Should We Continue to Use the Cockcroft-Gault Formula?

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Key Words

Cockcroft-Gault formula • Modification of diet in renal disease formula • Glomerular filtration rate • Chronic kidney disease • Creatinine clearance

Abstract

Background/Aims: Although the National Kidney Disease Education Program recommends use of the modification of diet in renal disease (MDRD) formula to estimate the glomerular filtration rate (GFR), most drug-dosing recommendations and clinical practices employ the Cockcroft-Gault (CG) formula. The quality score of the original MDRD study was better than that of the original CG study, although the imprecision sources were very similar between the formulas. To address whether CG should be abandoned in favour of MDRD in chronic kidney disease (CKD) management, we performed a literature review on the topic. **Methods:** We reviewed 27 articles comparing CG and MDRD in terms of bias, precision, accuracy, and the risk of misclassifying by two CKD stages. **Results:** In the chronic renal disease population, MDRD was more precise, safer and more accurate than CG at predicting the GFR, with two exceptions: CG was clearly superior in CKD patients with a normal serum creatinine (SCr) and results were discordant in patients with advanced renal failure. In diabetic populations with normal and near-normal GFR, the decline in renal function in diabetics was better screened by CG. In diabetics with renal impairment, MDRD is

more accurate than CG. In healthy patients, in subjects with normal SCr and in elderly patients, MDRD was not superior. Based on the risk of misclassifying by ≥ 2 CKD stages, neither formula could be safely applied in diabetic, low body mass index, advanced liver disease, chronic heart failure, or hospitalized patients. **Conclusions:** CG still has an interest in screening the decline in renal function in subjects with normal SCr who are at risk, such as diabetics and stage 1 and 2 CKD patients, as well as healthy subjects enrolled in clinical trials and pharmacokinetic studies. Thus, it may be early to replace CG by MDRD in drug studies. CG still is the better formula in the elderly. Both formulas are not safe in some populations.

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Introduction

The National Kidney Disease Education Program and other scientific communities recommend using the modification of diet in renal disease (MDRD) [1, 2] formula to approximate renal function through the glomerular filtration rate (GFR). However, most drug-dosing recommendations are based on the Cockcroft-Gault (CG) [3] formula, which estimates the creatinine clearance (CrCl). Additionally, CG remains widely used in clinical practice and recent articles and reviews continue to support its use [4–6, 45, 47, 63].

Table 1. a Comparison of the patient characteristics and methodologies used in deriving the CG and MDRD formulas

	CG	MDRD
Study population	Consecutive patients who had two or more 24-hour CrCls determined at Queen Mary Veterans Hospital	Patients enrolled in a multicenter, controlled trial of the effects of dietary protein restriction and blood pressure on the progression of kidney disease
Inclusion criteria	Being in steady state defined as values for SCr differed by <20%	Age of 18–70 years CrCl <70 ml/min/1.73 m ² Mean arterial pressure ≤125 mm Hg
Exclusion criteria		A body weight under 80% or over 160% of standard body weight Diabetes mellitus requiring insulin therapy ^a Urinary protein excretion exceeding 10 g/day
Total included patients	505	1,628 983 ♂/645 ♀
Training sample	236 (not randomly selected ^b) 236 ♂/0 ♀	1,070 (randomly selected)
Validation sample	505 ^c	558
Gold standard	CrCl	¹²⁵ I-iothalamate measured GFR
Renal function measurement	CrCl: 72.7 ± 36.6 ml/min	GFR: 40 ± 21 ml/min/1.73 m ²
Creatinine assay	Jaffé (Technicon Autoanalyser method N-11B)	Kinetic alkaline picrate (Beckman CX3)
Weight, kg	Mean: 72	Mean ± SD: 79.6 ± 16.8
Age	Range: 18–92	Mean ± SD: 51 ± 13
Statistical analysis	Simple linear regression by plotting age against creatininuria (mg · kg ⁻¹ · day ⁻¹)	Stepwise multiple regression of log-transformed data, based on demographic, serum, and urine variables
QUADAS score [8]	45% ^d	82%

^a Only 6% of the MDRD sample were diabetic.

^b Patients were rejected from the CG training sample if the difference between values for 24-hour creatinine excretion differed by >20% (n = 173), if the 24-hour creatinine excretion was <10 mg/kg (n = 31), or if the records were inadequate (n = 65).

^c Validation sample was not separate from the training sample.

^d Details of the Quality Assessment for Diagnostic Accuracy Studies (QUADAS) score determination are shown in Appendix 1.

Cockcroft and Gault derived their equation from a population of 236 male hospitalized patients who had 2 CrCl determinations that differed by <20%. The mean of 2 CrCl determinations were used to derive the formula, considering age and patient weight. A 15% reduction was recommended when applying the formula to women. Although the original purpose of the formula was to estimate CrCl, CG was later proposed to directly predict GFR [7]. In contrast, the 4-variable MDRD resulted from a retrospective multicentre controlled trial of the effects of dietary protein restriction and strict blood pressure control on kidney disease progression. The MDRD takes into account serum creatinine (SCr), age, gender and race.

The major weakness of the original CG study has been the non-separation between the training and validation samples. When comparing the quality of the original CG- and MDRD-deriving studies overall, the MDRD study clearly prevails (Appendix 1, table 1). However, this is of secondary importance if the CG formula performs at least comparably to the MDRD formula. Considering the success of the MDRD, the main goal of the present review was to determine whether the CG formula should be abandoned or if it still has a place in renal function analysis. In the original MDRD study, several subgroups were excluded or insufficiently represented, including the elderly, diabetics, patients with end-stage renal disease or

Table 1. b Sources of imprecision in the CG and MDRD formulas

	CG	MDRD
Age ^a	+	+
Weight ^b	++	0
Race ^c	0	++
Variability of SCr measurement methods and devices between laboratories ^d	++	+
Sex ^e	-/+	-/+
Serum albumin ^f	++	++

^a The dates of birth of two persons of the same age could differ by 364 days.

^b Weight imprecision has multiple sources: tool used and its imprecision, hour of measurement, clothes, rounding effect, etc.

^c It depends on which factor the physician would choose for multiracial subjects.

^d For the 4-variable MDRD, the SCr of the original sample was re-essayed in 2004 with an enzymatic method traceable to the IDMS assay, and the formula was re-expressed using standardized SCr values.

^e Although it seems strange that sex could be a source of imprecision, in this instance it is. Suppose that the reasons for dif-

ferences in the GFR between females and males are based on hormonal or muscular factors. These factors, or the force of their influence, are not constant at all ages. For instance, we wonder if the female corrective factor (0.85) in CG is necessary in the elderly, with the frequent sarcopenia in both sexes. We could say the same thing about the usefulness of a female factor in the very low BMI group or in cirrhotic patients.

^f Serum albumin level influences tubular creatinine secretion as in nephrotic syndrome, making the creatinine-based formulas overestimate the GFR [54]. In this case, the use of the original 6-variable MDRD may be more relevant, because it accounts for the albumin level.

renal disease with normal SCr levels, over- or underweight patients, dialysis patients, kidney transplant recipients, patients receiving immunosuppressive or corticosteroid treatment, frequently hospitalized patients, or patients with other serious medical conditions [9–11]. Additional studies have been performed to validate the MDRD in these subgroups. Therefore, an additional goal of our work was to compare the MDRD and CG formulas in some of these subgroups.

Methods

We reviewed 27 papers comparing CG and MDRD. Studies were included if they contained a gold-standard GFR measure, such as inulin or isotopic methods. We typically compared CG with the abbreviated 4-variable MDRD formula; however, in 6 articles [4, 5, 12–16] only the 6-variable MDRD formula was reported. Since the 2 MDRD formulas have relatively similar accuracies [1], we do not expect that the use of both the 4- and 6-variable formulas is a major limitation.

Because the sample populations and methods were quite variable across the studies, we avoided calculating a pooled bias or pooled accuracy. In addition, large-pooled means would not confirm the usefulness of a formula in a particular population. Instead, we conducted a ‘stratified’ review, studying gathered homogenous samples wherever possible. Results were grouped based on patient characteristics (geriatrics, diabetics, renal disorders, nutrition disorders, healthy and normal SCr, and others).

Although the correlation coefficient (*r*) was frequently reported, we did not use it for comparisons since *r* measures the strength of the relationship but not the agreement between 2 variables [17, 18]. The same issue applied to the determination coefficient *R*²; although sometimes considered to be a precision measure, *R*² is simply the square of the correlation coefficient in the simple linear regression.

CrCl estimated by CG as well as measured and estimated GFRs were adjusted for body surface area and expressed in ml/min/1.73 m² in all but 4 articles [4, 5, 13, 26]. In statistical tables, an empty cell indicates that information was not reported. Results using the MDRD are shown in bold or in italics (tables 2–7) if they over- or underperform those using CG.

We classified SCr measurement methods into: alkaline picrate methods (Jaffé methods) including modified ones, enzymatic methods and isotope-dilution mass spectrometry methods (IDMS).

Definitions of Performance Measures

Estimation bias, also called systematic error, refers to an estimation method for which the average of repeated estimates deviates from the true value [19]. *Precision* is the measure of the statistical variance of an estimation procedure [19]. Unlike bias, precision is a random error and has no direction [20]. Unbiased but imprecise estimates may arise when the measurement itself is imprecise or when key elements are missing. The missing elements may not lead to overall bias but may be relevant for a subgroup [21]. *Accuracy* is the closeness of the agreement between the measurement result and the true value [20, 22]. Like bias measures, accuracy measures typically consider the difference between the estimated and true values, but not the direction of this difference.

Table 2. a General characteristics of studies comparing the CG and MDRD formulas in CKD patients

Year	Authors	Number	Mean age $\pm$ SD	Age range	Gold standard	Mean measured GFR ml/min/1.73 m ²	SCr assay	Patient characteristics
2006	Levey et al. [1]	1,628	51 $\pm$ 13	?	Iothalamate	40 $\pm$ 21	Enzymatic	MDRD programme
2002	Bostom et al. [36]	109	43 $\pm$ 13	18–64	Iohexol	109	Jaffé	CKD patients with normal SCr
2003	Kingdon et al. [37]	26	58 (m)	12–80	EDTA	?	?	Scleroderma with renal impairment
2005	Poggio et al. [38]	828	56 $\pm$ 16	34–76	Iothalamate	32 $\pm$ 28	Jaffé	CKD
2005	Kuan et al. [26]	26	53 $\pm$ 13	30–70	Inulin	9 $\pm$ 4	?	End-stage renal disease
2005	Cirillo et al. [39]	380	?	18–88	Inulin	76	Jaffé	178 renal disease, 150 other disease, 52 healthy
2005	Froissart et al. [23]	2,095	53 $\pm$ 17	?	EDTA	61 $\pm$ 33	Jaffé	1,933 CKD and 162 healthy potential donors
2006	Fontseré et al. [28]	87	64 $\pm$ 12	28–83	EDTA	22 $\pm$ 7	Jaffé	CKD stage 4 and 5
2006	Barroso et al. [5]	99	62 $\pm$ 15	?	DTPA	16 $\pm$ 4	Jaffé	Advanced renal failure

Table 2. b Statistical characteristics of studies comparing the CG and MDRD formulas in CKD patients

Authors	Formula	r	R ²	ME	SD of ME		ME $\pm$ 2 SD	MAE	Lin Rc	CRMSE	MPE	Within values		Classification accuracy
					B	P	S	EA	EA	EA	B + P	EA	EA	CA
Levey et al. [1]	CG			-0.2 (m)	IQR: 10	IQR: 7.7					mPE: -0.5 (IQR: 30)	P30: 83%	P30: 90%	AUC: 0.94 ^a
	MDRD			-0.2 (m)										
Bostom et al. [36]	CG	0.41	0.17	-26.5	0.29	-41.7						P30: 59%	P30: 28%	
	MDRD	0.53		-41.7										
Kingdon et al. [37]	CG	0.71										P50: 65%	P50: 89%	
	MDRD	0.79												
Poggio et al. [38]	CG	0.89		3.5 (m)				5.6 (m)			mPE: 16%	mAPE: 23%	P30: 60%	
	MDRD	0.90		0.5 (m)										
Kuan et al. [26]	CG	0.48		3.3	3.75	3.25	10.8	7.1			MPE: 35%	P30: 46%	P30: 69%	
	MDRD	0.53		-1										
Cirillo et al. [39]	CG	0.81			0.87						MPE: 10.2%	MAPE: 27.1%	P30: 67%	
	MDRD	0.87												
Froissart et al. [23]	CG	0.89		1.9	± 15.4	± 13.7	32.7	Ø		15.5	MPE: 9; 11 $\pm$ 35%, 9; 8 $\pm$ 31%	P30: 79%	P30: 87%	misclassified: 32% ^b
	MDRD	0.91		-1										
Fontseré et al. [28]	CG			-1.1	± 8.7	± 7.5	18.5	0.52						
	MDRD			-3.8										
Barroso et al. [5]	CG	0.53		0.38 (m)							2.8 (mPE)	P30: 75%	P30: 70%	
	MDRD	0.62		-3.24 (m)										

CG performs better than MDRD, shown in italics; MDRD performs better than CG, shown in bold. MAE = Mean absolute error; CRMSE = combined root mean square error; MAPE = mean absolute percentage error; mAPE = median absolute percentage error; Lin Rc = Lin's coefficient; mPE = median percentage error; B = bias; P = precision; S = safety; EA = estimation accuracy; CA = classification accuracy; (m) = median instead of mean.

^a Cutoff level: 60 ml/min/1.73 m². ^b These results were extracted from the full text of Froissart et al. [23]. In their abstract, contradictory results were given.

Table 3. a General characteristics of studies comparing the CG and MDRD formulas in diabetic patients

Year	Authors	Number	Mean age $\pm$ SD	Age range	Gold standard	Mean measured GFR $\pm$ SD ml/min/1.73 m ²	SCr assay	Target population
2002	Vervooort et al. [12]	46	27 $\pm$ 7		Inulin	122 $\pm$ 18	Jaffé	Non-complicated type I diabetic patients
2005	Ibrahim et al. [27]	1,286	34 $\pm$ 7	20–39	Iothalamate	122 $\pm$ 23	Jaffé	Type I diabetic patients aged <39 years
2005	Rigalleau et al. [35]	122	66 $\pm$ 11	30–83	EDTA	45 $\pm$ 21	Jaffé	Type 1 and 2 diabetic patients with renal impairment
2005	Rigalleau et al. [33]	160	62 $\pm$ 14	19–83	EDTA	61 $\pm$ 36	Jaffé	Type 1 and 2 diabetic patients
2006	Fontseré et al. [40]	87	54 $\pm$ 9		EDTA	102 $\pm$ 36	Jaffé	Type 2 diabetic patients
2006	Macisaac et al. [31]	126	61 $\pm$ 11	22–84	DTPA	89 $\pm$ 34	?	Type 1 and 2 diabetic patients
2007	Rigalleau et al. [34]	200	63 $\pm$ 13	19–83	EDTA	56 $\pm$ 35	Jaffé	Type 1 and 2 diabetic patients

Table 3. b Statistical characteristics of studies comparing the CG and MDRD formulas in diabetic patients

Authors	Formula	r	R ²	ME	SD of ME	ME $\pm$ 2 SD		CRMSE	MPE	MAPE	90th percentile of absolute percentage error		Within values	Classification accuracy
						B	P	S	EA	B + P	EA	P	EA	CA
Vervooort et al. [12]	CG			-15.1 (m)								26.4%		
	MDRD			-18.8 (m)								31.9%		
Ibrahim et al. [27]	CG	0.33	0.11	-6	25	56 $\emptyset$				MAPE: 16%			P30: 88%	
	MDRD	0.36	0.13	-22	25	72 $\emptyset$				MAPE: 21%			P30: 78%	
Rigalleau et al. [35]	CG	0.56												
	MDRD	0.77												
Rigalleau et al. [33]	CG	0.74		4.8	26	56.8 $\emptyset$								AUC: 0.87 and 0.88 ^a
	MDRD	0.81		-6.1	22	48.1 $\emptyset$								AUC: 0.93 and 0.96
Fontseré et al. [40]	CG					56 $\emptyset$				MPE: 29.8 $\pm$ 16.6%				
	MDRD					61 $\emptyset$ ^b				MPE: -34.8 $\pm$ 17.2%				
Macisaac et al. [31]	CG	0.84	0.70	3.1	21	45.3 $\emptyset$			21.4				P30: 81%	
	MDRD	0.84	0.70	-2.2	18	38.2 $\emptyset$			18.4				P30: 89%	
Rigalleau et al. [34]	CG	0.75			25					MAPE: 44 $\pm$ 54%				AUC: 0.86 and 0.89
	MDRD	0.82			20					MAPE: 29 $\pm$ 37%				AUC: 0.92 and 0.95
	CG													Misclassified: 45%
	MDRD													Misclassified: 35%

CG performs better than MDRD, shown in *italics*; MDRD performs better than CG, shown in **bold**. CRMSE = Combined root mean square error; MAPE = mean absolute percentage error; B = bias; P = precision; S = safety; EA = estimation accuracy; CA = classification accuracy; (m) = median instead of mean.

^a Cutoff level: 60 ml/min/1.73 m². ^b The value of ME $\pm$ 2 SD was not provided by the authors. We calculated the approximate safety value from MPE and the mean GFR as follows: (|MPE $\pm$ 2 SD|) mean GFR = [0.298 + (2 $\times$ 0.166)] $\times$ 89 = 56 ml/min/1.73 m².

Definition of Errors (Differences)

The *arithmetic error* is the difference between the estimated and measured GFR values (estimated GFR – measured GFR¹). The *percentage error* or *relative error* is defined as the arithmetic error relative to the measured GFR (estimated GFR – measured GFR)/measured GFR, expressed as a percentage [21]. The *absolute error*² and *absolute percentage error* are defined as the absolute values of the arithmetic error and percentage error, respectively.

Measures of Performance

Bias Measures

- Mean error (ME) is the mean of all arithmetic errors [20].
- Median error is the median of all arithmetic errors; it replaces the ME in several articles.
- Mean percentage error (MPE) is the mean of all percentage errors.
- Median percentage error is the median of all percentage errors; it replaces the MPE in several articles.

Precision Measures

- Standard deviation (SD)³ of arithmetic, percentage, absolute, or absolute percentage errors [21].
- Interquartile range of errors, defined as the width of the 25th to the 75th percentile.
- The 90th percentile of the percentage absolute error (used in 3 studies) [2, 12, 15].
- Limits of agreement of the Bland-Altman [17, 18] plotting method⁴.

Estimation Accuracy Measures

- Mean absolute error (MAE) [20] or median absolute error (mAE).
- Mean absolute percentage error or median absolute percentage error.
- Lin's coefficient, also called the coefficient of concordance [24], measures accuracy (nearness of the reduced major axis of the data to the line of perfect concordance) and precision (tightness of the data around the reduced major axis). Lin's coefficient <0.90 indicates poor accuracy [25].
- Combined root mean square error is defined as:

$$\sqrt{\frac{\sum (EstimatedGFR - MeasuredGFR)^2}{N}} + SD^2$$

where SD is the standard deviation of the difference.

¹ We chose the order shown because it was used by all but 3 studies [1, 12, 13], which used the opposite order for this equation (measured GFR – estimated GFR). The sign of the results of these 3 studies has been changed only for the purpose of our review.

² Some authors preferred to call the arithmetic error the 'absolute bias', such as in table 6 of Froissart et al. [23]. However, the absolute error should have no sign and is not a measure of bias, but of accuracy.

³ Some authors provided the standard error of the mean (SEM) instead of SD [13, 16]. We calculated SD for these results as $SD = SEM \times \sqrt{N}$, where N is the number of patients.

⁴ Bland-Altman plots, which test bias uniformity over the whole range of values, were available in 15 studies. Limits of agreement ($ME \pm 2 SD$) were only provided in 12 studies [13, 16, 23, 26–34]. In articles that did not provide them, the SD of the ME and of the MPE were extracted from the distance between the limits of agreement of the Bland-Altman plot [26–29].

- P₃₀ is the percentage of estimates within 30% of the measured GFR [21]. Some authors calculated estimates within 15% (P₁₅) or 50% (P₅₀). P₅₀ was used when the P₃₀ was not provided. We focused on P₃₀ because the Kidney Disease Outcomes Quality Initiative guidelines recommend a P₃₀ value of 90% [46]. It should be noted that this value was not attained by MDRD or CG in the 27 articles, except in the MDRD validation sample [1].

Classification Accuracy Measures

Classification accuracy refers to the ability to classify patients into different chronic kidney disease (CKD) stages. Authors primarily used 2 cutoffs: 30 ml/min/1.73 m² and 60 ml/min/1.73 m². Accuracy measures included the sensitivity, specificity, area under the curve (AUC), and number of misclassified patients.

Acceptability or Safety Limits

No acceptability thresholds were proposed for any parameter in any of the reviewed articles. Therefore, we developed a safety tool for the purpose of this review. Whenever possible, we calculated the absolute value of the ME and 2 SDs: $|ME \pm 2 SD|$. Patients with acceptability threshold values >30 ml/min/1.73 m² (wideness of CKD stage 2 or 3) were at a significant risk of being misclassified by 2 stages (see Appendix 2 for more explanations). Such values were therefore flagged by the symbol $\emptyset$.

Results

Renal Disease Group

The MDRD was more precise, safe, and accurate than the CG in predicting the GFR in CKD, with 2 notable exceptions. In CKD patients with a normal SCr, the CG was clearly superior [36]; and in cases of advanced renal failure (GFR <30), the study results were discordant [5, 26, 28] (table 2). This discordance was also found in kidney transplant recipients in the review of White et al. [53].

Diabetics Group

In studies where the safety measure could be calculated [27, 31, 33, 40], neither formula was safe for use in diabetics (table 3). The MDRD always underestimated GFR, and in cases of normal or near-normal GFR [12, 27, 40], the decline in renal function in diabetics seemed to be better screened by CG.

It was unclear whether the diabetic sample populations were totally independent in 2 articles published by Rigalleau et al. [33, 34]. The settings, age range, and results (e.g. AUC and SD of the ME) were very similar. These characteristics led us to consider these 2 papers as a single study.

Diabetes was insufficiently represented in the original MDRD study, comprising only 6% of the sample [1]. A recent study using a pooled individual patient database

Table 4. a General characteristics of studies comparing the CG and MDRD formulas in healthy and normal SCr subjects

Year	Authors	Number	Mean age ± SD	Age range	Gold standard	Mean measured GFR ± SD ml/min/1.73 m ²	SCr assay	Patient characteristics
2002	Vervoort et al. [12]	46	28 ± 6		Inulin	107 ± 11	Jaffé	Healthy
2003	Lin et al. [41]	100	41 ± 10	18–62	Iothalamate/DTPA	113 ± 21	Jaffé	Healthy potential kidney donor
2005	Poggio et al. [38]	457	42 ± 10	28–55	Iothalamate	106 ± 18	Jaffé	Healthy potential kidney donor
2005	Verhave et al. [48]	850	48 ± 15	18–93	DTPA	99 ± 20	Enzymatic and Jaffé	Patients with normal SCr

Table 4. b Statistical characteristics of studies comparing the CG and MDRD formulas in healthy and normal SCr subjects

Authors	Formula	r	R ²	ME	SD of ME	ME ± 2 SD	MAE	MPE	90th percentile of absolute per- centage error	MAPE	Within values
				B			EA	B		EA	EA
Vervoort et al. [12] (subgroup)	CG			–13.1 (m)					26.6%		
	MDRD			–10.7					25.5%		
Lin et al. [41]	CG	0.24	0.06	16.8			37.9			mAPE: 23%	P30: 45%
	MDRD	0.15	0.02	–18.3			28.7			mAPE: 22%	P30: 65%
Poggio et al. [38] (subgroup)	CG	0.41		1.9 (m)			14.9 (m)	mPE: 2%		mAPE: 14%	P30: 85%
	MDRD	0.36		–9 (m)			<i>15.9 (m)</i>	<i>mPE: –9%</i>		<i>mAPE: 16%</i>	P30: 86%
Verhave et al. [48]											
Enzymatic SCr	CG		0.32	–4.9							P30: 87%
	MDRD		0.34	–12.4							P30: 89%
Jaffé SCr	CG		0.31	–20.6							P30: 71%
	MDRD		0.34	28.8							<i>P30: 51%</i>

CG performs better than MDRD, shown in italics; MDRD performs better than CG, shown in bold. (m) = Median instead of mean; MAE = mean absolute error; mPE = median percentage error; MAPE = mean absolute percentage error; mAPE = median absolute percentage error; B = bias; P = precision; S = safety; EA = estimation accuracy.

showed an improvement in MDRD accuracy in 3 diabetic cohorts after SCr calibration [49]. We did not include this study in our work, because the research did not include separate CG-MDRD comparisons for each cohort.

Healthy and Normal SCr Group

In all 4 studies reviewed that considered patients with healthy and normal SCr (table 4), the MDRD underestimated the GFR. The study by Vervoort et al. [12] compared CG to the 6-variable MDRD. To our knowledge, the accuracy between the 4- and the 6-variable MDRD formulas has not yet been tested in the healthy and normal SCr population. In the 3 other studies, CG was clearly less biased, while the accuracy results were often similar.

It is generally accepted that MDRD is inaccurate in subjects with low SCr values [50, author reply] or with high

GFR values, and that these inaccuracies persist even after SCr calibration [49]. For this reason, the National Kidney Disease Education Program and other organizations currently recommend reporting a numeric value only for MDRD-estimated GFR of <60 ml/min/1.73 m². There are two problems with this recommendation. First, although the above threshold is useful for defining CKD, it does not represent the lower limit of the normal GFR range [46]. Second, the GFR of an at-risk individual for CKD (due to diabetes, medications, high blood pressure, age, etc.) could drop by a third (e.g. from 90 to 60 ml/min/1.73 m²) without being detected by the MDRD estimations. Because pharmacokinetic studies and clinical trials are usually first conducted in a healthy population, it may still be too early to replace CG-estimated CrCl values with MDRD-estimated GFR values in drug studies [52].

Table 5. a General characteristics of studies comparing the CG and MDRD formulas in elderly patients

Year	Authors	Number	Mean age ± SD	Gold standard	Mean measured GFR ± SD ml/min/1.73 m ²	SCr assay	Patient characteristics
2003	Fehrman-Ekholm and Skeppholm [14]	52	82 ± NA	Iohexol	68 ± 11	?	Volunteer elderly healthy persons
2005	Lamb et al. [4]	46	80 ± 5	EDTA	54 ± 17	IDMS	Old patients
2005	Froissart et al. [23] (Strate)	595	73 ± 5	EDTA	46 ± 26 (females) 43 ± 29 (males)	Jaffé	Subgroup >65 years
2005	Burkhardt et al. [13]	61	75 ± 7	Inulin	96 ± 39	Jaffé	Geriatric inpatients

Table 5. b Statistical characteristics of studies comparing the CG and MDRD formulas in elderly patients

Authors	Formula	r	R ²	ME	SD of the ME	ME ± 2 SD	90th percentile of absolute error	90th percentile of abso- lute percentage error	AUC ^a
				B	P	S	P	P	CA
Fehrman-Ekholm and Skeppholm [14]	CG	0.71	0.50						
	MDRD	0.73	0.53						
Lamb et al. [4]	CG	0.88	0.77	-3.8	± 8	19.8			
	MDRD	0.91	0.82	8.6	± 10	28.6			
<i>Froissart et al. [23] groups^b</i>									
Males with low GFR	CG			-2.3	± 7.2	16.7	12	38%	
	MDRD			0.5	± 6.7	13.9	10	37%	
Males with high GFR	CG			-14.5	± 10.4	35.3	27	34%	
	MDRD			-5.9	± 12.1	30.1	22	26%	
Females with low GFR	CG			-0.1	± 8.0	16.1	12	41%	
	MDRD			1.2	± 8.2	17.6	13	39%	
Females with high GFR	CG			-10.7	± 12.2	35.1	24	30%	
	MDRD			-1.6	± 11.5	24.6	19	22%	
Burkhardt et al. [13]	CG			-40	± 56	152			0.89 and 0.87
	MDRD			-20	± 58	136			0.85 and 0.98

CG performs better than MDRD shown in italics; MDRD performs better than CG shown in bold. B = Bias; P = precision; S = safety; CA = classification accuracy.

^a AUC for cutoff levels at 90 and 60 ml/min, respectively. ^b Low GFR <60 ml/min/1.73 m² and high GFR >60 ml/min/1.73 m².

Geriatrics Group

We found 3 articles [4, 13, 14] that compared estimations using MDRD and CG to a gold standard in elderly populations. Additionally, a subgroup aged >65 years was extracted from Froissart et al. [23] (table 5). Fehrman-Ekholm et al. [14] did not report a statistical tool other than the coefficients of correlation and of determination. Burkhardt et al. [13] did not adequately explain their very large SD of the ME (the largest one found in our review) obtained using both MDRD and CG. This large value led us to question the precision of the gold standard in their

study; it was the only study that used one shot of inulin rather than a constant perfusion as a gold standard. The one-shot inulin method has been validated in children [43], but not in elderly patients. A previous paper by the same authors also reported a similarly large SD of ME [42]. In addition, the confidence interval of the mean measured GFR was 96 ± 39 ml/min/1.73 m². Thus, moderate and advanced CKD was not sufficiently represented in the elderly sample population.

When reviewing the Froissart et al. [23] study, we found that neither formula could be safely applied in el-

Table 6. a General and statistical characteristics of studies comparing the CG and MDRD formulas in low BMI patients

Year	Reference	Number	Gold standard	Definition	ME		± SD of ME	ME ± 2 SD	MPE
					B	P		S	
2005	Cirillo et al. [39]	45	Inulin	BMI <21	CG				MPE: -18%
					MDRD				MPE: -12%
2005	Froissart et al. [23]	94	EDTA	BMI <18.5	CG	6.5	± 17.7	42 Ø	
					MDRD	12	± 24.8	62 Ø	

Table 6. b General and statistical characteristics of studies comparing the CG and MDRD formulas in obese patients

Year	Reference	Number	Gold standard	Definition	ME		± SD	ME ± 2 SD	MPE
					B	P		S	
2005	Cirillo et al. [39]	91	Inulin	BMI >30	CG				MPE: 19%
					MDRD				MPE: -2%
2005	Froissart et al. [23]	279	EDTA	BMI >30	CG	9	18.7	46.4 Ø	
					MDRD	-2.5	11.6	25.7	

CG performs better than MDRD, shown in italics; MDRD performs better than CG, shown in bold. B = Bias; P = precision; S = safety. No accuracy measure was available.

derly males (aged >65 years) with a high GFR. However, it would have been preferable if the sample had been stratified from 75 years. In Western countries, the concept of an ‘old’ patient diverges from the World Health Organization definition. In France, the mean age in institutions for old persons is 85 years, and the Ministry of Health defines the geriatric department as a ward for patients older than 75 years.

Lamb et al. [4] used the gold standard of SCr measurements (IDMS) and EDTA as GFR reference method. Their mean age was 80 ± 5 years and mean GFR was 54 ± 17 ml/min/1.73 m². Until larger studies are performed, this article is the most relevant in elderly. It found that CG was safer and less biased than MDRD in this population.

The accordance of CG and MDRD is very poor in elderly populations (κ coefficient of 0.44), and these formulas cannot be used interchangeably to measure renal function in this population [51]. For these reasons, we recommend that only CG be used in elderly patients.

Nutrition Disorders Group

Body mass index (BMI) subgroups were adequately studied in 2 studies [23, 39] (table 6), and the results of these studies indicated that MDRD is safer and less biased when used in patients with a high BMI. Neither formula can be safely used in patients with a low BMI.

Other Groups

The results of other populations studied but not classified above are shown in table 7. The population targets studied included patients with rheumatoid arthritis, advanced liver disease, chronic heart failure, African-Americans with hypertension and a kidney disease cohort, hospitalized patients, heart transplant recipients, and former kidney donors. Except in cases of advanced liver disease, where CG is more biased but somewhat safer, more accurate, and more precise, in all other populations the MDRD prevailed. Neither formula was safe in heart transplant recipients, former kidney donors, or in patients with advanced liver disease. In hospitalized patients, we could not calculate the safety measure; however, with median absolute percentage errors of 71 and 53% for CG and MDRD, respectively, neither formula would be safe.

Discussion

Each time the average measured GFR of the sample was >90 ml/min/1.73 m² [12, 27, 36, 38, 40, 48], CG performed better than MDRD, except in one study [41]. We believe that CG remains relevant in those patient populations who generally have a normal SCr.

Table 7. a General characteristics of studies comparing the CG and MDRD formulas in non-classified populations

Year	Reference	Number	Mean age ± SD	Age range	Gold standard	Mean measured GFR (± SD), ml/min/1.73 m ²	SCr assay	Patient characteristics
2008	Karstila et al. [6]	81	66 ± 11	41–86	⁵¹ Cr-EDTA	44 (m)	Enzymatic	Rheumatoid arthritis
2006	MacAulay et al. [16]	57	50 ± 11	16–67	^{99m} Tc-DTPA	83	?	Advanced liver disease
2006	Smilde et al. [30]	110	58 ± 12		¹²⁵ I-iothalamate	73 ± 27	?	Chronic heart failure
2001	Lewis et al. [15]	1,703	54 ± 11		¹²⁵ I-iothalamate	57 ± 23	Jaffé	AASK cohort
2005	Poggio et al. [44]	107	65 ± 15	39–82	¹²⁵ I-iothalamate	17 ± 18	Jaffé	Hospitalized patients
2006	Delanaye et al. [29]	27	57 ± 12		⁵¹ Cr-EDTA	39 ± 15	Jaffé	Heart transplant recipients
2006	Ibrahim et al. [32]	112	40 ± 10		Iohecol	72 ± 12	Jaffé	Former kidney donors

Table 7. b Statistical characteristics of studies comparing the CG and MDRD formulas in non-classified populations

Reference	Formula	r	R ²	ME		ME ± 2 SD	MAE	MPE	Other accuracy measures	90th percentile of absolute per- centage error	
				B	P					P	A & P
Karstila et al. [6]	CG	0.90						20%	PPV ^a : 0.88 PPV: 0.90		
	MDRD	0.87						20%			
MacAulay et al. [16]	CG	0.80	0.65	15.4	± 26	67.4 ∅	23.6	15.7	P30: 65%		
	MDRD	0.87	0.76	3.5	± 32	67.5 ∅	23.4	4	P30: 62%		
Smilde et al. [30]	CG	0.79	0.63			41 ∅ ^b		−6 ± 25%	P30: 76%		
	MDRD	0.82	0.68			41 ∅		−12 ± 22.5%	P30: 80%		
Lewis et al. [15]	CG	0.85	0.72	−2.67			8.3 (m)		mAPE: 16.4%	39.6%	
	MDRD	0.91	0.82	−0.94			6.27		mAPE: 12.4%	31.6%	
Poggio et al. [44]	CG	0.66		8.2 (m)			8.3 (m)	71%	mAPE: 71%		0.46
	MDRD	0.71		6.2 (m)			7.2 (m)	53%	mAPE: 53%		0.57
Delanaye et al. [29]	CG	0.71	0.50	19.9	± 13.8	47.5 ∅			P30: 23%		
	MDRD	0.83	0.69	12	± 8.5	29			P30: 43%		
Ibrahim et al. [32]	CG	0.60	0.36	3.4	± 13.6	30.6 ∅		5.6 ± 21.5%	P30: 87%		
	MDRD	0.71	0.50	−6.6	± 9.5	25.6		−8.3 ± 14.1%	P30: 96%		

CG performs better than MDRD, shown in italics; MDRD performs better than CG, shown in bold. AASK cohort = African-American Study of hypertension and Kidney Disease; MAE = mean absolute error; Lin Rc = Lin's coefficient; B = bias; P = precision; S = safety; A = accuracy; (m) = median instead of mean; mAPE = median absolute percentage error.

^a Predictive positive value (PPV) for cutoff level at 90 ml/min/1.73 m². ^b The value of ME ± 2 SD was not provided by authors. We calculated the approximate safety value from MPE and mean GFR as follows: (|MPE ± 2 SD|) × mean GFR.

The major argument against the use of CG is that it cannot be re-expressed for IDMS-traceable SCr values. In addition, the SCr method used to develop the formula is no longer in use and samples from the study are not available [62]. However, the success of CG is not due to the original CG study itself (as the study contained several weaknesses), but to its validation in several later studies compared to both measured CrCl values and reference GFR measurement methods [7, 55–61]. Those

studies used different SCr methods; we believe that at least one could be re-expressed using IDMS-traceable SCr assay.

A study by Stevens et al. [64] showed that the MDRD had greater concordance with measured GFR for recommended drug dosage than the CG, for all subgroups tested, while the mean of CG-estimated CrCl was closer to the measured GFR than MDRD-estimated values in almost all subgroups, as well as in the whole population.

Regrettably, the ME $\pm$ SD for each formula were not reported. Beside the fact that it was a simulation and not a pharmacokinetics study, discordance exceeding 1 level of dosing was not calculated. Actually, 12 of 15 drugs tested had more than 2 levels of dosing. Missing more than 1 level reflects a high risk of toxicity and could be a consequence of the imprecision of a formula.

The main limitation of our study is that, although our review is the largest to date to compare CG and MDRD, it is still not exhaustive.

The CG formula remains of interest in screening declining renal function in subjects with normal SCr who

are at risk, including diabetics, patients with stage 1 or 2 CKD, and healthy subjects enrolled in pharmacokinetics studies or clinical trials. In elderly individuals, CG remains the most accurate formula. Neither formula was safe in some populations, including diabetics, patients with a low BMI, advanced liver disease, or chronic heart failure, and hospitalized patients. When applying the formulas in those populations, there was a significant risk of misclassifying patients by two stages. The CG may require an adjustment factor to be applied using SCr values measured by newly established assay procedures, as was done with the MDRD formula.

Appendix 1

Quality Assessment for Diagnostic Accuracy Studies questionnaire [8] for the original MDRD and CG studies.

1	Was the spectrum of patients representative of the patients who will receive the test in practice?
2	Were selection criteria clearly described?
3	Is the reference standard likely to correctly classify the target condition?
4	Is the time period between reference standard and index test short enough to be reasonably sure that the target condition did not change between the two tests?
5	Did the whole sample or a random selection of the sample, receive verification using a reference standard of diagnosis?
6	Did patients receive the same reference standard regardless of the index test result?
7	Was the reference standard independent of the index test (i.e. the index test did not form part of the reference standard)?
8	Was the execution of the index test described in sufficient detail to permit replication of the test?
9	Was the execution of the reference standard described in sufficient detail to permit its replication?
10	Were the index test results interpreted without knowledge of the results of the reference standard?
11	Were the reference standard results interpreted without knowledge of the results in the index test?
12	Were the same clinical data available when test results were interpreted as would be available when the test is used in practice?
13	Were uninterpretable/intermediate test results reported?
14	Were withdrawals from the study explained?

Questions	CG	MDRD
1	No: no women were included in the training sample. Of the entire sample, only 4% were women. Few elderly patients were included (only 17 patients were >80 years of age)	No: there were very strict eligibility and exclusion criteria [9–11]
2	No: patients excluded from the training sample were retained in the validation sample, including 65 patients with inadequate records	Yes
3	No: CrCl may be a reference estimator of renal function, but ‘the mean of two CrCl measurements separated by an unknown delay’ is not	Yes
4	No: the CG study was retrospective with the mean of 2 CrCl measurements used as reference. We do not know the delay between the 2 CrCl measurements. Weight and age are also important variables, and it is unknown whether they were ascertained at the first or second CrCl measurement	Yes
5–8	Yes	Yes
9	No: no detail was given about how and when urine was collected	Yes [9–11]
10–12	Not relevant	Not relevant
13	Yes	Yes
14	No: the training group was reduced in size from 249 to 236 individuals, without explanation	Yes

Appendix 2

We defined our safety condition as $|ME \pm 2 SD| < 30 \text{ ml/min/1.73 m}^2$. In the following 4 examples (fig. A–D) extracted from 2 articles studied in the current review, we show graphically that each time this threshold was exceeded, there was a significant risk of misclassifying those patients close to the edge of a given CKD stage by two stages.

Fig. A. Normal distribution of repeated CG-estimated GFR for a patient with a measured GFR of $59 \text{ ml/min/1.73 m}^2$ (stage 3 CKD) after applying an $ME \pm SD$ of $19.9 \pm 13.8 \text{ ml/min/1.73 m}^2$ [from 29]. Grey (online red) indicates estimates that misclassify the patient by two stages and also belong to the 95% confidence interval of the distribution.

Fig. B. Normal distribution of repeated MDRD-estimated GFR for the same patient as in figure A, after applying an $ME \pm SD$ of $12 \pm 8.5 \text{ ml/min/1.73 m}^2$ [from 29]. No grey is shown because there is no estimate that misclassifies the diagnosis by two stages and also belongs to the 95% confidence interval of the distribution.

Fig. C. Normal distribution of repeated CG-estimated GFR for a patient with a measured GFR of $59 \text{ ml/min/1.73 m}^2$ (stage 3 CKD) after applying an $ME \pm SD$ of $1.9 \pm 15.4 \text{ ml/min/1.73 m}^2$ [from 23]. Grey (online red) indicates estimates that misclassify the patient by two stages and also belong to the 95% confidence interval of the distribution.

Fig. D. Normal distribution of repeated MDRD-estimated GFR for a patient with a measured GFR of $61 \text{ ml/min/1.73 m}^2$ (stage 2 CKD) after applying an $ME \pm SD$ of $-1 \pm 13.7 \text{ ml/min/1.73 m}^2$ [from 23]. No grey is shown because no estimate misclassifies diagnosis by two stages and also belongs to the 95% confidence interval of the distribution. The curve is generated in the same direction as the bias (e.g. negative).

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Editorial Comment

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This article by Helou reviews a number of publications relating to the accuracy and bias of the two most commonly used formulae in Nephrology, namely the modification of diet in renal disease (MDRD) and Cockcroft-Gault equations. It highlights their respective merit and limitations. The review adds to the endless debate about the value and limitations of calculated glomerular filtration rate (GFR) at different stages of chronic kidney disease (CKD). New formulae, based on serum creatinine (CKD-Epi), cystatin C or a combination of both, are emerging all the time. It is important as practicing nephrologists to appreciate their value in providing approx-

imated GFR values but it is also imperative not to put too many unrealistic and unfounded expectations on such calculations; this is particularly true in individuals with renal function within the normal range, women and in the elderly. Concern has been expressed by some that the reported explosion of detected cases of CKD in communities in the last 10 years may be the consequence of over-interpretation or even misinterpretation of GFR values derived from currently used equations. To know the indications and limitations of calculated GFR is essential for an accurate assessment of the scale of the CKD problem.