A simplified Cockcroft-Gault formula to improve the prediction of the glomerular filtration rate in diabetic patients

V Rigalleau¹, C Lasseur², C Perlemoine³, N Barthe³, C Raffaitin¹, R de la Faille², C Combe², H Gin¹

SUMMARY

Aim: The National Kidney Foundation recommends stratification of renal failure into moderate (Glomerular Filtration Rate: GFR = 30-60 mL/min/1.73 m²), severe (15-30) or terminal (< 15) using the Cockcroft-Gault (CG) or the Modification of Diet in Renal Disease (MDRD) equations. We studied the biases in these methods in an attempt to improve the standard CG (MCG) and devise a strategy for stratification.

Methods: GFR was measured by 51Cr-EDTA clearance in 200 diabetic patients: 100 (Group 1: study of concordance) before 2003 and 100 thereafter (Group 2: validation of MCG). The CG was modified by replacing body weight by its mean value: 76.

Results: In group 1, the recommended equations only correctly stratified 50 patients. The CG, not the MDRD, underestimated GFR if BMI was normal, and overestimated it in obese patients. In group 2, the MCG was well correlated with GFR and not biased by weight. Over the whole population, the MCG and MDRD were more accurate for the diagnosis of moderate and severe renal failure. The MDRD showed the lowest differences with GFR, except if GFR > 60, where the MCG performed better. All formulae overestimated low GFR, the MDRD also underestimated high GFR. The best stratification (147/200) was obtained using the MCG if creatininemia < 120 µmol/l and the MDRD if creatininemia ≥ 120 µmol/l.

Conclusion: The CG is biased by weight, the MCG corrects this. The more accurate MDRD cannot be used in all patients as it underestimated high GFR. The best stratification was obtained using the MCG at low and the MDRD at high creatininemia.

Key-words: Diabetes · Chronic Renal failure · Body Mass Index · Glomerular Filtration Rate · Renal function.

RESUMÉ

Une formule de Cockcroft et Gault simplifiée pour améliorer la prédiction du débit de filtration glomérulaire chez les patients diabétiques

Objectif : La « National Kidney Foundation » recommande de stratifier l’insuffisance rénale chronique comme modérée (Débit de Filtration Glomérulaire : DFG = 30-60 mL/min/1,73 m²), sévère (DFG = 15-30) ou terminale (DFG<15) à l’aide de la formule de Cockcroft et Gault (CG) ou de l’équation de la « Modification of Diet in Renal Disease study » (MDRD). Nous avons étudié les biais de ces formules, dans l’objectif d’améliorer la formule de Cockcroft et Gault (CG Modifiée : MCG, simplement obtenue en remplacant le poids des sujets par sa valeur moyenne dans la population étudiée : 76 kg) et de proposer une stratégie de stratification.

Méthodes : Le DFG a été mesuré par une méthode de référence (clairence du 51Cr-EDTA) chez 200 patients diabétiques : 100 ont été étudiés avant 2003 (Groupe 1 : étude de concordance) et 100 ensuite (Groupe 2 : validation de la MCG).

Résultats : Dans le groupe 1, les deux formules recommandées n’ont permis une stratification exacte et concordante que chez 50 sujets. La prédiction par CG sous-estimait le DFG si le BMI était normal, et le surestimait en cas d’obésité ; la MDRD n’était pas affectée par ce biais. Dans le groupe 2, la prédiction par MCG était bien corrélée au DFG, et n’était pas biasée en fonction du BMI. Sur la population totale, les prédictions par MCG et MDRD étaient plus précises pour les diagnostics d’insuffisance rénale modérée ou sévère. Les différences les plus faibles avec les valeurs mesurées étaient obtenues avec la MDRD, sauf chez les sujets présentant un DFG > 60, chez qui la MCG était plus précise. Toutes les formules surestimaient les DFG bas, et la MDRD sous-estimait les DFG élevés. La stratification la plus exacte (147/200) a été obtenue en prédisant le DFG par la MCG si la créatininémie était < 120 µmol/L, et par la MDRD si la créatininémie était ≥ 120.

Conclusion : La formule de Cockcroft et Gault est biasée en fonction du poids, la modification simple que nous proposons avec la MCG corrige ce biais. Bien que plus précise, l’équation de la MDRD ne peut pas être utilisée chez tous les patients diabétiques car elle sous-estime les DFG normaux. La meilleure stratification que nous ayons pu obtenir a utilisé la MCG si la créatininémie était basse, et la MDRD si elle était élevée.

Mots-clés : Diabète · Insuffisance rénale chronique · Index de Masse Corporelle · Débit de filtration glomérulaire · Fonction rénale.

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Introduction

The determination of the Glomerular Filtration Rate (GFR) allows the stratification of Chronic Kidney Diseases (CKD), with practical implications [1,2]: complications must be evaluated and treated in patients with moderate renal failure (GFR < 60 ml/min/1.73 m²), while patients with severe renal failure (GFR < 30) must be referred to a nephrologist to start dialysis in cases of terminal renal failure (GFR < 15). Delayed referral and treatment are associated with poor prognosis [3].

GFR can be directly measured by infusion of external substances such as 51Cr-EDTA, but this is expensive and time-consuming. The use of prediction equations to estimate GFR from serum creatinine, like the Cockcroft-Gault formula (CG) [4] and the Modification of Diet in Renal Disease (MDRD) study equation [5], is therefore recommended by the National Kidney Foundation [1]. Although it is more complex than the CG, the MDRD equation seems more accurate, but some reports have not confirmed this advantage [6,7]. It is not known whether these two formulae give concordant stratification of CKD, and there is no consensus on the method of choice in clinical practice.

25-40% of diabetic patients present diabetic nephropathy [8]. In up to 25% of these patients, renal function declines in the absence of albuminuria [9], pointing to the importance of assessing GFR. The American Diabetes Association recommends to use the CG formula [10], but this equation calculates GFR as proportional to body weight, that varies widely among uremic diabetic patients [11]. In such patients, Solerte found that a 20% diet-induced weight loss was associated with a 20% increase in GFR [12]. This weight loss would decrease the predicted GFR by 20% according to the CG. The MDRD equation does not include body weight, but it is not validated in diabetic patients: the MDRD study only included 6% diabetic patients [5]. In a recent report, Vervoort failed to note any advantage of the MDRD equation in normoalbuminuric diabetic patients [6].

In order to improve the prediction of GFR in diabetic patients, we investigated whether the MDRD and CG estimations led to a correct stratification of renal failure in 100 diabetic patients with a wide range of isotopically determined GFR and widely dispersed BMI. As the CG was biased by BMI, we simplified it by replacing body weight by its mean value: 76. We then validated this simplification in another group of 100 patients. The performance of the three formulae was then compared for the whole (n=200) population. We propose a more efficient method for predicting GFR in diabetic patients using the corrected CG formula when serum creatinine is normal and the MDRD equation when it is high.

Subjects, materials and methods

Patients

Two hundred adult diabetic patients attending our clinic (Service de Nutrition-Diabétologie, Hôpital Haut-Lévêque, Pessac, France) were studied from January 2001 to January 2005. They were included if they had kidney failure or at least had kidney damage defined by an isotopic GFR below 90 ml/min/1.73 m² and microalbuminuria above 30 mg/24 h, and some diabetic subjects without renal damage were included in a study of the value of cystatin C. The patients from Group 1 (concordance study) were included from January 2001 to January 2003, and the patients from Group 2 (validation study) were included thereafter. The characteristics of the population are listed in table I. Dialysis, nephrotic proteinuria (> 3 g/24 h) or clinical edema were exclusion criteria.

Analytical methods

Serum creatinine was determined on a multiparameter analyzer (Olympus AU 640: Olympus Optical, Tokyo, Japan) using the Jaffé method with bichromatic measurements according to the manufacturer's specifications, and daily calibration of the analyser. This procedure did not change in our laboratory during the study. Clearance of the radionuclide marker was measured after intravenous injection of 51Cr-EDTA (Cis Industries, Gif/Yvette, France). All patients were studied in the morning at 9 am, after a light breakfast. After a single bolus of 100 µCi (3.7 MBq) of 51Cr-EDTA, 4 venous blood samples were drawn at 75, 105, 135 and 165 minutes, and urinary samples were collected at 90, 120, 150 and 180 minutes, as previously reported [11]. The determination of the Glomerular Filtration Rate (GFR) allows the stratification of Chronic Kidney Diseases (CKD), with practical implications [1,2]: complications must be evaluated and treated in patients with moderate renal failure (GFR < 60 ml/min/1.73 m²), while patients with severe renal failure (GFR < 30) must be referred to a nephrologist to start dialysis in cases of terminal renal failure (GFR < 15). Delayed referral and treatment are associated with poor prognosis [3].

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Table I

Main characteristics of the diabetic subjects from group 1, group 2, and the whole studied population.

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (concordance)</th>
<th>Group 2 (validation)</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>100</td>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>Gender (% men)</td>
<td>58%</td>
<td>61%</td>
<td>60%</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>63.0 ± 13.3</td>
<td>63.1 ± 13.9</td>
<td>63.0 ± 13.6</td>
</tr>
<tr>
<td>type of diabetes</td>
<td>29%</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>(% type 1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1 ± 13.3</td>
<td>76.8 ± 15.1</td>
<td>76.5 ± 14.2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166 ± 9</td>
<td>166 ± 8</td>
<td>166 ± 8</td>
</tr>
<tr>
<td>Body Mass Index</td>
<td>27.4 ± 4.1</td>
<td>27.6 ± 5.3</td>
<td>27.5 ± 4.7</td>
</tr>
<tr>
<td>(18.9-38.7)</td>
<td>(15.6-48.0)</td>
<td>(15.6-48.0)</td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.6 ± 1.7</td>
<td>8.6 ± 1.5</td>
<td>8.6 ± 1.6</td>
</tr>
<tr>
<td>Serum creatinine (µmol/L)</td>
<td>146 ± 75</td>
<td>147 ± 82</td>
<td>146 ± 79</td>
</tr>
<tr>
<td></td>
<td>(64-371)</td>
<td>(54-480)</td>
<td>(54-480)</td>
</tr>
</tbody>
</table>
described [13]. The final result was the mean of the 4 clearance values. If for one period the urine flow was too weak or if a clearance value was not within ±20% of the three other’s mean, this value was excluded and the mean calculated over the other 3 clearances. Less than 5% of the values were excluded this way. The 51Cr-EDTA radioactivity was measured in a gamma counter (COBRA 2, model 05003, Packard Instruments, Meriden, CT).

Estimation of renal function

A single creatinine determination was performed the day before the isotopic measurement of GFR, to calculate:

Cockcroft and Gault formula (CG):

\[ CG = \left( \frac{140 - \text{age\[yrs\]}}{\text{serum creatinine}\[\mu\text{mol/l}\]} \times \text{body weight}\[\text{kg}\] \times K \right) \frac{\text{mg/dl}}{\text{mg/dl}}\]

where K is a constant: 1.23 for men and 1.04 for women [4].

Modification of Diet in Renal Disease study equation (MDRD):

We used the abbreviated equation [5]

\[ \text{MDRD} = 186 \times (\text{serum creatinine}\[\mu\text{mol/l}\])^{1.154 \times (\text{yrs}) -0.203 \times (\text{weight}\[\text{kg}\])\times (\text{height}\[\text{cm}\])^{-0.321}} \]

The results of the CG, MCG and isotopic GFR were adjusted to body surface area using Dubois’ formula [14] before the comparisons. The results of the MDRD are directly expressed as adjusted to body surface area [5].

Categorization of the patients

For statistical analysis, the patients were categorized as a function of BMI and isotopic GFR. Renal failure was stratified as moderate (30 \(\leq\) GFR < 60 ml/min/1.73m²), severe (15 \(\leq\) GFR < 30), or terminal (GFR < 15) [1]. The patients were also categorized in deciles of GFR to determine bias as a function of GFR.

Statistical analysis

Results of the CG, MCG and MDRD formulae were compared to isotopic GFR by correlation, paired t tests, and a Bland & Altman procedure [15]. We also performed correlation studies to search for an association between BMI and GFR or its estimations. These calculations were performed using SPSS software, version 10.0. The sensitivity and specificity of the formulae were assessed from non-parametric receiver operating characteristic (ROC) curves, generated by plotting sensitivity versus 1-specificity, giving for the ideal test, a sensitivity of unity and a specificity of unity. Areas Under the Curve (AUC) were calculated and compared according to the procedure of Hanley and McNeil [16]. These analyses were performed using Medcalc software. The analysis of accuracy was determined by calculating the 50th-75th and 90th percentile of the percentage absolute differences between predicted and measured GFR [5]. Results are presented as means ± SD. P < 0.05 was considered significant.

Results

Group 1: concordance study and weight-related bias

Mean isotopic GFR in group 1 was 57.3 ± 37.5 mL/min/1.73 m². Both formulae were well correlated with GFR (CG: \(r = 0.81, P < 0.0001\); MDRD: \(r = 0.83, P < 0.0001\)), but led to an erroneous prediction: the CG overestimated GFR (CG: 62.2 ± 38.1, P < 0.05 vs isotopic), whereas the MDRD underestimated it (MDRD: 51.2 ± 4.2, P < 0.01 vs isotopic). Their performance for the stratification of renal failure is summarized in table II. More patients were well classified according to the MDRD (P < 0.01). Only 50% of the patients were well classified by both formulae (both wrong: 16% of the patients, discordant: 34%).

Isotopic GFR and the MDRD estimation were not correlated with BMI. The CG was correlated with BMI (\(r = 0.32, P < 0.005\)). In the 30 patients with normal body weight, the CG underestimated GFR (-12%, P < 0.05), the MDRD did not (-4%, NS). In the 23 obese patients, the CG overestimated GFR (+33%, P < 0.005), the MDRD did not (-14%, NS).

Group 1: correction of the CG formula

In an initial attempt to improve the CG formula, we replaced the real body weight of the patients by their ideal body weight (body weight for BMI = 22). Although the
correlation between this modified CG and the isotopic GFR was maintained ($r = 0.82$), this led to a marked underestimation (mean modified CG: $43.2 \pm 20.8$, P < 0.0001 vs isotopic). We therefore simply replaced body weight in the CG by its mean value: 76 kg, to calculate a new formula, MCG.

Mean MCG ($60.6 \pm 31.2$, NS vs isotopic) was well correlated with isotopic GFR ($r = 0.86$, P < 0.0001), and not correlated with BMI ($r = 0.13$, NS). The MCG did not differ significantly from isotopic GFR in patients with normal body weight (MCG: $51.2 \pm 21.4$ vs isotopic: $49.1 \pm 25.9$, NS) nor in the obese patients (MCG: $65.9 \pm 35.1$ vs isotopic: $60.0 \pm 46.7$, NS).

**Group 2: validation of the MCG formula**

Mean isotopic GFR was $55.6 \pm 32.2$ mL/min/1.73 m$^2$ in group 2. The MCG was well correlated with the isotopic GFR (mean MCG: $59.3 \pm 28.6$, NS vs isotopic, $r = 0.79$, P < 0.0001), and not correlated with BMI ($r = 0.01$, NS), unlike the CG ($r = 0.31$, P < 0.005). In the 37 patients with a normal BMI, the MCG did not differ from the isotopic GFR (MCG: $60.2 \pm 33.1$, isotopic: $59.3 \pm 33.8$, NS), whereas the CG underestimated GFR (CG: $50.9 \pm 33.8$, -14%; P < 0.05 vs isotopic). In the 30 obese patients, the MCG did not differ from the isotopic GFR (MCG: $61.0 \pm 29.3$, isotopic: $57.3 \pm 34.6$, NS), whereas the CG overestimated GFR (CG: $75.0 \pm 40.0$, + 31%; P < 0.001 vs isotopic).

**Whole population (n=200)**

Over the whole population, the mean isotopic GFR was $56.5 \pm 34.9$ mL/min/1.73 m$^2$, the mean CG, $61.2 \pm 35.6$ (P < 0.01 vs isotopic), mean MCG, $60.0 \pm 29.9$ (P < 0.05 vs isotopic) and the mean MDRD, $51.0 \pm 24.3$ (P < 0.001 vs isotopic). The MCG was better correlated with isotopic GFR than was the CG (CG: $r = 0.75$, MCG: $r = 0.83$; P < 0.05 vs CG, MDRD: $r = 0.82$; P = 0.068 vs CG).

The analysis of the ROC curves showed that the MDRD and the MCG had a better maximal accuracy for the diagnosis of moderate (n = 119; Area Under Curve: 0.866 for CG, 0.920 for MDRD, 0.921 for MCG; both P < 0.05 vs CG) and severe (n = 52; Area Under Curve: 0.891 for CG, 0.930 for MDRD, 0.942 for MCG; both P < 0.05 vs CG) renal failure.

The median differences between the predicted and measured GFR were -1.2 mL/min/1.73 m$^2$ for the MDRD, + 4.5 for the CG and + 4.6 for the MCG. As shown in figure 1, the 50th-75th-90th percentiles of percentage absolute differences between predicted and measured GFR were lower for the MDRD than for the CG, with intermediate results for the MCG. Interestingly, in patients with GFR > 60 mL/min/1.73 m$^2$, the MCG had the best accuracy.

The Bland & Altman procedure revealed a bias for the MDRD and MCG: the differences between the predicted and the measured GFR were correlated with their means (MDRD: $r = 0.54$, P < 0.0001; MCG: $r = 0.27$, P < 0.001). This was not apparent for the CG. The bias as a function of GFR is illustrated in figure 2, where the means ± SD estimations by the three formulae are represented as functions of the measured GFR, after categorizing them by deciles: under 50 ml/min/1.77 m$^2$, all the formulae overestimated GFR (particularly the CG and the MCG), whereas the MDRD underestimated higher GFR. This suggested a strategy.
Stratification of CKD on the whole population

As the MCG was more accurate for high GFR, and the MDRD was more accurate for low GFR, we used the MCG at low serum creatinine values and the MDRD at high values. We calculated the number of correct stratifications using this approach with ascending serum creatinine cut-offs: the best cut-off was at 120 µmol/l creatinine (147/200 well stratified). Table III summarizes the stratifications using each formula, and our approach. The choice of formula according to the creatinine level led to the best stratification (> 70% well classified).

Discussion

Our study confirms that both the Cockcroft and Gault (CG) and the MDRD formula are well correlated with the isotopic GFR, but the mean estimations differ from the mean reference GFR. More importantly, the simultaneous application of the two formulae provides a correct and concordant stratification of CKD in only 50% of the patients, which seems unacceptable.

French laboratories supply a CG estimation with serum creatinine according to the guidelines of the Agence Nationale d’Accréditation des Etablissements de Santé [2]. We show that this is not satisfactory. The CG is less accurate than the MDRD in renal insufficient diabetic [17] and non-diabetic patients [5,18]. This inaccuracy is partly due to the GFR prediction as proportional to weight by the CG, whereas it is not proportional to body weight in fact. The overestimation in obese diabetic patients leads to delayed referral or preparation of vascular access for hemodialysis. None of our patients was classified as presenting terminal renal failure by the CG, whereas eight had to start dialysis since the beginning of the study. As the prevalence of obesity is growing, this bias will rise, calling for a correction.

Better accuracy and the absence of any weight-related bias are important advantages of the MDRD equation, but its use should not be generalized to all diabetic patients. The calculation includes negative logarithms, requiring a scientific calculator, which is not suited for routine clinical practice. Moreover, the MDRD equation was established and validated in 1600 patients with renal insufficiency recruited in the MDRD study [5], which did not include patients with normal renal function. Fortunately, most diabetic patients have normal renal function. Their GFR will be underestimated by the MDRD, as we found. This underestimation may be partly explained by the 15-20 µmol/L lower creatinine levels obtained by the MDRD laboratory [18]. However five recent studies have recalibrated the creatinine result obtained by the Jaffé reaction as we used in the MDRD, and found that the MDRD equation still underestimates high GFR after recalibration [19-23]. Poggio et al have underlined the complexity of the calibration process [19]; for their 249 diabetic patients, the recalibrated MDRD was well fitted to the isotopic GFR, but they had severe CKD (mean measured GFR: 23 ± 18 ml/min/1.73 m²). The study from Ibrahim et al included 1286 type 1 diabetic subjects from the DCCT (mean measured GFR: 122 ± 23 ml/min/1.73 m²), and confirmed a large systematic underestimation by the MDRD, despite their creatinine measurements similar to those from the MDRD laboratory [21]. According to Rule et al, the creatinine recalibration only slightly improved the

Table III

<table>
<thead>
<tr>
<th>GFR (mL/min/1.73 m²)</th>
<th>≥ 60</th>
<th>30-60</th>
<th>15-30</th>
<th>≤ 15</th>
<th>Total</th>
</tr>
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<tr>
<td>N</td>
<td>81</td>
<td>67</td>
<td>36</td>
<td>16</td>
<td>200</td>
</tr>
<tr>
<td>Well stratified by both CG and MDRD</td>
<td>47</td>
<td>41</td>
<td>13</td>
<td>0</td>
<td>101</td>
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<tr>
<td>Well stratified by CG</td>
<td>59</td>
<td>44</td>
<td>15</td>
<td>0</td>
<td>118</td>
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<tr>
<td>Well stratified by MDRD</td>
<td>54</td>
<td>59</td>
<td>23</td>
<td>7</td>
<td>143</td>
</tr>
<tr>
<td>Well stratified by MCG</td>
<td>65</td>
<td>50</td>
<td>13</td>
<td>0</td>
<td>128</td>
</tr>
<tr>
<td>Well stratified by MCG &lt; 120 µM</td>
<td>60</td>
<td>57</td>
<td>23</td>
<td>7</td>
<td>147</td>
</tr>
<tr>
<td>- MCG if creatinine &lt; 120 µM</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>- MDRD if creatinine &gt; 120 µM</td>
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underestimation by the MDRD in healthy subjects, and it increased the bias in subjects with CKD [22]. Our main conclusions would therefore probably not differ with recalibration, and the results would not apply to a real life setting, where creatinine assays are not calibrated to the MDRD laboratory.

The drawbacks of each formula, and the confusion that arises when used simultaneously, led us to propose a correction of the CG, by removing body weight. This “MCG” has significant advantages: 1) being even simpler than the CG, it is readily calculated. 2) We have validated that it is not biased by BMI. Removing body weight protects the formula from the influence of its alterations. The choice of 76 may seem arbitrary, but it is near the mean body weights reported in previous studies concerning the prediction of GFR: 71 to 79 kg [5-7,18]. The MCG can be tested in other diabetic populations with different body weights: in view of the deleterious effect of weight on the CG estimation, it should perform better in such groups. 3) The MCG was well correlated with GFR: as expected due to the correction of the weight-related bias, r went up. Interestingly, this led to improved accuracy in the high range of GFR, where the MDRD fails.

The Bland and Altman procedures demonstrated that the biases in the prediction formulae were a function of GFR: low GFR were overestimated, whereas high GFR were underestimated, as reported for the CG [24]. The diagnostic performances of the formulae differed according to the range of GFR, enabling a strategy for the stratification of CKD. For most diabetic patients, GFR can be assumed as normal, in which case the MCG will be simple and accurate. When renal failure is suspected, the more accurate MDRD is justified. As the performances of the formulae differed according to the range of GFR, enabling a strategy for the stratification of CKD. For most diabetic patients, GFR can be assumed as normal, in which case the MCG will be simple and accurate.

In summary, the direct application of the two recommended formulae to predict GFR leads to a confused situation in diabetic patients: 50% of predictions were wrong or discordant. The CG formula is simple, but less accurate than the MDRD equation. As it is biased by weight, its inaccuracy will tend to rise in the future. Although it is more precise, and not biased by weight, the MDRD equation underestimates high GFR, its use can not be generalized to all diabetic patients. The simple modified CG formula as we propose is not biased by weight, is well correlated with isotopic GFR, and more accurate than the MDRD at high GFR. A prediction strategy using the MCG when serum creatinine is below 120 µmol/L, and the MDRD when it is higher, provided the most efficient stratification in our patients.

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