Monitoring Kidney Function in Type 2 Diabetic Patients With Incipient and Overt Diabetic Nephropathy

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OBJECTIVE — The purpose of this study was to assess agreement between glomerular filtration rate (GFR) and the decline in GFR estimated with the Modification of Diet in Renal Disease (MDRD) Study Group equation or the Cockcroft-Gault formula and measured by the plasma clearance of ^{51}Cr-EDTA.

RESEARCH DESIGN AND METHODS — We followed a cohort of 156 microalbuminuric type 2 diabetic patients for 8 years with four measurements of GFR and another cohort of 227 type 2 diabetic patients with overt diabetic nephropathy for 6.5 (range 3–17) years with seven (3–22) measurements of GFR.

RESULTS — For patients with microalbuminuria, mean ± SD baseline GFR was 117 ± 24 measured, 92 ± 20 estimated (MDRD equation), or 103 ± 24 ml · min^{-1} per 1.73 m^2 estimated (Cockcroft-Gault formula) (both $P < 0.001$); 95% limits of agreement were −66.1 to 20.3 (MDRD equation) and −58.7 to 30.7 (Cockcroft-Gault formula). The rate of decline in GFR was 4.1 ± 4.2 measured, 2.9 ± 2.8 estimated (MDRD equation), or 3.4 ± 3.2 ml · min^{-1} per 1.73 m^2 estimated (Cockcroft-Gault formula) (both $P < 0.001$). For patients with overt nephropathy, baseline GFR was 84 ± 30 measured, 73 ± 24 estimated (MDRD equation), or 81 ± 28 ml · min^{-1} per 1.73 m^2 estimated (Cockcroft-Gault formula) (both $P < 0.001$) with 95% limits of agreement −47 to 25 (MDRD equation) and −39 to 33 (Cockcroft-Gault formula). The rate of decline in GFR was 5.2 ± 4.1 measured, 4.2 ± 3.8 estimated (MDRD equation), and 4.6 ± 4.1 ml · min^{-1} per 1.73 m^2 estimated (Cockcroft-Gault formula) (both $P < 0.001$).

CONCLUSIONS — Particularly in microalbuminuric (hyperfiltering) patients, GFR is significantly underestimated with wide limits of agreement by the MDRD equation as well as by the Cockcroft-Gault formula. The rate of decline in GFR is also significantly underestimated with both equations. This makes GFR estimations based upon these equations unacceptable for monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy.

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The incidence of end-stage renal failure due to diabetes has increased dramatically during the past 2 decades. To prevent this increase, screening for chronic kidney disease and early intervention is necessary (1). In diabetic patients, the early detection of diabetic nephropathy has been focused on measurement of urinary albumin excretion rate, as the detection of elevated urinary albumin excretion rates within microalbuminuric levels (30–299 mg/24 h or a spot urine albumin-to-creatinine ratio of 30–299 mg/g) identifies patients with an increased risk for development of overt diabetic nephropathy with persistent macroalbuminuria. Once type 1 diabetic patients develop overt nephropathy, glomerular filtration rate (GFR) starts declining and should be measured regularly to monitor progression of disease, as these patients may eventually develop end-stage renal failure. Furthermore, impaired renal function may be present even in patients with a normal urinary albumin excretion rate (2).

In the U.S., the National Kidney Foundation recommends estimating GFR in subjects at risk of kidney disease (3) such as diabetic patients, and patients with chronic kidney disease are classified primarily on the basis of the level of GFR, with stage 1 representing patients with normal GFR but persistent signs of kidney damage (such as micro- or macroalbuminuria or hematuria). Furthermore, in patients with chronic kidney disease, it is recommended that kidney function be followed regularly. As the measurement of true GFR is time consuming, expensive, and difficult to perform and may involve radiation exposure and repeated blood or urine sampling and as the measurement of serum creatinine has well-known limitations and inaccuracies, this has lead to the development of formulas for estimation of GFR. The Cockcroft-Gault formula (4) estimating creatinine clearance has probably been applied most frequently. More recently the National Kidney Foundation has recommended using the Modification of Diet in Renal Disease (MDRD) Study Group formulas (5) for estimating GFR, as these estimates were found to be superior to the previous estimates (3). The Cockcroft-Gault formula was developed in nondiabetic subjects, and the MDRD formula was developed in patients with impaired renal function involving very few diabetic patients. These equations were shown to underestimate GFR in healthy subjects (6) and in macroalbuminuric type 2 diabetic patients (7), and they have not been evaluated in microalbuminuric type 2 diabetic patients. Furthermore, whether the rate of decline in GFR in these patients can be accurately determined from the rate of decline in the estimated GFR has not been validated.

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Abbreviations: BSA, body surface area; 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.

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Therefore, our aim was to evaluate the agreement between estimated or measured GFR and rate of decline in GFR in type 2 diabetic patients with micro- and macroalbuminuria. The GFR was estimated from the MDRD equation or from the Cockcroft-Gault formula and compared with the measurement of the plasma clearance of ^{51}Cr-EDTA, an accurate and precise measure of GFR (8).

RESEARCH DESIGN AND METHODS

— We included 156 microalbuminuric (39 women, BMI [means ± SD] 29.8 ± 4.4 kg/m^2, serum creatinine median 76 [range 41–164] μmol/l) (9) and 227 macroalbuminuric (60 women, BMI 30.0 ± 5.3 kg/m^2, serum creatinine 106 [45–276] μmol/l) type 2 diabetic patients from the Steno Diabetes Center (10). At least three measurements of GFR and at least 3 years of follow-up were required for patients to be eligible for the analysis. Since 1983 all patients with diabetes and persistent macroalbuminuria (urinary albumin excretion rate >300 mg/24 h) have had their kidney function monitored with one yearly determination of GFR at the Steno Diabetes Center. We included all (n = 227) patients fulfilling our requirements for measurements of GFR without clinical or laboratory evidence of nondiabetic kidney disease. Renal function was evaluated over a period of 6.5 years (3–17) with 7 (3–22) GFR determinations per patient. Data on the progression of nephropathy have recently been presented (10). The 156 type 2 diabetic patients with microalbuminuria (urinary albumin excretion rate of 30–300 mg/24 h) were followed as part of the Steno-2 study (9) for up to 8 years with a mean of 7.8 years with GFR measurements performed at baseline and after 2, 4, and 8 years, respectively (Table 1).

The GFR was measured after a single intravenous injection of edetic acid labeled with 3.7 MBq of sodium chromate-51 at 0900 by determining the radioactivity in venous blood samples taken at 180, 200, 220, and 240 min after the injection (8,11). The small underestimation (10%) of ^{51}Cr-EDTA clearance versus inulin clearance was corrected for by multiplying the ^{51}Cr-EDTA clearance by 1.10 (12). Extrarenal loss was corrected for by subtracting 3.7 ml/min. The mean day-to-day coefficient of variation in the GFR in our laboratory was 0.04 (13). Serum creatinine was measured using a time reaction technique (coefficient of variation 0.02), which reduces the interference from pseudo-creatinines (14).

We used the Cockcroft-Gault estimate of creatinine clearance based on age, sex, weight, and serum creatinine (4), and for the comparison with the MDRD equation, it was adjusted for body surface area (BSA) by multiplying by (1.73/BSA) using BSA at baseline throughout the follow-up period: Cockcroft-Gault Cl = 140 − age (years) × body wt (kg) × (1/plasma creatinine [μmol/l] × K × [1.73/BSA]) ml · min^{-1} per 1.73 m^2, where Cl is creatinine clearance and K = 1.23 for men and 1.05 for women.

We used the abbreviated MDRD study equation (all patients were Caucasian) (3): MDRD = 186 × (serum creatinine [mg/dl])$^{1.154}$ × (age)$^{0.203}$ × (0.742 if woman) × (1.210 if black) mm · min^{-1} per 1.73 m^2.

We also used the MDRD equation including serum albumin and blood urea nitrogen (5), but, as results were almost identical, data are not shown.

The investigations were carried out in accordance with the principles of the Declaration of Helsinki as revised in 2000.

Statistical analysis

Values are given as means ± SD or median (range). Albuminuria was logarithmically transformed before analysis due to the skewed distribution. Linear regression analysis (least-squares method) was used to determine the rate of decline in estimated creatinine clearance (Cockcroft-Gault formula) and estimated glomerular filtration rate (MDRD equation) and measured GFR (^{51}Cr-EDTA) for each patient. The stochastic variation was calculated as the residual SD and is expressed as a percentage of the corresponding value. The difference between the two methods was then plotted against the average of the two methods for each patient to give a further estimate of the agreement between the methods (Bland-Altman plot) (15). Limits of agreement were calculated as mean difference ± 1.96 of the differences. All calculations were made using SPSS 12.0 (SPSS, Chicago, IL). P values < 0.05 were considered significant (two tailed).

RESULTS

GFR at baseline

For type 2 diabetic patients with microalbuminuria, mean ± SD measured GFR (^{51}Cr-EDTA) was 117 ± 24, estimated MDRD value was 92 ± 20, and estimated Cockcroft-Gault value was 103 ± 24 ml · min^{-1} per 1.73 m^2 BSA (P < 0.001 for both) (Fig. 1). The differences between the methods were correlated with the means when the MDRD estimate (but not Cockcroft-Gault estimate) was used, with increasing underestimation at higher GFR (R = 0.22, P < 0.01). Linear regression analysis of estimated GFR on measured GFR reveals significant correlations (Fig. 2) (MDRD equation r = 0.52, P < 0.001; Cockcroft-Gault formula r = 0.55, P < 0.001). The residual SD was 15% of mean GFR for the MDRD equation and 17% of mean GFR for the Cockcroft-Gault formula.

For diabetic patients with overt nephropathy, baseline measured GFR was 84 ± 30) and MDRD estimate was 73 ± 24 or Cockcroft-Gault estimate was 81 ± 28 ml · min^{-1} per 1.73 m^2 (P < 0.01 for both) (Fig. 1). The differences between the methods were correlated with the means with increasing underestimation at higher GFR (Cockcroft-Gault formula R = 0.12, P = 0.049; MDRD equation R = 0.38, P < 0.001). Linear regression analysis of estimated GFR on measured GFR reveals significant correlations (Fig. 2) (MDRD equation r = 0.798, P < 0.001; Cockcroft-Gault formula r = 0.81, P < 0.001). The residual SD for the MDRD equation was 17% of mean GFR and for the Cockcroft-Gault formula was 19.5% of mean GFR.

Among the patients with diabetic nephropathy 47 (21%) had GFR <60 ml · min^{-1} per 1.73 m^2, which was observed in two (1%) patients with microalbuminuria. The sensitivities of the methods to detect chronic kidney disease (measured GFR <60 ml · min^{-1} per 1.73 m^2) (3) were 72% for the MDRD equation and 66% for he Cockcroft-Gault formula and the specificities were 82 and 91%, respectively. The predictive value of an estimated GFR <60 for having a measured GFR <60 was 51% (MDRD equation) or 66% (Cockcroft-Gault formula), whereas the predictive value of an estimated GFR >60 for having a measured GFR >60 was 92% (MDRD equation) or 91% (Cockcroft-Gault formula). In our study of the 227 patients with overt diabetic nephropathy, 79 patients died during follow-up; the presence of measured GFR <60 was a risk factor for death (hazard rate 1.7, P = 0.02) in a Cox regression analysis, whereas the MDRD or Cockcroft-Gault estimated GFR <60 was not a risk factor for death (P > 0.2). After adjustment for previously demonstrated risk factors for

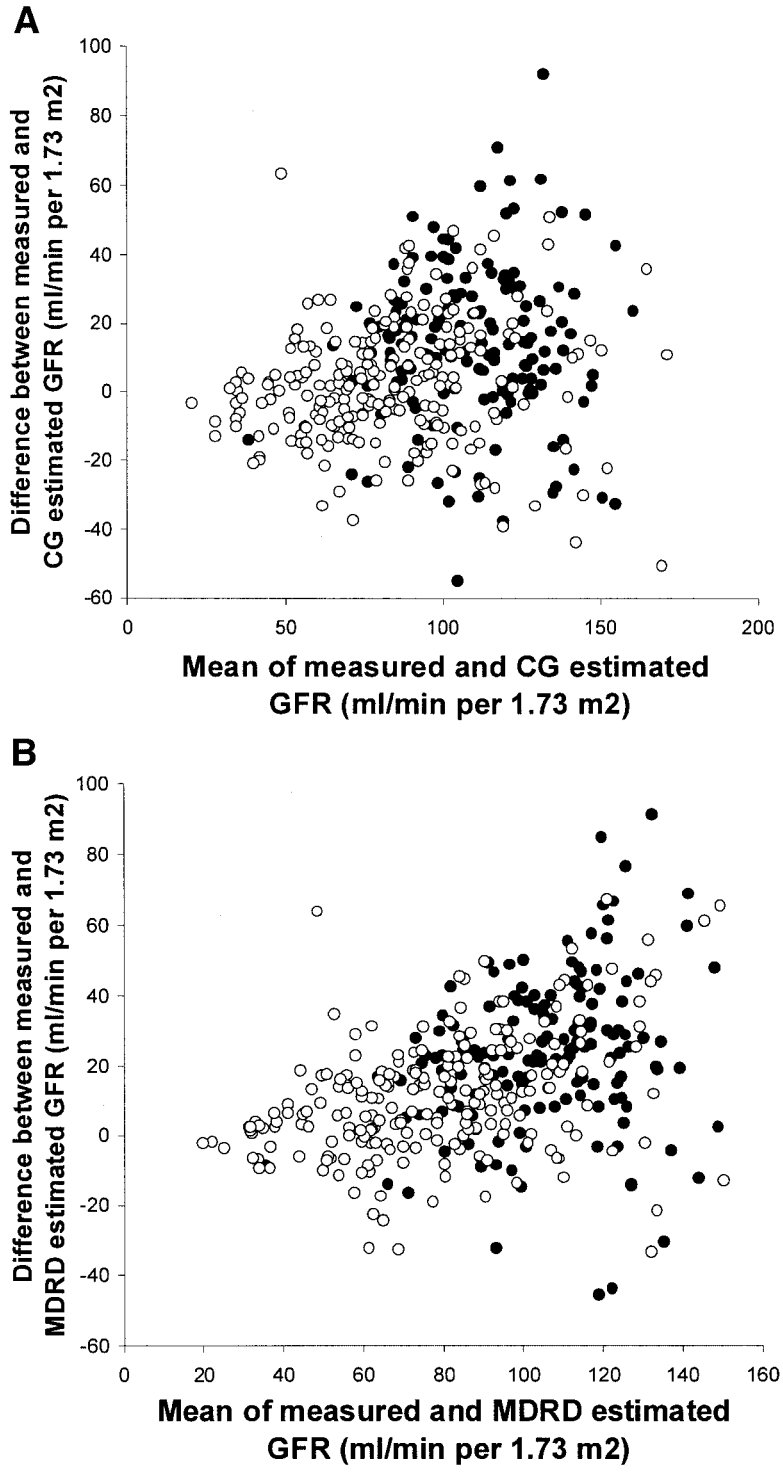

Figure 1—*Difference against mean of measured GFR (^{51}Cr-EDTA) and estimated GFR (*A*: Cockcroft-Gault [CG] formula,* B*: MDRD equation) in 156 microalbuminuric (●) and 227 macroalbuminuric (○) type 2 diabetic patients. The mean difference between the methods (the bias) in microalbuminuric patients was an underestimation of 14 ml · min^{-1} per 1.73 m^2 (95% limits of agreement −58.7 to 30.7) for the Cockcroft-Gault formula and an underestimation of 23 ml · min^{-1} per 1.73 m^2 (−66.1 to 20.3) for the MDRD equation compared with measured GFR. In patients with nephropathy, for the Cockcroft-Gault formula there was an underestimation of 3 ml · min^{-1} per 1.73 m^2 (−39 to 33) and for the MDRD equation there was an underestimation of 11 ml · min^{-1} per 1.73 m^2 (−47 to 25).*

mortality (albuminuria, age, systolic blood pressure, and HbA_{1c}), the presence of measured GFR <60 was no longer a risk factor for mortality.

Rate of decline in GFR

For patients with microalbuminuria, the measured decline in GFR (^{51}Cr-EDTA) was 4.1 ± 4.2 and the decline for the MDRD estimate was 2.9 ± 2.8 or for the Cockcroft-Gault estimate was 3.4 ± 3.2 ml · min^{-1} per 1.73 m^2 per year ($P <$ 0.001 for both) (Fig. 3). The differences between the methods increased with increasing mean rate of decline for GFR (Cockcroft-Gault formula $R = 0.33$, $P <$ 0.001; MDRD equation $R = 0.43$, $P <$ 0.001) and with increasing baseline measured GFR. Linear regression analysis of estimated decline in GFR on measured decline in GFR reveals significant correlations (MDRD equation $r = 0.50$, $P <$ 0.001; Cockcroft-Gault formula $r = 0.50$, $P < 0.001$). The residual SD for MDRD equation was 61% of mean decline in GFR and for Cockcroft-Gault formula was 68% of mean decline in GFR.

For diabetic patients with overt nephropathy, measured decline in GFR was 5.2 ± 4.1 and for the MDRD estimate was 4.2 ± 3.8) or for the Cockcroft-Gault estimate was 4.6 ± 4.1 ml · min^{-1} per 1.73 m^2 per year ($P < 0.001$ for both) (Fig. 3). The differences between the methods were not correlated with the means. Linear regression analysis of estimated decline in GFR on measured decline in GFR reveals significant correlations (MDRD equation $r = 0.769$, $P < 0.001$; Cockcroft-Gault formula $r = 0.765$, $P <$ 0.001). The residual SD for the MDRD equation was 47% of mean decline in GFR and for Cockcroft-Gault formula was 50% of mean decline in GFR.

CONCLUSIONS— In our cross-sectional study in micro- and macroalbuminuric type 2 diabetic patients we demonstrated that simple and rapid estimation of GFR using either the MDRD equation for determination of GFR or the Cockcroft-Gault formula for creatinine clearance (adjusted for BSA) correlated with GFR determined by ^{51}Cr-EDTA plasma clearance in the range from 20 to 178 ml · min^{-1} per 1.73 m^2. This is the first study to evaluate this specifically in microalbuminuric diabetic patients. Despite the correlation, the estimates significantly underestimated GFR in both micro- and macroalbuminuric patients, with increasing underestimation with in-

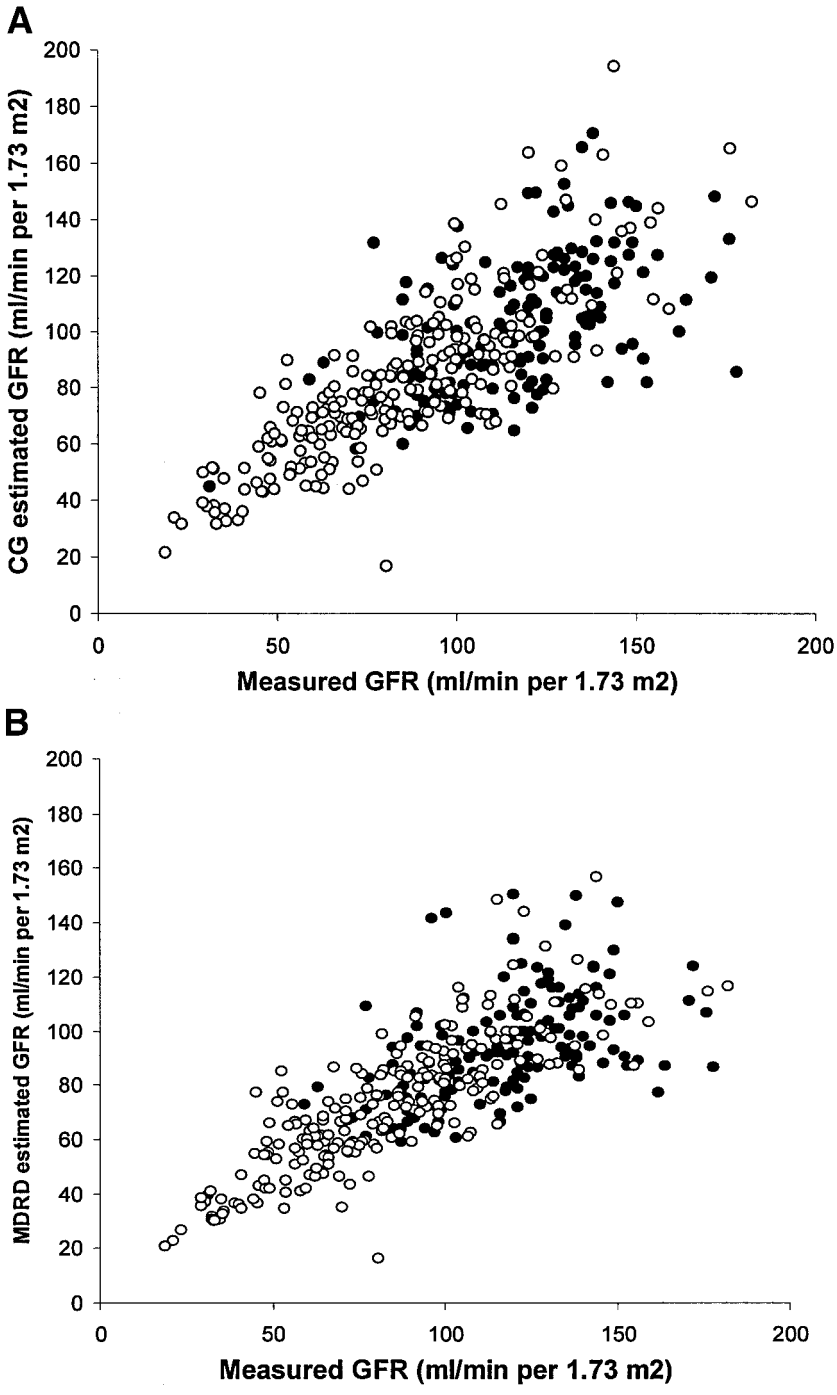

Figure 2—*Correlation between measured GFR (^{51}Cr-EDTA) and Cockcroft-Gault (CG) estimated GFR (A) and MDRD estimated GFR (B) in 156 microalbuminuric (●) (A: r = 0.55, P < 0.001, intercept 59;* B: r = *0.52,* P < *0.001, intercept 58) and 227 macroalbuminuric (○) type 2 diabetic patients (A: r = 0.81,* P < *0.001, intercept 11.7;* B: r = *0.798,* P < *0.001, intercept 8.2).*

creasing values (lack of accuracy) and as reflected by the wide limits of agreement. There was also lack of precision for both estimates. The underestimation was larger in microalbuminuric compared with macroalbuminuric patients. Furthermore, the sensitivity to detect impaired renal function (GFR <60 ml · min^{-1} per 1.73 m^2) was only 72% for the MDRD estimate and 66% with the Cockcroft-Gault estimate, and a prediction of impaired renal function with the estimates was only in accordance with measured GFR in 51 and 66% of the patients. In the longitudinal part of our study patients were followed for at least 3 years (a mean of 7 years), giving us the opportunity to evaluate, in a relatively large group of patients, whether long-term monitoring of type 2 diabetic patients with micro- and macroalbuminuria can be done with GFR estimated by the MDRD equation. Such an evaluation has not been done previously. The rate of decline in GFR was significantly underestimated with both equations in micro- and macroalbuminuric patients, and the limits of agreement were wide (lack of precision).

The MDRD equation was developed from a study of 1,628 patients with impaired renal function (mean GFR 40 ml · min^{-1} per 1.73 m^2) involving only 6% of patients with diabetes (5), whereas the Cockcroft-Gault formula was developed to predict creatinine clearance (4). This may explain the limitations of the equations in predicting renal function in healthy subjects and in patients with early diabetic nephropathy. Several researchers have tried to validate the Cockcroft-Gault formula (16–21) and the MDRD equation (7,22–24) in patients with diabetes and in healthy subjects (6,25–27). The results vary, but in general there is a lack of precision and often also of accuracy. The performance of the equations is often best in subjects with impaired renal function; thus, with increasing GFR the MDRD formula underestimates GFR to a larger extent. In a large study of 1,286 patients from the Diabetes Control and Complications Trial with uncomplicated type 1 diabetes, it was found that the Cockcroft-Gault formula underestimated GFR in patients with low GFR and overestimated GFR in patients with high GFR, in accordance with our previous study of type 1 diabetic patients (20). In contrast, in the present study of type 2 diabetic patients, there is an underestimation of GFR particularly in the microalbuminuric patients as in a previous study of type 2 diabetic patients (21), suggesting a difference between type 1 and 2 diabetic patients that could relate to body composition. Whether renal function should be standardized for BSA in obese subjects has also been questioned, but as the MDRD equation adjusts for BSA we have adjusted all results accordingly. The MDRD equation has not previously been evaluated in microalbuminuric patients with type 2 diabetes, an important subgroup with an increased risk for development of diabetic nephropathy and thus chronic kidney disease. According to the guidelines from the National Kidney Foundation (3), these patients should be monitored regu-

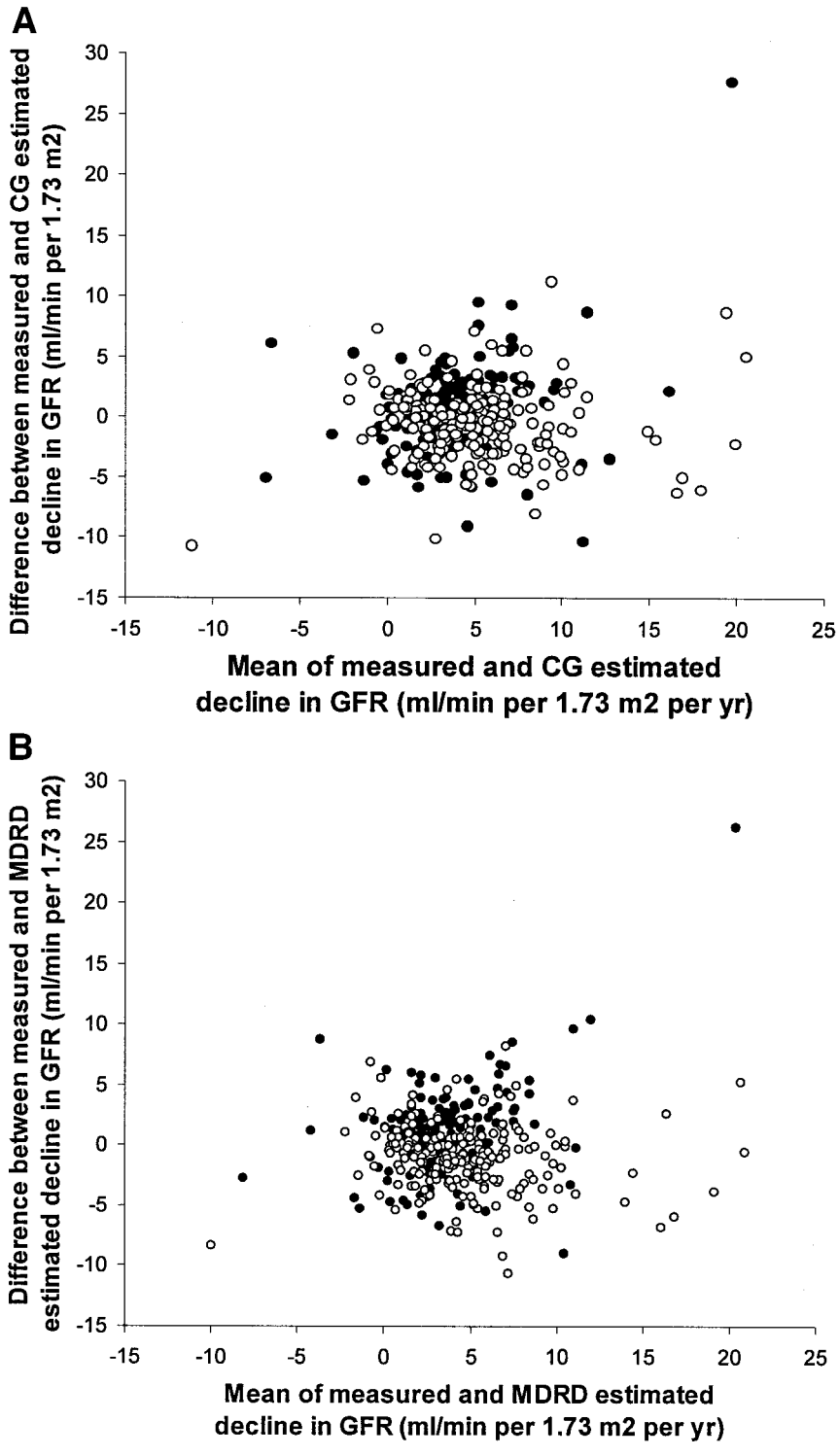

Figure 3—*Difference against mean of rate of decline in measured GFR (^{51}Cr-EDTA) and estimated GFR (*A*: Cockcroft-Gault [CG] formula,* B*: MDRD formula) in 156 microalbuminuric (●) and 227 macroalbuminuric (○) type 2 diabetic patients. The average difference between the methods (the bias) in microalbuminuric patients for the Cockcroft-Gault formula was an underestimation of decline of 0.7 (95% limits of agreement −8.15 to 6.85) and for the MDRD equation was an underestimation of 1.1 (−8.46 to 6.26) ml · min^{-1} per 1.73 m^2 per year compared with measured GFR. In patients with nephropathy, these was values were underestimations of 0.6 (−6.3 to 4.3) for the Cockcroft-Gault formula and 1.0 (−6.0 to 4.9) ml · min^{-1} per 1.73 m^2 per year for the MDRD equation.*

larly with estimation of GFR. Our study demonstrates that the sensitivity to detect impaired renal function is ≤72% (MDRD equation) and only 66% (Cockcroft-Gault formula) or 51% (MDRD equation) of the examined type 2 diabetic patients with impaired renal function have a measured GFR <60 ml · min^{-1} per 1.73 m^2, according to the estimates.

Despite the lack of precision and accuracy of the MDRD estimate, epidemiological studies using the MDRD estimates of renal function, which would not be feasible to perform with inulin or other measures of GFR, have been able to demonstrate that slightly impaired renal function (estimated GFR <60) has a significant impact on the risk for death and cardiovascular disease (28,29). Our study suggests that the risk estimates could be improved if measured GFR was applied instead of the applied estimates or if better estimates were developed. In our study estimated GFR was not a predictor of mortality in contrast to previous studies, a result that could be due to differences in the populations studied or lack of power in our study. As GFR is, on average, underestimated with the equations, the prevalence of impaired renal function would be overestimated in epidemiological studies applying the estimates; on the other hand, patients with incipient diabetic nephropathy and hyperfiltration, potentially having an increased risk for progression of the diabetic nephropathy, would be missed by the underestimation of GFR.

We have used the method for serum creatinine determination (modified Jaffe) as in the MDRD study and the study by Cockcroft and Gault. Our method has, however, not been calibrated to the MDRD study laboratory, which is a limitation of our study (6,30). Kemperman et al. (31) demonstrated that results with the Cockcroft-Gault formula could be improved by using cimetidine to block the tubular secretion of creatinine and by using an enzymatic technique for determination of plasma creatinine. The enzymatic creatinine determination method is more precise and accurate, but serum creatinine values are lower compared with the modified Jaffe method, leading to higher GFR estimates. A change in method and in reference values for a variable in the equations may necessitate a new formula (32). Instead of suggesting a new equation based on our population, we are participating in a global initiative, the Chronic Kidney Disease Epidemiol-

ogy Collaborative Study Group, which is attempting to obtain an easy and reliable estimate of GFR that can be used in different patient and ethnic populations based on creatinine and/or cystatin C.

It has been questioned whether it is possible to derive valid estimates of GFR as many other factors apart from glomerular filtration affect the serum creatinine level, including tubular secretion of creatinine, the impact of skeletal muscle mass, meat intake, and the inhibiting effect of medication on tubular secretion of creatinine (e.g., cimetidine) (33). Alternatively, it has been suggested that renal function be monitored using cystatin C (34), which may be more accurate in patients with normal renal function but at present does not allow estimation of GFR as suggested by National Kidney Foundation guidelines (3). Furthermore the tubular secretion of creatinine and extrarenal clearance of creatinine increase with declining renal function (35,36). A discrepancy between the rate of decline in GFR and decline in estimates of GFR based on the serum creatinine concentration could therefore be expected as observed in the present study, in which a significant underestimation of the decline in GFR by estimated GFR was observed in patients followed for an average of 7 years with a decline in GFR of 4–5 ml · min^{-1} · year^{-1} in micro- and macroalbuminuric type 2 diabetic patients. This was also observed in a study by Perkins et al. (24) in 30 type 2 diabetic subjects. In an analysis of the MDRD study (37), it was observed that changes in creatinine-based estimates of clearance was not explained by changes in measured GFR. We previously compared the rate of decline in measured GFR and GFR estimated by the Cockcroft-Gault formula in type 1 diabetic patients with overt diabetic nephropathy and found an unacceptable variability in estimated decline in GFR (20). In type 2 diabetic patients with normal renal function (and a small decline in GFR), an overestimation of the decline in GFR by the Cockcroft-Gault method was reported by Nielsen et al. (21). In contrast, recent data from 1,094 participants in the African American Study of Kidney Disease and Hypertension were analyzed using a new equation for the estimation of GFR based on the study data, and it was found that using creatinine-based estimates of renal function instead of iothalamate-measured GFR would not affect the conclusions of the study. However, the rate of decline in GFR was very low (<2 ml · min^{-1} · year^{-1}); thus, the expected changes in creatinine elimination are small and the observations may be specific for the African Americans with hypertensive nephrosclerosis enrolled in the study as discussed by the authors.

In the present study, we have used plasma clearance of ^{51}Cr-EDTA for determination of GFR. This method has been demonstrated to be precise and accurate (11). To account for the difference between inulin and EDTA clearance, a correction of 1.10 is used (12). To simplify sampling we have used the simplified sampling technique with six samples from 180 to 240 min (8). Results from more recent studies have confirmed the usefulness of this method but suggested that different sampling and modeling of data would give similar data although more accurate data in hyperfiltering patients (38), which could be a limitation of our study.

In summary, GFR is significantly underestimated with wide limits of agreement by the MDRD equation as well as by the Cockcroft-Gault formula, particularly in microalbuminuric (hyperfiltering) patients. The rate of decline in GFR is also significantly underestimated with both equations. This makes the present GFR estimations from applying the abovementioned equation or formula unacceptable for monitoring kidney function in type 2 diabetic patients with incipient and overt diabetic nephropathy.

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