Estimation of renal function in patients with diabetes

V. Rigalleau a,*, M.-C. Beauvieux b, C. Gonzalez a, C. Raffaitin a, C. Lasseur c, C. Combe c, P. Chauveau c, R. De la Faille c, C. Rigothier c, N. Barthe d, H. Ginja e

a Service de nutrition-diabétologie, hôpital Haut-Lévêque, avenue de Magellan, 33600 Pessac, France
b Service de biochimie, hôpital Haut-Lévêque, avenue de Magellan, 33600 Pessac, France
c Service de néphrologie, hôpital Pellegrin, place Amélie-Raba-Léon, 33000 Bordeaux, France
d Service de médecine nucléaire, hôpital Pellegrin, place Amélie-Raba-Léon, 33000 Bordeaux, France
e Université de Bordeaux 2 Victor Segalen, 33000 Bordeaux, France

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Abstract

Diabetes is the leading cause of chronic kidney disease (CKD), which makes estimation of renal function crucial. Serum creatinine is not an ideal marker of glomerular filtration rate (GFR), which also depends on digestive absorption, and the production of creatinine in muscle and its tubular secretion. Formulas have been devised to estimate GFR from serum creatinine but, given the wide range of GFR, proteinuria, body mass index and specific influence of glycaemia on GFR, the uncertainty of these estimations is a particular concern for patients with diabetes. The most popular recommended formulas are the simple Cockcroft–Gault equation, which is inaccurate and biased, as it calculates clearance of creatinine in proportion to body weight, and the MDRD equation, which is more accurate, but systematically underestimates normal and high GFR, being established by a statistical analysis of results from renal-insufficient patients. This underestimation explains why the MDRD equation is repeatedly found to give a poor estimation of GFR in patients with recently diagnosed diabetes and is a poor tool for reflecting GFR decline when started from normal, as well as the source of unexpected results when applied to epidemiological studies with a 60 mL/min/1.73 m2 threshold as the definition of CKD. The more recent creatinine-based formula, the Mayo Clinic Quadratic (MCQ) equation, and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) improve such underestimation, as both were derived from populations that included subjects with normal renal function. Determination of cystatin C is also promising, but needs standardisation.

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Keywords: Creatinine; Cystatin C; Glomerular filtration rate; Chronic kidney disease; Metformin; Diabetes; Review

Résumé

Estimation de la fonction rénale chez les patients diabétiques.

Le diabète est une cause majeure d’atteinte rénale, estimer la fonction rénale des patients diabétiques est donc crucial. La créatininémie n’est pas un marqueur idéal du débit de filtration glomérulaire (DFG), car elle dépend aussi de l’absorption digestive et de la production musculaire de créatinine, ainsi que de sa sécrétion tubulaire. Des équations intégrant des données anthropométriques doivent donc être utilisées pour estimer le DFG, avec des incertitudes particulières pour les patients diabétiques du fait du large éventail de DFG, de protéinurie, d’index de masse corporelle, et de l’effet propre de la glycéminie. Les plus utilisées et recommandées sont la formule de Cockcroft–Gault, simple mais peu précise et biaisée car elle estime la clairance de la créatinine comme proportionnelle au poids, et l’équation de la MDRD, plus précise mais qui sous-estime les DFG normaux car elle a été établie à partir d’une population d’insuffisants rénaux. Cette sous-estimation explique ses mauvaises performances pour estimer le DFG dans des groupes de patients diabétiques récents pour estimer le déclin du DFG en partant de valeurs normales, et aussi certains résultats inattendus d’études épidémiologiques ayant utilisé le seuil de 60 mL/min/1,73 m2 pour définir l’atteinte rénale. La sous-estimation est moindre avec les équations plus récentes (Mayo Clinic Quadratic, CKD-EPI) qui ont été établies à partir de populations incluant des sujets sans insuffisance rénale. La cystatine C est aussi un progrès pour l’estimation du DFG mais nécessite une standardisation.

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* Corresponding author. Tel.: +33 5 57 65 60 78; fax: +33 5 57 65 60 79.
E-mail address: vincent.rigalleau@chu-bordeaux.fr (V. Rigalleau).

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Diabetic nephropathy affects around one-third of patients with diabetes [1], and is the primary cause of end-stage renal disease in most countries [2]. According to the recommendations of the American Diabetes Association and National Kidney Foundation, the critical parameters for the detection [3] and follow-up [4] of chronic kidney disease (CKD) in patients with diabetes are the albumin excretion rate (AER) and glomerular filtration rate (GFR), which is poorly assessed by the sole determination of serum creatinine, as estimated (e-GFR) by either the Cockcroft–Gault (CG) or the Modification of Diet in Renal Disease (MDRD) equation. An increased AER reflects damage to the glomerular filtration barrier—specifically, endothelial cells, glomerular membrane and podocytes. A reduced GFR reflects impaired renal function. An e-GFR less or equal to 60 mL/min/1.73 m² and/or an AER greater than 30 mg/24 h suggest the diagnosis of CKD.

2. Serum creatinine is not an ideal marker of glomerular filtration rate

Serum creatinine does not depend solely on GFR (Fig. 1). Besides the exogenous source of ingested meat, creatinine is mainly produced from muscles and depends on muscle mass, which is higher in males and in black people, and lower with age in adults. This means that adjusting serum creatinine values for ethnic and anthropometric parameters, as performed by formulas, improves their relationship to GFR. The influence of muscle mass on serum creatinine is illustrated by the 20–30 μmol/L creatininemia usually found in patients with Duchenne myopathy [5]. However, whether more subtle reductions of muscle mass as seen, for example, in sedentary people can affect serum creatinine is not known. Less dramatically, drugs such as fibrates as seen, for example, in sedentary people can affect serum creatinine [6] and alter the muscle production of creatinine and alter [7]. This effect, however, does not explain the increased creatinine observed in the Helsinki Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, as cystatin C (CysC) was also increased in the patients treated with fenofibrate during the trial [8]. On the other hand, clearance of creatinine from plasma does not only rely on GFR, but also on its tubular secretion: creatinine clearance exceeds GFR by +10% in normal healthy subjects. This difference can increase to +60% in highly proteinuric nephropathies such as the nephrotic syndrome, with apparently normal serum creatinine masking frank alterations of GFR [9].

3. Serum creatinine is especially imperfect in patients with diabetes

A broad range of GFR can be encountered in diabetic patients, ranging from normal if they are not affected by diabetic nephropathy to high at the early ‘hyperfiltration stage’ [10] and to very low at the terminal predialysis stage. Proteinuria shifts from normal to the nephrotic range in the presence of CKD [11,12]. The consumption of red meat is higher in men with type 2 diabetes [13], and may become worse with the vogue for high-protein diets. The muscle mass of patients with diabetes is especially altered with age [14], and even more so in the case of renal insufficiency [15], while body weight varies according to the type of diabetes, which can influence the estimation of GFR. Variations in glycaemia can also directly influence GFR, as demonstrated in both normal subjects [16] and in those with type 1 (T1D) and type 2 diabetes (T2D) [17,18]. The importance of the glucose level was illustrated by the work of Remuzzi et al. [19], who measured GFR under conditions of controlled glycaemia in patients with T1D complicated by nephropathy: 35 mL/min/1.73 m² with a plasma glucose of 3.3 g/L vs 21 mL/min/1.73 m² with a plasma glucose of 0.93 g/L. These numerous influences make the estimation of GFR mandatory, but they also raise concerns over the validity of the formulas used in such a patient population.

4. The conventional formulas: Cockcroft–Gault or modification of diet in renal disease?

The recommended equations are the old Cockcroft–Gault formula, where CG = [(140 – age in years) × body weight in kg × K] divided by serum creatinine in μmol/L, and K is a constant: 1.23 for men and 1.04 for women [20], and the MDRD study equation [21], where MDRD = 175 [serum creatinine in mg/dL]^{-1.154 × (years)^{-0.203 × (0.742 if female) × (1.210 if African-American)}. The results of the MDRD are directly expressed adjusted to body surface area, whereas the results of the CG have to be adjusted, usually using the DuBois formula [22]. It should be noted that this correction is not always done in clinical practice. On comparing the results of both estimations to GFR measured by an isotope reference method (51Cr-EDTA) in 160 patients with both types of diabetes (n = 50 T1D, n = 110 T2D) and a wide range of renal function (serum creatinine 54–371 μmol/L, isotopic GFR 60.9 ± 36.3 mL/min/1.73 m²) [23], the MDRD was better correlated to GFR (r = 0.81) than was the CG (r = 0.74). Also, the receiver operating characteristic (ROC) curve analysis demonstrated greater diagnostic accuracy for the MDRD (Fig. 2). These results are in line with those of Froissard et al. [24], who also found the greater precision of the MDRD to be more effective in non-diabetic subjects (n = 2095), and of Poggio et al. [25], who found that, in 246 patients with diabetes and renal
Fig. 2. Receiver operating characteristic (ROC) curves for the diagnosis of moderate and severe renal insufficiency in 160 patients with diabetes show better performances of the Modification of Diet in Renal Disease (MDRD) equation compared with the Cockcroft–Gault (CG) formula.

From reference [23], with permission.

insufficiency (GFR 24 ± 21 mL/min/1.73 m²), ∼10% more subjects were within ± 30% of isotopic GFR with the MDRD than with the CG.

Four other studies of patients with diabetes, including the US Diabetes Control and Complications Trial (DCCT) [26], failed to detect any advantages with the MDRD; however, these studies included subjects with normal renal function, whose GFR (∼100 mL/min/1.73 m²) is underestimated by the MDRD [27–29]. These studies showed that, for those with normal renal function, both formulas are imprecise, with less than one-third of estimations being within ± 10% of isotopic GFR. Some guidelines even propose that the value of the e-GFR should not be used if it is greater than 60 mL/min/1.73 m² [30] because it is both false and confusing, and differs among estimations.

Furthermore, errors in the CG and MDRD estimations of normal GFR are not the same, as determined by Ibrahim et al. [26]: the mean error of the CG is smaller but biased, with a low-to-normal CG being underestimated while a high CG is overestimated. Most of the 110/1286 subjects in the DCCT who had CG > 140 mL/min/1.73 m² (‘hyperfiltration’) were overestimated by more than 20 mL/min/1.73 m². The bias of the MDRD is also important, but more predictable as a systematic underestimation: 71% of the patients included in the DCCT had an MDRD below the isotopic GFR of less than 10 units, and MDRD-determined ‘hyperfiltration’ was an exception, despite the fact that more than 20% of these young patients with T1D had isotopic GFRs > 140 mL/min/1.73 m². Underestimations of GFR by the MDRD have also been reported in studies of patients with T2D [29,31], which perhaps is to be expected, as the equation was built through logistic regression of the results from the renal-insufficient participants of the Modification of Diet in Renal Disease study (mean GFR: 40 ± 21 mL/min) [21]. Given the inaccuracy of the CG and underestimations of the MDRD, these equations cannot be used in the diagnosis of glomerular hyperfiltration. The frequently underestimated MDRD of ∼60 mL/min/1.73 m² should be borne in mind when interpreting epidemiological studies that use this threshold for the diagnosis of CKD [32], as further discussed below.

The poor precision of the CG is not to be considered merely the price of its simplicity: the formula is intrinsically flawed, as it estimates GFR in proportion to body weight. As shown in Fig. 3, this leads to overestimation of GFR in patients who are overweight or obese, and underestimation in lean or malnourished patients [33,34]; replacing the measured body weight by

Fig. 3. Glomerular filtration rate (GFR) and its estimations in patients with diabetes and normal body weight, overweight and obesity show that the Cockcroft–Gault formula is biased.

From reference [33], with permission.

the mean value for the studied population would improve the results of the CG formula [35]. In addition, this error is becoming worse at present in the light of the current obesity epidemic, which does not spare patients with CKD [36]. It has also been shown that the accuracy of the CG is lower in patients with poorly controlled diabetes (HbA1c < 8%) [37], although the influence of the HbA1c on GFR (+6 mL/min/1.73 m² for every +1% of HbA1c) can be detected in estimations.

In summary, the main value of the CG is its simplicity, but it is wrong, and the error is worsening because of the obesity epidemic, whereas the MDRD is more accurate for the renal-insufficient, but erroneously underestimates normal-to-high GFR. These flaws are of practical importance in their clinical use for:

- the diagnosis of CKD, as the underestimated MDRD also contaminates the 45–60 mL/min/1.73 m² range that, in our experience, means that around one-third of such MDRD e-GFRs are, in fact, > 60 mL/min/1.73 m² (unpublished data);
- the follow-up of renal function decline, as the inaccurate CG and biased MDRD poorly (under) estimate such a decline [31], although estimations improve for the later stages of disease [38,39]. Clearly, there is considerable room for improvement in the estimation of GFR.

5. Improved creatinine-based formulas

Direct measurement of creatinine clearance has poor reproducibility due to the 15% day-to-day variations seen for urinary creatinine, even in hospitalised patients where specific procedures improve the collection of urine [40]. Serum creatinine dosage, commonly performed with the Jaffe method run on an automated analyser, has to be calibrated to the gold-standard method that is ‘IDMS (isotope dilution mass spectrometry)-traceable’, as recommended by the French Society of Nephrology [41]. Efforts to standardize serum creatinine assays by establishing calibration traceability to an IDMS reference measurement have been underway since 2005. All major global manufacturers have completed recalibration to be traceable to an IDMS reference measurement procedure, and all inventory with the older calibration is expected to no longer be in use by the first half of 2010. Previously, there was wide variability in serum creatinine results among clinical laboratories, with an overall positive bias of approximately 10–20% across the laboratories surveyed [42]. Non-standardized serum creatinine is usually 10–15 μmol/L higher than a 90 μmol/L serum creatinine. Unfortunately, the serum samples on which Cockcroft and Gault based their equation are not available for analysis by an IDMS-traceable assay method, so the CG equation cannot be reformulated for IDMS-traceable creatinine values. The US-based National Kidney Disease Education Program maintains that it is not possible to have a single, uniform conversion formula or factor to relate IDMS-standardised creatinine values back to non-IDMS-traceable values [43]. However, the use of the ‘175’ abbreviated version of the MDRD equation with a standardised creatinine, as presented here, slightly reduces the underestimation of GFR [44].

Some new formulas have been constructed, using a statistical approach like the MDRD based on populations not excluding subjects with normal renal function to correct its underestimation. Ibrahim et al. [26] recalculated the equation based on DCCT data, but the validity of this refitted MDRD for renal insufficiency is questionable. The most recent report of e-GFR decline in the DCCT–EDIC (Epidemiology of Diabetes Interventions and Complications) study used the conventional abbreviated MDRD [45]. Based on the GFR of patients with CKD and healthy kidney donors, the Mayo Clinic group has calculated a ‘Mayo Clinic Quadratic’ (MCQ) equation [46]. On testing the MCQ in 200 patients with diabetes, its correlation with isotopic GFR was similar to the MDRD, while the underestimation of a high MCQ was clearly reduced, thus allowing homogeneous evaluation of the whole GFR range [47] (Fig. 4). This is advantageous for monitoring e-GFR decline, which could be related to the outcome of the AER with only the MCQ during the 3-year follow-up of 63 patients [48]. On the other hand, the precision of the MCQ was less than that of the MDRD, which led to a lower proportion of well-stratified patients in the critical KDQO/I stage 3 (30–60 mL/min/1.73 m²). More recently, the CKD Epidemiology Collaboration multicentre initiative developed a ‘CKD-EPI’ equation, built on measurements taken from 8,254 patients and validated in 3,896 other subjects, which should become the reference method [49]. The formula is complicated, with eight different variations according to race and gender, and whether or
Fig. 5. Correlation between measured change (2-year follow-up initially) in renal function, as determined by isotopic glomerular filtration rate (i-GFR) and four estimated creatinine-based formulas in 20 diabetic patients: (A) CG (Cockroft–Gault); (B) Modification of Diet in Renal Disease (MDRD); (C) Mayo Clinic Quadratic (MCQ) equation; and (D) cystatin C (CysC)-derived equation (Rule’s equation). The Cys-C-derived measure had the best correlation.

From reference [61], with permission.

not the IDMS-traceable creatinine is greater than 62 \mu mol/L and greater than 80 \mu mol/L in women and men, respectively, so the calculation must be computer-assisted. However, the validity of the CKD-EPI for patients with T2D has already been questioned [50]. Thus, as these attempts have still not resolved the issue, another marker of renal function, CysC, has been tested over the past few years.

6. Cystatin C and the derived equations

CysC is produced at a constant rate by nucleated cells, and is freely filtered and degraded, but not secreted, by proximal tubular cells. For this reason, extrarenal factors that modulate creatinine have less of an impact on CysC [51], which can be considered an endogenous marker of GFR [52,53] that is of particular interest when GFR is normal or slightly reduced [54,55].

Rule et al. [56] proposed the following CysC thresholds for the stratification of CKD:

- stage 1: \leq 0.80 mg/L (GFR \geq 90 and AER > 30 mg/24 h);
- stage 2: 0.80–1.09 mg/L (GFR 60–89 and AER > 30 mg/24 h);
- stage 3: 1.10–1.86 mg/L (GFR 30–59);
- stage 4: 1.87–3.17 mg/L (GFR 15–29);
- stage 5: > 3.17 mg/L (GFR < 15).

In our patients with diabetes, the best overall proportions of correctly stratified subjects based on these thresholds were 72.6% with CysC vs 66.9% with the MDRD, 62.9% with the MCQ and 54% with the CG [57]. The 1.10 mg/L CysC threshold for the diagnosis of CKD offers the advantage of excluding those without CKD from the estimation of a false underestimated MDRD if < 1.1 mg/L, and may even correct it by simply dividing the MDRD by CysC; in our patients, this relatively simple approach corrected the MDRD bias without diminishing its accuracy in the low GFR range [57].

To the best of our knowledge so far, four equations have been derived to estimate GFR from CysC [56,58–60], but have proved to have no advantage over the MDRD in either T1D [59] or T2D [60,61] patients: the inclusion of demographic parameters such as age and gender markedly improved the relationship between 1/sCr (serum creatinine) and GFR, although there appears to be less of an improvement with CysC, presumably because it does not depend as much on body composition [62]. Including both serum creatinine and CysC in the equation, as proposed by Rule et al. [56], can, however, further improve correlation with GFR [57].

Although not more accurate than the MDRD, the CysC-derived formulas are less biased, according to Bland–Altman procedures [61], which is advantageous for the follow-up of GFR decline as suggested by longitudinal studies of T1D [63,64] and T2D [65]. As shown in Fig. 5, after relating the
progressive decline of isotopic GFR in 20 patients with diabetes (-8.5 ± 17.9 mL/min/1.73 m² after two years) to their creatinine- and CysC-based estimations, we found that the correlations were not significant with the creatinine-based equations (except the MCQ), and were considerably better with the CysC-based formulas [62]. However, although promising [66], because CysC measurement procedures do not produce uniform results, the estimating equations are restricted to use with only the results from the specific method used to develop them. Consequently, there is a need to standardize CysC calibration to enable the more widespread use of e-GFR estimating equations using this parameter in the calculation. For this reason, recent guidelines have stated that the CysC-based prediction equation cannot yet be recommended for use in clinical practice [67].

7. Practical implications: the example of metformin

Neither the imputability of lactic acidosis to metformin nor the potential protective effect of metformin during lactic acidosis [68] is discussed here, as these points are outside the scope of the present review. At this time, metformin is contraindicated in cases of renal insufficiency, and our topic is the use of the estimation of renal function for this purpose.

The extended application of the MDRD equation has led to numerous epidemiological studies in which the diagnosis of moderate renal failure relied on an e-GFR less than 60 mL/min/1.73 m² as recommended. These studies usually show that the reduction of e-GFR, even if only moderate, is associated with an increased risk of cardiovascular events [69,70], although whether this relationship remains after taking the AER into account is debatable [71]. However, one important piece of information from these studies is the high proportion of MDRD e-GFR less than 60 mL/min/1.73 m² seen in patients with diabetes (about 30%) [71,72]. This makes the withdrawal of metformin at the 60 mL/min/1.73 m² MDRD threshold problematic, as underscored by Warren et al. [73], who proposed a 40 mL/min/1.73 m² threshold to exclude metformin in a similar proportion of patients as with the previous serum creatinine threshold (150 μmol/L) recommended in the UK.

On examining the consequences of using these distinct cut-off values to stop metformin in our patients with T2D [74] (Table 1), we found that metformin was contraindicated in 30% of patients if based on a serum creatinine greater than 150 μmol/L, considered safe according to a survey in the UK. However, 15% of the indications/contraindications were erroneous, according to the actual GFRs measured with this 40 mL/min/1.73 m² threshold. This proportion of error decreased to 11% when the contraindication was based on a 40 mL/min/1.73 m² MDRD threshold, a significant advantage, whereas excluding metformin on the basis of a CG less than 40 mL/min/1.73 m² was wrong in 19% of cases, more than with creatinine alone. On the other hand, the use of a 60 mL/min/1.73 m² MDRD threshold led to the exclusion of metformin in 75% of patients and erroneously classified 19% of them, suggesting that the threshold must be lower if based on the MDRD. The MDRD errors in the 45–59 mL/min/1.73 m² range are probably also the explanation for some unexpected epidemiological results, such as the reduced mortality in subjects with very moderate reductions of GFR (50–59 mL/min/1.73 m²) after the age of 65 [75], two times more CKD in women than in men with diabetes [72] and discordances with cardiovascular risk factors [76].

8. Conclusion

GFR must be estimated in patients with diabetes, the primary cause of renal insufficiency worldwide. Serum creatinine is not sufficient, as it also depends on the production and tubular secretion of creatinine. The simplest estimation of GFR is by calculation of the CG formula, but this is not accurate, and it falsely estimates the clearance of creatinine in proportion to body weight. The MDRD equation is more accurate, but it always underestimates GFR if it is greater than 60 mL/min/1.73 m², and sometimes if it is between 45 and 60 mL/min/1.73 m². New equations can improve this estimation, but they are far more complicated. CysC is a promising step forward, but needs standardisation.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References

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