Estimation of Glomerular Filtration Rate in Diabetic Subjects

Cockcroft formula or Modification of Diet in Renal Disease study equation?

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OBJECTIVE — The Cockcroft-Gault formula is recommended for the evaluation of renal function in diabetic patients. The more recent Modification of Diet in Renal Disease (MDRD) study equation seems more accurate, but it has not been validated in diabetic patients. This study compares the two methods.

RESEARCH DESIGN AND METHODS — In 160 diabetic patients, we compared the Cockcroft-Gault formula and MDRD equation estimations to glomerular filtration rates (GFRs) measured by an isotopic method (^{51}Cr-EDTA) by correlation studies and a Bland-Altman procedure. Their accuracy for the diagnosis of moderately (GFR <60 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}) or severely (GFR <30 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}) impaired renal function were compared with receiver operating characteristic (ROC) curves.

RESULTS — Both the Cockcroft-Gault formula ($r = 0.74$; $P < 0.0001$) and MDRD equation ($r = 0.81$; $P < 0.0001$) were well correlated with isotopic GFR. The Bland-Altman procedure revealed a bias for the MDRD equation, which was not the case for the Cockcroft-Gault formula. Analysis of ROC curves showed that the MDRD equation had a better maximal accuracy for the diagnosis of moderate (areas under the curve [AUCs] 0.868 for the Cockcroft-Gault formula and 0.927 for the MDRD equation; $P = 0.012$) and severe renal failure (AUC 0.883 for the Cockcroft-Gault formula and 0.962 for the MDRD equation; $P = 0.0001$). In the 87 patients with renal insufficiency, the MDRD equation estimation was better correlated with isotopic GFR (Cockcroft-Gault formula $r = 0.57$; the MDRD equation $r = 0.78$; $P < 0.01$), and it was not biased as evaluated by the Bland-Altman procedure.

CONCLUSIONS — Although both equations have imperfections, the MDRD equation is more accurate for the diagnosis and stratification of renal failure in diabetic patients.

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Abbreviations: AUC, area under the curve; ESRD, end-stage renal disease; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; ROC, receiver operating characteristic.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Diabetic nephropathy affects 25–40% of diabetic patients (1), and diabetes is the leading cause of end-stage renal disease (ESRD) in developed countries (2). Mainly because of the high prevalence and increased life expectancy of type 2 diabetic patients (3), the proportion of patients with both diabetes and ESRD is dramatically growing in developed countries (4). Survival rates are low in such patients because of high cardiovascular risk (5), and medical costs are high (6).

The evaluation of renal function is therefore of critical importance in diabetic subjects. Glomerular filtration rate (GFR) is the best measure of overall kidney function in health and disease (7). Serum creatinine concentration is widely used as an indirect marker of GFR, but it is influenced by muscle mass and diet (8). GFR can be directly measured by infusion of external substances such as inulin or ^{51}Cr-EDTA (9), but these methods are expensive and time consuming. The use of prediction equations to estimate GFR from serum creatinine and other variables (age, sex, race, and body size) is therefore recommended by the National Kidney Foundation for the diagnosis and stratification of chronic kidney diseases (10). According to these guidelines, renal function is moderately decreased if GFR is <60 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2} and severely decreased if GFR is <30 ml $\cdot$ min^{-1} $\cdot$ 1.73 m^{-2}.

The proposed equations are the Cockcroft-Gault formula (11), as recommended by the American Diabetes Association (12), and the Modification of Diet in Renal Disease (MDRD) study equation (13). The more recent MDRD equation seems more accurate, but it has not been validated in diabetic kidney disease (10). Its superiority over the Cockcroft-Gault formula has been mentioned in some (14), but not all (15,16), recent reports.

We compared Cockcroft-Gault formula and MDRD equation estimates of GFR with ^{51}Cr-EDTA measurement in

160 diabetic subjects with a wide range of GFRs (8–164 ml · min^{-1} · 1.73 m^{-2}). We studied the correlation between both estimations and isotopic measurement of GFR and performed a Bland-Altman procedure (17). Their sensitivity and specificity for the diagnosis of moderately or severely impaired renal function were assessed from receiver operating characteristic curves (ROC). Correlation studies and Bland-Altman procedures were also performed on the renal insufficient group in relation to isotopic GFR (n = 87).

RESEARCH DESIGN AND METHODS

— The study group consisted of 160 diabetic patients attending our clinical unit. Both sexes (91 men and 69 women) and types of diabetes (50 type 1 and 110 type 2) were represented. Mean ± SD HbA_{1c} was 8.6 ± 1.7%. A wide range of ages (19–83 years; 62.2 ± 13.7 years), BMIs (15.6–48.9 kg/m^2; 27.5 ± 4.6 kg/m^2), and serum creatinine levels (54–371 μmol/l; 136.0 ± 69.1 μmol/l) were represented. Mean proteinuria was 523 ± 260 mg/24 h. Subjects with nephrotic proteinuria (>3 g/24 h) or clinical edema were excluded. No subject was treated by dialysis at the time of the study.

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. Clearance of the radionuclide marker was measured after intravenous injection of ^{51}Cr-EDTA (Cis Industries, Gif/Yvette, France). All patients were studied at 9:00 A.M. after a light breakfast. After a single bolus of 100 μCi (3.7 MBq) of ^{51}Cr-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 (18). The ^{51}Cr-EDTA radioactivity was measured on a γ counter (COBRA 2, model 05003; Packard Instruments, Meriden, CT).

Estimations of renal function

A single creatinine determination was performed the day before the isotopic measurement of GFR to calculate the Cockcroft-Gault formula as follows.

$$\frac{(140 - \text{age [years]}) \times \text{body weight (kg)} \times K}{\text{serum creatinine (μmol/l)}} \quad (1)$$

where K is a constant of 1.23 for men and 1.04 for women (11).

Before comparison, Cockcroft-Gault formula results were adjusted to body surface area using Dubois' formula (19).

To calculate the MDRD equation, we used the following abbreviated equation (13).

$$186 \times (\text{serum creatinine [mg/dl]})^{-1.154} \times ([\text{years}])^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

Statistical analysis

Results of the Cockcroft-Gault formula and the MDRD equation were compared with isotopic GFR by correlation, paired t tests, and Bland-Altman procedures. These calculations were performed with SPSS software, version 10.0. The sensitivity and specificity of both formulas were assessed from nonparametric ROC curves generated by plotting sensitivity versus 1 − specificity, giving the ideal test a sensitivity = 1 and specificity = 1. Areas under the curve (AUCs) were calculated and compared according to the procedure of Hanley and McNeil (20). AUC is commonly >0.5 with values ranging from 1 (ideal perfect separation of the tested values) to 0.5 (no apparent distribution difference between the tested groups). These analyses were performed using Medcalc software. Results are presented as means ± SD. $P < 0.05$ was considered significant.

RESULTS

— Mean isotopic GFR was 60.9 ± 36.3 ml · min^{-1} · 1.73 m^{-2}. The mean Cockcroft-Gault formula overestimated GFR (65.6 ± 37.5 ml · min^{-1} · 1.73 m^{-2}; $P < 0.05$ vs. isotopic GFR) and the mean MDRD equation underestimated GFR (54.7 ± 25.1 ml · min^{-1} · 1.73 m^{-2}; $P < 0.001$ vs. isotopic GFR). As shown in Fig. 1*A*, both estimations were well correlated to isotopic GFR with a slight advantage for the MDRD equation (Cockcroft-Gault formula $r = 0.74$, $P < 0.0001$; MDRD equation $r = 0.81$, $P < 0.0001$; $P = 0.12$ between r values). The Bland-Altman procedure (Fig. 1*B*) revealed a bias for the MDRD equation as the estimation minus GFR (mean −6.1 ml · min^{-1} · 1.73 m^{-2}, 2 SDs 43.0) was negatively correlated to the mean ($r = -0.54$, $P < 0.001$), which was not the case for the Cockcroft-Gault formula (mean +4.8 ml · min^{-1} · 1.73 m^{-2}, 2 SDs 52.4, $r = 0.04$, $P = 0.64$).

For the 50 type 1 diabetic subjects (BMI 24.6 ± 2.9 kg/m^2), both estimations did not differ from isotopic GFR (isotopic 65.5 ± 34.2 ml · min^{-1} · 1.73 m^{-2}; Cockcroft-Gault formula 66.6 ± 35.4 ml · min^{-1} · 1.73 m^{-2}; MDRD equation 62.4 ± 29.7 ml · min^{-1} · 1.73 m^{-2}; NS). For the 110 type 2 diabetic subjects (BMI 28.9 ± 4.8 kg/m^2; $P < 0.0001$ vs. type 1), isotopic GFR was 58.7 ± 37.2 ml · min^{-1} · 1.73 m^{-2}. The Cockcroft-Gault formula gave an overestimated GFR (65.2 ± 38.5 ml · min^{-1} · 1.73 m^{-2}; $P < 0.01$ vs. isotopic) and the MDRD equation gave an underestimated GFR (51.2 ± 22.0 ml · min^{-1} · 1.73 m^{-2}; $P < 0.001$ vs. isotopic). In both subgroups, correlation coefficients between estimated and measured GFR were not significantly, but were consistently, higher for the MDRD equation (type 1: $r = 0.72$ for the Cockcroft-Gault formula and 0.83 for the MDRD equation; type 2: $r = 0.76$ for the Cockcroft-Gault formula and 0.83 for the MDRD equation).

The ROC curve analysis (Fig. 2) showed that the maximum diagnostic accuracy of the Cockcroft-Gault formula for the diagnosis of moderate renal failure (GFR <60 ml · min^{-1} · 1.73 m^{-2}) was lower than the MDRD equation (Cockcroft-Gault formula AUC 0.868, cutoff limit 56.5; MDRD equation AUC 0.927, cutoff limit 54.7; $P < 0.05$). This was mainly due to a better sensitivity of the MDRD equation estimation (Cockcroft-Gault formula sensitivity 77.9% and specificity 81.1%; MDRD equation sensitivity 91.9% and specificity: 78.4%). For the diagnosis of severe renal failure (GFR <30 ml · min^{-1} · 1.73 m^{-2}) (Fig. 3), the maximum diagnostic accuracy of the Cockcroft-Gault formula was lower than that of the MDRD equation (Cockcroft-Gault formula AUC 0.883, cutoff limit 43.9; MDRD equation AUC 0.962, cutoff limit 42.4; $P < 0.0001$) because of improved sensitivity and specificity (Cockcroft-Gault formula sensitivity 78.9% and specificity 84.4%; MDRD equation sensitivity 94.7% and specificity 90.2%).

In the 87 renal-insufficient patients (GFR <60 ml · min^{-1} · 1.73 m^{-2}; mean isotopic GFR 33.7 ± 14.7 ml · min^{-1} · 1.73 m^{-2}), both the Cockcroft-Gault for-

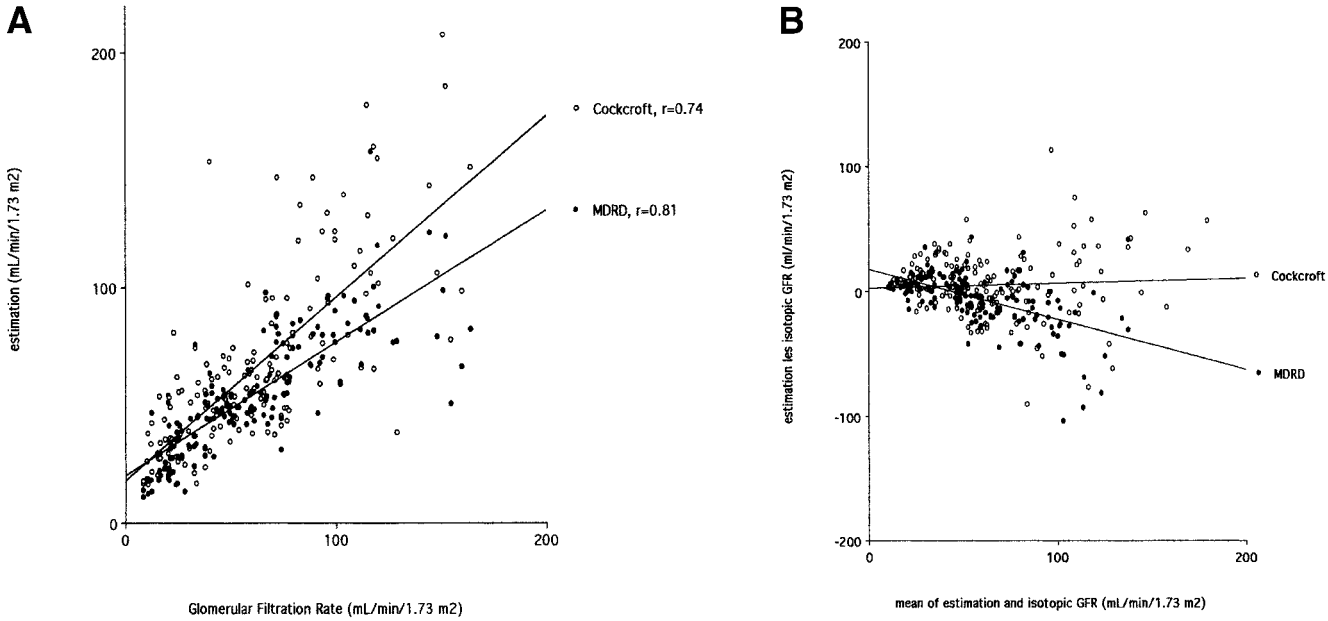

Figure 1—A: *Estimated GFR as a function of its isotopic measurement (milliliters per minute per 1.73 m^2) in 160 diabetic subjects.* B: *Bland-Altman plots of differences between estimated GFR and measured with ^{51}Cr-EDTA as a function of average GFR by both methods in 160 diabetic subjects.* ○, *Cockcroft-Gault formula;* ●, *MDRD equation.*

mula and the MDRD equation overestimated GFR (Cockcroft-Gault formula 45.3 ± 21.0 ml · min^{-1} · 1.73 m^{-2}; MDRD equation 38.4 ± 14.0 ml · min^{-1} · 1.73 m^{-2}; both $P < 0.0001$ vs. isotopic GFR), but the overestimation was more pronounced with the Cockcroft-Gault formula ($P < 0.0001$ vs. the MDRD equation). As shown in Fig. 4*A*, the correlation with isotopic GFR was lower for the Cockcroft-Gault formula (Cockcroft-Gault formula $r = 0.57$, $P < 0.001$; MDRD equation $r = 0.78$, $P < 0.0001$; $P < 0.01$ between r values). As shown in Fig. 4*B*, the Cockcroft-Gault formula overestimated high values of GFR according to the Bland-Altman procedure (mean +11.6 ml · min^{-1} · 1.73 m^{-2}, 2SD 37.1, $r = 0.38$, $P < 0.001$); this was not the case for the MDRD equation (mean +4.7 ml · min^{-1} · 1.73 m^{-2}, 2SD 20.6, $r = 0.07$, $P = 0.49$).

CONCLUSIONS — The Cockcroft-Gault formula is a simple, widely used, and recommended means to assess renal function. The estimation by the Cockcroft-Gault formula is well correlated (r = 0.75–0.93) with GFR as determined by infusion of external substances such as ^{99}Tc-diethylenetriaminepentaacetate (21,22), iothamalate (13,23–26), inulin (27), iohexol (28), and ^{51}Cr-EDTA (29). Studies in diabetic patients (24,30–32) have examined smaller numbers of patients (n = 49–136) and reported slightly lower correlation coefficients (r = 0.69–0.88). A correlation coefficient of 0.74 and a slight overestimation of GFR (24), as we also found, were therefore not unexpected. The normalization of the Cockcroft-Gault formula to body surface area as carried out is known to improve its diagnostic performance (33).

Previous studies found the main problem with the Cockcroft-Gault formula to be overestimation when GFR values are low (21,22), which we also found to be true, particularly in the 87 diabetic patients with renal insufficiency. Our results show that this overestimation alters the sensitivity of the Cockcroft-Gault formula for the diagnosis of moderate and severe renal failure. Late diagnosis of severe renal failure can retard the referral to the nephrologist or the indication for dialysis or transplantation, which worsens the prognosis (34). The National Kidney Foundation recommends that patients

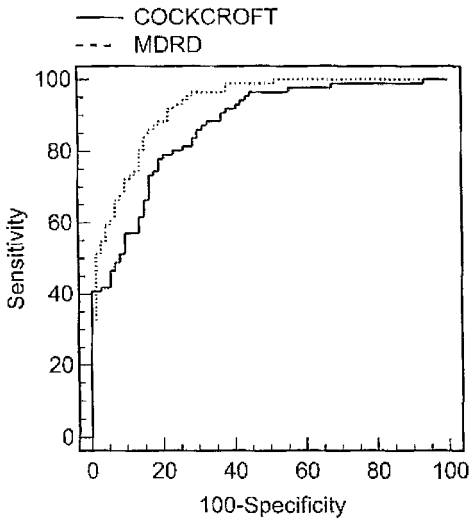

Figure 2—*ROC curves comparing AUCs of the Cockcroft-Gault formula and the MDRD equation for the diagnosis of moderate renal failure (GFR <60 ml · min^{-1} · 1.73 m^2).*

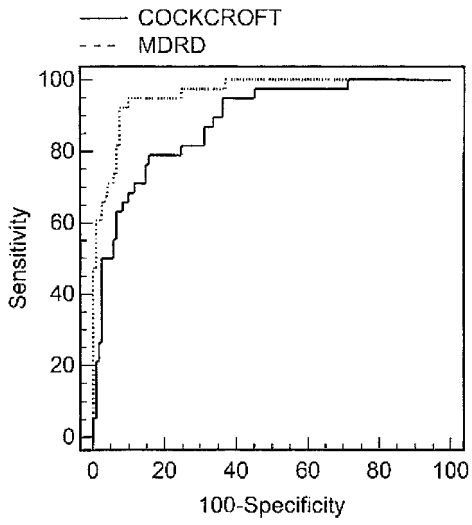

Figure 3—*ROC curves comparing AUCs of the Cockcroft-Gault formula and MDRD equation for the diagnosis of severe renal failure (GFR <30 ml · min^{-1} · 1.73 m^{-2}).*

should be referred to a nephrologist when GFR is <30 ml · min^{-1} · 1.73 m^{-2} and prepared for dialysis (including access placement) when GFR is <25 ml · min^{-1} · 1.73 m^{-2}. Delayed referral would have affected 52 and 34% of the 38 subjects with isotopic GFR <30 ml · min^{-1} · 1.73 m^{-2} using the Cockcroft-Gault formula and the MDRD equation, respectively. Delayed access would have affected 64 and 45% of the 31 subjects with isotopic GFR <25 ml · min^{-1} · 1.73 m^{-2} using the Cockcroft-Gault formula and the MDRD equation, respectively.

The presence of weight in the equation is probably another important cause of error, especially for diabetic patients whose BMIs are widely dispersed. In type 2 diabetes, a high proportion of these patients with renal insufficiency are obese, even at the stage of hemodialysis (35). GFR is proportional to body weight in the Cockcroft-Gault formula. However, most of the excessive body weight in obesity is fat, which does not produce creatinine. According to a proportional relationship, an obese diabetic patient who intentionally loses 20% of his body weight would lose 20% of his or her GFR. In 24 moderately obese diabetic patients, Solerte et al. (36) found that a 20% diet-induced weight loss was associated with a 20% increase in GFR. Body weight in the Cockcroft-Gault formula therefore influences the estimation in an opposite way from the clinical evidence: intentional weight loss is beneficial in diabetic patients (37) and nothing suggests that it deteriorates renal function. The 10% overestimation of GFR that we found by the Cockcroft-Gault formula in type 2 diabetic patients (but not in type 1) is probably due to this influence of weight.

The MDRD equation is derived from the results of 1,070 renal-insufficient patients and validated in 558 other patients. It was clearly more accurate than the Cockcroft-Gault formula in this population (13), and it does not require body weight. However, the MDRD equation has not been validated in individuals without renal disease (13). We show that it underestimates GFR at high levels, as already reported by Hallan et al. (14) in nondiabetic patients by a Bland-Altman plot quite similar to ours. This underestimation explains why Vervoort et al. (15), who studied 46 type 1 diabetic patients with normal GFR (>88 ml · min^{-1} · 1.73 m^{-2}), did not find any advantage of the MDRD equation over the Cockcroft-Gault

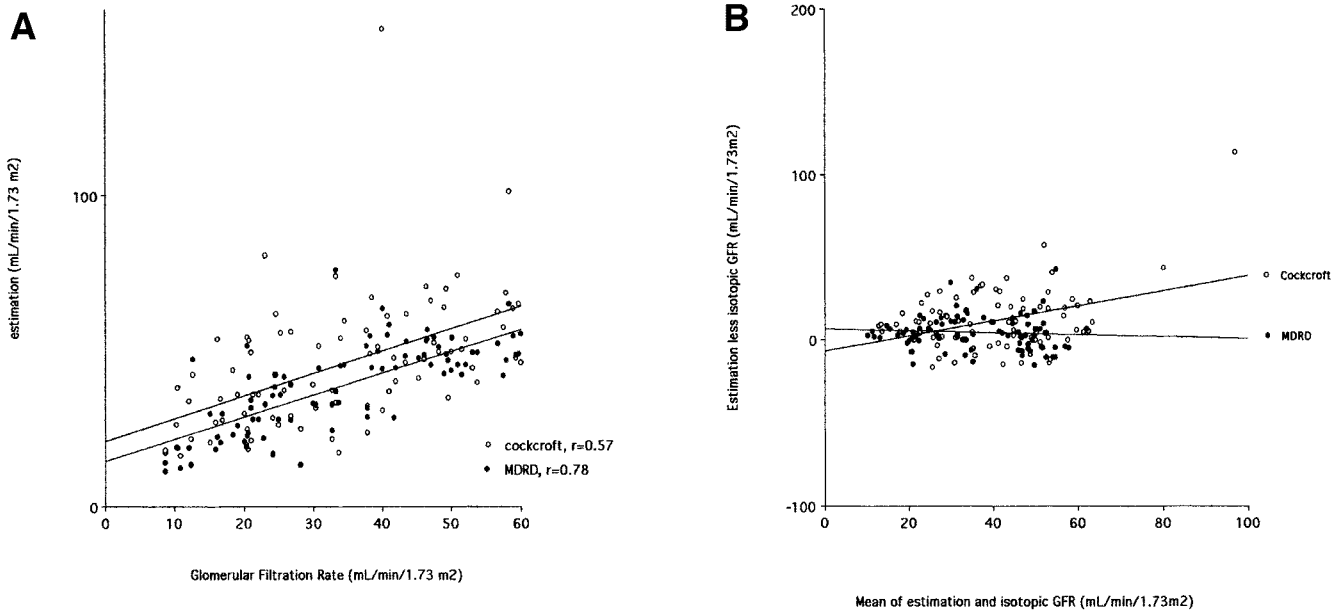

Figure 4—A: *Estimated GFR as a function of its isotopic measurement (milliliters per minute per 1.73 m^2) in 87 renal-insufficient diabetic subjects.* B: *Bland-Altman plots of differences between estimated GFR and measured with ^{51}Cr-EDTA as a function of average GFR by both methods in 87 renal-insufficient diabetic subjects.* ○, *Cockcroft-Gault formula;* ●, *MDRD equation.*

formula. However, an important practical utility of a GFR predictive formula is to diagnose and stratify chronic renal failure in patients with renal diseases. Our work shows better precision and improved diagnostic accuracy for the MDRD equation, particularly in diabetic subjects with renal insufficiency. This advantage may be offset by the requirement of a scientific calculator because the MDRD equation calculation includes negative logarithms, whereas the Cockcroft-Gault formula can be calculated using a simple calculator or by mental arithmetic. As suggested by the National Kidney Foundation recommendations (10), the calculation of the estimated GFR can be performed by clinical laboratories; according to French recommendations (33), laboratories give an estimation of GFR together with the result of serum creatinine measurement using the Cockcroft-Gault formula. If other reports confirm the practical interest of the MDRD equation, it will be possible to request a MDRD equation calculation from the laboratory.

Although the error is halved when compared with the Cockcroft-Gault formula, low GFR was still overestimated with the MDRD equation. The relationship between serum creatinine and GFR is not simple in severe renal insufficiency. The clearance of creatinine does not depend only on GFR (38) as tubular excretion of creatinine occurs. This tubular excretion varies with the degree of renal failure (39), thus limiting the possibility of using 24-h creatinine clearance, which is not recommended by the National Kidney Foundation as a substitute for prediction equations (10). The serum level of creatinine not only depends on its clearance; lower creatinine production due to decreased lean body mass (40) may reduce creatinine production in some renal insufficient patients as renal function declines. A lower creatinine generation has indeed been mentioned in hemodialyzed diabetic subjects (35). Further improved formulas are therefore warranted and the use of reference methods with infusion of external substances can still be useful to evaluate renal function in some renal-insufficient diabetic patients.

In summary, both equations have imperfections. Overestimation at low GFR levels and the influence of weight reduce the sensibility and the accuracy of the Cockcroft-Gault formula. The MDRD equation is more difficult to calculate in clinical practice and underestimates GFR at high levels, but it has better accuracy in diagnosing and stratifying chronic renal failure in diabetic patients, which is an important advantage for a prediction formula.

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