Microalbuminuria and the Risk for Early Progressive Renal Function Decline in Type 1 Diabetes

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This study aimed to establish the time of initiation and the determinants of renal function decline in type 1 diabetes. Until now, such decline has been assumed to be a late-occurring event associated with proteinuria. A total of 267 patients with normoalbuminuria and 301 patients with microalbuminuria were followed for 8 to 12 yr. Linear trends (slopes) in GFR were estimated by serial measurement of serum cystatin C. Cases of early renal function decline were defined by loss in cystatin C GFR that exceeded −3.3%/yr, a threshold that corresponds to the 2.5th percentile of the distribution of GFR slopes in an independent nondiabetic normotensive population. Cases of early renal function decline occurred in 9% (mean slope −4.4; range −5.9 to −3.3%/yr) of the normoalbuminuria group and 31% (mean slope −7.1; range −23.8 to −3.3%/yr) of the microalbuminuria group ($P < 0.001$). Risk for early renal function decline depended on whether microalbuminuria regressed, remained stable, or progressed, rising from 16 to 32 and 68%, respectively ($P < 0.001$). In multivariate analysis, risk for decline was higher after age 35 yr or when glycosylated hemoglobin exceeded 9% but did not vary with diabetes duration, smoking, BP, or angiotensin-converting enzyme inhibitor treatment. Contrary to the existing paradigm of diabetic nephropathy, progressive renal function decline in type 1 diabetes is an early event that occurs in a large proportion of patients with microalbuminuria. Together with testing for microalbuminuria, clinical protocols using cystatin C to diagnose early renal function decline and track response to therapeutic interventions should be developed.

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The lifetime risk for ESRD approaches 25% in patients with type 1 diabetes (1). Our knowledge of renal function loss in diabetic nephropathy is mostly limited to late stages, after the GFR is <60 ml/min (2–4). Clinical proteinuria, which is typically present by then, has been assumed to be necessary for the process. Some authors extend this assumption to include microalbuminuria as well (5–8), whereas others question the necessary role of albumin altogether, pointing to evidence that the process can occur despite normoalbuminuria (9–11).

This uncertainty about urinary albumin's role in renal function decline was spotlighted by our demonstration that remission of microalbuminuria is more frequent than its progression to proteinuria (12). The obvious follow-up question is, "Does regression of microalbuminuria imply that renal function is also spared?" (13).

At this early stage of nephropathy, the answer to the question requires a technique for distinguishing systematic decreases in renal function over the long term from short-term variations in normal renal function. To avoid confusion with the progressive loss of function in the late stages of nephropathy, we refer to a systematic decline that occurs while renal function is in the normal range as "early progressive renal function decline."

The introduction of a commercial assay for serum cystatin C to estimate renal function in clinical research opened the way for evaluating early renal function decline in patients with diabetes (14,15). Therefore, we sought to answer the question by measuring the long-term trends in renal function in the 12-yr follow-up data of the same study population that yielded the demonstration of regression of microalbuminuria.

Materials and Methods

Study Participants

Patients who were enrolled in the Joslin Study of the Natural History of Microalbuminuria in Type 1 Diabetes were eligible for this study (12,16–18). The protocol and consent procedures were approved by the Committee on Human Studies of the Joslin Diabetes Center.

Urine samples from every second patient who had type 1 diabetes and was 15 to 44 yr of age and seen at the Joslin Clinic between January 1991 and April 1992 were examined for albumin excretion (1602 patients). During the first 2 yr of observation, their repeat urine samples were examined to establish their urinary albumin excretion status and eligibility for follow-up. The 347 patients who already had proteinuria or ESRD were not followed, but the rest were followed for 8 to 12 yr with frequent urine examinations (average of three per 2-yr interval). The 312 patients with microalbuminuria already present in the initial 2-yr interval (prevalent microalbuminuria) were invited to give a blood sample and be examined. Thereafter, they were invited biennially for

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reexamination. Within 4 yr after the initial evaluation, new-onset microalbuminuria developed in 109 of the 943 patients with normoalbuminuria (18). These patients were invited to give a blood sample and be examined, and biennially they were invited for reexamination along with the 312 prevalent cases of microalbuminuria. Together, they composed the cohort of 421 patients with microalbuminuria studied previously to determine the frequency of microalbuminuria regression (12). As a comparison group for the microalbuminuria cohort, we invited a random sample of 414 of the remaining 834 patients with normoalbuminuria for biennial examinations and blood samples.

For the analysis of trends in renal function, we selected all individuals with at least two (on average four) archived serum samples that spanned a minimum of 4 yr. Those who were available for this analysis were 301 (71%) of the 421 patients in the microalbuminuria cohort and 305 (74%) of the 414 patients in the normoalbuminuria group who had been invited for biennial examinations. In the latter group, we excluded from this analysis 38 individuals in whom microalbuminuria developed late in follow-up. Therefore, the reference group includes only the 268 patients with persistent normoalbuminuria throughout 8 to 12 yr of follow-up.

Assessment of Urinary Albumin Excretion and Exposure Variables

The albumin excretion rate (in micrograms per minute) was estimated from the albumin-to-creatinine ratio in random urine samples, as described previously (12,16). Briefly, individual determinations of the albumin excretion rate were transformed to the logarithmic scale (base 10) for analysis. Follow-up observation was organized into 2-yr intervals, and patients were assigned a urinary albumin excretion status for each interval according to the geometric mean of their determinations in that interval: Normoalbuminuria was defined as an excretion rate <30 μg/min, microalbuminuria 30 to 299 μg/min, and proteinuria ≥ 300 μg/min. The examination of exposure variables was described previously (16). Briefly, this included a medical history that emphasized use of angiotensin-converting enzyme inhibitors (ACEI) and other antihypertensive medications, measurement of BP, and phlebotomy for assaying cholesterol profile and glycosylated hemoglobin (HbA_{1c}).

GFR Estimated by Serum Cystatin C

Cystatin C is a nonglycosylated basic protease inhibitor that is produced at a constant rate by all nucleated cells, freely filtered by the glomerulus, and stable in frozen serum or plasma (19–23). GFR is estimated by the reciprocal of cystatin C (in mg/L) multiplied by 100. The validity of cystatin C in tracking trends in renal function accurately—when patients have elevated or normal GFR—has been well demonstrated for individuals with diabetes (14,15,24). For the measurement of GFR when it is already impaired, estimates that are based on serum cystatin C (cC-GFR) are similar to creatinine-based estimates.

Residual variation of the cystatin C estimates around the fitted linear trends was 9.1% in this study. As in an earlier study, this is smaller than the residual variation of 12.1% for estimates that are based on iothalamate clearance (14). This is likely because short-term fluctuations in the true GFR affect direct measurements (25) but are averaged out by methods that are based on clearance of the pool of an endogenous metabolite, such as cystatin C. The difference is analogous to the difference between direct measurements of plasma glucose and measurements of HbA_{1c}, which averages out fluctuations in glucose concentration over the lifespan of red blood cells.

In this study, all serum samples were stored at -70°C until the day of assay and were analyzed for cystatin C concentration (Dade Behring Diagnostics, Newark, DE) on a BN Prospec System nephelometer (Dade Behring Diagnostics). The assay's range of detection is 0.30 to 7.50 mg/L, with the reference range for young, healthy individuals reported as 0.53 to 0.95 mg/L. In our laboratory, the intraindividual coefficient of variation for individuals with diabetes was 3.8 to 3.0% in samples from the lowest and highest quartiles of the cystatin C distribution, respectively (14). Furthermore, assay results for replicate aliquots of serum samples that were stored at -85°C for 6 mo or in the refrigerator for up to 2 wk were equivalent to results that were obtained on fresh samples.

Determination of Abnormal Decline in Renal Function ("Early Renal Function Decline")

All serial measurements of serum cystatin C concentration were examined for trends in renal function during 8 to 12 yr of follow-up. Patients from the normoalbuminuria and microalbuminuria groups provided, on average, 3.4 and 4.8 serum samples, respectively. In plots of each participant's data, renal function seemed stable during follow-up or declined linearly over time. Figure 1 demonstrates the nature of the data and magnitude of change observed by showing examples that were selected to represent the mean slopes and the extremes of the distributions.

To avoid the skewness that is inherent in the reciprocal of a random variable, data were transformed to the logarithmic scale (base 10) for analysis. The slopes were estimated by the regression coefficient for the

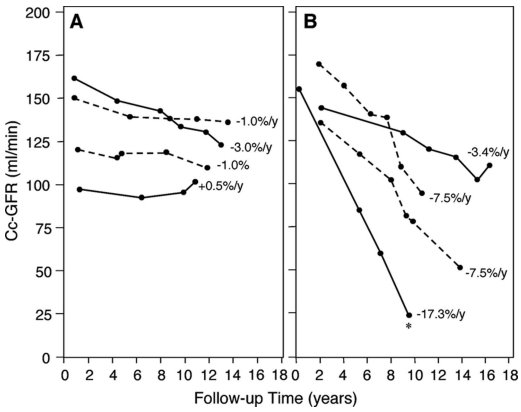

Figure 1. Serial estimates cC-GFR for four patients with stable renal function (A) and four patients with early progressive renal function decline (B). The hatched lines represent individuals with annual percentage changes in GFR estimated by 100/serum cystatin C (in mg/ml; cC-GFR) that approximate the mean values for control subjects with stable renal function (A) and for case patients with early progressive renal function decline (B); the solid lines represent individuals in the outer quartiles of the distributions. The mean slope for control subjects was -1.0%/yr, whereas the mean slope for case patients was -7.1%/yr. The fixed threshold for case definition was -3.3%/yr. The individual with a slope of -17.3%/yr is representative of the lowest quartile of annual change in case patients. Beginning with a cC-GFR value of 155 ml/min, within 10 yr, this individual reached ESRD (*). Overall, residual variation of the data points around the fitted regression lines for the 568 participants was 9.1 ± 8.7%, indicating that trends were generally linear. Residual variation was not significantly different in the microalbuminuria and normoalbuminuria groups.

time variable and then converted from the logarithmic scale to produce the annual percentage change in cC-GFR for an individual (26).

Because the reference distribution for evaluating whether a negative slope or trend in renal function qualified as an abnormal rate of decline, we used the longitudinal data that were available from the Baltimore Aging Study (27). Using the weighted mean and variances for the participants who were aged 30 to 59.9 yr, we determined the range that included 95% of the distribution (−3.3 to 2.8%/yr) and selected the 2.5th percentile (the lower limit) as the threshold to define cases of early progressive renal function decline.

Statistical Analyses

Analyses were performed in SAS (version 8.02 for Windows; SAS Institute, Cary, NC). Significance was based on an α level of 0.05 throughout. Differences between case patients and control subjects at baseline were assessed using χ^2 tests for categorical variables or t test for continuous variables. Case patients with early renal function decline and control subjects with slopes within the normal range were determined according to the fixed cutoff value of −3.3%, whose derivation was described previously. Variables that were significantly related to case-control status in univariate analyses were examined in a multiple logistic analysis. Characteristics such as gender, age, and an indicator variable that distinguished incident from prevalent microalbuminuria were forced into the multivariate model, and manual forward and backward selection procedures were used to determine which additional explanatory variables had significant effects on the presence of early renal function decline. Given that the use of a fixed threshold for defining case patients and control subjects has inherent problems, we performed a confirmatory mixed-effects model (28) including random effects for the baseline GFR (the intercept) and the slope (data not shown). This maximum likelihood–based method can properly handle unbalanced, incomplete data so that irregular sampling times during the follow-up were not problematic. The frequency of early progressive renal function decline and its determinants did not differ from the estimates shown for the fixed threshold analysis presented next.

Results

Characteristics of the study participants at baseline are summarized in Table 1 according to their urinary albumin excretion status. Participants with microalbuminuria were not different from those with normoalbuminuria with regard to gender or age, but they had longer diabetes duration, included more current or past cigarette smokers, and had higher BP and HbA_{1c} values. By design, they had higher urinary albumin excretion rates than those with normoalbuminuria. As a group, though, they had "early microalbuminuria" in that their levels of urinary albumin excretion were in the lower range and many had the new onset of microalbuminuria. Their cystatin C values at baseline were higher; consequently, the average cC-GFR was approximately 14 ml/min lower than that in the normoalbuminuria group.

The normoalbuminuria group was followed for 8 to 12 yr with 3.4 ± 0.9 estimates of cC-GFR per patient. A test for departure of the trends from linearity was NS, and the distribution of slopes was approximately normal (Figure 2). The mean (−1.0%/yr) was comparable to populations without diabetes (27). However, the slopes for 24 (9.0%) individuals exceeded an annual decline in renal function of 3.3%—they ranged from a maximum change of −5.9%/yr to a minimum of

Table 1. Baseline characteristics of patients with type 1 diabetes according to the presence of microalbuminuria[a]

Characteristic	Patients with Normoalbuminuria (n = 267)	Patients with Microalbuminuria (n = 301)	P[b]
Female gender (%)	55	50	0.16
Age at baseline (yr)	30 ± 7	31 ± 8	0.12
Diabetes duration (yr)[c]	14 ± 8	18 ± 9	<0.001
Current or past smoking (%)	35	53	<0.001
SBP (mmHg)	117 ± 14	122 ± 14	<0.001
DBP (mmHg)	70 ± 9	75 ± 8	<0.001
HbA_{1c} (%)	8.1 ± 1.3	9.0 ± 1.5	<0.001
Total cholesterol (mg/dl)[d]	192 ± 45	199 ± 42	0.10
AER (μg/min)			<0.001
median	12	59	
IQR	11 to 13	37 to 105	
Cystatin C (mg/L)	0.66 ± 0.09	0.76 ± 0.40	<0.001
cC-GFR (mg/L)[e]	155 ± 22	141 ± 29	<0.001

[a]Except for albumin excretion rate (AER), data are means ± SD or %. Follow-up was 10.6 ± 2.3 yr for the normoalbuminuria group and 8.9 ± 2.9 yr for microalbuminuria group after the detection or onset of microalbuminuria. Of those with microalbuminuria, 89 (30%) were of new onset. For the normoalbuminuria and microalbuminuria groups, respectively, the number of cystatin C determinations during follow-up were 3.4 ± 0.9 and 4.8 ± 1.6. cC-GFR, GFR estimated by 100/cystatin C (mg/L); DBP, diastolic BP; HbA_{1c}, glycosylated hemoglobin; IQR, interquartile range; SBP, systolic BP.

[b]Categorical variables report P values for χ^2 test statistics, and continuous variables report P values for ANOVA, both without ordering.

[c]Duration for patients with prepubertal diabetes onset is calculated from age 11 yr.

[d]To convert to millimoles per liter, multiply by 0.02586.

[e]Range 75 to 225 ml/min.

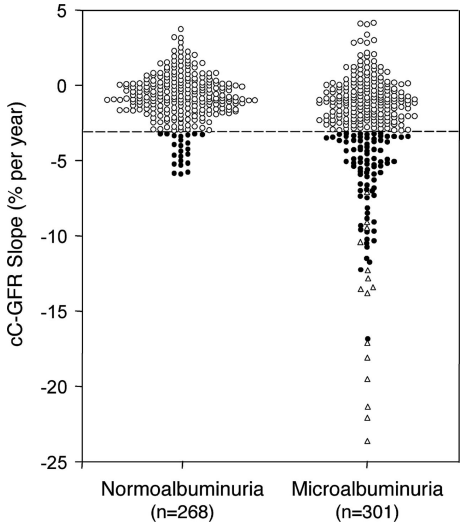

Figure 2. Distribution of GFR slopes over time (in %/yr) according to the presence of microalbuminuria. ○, individuals with stable renal function; ●, cases of early progressive renal function decline; △, cases with clinical ESRD (15 individuals required hemodialysis or renal transplantation) by the end of follow-up. In individuals with normoalbuminuria, who had mean baseline cC-GFR of 155 ± 22 ml/min, 9% had early progressive renal function decline. In the patients with microalbuminuria, however, for whom mean baseline cC-GFR was 143 ± 26, 31% had early progressive renal function decline.

−3.3%/yr (mean −4.4%/yr), as shown in Figure 2. The clinical characteristics of these 24 individuals did not distinguish them from the rest of the normoalbuminuria group.

The distribution of the slopes in cC-GFR in the microalbuminuria group is shown in Figure 2. These individuals were followed for 8 to 12 yr—after the enrollment of individuals with prevalent microalbuminuria or after the detection of new-onset microalbuminuria—and had a mean of 4.8 ± 1.6 estimates of cC-GFR per person. Although the distribution of slopes was more negatively skewed than in the normoalbuminuria group, the individual trends in cC-GFR were still well represented by lines (Figure 1). The distributions of slopes in the two groups largely overlapped, but 94 (31%) slopes in the microalbuminuria group qualified as early progressive renal function decline (Figure 2). This significantly exceeds their frequency in the normoalbuminuria group (31 *versus* 9%; $P < 0.001$).

To identify determinants of early progressive renal function decline, we compared the 94 case patients in the microalbuminuria group with the rest of the microalbuminuria group as control subjects (Table 2). To illustrate patient characteristics that also changed as renal function was changing during follow-up, Table 2 includes values for baseline and the second follow-up interval values (4 yr later). Case patients and control subjects did not differ with regard to gender, duration of diabetes, proportion of cigarette smokers, or the proportion using ACEI. However, case patients were significantly older and had higher HbA_{1c} and total cholesterol values at baseline and during the second interval of follow-up. Systolic BP was higher during follow-up for case patients as compared with control subjects, despite no difference in baseline values. No difference in urinary albumin excretion was observed in case patients and control subjects at baseline, but by the second follow-up interval, it had increased significantly in case patients and decreased substantially in control subjects (Table 2).

To investigate this relationship between early progressive renal function decline and the course of urinary albumin excretion, we stratified the group according to whether microalbuminuria regressed, progressed, or remained stable during the first 4 yr of follow-up (Figure 3). This allowed sufficient observation time to evaluate the subsequent trend in renal function. Regression was defined as a halving of the albumin excretion rate (decrease exceeding 50%) (12), whereas progression of microalbuminuria was defined as a doubling (increase exceeding 100%). Anything in between was considered stable. Microalbuminuria regression was associated with a significant reduction in the frequency of early renal function decline in comparison with progression or stable microalbuminuria (χ^2 test $P = 0.002$ and $P < 0.001$, respectively). The frequency of early progressive renal function decline in those with microalbuminuria regression was higher than those with longstanding normoalbuminuria (16.2 *versus* 9.0%, respectively; $P = 0.06$).

We examined the independent contribution of these determinants of early progressive renal function decline in patients with microalbuminuria in multiple logistic model (Table 3). We excluded from this model the nonbaseline clinical variables except for two variables of interest: Urinary albumin excretion and HbA_{1c}. The multivariate logistic model was associated with a χ^2 in a log-likelihood test of 68.1 ($P < 0.001$). The risk for early progressive renal function decline was reduced for those with longer diabetes duration, but the effect was NS. Independent of diabetes duration, age was the variable that increased the risk for early renal function decline but only in the highest tertile. The course of microalbuminuria during the first 4 yr of follow-up had a very strong effect on the risk. Relative to stable microalbuminuria, regression of microalbuminuria significantly decreased the risk (odds ratio [OR] 0.3; $P = 0.01$), whereas progression of microalbuminuria significantly increased it (OR 6.5; $P < 0.001$). The risk increased linearly with the HbA_{1c} value, but for ease of interpretation, it is shown dichotomized at the median, 9.0%. The odds of early progressive renal function decline for those at or above the median were 2.5 times the odds for those below the median. To investigate the role of hyperglycemia further, we identified patients whose HbA_{1c}, regardless of baseline value, increased 1 percentage point or more between baseline and the second follow-up interval. Their risk was not significantly increased (OR 1.1; $P = 0.40$).

Use of ACEI treatment was associated with protection from early renal function decline. The effect, however, was not statistically significant. Elevated systemic BP were associated with declining renal function, but these differences were similarly not statistically significant.

Discussion

This study showed that the process of progressive renal function decline in type 1 diabetes frequently begins during the

Table 2. Characteristics of patients with type 1 diabetes and microalbuminuria according to case-control status[a]

Characteristic	Renal Function		*P*
	Stable (Controls; $n = 207$)	Declined (Cases; $n = 94$)	
Serum cystatin C (mg/L)			
at baseline	0.74 ± 0.15	0.70 ± 0.16	—[e]
at end of follow-up	0.82 ± 0.17	1.36 ± 0.90	—[e]
change (follow-up minus baseline)	0.08 ± 0.15	0.66 ± 0.86	—[e]
cC-GFR (mg/L)			
at baseline	140 ± 25	149 ± 30	—[e]
at end of follow-up	126 ± 25	91 ± 34	—[e]
change (follow-up minus baseline)	−14 ± 22	−60 ± 31	—[e]
cC-GFR slope (%/yr)[b]	−0.7 ± 3.5	−7.1 ± 4.4	—[e]
Female (%)	51	49	NS
Age at baseline (yr)	30 ± 7	32 ± 8	0.04
Diabetes duration (yr)	18 ± 8	17 ± 9	NS
Current or past smoker (%)	51	56	NS
HbA_{1c} (%)			
baseline	8.8 ± 1.5	9.6 ± 1.5	<0.001
second follow-up[c]	8.7 ± 1.3	9.4 ± 1.6	<0.001
Total cholesterol[d]			
baseline	195 ± 42	207 ± 40	0.03
second follow-up[c]	194 ± 37	208 ± 45	0.02
ACEI use (%)			
baseline	25	23	NS
second follow-up[c]	46	55	NS
SBP (mmHg)			
baseline	122 ± 14	122 ± 15	NS
second follow-up[c]	123 ± 15	128 ± 16	0.02
DBP (mmHg)			
baseline	75 ± 8	75 ± 9	NS
second follow-up[c]	75 ± 8	77 ± 9	0.09
AER (μg/min)			
baseline			
median	57	62	NS
IQR	37 to 101	40 to 131	
second follow-up[c]			
median	36	115	<0.001
IQR	17 to 88	29 to 340	

[a]Except for AER, data are means ± SD or %. ACEI, angiotensin-converting enzyme inhibitor.
[b]Calculated by linear regression (see Materials and Methods).
[c]Four years after baseline.
[d]To convert to millimoles per liter, multiply by 0.02586.
[e]Because cystatin C was involved in defining case patients and control subjects, these variables were not tested.

microalbuminuria stage, and renal function may be elevated above normal when the process starts. The risk for decline is very high in patients whose microalbuminuria progresses to higher levels, intermediate when microalbuminuria is stable, and low when microalbuminuria regresses. Also the risk increases after age 35 yr and with increasing HbA_{1c}. That the process is detectable so early in the course of diabetic nephropathy not only provides motivation for research on the underlying mechanisms of early progressive renal function decline but also justifies the development of new interventions for protecting renal function while it is still normal or even elevated. Toward this end, the serial estimation of a valid measure of GFR—such as the serum concentration of cystatin C—could be included in routine clinical practice to complement screening for microalbuminuria and produce more accurate prediction of the onset of impaired renal function and subsequent ESRD.

This large study of the natural history of early renal function decline in type 1 diabetes became feasible only after an assay for serum cystatin C became commercially available (19,23,29)

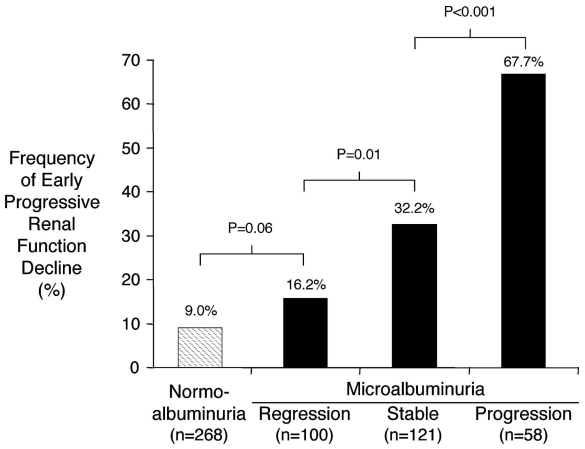

Figure 3. Frequency (in %) of early progressive renal function decline in patients with normoalbuminuria and microalbuminuria divided according to the 4-yr course of microalbuminuria. Regression is defined as a halving (decrease by 50% or more) of the urinary albumin excretion rate (in μg/min; $n = 100$) (12). Stable is defined as no change or greater than a halving or doubling of the urinary albumin excretion rate ($n = 121$). Progression is defined as a doubling (increase by 100% or more) of the urinary albumin excretion rate ($n = 58$). Twenty-two individuals had insufficient urine samples in the second follow-up interval to determine the course of their microalbuminuria.

and once it was proved to be a feasible measure in large-scale studies (24,30). A tool was needed for tracking temporal trends in renal function in patients with diabetes and a normal or elevated GFR. For this purpose specifically, the estimation of GFR by 100/cystatin C has been validated against direct measurements of the GFR by iothalamate clearance and outperforms creatinine-based estimates of renal function such as the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) equations (14,15,31).

Early progressive renal function decline occurs in patients with normoalbuminuria, but it is less frequent and, if it develops, does not decline rapidly. The mean of −1.0% decline per year in this group is comparable to populations without diabetes (27). The slopes for 24 (9.0%) individuals exceeded the limits of normal variation. This finding is consistent with previous reports of a low frequency of impaired renal function in patients with type 1 diabetes and normoalbuminuria (10,11,32).

In our study, early progressive renal function decline occurred in a large proportion (one third) of the patients with microalbuminuria, despite their having normal or elevated baseline renal function. Once the process of decline began, it progressed relentlessly and reached impaired renal function or ESRD in many patients during the study period. The linearity of decline suggests that progressive renal function loss begins not during the proteinuria stage (2–4,33), but 10 to 15 yr earlier during the microalbuminuria stage.

Previous studies suggested that significant decline in the GFR can occur in patients with microalbuminuria (5–8,34). However, it was not clear from those small studies whether changes in the GFR were the result of methodologic shortcomings, short-term variations, or a truly irreversible process of renal function loss. With attention to these issues—using serial measurements and long follow-up—we established that early progressive renal function decline in type 1 diabetes begins in approximately one third of individuals with microalbuminuria even while their renal function is normal or elevated.

The mechanisms that are responsible for initiating and sustaining the early progressive decline in renal function are unknown. The usual assumption is that morphologic lesions in the kidney underlie this decline (35). However, our finding that progressive renal function decline begins during microalbuminuria is not consistent with this hypothesis. In previous studies, patients with short duration of microalbuminuria had only small glomerular lesions in comparison with patients with normoalbuminuria (36–39). Furthermore, morphologic changes are most pronounced in individuals with long diabetes duration, but the risk for early renal function decline in this study was not associated with long duration of diabetes.

From a clinical perspective, the putative process of early progressive renal function decline is very strongly associated with microalbuminuria and the subsequent course of urinary albumin excretion. Recently, the view that microalbuminuria represents a committed step toward the development of proteinuria and subsequent renal function loss (39–42) has been put in question by data that characterize microalbuminuria as a process of dynamic, rather than fixed, renal injury (43). The incidence of microalbuminuria regression far outweighs that of progression to proteinuria (12,44,45). This regression is significantly more frequent in individuals with salutary factors—that is, low levels of total cholesterol, triglyceride, HbA_{1c}, and systolic BP (12). That regression of microalbuminuria in this study is independently associated with protection from early renal function decline, even compared with those with stable microalbuminuria, provides compelling justification for a clinical trial. Ultimately, a clinical protocol for inducing microalbuminuria regression—by modifying every one of the salutary factors—may be the most valuable intervention for preventing impaired renal function and ESRD in individuals with type 1 diabetes and microalbuminuria.

Consistent with studies of the prevention of microalbuminuria in type 1 diabetes (46,47), this study demonstrates that poor glycemic control increases the risk for early progressive renal function decline. Significant hyperglycemia and high HbA_{1c} usually accompany the onset of type 1 diabetes, and they are associated with renal hyperfiltration (48). Subsequent improvement in glycemic control restores normal renal function, mimicking early renal function decline (49). However, this decline is not progressive, and it is distinct from the early progressive renal function decline that was found in this study of patients long after their diabetes onset. The risk for early progressive renal function decline was significantly associated with high baseline levels of HbA_{1c}. Moreover, subsequent worsening of glycemic control—rather than maintaining hyperfiltration (48)—increased the risk for early renal function decline, although the effect was not quite significant statistically.

Elevated systemic BP is associated with the risk for progressive renal function decline during the advanced stages of dia-

Table 3. Results of the multiple logistic analysis of early progressive renal function decline in the 301 patients with microalbuminuria[a]

Determinant	OR (95% CI)	*P*
Baseline duration of diabetes (≥16 *versus* <16 yr)[b]	0.7 (0.3 to 1.7)	0.51
Baseline age (yr; by tertiles)		
15 to 27	1.0 (reference)	—
28 to 35 (*versus* 15 to 27)	1.3 (0.5 to 3.6)	0.57
36 to 48 (*versus* 15 to 27)	4.1 (1.5 to 11.8)	0.01
Course of urinary albumin excretion[c]		
microalbuminuria regression (*versus* stable)	0.3 (0.1 to 0.8)	0.01
stable microalbuminuria	1.0 (reference)	—
microalbuminuria progression (*versus* stable)	6.5 (2.4 to 17.5)	<0.001
HbA_{1c}		
baseline (≥9 *versus* <9%)[d]	2.5 (1.2 to 5.4)	0.02
change from baseline to second follow-up interval (≥1% increase *versus* <1% increase)	1.1 (0.9 to 1.5)	0.40
Baseline ACEI use (*versus* no ACEI use)	0.7 (0.3 to 1.6)	0.33
Baseline SBP (≥115 *versus* <115 mmHg)	0.8 (0.3 to 1.9)	0.59
Baseline DBP (≥75 *versus* <75 mmHg)	0.6 (0.3 to 1.3)	0.11

[a]Model adjusted for gender; smoking; new-onset microalbuminuria (*versus* prevalent); and baseline values of urinary AER, estimated GFR, and serum cholesterol. In multivariate analysis, these additional variables were not associated with the odds of early renal function decline. Odds ratios (OR) represent the adjusted odds of early renal function decline for those with the determinant relative to those without. For example, participants with baseline HbA_{1c} ≥9 have 2.5 times the odds of early renal function decline relative to those with baseline levels <9%. Median value was 115 for SBP and 75 mmHg for DBP. CI, confidence interval.

[b]Duration for patients with prepubertal diabetes onset is calculated from age 11 yr.

[c]See Figure 3 legend for definitions.

[d]The relationship of HbA_{1c} with frequency of early renal function decline is linear. For example, the OR is 2.6 for those with values ≥8% as compared with below, and 2.2 for those with values ≥7% as compared to below.

betic nephropathy (50–53). However, its association with the risk for early progressive renal function decline was NS in this study. Most likely, this is related to the lack of precision of BP measurements in a clinical setting and possibly the subtlety of the effect at this early stage. Although ACEI therapy was associated with a lower risk for renal function decline, the effect was NS and did not share the magnitude of effect that was seen with lower levels of HbA_{1c} or the regression of microalbuminuria.

This study contributes toward the goal of establishing a clinical algorithm for early identification of patients who are at risk for ESRD. On the basis of a low risk for early renal function decline, a patient with type 1 diabetes can expect to have a low risk for developing ESRD if microalbuminuria has never developed or if it has regressed after its onset. However, those who develop persistent microalbuminuria warrant screening for early renal function decline using cystatin C.

The results of this study must be considered in light of two potential limitations. First, the study consisted of a relatively young population with type 1 diabetes, and, therefore, the results may not be generalizable to the elderly or to those with type 2 diabetes. Second, the accuracy of serum cystatin C at estimating changes in GFR in the low ranges—when it is already impaired—has not been sufficiently studied. For example, the advantages of 100/cystatin C formula may diminish as GFR falls into the impaired range; as such, other proposed equations using cystatin C tend to adjust the estimated GFR to even lower values (54). Although the best strategy for estimating GFR from cystatin C in the impaired range has yet to be determined, use of the equation 100/cystatin C rather than an alternative estimating equation (54) would be predicted to underestimate conservatively the magnitude of early progressive renal function decline in this population rather than to overestimate it.

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Disclosures

None.

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See the related editorial, "Glomerular Filtration Rate and Albuminuria: Twin Manifestations of Nephropathy in Diabetes," on pages 1036–1037.