How Reliable Is Estimation of Glomerular Filtration Rate at Diagnosis of Type 2 Diabetes?

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OBJECTIVE — The Cockcroft-Gault (CG) and Modification of Diet in Renal Disease (MDRD) equations previously have been recommended to estimate glomerular filtration rate (GFR). We compared both estimates with true GFR, measured by the isotopic ^{51}Cr-EDTA method, in newly diagnosed, treatment-naïve subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS — A total of 292 mainly normoalbuminuric (241 of 292) subjects were recruited. Subjects were classified as having mild renal impairment (group 1, GFR <90 ml/min per 1.73 m^2) or normal renal function (group 2, GFR ≥90 ml/min per 1.73 m^2). Estimated GFR (eGFR) was calculated by the CG and MDRD equations. Blood samples drawn at 44, 120, 180, and 240 min after administration of 1 MBq of ^{51}Cr-EDTA were used to measure isotopic GFR (iGFR).

RESULTS — For subjects in group 1, mean (±SD) iGFR was 83.8 ± 4.3 ml/min per 1.73 m^2. eGFR was 78.0 ± 16.5 or 73.7 ± 12.0 ml/min per 1.73 m^2 using CG and MDRD equations, respectively. Ninety-five percent CIs for method bias were –11.1 to −0.6 using CG and –14.4 to –7.0 using MDRD. Ninety-five percent limits of agreement (mean bias ± 2 SD) were −37.2 to 25.6 and −33.1 to 11.7, respectively. In group 2, iGFR was 119.4 ± 20.3 ml/min per 1.73 m^2. eGFR was 104.4 ± 26.3 or 92.3 ± 18.7 ml/min per 1.73 m^2 using CG and MDRD equations, respectively. Ninety-five percent CIs for method bias were –17.4 to –12.5 using CG and –29.1 to –25.1 using MDRD. Ninety-five percent limits of agreement were −54.4 to 24.4 and −59.5 to 5.3, respectively.

CONCLUSIONS — In newly diagnosed type 2 diabetic patients, particularly those with a GFR ≥90 ml/min per 1.73 m^2, both CG and MDRD equations significantly underestimate iGFR. This highlights a limitation in the use of eGFR in the majority of diabetic subjects outside the setting of chronic kidney disease.

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The prevalence of chronic kidney disease (CKD) continues to escalate at an alarming rate (1–3). In the U.K., the incidence of end-stage renal disease (ESRD) has doubled in the past 10 years and this increase is projected to continue to rise at a rate of 5–8% per annum (2). In the U.S. in 2003, there were 325,000 individuals receiving renal replacement therapy (RRT) at a cost of $18.1 billion per annum, 45% of these were diabetic patients (3). The number receiving RRT in the U.S. is anticipated to double by 2010 (4), clearly producing a significant economic burden. The number of patients with ESRD underestimates the entire burden of CKD. Whole-population screening surveys performed in Europe (5) and the U.S. (6) have identified that between 6 and 11% of this population have a degree of CKD; this number increases to 50–60% when at risk groups are screened (6).

Diabetes is the leading cause of ESRD in developed countries, accounting for 18 and 36% of new cases of RRT in the U.K. and Germany, respectively, in 2001 (7) and 45% of new cases in the U.S. in 2003 (3). Differences in incidence between developed countries are likely a reflection of racial and ethnic mix. In the U.S., the incidence of ESRD is lower among Caucasian compared with African-American people (7). Racial factors also play a role in the greater susceptibility of African and Native Americans to CKD related to diabetes and hypertension (8), as well as the more rapid rate of progression of CKD seen in these groups (9). Other contributory factors related to lower disease prevalence, underreferral of patients, better management of diabetes, and higher death rates from cardiovascular disease (10) may account for the differences in incidence of ESRD seen between European countries.

There is strong evidence to show that early detection of diabetic nephropathy, resulting in timely intervention with particular attention to blood pressure control (thus limiting proteinuria), glycemic control, smoking cessation, and attenuation of cardiovascular risk, can improve long-term outcomes (11–21) and retard progression to ESRD (19,20). The clear implication of this evidence is that to achieve maximum benefit, current health care strategies must ensure detection of diabetic nephropathy as early as possible.

Although not universally accepted, the National Service Framework for Renal Services in the U.K. recommends the adoption of formula-derived estimates of GFR (eGFR) in the annual evaluation of all patients with diabetes (22). It is anticipated that this process will aid early identification and therefore improve long-term outcomes for those with diabetic nephropathy. The recently developed four-variable Modification of Diet in Renal Disease (MDRD) equation (23), which estimates GFR according to serum creati-

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Abbreviations: BSA, body surface area; CG, Cockcroft-Gault; CKD, chronic kidney disease; eGFR, estimated GFR; GFR, glomerular filtration rate; ESRD, end-stage renal disease; iGFR, isotopic GFR; MDRD, Modification of Diet in Renal Disease; RRT, renal replacement therapy.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.
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Table 1—*Demographic data*

	All subjects	Group 1 (iGFR <90)	Group 2 (iGFR ≥90)
n	292	37	255
Men/women	219/73	25/12	194/61
Age (years)	55.3 ± 9.4	62.8 ± 6.4	54.2 ± 9.3*
Weight (kg)	92.0 ± 17	88.0 ± 16.7	92.5 ± 17.0
BMI (kg/m^2)	31.5 ± 5.6	30.9 ± 6.0	31.6 ± 5.5
A1C (%)	7.79 ± 2.00	7.16 ± 1.83	7.88 ± 2.01*
Fasting plasma glucose (mmol/l)	9.70 ± 3.09	8.44 ± 2.49	9.87 ± 3.13*
Creatinine (μmol/l)	79.9 ± 14.8	90.7 ± 16.1	78.4 ± 14.0*
Systolic blood pressure (mmHg)	136 ± 20	144 ± 22	135 ± 19*
Diastolic blood pressure (mmHg)	81 ± 10	80 ± 10	82 ± 10

Data are means ± SD. *$P < 0.05$ for difference between means of group 1 and group 2.

nine, age, sex, and ethnic origin, is being widely advocated (22,24).

eGFR values derived by the MDRD and the traditional Cockcroft-Gault (CG) equations have been validated in CKD (25–30); however, there is concern that they underestimate GFR in the vast majority of individuals with normal or near-normal renal function (31,32). Recent work by Parving and colleagues (33) in type 2 diabetic subjects with incipient and established nephropathy found the performance of eGFR to be unacceptable for monitoring kidney function in type 2 diabetic patients. Our study was designed to explore the relationship between the CG- and MDRD-derived eGFR and the reference ^{51}Cr-EDTA isotopically measured GFR in newly diagnosed, treatment-naïve subjects with type 2 diabetes.

RESEARCH DESIGN AND METHODS

— Subjects for this study were recruited from a long-term, local ethics committee–approved follow-up study of type 2 diabetic subjects performed at the University Hospital of Wales, Heath Park, Cardiff, U.K., and Llandough Hospital, Cardiff, U.K. The study population consisted of 292 newly diagnosed, treatment-naïve type 2 diabetic subjects recruited between 1996 and 2005 who had a reference isotopic ^{51}Cr-EDTA GFR (iGFR) measurement and sufficient clinical and biochemical data for inclusion. Subjects were diagnosed according to World Health Organization criteria at the time of recruitment into the study (34,35). The vast majority of subjects were Caucasian, and no subjects were of African-American origin.

Clinical methods

At 0830 h, following an overnight fast, a urine specimen was collected, anthropometric measurements taken, and blood pressure measured in the recumbent position after 10 min rest. Subjects were intravenously cannulated and blood samples drawn for blood glucose, A1C, and serum creatinine. Subsequently, a single intravenous injection containing 1 MBq ^{51}Cr-EDTA was administered at 0 min, with further blood sampling at 44, 120, 180, and 240 min. Blood was collected into heparinized tubes and centrifuged at 4°C.

Laboratory methods

The reference iGFR was obtained by a single-injection plasma clearance method corrected for body surface area (BSA). The simplified ^{51}Cr-EDTA clearance method used has been validated against plasma clearance determined by multiple sampling (36). The four-sample method used allowed estimation using a two-compartment model. A close correlation between total plasma clearance of ^{51}Cr-EDTA and insulin clearance determined by the classical technique has been shown previously (37).

Serum creatinine levels were determined using the OCD (J&J) dry-slide system on the Vitros 750 × RC and 950 analyzer. The laboratory reported that the coefficient of variation of the assay was 4.2% at a creatinine concentration of 103 μmol/l and 1.92% at a creatinine concentration of 516 μmol/l. Creatinine measurement in our hospital was validated at intervals by measurement of samples from the Welsh External Quality Assurance Scheme.

Estimation of GFR

To estimate GFR, the CG formula for creatinine clearance corrected for BSA and the four-variable abbreviated MDRD formula, as recommended for use in the U.K. CKD guidelines (24), were used. The formulas are as follows: *1*) CG formula (27): eGFR (ml/min per 1.73 m^2) = [140 − age (years)] × weight (kg) × k × c serum creatinine (μmol/l), where k is 1.23 for men and 1.04 for women and c adjusts for BSA (33). c = 1.73/BSA, with BSA calculated using the following DuBois (38) formula: BSA (m^2) = [weight (kg)]$^{0.425}$ × [height (cm)]$^{0.725}$ × 0.007184; and 2) the abbreviated four-variable MDRD formula (23): eGFR (ml/min per 1.73 m^2) = 186 × [serum creatinine (μmol/l)/88.4]$^{-1.154}$ × [age (years)]$^{-0.203}$ × (0.742 if female) × (1.210 if African American).

Statistical analysis

Data were assessed graphically for serial correlation. Subjects were grouped by iGFR, with group 1 having iGFR 60–89 ml/min per 1.73 m^2 and group 2 having iGFR ≥90 ml/min per 1.73 m^2. eGFR results derived by the CG and MDRD formulas were compared with iGFR by means of two-tailed, paired *t* tests (confirmed by nonparametric equivalents for nonnormal distributions), χ^2 test for proportions, linear regression, and the κ statistic for rater agreement. Regression goodness of fit and other statistical method assumptions were checked graphically and by use of relevant statistics as appropriate. All calculations were performed using SPSS (version 12.0.1; SPSS) and S-PLUS (version 7.0; Insightful) software packages. Results are presented as means ± SD (95% CI), unless otherwise indicated. $P < 0.05$ was taken to indicate statistical significance. Sample size calculations indicated that the study had at least 80% power to detect a mean difference in GFR of 5 ml/min per 1.73 m^2.

RESULTS

— The demographic characteristics of the 292 study participants are summarized in Table 1. Study subjects were largely normoalbuminuric (241 of 292 [83%]). Table 1 shows that subjects in group 1 had a higher mean age than those in group 2. There was no significant difference in weight or BMI between the groups. However, consistent with a lower iGFR, mean serum creatinine concentration was greater in group 1 than group 2.

The performance of the CG and MDRD formula–derived eGFR to estimate iGFR is presented in Table 2. Performance was assessed by use of bias (mean difference between eGFR and iGFR), precision (SD of the bias), accuracy (proportion of eGFR results within 10 and 30% of

Table 2—*Predictive performance of the CG and the MDRD formulae*

	All subjects (n = 292)		Group 1 (iGFR <90; n = 37)		Group 2 (iGFR ≥90; n = 255)	
iGFR [median (interquartile range)]	114.9 (22.4)		83.8 (4.3); 84 (81–88)		119.4 (20.3); 115 (103–133)	
Formula	CG	MDRD	CG	MDRD	CG	MDRD
eGFR [median (interquartile range)]	101.1 (26.8)	89.9 (19.0)	78.0 (16.5); 76 (69–88.5)	73.7 (12.0); 73 (64–82)	104.4 (26.3); 100 (87–120)	92.3 (18.7); 89 (78–103)
Bias	−13.8 (−16.1 to −11.6)	−25.0 (−26.9 to −23.1)	−5.8 (−11.1 to −0.6)	−10.7 (−14.4 to −7.0)	−15.0 (−17.4 to −12.5)	−27.1 (−29.1 to −25.1)
Precision	19.5	16.6	15.7	11.2	19.7	16.2
95% limits of agreement	(−52.8 to 25.2)	(−58.2 to 8.2)	(−37.2 to 25.6)	(−33.1 to 11.7)	(−54.4 to 24.4)	(−59.5 to 5.3)
Accuracy 10%	29% (24–35)	15% (11–19)	32% (19–50)	27% (14–44)	29% (23–35)	13% (9–18)
Accuracy 30%	86% (81–89)	79% (74–83)	86% (17–95)	95% (80–99)	85% (80–89)	76% (71–81)
R^2	0.490	0.476	0.093*	0.119	0.450	0.429
Gradient	0.59 (0.52–0.65)	0.81 (0.71–0.91)	0.08 (−0.01 to 0.17)	0.13 (0.01–0.24)	0.52 (0.45–0.59)	0.71 (0.61–0.81)
Intercept	55.7 (48.5–63.0)	41.9 (32.9–51.0)	77.6 (70.8–84.4)	74.7 (66.1–83.3)	65.6 (57.9–73.2)	53.8 (44.2–63.3)

Data are means ± SD (95% CI), unless otherwise indicated. All R values were positive and, with one exception*, significantly different from zero.

iGFR), and linear regression (R^2 values, regression equation gradient and intercept for iGFR versus eGFR).

Positive correlations were observed between eGFR and iGFR for all groups, although these were reduced for the lower iGFR group. In Table 2, the R^2 values indicate that there were significant proportions of iGFR variability unexplained by either formula (over 50% in all cases). Values for bias show that on average the formulas significantly underestimated iGFR, while the precision and accuracy data indicate wide prediction intervals of iGFR for a given eGFR. The wide 95% limits of agreement, which range from negative to positive values, further highlights the poor estimates provided by the CG and MDRD methods. Gradient and intercept results also highlight scale and location differences. These are further illustrated in Fig. 1.

A comparison of eGFR- and iGFR-derived U.K. CKD stages was also made, and the percentage agreements in classification are shown in Table 3. The κ values, which reflect the degree of agreement above chance between eGFR and iGFR classification, indicate poor agreement using the MDRD formula and only fair agreement when the CG formula is used (39).

CONCLUSIONS — Formula-derived eGFR results have become widely used in clinical practice. The CG and MDRD equations have been validated in patients with CKD and are currently used to stratify CKD in Europe and North America (24,40,41). However, these equations do have recognized limitations, including a tendency to significantly underestimate higher levels of GFR (26,31,33,42,43). Additionally, Parving and colleagues (33) demonstrated that in type 2 diabetic subjects with macroalbuminuria eGFR had a poor sensitivity to detect GFR values <60 ml/min per 1.73 m^2.

In our study of newly diagnosed, treatment-naïve type 2 diabetic subjects, statistically significant correlations between eGFR derived by the CG and four-variable MDRD formulas with iGFR measured by ^{51}Cr-EDTA were observed. Despite this, the performance of formula-derived eGFRs to estimate measured iGFR results generally was poor in terms of bias, precision, and accuracy.

Both formulas introduced significant biases and underestimated iGFR. This was most pronounced when applying either formula to subjects with iGFR >90 ml/

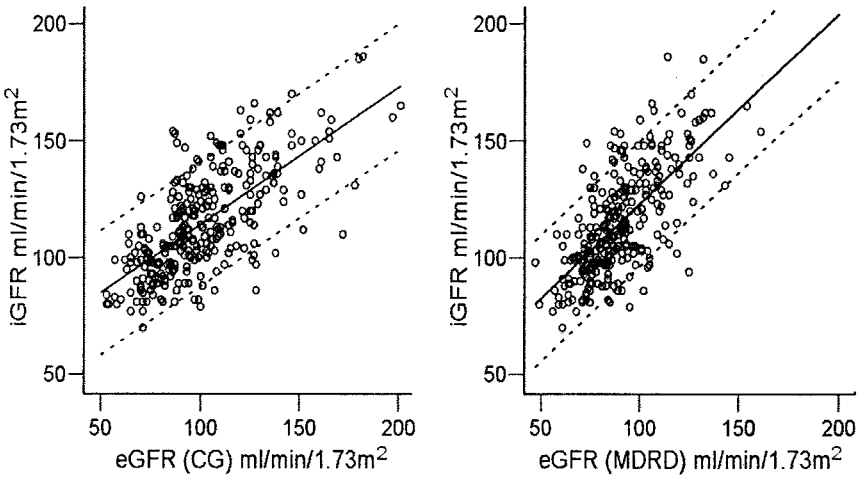

Figure 1—*Relation of CG- and MDRD-calculated eGFR with ^{51}Cr-EDTA–measured iGFR. The solid line represents the regression line, and the dotted lines represent 95% prediction intervals for iGFR based on eGFR.*

min per 1.73 m^2. These findings echo and extend those of Parving and colleagues (33) who studied type 2 diabetic subjects with incipient or overt nephropathy.

Both formulas lacked precision, with wide prediction intervals for iGFR based on eGFR as illustrated in Fig. 1. Overall, the performance was particularly poor for subjects with iGFR in the range of 60–89 ml/min per 1.73 m^2. While the difficulty in interpreting eGFR values has been demonstrated in other patient groups (33,44,45), this is the first large study to show this in newly diagnosed, treatment-naïve and mainly normoalbuminuric type 2 diabetic subjects.

The eGFR formulae were designed for application in patients with GFR <60 ml/min per 1.73 m^2 (27,28). They also have been shown to be reliable in type 2 diabetic patients with severe renal impairment (46). However, in the U.K. the National Service Framework for Renal Services now recommends the use of eGFR for renal assessment in all diabetic patients (22). This may be problematic, as this is a different population from which the equations were derived. In our study, there was little agreement above chance between the eGFR-derived stage of CKD and that derived using iGFR, as reflected by the low κ scores.

Diabetic patients, although at higher risk of CKD than the normal population, generally have normal renal function. According to our results, use of these equations in isolation as a screening tool will lead to an overestimation of the number of diabetic patients with renal impairment. From our study, 14% of patients with GFR between 60 and 89 ml/min per 1.73 m^2 would be classed as stage 3 U.K. CKD with either formula. In isolation this would be misleading considering the low sensitivity of these tests to detect impaired renal function. Parving and colleagues (33) demonstrated only 72% sensitivity for the MDRD formula and 66% for the CG formula to detect GFR values <60 ml/min per 1.73 m^2.

Assessment of serum creatinine clearly plays a significant role in the eGFR formulae. There are reports (47–49) of the impact of variation in calibration of the creatinine assay having an adverse impact on the performance of eGFR to estimate GFR, particularly at low levels of serum creatinine (50). Creatinine assays can be calibrated by gas chromatography isotope dilution mass spectrometry to give a gold standard creatinine value. In the U.S., the National Kidney Education Program has initiated a standardization program to minimize this variation of creatinine measurement (50), and the program is expected to be complete by 2008. Despite being more precise and accurate, these methods give serum creatinine values, which are lower compared with the widely used modified Jaffe method (50). Use of the standardized values would then give higher GFR estimates. This has led to the MDRD equation being reexpressed in 2005 for use with a standardized serum creatinine assay (51). The authors of the updated equation recommend that the original four-variable MDRD equation should continue to be used until the standardization of creatinine assays is complete (49). During the course of our study, creatinine measurements were standardized by measurement of common samples in the Welsh External Quality Assurance Scheme but were not calibrated to the MDRD laboratory. This is a potential limitation of our study; however, until standardization is widespread our results reflect current clinical practice.

Due to the recognized deficiencies of serum creatinine to detect mild renal impairment, even when used with prediction equations (26,31,33,42,43), there is interest in cystatin C, a nonglycosylated basic protein, as a potential endogenous filtration marker of GFR. There is supportive evidence that the reciprocal of cystatin C correlates more closely with isotopic GFR than the CG or MDRD equa-

Table 3—*U.K. CKD staging of subjects in groups 1 and 2*

	CG eGFRκ = 0.24			MDRD eGFRκ = 0.15		
	U.K. CKD stage 3 (GFR <60)	U.K. CKD stage 2 (GFR 60–89)	U.K. CKD stage 1 (GFR ≥90)	U.K. CKD stage 3 (GFR <60)	U.K. CKD stage 2 (GFR 60–89)	U.K. CKD stage 1 (GFR ≥90)
n	6	100	186	7	156	129
Group 1 (GFR 60–89; *n* = 37)	5/37 (14)	24/37 (65)	8/37 (21)	5/37 (14)	29/37 (78)	3/37 (8)
Group 2 (GFR ≥90; *n* = 255)	1/255 (1)	76/255 (30)	178/255 (69)	2/255 (1)	127/255 (50)	126/255 (49)

Data are *n* (%).

tions in subjects with mild renal impairment (52). However, concerns remain regarding intrapatient variation and the effect of certain drugs and hormonal levels on cystatin C concentration (53). While it remains an interesting potential tool for clinical use, substantially more work is needed in different patient subgroups before cystatin C can be considered as an alternative to serum creatinine.

In summary, for patients with diabetes and preserved renal function we recommend that eGFR results not be considered in isolation but together with other indicators of CKD such as microalbuminuria, proteinuria, hematuria, or changes in creatinine concentration. It may be appropriate only to quantify eGFR results <60 ml/min per 1.73 m^2, since U.K. CKD stage 3 CKD has increased clinical significance, necessitating additional intervention. Unfortunately, even this is problematic due to the over diagnosis of CKD stage 3 by eGFR demonstrated in this study.

eGFR is being widely, but not universally, used in patients with and without CKD. The U.K. CKD guidelines advocate the four-variable MDRD equation because it is most accurate in CKD and most easily applicable in clinical practice. However, the current study highlights that while eGFR maybe useful in the assessment of CKD it does have significant limitations outside of this setting.

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