Influence of Body Weight on the Performance of Glomerular Filtration Rate Estimators in Subjects With Type 2 Diabetes

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The American Diabetes Association recommends estimation of glomerular filtration rate (GFR) (1) by either the Cockcroft-Gault (2) or the Modification of Diet in Renal Disease (MDRD) (3) equation in all patients with diabetes. The implication is that these equations provide similar results. Body weight is a numerator in the Cockcroft-Gault equation; however, it is absent from the MDRD equation. This may explain some of the difference in the ability of these equations to estimate GFR in patients with type 2 diabetes, over 80% of whom are obese (4), and may lead to discrepancies in reporting of chronic kidney disease stage (5). Our study was designed to identify whether body weight may explain variability in performance between the Cockcroft-Gault and MDRD equations in patients newly diagnosed with type 2 diabetes.

RESEARCH DESIGN AND METHODS— The study population consisted of 293 subjects newly diagnosed with type 2 diabetes; 96% were Caucasian and the remainder of South Asian origin. No African-American subjects were included.

Following an overnight fast, anthropometric and biochemical measurements were made. Subjects were intravenously cannulated, and 1 MBq ^{51}Cr-EDTA was administered at 0 min, with further blood sampling at 44, 120, 180, and 240 min.

The ^{51}Cr-EDTA plasma clearance method for GFR measurement, corrected for body surface area (BSA), has been validated previously (6). This allows estimation of a two-compartment model. A close correlation exists between total plasma clearance of ^{51}Cr-EDTA and inulin clearance determined by the classical technique (7).

Creatinine levels were determined using the OCD (Johnson & Johnson) dry slide system on the Vitros 750 × RC and 950 analyzer. The coefficients of variation were 4.2% at a creatinine concentration of 103 μmol/l and 1.92% at 16 μmol/l.

Estimated GFR (eGFR) (in milliliters per min per 1.73 meters squared) was calculated by the Cockcroft-Gault formula, corrected for BSA (2), and the MDRD formula (3), both of which are shown below:

Cockcroft-Gault formula:

$$\frac{[140 - \text{age (years)}] \times \text{weight (kg)} \times k \times c}{\text{serum creatinine } (\mu\text{mol/l})} \qquad \text{(eq. 1)}$$

where k is 1.23 for men and 1.04 for females and c adjusts for BSA. $c = 1.73/\text{BSA}$ with BSA calculated using the DuBois formula (8):

$$\text{BSA (m}^2) = [\text{weight (kg)}]^{0.425} \times [\text{height (cm)}]^{0.725} \times 0.007184 \qquad \text{(eq. 2)}$$

MDRD formula:

$$186 \times [\text{serum creatinine } (\mu\text{mol/l})/88.4]^{-1.154} \times [\text{age (years)}]^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American}) \qquad \text{(eq. 3)}$$

Statistical analysis

To compare formula performance over different body weight ranges while maintaining group sizes suitable to make the calculations, subjects were grouped into tertiles according to body weight. Other comparisons were made using the full ranges of the relevant data. eGFR results derived by the Cockcroft-Gault and MDRD formulae were compared with isotopic GFR by means of two-tailed paired and unpaired t tests as appropriate (confirmed by nonparametric equivalents for abnormal distributions) and χ^2 test for proportions and linear regression. Statistical test assumptions were checked graphically and by use of suitable statistics as required. All calculations were performed using SPSS (version 12.0.1). Results are presented as mean ± SD unless otherwise indicated. $P < 0.05$ was taken to indicate statistical significance.

RESULTS— Demographic characteristics of study participants are summarized in Table 1. Normoalbuminuric subjects comprised 91% of participants. A positive correlation between GFR and body weight ($r = 0.194$) was found and was also seen across weight groups. Mean fasting plasma glucose and A1C were similar between groups.

Performance of Cockcroft-Gault– and MDRD formulae–derived eGFRs according to body weight is presented in Table 1. Bias values show that eGFR significantly underestimates isotopic GFR. However,

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Abbreviations: BSA, body surface area; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

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

Table 1—*Demographic data and performance of GFR estimation equations*

	All subjects		Group 1		Group 2		Group 3	
n	293		99		97		97	
Mean weight (kg)	91.9		74.3		91.2		110.5	
Male/female	221/72		61/38		71/21		84/13	
Age (years)	55.2 ± 9.4 (55.0 [49.0–62.8])		57.3 ± 9.9 (60.0 [50.8–65.0])		56.3 ± 8.6 (57.0 [50.0–63.0])		51.9 ± 8.9 (51.0 [46.5–58.0])	
Weight (kg)	91.9 ± 17.0 (91.5 [80.3–102.5])		74.3 ± 7.8 (75.8 [69.9–80.4])		91.2 ± 4.1 (91.5 [87.3–94.8])		110.5 ± 11.6 (106.9 [102.5–114.3])	
A1C (%)	7.79 ± 2.00 (7.2 [6.3–9.1])		7.87 ± 2.18 (7.2 [6.2–9.3])		7.69 ± 1.74 (7.4 [6.4–9.1])		7.81 ± 2.06 (7.0 [6.5–9.0])	
Fasting plasma glucose (mmol/l)	9.67 ± 3.04 (8.7 [7.4–11.4])		9.69 ± 3.29 (8.6 [7.3–11.7])		9.48 ± 2.75 (8.9 [7.1–11.4])		9.83 ± 3.07 (9.0 [7.7–11.2])	
Creatinine (μmol/l)	80.0 ± 14.8 (80.0 [69.3–90.0])		76.8 ± 14.3 (76.0 [66.8–86.3])		81.1 ± 15.3 (80.0 [70.0–89.0])		82.0 ± 14.3 (83.0 [71.5–92.5])	
AER (mg/day)	10.9 ± 34.7		7.2 ± 15.2		9.6 ± 22.4		16.1 ± 42.8	
iGFR	114.9 ± 22.4 (111.0 [98.0–130.0])		110.8 ± 20.4 (107.0 [96.0–125.0])		113.8 ± 21.8 (109.0 [98.0–130.50])		120.1 ± 24.0 (116.0 [102.0–138.5])	
	CG	MDRD	CG	MDRD	CG	MDRD	CG	MDRD
eGFR	101.2 ± 26.8	89.9 ± 19.0	90.2 ± 20.5	89.5 ± 17.6	99.1 ± 24.3	89.0 ± 19.9	114.5 ± 29.4	91.2 ± 19.5
Bias (95% CI)	−13.7 (−16.0 to −11.4)	−25.0 (−26.9 to −23.1)	−20.6 (−23.9 to −17.3)	−21.3 (−24.6 to −18.0)	−14.7 (−18.5 to −10.9)	−24.8 (−28.1 to −21.5)	−5.6 (−9.8 to −1.4)	−28.9 (−32.1 to −25.7)
Precision (95% LOA)	19.7 (−52.3 to 24.9)	16.6 (−57.5 to 7.6)	16.3 (−52.6 to 11.4)	16.6 (−53.7 to 11.2)	18.9 (−51.8 to 22.3)	16.5 (−57.1 to 7.5)	20.9 (−46.6 to 35.3)	16.0 (−60.3 to 2.5)
10% accuracy	30 (24–35)	15 (11–19)	20 (12–28)	20 (12–28)	30 (21–39)	14 (7–22)	39 (29–49)	10 (4–16)
30% accuracy	86 (82–90)	79 (74–84)	80 (72–88)	88 (81–94)	84 (76–91)	74 (65–83)	94 (89–99)	74 (65–83)
r^2	0.481	0.475	0.465	0.396	0.443	0.478	0.505	0.558

Data are means ± SD, median [interquartile range], or percent (95% CI) unless otherwise indicated. All r^2 values were positive and statistically significantly different from zero. Bias is calculated as the mean difference between eGFR and measured (isotopic GFR [iGFR]) values. Precision is the SD of the bias (95% limits of agreement [LOA]) of eGFR and isotopic GFR. Accuracy reflects the proportion of eGFR values within 10% and 30% of isotopic GFR. r^2 values of eGFR vs. isotopic GFR are shown. AER, albumin excretion rate; CG, Cockcroft-Gault.

the negative bias of the Cockcroft-Gault equation reduced toward zero with increasing body weight, whereas the negative bias of the MDRD equation increased with increasing body weight.

Precision values are similar in all groups. Wide 95% limits of agreement, which range from negative to positive values, were seen for both equations regardless of body weight. Accuracy of the Cockcroft-Gault equation improved with increasing body weight, contrasting with the MDRD equation, with which accuracy declined with increasing weight.

CONCLUSION — eGFR is used for assessment of kidney function in patients with diabetes. Despite validation in chronic kidney disease (9,10), eGFR has limitations in patients with preserved kidney function (11).

Inclusion of weight in the Cockcroft-Gault equation and its absence from the MDRD equation led us to speculate that this may explain some of the variability in eGFR results. In obese patients with established kidney disease, the Cockcroft-Gault equation overestimates GFR while underestimating GFR in lean subjects; performance of the MDRD equation in such patients was consistent regardless of weight (12).

We found that both formulae introduced significant biases and, in average terms, underestimated GFR. Consistent with previous studies (12,13), bias of the Cockcroft-Gault formula was most pronounced in lean subjects, diminishing with increasing body weight. Conversely, bias of the MDRD equation increased with increasing body weight. Improvement in accuracy of the Cockcroft-Gault equation was seen with increasing weight, while accuracy of the MDRD equation was better in lean subjects.

In obese patients, excess body weight is mainly adipose tissue, whereas creatinine is primarily generated by muscle. In the Cockcroft-Gault equation, body weight is proportional to GFR; therefore, increasing body weight without a proportional increase in creatinine generation will tend to increase the estimation of GFR. This may explain the attenuation in underestimation of GFR seen by the Cockcroft-Gault equation in obese patients. However, weight is not included in the MDRD equation and therefore cannot influence performance.

This study of predominantly male Caucasian subjects with type 2 diabetes and normoalbuminuria found the Cockcroft-Gault equation to be influenced by body weight, whereas the MDRD is to a far lesser degree. This may lead to significant differences in eGFR results.

Although the MDRD equation underestimates GFR, unlike the Cockcroft-Gault equation its performance is not greatly affected by body weight. However, the Cockcroft-Gault equation did provide a more accurate estimation of GFR in obese subjects with newly diagnosed type 2 diabetes, a substantial clinical population.

Currently, improved estimators of GFR for use in patients with diabetes are being developed (14). While we await these improvements, clearly the Cockcroft-Gault and MDRD equations cannot be used interchangeably. A consensus on estimation of GFR in patients with diabetes is required.

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