New Predictive Equations Improve Monitoring of Kidney Function in Patients With Diabetes

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OBJECTIVE — The Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations poorly predict glomerular filtration rate (GFR) decline in diabetic patients. We sought to discover whether new equations based on serum creatinine (the Mayo Clinic Quadratic [MCQ] or reexpressed MDRD equations) or four cystatin C–based equations (glomerular filtration rate estimated via cystatin formula [Cys-eGFR]) were less biased and better predicted GFR changes.

RESEARCH DESIGN AND METHODS — In 124 diabetic patients with a large range of isotopic GFR (iGFR) (56.1 ± 35.3 ml/min per 1.73 m^2 [range 5–164]), we compared the performances of the equations before and after categorization in GFR tertiles. A total of 20 patients had a second determination 2 years later.

RESULTS — The Cockcroft-Gault equation was the least precise. The MDRD equation was the most precise but the most biased according to the Bland-Altman procedure. By contrast with the MDRD and, to a lesser extent, the MCQ, three of the four Cys-eGFRs were not biased. All equations overestimated the low GFRs, whereas only the MDRD and Rule's Cys-eGFR equations underestimated the high GFRs. For the subjects studied twice, iGFR changed by −8.5 ± 17.9 ml/min per 1.73 m^2. GFR changes estimated by the Cockcroft-Gault (−4.5 ± 6.8) and MDRD (−5.7 ± 6.2) equations did not correlate with the isotopic changes, whereas new equation-predicted changes did: MCQ: −8.7 ± 9.4 ($r = 0.44$, $P < 0.05$) and all four Cys-eGFRs: −6.2 ± 7.4 to −7.3 ± 8.4 ($r = 0.60$ to 0.62, all $P < 0.005$), such as 100/cystatin-C ($r = 0.61$, $P < 0.005$).

CONCLUSIONS — The new predictive equations better estimate GFR than the Cockcroft-Gault equation. Although the MDRD equation remains the most accurate, it poorly predicts GFR decline, as it overestimates low and underestimates high GFRs. This bias is lesser with the MCQ and Cys-eGFR equations, so they better predict GFR changes.

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Chronic kidney disease (CKD) is a major health problem worldwide, with dramatically rising incidence and prevalence. Patients with diabetes are particularly affected by this negative development. It is necessary to stratify CKD and estimate its progression because diabetes is the leading cause of end-stage renal disease (1). The National Kidney Foundation guidelines recommend estimating glomerular filtration rate (GFR) in subjects with CKD (2). According to the National Kidney Foundation and the American Diabetes Association, GFR can be estimated in adults by using the Cockcroft-Gault or the Modification of Diet in Renal Disease (MDRD) equations (1,3). Neither of these equations, based on serum creatinine, is highly predictive of GFR. The Cockcroft-Gault equation is less accurate (4), biased by body weight (5), and less robust in patients with poor glycemic control (6). The simplified MDRD equation allows renal function to be classified with acceptable precision and requires only usual information about the patient. However, adjustment may be required to avoid error due to creatinine assays and calibrators (7). Moreover, the MDRD is known to underestimate high or normal GFR, leading to dramatic inaccuracy, as evidenced in the Diabetes Control and Complications Trial cohort (8). Only 70% of subjects overall may be considered well stratified, according to the Kidney Disease Outcomes Quality Initiative, with these equations (9). Their precision seems even worse for estimating CKD progression, leading to unacceptable inaccuracy (10). The estimated equations reflected the measured GFR decline only in the most advanced (Kidney Disease Outcomes Quality Initiative stage 3) cases (11), suggesting that variable predictive performance due to GFR level may play a role in this imprecision.

New predictive equations therefore need to be developed and validated. They could be based on the results of serum creatinine in subjects with (as in the MDRD) or without renal impairment. The Mayo Clinic Quadratic (MCQ) equation was established this way (12). Another means of measurement is to include the

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Abbreviations: CKD, chronic kidney disease; Cys-eGFR, glomerular filtration rate estimated via cystatin formula; GFR, glomerular filtration rate; iGFR, isotopic GFR; MCQ, Mayo Clinic Quadratic; MDRD, Modification of Diet in Renal Disease; rMDRD, reexpressed MDRD; ROC, receiver-operating characteristic.

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

promising new renal marker cystatin-C in formulae based solely on a serum level, without requiring any clinical information (13). In 30 type 2 diabetic subjects during a 4-year study, there was a close relationship between longitudinal trends in iothalamate clearance and trends in renal function, as estimated by the mean of 100/cystatin-C (14), in contrast to creatinine-based estimates of GFR (Cockcroft-Gault and MDRD equations). It appears of particular interest, therefore, to study the known cystatin-C–based equations and to compare them with recent creatinine-based formula to determine whether these new predictive equations are less biased according to the GFR level and whether they allow GFR trends to be established in diabetic subjects.

We compared the estimation of GFR by conventional (Cockcroft-Gault and MDRD) and new (reexpressed MDRD [rMDRD] [7], MCQ, and cystatin-C–based) equations to 51Cr-EDTA–measured GFR in 124 diabetic patients with a large range of renal function. The four cystatin-based equations were recently proposed *1*) in the general population by Rule et al. (15) and Arnal and colleagues (16,17) and *2*) in diabetic patients by Tan et al. (18) and MacIsaac et al. (19). To focus on biases according to GFR level, we performed a Bland-Altman procedure and repeated the comparison after categorizing the subjects in tertiles of GFR levels. In 20 patients, GFR was also measured and predicted 2 years later to investigate whether the new equations were more efficient in predicting GFR change.

RESEARCH DESIGN AND METHODS

A total of 124 adult diabetic patients attending our clinical unit (Service de Nutrition-Diabétologie, Hôpital Haut-Lévêque, Pessac, France) were studied, most of whom were men (n = 78), with type 2 diabetes (n = 88), mean ± SD age 62 ± 13 years (range 19–83), BMI 27.5 ± 4.6 kg/m^2 (15.6–40.7), and albumin excretion rate 575 ± 864 mg/24 h (5–4,000). No patient was dialyzed during the study.

Analytical methods

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 the analyzer was calibrated and controlled daily. The procedure remained constant throughout the study. The results were obtained in micromols/liter and converted into milligrams/deciliter to perform the predictive equations. Serum cystatin-C was determined on a nephelometric analyzer (Behring Nephelometer 2; Paris La Défense Cedex, Paris, France) by means of particle-enhanced immunonephelometry (N latex CysC; Dade Behring, Marburg, Germany) after calibration and control. Clearance of the radionuclide marker was measured after intravenous injection of 51Cr-EDTA (Cis Industries, Gif/Yvette, France). Patients were studied in the morning at 9:00 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 collected at 90, 120, 150, and 180 min, as previously described (20). The final result was the mean of the four clearance values. If urinary flow was too weak in any period or if a clearance value was not within ±20% of the mean of the other three, the value was excluded and the mean calculated on the other three clearances; <5% of the values were thus excluded. 51Cr-EDTA radioactivity was measured in a gamma counter (COBRA 2, model 05003; Packard Instruments, Meriden, CT).

Estimation of renal function

Single serum creatinine and cystatin-C measurements were performed the day before the isotopic measurement of GFR.

Creatinine-based formulae

Cockcroft-Gault formula: [(140 − age [years]) × body weight [kg] × K] serum creatinine [μmol/l], where K is a constant (1.23 for men and 1.04 for women) (21).

MDRD equation. We used the simplified equation (22): 186 × (serum creatinine [mg/dl])$^{-1.154}$ × (years)$^{-0.203}$ × 0.742 (if female) × 1.210 (if African American).

rMDRD equation. As significant error is introduced when the MDRD equation is used with different creatinine assays or calibration, the simplified MDRD was recently recalculated with serum creatinine measurements calibrated to an enzymatic assay (7): 175 × (serum creatinine [mg/dl])$^{-1.154}$ × (years)$^{-0.203}$ × 0.742 (if female) × 1.212 (if African American).

MCQ equation. We used the MCQ equation as described by Rule et al. (12): exp. (1.911 + 5.249/SCr − 2.114/SCr^2 − [0.00686 × age (years)] −0.205 if female, where SCr is serum creatinine [in milligrams per deciliter].

Cystatin-C–based formulae. Several cystatin-C–based predictive equations for calculating GFR have recently been published and evaluated with different cystatin-C assays; they may lead to inaccurate GFR estimates if an inappropriate formula is used (23). We chose formulae by using our own methodology to measure serum cystatin-C (immunonephelemetry; Dade Behring). As a disease-specific formula has been tested in diabetes for estimating GFR (18) using a different methodology (immunoturbidimetric method; Dako, High Wycombe, U.K.) on a Cobas FARA analyzer (Roche Diagnostics, Lewes, U.K.), we have tested this formula, but accurately comparing different methodologies is classically difficult. In all formulae, CysC is serum cystatin-C (in milligrams per liter).

Cystatin-estimated GFR according to Arnal and colleagues. The cystatin-estimated GFR (Cys-eGFR) according to Arnal and colleagues (16,17) was used in 208 patients aged 1–80 years with various etiologies and with insulin determination of GFR as follows: Cys-eGFR (Arnal-Dade) = 74.835/(CysC$^{1.333}$).

Cys-eGFR according to Rule et al. This equation (15) was derived from patients with native kidney disease (n = 204) having hypertension as a mean suspected etiology: Cys-eGFR (Rule) = 66.8× (CysC)$^{-1.30}$. Isotopic GFR (iGFR) was measured by iothalamate clearance.

Cys-eGFR according to MacIsaac et al. In the study by MacIsaac et al. (19), in 126 diabetic patients (mainly type 2 diabetes), the iGFR was measured by clearance of ^{99m}Tc-diethylene-triamine-penta-acetic acid (88 ± 2 ml/min per 1.73 m^2, with 78% >60 ml/min per 1.73 m^2). The equation according to MacIsaac et al. is as follows: Cys-eGFR (MacIsaac) = (84.6/CysC) − 3.2.

Cys-eGFR according to Tan et al. In the study by Tan et al. (18), an unbiased conversion algorithm between plasma cystatin-C and iGFR measured by iohexol clearance was used in type 1 diabetes, including a subgroup of healthy subjects. The equation is as follows: Cys-eGFR (Tan) = (87.1/plasma CysC) − 6.87.

The results of the Cockcroft-Gault and iGFR were adjusted to body surface area using Dubois' formula (24) before comparisons. The results of the MDRD, rMDRD, MCQ, and cystatin-based formulae are directly expressed as adjusted to body surface area.

Statistical analysis

The results of the predictive equations were compared with iGFR by regression analysis, paired *t* tests, and Bland-Altman procedures. The regression analysis and paired *t* tests were repeated after categorizing the subjects in tertiles according to their measured GFR. The precision of the equations was assessed by the absolute differences between their results and the iGFR and by the percentage of estimations within ±15, ±30, and ±50% of the iGFR. The sensitivity and specificity for the diagnosis of moderate (GFR <60 ml/min per 1.73 m^2) and severe (GFR <30 ml/min per 1.73 m^2) 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 as published (25). In the 20 subjects who were studied twice, the two measured and predicted GFRs were compared by paired *t* tests and the measured and predicted GFR changes compared by regression analysis. These calculations were performed with SPSS, version 10.0, and MedCal software. Results are presented as means ± SD; $P < 0.05$ was considered significant.

RESULTS

Overall performances of predictive equations

Serum creatinine was 148 ± 79 μmol/l and serum cystatin-C 1.56 ± 0.84 mg/l (range 0.49–5.48). Mean iGFR was 56.1 ± 35.3 ml/min per 1.73 m^2 (8.5–164). The results of the eight predictive equations are presented in Table 1. The mean Cys-eGFR (Arnal-Dade) alone did not differ from the reference iGFR and was not biased. Such was also the case to a lesser extent with Cys-eGFR (MacIsaac and Tan), according to the Bland-Altman plots. The highest absolute difference with the iGFR was obtained with the Cockcroft-Gault equation, while the lowest was obtained with the MDRD, rMDRD, and Cys-eGFR (Rule) equations.

The area under the ROC curve (Table 1) was significantly lower with the Cockcroft-Gault equation than with the others for the diagnosis of moderate renal failure (GFR <60 ml/min per 1.73 m^2). For the diagnosis of severe renal failure (GFR <30 ml/min per 1.73 m^2), the best area under the curve was that by the MDRD equation.

Type of diabetes

The study involved both type 1 ($n = 36$; BMI 25.0 ± 3.1 kg/m^2) and type 2 ($n = 88$; BMI 28.5 ± 4.7 kg/m^2; $P < 0.001$ vs. type 1) diabetic subjects having iGFRs of 62.9 ± 34.3 (range 10–145) and 53.3 ± 35.5 ml/min per 1.73 m^2 (range 8–164), respectively. The Cockcroft-Gault formula was not biased according to the Bland-Altman procedure but was characterized by the highest absolute percentage of difference with iGFR in the two types of diabetes. The MDRD and rMDRD equations were biased in type 1 ($r = −0.57$, $P < 0.001$) and type 2 ($r = −0.64$, $P < 0.001$) diabetic subjects, whereas the MCQ equation was biased only in type 2 diabetic subjects ($r = −0.26$, $P < 0.01$). The Cys-eGFR (Rule) equation alone was biased only in type 2 diabetic subjects ($r = −0.28$, $P < 0.01$). The influence of lean mass in cystatin-C equations has been demonstrated especially in patients with extreme body composition (26); the lack of systematic significant observed difference in the cys-eGFR formulae suggests that cystatin-C is unaffected by the body composition of our subgroups of diabetic subjects.

Prediction of GFR according to GFR tertiles

The performances of all estimations are presented in Table 2. All of the predictive equations overestimated low GFR, and the MDRD, rMDRD, and Cys-eGFR (Rule) equations also underestimated high GFR (−21, −25, and −11.5%, respectively). In the medium GFR tertile, only the MDRD and Cys-eGFR (Arnal-Dade) equations did not significantly differ from iGFR. The Cys-eGFR (Arnal-Dade) equation gave *1*) a correct estimation of GFR in both the high and medium tertiles and *2*) one of the lowest (+25%) overestimations in the low tertile.

Prediction of CKD progression

The 20 subjects who underwent a second evaluation were mainly men ($n = 16$) with type 2 diabetes ($n = 13$), having an iGFR change of −8.5 ± 17.9 ml/min per 1.73 m^2. Their mean initial age was 68 ± 10 years and BMI 25.8 ± 4.1 kg/m^2. Serum creatinine and cystatin-C significantly increased after 2 years ($P < 0.001$ and $P < 0.003$, respectively [viewable in an online appendix, available at http://dx.doi.org/10.2337/dc06-2637]). The characteristics of the eight tested formulae with the mean difference in their changes are shown in Appendix 1. The relations between measured and estimated renal function changes are depicted in Fig. 1 (completed in Appendix 2). The rate of iGFR change was significantly correlated with its estimations by the MCQ equation ($r = 0.45$, $P < 0.05$) (Fig. 1*C*) and by the four Cys-eGFR equations ($P < 0.005$) [$r = 0.60$ for Cys-eGFR (Arnal-Dade) (Fig. 1*D*); 0.61 for Cys-eGFR (MacIsaac) and Cys-eGFR (Tan) and 0.62 for Cys-eGFR (Rule) (all three viewable in Appendix 2)], whereas the correlation with the Cockcroft-Gault ($r = 0.35$) (Fig. 1*A*), MDRD ($r = 0.41$) (Fig. 1*B*), and rMDRD ($r = 0.41$) (Appendix 2*A*) equations did not reach significance. The iGFR changes correlated with the trend in 100/cystatin-C ($r = 0.61$, $P < 0.005$) (Fig. 1*E*), whereas the correlation with the trend in 100/creatinine did not reach significance ($r = 0.41$).

CONCLUSIONS

— While conventional GFR predictive equations are known to lack predictive power, the diabetic population represents a specific challenge. The effects of hyperglycemia (6) and BMI-related bias (5) have led most investigators to avoid using the Cockcroft-Gault equation in recent reports (27,28). As the Cockcroft-Gault equation calculates GFR proportional to body weight, it considerably overestimates obese subjects. This tendency is likely to increase because the mean BMI of subjects entering dialysis is increasing twice as fast as the BMI of the U.S. general population, as recently reported (29). Because a high BMI seems to be an important risk factor for end-stage renal disease (30), this error is unacceptable. Replacing the Cockcroft-Gault with the MDRD equation is not necessarily the solution. Although diabetic nephropathy is quite a common cause of CKD, most diabetic subjects retain normal renal function during their lifetime. High GFR may also be present at the earliest stage of diabetic nephropathy. Owing to its underestimation of normal and high GFR (14,19), the MDRD equation is not adequate, so new formulae are required.

Although this work confirms that some cystatin-based equations have a predictive potential similar to those of the Cockcroft-Gault and MDRD equations in diabetic subjects (19), the use of complicated or expensive tools (cystatin-C determination is nowadays 10-fold more expensive than creatinine determination) is not justified unless they demonstrate a clear advantage; however, if measuring

Table 1—*Results of predictive equations in the entire diabetic population* (n = *124) divided into formulae related to creatinine and cystatin*

	Creatinine-based formula			
	CG	MDRD	rMDRD	MCQ
Mean ± SD (ml/min per 1.73 m^2)	63.3 ± 37.7	51.4 ± 24.3	48.3 ± 22.9	60.9 ± 32.2
Range	16–208	10–123	10–116	10–153
Correlation coefficient with iGFR	0.79	0.87	0.87	0.87
Difference with iGFR (nonparametric)	<0.001	<0.05	<0.001	<0.001
Median absolute percent difference with iGFR	45.2 ± 52.0	27.7 ± 24.6	26.2 ± 21.7	31.9 ± 34.4
Bland-Altman				
r	+0.10	−0.62	−0.68	−0.18
P	NS	<0.001	<0.001	<0.05
2 SD	69.0	36.4	37.4	34.8
Accuracy (%)				
Within ± 15	29	33	36	34
Within ± 30	50	68	64	62
Within ± 50	72	89	89	82
AUC*				
iGFR <60 ml/min per 1.73 m^2 (*n* = 76)	0.87†	0.94	0.94	0.94
Sensitivity	88.2	85.5	85.5	81.6
Specificity	68.7	87.5	87.5	91.7
Criterion	≤67.2	≤53.4	≤58.3	≤62.3
AUC				
iGFR <30 ml/min per 1.73 m^2 (*n* = 36)	0.89	0.97	0.97	0.95
Sensitivity	75.0	94.4	94.4	88.9
Specificity	92	92	92	92
Criterion	≤38.3	≤41.8	≤39.3	≤45.1

	Cystatin-based formula			
	Arnal-Dade	MacIsaac	Tan	Rule
Mean ± SD (ml/min per 1.73 m^2)	55.7 ± 34.7	66.1 ± 32.9	63.8 ± 33.1	52.4 ± 31.6
Range	6–195	11–172	9–170	7–166
Correlation coefficient with iGFR	0.76	0.82	0.82	0.81
Difference with iGFR (nonparametric)	NS	<0.001	<0.001	<0.01
Median absolute percent difference with iGFR	31.2 ± 33.0	42.9 ± 45.4	38.3 ± 41.0	27.1 ± 27.4
Bland-Altman				
r	−0.02	−0.12	−0.11	−0.18
P	NS	NS	NS	<0.05
2 SD	47.8	40.6	40.6	41.4
Accuracy (%)				
Within ± 15	31	32	30	39
Within ± 30	64	55	59	67
Within ± 50	87	72	77	89
AUC*				
iGFR <60 ml/min per 1.73 m^2 (*n* = 76)	0.95	0.96	0.96	0.96
Sensitivity	90.8	92.1	92.1	92.1
Specificity	89.6	87.5	87.5	87.5
Criterion	≤61.9	≤71.8	≤69.5	≤55.7
AUC				
iGFR <30 ml/min per 1.73 m^2 (*n* = 36)	0.93	0.94	0.94	0.94
Sensitivity	88.9	80.6	80.6	80.6
Specificity	85.2	94.3	94.3	94.3
Criterion	≤35.4	≤42.4	≤40.0	≤29.5

For the Bland-Altman comparison, *r* and *P* represent the correlation and its specificity between [average (tested equation + iGFR)] and (tested equation − iGFR). iGFR = 56.1 ± 35.3 ml/min per 1.73 m^2 (range 8–164). *For the ROC curves for the estimated equations, AUC = area under the ROC curves. †$P < 0.05$ vs. other areas under the curve. CG, Cockroft-Gault.

cystatin-C proves to be a simple and accurate way of detecting CKD, its current use should lead to a significant reduction in its cost. Many studies have demonstrated the interest of cystatin-C as a marker of renal function in diabetic patients, but fewer investigations have compared various CysC-eGFR formulae with updated creatinine-based formulae, espe-

Table 2—*Performance of predictive equations*

	Low GFR tertile	Medium GFR tertile	High GFR tertile
n	41	42	41
iGFR	21.4	49.8	97.2
Range	8–34	34–67	67–164
Creatinine-based formula			
CG	35.6	56.1	98.4
Range	16–80	23–102	37–208
r	0.37*	0.25	0.59†
P vs. iGFR	†	‡	NS
MDRD	28.2	49.0	77.0
Range	10–76	28–81	42–123
r	0.59†	0.39*	0.65†
P vs. iGFR	†	NS	†
rMDRD	26.5	46.1	72.5
Range	10–71	26–77	39–116
r	0.60†	0.39*	0.65†
P vs. iGFR	†	‡	†
MCQ	29.9	57.6	95.4
Range	10–80	26–94	56–153
r	0.56†	0.41*	0.60†
P vs. iGFR	†	†	NS
Cystatin-based formula			
Arnal-Dade	26.7	49.6	91.1
Range	6–70	21–81	49–195
r	0.62†	0.21	0.30‡
P vs. iGFR	†	NS	NS
MacIsaac	36.4	60.9	101.3
Range	11–77	33–133	67–172
r	0.64†	0.27	0.42*
P vs. iGFR	†	†	NS
Tan	33.9	58.5	99.1
Range	9–75	30–131	65–170
r	0.64†	0.27	0.42*
P vs. iGFR	†	*	NS
Rule	25.2	46.1	86.0
Range	7–61	19–120	51–166
r	0.62†	0.24	0.41*
P vs. iGFR	‡	‡	*

‡$P < 0.05$; *$P < 0.01$; †$P < 0.001$. CG, Cockroft-Gault.

cially to follow the trends of renal function. To our knowledge, this study is the first to incorporate a comparison of four Cys-eGFR with four creatinine-based GFR equations.

For our patients, all creatinine- or cystatin-based formulae were more accurate than the Cockcroft-Gault equation in diagnosing renal failure, as demonstrated by areas under the ROC curves. Based on precision (calculated as the absolute percentage variation from iGFR), the most accurate tool for estimating GFR in renally insufficient diabetic patients remains the MDRD (similar to the rMDRD) and the Cys-eGFR (Rule) formulae. The precision of the MCQ and Cys-eGFR (Arnal-Dade) were slightly lower than with the MDRD and Rule equations. Of particular interest, cystatin-C–based formulae did not underestimate high GFR [except for Cys-eGFR (Rule)], in contrast with the MDRD (−21%) and rMDRD (−25%) equations, which is as expected because they were not biased.

Obtaining a low bias seems crucial in determining CKD progression; a predictive formula that underestimates normal GFR by −20% (42–123 ml/min per 1.73 m^2) and overestimates low GFR by +33% (10–76 ml/min per 1.73 m^2) (as did the MDRD equation) will underestimate GFR change, as recently reported (10,14). We found no significant improvement in prediction by using the reexpressed MDRD equation. The better value of the MDRD equation at more advanced CKD stages reported elsewhere (11) was not unexpected, as MDRD equation performance improves when GFR declines. The absence of bias according to the GFR level is an obvious advantage for determining CKD progression with Cys-eGFR. Cys-eGFR (Arnal-Dade) was especially interesting as it gave *1*) a correct estimation of GFR in both high and medium tertiles and *2*) one of the lowest (+25%) overestimations in the low tertile. The creatinine-based MCQ gave an intermediate performance, as could be expected because it has been established from the results of a mixed population that was not limited to renally insufficient subjects (12), unlike the MDRD equation.

Although the follow-up involved only 20 patients, significant results obtained in a small cohort suggest that better accuracy would be achieved in a larger one. Our results are in line with those of Perkins et al. (14), who reported better agreement of 100/cystatin than of 100/creatinine with GFR decline in 30 type 2 diabetic patients with high baseline GFR (>120 ml/min per 1.73 m^2). We extend this finding to renally insufficient diabetic patients, with mean GFR changing about −4 ml/min per 1.73 m^2, as usually reported (10,11); moreover, it appears that changes in GFR as estimated by 100/cystatin predicted changes in isotopic GFR equally as well as the cystatin prediction equations. These results, obtained in 20 variable patients, are not sufficient to affirm that the less-biased Cys-eGFR (Arnal-Dade) equation can estimate changes in GFR on an individual basis. However, our findings, like those of others, point to the usefulness of CysC as a marker of GFR and should lead to larger population studies with further validation. Finally, any calibration differences between the Dade-Behring BNII nephelemeter used in this study and other cystatin-C assays can lead to inaccurate GFR estimates, a well-described problem with creatinine equations. Further work is needed to improve *1*) cystatin-C measurement by harmonization of methods and calibration, as in recent work concerning standardization of creatinine (7), and *2*) the precision of cystatin-C–derived formulae.

Besides estimating renal function, it would be of interest to measure serum cystatin-C in diabetic subjects because cystatin-C predicts increased cardiovascular risks that may be missed by measurement of kidney function using serum

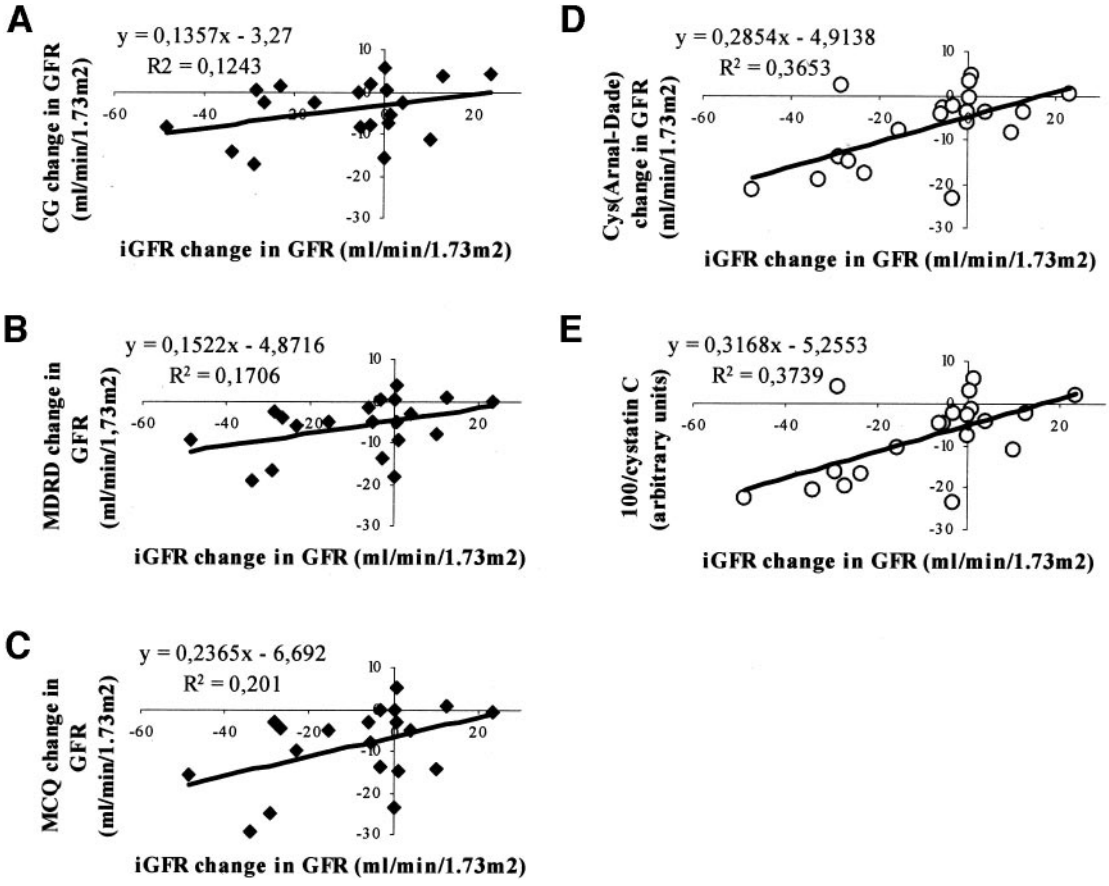

Figure 1— *Correlation between measured change (between initial measurements and those at a 2-year follow-up) in renal function as determined from iGFR and five estimated formulae in 20 diabetic patients based on creatinine (Cockcroft-Gault [CG] [A], MDRD [B], and MCQ [C]; $P < 0.05$) or based on cystatin-C (according to the Arnal-Dade Behring formula [D] [refs. 16 and 17] and according to the 100/cystatin-C formula [E] published by Perkins et al. [ref. 14]). Points in the lower-right quadrant of a plot represent false-positive results for renal function for the measured iGFR (iGFR > 0 ml/min per 1.73 m^2) and indicate an underestimation of renal change. Points in the upper-left quadrant of a plot represent false-negative results for renal function change for the measured iGFR (iGFR < 0 ml/min per 1.73 m^2).*

creatinine (31). Our work mainly shows that it is promising to evaluate CKD progression in diabetic subjects with various Cys-eGFR equations, in agreement with the point of view that specific prediction formulae could be used for particular patient groups (32). Disease-specific formulae have to be restricted to specific medical prescription owing to the frequent lack of clinical information concerning referred patient samples in laboratories (16). This study provides a kinetic basis for previous static work reporting that serum cystatin-C is valuable in detecting early or mild diabetic nephropathy (33) for screening early impairment of renal function at a time when active management is important. The fact that the highest and medium GFRs were well estimated and that the lowest GFRs were less overestimated by the Cys-eGFR (Arnal-Dade) in particular means, in particular, that it is possible to obtain a global estimation of the change (high GFR becoming a low GFR) close to that measured by iGFR. If the cost of determining GFR by cystatin-C is prohibitive or unavailable, then the MCQ seems to be a good alternative to the MDRD for the most obese and/or poorly controlled patients, whose Cockcroft-Gault equation would otherwise be imprecise and biased.

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