Longitudinal Changes in Estimated and Measured GFR in Type 1 Diabetes

Ian H. de Boer,* Wanjie Sun,† Patricia A. Cleary,† John M. Lachin,† Mark E. Molitch,‡ Bernard Zinman,§ and Michael W. Steffes,‖ for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group

*Division of Nephrology and Kidney Research Institute, University of Washington, Seattle, Washington; †The Biostatistics Center, George Washington University, Rockville, Maryland; ‡Division of Endocrinology, Northwestern University, Chicago, Illinois; §Samuel Lunenfeld Research Institute, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada; and ‖Department of Laboratory Medicine and Pathology, University of Minnesota, Minneapolis, Minnesota

ABSTRACT

Estimation of GFR from serum concentrations of creatinine and cystatin C has been refined using cross-sectional data from large numbers of people. However, the ability of the improved estimating equations to identify changes in GFR within individuals over time has not been rigorously evaluated, particularly within the normal range of GFR. In cross-sectional and longitudinal analyses of 1441 participants in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study with type 1 diabetes, we compared GFR estimated from creatinine ($eGFR_{Cr}$), cystatin C ($eGFR_{Cys}$), or both ($eGFR_{Cr+Cys}$) with iothalamate GFR (iGFR), including changes in each over time. Mean (SD) iGFR was 122.7 (21.0) ml/min per 1.73 m^2. In cross-sectional analyses, $eGFR_{Cr+Cys}$ estimated iGFR with the highest correlation (r=0.48 versus 0.39–0.42), precision, and accuracy. In longitudinal analyses, change in $eGFR_{Cr+Cys}$ best estimated change in iGFR; however, differences between estimates were small, and no estimate accurately classified change in iGFR. Over a median 23 years of follow-up, mean rate of change in eGFR was similar across estimates of $eGFR_{Cr}$, $eGFR_{Cys}$, and $eGFR_{Cr+Cys}$ (−1.37, −1.11, and −1.29 ml/min per 1.73 m^2 per year, respectively). Associations of BP and hemoglobin A1c with change in eGFR were strongest for $eGFR_{Cys}$ and $eGFR_{Cr+Cys}$. Together, these results suggest that the addition of cystatin C to creatinine to estimate GFR may improve identification of the causes and consequences of GFR loss in type 1 diabetes, but may not meaningfully improve the tracking of GFR in clinical care.

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Reduced GFR leads to ESRD and metabolic complications of CKD. Estimation of GFR from serum concentrations of creatinine and cystatin C has been refined using cross-sectional data from large numbers of people.[1] As a result, individuals with reduced GFR and increased risk of adverse clinical outcomes can be more accurately identified within populations.[1,2] However, the ability of the improved estimating equations to identify changes in GFR within individuals over time has not been rigorously evaluated, particularly within the normal range of GFR (≥60 ml/min per 1.73 m^2). Detecting changes in GFR within individual patients is important to develop, evaluate, and implement strategies to prevent CKD.

Identifying changes in GFR within individuals may be particularly useful in type 1 diabetes. Patients with type 1 diabetes often have GFR higher than normal early in the course of disease (hyperfiltration).[3] Over many years of follow-up, some of these patients develop overtly reduced GFR (<60 ml/min per 1.73 m^2).[4,5]

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Correspondence: Dr. Ian H. de Boer, Kidney Research Institute and Division of Nephrology, University of Washington, Box 359606, 925 9th Avenue, Seattle, WA 98104. Email: deboer@u.washington.edu

Tracking GFR during this interval is challenging, because large changes in GFR may cause only small changes in serum creatinine and cystatin C concentrations. In addition, it is now clear that macroalbuminuria (urine albumin excretion≥300 mg/d) is not a sensitive marker of early GFR loss. Rather, some patients lose substantial GFR with microalbuminuria (30–299 mg/d) or even normoalbuminuria (<30 mg/d).[5–7]

In this study, we evaluated longitudinal changes in estimated and measured GFR among participants in the Diabetes Control and Complications Trial (DCCT) and its observational extension, the Epidemiology of Diabetes Interventions and Complications (EDIC) study. The DCCT/EDIC study included participants with type 1 diabetes who had normal or high GFR at baseline.[8,9] In this population, we used two complementary approaches to compare GFR estimated from serum concentrations of creatinine and cystatin C combined with GFR estimated from either creatinine or cystatin C alone. First, we compared each GFR estimate with GFR measured as the urinary clearance of ^{125}Iiothalamate. We hypothesized that change in GFR estimated from serum creatinine and cystatin C together would most accurately and precisely correlate with, and most accurately classify, change in measured GFR. Second, we tested associations of known risk factors for GFR loss with change in each GFR estimate over long-term follow-up (median of 23 years). We hypothesized that higher BP and hemoglobin A1c would be most strongly associated with change in GFR estimated from creatinine and cystatin C combined. Substantial improvements in accuracy, precision, classification, and association would suggest that the addition of cystatin C to creatinine to estimated GFR may improve the tracking of GFR within its normal range in type 1 diabetes.

RESULTS

Cross-Sectional Comparisons of Estimated and Measured GFR

The 1441 participants in the DCCT had a mean age of 26.8 years and mean diabetes duration of 5.9 years at baseline (Table 1). Mean or median values of albumin excretion rate (AER), creatinine clearance, and serum creatinine and cystatin C concentrations were in the normal range.

Of 1441 participants, 1334 (93%) participants had at least one measurement of iothalamate GFR (iGFR) during the DCCT and were included in cross-sectional comparisons of estimated and measured GFR. These 1334 participants contributed a total of 2592 iGFR measurements with concurrent measurements of creatinine clearance and serum creatinine and cystatin C concentrations: 357, 694, and 283 participants contributed sets of measurements at one, two, and three visits during the DCCT, respectively.

Mean (SD) iGFR was 122.7 (21.0) ml/min per 1.73 m^2. Mean values of each GFR estimate and creatinine clearance were similar, with creatinine clearance and GFR estimated from creatinine having the smallest bias (Table 2). All measures tended to overestimate the iGFR in the low normal range (<90 ml/min per 1.73 min^2) and underestimate the iGFR in the high range (≥130 ml/min per 1.73 min^2) (Figure 1). Compared with iGFR, variance was higher for creatinine clearance and lower for other GFR estimates.

Correlations of creatinine clearance and GFR estimated from creatinine ($eGFR_{Cr}$), cystatin C ($eGFR_{Cys}$), or both ($eGFR_{Cr+Cys}$) with iGFR ranged from 0.36 to 0.48, and they were highest for $eGFR_{Cr+Cys}$ (Table 2). Precision and accuracy were least favorable for creatinine clearance and most

Table 1. Participant characteristics at DCCT baseline

Characteristic	All Participants	By Number of iGFR Measurements		
		Participants with Two or Three iGFR Measurements	Participants with One iGFR Measurement	Participants with No iGFR Measurements
n	1441	977	357	107
Age (yr)	26.8 (7.1)	27.2 (6.9)	25.7 (7.5)	26.6 (7.3)
Women	680 (47.2%)	422 (43.2%)	195 (54.6%)	63 (58.9%)
Caucasian race	1390 (96.4%)	941 (96.3%)	346 (96.9%)	103 (96.3%)
Duration of diabetes (yr)	5.9 (4.2)	5.5 (4.0)	6.7 (4.4)	6.5 (4.3)
DCCT treatment assignment				
Intensive	711 (49.3%)	486 (49.7%)	174 (48.7%)	51 (47.7%)
Conventional	730 (50.7%)	491 (50.3%)	183 (51.3%)	56 (52.3%)
Active smoking	304 (21.1%)	204 (20.9%)	77 (21.6%)	23 (21.5%)
Body mass index (kg/m^2)	23.5 (2.8)	23.6 (2.8)	23.2 (2.8)	23.3 (3.0)
Systolic BP (mmHg)	114.5 (11.4)	114.5 (11.3)	114.5 (11.3)	114.8 (12.0)
Diastolic BP (mmHg)	73.0 (8.5)	73.3 (8.3)	72.5 (8.8)	72.9 (8.4)
Hemoglobin A1c	9.1 (1.6)	9.0 (1.6)	9.2 (1.7)	9.2 (1.6)
Albumin excretion rate (mg/d)	11.5 (7.2, 18.7)	10.1 (5.8, 17.2)	11.5 (5.8, 23.0)	11.5 (7.2, 21.6)
Creatinine clearance (ml/min per 1.73 m^2)	128.4 (29.8)	128.2 (28.9)	129.0 (32.2))	128.1 (29.4)
Serum creatinine (mg/dl)	0.68 (0.14)	0.69 (0.13)	0.65 (0.15)	0.65 (0.15)
Serum cystatin C (mg/L)	0.62 (0.10)	0.64 (0.10)	0.59 (0.08)	0.58 (0.07)

Cell contents are mean (SD), *N* (%), or median (IQR) for albumin excretion rate.

Table 2. Cross-sectional correlations of eGFR and creatinine clearance with measured GFR evaluated using 2592 sets of measurements among 1334 participants

Variable	iGFR	Creatinine Clearance	$eGFR_{Cr}$	$eGFR_{Cys}$	$eGFR_{Cr+Cys}$
Summary statistics					
Mean (SD), ml/min per 1.73 m^2	122.7 (21.0)	121.9 (26.9)	119.3 (13.0)	113.6 (15.8)	117.6 (14.1)
Median (quartile 1, quartile 3), ml/min per 1.73 m^2	121.5 (109.8, 134.0)	119.0 (106.0, 134.0)	119.6 (112.1, 127.3)	116.4 (105.7, 124.1)	118.4 (109.2, 126.7)
Comparisons with iGFR					
Pearson *r*		0.36	0.38	0.40	0.47
Spearman *r*		0.42	0.39	0.42	0.48
Median difference (ml/min per 1.73 m^2)		1.1	2.6	7.4	4.3
Median percent difference		0.9	2.2	6.1	3.5
IQR of the difference (ml/min per 1.73 m^2)		27.2	22.9	23.7	21.7
IQR of the percent difference		22.8	18.4	18.6	17.5
P_{30} (%)		87.8	95.0	93.2	96.0
P_{20} (%)		73.6	82.5	79.6	85.3

The median difference between iGFR and creatinine clearance or eGFR was calculated on the natural and relative scales as measures of bias, with lower values reflecting lower bias. The IQR of the difference between iGFR and creatinine clearance or eGFR was calculated on the natural and relative scales as measures of precision, with lower values reflecting greater precision. The proportion of participants with creatinine clearance or eGFR values within 30% or 20% of iGFR (P_{30} or P_{20}, respectively) were calculated as measures of accuracy, with higher numbers reflecting greater accuracy.

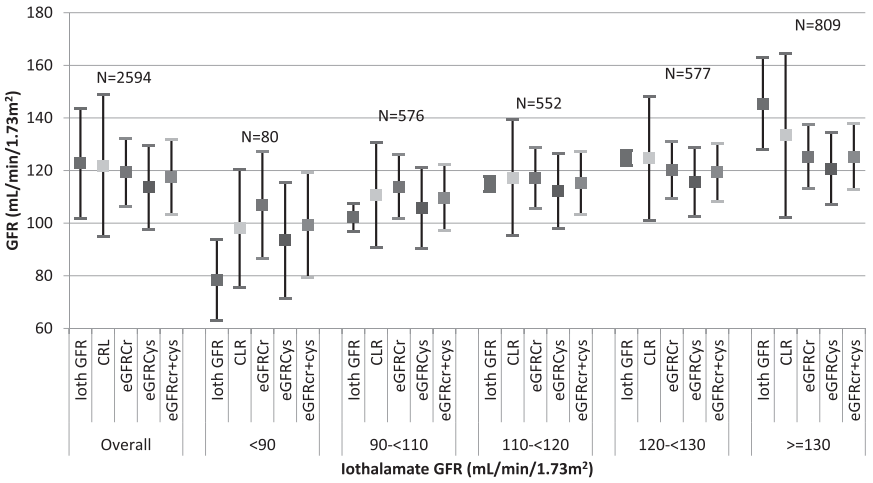

Figure 1. Distributions of iGFR (ioth GFR), $eGFR_{Cr}$, $eGFR_{Cys}$, $eGFR_{Cr+Cys}$, and creatinine clearance (CLR) stratified by level of iGFR. Data points and bars represent median and interquartile range.

favorable for $eGFR_{Cr+Cys}$. However, differences among GFR estimates were small. For example, the interquartile range (IQR) of the difference between estimated GFR (eGFR) and iGFR was 21.7 versus 22.9 ml/min per 1.73 m^2 for $eGFR_{Cr+Cys}$ versus $eGFR_{Cr}$, and the proportion of participants with eGFR values within 20% of iGFR (P_{20}) was 85.3% versus 82.5%, respectively.

Longitudinal Comparisons of Changes in eGFR and Measured GFR

During the DCCT, 977 participants contributed more than one set of iGFR, creatinine clearance, and serum creatinine and cystatin C measurements. Baseline characteristics of these 977 participants were similar to those characteristics of the full DCCT population (Table 1).

The 977 participants contributed a total of 1260 time intervals bracketed by GFR measurements. Mean duration of the intervals was 3.1 years (range=1–6 years, IQR=2–4 years). Mean (SD) difference in iGFR over the intervals was −4.1 (20.4) ml/min per 1.73 m^2. Using change in iGFR as reference, bias was small for change in each GFR estimate and change in creatinine clearance, with the smallest bias for GFR estimates that included cystatin C (Table 3). Compared with change in iGFR, the variance of change in creatinine clearance was higher, and the variances of changes in GFR estimates were lower.

Correlations of changes in creatinine clearance and GFR estimates with change in iGFR ranged from 0.11 to 0.18. Within this range, correlation was greater for GFR estimates that included cystatin C compared with $eGFR_{Cr}$. Precision was also poor for creatinine clearance and each GFR estimate. For each, the IQR of the difference between change in eGFR and change in iGFR (22.6–37.6 ml/min per 1.73 m^2) was larger than the IQR of change in iGFR itself (20.9 ml/min per 1.73 m^2). Accuracy, defined as the difference in change in eGFR versus change in iGFR less than 15 ml/min per 1.73 m^2, was good for creatinine clearance and each GFR estimate. However, the median absolute value of this difference was large (11.4–18.8 ml/min per 1.73 m^2) compared with median change in iGFR (−3.0 ml/min per 1.73 m^2).

Table 3. Longitudinal correlations of changes in eGFR and measured GFR evaluated using 1260 time intervals among 977 participants

Variable	Change in iGFR	Change in Creatinine Clearance	Change in $eGFR_{Cr}$	Change in $eGFR_{Cys}$	Change in $eGFR_{Cr+Cys}$
Summary statistics					
Mean (SD), ml/min per 1.73 m^2	−4.1 (20.4)	−2.7 (32.3)	−4.2 (11.2)	−3.3 (12.4)	−3.9 (10.4)
Median (quartile 1, quartile 3), ml/min per 1.73 m^2	−3.0 (−14.1, 6.8)	−2.0 (−17.0, 14.0)	−2.7 (−9.8, 2.4)	−3.2 (−9.6, 3.9)	−3.8 (−9.7, 2.5)
Comparisons with iGFR					
Pearson *r*		0.15	0.12	0.15	0.18
Spearman *r*		0.15	0.11	0.16	0.17
Median difference (ml/min per 1.73 m^2)		−1.3	0.7	−0.1	0.4
IQR of the difference (ml/min per 1.73 m^2) with 95% CI		37.6 (35.4 to 39.9)	23.7 (21.9 to 25.3)	23.4 (21.6 to 25.1)	22.6 (21.3 to 24.3)
Proportion of values within 15 ml/min per 1.73 m^2 of iGFR (%)		48.6	81.2	77.3	83.8
Median absolute value of the difference (ml/min per 1.73 m^2)		18.8 (8.5, 32.7)	11.8 (5.7, 20.8)	11.6 (5.5, 21.5)	11.4 (5.5, 20.1)

Changes were evaluated over a mean interval of 3.1 years (range=1–6 years, IQR=2–4 years). The median difference between change in iGFR and change in creatinine clearance or eGFR was calculated as a measure of bias, with lower values reflecting lower bias. The IQR of the difference between change in iGFR and change in creatinine clearance or eGFR was calculated as a measure of precision, with lower values reflecting greater precision and 95% CIs listed in parentheses. The proportion of participants with change in creatinine clearance or eGFR values within 15 ml/min per 1.73 m^2 of change in iGFR was calculated as a measure of accuracy, with higher numbers reflecting greater accuracy. The median of the absolute value of difference between change in iGFR and change in creatinine clearance or eGFR was calculated as a measure of precision and accuracy, with lower values reflecting better performance.

Changes in iGFR<-15 and >15 ml/min per 1.73 m^2 were observed for 297 and 160 intervals, respectively. Categorized changes in GFR estimates and creatinine clearance did not reliably agree with these changes in iGFR (Table 4).

Long-Term Longitudinal Changes in eGFR

Comparisons of long-term changes in eGFR without reference to iGFR were performed among all 1441 DCCT/EDIC participants. In this population, the median duration of combined DCCT/EDIC follow-up, including only study visits with simultaneous measurement of serum creatinine and serum cystatin C, was 23 years (range=1–27 years). The median number of follow-up measurement sets per participant was 10 (range=1–13). Mean rates of change in eGFR (in milliliters per minute per 1.73 m^2 per year) were −1.37 (95% confidence interval [95% CI], −1.41 to −1.33) for $eGFR_{Cr}$, −1.11 (95% CI, −1.16 to −1.06) for $eGFR_{Cys}$, and −1.29 (95% CI, −1.33 to −1.24) for $eGFR_{Cr+Cys}$ (Figure 2).

Baseline age≥30 years, higher time-updated systolic BP, higher mean DCCT hemoglobin A1c, and greater time-updated AER were each associated with more rapid loss of eGFR over time, regardless of the method used to estimate GFR (Table 5). However, for age, systolic BP, and particularly hemoglobin A1c, magnitudes of association were greater when $eGFR_{Cys}$ or $eGFR_{Cr+Cys}$ was used to track GFR compared with $eGFR_{Cr}$.

DISCUSSION

In a large type 1 diabetes population with normal or high measured GFR, a validated equation using cystatin C and creatinine together estimated GFR and its change over time with modestly greater precision and accuracy than an equation based on creatinine alone. In addition, associations of known risk factors (higher BP and hemoglobin A1c) with GFR loss were stronger when GFR was estimated using cystatin C and creatinine together versus creatinine alone. These results suggest that the addition of cystatin C to creatinine to estimate GFR may improve the identification of causes and consequences of GFR loss. However, the incremental value of adding cystatin C to creatinine to estimate GFR was subtle and did not improve classification of participants with regard to GFR loss over time. These findings suggest that incorporating cystatin C into the estimation of GFR may not meaningfully improve the tracking of GFR in clinical care.

In cross-sectional analyses, compared with results from the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) consortium,[1] our estimates of GFR generally had greater accuracy (range of P_{20}=79.6%–85.3% versus 67.1%–77.2%) and less precision (IQRs of differences=21.7–23.7 versus 13.4–16.4 ml/min per 1.73 m^2) relative to measured GFR. This finding likely reflects the high range of GFR in our study (mean=122 versus 70 ml/min per 1.73 m^2). With high GFR, accuracy seems improved, because differences are evaluated on the relative scale; additionally, precision is reduced, because small differences in serum concentrations of creatinine and cystatin C yield large differences in eGFR. Despite these differences, $eGFR_{Cr}$ performed reasonably well in both studies, and $eGFR_{Cr+Cys}$ offered marginal improvements in precision and accuracy. Smaller studies of people with diabetes have also suggested improved estimation of measured GFR using cystatin C.[10,11] Our data, therefore, confirm reasonable

Table 4. Agreement of change in eGFR versus change in measured GFR evaluated using 1260 time intervals among 977 participants

Estimate of Change in GFR	Change in iGFR (ml/min/1.73 m^2)				
	<−15 (*N*=297)	−15 to +15 (*N*=800)	>15 (*N*=160)	Weighted κ	Diagonal Agreement (%)
Change in creatinine clearance (ml/min/1.73m^2)				0.08	43.3
<−15	106 (8.4%)	211 (16.8%)	34 (2.7%)		
−15 to +15	143 (11.4)	392 (31.2%)	79 (6.3%)		
>15	48 (3.8%)	197 (15.7%)	47 (3.7%)		
Change in $eGFR_{Cr}$ (ml/min/1.73m^2)				0.03	57.8
<−15	46 (3.7%)	104 (8.3%)	20 (1.6%)		
−15 to +15	241 (19.1%)	671 (53.3%)	131 (10.4%)		
>15	10 (0.8%)	26 (2.1%)	10 (0.8%)		
Change in $eGFR_{Cys}$ (ml/min/1.73m^2)				0.06	57.3
<−15	54 (4.3%)	106 (8.4%)	13 (1.0%)		
−15 to +15	220 (17.5%)	653 (51.9%)	134 (10.6%)		
>15	23 (1.8%)	42 (3.3%)	14 (1.1%)		
Change in $eGFR_{Cr+Cys}$ (ml/min/1.73m^2)				0.04	58.9
<−15	47 (3.7%)	87 (6.9%)	10 (0.8%)		
−15 to +15	240 (19.1%)	687 (54.6%)	144 (11.4%)		
>15	10 (0.8%)	27 (2.1%)	7 (0.6%)		

Cell contents are *N* (%), except for weighted κ-statistics and diagonal agreement proportions.

performance of creatinine-based GFR estimates in type 1 diabetes as well as a modest improvement with the added use of cystatin C.

In contrast, in longitudinal analyses, change in GFR estimates did not compare favorably with change in iGFR. Mean (SD) change in iGFR was −4.1 (20.4) ml/min per 1.73 m^2 over a mean interval duration of 3.1 years. Change in each GFR estimate reflected change in iGFR with little bias, but the variance in change of each GFR estimate was substantially smaller than the variance of change in iGFR; also, correlation and precision were poor. For example, the IQR of the difference between change in $eGFR_{Cr+Cys}$ and change in iGFR was 22.6 ml/min per 1.73 m^2, which is larger than the IQR of change in iGFR itself (20.9 ml/min per 1.73 m^2). In addition, the median absolute value of this difference was 11.4 ml/min per 1.73 m^2, which is substantially larger than the median change in iGFR (−3.0 ml/min per 1.73 m^2). These data suggest that changes in eGFR over a clinically relevant period of approximately 3 years may not reliably reflect changes in iGFR within its normal range.

Our poor longitudinal correlations of change in eGFR versus measured GFR contrast with the correlations of a study of 30 Pima Indians with type 2 diabetes.[12] Each of the Pima participants contributed four to eight longitudinal measurements of iGFR, creatinine, and cystatin C over 4 years of follow-up. The slope of the reciprocal of cystatin C correlated strongly with the slope of iGFR (Spearman r=0.77 versus 0.32 for GFR estimated from serum creatinine). All participants had albuminuria at baseline, and mean change in iGFR was −4.4% per year. In this setting, participants seemed to have a relatively large and steady rate of GFR loss that was well approximated using linear slopes, and the use of such slopes likely smoothed out variability in individual GFR estimates and measurements. Similar results were observed among 85 Australian subjects with type 1 diabetes who underwent an average of 5.6 iGFR measurements. In this study, change in $eGFR_{Cys}$ identified a subset of 19 decliners (change in iGFR<−3.3 ml/min per 1.73 m^2 per year) with sensitivity superior to $eGFR_{Cr}$.[13] In the subset of decliners, $eGFR_{Cys}$ also estimated the rate of change (slope) with reduced bias.

We have observed nonlinear declines in GFR in the DCCT/EDIC population,[14] and few DCCT/EDIC participants had more than two iGFR measurements. Therefore, we evaluated windows bracketed by two iGFR measurements rather than slopes. Inherent variability in the smaller number of GFR measurements and estimates per participant combined with slow actual GFR loss over time likely contributed to weak correlations. It is important to note that iGFR, like any physiologic parameter, is measured with error.[15] In addition, GFR can change over minutes to hours because of factors such as position and diet. As a result, intraindividual variation in iGFR can be large in the absence of a systematic trend. Clearly, replicating such noise accurately and precisely may be neither feasible nor desirable. Our data highlight the substantial intraindividual variability in eGFR and measured GFR within the normal range and the difficulty of identifying meaningful short-term GFR changes for individuals.

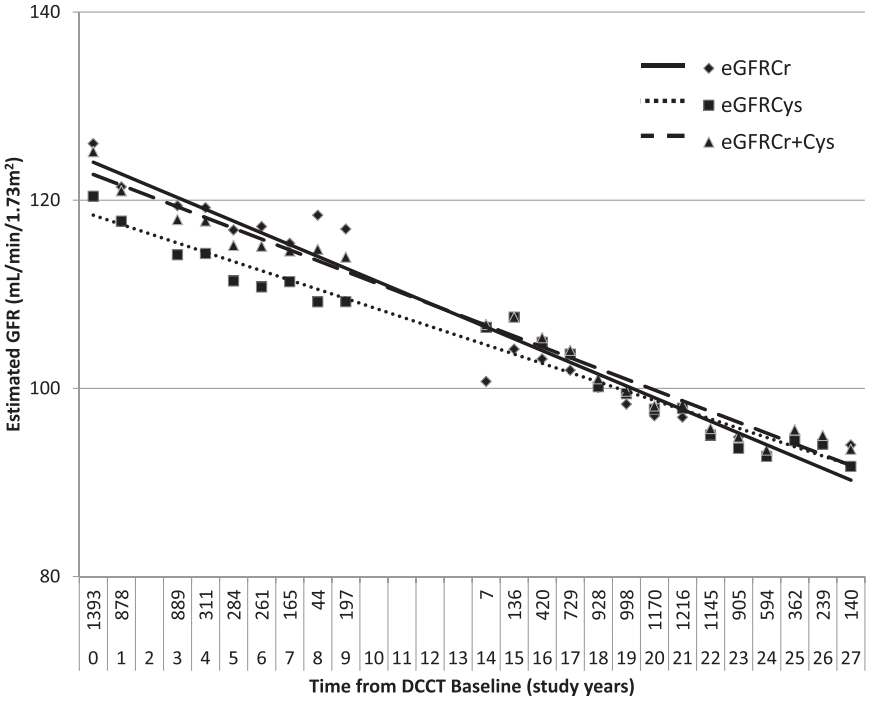

Figure 2. Mean eGFR over time during combined DCCT/EDIC follow-up. GFR was estimated using $eGFR_{Cr}$, $eGFR_{Cys}$, or $eGFR_{Cr+Cys}$. Different sets of participants were included for each year of follow-up. Numbers of participants included at each time point are listed above each study year.

In our study, the performance of creatinine clearance versus iGFR was not better than the performance of eGFR versus iGFR. Creatinine clearance and change in creatinine clearance had larger variances than iGFR, eGFR, and changes in iGFR and eGFR. These results suggest large intraindividual variability, perhaps because of, in part, inaccurately timed urine collections. DCCT urine collections were performed under supervision, which would be expected to improve accuracy, but the relatively short duration (4 hours) may decrease accuracy. The performance of creatinine clearance may vary under different collection protocols.

Over long-term follow-up (median=23 years), mean rates of GFR loss were comparable when we estimated GFR using serum creatinine, cystatin C, or both. This result contrasts with data from older adults, in whom cystatin C estimated substantially larger declines in GFR than creatinine.[16] Our data do not support the notion that $eGFR_{Cys}$ routinely captures changes in GFR that are missed by $eGFR_{Cr}$ among young people with type 1 diabetes and normal GFR. However, associations of known risk factors with eGFR loss were modestly stronger when GFR was estimated using cystatin C. One potential explanation is that GFR loss was better classified using cystatin C, generating estimates with lower bias.

This study has a number of important strengths, including the evaluation of a large type 1 diabetes population with high/normal GFR at risk of GFR loss, simultaneous evaluation of serum creatinine, serum cystatin C, and creatinine clearance, careful calibration of serum creatinine and cystatin C concentrations, and a large number of longitudinal data included in the analyses. Given known variation in cystatin C calibrators over time,[17] our calibration of cystatin C concentrations over more than a decade of measurement was key to the implementation of this study, and it documents an approach that could be modeled by other longitudinal studies.

Our study also has a number of limitations. Our data are not independent of the data used to develop the CKD-EPI equations, because a subset of DCCT/EDIC data were included in that process.[1] We focused on population-level trends rather than characterizing individual patterns of change in detail. In addition, we lacked data on some covariates, which may affect serum creatinine or cystatin C concentrations. Direct GFR measurements were not obtained over long-term follow-up, and few participants progressed to very low GFR. We did not test associations of GFR estimates with clinical outcomes, and GFR was the only one of many aspects of kidney function/damage that was evaluated.

Our data suggest that the increased precision of $eGFR_{Cr+Cys}$ may improve the ability to identify risk factors for GFR loss and reduce bias when testing associations of eGFR with CKD complications in clinical research. For clinical care, our data confirm that it is difficult to accurately ascertain changes in GFR within its normal range and suggest that the addition of cystatin C to creatinine does not substantially improve the tracking of GFR in this setting. Other biomarkers of GFR and related kidney functions may be needed to identify patients with type 1 diabetes at high risk of progressive CKD. Until such biomarkers are available, regular monitoring of albuminuria and serum creatinine remains the clinical standard in diabetes care.[18,19]

CONCISE METHODS

Study Population

The DCCT enrolled 1441 persons with type 1 diabetes from 1983 to 1989 to determine the effects of intensive diabetes therapy on the long-term complications of diabetes.[8] The trial included two cohorts. The primary prevention cohort was characterized by diabetes duration of 1–5 years, AER$<$40 mg per 24 hours, and no retinopathy by fundus photography. The secondary intervention cohort was characterized by diabetes duration of 1–15 years, AER$\leq$200 mg per 24 hours, and at least one microaneurysm in either eye (but no more than moderate nonproliferative retinopathy). For both cohorts, serum creatinine$<$1.2 mg/dl or creatinine clearance$>$100 ml/min per 1.73 m^2

Table 5. Associations of selected clinical characteristics with change in GFR estimated from serum concentrations of creatinine, cystatin C, or both among all 1441 participants over combined DCCT/EDIC follow-up

Risk Factor	Difference in Change in $eGFR_{Cr}$ (ml/min per 1.73 m^2 per year)	Difference in Change in $eGFR_{Cys}$ (ml/min per 1.73 m^2 per year)	Difference in Change in $eGFR_{Cr+Cys}$ (ml/min per 1.73 m^2 per year)
Age at DCCT baseline (yr)			
<20	0 (Reference)	0 (Reference)	0 (Reference)
20–29	−0.15 (−0.26 to −0.05)	−0.18 (−0.31 to −0.06)	−0.13 (−0.25 to 0.01)
≥30	−0.52 (−0.62 to −0.41)	−0.64 (−0.77 to −0.51)	−0.56 (−0.68 to −0.44)
F values (df=2)	62.7	63.3	58.6
P value	<0.001	<0.001	<0.001
Sex			
Women	0 (Reference)	0 (Reference)	0 (Reference)
Men	0.01 (−0.07 to 0.08)	0.03 (−0.06 to 0.12)	0.06 (−0.14 to 0.03)
t value (df=1)	0.21	0.62	1.30
P value	0.83	0.54	0.19
Time-updated systolic BP (mmHg)			
<120	0 (Reference)	0 (Reference)	0 (Reference)
120–129	−0.03 (−0.08 to 0.03)	−0.07 (−0.14 to 0.01)	−0.04 (−0.10 to 0.03)
≥130	−0.12 (−0.18 to −0.05)	−0.22 (−0.30 to −0.14)	−0.17 (−0.24 to −0.09)
F values (df=2)	6.84	14.4	10.1
P value	0.001	<0.001	<0.001
Mean DCCT hemoglobin A1c (%)			
<7	0 (Reference)	0 (Reference)	0 (Reference)
7–7.9	0.07 (−0.03 to 0.17)	−0.06 (−0.18 to 0.06)	−0.00 (−0.11 to 0.11)
8–8.9	−0.07 (−0.18 to 0.04)	−0.23 (−0.36 to −0.09)	−0.18 (−0.30 to −0.05)
9–9.9	−0.22 (−0.34 to −0.10)	−0.44 (−0.59 to −0.29)	−0.39 (−0.53 to −0.25)
≥10	−0.43 (−0.56 to −0.30)	−0.79 (−0.95 to 0.64)	−0.71 (−0.86 to −0.56)
F values (df=2)	18.5	31.3	31.2
P value	<0.001	<0.001	<0.001
Time-updated albumin excretion rate (mg/d)			
<30	0 (Reference)	0 (Reference)	0 (Reference)
30–299	−0.07 (−0.07 to −0.08)	−0.12 (−0.13 to −0.12)	−0.08 (−0.09 to −0.07)
≥300	−0.44 (−0.37 to −0.48)	−0.54 (−0.64 to −0.45)	−0.44 (−0.52 to −0.37)
F values (df=2)	68.7	70.1	64.5
P value	<0.001	<0.001	<0.001

Mean changes in eGFR (ml/min per 1.73 m^2) with 95% CI were −1.37 (−1.41 to −1.33) for $eGFR_{Cr}$, −1.11 (−1.16 to −1.06) for $eGFR_{Cys}$, and −1.29 (−1.33 to −1.24) for $eGFR_{Cr+Cys}$. df, degrees of freedom.

was required for eligibility. Participants were randomly assigned to intensive diabetes therapy aimed at lowering glucose concentrations as close as safely possible to the normal range or conventional therapy aimed at preventing symptoms of hyperglycemia and hypoglycemia. In 1994, after completion of the DCCT, 1375 participants (96% of the surviving cohort) agreed to participate in the EDIC study. During EDIC, diabetes therapy and glycemic control as measured by hemoglobin A1c became similar in the two original DCCT treatment groups, and yearly follow-up has continued through the present.[14]

Measured GFR

Beginning in 1986, the DCCT added scheduled iGFR measurements to remaining baseline study visits and study visits at DCCT year 3 and DCCT closeout (in 1993).[9] Additional iGFR measurements were obtained at EDIC year 1 or 2, but cystatin C was not measured concurrently, and the EDIC iGFR measurements are, therefore, not included in this study. GFR was measured as the urinary clearance of ^{125}Iiothalamate after a subcutaneous injection of 35 μCi without epinephrine.[9] After an equilibration period of at least 1 hour, four consecutive urine collections were obtained by voluntary voiding, and five serum samples were drawn bracketing the urine collections. The overall GFR was calculated as if the clearance periods were one long period. Median intratest coefficient of variation (CV) was 11.7%. GFR was corrected for body surface area.[20]

eGFR

We estimated GFR from $eGFR_{Cr}$, $eGFR_{Cys}$, or $eGFR_{Cr+Cys}$ using equations developed and validated by the CKD-EPI consortium.[1]

Serum creatinine was measured yearly throughout DCCT/EDIC at the DCCT/EDIC Central Biochemistry Laboratory, University of Minnesota. Overall interassay CV was <3%, and overall coefficient of reliability was >0.98. All serum creatinine results were calibrated to National Institute of Standards and Technology Isotope Dilution Mass Spectrometry assigned values.[14]

Serum cystatin C was measured for all DCCT study visits that included iGFR measurement and all EDIC study visits from 2002 to 2012. Serum samples were stored at −80°C at the DCCT/EDIC Central Biochemistry Laboratory until measurement. From 2003 to 2012, cystatin C was measured using a Dade Behring nephelometer (interassay CV=3.0%). We observed evidence of calibrator drift in these assays, with variable and decreasing mean values over time (Supplemental Material). In 2011–2012, cystatin C was measured using an immunoturbidimetric assay manufactured by Gentian and performed on the Roche ModP Analyzer. The Gentian assay was calibrated to reference materials developed by the International Federation for Clinical Chemistry/Institute for Reference Materials and Measurements (IFCC/IRMM).[21] In 2012, we remeasured cystatin C using the Gentian assay for 26–35 samples drawn from each Dade Behring nephelometer calibrator lot. We used these data (n=347) to calibrate all cystatin C measurements to those measurements obtained with the IFCC/IRMM-calibrated Gentian platform (Supplemental Material).

Creatinine Clearance

Creatinine clearance was determined from supervised 4-hour urine collections.[9] Water intake was encouraged to maintain urine output throughout the collection period. Urine creatinine was measured at the DCCT/EDIC Central Biochemistry Laboratory using a modified Jaffe reaction (interassay CV=3.0%). Like iGFR, creatinine clearance was standardized to body surface area.

Other Clinical Characteristics

Demographic characteristics were ascertained by questionnaire. Hemoglobin A1c was measured quarterly during the DCCT using HPLC.[22] AER was measured yearly during the DCCT and every other year during EDIC by 4-hour timed urine collection using a fluoroimmunoassay (interassay CV=9.4%).[9]

Statistical Analyses

For comparisons of GFR estimates and creatinine clearance with iGFR, we included only study visits for which serum creatinine, serum cystatin C, creatinine clearance, and iGFR were all measured. We performed both cross-sectional and longitudinal comparisons, to which some participants contributed multiple sets of measurements. Longitudinal analyses evaluated differences in GFR estimates, creatinine clearance, and iGFR between two consecutive sets of these measurements.

Using iGFR or change in iGFR as the standard, we assessed agreement using Pearson and Spearman correlation. Precision was ascertained using the interquartile ranges of paired differences. Nonparametric CI of precision was determined by bootstrapping.[23] Accuracy was ascertained as the proportion of values within clinically relevant proximity of iGFR values. Bias was ascertained as the median of paired differences. We categorized changes in iGFR over time as <-15, -15 to 15, and >15 ml/min per 1.73 m^2 to reflect clinically relevant changes in GFR and compared agreement with categorized changes in GFR estimates and creatinine clearance using diagonal agreement and the weighted κ-statistic.

For comparison of long-term changes in GFR estimates, we estimated the rate of change in each GFR estimate over time using linear mixed effect models. We included only time points for which both creatinine and cystatin C were measured. Associations of relevant clinical characteristics with rates of change in GFR estimated from creatinine, cystatin C, or both were tested in parallel models, one characteristic at a time. As in prior analyses, hemoglobin A1c was evaluated as DCCT mean hemoglobin A1c,[5,14] and AER was updated over time.[7] For participants who reached ESRD (maintenance dialysis or kidney transplantation), eGFR was set to 10 ml/min per 1.73 m^2 at the onset of ESRD and missing thereafter.

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A complete list of participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group can be found in ref. 14.

DISCLOSURES

None.

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