

# Glucose Control Influences Glomerular Filtration Rate and Its Prediction in Diabetic Subjects

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**OBJECTIVE** — Hyperglycemia increases glomerular filtration rate (GFR), but the influence of HbA<sub>1c</sub> (A1C) on GFR and GFR's prediction by recommended equations remains to be determined.

**RESEARCH DESIGN AND METHODS** — In 193 diabetic patients, we searched for an association between A1C and isotopically measured GFR (51Cr-EDTA) and their predictions by the Cockcroft and Gault formula (CG) and the modification of diet in renal disease (MDRD) equation. Their accuracy for the diagnosis of moderate (GFR <60 ml/min per 1.73 m<sup>2</sup>) or severe (GFR <30 ml/min per 1.73 m<sup>2</sup>) renal failure was compared from receiver operating characteristic (ROC) curves, before and after categorizing the patients as well (A1C ≤8%) or poorly controlled.

**RESULTS** — The mean GFR was 57.0 ± 34.8 ml/min per 1.73 m<sup>2</sup> and was well correlated with both estimations (CG  $r = 0.75$ , MDRD  $r = 0.83$ ;  $P < 0.05$ ). The areas under the ROC curves were higher with the MDRD ( $P < 0.05$ ). A1C was correlated ( $P < 0.001$ ) with the GFR ( $r = 0.29$ ), MDRD ( $r = 0.38$ ), CG ( $r = 0.26$ ), and the absolute differences between the GFR and their CG but not MDRD estimations ( $r = 0.17$ ,  $P < 0.05$ ). Each +1% A1C was associated with +6.0 ml/min per 1.73 m<sup>2</sup> GFR (CG +5.6, MDRD +5.3). After separating well-controlled ( $n = 88$ , A1C 7.0 ± 0.7%) and poorly controlled ( $n = 105$ , 9.6 ± 1.3%) patients, the diagnostic accuracies were better ( $P < 0.05$ ) for the MDRD, except for the diagnosis of moderate renal failure in well-controlled patients (NS).

**CONCLUSIONS** — GFR and its estimations correlate with A1C. Although the relations between GFR and its estimations were not affected by the degree of glucose control, the precision and diagnostic accuracy of the CG formula were diminished for A1C >8%. The MDRD equation was more accurate and robust in diabetic patients with impaired renal function.

*Diabetes Care* 29:1491–1495, 2006

The Kidney Disease Outcome Quality Initiative guidelines (1) recommend estimating glomerular filtration rate (GFR) in patients with chronic kidney disease using the Cockcroft and Gault formula (CG) (2) or the modification of diet in renal disease (MDRD) study equation (3). This enables stratification of chronic renal failure as moderate (GFR <60 ml/

min per 1.73 m<sup>2</sup>) or severe (GFR <30 ml/min per 1.73 m<sup>2</sup>). The original MDRD study (3) and more recent ones (4,5) found that the MDRD equation was more accurate than the CG for GFR prediction, although both underestimate GFR in healthy individuals (6).

Diabetes is the leading cause of end-stage renal disease in the Western world

(7). Both the CG and MDRD predictions can be used according to the recent recommendations for clinical practice of the American Diabetes Association (8); some reports favor the MDRD equation for diabetic patients (9,10), while others do not (11,12). Apart from the presence of body weight in the CG calculation, leading to a BMI-related bias and an overestimation for type 2 diabetic patients (13), the impact of glucose control on GFR may be another diabetes patient-specific cause of error.

Acute hyperglycemia is known to increase GFR in normal (14) and type 1 (15) and type 2 (16) diabetic patients with normal renal function and in type 1 diabetic patients with overt nephropathy (17). In type 2 diabetic patients, the reduction in HbA<sub>1c</sub> (A1C) after a few months of treatment is associated with a reduction in GFR (18,19), and GFR correlates with A1C in early type 1 diabetic patients (20). This relationship between GFR and A1C has not, however, been reported in diabetic patients with impaired renal function, and it is not known whether glucose control influences the prediction of GFR using the recommended equations.

In 193 diabetic patients with a wide range of renal function, we measured GFR by 51Cr-EDTA clearance, predicted it by the CG and MDRD equations, and examined whether GFR was correlated with A1C. GFR and its predictions were compared after categorizing the patients as well (A1C ≤8%,  $n = 88$ ) or poorly (A1C >8%,  $n = 105$ ) controlled. Because the mean GFR of these two groups differed, the comparison was also performed after exclusion of extreme GFR on GFR-matched groups ( $n = 80$  for each).

## RESEARCH DESIGN AND METHODS

One hundred ninety-three nondialyzed diabetic patients (115 men, 134 type 2 diabetes, mean age 63 ± 13 years, BMI 27.5 ± 4.6 kg/m<sup>2</sup>) were studied. Mean albumin excretion rate was 520 ± 839 mg/24 h. A wide range of renal function (serum creatinine 146 ± 79 μmol/l, range 54–492) and A1C (8.4 ± 1.6%, 5.2–15.1) were repre-

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Received for publication 21 February 2006 and accepted in revised form 30 March 2006.

**Abbreviations:** CG, Cockcroft and Gault formula; GFR, glomerular filtration rate; MDRD, modification of diet in renal disease; ROC, receiver operating characteristic.

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

DOI: 10.2337/dc06-0407

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Table 1—Mean GFR and its prediction in well- and poorly controlled diabetic patients

	A1C ≤8%	A1C >8%	P
n	88	105	
Type 1/type 2 diabetes	21/67	38/67	NS
A1C	7.0 ± 0.7%	9.6 ± 1.3%	<0.001
GFR (ml/min per 1.73 m <sup>2</sup> )	45.4 ± 27.4	66.8 ± 37.4	<0.001
CG estimation	52.0 ± 25.9	69.8 ± 40.7	<0.001
Correlation with GFR	0.70	0.74	NS
Difference with GFR	P < 0.005	NS	
Area under ROC curve for GFR <60	0.85	0.85	
Area under ROC curve for GFR <30	0.89	0.89	
MDRD estimation	43.2 ± 20.3	58.0 ± 23.7	<0.001
Correlation with GFR	0.82	0.81	NS
Difference with GFR	NS	P < 0.001	
Area under ROC curve for GFR <60	0.88	0.93*	
Area under ROC curve for GFR <30	0.96*	0.95*	

Data are means ± SD, unless otherwise indicated. \*Improved accuracy of the MDRD versus the CG estimations (P < 0.05).

sented. A total of 160 of the 193 subjects were included in a previous study about the accuracy of GFR prediction in diabetes (9).

**Analytical methods**

A1C was measured by high-performance liquid chromatography with a Menarini analyzer. Serum creatinine was determined on a multiparameter analyzer (Olympus AU 640; Olympus Optical, Tokyo, Japan) using the Jaffé method with bichromatic measurements according to the manufacturer's specifications and daily calibration of the analyzer. This procedure was used throughout the study. Clearance of the radionuclide marker was measured after intravenous injection of 51Cr-EDTA (Cis Industries, Gif/Yvette, France). All patients were studied in the morning at 9 A.M., after a light breakfast. After a single bolus of 100 µCi (3.7 MBq) of 51Cr-EDTA, four venous blood samples were drawn at 75, 105, 135, and 165 min, and urinary samples were collected at 90, 120, 150, and 180 min, as previously described (21). The final result was the mean of the four clearance values. If for one period the urine flow was too low or if a clearance value was not within ±20% of the mean of the other three, this value was excluded and the mean calculated over the other three clearances. Less than 5% of the values were excluded in this way. The 51Cr-EDTA radioactivity was measured in a gamma counter (COBRA 2, model 05003; Packard Instruments, Meriden, CT).

**Estimation of renal function**

A single creatinine determination was performed the day before the isotopic measurement of GFR to calculate CG: CG = (140 - age [years]) × body weight [kg] × K serum creatinine [µmol/l], where K is the constant 1.23 for men and 1.04 for women (2).

**MDRD study equation**

We used the abbreviated equation (3): MDRD = 186 × serum creatinine [mg/dl]<sup>-1.154</sup> × years<sup>-0.203</sup> × (0.742 if female) × (1.210 if African American).

The results of the CG and isotopic GFR were adjusted to body surface area using Dubois' formula (22) before the comparisons. The results of the MDRD are directly expressed as adjusted to body surface area (3).

**Statistical analysis**

Results of the CG and MDRD formulas were compared with isotopic GFR by correlation and paired t tests. Linear regression analysis was used to identify associations between GFR, its predictions, the absolute difference between predicted and measured GFR, and A1C. Results from well- and poorly controlled patients were compared by ANOVA and unpaired t tests. The sensitivity and specificity of both formulae for the diagnosis of moderate and severe renal failure were assessed from nonparametric receiver operating characteristic (ROC) curves, generated by plotting sensitivity versus 1-specificity, giving the ideal test a sensitivity equal to 1 and a specificity equal to

1. Areas under the curve were calculated and compared according to the procedure of Hanley and McNeil (23). These calculations were performed with SPSS software, version 10.0. Results are presented as mean ± SD, and P < 0.05 was considered significant.

**RESULTS**

The mean GFR was 57.0 ± 34.8 ml/min per 1.73 m<sup>2</sup>. The CG overestimated GFR (61.7 ± 35.8, P < 0.01), whereas the MDRD underestimated it (51.3 ± 23.3, P < 0.001). Both estimations correlated with the GFR (r = 0.75 for CG, r = 0.83 for MDRD; P < 0.05). The areas under the ROC curves for the diagnosis of moderate (CG 0.86, MDRD 0.91) and severe (CG 0.89, MDRD 0.96) renal failure were higher with the MDRD estimations (both P < 0.05).

**Relationship between renal function and A1C**

A1C was positively correlated with GFR (r = 0.29), MDRD (r = 0.38), and CG (r = 0.26) and negatively correlated with serum creatinine (r = -0.36) (all P < 0.001). According to the regression analysis, each +1% A1C was associated with +6.0 ml/min per 1.73 m<sup>2</sup> GFR, +5.6 with the CG and +5.3 for the MDRD. The correlation between A1C and GFR were also significant for the type 1 (r = 0.32, P < 0.01) and type 2 diabetic patients (r = 0.28, P < 0.001) considered separately. A1C also correlated with the absolute differences between the GFR and their CG estimations (r = 0.17, P < 0.05), whereas the correlation with the absolute differences between the GFR and their MDRD estimations did not reach significance.

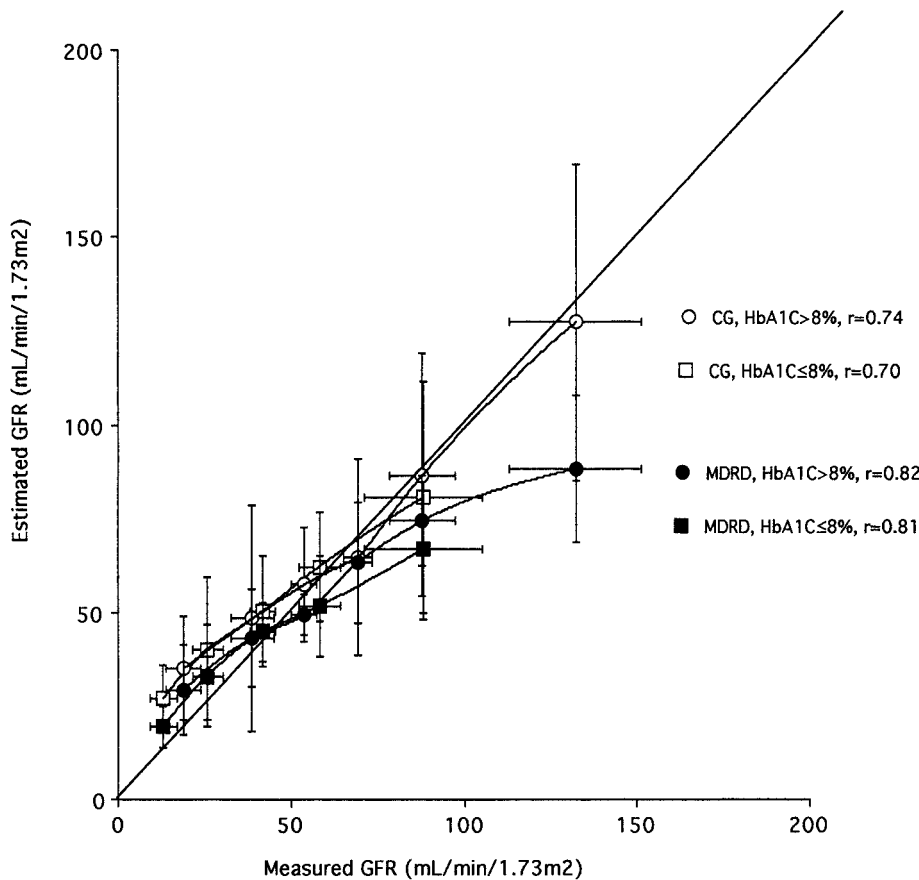
**GFR prediction in poorly versus well-controlled patients**

As shown in Table 1, GFR and its estimations were significantly higher in poorly controlled patients (n = 193). The correlation coefficients between GFR and its estimations were higher with the MDRD and were not modified by glucose control. The maximal diagnostic accuracy (ROC curves) was better for the MDRD, except for the diagnosis of moderate renal failure in well-controlled patients where they did not differ. Figure 1 depicts the estimations as a function of measured GFR after categorizing the patients as GFR quintiles (A1C ≤8%) and sextiles (A1C >8%) to obtain similar-sized subgroups (n = 17 or 18); both estimations overestimated low GFR (<50 ml/min per 1.73 m<sup>2</sup>), although

lower diagnostic accuracy of the CG in poorly controlled patients.

**CONCLUSIONS** — In our 193 diabetic patients, the GFR was correlated to the A1C. The association between poor glycemic control and increased GFR is well known in early diabetes. We show that this relationship extends to both types of diabetes and persists at more advanced stages of renal impairment. Concerning the estimation of GFR through predictive equations, our first finding is that the widely used estimates of GFR, the CG, and especially the MDRD equation estimate these changes as well when compared with isotopically measured GFR. Our second finding is the better accuracy of the MDRD equation when glucose control is poor.

The increase in GFR with hyperglycemia is well recognized and probably explains glomerular hyperfiltration in the early phase of renal involvement in type 1 (24) and perhaps also in type 2 diabetes (25). Indeed the reduction in A1C after a few months on diet or oral hypoglycemic agents is associated with a significant reduction in GFR (18,19). The persistence of this effect has been documented in renal insufficient type 1 diabetic patients (17), and GFR correlates with A1C in short-duration type 1 diabetic patients (20). Our study shows that this correlation can be extended to both types of diabetes and to more advanced stages of renal impairment. Renal failure may influence the A1C measurement. Interference by urea (26) and the presence of carbamy-



**Figure 1**—Estimated GFR (CG white, MDRD black) in well- (squares, n = 88) and poorly controlled (circles, n = 105) patients, as a function of the measured isotopic GFR, categorized by quintiles (well controlled) and sextiles (poorly controlled).

this was more pronounced with CG. At high GFR, the MDRD underestimated GFR. The precision of the prediction formulas therefore depends on the GFR level, so we repeated the comparison after excluding extreme GFR values to obtain two groups with differing A1C but similar mean GFR.

**GFR prediction in poorly versus well-controlled patients with matched GFR**

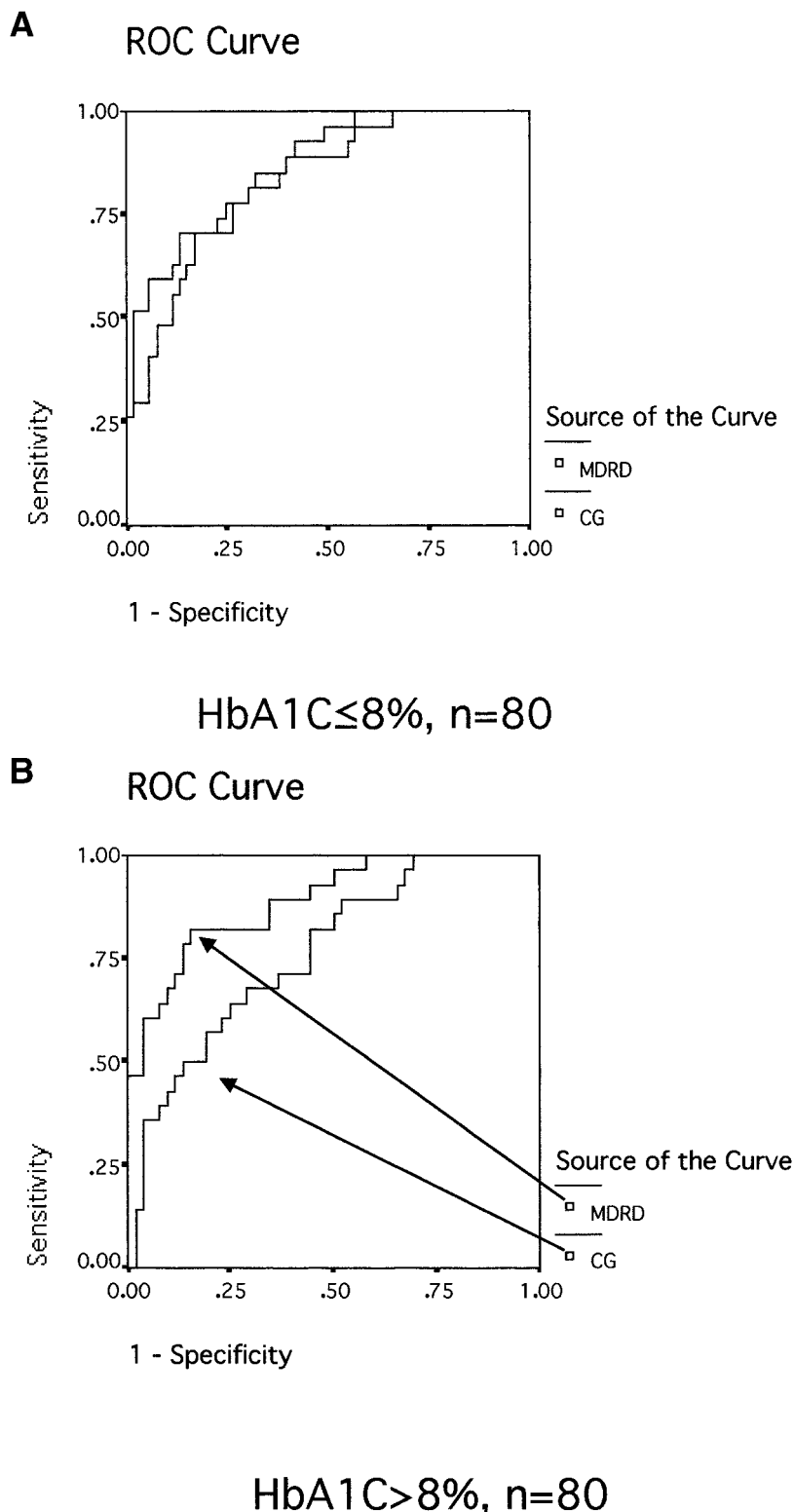
The results of the 8 patients with the lowest GFR in the well-controlled group and the 25 patients with the highest GFR in the poorly controlled group were excluded to obtain similar mean GFR in the two groups (Table 2). GFR and its estimations did not differ in the well- and poorly controlled groups. The CG overestimated GFR, whereas the MDRD did not. The correlation coefficients between GFR and its estimations were lower with the CG, especially in the poorly controlled group (r = 0.56). The maximal diagnostic accuracy (ROC curves) was better for the MDRD, except for the diagnosis of mod-

erate renal failure in well-controlled patients where they did not differ. The ROC curves for the diagnosis of moderate renal failure are depicted in Fig. 2, showing the

**Table 2**—Mean GFR and its prediction in well- and poorly controlled diabetic patients, after matching the groups for GFR

	A1C ≤8%	A1C >8%	P
n	80	80	
Type 1/type 2 diabetes	20/60	28/52	NS
A1C	7.0 ± 0.7%	9.6 ± 1.3%	<0.001
GFR (ml/min per 1.73 m <sup>2</sup> )	48.9 ± 26.1	49.9 ± 21.6	NS
CG estimation	54.8 ± 25.5	55.6 ± 28.3	NS
Correlation with GFR	0.65	0.56	NS
Difference with GFR	P < 0.05	P < 0.05	
Area under ROC curve for GFR <60	0.83	0.76	
Area under ROC curve for GFR <30	0.86	0.84	
MDRD estimation	45.7 ± 19.5	49.5 ± 18.3	NS
Correlation with GFR	0.79	0.79	NS
Difference with GFR	NS	NS	
Area under ROC curve for GFR <60	0.86	0.89*	
Area under ROC curve for GFR <30	0.95*	0.93*	

Data are means ± SD, unless otherwise indicated. \*Improved accuracy of the MDRD versus the CG estimations (P < 0.05).



**Figure 2**—ROC curves. Comparison of AUC between CG and MDRD equation for the diagnosis of moderate renal failure ( $GFR < 60$  ml/min per  $1.73$  m<sup>2</sup>), in well-controlled (A,  $n = 80$ ) and poorly controlled subjects (B,  $n = 80$ ) with similar mean GFR.

lated hemoglobin (27) both tend to increase the value of A1C, which would impair the relationship rather than explain it (carbamylation does

not interfere with the A1C measurement by the Menarini analyzer we used here).

The positive relationship between A1C and GFR is of practical importance;

overt nephropathy has long been considered a point of no return based on negative reports on the effect of long-term glucose control (28,29). Some authors challenge this pessimistic view in type 1 (30,31,32) and type 2 diabetes (33), but it is not easy to discriminate a long term  $-1$  ml/min per  $1.73$  m<sup>2</sup>/year GFR decline per  $-1\%$  A1C (30,31), when the natural relation is a reduction of  $-6$  ml/min per  $1.73$  m<sup>2</sup> GFR per  $-1\%$  A1C as we found here. However, it should be kept in mind that other nephroprotective interventions such as blood pressure control and protein restriction are associated with a short-term reduction in GFR (34).

Our main objective was to determine whether blood glucose control affects the prediction of GFR. This was not the case at first sight, as the CG and MDRD estimations were also related to A1C and the relation between measured and predicted GFR were not greatly modified, as shown on Fig. 1. However, the differences between the CG and GFR increased with increase in A1C. This probably explains why poor glucose control reduces the accuracy for the diagnosis of moderate renal failure with the CG, as shown by the analysis of the ROC curves.

In the two groups matched for GFR, the CG but not the MDRD overestimated GFR. The MDRD underestimated mean GFR in the non-GFR-matched poorly controlled group, which would be expected due to the MDRD underestimation of high GFR, as reported by us and others (9,10,12). This underestimation explains why the CG better fitted to the high GFR of the type 1 diabetic patients in the Diabetes Control and Complications Trial (12); the MDRD equation was originally derived from the results of renal insufficient patients, and its use is problematic in patients with normal renal function (10). High GFR levels and glucose control (5–8 mmol/l) during the study undoubtedly advantaged the CG in the study of Vervoort et al. (11).

In day-to-day clinical practice, the prediction of GFR becomes crucial when renal function declines, and many diabetic patients are often poorly controlled. In these conditions, we have shown that the MDRD has a better diagnostic accuracy (9), and our present results show that this accuracy was not altered by poor glucose control, whereas the CG becomes less accurate when A1C is over 8%. Despite its limitations, especially at high GFR, we think that the MDRD equation is preferable for the diagnosis of moderate

and severe renal failure in diabetic patients, as it is more accurate than the CG and more robust when glucose control is not optimal.

**Acknowledgments**—We would like to thank Dr. S. Jarman for revision of the English manuscript.

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