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The Mayo Clinic quadratic equation improves the prediction of glomerular filtration rate in diabetic subjects

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Abstract

Background. Although recommended, both the Cockcroft and Gault formula (CG) and the modification of diet in renal disease (MDRD) equation are not ideally predictive of glomerular filtration rate (GFR) in diabetic subjects; we tested whether the new Mayo Clinic Quadratic (MCQ) equation performed better.

Methods. In 200 diabetic subjects with a wide range of renal function, GFR was measured by 51Cr-EDTA clearance, and compared with the results of the three predictive equations by regression analysis and Bland and Altman procedures. The correlations with body mass index, age and albumin excretion rates were tested. The precisions (absolute difference as percentage), diagnostic accuracies [receiver operating characteristic (ROC) curves for the diagnosis of moderate and severe chronic kidney disease (CKD)], and the results of stratification according to the KDOQ classification were compared.

Results. The CG and MCQ overestimated mean GFR, whereas the MDRD underestimated it. Correlation coefficients and areas under the ROC curves were better for the MDRD and the MCQ as compared with the CG, which was biased by body weight (+30% overestimation in obese diabetic subjects). The absolute differences with true GFR were slightly lower for the MDRD than the MCQ, and both better than the CG. Both the MDRD and MCQ correctly stratified 65% of the subjects (CG: 55%, $P < 0.05$). In contrast with the MDRD, the MCQ did not underestimate normal GFR, and its performance for stratification was uniformly good over a wide GFR range.

Conclusions. In diabetic subjects, the MCQ has a similar diagnostic performance to the MDRD, but it does not underestimate normal GFR, which is an important advantage.

Keywords: body mass index; diabetes mellitus; GFR; prediction equations; renal function

Introduction

The National Kidney Foundation (NKF) recommends stratification of chronic kidney disease (CKD) in stages 1–5 [1], based on estimated glomerular filtration rate (GFR). This can be estimated by the Cockcroft and Gault formula (CG) [2] or the modification of diet in renal disease (MDRD) study equation [3], as indicated by the NKF and the American Diabetes Association [4].

Diabetes is the primary cause of CKD, and since 2001, most patients entering dialysis in the US are diabetic [5]. The validity of GFR-predictive equations must be verified in the diabetic population, as both equations were developed from the results of non-diabetic subjects. We have demonstrated clear advantages for the MDRD estimation in diabetic patients, as it is more accurate [6], not biased by body mass index (BMI) [7] and more robust when glucose control is poor [8]. The BMI-related bias of the CG, that estimates renal function as proportional to body weight [7], is of special importance for diabetic subjects; most of them are type 2, with a high prevalence of overweight and obesity. However, a drawback of the MDRD is the underestimation of high GFR [9,10] as it has been established and validated in patients with renal insufficiency [3]. This recently led the group of the Mayo Clinic to develop a new 'Mayo Clinic Quadratic' (MCQ) equation, based on the results of both healthy subjects and subjects with CKD [11]. However, only 13% of their 320 patients

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with CKD were diabetic, and the validity of the MCQ for patients outside the Mayo Clinic has been questioned [12].

We therefore tested the MCQ against isotopic GFR, as compared with the recommended MDRD and CG, in 200 diabetic patients of both types, with a large range of GFR (8.5–164 ml/min/1.73 m^2).

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 mainly men ($n = 118$), with type 2 diabetes ($n = 139$, type 2; $n = 61$ type 1), aged 63 ± 13 years (19–83), with a BMI of 27.5 ± 4.7 (15.6–48.9; $n = 50$ obese subjects) and 8.6 ± 1.6 HbA1C (5.2–15). They were included if they were renal insufficient or at least had kidney damage, defined by an isotopic GFR <90 ml/min/1.73 m^2 and microalbuminuria >30 mg/24 h, and some diabetic subjects without renal damage were included in a study of the value of cystatin C. Patients with nephrotic proteinuria (>3 g/24 h) or clinical oedema were excluded to avoid the influence of hyperhydratation on renal function. No patient was treated by dialysis at the time of the study, and no patient used agents known to influence the tubular secretion of creatinine as cimetidine or cotrimoxazole.

Analytical methods

Serum creatinine (SCr) was determined on a multiparameter analyser (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 radionucleide marker was measured after intravenous injection of 51Cr-EDTA (Cis Industries, Gif/Yvette, France). All patients were studied at 9 in the morning, after a light breakfast. After a single bolus of 100 μCi (3.7 MBq) of 51Cr-EDTA, four venous blood samples were drawn at 75, 105, 135 and 165 min, and urinary samples were collected at 90, 120, 150 and 180 min, as previously described [13]. The final result was the mean of the four clearance values. If for one period the urine flow was too low or if a clearance value was not within ±20% of the mean of the other three, this value was excluded and the mean was calculated over the other three clearances. In this way <5% of the values were excluded. The 51Cr-EDTA radioactivity was measured in a γ counter (COBRA 2, model 05003, Packard Instruments, Meriden, CT). The albumin excretion rate (AER) was determined on an immunonephelometric analyser (Behring Nephelometer 2) using an appropriate kit (Nantiserum VO human albumin, Dade Behring).

Estimation of renal function

A single creatinine determination [SCr (mg/dl)] was performed on the day before the isotopic measurement of GFR, to calculate:

Cockcroft and Gault formula (CG) [2].

$$CG = \frac{[140 - \text{age (years)}] \times \text{body weight (kg)} \times 72 \times (0.85 \text{ if female})}{SCr}$$

Modification of Diet in Renal Disease study equation (MDRD). We used the abbreviated equation [11]:

$MDRD = 186 \times (SCr)^{-1.154} \times [\text{age(years)}]^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African–American})$

Mayo Clinic Quadratic (MCQ) equation [11].

$MCQ = \exp [1.911 + 5.249/SCr - 2.114/SCr2 - 0.00686 \times \text{age (years)} - 0.205 \text{ if female}]$

The results of the CG and isotopic GFR were adjusted to body surface area using Dubois' formula [14] before the comparisons. The results of the MDRD and MCQ are expressed directly after adjustment to body surface area.

Categorization of the patients

For the statistical analysis, the patients were categorized as a function of GFR and AER: CKD was stratified as stage 1 (GFR ≥ 90 ml/min/1.73 m^2, with AER ≥ 30 mg/24 h), stage 2 ($60 \leq GFR < 90$, with AER ≥ 30 mg/24 h), stage 3 ($30 \leq GFR < 60$), stage 4 ($15 \leq GFR < 30$) or stage 5 ($GFR < 15$); the remaining patients were 'at increased risk' of CKD due to diabetes [1]. The patients were also categorized in deciles of estimated GFR to determine bias as a function of GFR.

Statistical analysis

The results of the predictive equations were compared with isotopic GFR by paired *t*-tests, and linear regression analysis and Bland and Altman procedures were performed. We tested whether the relation between Ln(isotopic GFR) and 1/SCr followed a linear, logarithmic (as in the MDRD) or quadratic (as in the MCQ) pattern. Ln(isotopic GFR) were also regressed with the CG (1/SCr, 140−age, gender, body weight), MDRD [Ln(SCr), Ln(age), gender] and MCQ (1/SCr, 1/SCr^2, age, gender) models. Linear regression analysis was employed to identify associations between GFR, its predictions and important factors as BMI, age and the AER. The precision of the equations was assessed by the absolute differences between their results and the isotopic GFR. The sensitivity and specificity of each equation for the diagnosis of moderate (GFR <60 ml/min/1.73 m^2) and severe ($GFR < 30$) renal failure were assessed from non-parametric receiver operating characteristic (ROC) curves, generated by plotting sensitivity *vs* 1-specificity, giving the ideal test a sensitivity equal to 1 and a specificity equal to 1. Areas under the curve (AUC) were calculated and compared according to the procedure of Hanley and McNeil [15]. The number of correctly stratified subjects with each equation were compared by χ^2 tests. These calculations were performed

Table 1. Mean ± SD estimated GFR by the three equations, compared with the isotopic GFR

	CG	MDRD	MCQ
Estimated GFR (ml/min/1.73 m^2)	61.2 ± 35.6	51.2 ± 24.4	60.5 ± 31.4
P vs isotopic GFR (paired *t*-test)	0.007	0.0001	0.001
Correlation with isotopic GFR	$R = 0.75$	$R = 0.82$*	$R = 0.84$*
Absolute difference with isotopic GFR: mean±SD	44.2 ± 53.8%	29.3 ± 36.6%**, ***	32.5 ± 44.6%**
(5th-95th centiles)	(1–157%)	(1–73%)	(1–88%)

Isotopic GFR: 56.5 ± 34.9 ml/min/1.73 m^2.
*$P < 0.05$, **$P < 0.001$ *vs* CG, ***$P < 0.05$ *vs* MCQ.

with SPSS software, version 10.0. Results are presented as mean ± SD, and $P < 0.05$ was considered significant.

Results

The mean isotopic GFR was 56.5 ± 34.9 ml/min/1.73 m^2. The mean results of the estimations, their correlation to isotopic GFR and their mean absolute differences with isotopic GFR are listed in Table 1: the MDRD underestimated GFR, whereas the CG and MCQ overestimated it. The MDRD and MCQ were both better correlated to the isotopic GFR, than was the CG. The Bland and Altman plots for the three estimations are depicted on Figure 1: the limits of agreement were wider with the CG (2SD: 49.2 ml/min/1.73 m^2 for the CG, 40.4 for the MDRD, 37.6 for the MCQ). Both the MDRD ($R = -0.54$, $P < 0.001$) and the MCQ ($R = -0;19$, $P<0.01$) underestimated high GFR, but this was more pronounced for the MDRD. According to the absolute differences, both the MDRD and the MCQ were more precise than the CG, with a slight advantage for the MDRD.

Performances according to GFR

Figure 2 depicts 51Cr-EDTA measured GFR as a function of their estimations categorized by deciles. The CG overestimated high GFR ($P < 0.001$ for the highest decile). The MDRD underestimated them ($P < 0.001$ for the 8th decile, $P < 0.05$ for the 9th decile), whereas this did not occur with the MCQ.

When plotting Ln(isotopic GFR) against 1/SCr, the best-fitting model for curve estimation was quadratic ($R^2 = 0.684$), followed by logarithmic ($R^2 = 0.678$) and linear ($R^2 = 0.639$). Accordingly, Ln(isotopic GFR) best fitted to the MCQ model ($R^2 = 0.765$; B = 4.31 for 1/SCr, −1.5 for 1/SCr2, −0.0084 for age, −0.32 for gender; all $P < 0.001$). The overall performance of the MDRD model was near ($R^2 = 0.750$; B = −1.32 for Ln(SCr), −0.38 for Ln(age), −0.32 for gender; all $P < 0.001$), whereas the CG model was less adequate, erronously taking account of body weight [$R^2 = 0.711$; B = 1.99 for 1/SCr, 0.0069 for (140−age), −0.32 for gender; 0.006 for body weight; all $P < 0.001$ except body weight: $P = 0.738$].

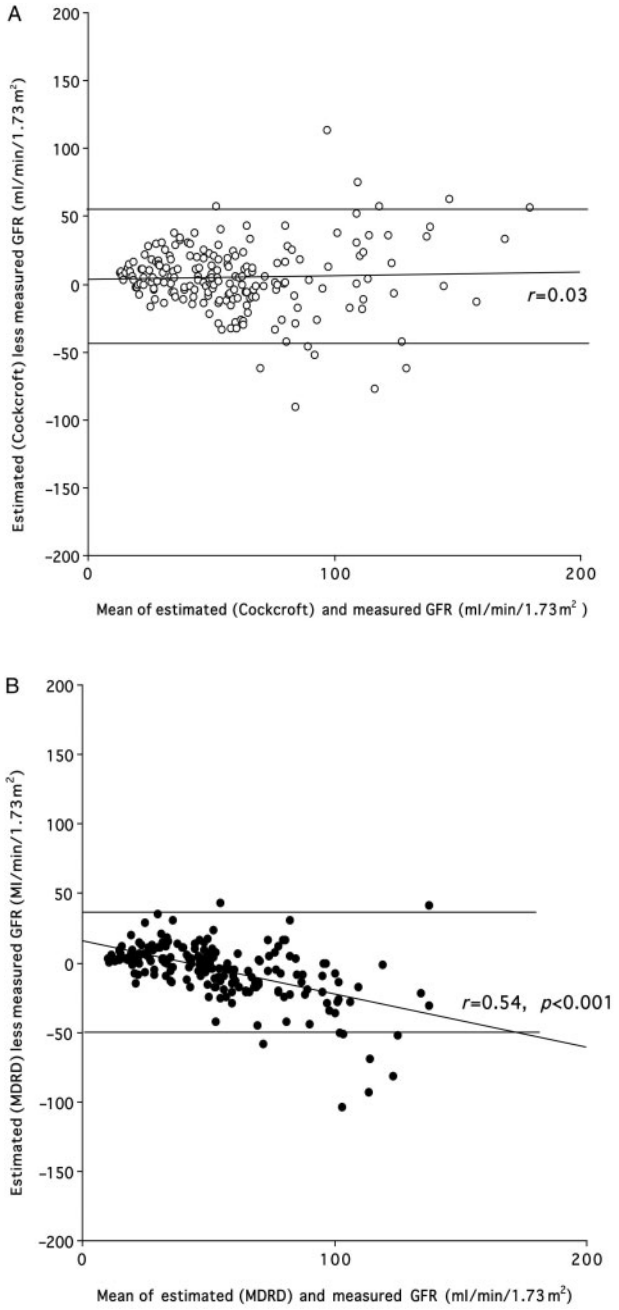


Fig. 1. Bland and Altman plots for the CG [(A) open circles], the MDRD [(B) closed circles] and the MCQ [(C) open squares] estimations of GFR.

Influence of other factors

Isotopic GFR was not correlated with BMI ($R = 0.01$). The MDRD and MCQ estimations were also not

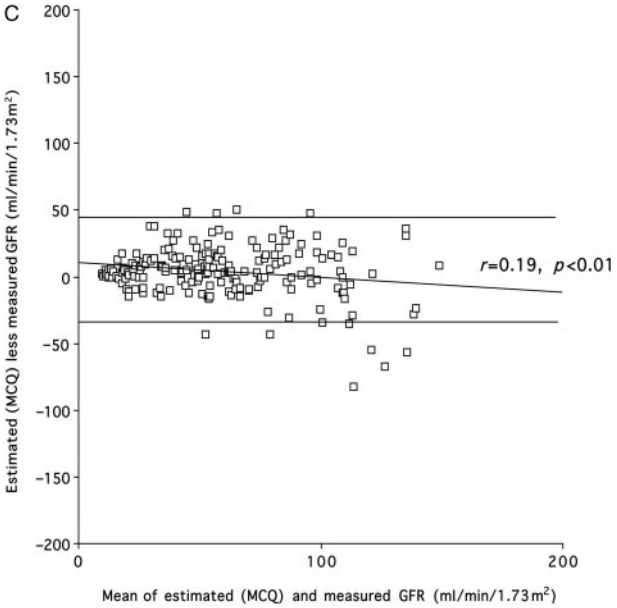


Fig. 1. Continued.

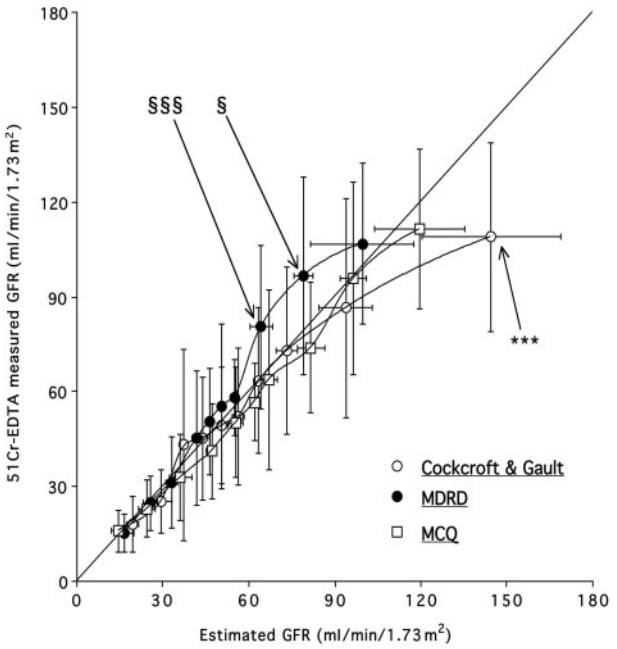
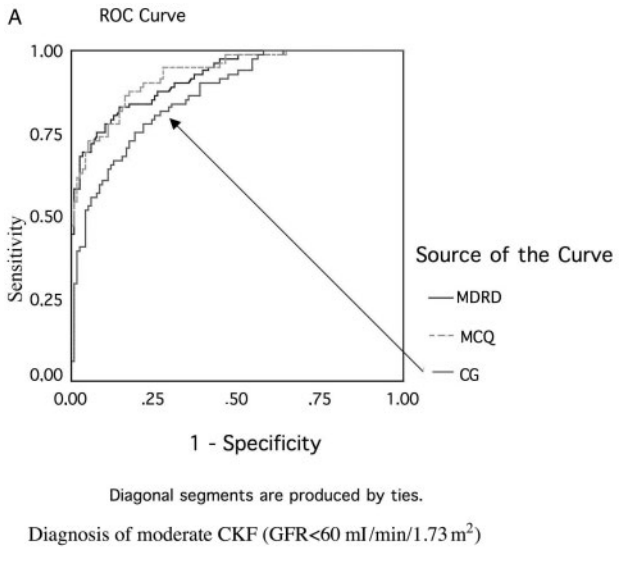


Fig. 2. 51Cr-EDTA measured GFR as a function of their estimations (CG open circles; MDRD closed circles; MCQ open squares) categorized by deciles.



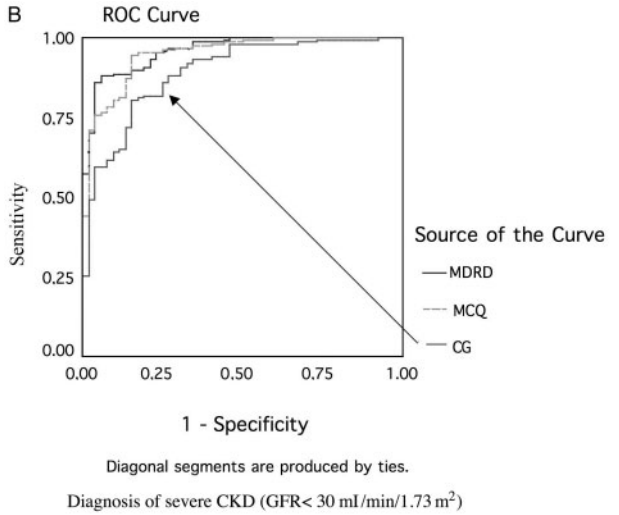


Fig. 3. ROC curves for the diagnosis of moderate [GFR < 60 ml/min/1.73 m^2; (A)] and severe [GFR < 30 ml/min/1.73 m^2; (B) chronic kidney failure by the three predictive equations.

correlated with BMI ($R = 0.04$ for the MDRD, $R = 0.01$ for the MCQ), whereas the CG was correlated with BMI ($R = 0.31$, $P < 0.001$). For the 52 obese subjects, the CG overestimated GFR by +32%, the MDRD underestimated it by −16%, whereas the MCQ estimation did not differ from the measured GFR (isotopic: 58.1 ± 40.2; MCQ: 58.8 ± 40.2; NS).

Isotopic GFR was negatively correlated to age ($R = -0.34$, $P < 0.001$), as were its estimations (CG: $R = -0.41$, MDRD: $R = -0.32$, MCQ: $R = -0.35$; all $P < 0.001$).

The mean AER was 511 ± 754 mg/24 h (5-3000). Isotopic GFR was negatively correlated to the AER ($R = -0.36$, $P < 0.001$), as were its estimations (CG: $R = -0.30$, MDRD: $R = -0.38$, MCQ: $R = -0.42$; all $P < 0.001$).

Diagnostic accuracy and quality of stratification

The ROC curves for the diagnosis of moderate (GFR < 60) and severe (GFR < 30) CKD are depicted in Figure 3. In both cases, the AUC of the MDRD and the MCQ were similar (0.92 for moderate and 0.95 for severe CKD), and significantly better than the CG (0.86 for moderate and 0.89 for severe CKD).

Table 2. Stratification of the 200 diabetic patients according to the KDOQI, using the three predictive equations *vs* the isotopic GFR

Stratified by isotopic measure : ⇨			At increased risk	1	2	3	4	5
Stratified by estimation:		*n*	31	21	29	67	36	16
⇩			31	21	29	67	36	16
At	CG	32	**80.6%**		3.4%	8.9%		
increased	MDRD	24	**70.9%**		3.4%	1.5%		
risk	MCQ	37	**83.8%**		3.4%	14.9%		
1	CG	20		**66.6%**	13.7%	2.9%		
	MDRD	9		**42.8%**	0	0		
	MCQ	23		**80.9%**	17.2%	1.5%		
2	CG	29		12.9%	**37.9%**	17.9%	5.5%	
	MDRD	24		47.6%	**41.3%**	3.0%	0	
	MCQ	36		14.2%	**65.5%**	19.4%	2.7%	
3	CG	89	19.4%	9.6%	44.8%	**65.6%**	50.0%	31.3%
	MDRD	101	29.1%	9.5%	55.1%	**88.1%**	36.1%	12.5%
	MCQ	62	16.2%	4.7%	13.7%	**56.7%**	33.3%	12.5%
4	CG	30				4.5%	**44.4%**	68.8%
	MDRD	34				7.5%	**61.1%**	43.8%
	MCQ	31				7.5%	**58.3%**	31.3%
5	CG	0					0	**0**
	MDRD	8					2.7%	**43.8%**
	MCQ	11					5.5%	**56.3%**

The percentage of rightly stratified subjects are in bold.

Table 2 shows how the three predictive equations stratified the subjects according to the KDOQI stratification. The CG did not enable diagnosis of stage 5, and missed most of the stage 4 CKD. Most of the stage 1 and 2 CKD were misclassified into the following stage by the MDRD. The classification by the MCQ was more homogeneous, as it was correct for more than 50% of the subjects in each stratum. Overall, the CG correctly stratified 55% of the subjects (110/200), whereas both the MDRD and the MCQ correctly stratified 65% subjects (131/200 for the MDRD, 130/200 for the MCQ; both $P < 0.05$ *vs* CG by χ^2).

Discussion

Our findings show the poor performance of the CG formula: it overestimated GFR, especially in the low range, and it was less well correlated with the measured values, with a lower precision and diagnostic accuracy than the other two equations. Although the limited effective needs cautious interpretation, most of the patients with stage 4 (and all stage 5) CKD were missed by the CG. As it calculates GFR as proportional to body weight, it largely overestimates GFR in obese subjects. This bias will tend to increase with time as the mean BMI of subjects entering dialysis is increasing twice as fast as the BMI of the general population in the USA [5]. As a high BMI appears to be an important risk factor for end-stage renal disease [16], this error appears unacceptable.

However, replacing the CG by the MDRD equation may not be the best solution: its underestimation of high GFR will falsely identify a high proportion of diabetics as renal insufficient. This error has been noted in several epidemiological studies [17,18]: for example, older subjects with slight renal impairment according to the MDRD seem to have a paradoxically better prognosis than subjects with normal renal function [18]. The underestimation of high (and overestimation of low) GFR also impairs the follow-up of GFR decline in diabetic patients [19]. This underestimation may be partly explained by the 15–20 μmol/l lower creatinine levels obtained by the MDRD laboratory [20]. However, recent studies have recalibrated the creatinine result obtained by the Jaffé reaction as we used to the MDRD, and found that the MDRD equation still underestimates high GFR after recalibration [9–11,22]. 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 m^2). The study from Ibrahim *et al*. included 1286 type 1 diabetic subjects from the DCCT (mean measured GFR: 122 ± 23 ml/min/1.73 m^2), and confirmed a large systematic underestimation by the MDRD, despite their creatinine measurements similar to those from the MDRD laboratory [9]. According to Rule *et al*. [11] the creatinine recalibration only slightly improved the underestimation by the MDRD in healthy subjects, and it increased the bias in subjects with CKD. Although the non-MDRD calibration of the creatinine assay is a limitation, 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.

Although we noted a lower precision, the new MCQ avoided this underestimation, and we found that it homogeneously stratified CKD in diabetic subjects with a wide range of renal function. This permits the use of a single formula, whereas for correct use, the MDRD may require the pre-selection of patients with renal impairment [23].

Although the MCQ improves prediction of GFR in diabetics, more work is needed. Indeed around 35% of diabetic subjects are KDOQI misclassified with the MDRD and the MCQ, and the generalized over-estimation of low GFR leaves room for the more expensive isotopic or inulin determination of GFR in some cases.

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Conflict of interest statement. None declared.

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