Improvements in the use of plasma creatine as a marker of the glomerular filtration rate
Kemperman, F.A.W.

Citation for published version (APA):
Kemperman, F. A. W. (2001). Improvements in the use of plasma creatine as a marker of the glomerular filtration rate
Chapter 1

Formula-derived prediction of the glomerular filtration rate from plasma creatinine concentration

Frits AW Kemperman, Raymond T Krediet, Lambertus Arisz.

Department of Internal Medicine and Nephrology of the Academic Medical Center, University of Amsterdam, The Netherlands

Nephron, in press
A review is given of the various published formulas to predict GFR from plasma creatinine concentration. Special attention is given to their accuracy and precision in various patient groups. The accuracy (or bias) and precision was good in patients with mild to moderate renal insufficiency and with Child A liver cirrhosis. The accuracy was less in African American patients and in healthy subjects. Precision was less in diabetic patients. Both accuracy and precision were poor in severe chronic renal failure, in Child C cirrhosis and in the elderly. Administration of cimetidine to inhibit tubular creatinine secretion and the use of an enzymatic creatinine assay that lacks interference lead to an improvement of GFR-prediction and follow-up. It corrects overestimation in the low GFR-range and underestimation in the high GFR-range, often reported in studies of prediction formulas. Formulas for GFR-estimation can only be applied when plasma creatinine is stable and when patients are not severely wasted or obese. The formula of Cockcroft and Gault is still the most widely used for GFR-estimation. Newer formulas did not improve the precision in a meaningful way.
Introduction

Estimation of the glomerular filtration rate (GFR) in individual patients is required for the assessment of the severity of renal disease, for dosing regimens of various drugs and for appraisal of renal involvement in systemic diseases, such as diabetes mellitus or systemic lupus erythematosus. In clinical practice an approximation of GFR is often obtained from the plasma creatinine concentration. This may give unreliable results, because plasma creatinine is not only dependent on GFR, but also on muscle mass, which varies with age, weight and gender [1]. In case of paraplegia or muscle diseases, plasma creatinine is low because of reduced muscle mass [2]; in patients with liver cirrhosis muscle mass is reduced and in addition a decreased ability to produce creatinine is important [3,4]. Conversely, a high protein intake can lead to a 10% increase in creatinine production and the ingestion of large amounts of cooked muscle meat increases plasma creatinine because of absorption of ingested creatinine in the bowel [5,6].

Furthermore, a marked reduction in GFR can be present before it is reflected in a plasma creatinine concentration above the upper limit of the normal range. This is due to 3 causes: (1) the power relationship of GFR and plasma creatinine [7]; (2) an increase of plasma creatinine within the normal range in an individual patient; (3) tubular secretion of creatinine, which is relatively more important when GFR is lower [8]. Moreover, GFR can remain in the normal range while functional reserve capacity is reduced or when hyperfiltration occurs in a lower total nephron mass [9]. And finally, in severe chronic renal failure (GFR < 10 ml/min) creatinine can be excreted or metabolized by extrarenal pathways, probably the intestinal microflora. This may account for up to 66% of the daily creatinine production in these patients [10-12].

The laboratory assay used is important when GFR is estimated from plasma creatinine. Most laboratories still use the alkaline picrate assay based on a colour reaction [13], which despite modifications, gives a falsely high plasma creatinine concentration. This is due to non-creatinine chromogens and may increase measured plasma creatinine up to 120 % of the true value in the normal range [5,14,15]. Also some drugs, especially cephalosporins, and endogenous substances such as glucose and acetoacetate interfere positively with the alkaline picrate assay [16]. In case of diabetic or alcoholic ketoacidosis plasma creatinine concentrations can be falsely elevated by 35-389 µmol/l, depending on the type of analyzer, the concentration of acetoacetate and to a lesser extent that of glucose [17,18]. Enzymatic assays lack this interference, except for dopamine and 5-flucytosine, and give identical results to the reference method that uses high-performance liquid
chromatography[16,19-21] Bilirubin, even in a slightly enhanced concentrations of 10-50 μmol/l, interferes negatively with both alkaline picrate and enzymatic assays [5,16,22].

The use of endogenous creatinine clearance as an estimate of GFR, introduced by Popper and Mandel in 1937, also has major shortcomings [23-28]. In addition to the necessity for accurate urine collections, creatinine clearance overestimates GFR because of tubular secretion of creatinine. In normal renal function this accounts for 10-40 % of the GFR [29-31] with marked interindividual variability. Tubular secretion can increase to more than 100 % in patients with a GFR of about 40 ml/min/1.73m², especially in glomerulopathic and proteinuric patients [8,32,33]. When GFR is reduced below 20 ml/min this percentage decreases again [30,34]. Tubular reabsorption of creatinine in humans has only been demonstrated in case of dehydration and very low urine flow [29,35,36].

Tubular creatinine secretion can be inhibited by administration of cimetidine, trimethoprim, high dose salicylates or pyrimethamine [37-39]. Already in 1935 Shannon described inhibition of tubular creatinine secretion in humans by phlorizin [40]. Cimetidine has a higher affinity for the organic cation transporter at the luminal side of proximal tubular cells and may inhibit creatinine secretion completely [41-44]. Famotidine and ranitidine do not have this effect, probably due to a lower affinity for the transport carrier [45,46]. Other drugs also increase plasma creatinine concentration either due to an influence on the production rate and release of creatinine, such as corticosteroids and active vitamin D metabolites, or by a decrease in the distribution volume of creatinine due to inhibition of creatinine influx into the erythrocytes [47]. This has been described for phenacemide [48].

To improve GFR-estimation from plasma creatinine concentration, formulas or nomograms which incorporate variables such as age, weight and gender can be used. These have been designed to estimate creatinine clearance for adequate drug-dosing without the necessity of accurate urine collection [1,7,49-57]. The value of these formulas for GFR-prediction is likely to increase when an accurate plasma creatinine assay and inhibition of tubular secretion is performed.

The aim of this review is to analyze the accuracy and precision of formula-derived GFR-estimations on the basis of plasma creatinine concentration, in situations with normal and impaired GFR and in different patient groups. First, we will briefly refer to formulas for estimation of creatinine clearance. The use of other endogenous GFR-markers, such as the concentrations of serum β₂-microglobulin or cystatin-C, will not be discussed.
Creatinine clearance prediction formulas

Several formulas have been developed for bedside estimation of creatinine clearance, most often to facilitate drug dosing (Table 1) [1,7,49-55]. These formulas use individual variables to give an estimate of creatinine production per unit of time. This estimate is then divided by the plasma creatinine concentration to obtain a clearance value. Several authors performed 24-hour urine collections of patients without overt renal disease in different age groups [1,50,51,56-58]. The urinary creatinine excretion per kg of body weight was shown to decrease with age, so most formulas had age and body weight in the numerator. A 10-20% reduction of the numerator has been suggested for female patients, because of a lower muscle mass/body weight ratio [1,50,51]. Lott et al. suggested that lean body mass (LBM) should be used instead of body weight [58]. However, the formula to calculate LBM is more difficult than the prediction formula itself. Therefore, this approach has not been generally adopted. Siersbaeck-Nielsen et al. and later Bjornsson et al. constructed nomograms to estimate creatinine clearance [56,57].

Other authors designed formulas for specific patient groups, such as those with paraplegia, obesity, cancer, severe infections or trauma [2,55,59-61]. For paraplegic patients Mirahmadi et al. suggested a correction factor for the Cockcroft-Gault formula of 0.8, because of a lower muscle mass/body weight ratio, but later Thakur et al. proposed that compensatory muscle hypertrophy due to intensive physical therapy obviated the need of a correction factor in younger paraplegic patients [2,62]. In obese patients more importance has been attributed to height instead of weight [55]. Also, formulas for a changing plasma creatinine concentration were designed, calculating the creatinine clearance from a change in creatinine output, assuming that the change in creatinine concentration is equal over the whole volume of distribution [63,64]. It was suggested that in this way, there was no need to wait for a new steady state of plasma creatinine to be reached, which is required for all other formulas. In a study of elderly patients Goldberg et al. concluded that no acceptable formula existed for bedside estimation of creatinine clearance in this patient group [65]. The same holds true for patients with liver disease [54]. In hospitalized patients with advanced HIV disease each of the existing formulas overestimated creatinine clearance, even after correction for lean body mass [66]. For healthy individuals and renal patients the formula of Cockcroft and Gault gave the best estimate of creatinine clearance [67]. In cardiac patients, who were often older, obese and had diabetes, the more complicated formula of Salazar and Corcoran was slightly better [68].
### Table 1 Formulas for rapid estimation of creatinine clearance ($C_r$).

<table>
<thead>
<tr>
<th>Author(-s)</th>
<th>Formula for $C_r$</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards and Whythe</td>
<td>$\frac{94.3}{S_c} - 1.8$ (\frac{69.9}{S_c} + 2.2) (\frac{100}{S_c} - 12) (\frac{80}{S_c} - 7) (\frac{14.4}{S_c})</td>
<td>(ml/min) [49]</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>$\frac{14.4}{S_c} \text{ age-20}$ (\frac{98.16}{S_c})</td>
<td>(ml/min/1.73m²) [50]</td>
</tr>
<tr>
<td>Mawer et al.</td>
<td>$\frac{B W^a(29.3 - 0.203 \text{age})^b(1 - 0.03 \text{S}_c)}{14.4 \text{S}_c}$ (\frac{B W^a(25.3 - 0.175 \text{age})^b(1 - 0.03 \text{S}_c)}{14.4 \text{S}_c}) (\frac{14.4 \text{S}_c}{\text{age-20}})</td>
<td>(ml/min) [52]</td>
</tr>
<tr>
<td>Jelliffe</td>
<td>$\frac{14.4 \text{S}_c}{\text{age-20}}$ (\frac{14.4 \text{S}_c}{\text{age-20}}) (\frac{98.16}{S_c})</td>
<td>(ml/min/1.73m²) [51]</td>
</tr>
<tr>
<td>Cockcroft and Gault</td>
<td>$\frac{140-\text{age}^c\text{BW}}{S_c^d72}$ (\frac{27 - (0.175 \text{age})^e\text{BW}^f0.07}{S_c^g})</td>
<td>(ml/min) [1]</td>
</tr>
<tr>
<td>Bjornsson</td>
<td>$\frac{140-\text{age}^c\text{BW}}{S_c^d72}$ (\frac{27 - (0.175 \text{age})^e\text{BW}^f0.07}{S_c^g})</td>
<td>(ml/min) [53]</td>
</tr>
<tr>
<td>Hull et al.</td>
<td>$\frac{145-\text{age}^c\text{BW}}{S_c^d72}$ (\frac{27 - (0.175 \text{age})^e\text{BW}^f0.07}{S_c^g})</td>
<td>(ml/min/70kg) [54]</td>
</tr>
<tr>
<td>Gates</td>
<td>$\frac{89.4 + (55-\text{age})^a(0.005^b89.4)}{S_c^d1.2}$ (\frac{60 + (56-\text{age})^a(0.005^b60)}{S_c^d1.1})</td>
<td>(ml/min/1.73m²) [7]</td>
</tr>
<tr>
<td>Salazar and Corcoran</td>
<td>$\frac{137-\text{age}^a(0.285^b\text{BW})^a(12.1^b\text{Ht})}{S_c^d1.1}$ (\frac{146-\text{age}^a(0.287^b\text{BW})^a(9.74^b\text{Ht})}{S_c^d1.1})</td>
<td>(ml/min) [55]</td>
</tr>
</tbody>
</table>

$S_c = \text{serum creatinine (mg/dl)}$; BW = body weight (kg); Ht = height (m).
Table 2  Formulas for GFR-estimation obtained from multiple regression analyses.

<table>
<thead>
<tr>
<th>Authors</th>
<th>GFR-estimation formula</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walser et al.</td>
<td>[ 7570 \left( \frac{P_{cr}}{P_{cr}} - 0.103^{\text{age}} + 0.096^{\text{BW}} - 6.66 \right) \text{ (ml/min/3m}^2) ]</td>
<td>[72]</td>
</tr>
<tr>
<td>Agarwal et al.</td>
<td>[ 6050 \left( \frac{P_{cr}}{P_{cr}} - 0.08^{\text{age}} + 0.08^{\text{BW}} + 4.81 \right) \text{ (ml/min/1.73m}^2) ]</td>
<td>[76]</td>
</tr>
<tr>
<td>Nankivel et al.</td>
<td>[ 163.95\text{age}^{\text{BW}^{1.057}} \left( \frac{P_{cr}}{P_{cr}} \right) \text{ (ml/min)} ]</td>
<td>[73]</td>
</tr>
<tr>
<td>Nankivel et al.</td>
<td>[ 190.43\text{age}^{\text{BW}^{0.707}} \left( \frac{P_{cr}}{P_{cr}} \right) \text{ (ml/min)} ]</td>
<td>[74]</td>
</tr>
<tr>
<td>Nankivel et al.</td>
<td>[ 5520 \left( \frac{5520}{\text{age}} + 0.27^{\text{BW}} - 2 - 0.29^{\text{height(cm)}} \right) \text{ (ml/min/1.73m}^2) ]</td>
<td>[71]</td>
</tr>
<tr>
<td>Nguyen et al.</td>
<td>[ 218.1 - 0.916^{\text{age}} - 0.635^{\text{BMI} - 30} \left( \frac{P_{cr}}{P_{cr}} \right) \text{ (ml/min/1.73m}^2) ]</td>
<td>[70]</td>
</tr>
<tr>
<td>Baracska et al.</td>
<td>[ 4420 \left( \frac{4420}{\text{age}} + 88 \right) \text{ (ml/min)} ]</td>
<td>[75]</td>
</tr>
<tr>
<td>Levey et al.</td>
<td>[ 15028 \left( \frac{P_{cr}^{0.999^{\text{age}}^{2.179} + \text{Urea(mg/dl)}^{0.17} \times \text{albumin(g/dl)}^{0.318} \times \text{correction factor 0.762} \times \text{african american factor 1.180}}{P_{cr}} \text{ (ml/min/1.73m}^2) ]</td>
<td>[69]</td>
</tr>
</tbody>
</table>

\( P_{cr} = \) plasma creatinine (\text{mmol/l}); \( BW = \) body weight (kg); \( BMI = \) body mass index (kg/m\(^2\)).

Walser et al. used squared height instead of body surface area to standardize the GFR-estimate. Nankivel et al. studied 33 patients after a combined pancreas-kidney transplant [73] and 146 patients after a kidney transplant [74]. The study of Nguyen et al. comprised 122 recently diagnosed diabetic patients. The studygroups of Walser et al., Toto et al. and Baracska et al. are described in Table 3 and the text, that of Levey et al. in the text only.
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Formulas used for GFR-estimation

The plasma creatinine concentration has also been used for direct estimation of GFR. This has been investigated in a number of studies. GFR was measured as the plasma or renal clearance of inulin or radiotracers. This was then compared with formulas, already in use for creatinine clearance or with newly designed formulas. The latter were based on plasma concentrations of solutes - in most cases only plasma creatinine - and individual variables that correlated with GFR in multiple regression analyses [69-76]. These formulas are shown in Table 2.

All studies that compared the renal clearance of a tracer to the result of a GFR-estimation formula in terms of accuracy (or bias: mean difference between formula-estimate and GFR) and precision (SD of this difference) [77,78] are shown in Table 3 and will be discussed below [71,72,75,79-84]. We excluded studies that used the plasma clearance of a tracer for GFR-determination as gold standard [73,74,85-94], studies that only provided the mean ratio estimate/GFR and its SD [95-99] or that provided no or insufficient information concerning both the accuracy and precision of their estimation [69,70,100-112]. Studies of intensive care patients were also excluded, because of the possible interference of bilirubin or dopamine with both the alkaline picrate and enzymatic plasma creatinine assay [113-115]. Most studies still used the formula of Cockcroft and Gault (CG) for GFR-estimation.

Rolin et al. investigated a group of patients with a wide range of GFR [84]. GFR-estimation by CG was not only inaccurate, but especially imprecise (Table 3). The accuracy improved after correction of CG for body surface area, but the precision did not. The authors concluded that the use of a formula was only justified in case immediate action was necessary. Later studies with more distinct patient groups showed better results with coefficients of variation ranging between 13 and 22 % [71,79,82,83]. In case of diabetes a larger variability has been reported (26 %) [82]. It is speculative whether this was caused by an inappropriate reflection of muscle mass by body weight in these patients. Even more variability has been shown in elderly patients and in patients with advanced renal disease [72,75]. The mean overestimation of GFR by CG was 45 % in the latter patient group. This was most likely due to a relatively higher degree of tubular creatinine secretion in these patients. In the African American patients the CG-formula underestimated GFR [71]. This might be due to the relatively large muscle mass compared to body weight in these patients, leading to an underestimation of creatinine production from body weight [116].
Table 3 Nine studies in chronologic order, which reported accuracy (or bias) and precision and in which GFR was measured as the renal clearance of a tracer (ml/min/1.73m²); GFR was compared with four GFR-estimation formulas; the last two studies were done with cimetidine administration.

<table>
<thead>
<tr>
<th>Method of GFR determination</th>
<th>P Cr assay</th>
<th>formula for GFR estimation</th>
<th>Patient group (mean GFR ± SD) and range</th>
<th>n</th>
<th>Accuracy ± Precision</th>
<th>CV (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>IOT s.c.</td>
<td>alkaline</td>
<td>CG</td>
<td>renal (71 ± 35) range 6-170</td>
<td>394</td>
<td>+ 9.8 ± 34.2</td>
<td>48.1</td>
<td>[84]</td>
</tr>
<tr>
<td></td>
<td>picrate</td>
<td>CG + bsa corr.</td>
<td></td>
<td></td>
<td>+ 3.1 ± 29.7</td>
<td>41.8</td>
<td></td>
</tr>
<tr>
<td>IOT i.v.</td>
<td>alkaline</td>
<td>CG</td>
<td>DM 1(78 ± 35) healthy (117)</td>
<td>132</td>
<td>+ 2 ± 20</td>
<td>25.6</td>
<td>[82]</td>
</tr>
<tr>
<td>Inulin contin.</td>
<td>picrate</td>
<td>CG</td>
<td></td>
<td>110</td>
<td>- 8 ± 16</td>
<td>13.7</td>
<td></td>
</tr>
<tr>
<td>DTPA i.v.</td>
<td>alkaline</td>
<td>CG</td>
<td>CRF (13) range 2-37</td>
<td>85</td>
<td>+ 5.9 ± 4.4</td>
<td>33.8</td>
<td>[72]</td>
</tr>
<tr>
<td></td>
<td>picrate</td>
<td>Walser</td>
<td></td>
<td></td>
<td>0.0 ± 3.0</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>IOT i.m.</td>
<td>alkaline</td>
<td>CG</td>
<td>&gt;65jr (71 ± 21) range 36-124</td>
<td>41</td>
<td>- 1.1 ± 23.8</td>
<td>33.5</td>
<td>[75]</td>
</tr>
<tr>
<td></td>
<td>picrate</td>
<td>Baracsay</td>
<td></td>
<td></td>
<td>+ 0.5 ± 16.4</td>
<td>23.1</td>
<td></td>
</tr>
<tr>
<td>IOT s.c.</td>
<td>alkaline</td>
<td>CG</td>
<td>afr.am.(69 ±26) range 11-126</td>
<td>193</td>
<td>- 9.6 ± 14.9</td>
<td>21.6</td>
<td>[71]</td>
</tr>
<tr>
<td></td>
<td>picrate</td>
<td>Toto</td>
<td></td>
<td></td>
<td>+ 0.1 ± 12.8</td>
<td>18.6</td>
<td></td>
</tr>
<tr>
<td>IOT s.c.</td>
<td>alkaline</td>
<td>CG</td>
<td>afr.am.(65 ±26) range 11-122</td>
<td>110</td>
<td>- 8.9 ± 14.5</td>
<td>22.3</td>
<td>[79]</td>
</tr>
<tr>
<td>Inulin i.v.</td>
<td>enzym</td>
<td>CG</td>
<td>healthy(98 ±16) cirrhA (95 ±16) cirrhC(102 ±18)</td>
<td>10</td>
<td>- 6.5 ± 12.3</td>
<td>12.6</td>
<td>[83]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>- 5.4 ± 12.7</td>
<td>13.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>+23.7 ± 19.7</td>
<td>19.3</td>
<td></td>
</tr>
<tr>
<td>IOT contin.</td>
<td>enzym</td>
<td>CG + cimetidine</td>
<td>renal (72 ± 31) range 20-120</td>
<td>19</td>
<td>- 2.5 ± 7.1</td>
<td>9.9</td>
<td>[80]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>- 3.8 ± 14.8</td>
<td>16.6</td>
<td>[81]</td>
</tr>
</tbody>
</table>

Accuracy: mean difference between estimate and real GFR; precision: SD of this difference. Abbreviations: CV = coefficient of variation; SD/mean GFR; IOT = 125I-iothalamate; DTPA = 99mTc-diethylene-triamine-pentacetic acid; contin. = continuous i.v. infusion; s.c. = subcutaneous injection; i.v. = intravenous bolus; enzym. = enzymatic; CG = Cockcroft-Gault; + bsa corr. = after correction for body surface area; SLE = systemic lupus erythematosus; DM 1/2 = diabetes mellitus type 1/2; CRF = chronic renal failure; afr.am. = african american; cirrhA/C = liver cirrhosis Child class A/C.
CG slightly underestimated GFR in patients with Child A cirrhosis, whereas in Child C patients it overestimated GFR by 23% and the precision was worse than in Child A patients [83]. These findings could be explained by a lower muscle mass, a reduced ability to produce creatinine and the presence of ascites in these patients, making body weight an inaccurate estimate of the muscle mass. The possibility of a negative interference of the enzymatic plasma creatinine assay by even a relatively low concentration of bilirubin had not been taken into account in this study.

New formulas have been proposed for African American patients, patients with advanced renal disease and elderly patients. These formulas used multiple regression techniques to improve the accuracy and precision [71,72,75]. The mean difference of the formula-estimate and GFR approached zero, indicating a high accuracy. However, the population from which the formula was derived and the test population were the same in these studies. In patients with advanced renal disease and in elderly patients the new formula had a slightly better precision than the CG-formula (coefficient of variation 23% instead of 34%). The formula proposed by Toto et al. was not better than CG in a follow-up study of Coresh et al. [79]. Also in cancer patients a new formula has been constructed using a multiple regression technique [98]. Although the accuracy improved, the precision did not.

Recently, a new formula has been developed in a large patient group participating in the Modification of Diet in Renal Disease study group [69]. It was derived from 1070 patients and incorporated age, gender, ethnicity and serum concentrations not only of creatinine, but also of albumin and urea (Table 2). It was tested in a different population from the one used for deriving the formula (n = 558, GFR range 8-110 ml/min/1.73m²). The accuracy and precision of this formula was better compared to CG, but no SD of the difference between the formula-estimate and GFR was given. Consequently, no definite comparison with the studies mentioned in Table 3 could be made. Although this formula was derived from patients with a wide GFR-range and excluding insulin requiring diabetic patients, it has also been used for end stage renal disease patients [117] and patients with type 2 diabetes mellitus or impaired glucose tolerance [118]. Besides, it incorporates laboratory determinations which can vary independently of GFR, such as serum albumin and urea. The plasma urea concentration is dependent on protein intake, catabolism, hydration state and urine production [5]. The assay for serum albumin has a high interlaboratory variability, which makes it difficult to adopt the formula in other laboratories [119].
Inhibition of tubular creatinine secretion

Cimetidine can be used to inhibit the increasing amount of tubular creatinine secretion as GFR decreases [8]. This could improve the accuracy and precision of GFR-estimation. Most studies have been done comparing GFR, measured with inulin or radiotracers, to creatinine clearance (C\textsubscript{r}) after cimetidine administration. Different cimetidine dosing regimes have been suggested in these studies. Roubenoff et al. studied 24-hour C\textsubscript{r} after cimetidine comparing it to a 4-hour GFR measurement [95]. This approach did not take into account the circadian rhythm of C\textsubscript{r} after administration of cimetidine [120]. Despite this, it was shown that the ratio 24-hour C\textsubscript{r}/GFR decreased from 1.33 to 1.07 and the SD of the ratio from 0.32 to 0.10 [95]. The coefficient of variation was lower than that of the formula-derived GFR-estimation without cimetidine. Similar results of the simultaneous C\textsubscript{r}/GFR ratio were obtained in the study of Hilbrands et al.: 1.23 ± 0.20 before and 0.96 ± 0.08 after a rather complicated cimetidine dosing schedule [121]. This seems to indicate a better inhibition than in the previously mentioned study, but the tubular secretion was less elevated in this patient group and therefore probably easier to inhibit. Van Acker et al. studied a glomerulopathic patient group with a mean GFR of 40 ml/min/1.73m\textsuperscript{2}. The ratio C\textsubscript{r}/GFR in that study ranged from 1.14 to 2.27 [32]. After administration of cimetidine this ratio approached unity in half of the patients (1.02 ± 0.03), indicating complete inhibition of tubular creatinine secretion. In the other patients the ratio remained elevated (1.33 ± 0.14), due to a high renal cimetidine clearance. However, a single high cimetidine dose of 1200 mg inhibited tubular secretion completely from the third to sixth hour after administration in patients with a plasma creatinine less than 220 μmol/l. Choi et al. showed that the ratio after cimetidine was higher in patients with a GFR below 40 ml/min/1.73m\textsuperscript{2} : 1.22 opposed to 1.09 in patients with a GFR of 40-80 ml/min/1.73m\textsuperscript{2} and 1.10 above 80 ml/min/1.73m\textsuperscript{2}. This indicates decreased inhibition of tubular secretion in more advanced renal failure [122].

The use of cimetidine has also been studied in renal transplant patients. A single intravenous bolus of cimetidine 5 mg/kg reduced the ratio C\textsubscript{r}/GFR from 1.43 to 1.03 two hours later [123]. Zaltzman et al. performed a 3-hour urine collection period one hour after a single oral 800 mg cimetidine dose [124]. The C\textsubscript{r}/GFR ratio decreased from 1.53 to 1.12. The reason it did not decrease to unity was probably the early timing of urine collection and an insufficient dose of cimetidine. Hirata-Dulas et al. were also unable to inhibit tubular creatinine secretion completely
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in transplant patients with \( C_t \), below 60 ml/min, probably because the cimetidine dose was
reduced according to renal function and therefore insufficient [125].

Although the creatinine clearance during a timed collection period after cimetidine has been
advocated as an alternative for the clearance of inulin or radiotracers [28,32], the necessity of
either a short supervised or a 24-hour unsupervised urine collection period makes these methods
less practical for clinical routine. The formula derived GFR-estimation is expected to improve
after inhibition of tubular secretion by a sufficient dose of cimetidine. The Cockcroft-Gault
formula (CG) after cimetidine administration has been studied using an enzymatic plasma
creatinine assay [80,81]. Ixkes et al. studied patients with various renal diseases and found a very
good accuracy and precision of CG (Table 3) [80]. The accuracy and precision were the same as
in the early creatinine clearance studies after cimetidine [95,121]. In two patients with a GFR
below 40 ml/min/1.73m\(^2\), tubular secretion was not completely inhibited. This study also
showed that a new steady state of elevated plasma creatinine could only be expected within 24
hours when plasma creatinine concentration was less than 180 \( \mu \)mol/l. This is because a new
steady state is reached after 3-4 plasma creatinine half lives. The half life proved to be short
enough to obtain this situation within 24 hours in patients with a plasma creatinine of less than
180 \( \mu \)mol/l [80]. It is in this range of renal function that a higher sensitivity of clinical GFR-
estimation is needed, because it may have important consequences for the management of
patients.

A creatinine concentration < 180 \( \mu \)mol/l was also an inclusion criterion in the second larger
study of type 2 diabetic patients with normo-, micro- and macroalbuminuria [81]. After
cimetidine, the accuracy of CG was similar to that in patients with a primary renal disease, but the
precision was lower (coefficient of variation 17 instead of 10 \%, Table 3), but still much better
than that of a 24-hour outpatient creatinine clearance. It remains speculative whether this was
due to the inappropriate reflection of muscle mass by body weight in this type 2 diabetic
population. In renal transplant patients the ratio CG/GFR was found to decrease from 1.30 to
1.10 after cimetidine administration [126]. The explanation for the incomplete inhibition of
tubular secretion in these patients was probably the low GFR-range, with a mean GFR of 38
ml/min/1.73m\(^2\).
Follow-up of GFR by formula estimations

In 1976 Mitch et al. proposed a simple method for estimating progression of chronic renal failure [127]. When the urinary creatinine excretion remains constant, the decline of creatinine clearance should correspond with the reciprocal plasma creatinine concentration. This decline of reciprocal plasma creatinine was concluded to be linear in 31 of 34 patients and could be used to predict when dialysis would become necessary. Tougaard et al. designed an individual nomogram for follow-up of GFR from reciprocal plasma creatinine, using a single GFR-determination and assuming that the urinary creatinine excretion remained constant as GFR decreased [128]. Later studies, in which radiotracer measured GFR was used instead of creatinine clearance, showed that the change in reciprocal plasma creatinine only had a weak correlation with the change in GFR in patients with diabetic nephropathy and that reciprocal plasma creatinine gave inaccurate estimations of the rate or even the presence of progression in chronic renal failure [129,130]. This was caused by the varying degree of tubular creatinine secretion among individuals and a decrease in total renal excretion of creatinine in advanced renal failure due to extrarenal metabolism [131,132]. Moreover, a change of diet also changes the relationship between GFR and reciprocal plasma creatinine [131]. Therefore, reciprocal plasma creatinine can not be used for follow-up of GFR in both (dietary) intervention trials and clinical practice.

The Cockcroft-Gault formula has been used for follow-up of GFR in diabetic and transplant patients [91,99,110,133-135]. The mean rate of decline of the CG-estimate was similar to the decline of GFR in type 1 diabetic patients with nephropathy [91], but overestimated this in type 2 diabetic patients without nephropathy [133]. However, the variability of CG for follow-up was unacceptably high [91,133]. The same variability was found in a study of renal transplant patients, probably due to the variable amount of tubular secretion, whereas no data of the variability were given in heart transplant patients [99,110]. In lung transplant recipients CG underestimated the rate of GFR decline [135]. The formula proposed by Levey et al. was slightly better to detect a small decrease in GFR in these patients [69]. One study used cimetidine and an enzymatic plasma creatinine assay for follow-up of GFR with the CG-formula in type 2 diabetic patients with all stages of albuminuria [134]. The discrepancy between CG and GFR remained constant over time and the change in GFR was reflected by the change in CG. This might make CG, when plasma creatinine is determined enzymatically after cimetidine administration, a suitable parameter for the clinical follow-up of GFR.
Pitfalls in formula derived GFR-estimation

A major problem of GFR-estimation is that it is less precise in the normal range, above 70-100 ml/min [28,90,103,133]. In general, estimates by the Cockcroft-Gault and other formulas tend to overestimate GFR at low values and to underestimate it at high values [89,100,136]. This explains the finding that in diabetic patients with normal to elevated GFR CG underestimated GFR [70,104,137,138]. The overestimation at low values is partly caused by the increasing amount of tubular secretion at low GFR-values, which can be improved with cimetidine administration. However, the underestimation at higher GFR-values can not be improved with cimetidine administration, when an alkaline picrate creatinine assay is used [21,97]. This is explained by the fact that non-creatinine chromogens have a greater percentual impact on the false elevation of plasma creatinine at low-normal values, corresponding with normal-high GFR-values [5]. When calculating CG - and other formulas in which plasma creatinine is in the denominator - this falsely high plasma creatinine leads to a falsely low value for estimated GFR. This can be overcome using a plasma creatinine assay that lacks influence by non-creatinine chromogens, such as an enzymatic or HPLC assay. The possibility exists that CG over- instead of underestimates GFR when only an enzymatic assay is used [139]. However, the administration of cimetidine prevents this overestimation.

Another important subject is the reproducibility of GFR-measurements and its estimates. GFR can be measured with a day-to-day variability of 2-3 % as the renal clearance during continuous infusion of $^{125}$I-iothalamate and $^{131}$I-hippuran [140,141]. The simultaneous infusion of $^{131}$I-hippuran makes it possible to correct for inaccurate urine collection [140]. A correction can also be made for a changing plasma concentration of inulin or radiotracers during constant infusion, caused by the circadian rhythm of GFR or by an inappropriate infusion rate [142,143]. Studies that reported a higher day-to-day variability of GFR-measurements, up to 17 %, did not use these corrections [71,97,111,144]. This variability in 'gold standard' implies that the outcome for a study comparing GFR with formula-estimations can be hampered. The coefficient of variation of the enzymatic plasma creatinine assay is less than 3 % and therefore the analytical variability has a minor influence on CG and other formulas using plasma creatinine only [16,120]. The coefficient of variation of CG was reported to be 5 to 6 % without the use of cimetidine and 5 % with cimetidine [92,97,111]. Moreover, the most important advantage of the formula derived
estimations over GFR measurements is the convenience to obtain it as often as necessary during follow-up of patients.

Conclusion and Recommendations

In this review we discussed studies that used plasma creatinine in the denominator of formulas, originally developed for bedside drug dosing, for prediction of GFR in various adult patient groups. The inaccuracy of these formulas was mainly due to tubular secretion of creatinine, causing overestimation of GFR in the low range, and the use of the alkaline picrate creatinine assay, causing underestimation of GFR in the normal to high range due to falsely high plasma creatinine values. The accuracy of GFR-estimation improved by administration of cimetidine applied to the formula of Cockcroft and Gault [21,80,81,122]. Other, newer formulas did not improve the precision in a meaningful way [71,72,75]. The variability of CG was too high to obtain an acceptable estimate of the decline in GFR in follow-up studies [91,133,135]. However, CG after cimetidine administration, using an enzymatic plasma creatinine assay might be suitable for follow-up [134].

Before using plasma creatinine in prediction formulas of GFR one must bear in mind some limitations mentioned earlier in this paper, also described in previous articles [89,107,145]. First of all, plasma creatinine needs to be in steady state. In patients with acute renal failure or in hospitalized patients with diseases or interventions affecting plasma creatinine, formulas cannot be used. Shortly after strenuous exercise or a (cooked) meat meal plasma creatinine increases. Formulas are also inaccurate in patients with liver disease or muscle wasting and in extreme adipose (BMI above 35 kg/m²) or edematous patients. Furthermore, the plasma creatinine assay is important. Although the formulas originally used alkaline picrate creatinine values, recent studies showed that GFR is estimated more accurately with an enzymatic plasma creatinine assay [21,80,81,83,134]. Still, bilirubin, dopamine and 5-flucytosine can interfere with the enzymatic assay, making formula estimations inappropriate [16]. Finally, the formulas described in this article were studied in adult patients most often younger than 70 years of age, except for 3 studies [75,86,112]. Consequently, these formulas are not well validated for GFR-estimation in elderly patients.

Appreciating these limitations, GFR can estimated with reasonable accuracy and precision using the Cockcroft-Gault formula, preferably using an enzymatic plasma creatinine assay and
inhibition of tubular creatinine secretion by cimetidine administration. In African Americans and patients with advanced renal failure or advanced liver cirrhosis, there is a larger inaccuracy. In diabetic patients the precision is less. If the individual effect of an intervention has to be known, then GFR should be measured. For routine clinical practice of patients, likely to suffer from renal dysfunction in the future, or for population studies GFR-prediction by formulas is sufficient.
References


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GFR-estimation from plasma creatinine


Chapter 1


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GFR-estimation from plasma creatinine


GFR-estimation from plasma creatinine


