An audit of 24-hour creatinine clearance measurements at Tygerberg Hospital and comparison with prediction equations

Mia le Riche, Annalise E Zemlin, Rajiv T Erasmus, M Razeen Davids

Background. Internationally, clinical guidelines recommend the use of creatinine-based equations to estimate glomerular filtration rate (GFR) for assessment and follow-up of kidney disease. The routine use of 24-hour creatinine clearances (CrCl) is no longer advocated.

Objectives. To examine the indications for requesting CrCl at Tygerberg Hospital, identify problems associated with the procedure, and evaluate the utility of the Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations with different levels of renal dysfunction in the ethnic groups of the Western Cape.

Methods. A clinical audit of CrCl was performed. The estimated GFR as predicted by the modified CG and MDRD formulae was compared with CrCl in 252 patients, representing three local ethnic groups. MDRD formulae with and without the correction factor for black ethnic group (MDRD-B) were evaluated.

Results. Problems with urine collection or data supplied were identified in one-third of CrCl requests, leading to unreliable results. The CG correlated best with CrCl in the group as a whole. The average absolute and percentage differences from CrCl in the different ethnic groups were as follows: coloured (mixed ethnicity) (N = 186) – CG 13.4 ml/min/1.73 m^2 (18%), MDRD 16.8 ml/min/1.73 m^2 (23%) and MDRD-B 27.9 ml/min/1.73 m^2 (38%); black (N = 21) – CG 14.8 ml/min/1.73 m^2 (19%), MDRD 12.9 ml/min/1.73 m^2 (17%) and MDRD-B 25.1 ml/min/1.73 m^2 (33%); white (N = 45) CG 13.5 ml/min/1.73 m^2 (19%), MDRD 15.3 ml/min/1.73 m^2 (21%) and MDRD-B 24.8 ml/min/1.73 m^2 (35%). Throughout the renal function levels (chronic kidney disease stages 1 - 5) CG correlated better with CrCl than MDRD.

Conclusions. Possible reasons for poor correlations include a high prevalence of obesity, underweight and normal GFR in the study population. There is a need for further research, using a gold standard, into the accuracy of these prediction equations in our unique patient populations before firm recommendations can be made regarding their use. Until then CrCl will continue to be widely used. Greater efforts at patient and health care worker education are required to ensure proper collections.

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Current international guidelines for the detection, evaluation, and management of chronic kidney disease (CKD) recommend using creatinine-based prediction equations to estimate glomerular filtration rate (GFR) rather than using 24-hour creatinine clearance (CrCl) measurements.[1,2] Several such equations have been described, most of which take into account age, gender, race, weight and/or other variables that determine muscle mass and may affect the relationship between serum creatinine and GFR. In adults, the Modification of Diet in Renal Disease (MDRD) study equations (in particular the 4-variable version) and the Cockcroft-Gault (CG) equation are recommended.[1,2]

However, in certain situations the equations have not been validated and the use of CrCl is still recommended. These include pregnancy, and patients with unusual body habitus (obesity, amputations, muscle wasting) or diet (vegetarians). CrCl is also recommended to assess renal function before initiating chemotherapy or prescribing renally excreted drugs with a narrow therapeutic margin, for the assessment of potential kidney donors and patients with normal or near-normal renal function, and in patients with end-stage renal disease.[2-8]

The problems of using the CrCl are well documented – it is time-consuming and cumbersome, inaccuracies may result from incomplete urine collections or from over-collections, and the tubular secretion of creatinine causes this method to overestimate GFR.

Prediction equations need to be validated for the population in which they are to be used. Racial differences affect serum creatinine because of differences in muscle mass and renal handling of creatinine.[7] Therefore, with an equivalent GFR, blacks have higher serum creatinine levels, while Hispanic and

Department of Pathology, Division of Chemical Pathology, National Health Laboratory Service, Tygerberg Hospital and Stellenbosch University, Tygerberg, W Cape
Mia le Riche, MB ChB
Annalise E Zemlin, MB ChB, FC Path (Chem), MMed (Chem Path)
Rajiv T Erasmus, MB BS, FMC Path, FACB, DABCC, DHSM

Division of Nephrology and Department of Medicine, Stellenbosch University, Tygerberg, W Cape
M Razeen Davids, MB ChB, FCP (SA), MMed (Int Med)

Corresponding author: *A Zemlin (azemlin@sun.ac.za)*

Asian individuals have lower creatinine levels.[9] There is still a paucity of published data on the applicability of the CG and MDRD formulae in many ethnic groups other than Caucasians and African-Americans, the groups in which these equations were originally derived.

We report the findings of a clinical audit of 1 000 CrCl requests received at Tygerberg Hospital and also report the results of a comparison of estimated GFR derived from CrCl with that from the CG and MDRD equations in a group of 186 patients of mixed ethnicity (coloured).

Methods

A retrospective audit was performed of 1 000 consecutive requests received at our laboratory between October 2002 and April 2003. Laboratory data and medical records of the patients involved were reviewed, and demographic and diagnostic data recorded. Collection errors, based on the reference range for 24-hour creatinine excretion for sex and body mass,[10] and other related problems were identified.

We then compared the estimated GFR derived from the CrCl with that from the CG and MDRD equations in the adult coloured patients – too few samples were received from patients of other race groups to allow for meaningful comparisons. Samples from patients who were pregnant, under the age of 18 years, or who had obvious errors as described above were excluded. We excluded these samples and samples that were not suitable for analysis (N = 187) and those of unknown race (N = 33). This left us with samples from 252 patients, of whom 186 were coloured. To enable comparison with the MDRD equation, which estimates GFR corrected for standard body surface area (BSA), we corrected the CG and CrCl results for BSA and also employed a correction factor of 0.9 (as used in similar studies[5]) in an attempt to compensate for tubular secretion of creatinine. These calculated estimates are referred to as CrCl-GFR and CG-GFR. We used the 4-variable MDRD equations without (MDRD) and with the correction factor of 1.212 for black ethnicity (MDRD-B).

Results

We received 1 000 samples from 674 patients; of these, 482 (71.5%) were female, and 192 (28.5%) male. There were 15 samples from children under the age of 18 years (1.5%), and 187 samples (19%) from pregnant subjects. Most of the patients (74%) were coloured, reflecting the population served by Tygerberg Hospital.

The Division of Endocrinology was responsible for 210 (21%) of the requests, most often for the evaluation of renal function in patients with diabetes mellitus. The Department of Obstetrics and Gynaecology submitted 187 requests (19%) from pregnant patients, with the most common diagnosis in this group being pre-eclampsia (58%). The third most common origin for the requests was the Department of Oncology where patients were being evaluated before chemotherapy (151 patients, 15%), with bronchus carcinoma being the most common neoplasia (41% of these). Interestingly, very few samples were received from the Division of Nephrology (N = 10; 1%), reflecting a change in their practice to rely mainly on calculated estimates of GFR and also on the protein/creatinine ratio on spot urine samples instead of the 24-hour urine for quantifying proteinuria in patients with CKD.

Problems were encountered with 326 (32.6%) CrCl requests received; 113 (11.3%) had inadequate information on the request form (no weight or height) or no serum sample provided, 172 (17.2%) were probably undercollected, and 41 (4.1%) were probably overcollected. In 55 patients (8% of 674 patients) more than one request had one of these errors. Even after excluding these samples, there was still poor correlation between consecutive CrCl samples obtained within a 7-day period (N = 105; r = 0.67). Weights (r = 0.99), heights (r = 0.97) and serum creatinine values (r = 0.97) from these samples were closely correlated.

Most of the samples were from patients with normal or near-normal renal function, with 35% of the samples from adult patients (including pregnant subjects) having a CrCl-GFR > 90 ml/min/1.73 m^2; 40% were in the 60 - 90 range, 19% in the 30 - 60 range, 4% between 15 and 30, and only 2% less than 15.

When comparing the CrCl-GFR with prediction equations in valid samples from coloured patients (N = 186), the CG-GFR had the best agreement with the CrCl-GFR (Table I, Figs 1 and 2). There was better agreement when using the MDRD equation without correcting for black ethnicity than when using the correction factor. Although the mean value obtained by the CG-GFR is similar to the mean CrCl-GFR (Table I), the Bland-Altman difference plots are more informative about agreement across the range of GFR. There was a clear increase in difference of CG-GFR versus CrCl-GFR at higher levels of GFR (Fig. 1) – a similar distribution was seen with the 2 MDRD formulae (data not shown). The mean difference was 0.03 ml/min/1.73 m^2 (± 1.96 standard deviation (SD) of 35.2), while the mean percentage difference was 0% (± 1.96 SD of 52%).

Discussion

The difficulties associated with using 24-hour urine collections to determine CrCl are clearly illustrated in this study, with problems identified in approximately one-third of samples. Because the tests are usually repeated, this is costly and may prolong hospital stays. Where insufficient anthropometric data were received, CrCl results reported by our laboratory could not be corrected for BSA. Where no blood sample was received no CrCl result could be calculated. In cases of over- or undercollection, a comment was included that the results probably overestimated or underestimated GFR. Our findings underscore the need to educate patients and medical staff regarding the procedures for performing an accurate 24-hour urine collection.

Table I. Comparison of different measures of GFR in samples obtained from non-pregnant coloured adults (*N* = 186)

Method of GFR estimation	Mean (± 1 SD)	Average difference from CrCl-GFR (ml min/1.73 m²) (%)
CrCl-GFR	72.5 (31.0)	-
CG-GFR	72.4 (32.1)	13.4 (18)
MDRD	81.6 (35.6)	16.8 (23)
MDRD-B	98.9 (43.2)	27.9 (38)

GFR = glomerular filtration rate; CrCl = creatinine clearance; CG = Cockcroft-Gault equation; MDRD = Modification of Diet in Renal Disease equation; MDRD-B = MDRD for black ethnicity; SD = standard deviation.

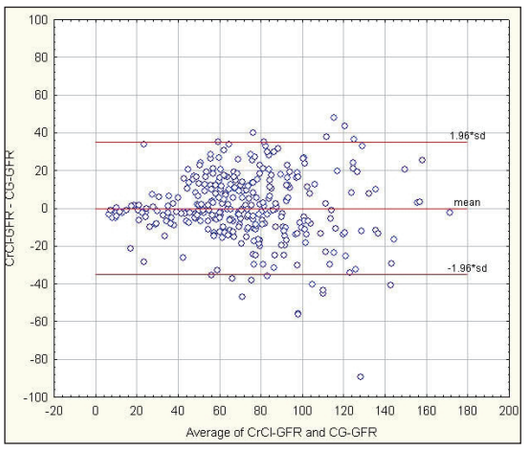

*Fig. 1. Bland-Altman plot showing the agreement between CrCl-GFR and CG-GFR in samples from non-pregnant coloured adults (*N = *186). Differences are absolute in ml/min/1.73 m².*

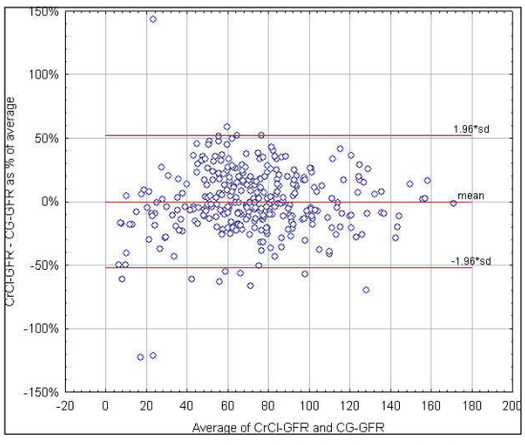

*Fig. 2. A percentage-transformed Bland-Altman plot showing the agreement between CrCl-GFR and CG-GFR in samples from non-pregnant coloured adults (*N = *186). Differences are reflected in percentages.*

The study revealed a swing towards the use of prediction equations in patients with CKD but also highlighted cases where the equations could not have replaced CrCl. There were many samples from patients with normal renal function, including pregnant patients, and patients evaluated for chemotherapy. Underweight (21%) and obese patients (25.8%) also comprised a large proportion of the requests.

The differences obtained between estimated GFR and CrCl-GFR were clinically significant, being up to 52% (the ± 1.96 SD level). This is seen especially in patients with higher GFR values, and may clearly result in patients being placed in the wrong CKD category. Because we compared the new method (the prediction equations) with a method beset by many problems, it is impossible to draw conclusions about the accuracy of these equations from this audit. The finding that there was such poor correlation between consecutive CrCl-GFRs from the same patients, underscores the lack of reliability of this method.

There is clearly a need for research to evaluate the CG and MDRD prediction equations in the different South African ethnic groups, but a gold standard method must be used for comparison. In the meantime, we suggest using either the CG or standard MDRD equations in coloured patients. Although we are still not sure whether these equations will yield results closely approximating the 'true GFR' in our patient populations, it must be emphasised that the correlation between repeated estimates of GFR using these equations is excellent, in stark contrast to our experience with consecutive 24-hour urine collections. Estimated GFR is therefore more than adequate for following the trend of renal function in the routine management of most patients.

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