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Cockcroft-Gault formula is biased by body weight in diabetic patients with renal impairment

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Abstract

The Cockcroft-Gault (CG) formula and the modification of diet in renal disease (MDRD) equation are commonly used to estimate glomerular filtration rate (GFR), but their validity at extreme body weight is questionable. This may be significant for diabetic patients. In 122 diabetic patients with renal damage, we compared both estimates to isotopically determined GFR by correlation studies and a Bland and Altman procedure before and after categorizing the patients according to body mass index (BMI). Over the whole population, the CG overestimated GFR (CG, 51.4 ± 23.1 mL/[min · 1.73 m^2]; isotopic GFR, 44.6 ± 21.1 mL/[min · 1.73 m^2], $P < .0001$). The MDRD (45.2 ± 17.9; NS vs isotopic GFR) did not overestimate GFR, but it underestimated high GFR as revealed by the Bland and Altman procedure ($r = -0.26$, $P < .005$). The CG underestimated GFR in patients with normal BMI (−14%, $P < .01$) and overestimated it in overweight (15%, $P < .005$) and obese patients (55%, $P < .0001$); the result and the error of the estimation were correlated with BMI. This bias did not affect the MDRD. The use of ideal instead of measured body weight improved the CG prediction, but underestimated GFR. As the BMI of the 87 type 2 diabetic subjects was higher, the CG overestimated their mean GFR by 18% ($P < .001$), whereas the MDRD did not. There were 25% fewer patients with delayed referral using the MDRD than with the CG. Because the estimate of GFR by the CG is proportional to body weight, it is not suited for obese diabetic patients. Although it is less easy to calculate, the MDRD is not affected by weight, and its use would avoid delay in referral to nephrologists.

1. Introduction

The evaluation of renal function is crucial in patients with chronic kidney disease [1]. Glomerular filtration rate (GFR) is traditionally considered the best overall index of renal function in health and disease [2]. According to recent guidelines [3,4], the determination of GFR allows the diagnosis and the stratification of chronic renal failure (CRF), which has practical implications. Complications should be evaluated and treated in patients with moderate renal failure (GFR <60 mL/[min · 1.73 m^2]), whereas patients with severe renal failure (GFR <30 mL/[min · 1.73 m^2]) must be referred to a nephrologist with a view to dialysis. Delayed referral and treatment are associated with poor prognosis [5].

Serum creatinine concentration is widely used as an indirect marker of GFR, but it is influenced by muscle mass and diet [6]. It should not be used as the sole index of kidney function [3]. GFR can be directly measured by infusion of external substances such as inulin or ^{51}Cr-EDTA [7], 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 [3]. The proposed equations are the Cockcroft-Gault (CG) formula [8] and the modification of diet in renal disease (MDRD) study equation [2]. However, these equations have not been validated in conditions of extreme body size or severe malnutrition. Their predictive values have not been

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compared, and GFR may need to be measured directly in such cases [3].

Diabetes is the leading cause of end-stage renal disease in the Western world [9]. Mainly because of the high prevalence and better life expectancy of type 2 diabetic patients [10], the proportion of patients with both diabetes and end-stage renal disease is rising dramatically in developed countries [11]. The use of the CG formula to assess renal function is recommended by the American Diabetes Association [12], but this equation includes weight, which varies widely among diabetic patients; both obesity and malnutrition are more frequent in hemodialyzed diabetic patients [13]. The more recent MDRD equation does not include body weight, but it has not been validated in diabetic kidney disease [2]. Its superiority over the CG has been mentioned in some [14], but not all [15], recent reports. None of these studies included diabetic patients with kidney damage.

In 122 diabetic patients with kidney damage, we compared CG- and MDRD-estimated GFR to values measured by a reference method (^{51}Cr-EDTA). We studied the correlation between both estimates and isotopic measurement of GFR, and we performed a Bland and Altman procedure [16]. To determine the influence of body weight on the estimations, we repeated the comparison and the correlation studies after the patients were categorized as normal (body mass index [BMI] <25 kg/m^2), overweight (BMI ≥25 to <30 kg/m^2), or obese (BMI ≥30 kg/m^2), and we calculated the CG based on the ideal body weight of the subjects (as defined by body weight for BMI = 22 kg/m^2). Comparisons and correlations were also studied separately in types 1 and 2 diabetic patients.

2. Methods

2.1. Patients

One hundred twenty-two adult diabetic patients attending our clinical unit were studied. The patients were included if they were renal insufficient, indicated by an isotopic GFR below 60 mL/(min · 1.73 m^2) (n = 87) or if they had at least some kidney damage as defined by an isotopic GFR below 90 mL/(min · 1.73 m^2) and microalbuminuria of more than 30 mg/24 hours (n = 35). Patients with nephrotic proteinuria (>3 g/24 hours) or anasarca were excluded. No patient was treated by dialysis at the time of the study.

2.2. Analytical methods

Serum creatinine was determined on a multiparameter analyzer (Olympus AU 640, Olympus Optical, Tokyo, Japan) using the Jaffe method with bichromatic measurements according to the manufacturer's specifications and daily calibration of the analyzer. Clearance of the radionuclide marker was measured after intravenous injection of ^{51}Cr-EDTA (Cis Industries, Gif/Yvette, France). All patients were studied in the morning at 9:00 AM, after a light breakfast. After a single bolus of 100 μCi (3.7 MBq) of ^{51}Cr-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 described [17]. The ^{51}Cr-EDTA radioactivity was measured in a γ counter (COBRA 2, model 05003, Packard Instruments, Meriden, CT).

2.3. Estimation of renal function

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

$$\mathrm{CG} = \frac{(140\text{-age [years]}) \times \text{body weight [kg]} \times K}{\text{serum creatinine [mg/dL]}}$$

where K is a constant, 0.72 for men and 0.85 for women [8].

The calculation was also performed after replacing the measured body weight of the patients by their ideal body weight, calculated as their body weight for BMI = 22 kg/m^2, leading to CG(IBW):

$$\mathrm{IBW} = 22 \times \left(\text{height [m]}^2\right)$$

Before comparison, CG and CG(IBW) results were adjusted to body surface area using the formula of DuBois and DuBois [18].

We used the abbreviated MDRD equation [2]:

$$\begin{aligned}\mathrm{MDRD} = {} & 186 \times (\text{serum creatinine [mg/dL]})^{-1.154} \\ & \times (\text{age [years]})^{-0.203} \times (0.742 \quad \text{if female}) \\ & \times (1.210 \quad \text{if African American})\end{aligned}$$

2.4. Statistical analysis

Results of the CG, CG(IBW), and MDRD formulas were compared with isotopic GFR by correlation, paired t tests, and a Bland and Altman procedure. The patients were then categorized according to BMI as normal (BMI <25 kg/m^2), overweight (BMI ≥25 to <30 kg/m^2), and obese (BMI ≥30 kg/m^2), according to the type of diabetes, and according to the degree of renal insufficiency; correlation studies and paired t tests were performed in each subgroup. We also performed correlation studies to search for an association between BMI and GFR or its estimations and BMI and the differences (estimate minus isotopic GFR). These calculations were performed using SPSS software, version 10.0 (Paris-La-Défense, France).

3. Results

Both sexes (67 men, 55 women) and types of diabetes (35 type 1, 87 type 2) were represented. Mean hemoglobin A_{1c} was 8.4% ± 1.6%. A wide range of age (30-83 years; mean ± SD, 65.6 ± 11.3 years), BMI (15.6-48.9 kg/m^2;

Table 1
Isotopically determined GFR and its estimation by the CG formula and the MDRD equation in normal-weight, overweight, and obese diabetic patients in types 1 and 2 diabetic patients and in subgroups established according to the degree of renal insufficiency

	n	BMI	GFR	Cockcroft	*r*	*P*	CG(IBW)	*r*	*P*	MDRD	*r*	*P*
Normal	42	22.7 ± 1.9	46.5 ± 20.2	40.3 ± 13.9	0.69	.009	38.8 ± 12,3	0.70	.001	45.5 ± 14.4	0.70	NS
Overweight	47	27.6 ± 1.3	44.1 ± 22.3	50.8 ± 19.5	0.77	.003	40.7 ± 16.2	0.78	NS	45.6 ± 21.2	0.84	NS
Obesity	33	33.6 ± 3.8	42.7 ± 22.1	66.3 ± 28.9	0.59	.0001	43.1 ± 17.7	0.68	NS	44.4 ± 17.1	0.75	NS
Diabetes												
Type 1	35	24.8 ± 2.9	47.6 ± 22.2	51.0 ± 24.0	0.50	NS	44.7 ± 17.7	0.61	NS	49.2 ± 20.2	0.71	NS
Type 2	87	28.6 ± 5.1	43.4 ± 20.7	51.5 ± 22.8	0.59	.0001	39.0 ± 14.1	0.76	.004	43.6 ± 16.7	0.80	NS
GFR												
≥60	35	26.6 ± 3.8	70.6 ± 5.5	65.9 ± 21.6	0.13	NS	53.8 ± 13.8	0.19	.0001	61.5 ± 15.5	0.25	.001
≥30 to <60	47	27.8 ± 5.4	45.0 ± 8.7	53.6 ± 21.5	0.26	.007	41.6 ± 10.6	0.36	.04	47.3 ± 9.7	0.33	NS
<30	40	28.0 ± 5.0	19.5 ± 5.7	34.8 ± 14.9	0.32	.0001	27.0 ± 9.6	0.37	.0001	27.3 ± 10.2	0.46	.001

r indicates the correlation coefficients between the estimated and measured GFR; *P*, significance of the differences between the estimated and measured GFR.

mean ± SD, 27.5 ± 4.8 kg/m^2), and serum creatinine levels (67-371 μmol/L; mean ± SD, 152 ± 71 μmol/L) were represented. Mean proteinuria was 626 ± 947 mg/24 hours.

Mean isotopic GFR was 44.6 ± 21.1 mL/(min · 1.73 m^2). Mean CG overestimated GFR (51.4 ± 23.1 mL/[min · 1.73 m^2], $P < .0001$ vs isotopic GFR), mean CG(IBW) underestimated GFR (40.7 ± 15.4 mL/[min · 1.73 m^2], $P < .005$ vs isotopic GFR), whereas mean MDRD did not (45.2 ± 17.9 mL/[min · 1.73 m^2]; NS vs isotopic GFR). All estimates were correlated with isotopic GFR, but the association was weaker for the CG (CG, $r = 0.56$, $P < .0001$; CG(IBW), $r = 0.71$, $P < .0001$; MDRD, $r = 0.77$, $P < .0001$, $P < .01$ between r for CG and MDRD). The Bland and Altman procedure revealed a bias for the MDRD equation and the CG(IBW), as the estimates minus GFR were negatively correlated with their means (MDRD, $r = -0.26$, $P < .01$; CG(IBW), $r = -0.41$, $P < .005$), which was not the case for CG ($r = 0.09$, $P = .29$).

In each category of BMI, the mean CG significantly differed from the mean isotopic GFR, as shown in the Table 1. But the error varied widely; as represented in Fig. 1, the CG led to a moderate underestimate (−14%) in patients with normal weight, a moderate overestimate (15%) in overweight patients, and a marked overestimate in obese patients (55%). This marked overestimation did not concern the CG(IBW), but the correction by ideal body weight underestimated GFR in patients with normal weight and in type 2 diabetic patients. The MDRD estimates did not differ from isotopic GFR in each category of BMI, and the correlation coefficients between the estimated (formula) and the measured (isotopic) GFR were consistently, albeit nonsignificantly, higher with the MDRD than with the CG in each subgroup.

Over the whole population, the CG estimate increased with increasing BMI (correlation, $r = 0.48$, $P < .001$), whereas the isotopic GFR ($r = 0.09$, $P = .30$) or the MDRD estimate ($r = 0.006$, $P = .94$) was not correlated with BMI. The CG(IBW) was not correlated with BMI ($r = 0.09$, $P = .32$). The error of the prediction formula (estimated minus measured GFR) was correlated with BMI for the CG ($r = 0.63$, $P < .0001$), but not for the MDRD ($r = 0.14$, NS).

Mean BMI was higher in type 2 diabetes (type 1, 24.8 ± 2.9 kg/m^2; type 2, 28.6 ± 5.1 kg/m^2, $P < .001$), but the isotopic GFR did not differ between types 1 and 2 diabetic patients (type 1, 47.6 ± 22.2 mL/[min · 1.73 m^2]; type 2, 43.4 ± 20.7 mL/[min · 1.73 m^2], NS). In both types of diabetes, the CG overestimated GFR, but the difference was significant only in type 2 diabetes (type 1, 51.0 ± 24.0, 7%, $P = .39$; type 2, 51.5 ± 22.8, 18%, $P < .0001$). The MDRD estimates did not differ from isotopic GFR (type 1, 49.2 ± 20.2, 3%, NS; type 2, 43.6 ± 16.7, 0.5%, NS). Again, the correlation coefficients between the estimated (formula)

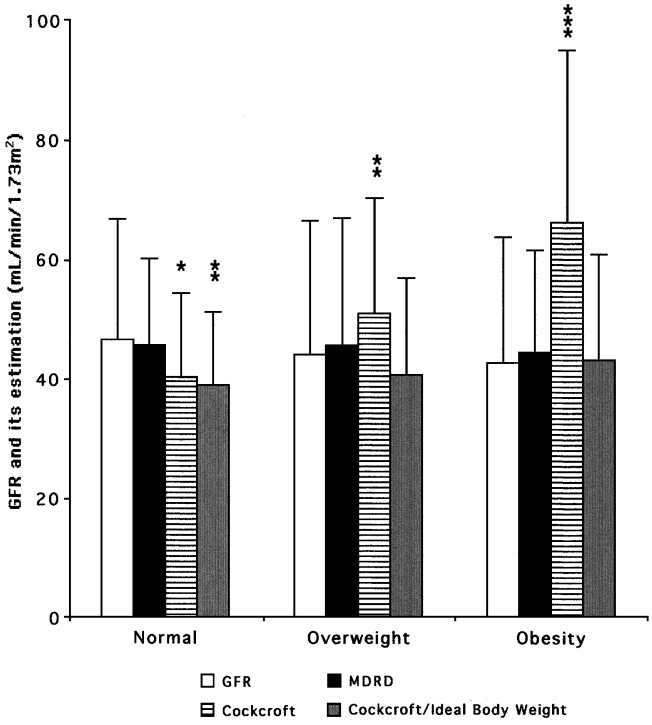

Fig. 1. Isotopically determined GFR (white bars) and its estimation by the CG formula using the measured (lined bars) or the ideal (gray bars) body weight and the MDRD equation (black bars) in normal-weight, overweight, and obese diabetic patients. *$P < .01$, **$P < .005$, ***$P < .0001$ vs isotopic GFR, respectively.

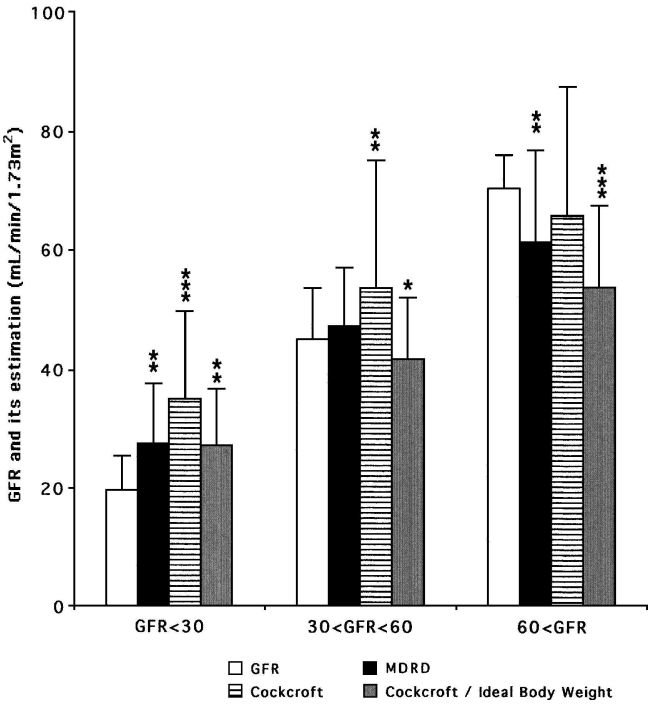

Fig. 2. Isotopically determined GFR (white bars) and its estimation by the CG formula using the measured (lined bars) or the ideal (gray bars) body weight and the MDRD equation (black bars) in diabetic patients with varying degree of renal insufficiency according to isotopic GFR. *$P < .01$, **$P < .005$, ***$P < .0001$ vs isotopic GFR, respectively.

and the measured (isotopic) GFR were higher with the MDRD (type 1, $r = 0.71$; type 2, $r = 0.80$) than with the CG (type 1, $r = 0.50$; type 2, $r = 0.59$) in each subgroup ($P = .17$ between r for type 1 diabetes, $P < .01$ between r for type 2 diabetes).

As shown in Fig. 2, all the prediction formulas overestimated low GFR and underestimated high GFR, with significant differences except for the CG in patients with normal renal function. In the patients with moderate renal insufficiency, the CG overestimated GFR, whereas its calculation with the ideal body weight led to an underestimate.

4. Discussion

Our comparison between the CG and MDRD estimations of GFR in diabetic patients with renal impairment is clearly in favor of the MDRD formula. The mean MDRD estimates were close to isotopically measured GFR, with higher correlation coefficients, and no bias because of BMI. These results are in line with those of the original MDRD study [2] and the more recent report from Hallan et al [14]. These studies however included a marginal proportion of diabetic patients (6% in the MDRD, not reported in the study of Hallan et al). We have recently reported that the MDRD equation was more accurate than the CG in diabetic patients [19], but we did not specifically address the influence of body weight in patients with kidney damage. The present study specifically addressed the prediction of GFR in diabetic patients with renal damage, who are often overweight or obese.

The better performance of the MDRD has practical implications. The National Kidney Foundation recommends that patients should be referred to a nephrologist when the GFR is below 30 mL/(min · 1.73 m^2) and prepared for dialysis including access placement when the GFR is below 25 mL/(min · 1.73 m^2). Delayed referral would have involved 52% of the 38 patients with an isotopic GFR below 30 mL/(min · 1.73 m^2) using the CG formula and 34% using the MDRD. Delayed access would have involved 64% of the 31 patients with an isotopic GFR below 25 mL/(min · 1.73 m^2) using the CG formula and 45% using the MDRD. In our population, the use of the MDRD would have avoided the omission by the CG in 9 of 38 referral indications and in 9 of 31 access indications, with no more false positives than the CG. Delayed referral worsens the prognosis in CRF [20].

The overestimate of low GFR by the CG as we found has been reported by other authors [21,22] and undoubtedly contributes to its poor sensitivity for the diagnosis of severe CRF. This is not surprising, because the CG formula was originally derived from patients who had no renal disease [8]. We show that this effect is particularly important in overweight and even more in obese diabetic patients, leading to a poor performance in type 2 diabetic patients; the 9 referral and access indications missed by the CG and not by the MDRD were obese (BMI, 32.2 ± 2.7 kg/m^2) type 2 (except 1) diabetic patients. The error by the CG was correlated with BMI. The presence of weight in the equation is an important cause of error, especially for diabetic patients whose BMIs are widely dispersed; in type 2 diabetes, a high proportion of patients is obese, even at the stage of hemodialysis [13]. GFR is proportional to body weight in the CG formula, so the correlation between BMI and the CG estimate was not unexpected. But the isotopic GFR (and the estimate by the MDRD) did not correlate with BMI. Most of the excess body weight in obesity is fat; although creatinine is produced by many organs, its largest stores are in muscles. Assuming a proportional relationship, an obese diabetic patient who intentionally loses 20% of his body weight would lose 20% of his GFR. In 24 moderately obese diabetic patients, Solerte et al [23] found that a 20% diet-induced weight loss was associated with a 20% increase in GFR. Body weight in the CG formula therefore influences the estimation in an opposite way to clinical evidence; intentional weight loss is beneficial in diabetic patients [24], and nothing suggests that it deteriorates renal function. Previous studies comparing the CG prediction to 24-hour urine creatinine clearance in nondiabetic [25] or type 2 diabetic [26] obese patients were also in favor of this BMI-related overestimation by the CG formula. The use of ideal instead of measured body weight in the formula corrected this bias, but this underestimated GFR, with a bias according to the Bland and Altman procedure.

Despite its advantages, the MDRD formula cannot be considered as an ideal predictor of GFR. The Bland and

Altman procedure showed that it underestimated GFR at high levels, as described in nondiabetic patients [14] and in type 1 diabetic patients with normal GFR [15]. This explains why the MDRD is not better than the CG in patients with normal renal function [15]; the MDRD formula has been established and validated in 1600 patients with renal insufficiency recruited in the MDRD study, which did not include patients with normal renal function. However, an important practical utility of a GFR predictive formula is to estimate renal function in patients with renal insufficiency. Despite the fact that fewer individuals were missed using the MDRD than by the CG, one third of our patients with severe renal failure were still not diagnosed by the MDRD; improved formulas are required.

In summary, the CG formula estimates GFR in proportion to body weight, leading to a marked overestimate in obese type 2 diabetic patients. With the rising incidence of obesity [27], the CG formula will need to be corrected or replaced. The MDRD equation is not affected by this bias, and its use would avoid delay in referral to nephrologists.

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