times 1.73/\text{BSA} \).

The MDRD-4 variable equation was used to obtain eGFR\( \text{MDRD} \) in ml/min per 1.73 m² by the following formula:

\[
eGFR_{\text{MDRD}} = 175 \times \text{SCr}^{1.154} \times \text{age}^{0.203} \times 1.212 \text{ (if of African descent) } \times 0.742 \text{ (if female)}/\text{SCr in µmol/L.
\]
30.54 (20.21–163.92) of the studied subjects.

The eGFRMDRD, eGFRmCG, and eGFRCG correlated significantly with CCLCr, with a slightly stronger correlation with eGFRMDRD ($r = 0.701, 0.658$ and $0.605$, respectively; $P < 0.001$).

Studying eGFRMDRD, eGFRmCG, and eGFRCG at a known cut-off value of 90 found that eGFRmCG had a higher validity than eGFRCG and that eGFRMDRD had a higher sensitivity and lower specificity than either eGFRmCG or eGFRCG (sensitivity = 97.4, 93.6 and 92.3; specificity = 22.5%, 27.5% and 26.3%, respectively).

The ROC curve analysis showed that the diagnostic accuracy of eGFRmCG for a diagnosis of CKD was higher than that of eGFRCG. The eGFRMDRD had a higher area under the curve (AUC) and higher sensitivity and lower specificity than either eGFRmCG or eGFRCG [Figure 1 and Table 1].

Regression analysis was performed to predict renal impairment by using eGFRCG adjusted for age, sex, obesity and DM. A regression equation was applied to calculate the predicted score for each patient (ranging from 0–100). The predicted score was entered in a ROC curve to detect its validity as well as to determine the best cut-off value for diagnosing renal impairment. The same was done for eGFRmCG and eGFRMDRD for comparison. A ROC curve analysis showed that the eGFRmCG score had a higher AUC, sensitivity, negative predictive value (NPV) and total accuracy (TA), and lower specificity and positive predictive value (PPV) than the eGFRCG score. Additionally, the eGFRMDRD score had a higher validity than the eGFRmCG score [Figure 2 and Table 2].

Regarding the validity among the studied groups, the eGFRMDRD had a higher validity than either eGFRCG or eGFRmCG in the obese, diabetic, male or the ≥70-year-old subjects. Comparing the validity of eGFRmCG and eGFRCG, this study also showed that eGFRmCG had higher validity in the

| Table 1: The validity of eGFR, eGFRmC-G and eGFRMDRD as a diagnostic tool for renal impairment after receiver operating characteristic curve analysis |
|---------------------------------|-----|---------|--------|--------|--------|--------|--------|
|                                | AUC | $P$ value | Cut-off values* | Sensitivity | Specificity | PPV | NPV | TA |
| eGFR$_{CG}$                     | 0.791 | <0.001 | ≤59.5 | 73.1 | 80.0 | 78.1 | 75.3 | 76.6 |
| eGFR$_{mCG}$                    | 0.831 | <0.001 | ≤58.3 | 75.6 | 85.0 | 83.1 | 78.2 | 80.4 |
| eGFR$_{MDRD}$                  | 0.846 | <0.001 | ≤61.9 | 82.1 | 72.5 | 74.4 | 80.6 | 77.2 |

*mg/min for eGFR$_{CG}$ and mg/min/1.73 m$^2$ for eGFR$_{mCG}$ and eGFR$_{MDRD}$. 

AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value; TA = total accuracy; eGFR$_{CG}$ = estimated glomerular filtration rate by Cockcroft-Gault equation; eGFR$_{mCG}$ = estimated glomerular filtration rate by modified Cockcroft-Gault equation; eGFR$_{MDRD}$ = estimated glomerular filtration rate by modification of diet in renal disease.
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Table 2: The validity of eGFR_{C-G}, eGFR_{mC-G} and eGFR_{MDRD} as a diagnostic tool for the assessment of kidney function after adjustment for age, sex, weight and diabetes

<table>
<thead>
<tr>
<th></th>
<th>AUC</th>
<th>P value</th>
<th>Cut-off values*</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR_{C-G}</td>
<td>0.806</td>
<td>&lt;0.001</td>
<td>≥48.7</td>
<td>80.8</td>
<td>73.8</td>
<td>75.0</td>
<td>79.7</td>
<td>77.2</td>
</tr>
<tr>
<td>eGFR_{mC-G}</td>
<td>0.841</td>
<td>&lt;0.001</td>
<td>≥46.3</td>
<td>84.6</td>
<td>71.3</td>
<td>74.2</td>
<td>82.6</td>
<td>77.8</td>
</tr>
<tr>
<td>eGFR_{MDRD}</td>
<td>0.853</td>
<td>&lt;0.001</td>
<td>≥48.4</td>
<td>84.6</td>
<td>73.8</td>
<td>75.9</td>
<td>83.1</td>
<td>79.1</td>
</tr>
</tbody>
</table>

AUC = area under the curve; PPV = positive predictive value; NPV = negative predictive value; TA = total accuracy; eGFR_{C-G} = estimated glomerular filtration rate by Cockcroft-Gault equation; eGFR_{mC-G} = estimated glomerular filtration rate by modified Cockcroft-Gault equation; eGFR_{MDRD} = estimated glomerular filtration rate by modification of diet in renal disease.

*mg/min for eGFR_{C-G} and mg/min/1.73 m² for eGFR_{mC-G} and eGFR_{MDRD}.

≥70-year-old, male and diabetic subjects; however, in the obese subjects, eGFR_{mC-G} was more sensitive but had less specificity, PPV, NPV and TA than in eGFR_{C-G} [Table 3].

Discussion

GFR is the best index of renal function in health and disease. It can be estimated by measuring the renal clearance of certain substances using exogenous (radioisotopic and non-radioisotopic) filtration markers. However, these methods are impractical and expensive. Endogenous markers such as creatinine have also been used to assess GFR. The accuracy of CL_{cr} may be limited by inaccurate urine collection and creatinine secretion. Not only is urine collection time-consuming and cumbersome, but incomplete collection leads to a reduced CL_{cr} while over-collection leads to an increased CL_{cr}. Moreover, CL_{cr} overestimates the GFR due to tubular creatinine secretion. To compensate for these previous limitations, investigators have devised equations that predict GFR based on SCr, gender, body size, race and age. The most widely used equations are the C-G equation, which produces GFR values in ml/min, and the MDRD equation, which produces GFR values in ml/min per 1.73 m². The C-G equation should be adjusted for BSA to increase its accuracy and enable a comparison with normal values.

In this study, we evaluated the performance of the C-G and MDRD equations for estimating the GFR in a cohort of 158 subjects. An important characteristic of the cohort is that it included subjects whose CCL_{cr} ranged from 10.3–196.5 ml/min per 1.73 m² with sufficient numbers of subjects having CCL_{cr} >60 and <60 (84 and 74, respectively). Thus, the performance of these equations could be assessed over a wide range of kidney function.

Furthermore, because all patients included in this study were Arab, the performances of the C-G and MDRD equations could be assessed in a group of subjects whose anthropometric characteristics are slightly different from those of American or European subjects.

With these different anthropometric characteristics in mind, we compared eGFR_{MDRD}, eGFR_{mC-G} and eGFR_{C-G} with CCL_{cr}. It was found that these equations underestimated GFR in comparison to CCL_{cr} (mean CCL_{cr}, eGFR_{MDRD}, eGFR_{mC-G} and eGFR_{C-G} were 69.52, 62.89, 66.37 and 66.87, respectively). This can be explained by the fact that CCL_{cr} exceeds the true GFR by 19% because of tubular secretion. In their study, Froissart et al. showed that there was a very good global agreement between measured GFR and both eGFR_{MDRD} and eGFR_{mC-G}. On average, eGFR_{MDRD} was only 1.0 ml/min per 1.73 m² less than measured GFR; eGFR_{mC-G} was only 1.9 ml/min per 1.73 m² greater than measured GFR. However, Froissart et al.'s study compared eGFR_{MDRD} and eGFR_{mC-G} against GFR measured by 51Cr-EDTA renal clearance, and not CCL_{cr}, and did not evaluate eGFR_{C-G}. Similarly, in 1999, Levey et al. documented that the C-G formula largely overestimated measured GFR.

The current study demonstrated that eGFR_{MDRD}, eGFR_{mC-G} and eGFR_{C-G} can replace CCL_{cr} in practice, avoiding the limitations of CCL_{cr} as evidenced by the significant correlation between them, with a stronger correlation with eGFR_{MDRD} (r = 0.701, 0.658 and 0.605, respectively; P <0.001). These results are supported by a Pakistani study which compared eGFR_{MDRD} and eGFR_{C-G} with CCL_{cr} in 369 cases, revealing a significant correlation between them, with a stronger correlation with eGFR_{MDRD} (r = 0.788 for eGFR_{MDRD} and r = 0.775 for eGFR_{C-G}). However, that study did not evaluate eGFR_{mC-G}. In 2006, Shoker et al. compared...
eGFR\textsubscript{mc-G} and eGFR\textsubscript{C-G} with CCL\textsubscript{cr}, documenting that eGFR\textsubscript{mc-G} gave superior results compared to eGFR\textsubscript{C-G}, with an overall accuracy in the general and subgroup analysis. Similarly, our results showed that eGFR\textsubscript{mc-G} had a stronger correlation with CCL\textsubscript{cr} than eGFR\textsubscript{C-G} emphasizing that the correction for BSA increases the validity of the C-G equation. The difference between the two studies is that eGFR\textsubscript{mc-G} and eGFR\textsubscript{C-G} were compared with CCL\textsubscript{cr} in the Shoker et al. study, but in our study they were compared with CCL\textsubscript{cr}, which is more accurate. In 2012, Alcântara et al. compared eGFR\textsubscript{C-G} with CCL\textsubscript{cr} and no significant difference was found between the mean eGFR\textsubscript{C-G} (64.7 ± 27.4) and the mean CCL\textsubscript{cr} (68.4 ± 32.6) and a correlation between them was found ($r = 0.68; P < 0.001$). Using lean body weight instead of total body weight to obtain the eGFR\textsubscript{C-G}, the correlation coefficient was increased to 0.75 ($P < 0.001$). However, Alcântara et al.’s study did not evaluate eGFR\textsubscript{mc-G} and eGFR\textsubscript{MDRD} as in our study.

In studying eGFR\textsubscript{MDRD}, eGFR\textsubscript{mc-G} and eGFR\textsubscript{C-G} as a diagnostic tool for renal impairment, as
detected by CCL_{cr} and at a known cut-off value of 90, it was found that eGFR_{mc-G} had a higher validity than eGFR_{C-G}. This emphasises that correction for BSA increases the validity of the C-G equation and that eGFR_{MDRD} had a higher sensitivity and lower specificity than either eGFR_{mc-G} or eGFR_{C-G}. A ROC curve analysis showed that the diagnostic accuracy of eGFR_{mc-G} for diagnosing CKD was higher than that of eGFR_{C-G}, and that eGFR_{MDRD} had a higher sensitivity, higher AUC and a lower specificity than either eGFR_{C-G} or eGFR_{mc-G}. By doing a regression analysis to predict renal impairment, using eGFR_{C-G}, eGFR_{mc-G} and eGFR_{MDRD} adjusted for age, sex, obesity and DM, the ROC curve analysis showed that the eGFR_{mc-G} score had a higher AUC, sensitivity, NPV and TA, and a lower specificity and PPV than that of the eGFR_{C-G} score. Additionally, it showed that the eGFR_{MDRD} score had a higher validity than the eGFR_{mc-G} score. Our results supported those of Srinivas et al., whose study compared eGFR_{MDRD} and eGFR_{mc-G} with GFR measured by 99mTc-DTPA renal clearance in 599 renal donors; this study demonstrated that eGFR_{MDRD} performed better in terms of global bias, precision, correlation and accuracy than eGFR_{mc-G}.^{21}

Regarding the validity among studied groups, our study showed that eGFR_{MDRD} had a higher validity than either eGFR_{C-G} or eGFR_{mc-G} in males, those with DM, individuals ≥70 years of age and those who were obese. The eGFR_{mc-G} had higher validity in diabetics, males and those ≥70 years of age than eGFR_{C-G}; however, in the obese subjects, eGFR_{mc-G} was more sensitive but had less specificity, PPV, NPV and TA than eGFR_{C-G}. This was similar to Froissart et al’s study, which showed that eGFR_{mc-G} had the lowest level of precision for obese subjects.^{19}

In 2005, Rigalleau et al. compared eGFR_{MDRD} and eGFR_{mc-G} with measured GFR in 160 diabetic patients, and revealed that eGFR_{MDRD} and eGFR_{mc-G} correlated well with measured GFR, while eGFR_{MDRD} underestimated and eGFR_{mc-G} overestimated it. The ROC curve analysis showed that the maximum diagnostic accuracy of eGFR_{mc-G} for diagnosing CKD was lower than that of eGFR_{MDRD}. It was concluded that the MDRD equation is more accurate for the diagnosis of renal failure in diabetic patients.^{22} However, eGFR_{MDRD} and eGFR_{mc-G} were evaluated against measured GFR by 51Cr-EDTA clearance and not against CCL_{cr}. The eGFR_{C-G} was not evaluated.

Based on the current study, as well as other studies, it is clear that the measurement of Cl_{cr} using a 24-hour urine collection system does not improve the estimate of GFR compared to that provided by the C-G and MDRD equations. Nevertheless, this system provides useful information for the estimation of GFR in individuals with unusual dietary intake (for example in subjects with vegetarian diets or those taking creatine supplements), or abnormal muscle mass (for instance as a result of an amputation, malnutrition or muscle wasting). It is also useful for the assessment of diet and nutritional status, and for assessing the patient’s status when there is a need to start dialysis.^{9}

There are several limitations to this study. First, Cl_{cr} was used as the reference method for GFR although the measurement of Cl_{cr} has many theoretical and practical difficulties. Ideally it should be substituted by inulin or isotope clearances as a reference to verify the accuracy of the results. Second, it would be more relevant to compare C-G and MDRD formulas in a multicentre environment.

**Conclusion**

C-G and MDRD equations can be used as an alternative to the Cl_{cr} test for assessing GFR, thereby avoiding the cumbersome, time-consuming and expensive GFR test. The MDRD formula had better validity in this study than the C-G equation and the validity of the C-G equation was improved by an adjustment to the BSA.

**References**


