Long-term Renal Outcomes of Patients With Type 1 Diabetes Mellitus and Microalbuminuria

An Analysis of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Cohort

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Background: Microalbuminuria is a common diagnosis in the clinical care of patients with type 1 diabetes mellitus. Long-term outcomes after the development of microalbuminuria are variable.

Methods: We quantified the incidence of and risk factors for long-term renal outcomes after the development of microalbuminuria in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. The DCCT randomly assigned 1441 persons with type 1 diabetes to intensive or conventional diabetes therapy, and participants were subsequently followed up during the observational EDIC study. During the DCCT/EDIC study, 325 participants developed incident persistent microalbuminuria (albumin excretion rate, ≥30 mg/24 h at 2 consecutive study visits). We assessed their subsequent renal outcomes, including progression to macroalbuminuria (albumin excretion rate, ≥300 mg/24 h at 2 consecutive visits), impaired glomerular filtration rate (estimated glomerular filtration rate, <60 mL/min/1.73 m^2 at 2 consecutive study visits), end-stage renal disease, and regression to normoalbuminuria (albumin excretion rate, <30 mg/24 h at 2 consecutive visits).

Results: The median follow-up period after persistent microalbuminuria diagnosis was 13 years (maximum, 23 years). Ten-year cumulative incidences of progression to macroalbuminuria, impaired glomerular filtration rate, end-stage renal disease, and regression to normoalbuminuria were 28%, 15%, 4%, and 40%, respectively. Albuminuria outcomes were more favorable with intensive diabetes therapy, lower glycated hemoglobin level, absence of retinopathy, female sex, lower blood pressure, and lower concentrations of low-density lipoprotein cholesterol and triglycerides. Lower glycated hemoglobin level, absence of retinopathy, and lower blood pressure were also associated with decreased risk of impaired glomerular filtration rate.

Conclusions: After the development of persistent microalbuminuria, progression and regression of kidney disease each commonly occur. Intensive glycemic control, lower blood pressure, and a more favorable lipid profile are associated with improved outcomes.

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MICROALBUMINURIA (urine albumin excretion rate [AER], 30-300 mg/24 h) is a common diagnosis in the clinical care of patients with type 1 diabetes mellitus, with a lifetime cumulative incidence of 20% to 40%.[1-4] Clinical guidelines recommend regular screening for microalbuminuria because it is common, is known to be associated with adverse renal and cardiovascular outcomes, and can be treated with antagonists of the renin-angiotensin-aldosterone system (RAAS).[4]

The Diabetes Control and Complications Trial (DCCT) demonstrated that hyperglycemia is a risk factor for developing microalbuminuria and that intensive diabetes therapy can prevent or delay the development of microalbuminuria.[5,6] Additional risk factors for microalbuminuria have been well described and include older age, male sex, long duration of diabetes, smoking, obesity, elevated blood pressure, and genetic predisposition.[7-13]

Less is known about long-term renal outcomes of individuals with type 1 diabetes after microalbuminuria develops, in part because few studies are able to accurately ascertain the time at which microalbuminuria occurs and to perform detailed follow-up among participants for long subsequent periods. Accurate characterization of long-term renal outcomes is critically important to provide prognosis for patients with type 1 diabetes and to identify opportunities for therapeutic intervention.

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The DCCT and its observational extension, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, offer a unique opportunity to assess long-term clinical renal outcomes after the development of microalbuminuria because the time of albuminuria onset can be precisely defined using extensive longitudinal measurements and because participants have been followed up for more than 2 decades using standardized methods.[5,6] In this study, we describe long-term renal outcomes of persistent microalbuminuria (PMA) in the DCCT/EDIC cohort and assess risk factors for progression and regression of kidney disease. We focus on the potential effect of glycemia because the DCCT was a randomized trial of intensive diabetes therapy and because detailed longitudinal glycated hemoglobin data were collected during the DCCT/EDIC study.

METHODS

THE DCCT/EDIC STUDY

The DCCT was a multicenter clinical trial among patients with type 1 diabetes mellitus examining the effects of intensive diabetes therapy that was aimed at lowering glycemia as close as safely possible to the nondiabetic range compared with conventional therapy.[5,6] The trial included 2 cohorts, a primary prevention cohort (1-5 years' duration of diabetes, AER of <40 mg/24 h, and no retinopathy by fundus photography) and a secondary intervention cohort (1-15 years' duration of diabetes, AER of ≤200 mg/24 h, and ≥1 microaneurysm in either eye but no more than moderate nonproliferative retinopathy). Between August 23, 1983, through June 30, 1989, a total of 1441 persons aged 13 to 39 years were enrolled and randomly assigned to intensive or conventional diabetes therapy. Intensive therapy included 3 or more insulin injections daily or the use of an insulin pump, with the aim of achieving glycated hemoglobin levels of less than 6.05% (to convert glycated hemoglobin level to proportion of total hemoglobin, multiply by 0.01). The goal of conventional therapy was the prevention of hyperglycemic and hypoglycemic symptoms using 1 or 2 daily injections of insulin. Participants were followed up for a mean of 6.5 years until the DCCT closeout in 1993.

At the end of the DCCT, all former conventional treatment participants were offered instruction in intensive therapy, and all participants returned to their personal health care providers for ongoing diabetes care. All DCCT participants were invited to join the EDIC study, an observational extension of the DCCT, and 1375 of 1428 (96.3% of the surviving cohort) agreed to participate. During the EDIC study, the mean glycated hemoglobin levels, which had been separated by approximately 2% between the conventional and intensive therapy groups during the DCCT, converged between the former treatment groups.[6] The DCCT/EDIC study procedures were approved by the institutional review boards of participating centers, and all participants provided written informed consent. The study described herein includes data from the DCCT baseline through year 14 of the EDIC study (ending May 30, 2008).

COHORT WITH PMA

This analysis focuses on 325 DCCT/EDIC study participants who developed incident PMA during the course of the DCCT/EDIC study observation. For this and other epidemiological studies of the DCCT/EDIC cohort,[13-15] PMA is defined as an AER of at least 30 mg/24 h at 2 consecutive study visits. This definition of PMA differs from the original DCCT definition of microalbuminuria used for the assessment of treatment effect (AER, ≥40 mg/24 h at a single visit) to reflect current American Diabetes Association[4] and National Kidney Foundation[16] recommendations, which include a threshold of 30 mg/24 h and persistence, and to reduce the effect of measurement error on the diagnosis of microalbuminuria. The AER was measured yearly during the DCCT and every 2 years during the EDIC study. Urine was collected for 4 hours during a water diuresis, and albumin was measured by fluoroimmunoassay (coefficient of variation, 9.4%).[5] A diagnosis of PMA was based on 2 consecutive DCCT AER measurements, the last DCCT and first EDIC study AER measurements, or 2 consecutive EDIC study measurements. The cohort of 325 participants with incident PMA did not include 68 separate participants with an AER of at least 30 mg/24 h at their first 2 DCCT visits (prevalent microalbuminuria).

DEFINITIONS OF LONG-TERM RENAL OUTCOMES

Among the PMA cohort, we assessed progression to macroalbuminuria, development of impaired glomerular filtration rate (GFR), development of end-stage renal disease (ESRD), and regression to normoalbuminuria. Progression to macroalbuminuria was defined as an AER of at least 300 mg/24 h at 2 consecutive study visits. Impaired GFR was defined as an estimated GFR of less than 60 mL/min/1.73 m^2 at 2 consecutive study visits.[4,16] Regression to normoalbuminuria was defined as an AER of less than 30 mg/24 h at 2 consecutive study visits. Serum creatinine level was measured yearly during the DCCT/EDIC study using the modified Jaffe reaction, and the estimated GFR was calculated using the Modification of Diet in Renal Disease formula.[17] End-stage renal disease was defined as the initiation of maintenance dialysis (n=13) or kidney transplantation (n=8), assessed yearly by questionnaire. Renal outcomes were not mutually exclusive.

COVARIATES

Demographic data and smoking were assessed by self-report. Body mass index was calculated as weight in kilograms divided by height in meters squared. Blood pressure was measured by trained personnel.[18] All laboratory measurements were completed at the DCCT/EDIC study central biochemistry laboratory. Glycated hemoglobin level was measured using high-performance ion-exchange liquid chromatography (coefficient of variation, <4%).[19] Plasma lipids were measured using conventional enzymatic methods, with low-density lipoprotein cholesterol concentration calculated using the Friedewald formula. Prevalence of any retinopathy (≥1 microaneurysm in either eye) was assessed using 7-field stereofundus photography.

Medication use was assessed yearly by self-report only during the EDIC study. The use of angiotensin-converting enzyme inhibitors was discouraged during the DCCT, and only 6.2% reported angiotensin-converting enzyme inhibitor use at their first EDIC study visit. Angiotensin receptor blockers were available for clinical use only during the EDIC study. RAAS inhibitors (angiotensin-converting enzyme inhibitors and angiotensin receptor blockers) were combined and analyzed as a class. Hydroxymethylglutaryl coenzyme A reductase inhibitors became available at the end of the DCCT (beginning in 1989), and the use of a lipid-lowering agent was reported by only 2.2% of participants at their first EDIC study visit.

STATISTICAL ANALYSIS

To describe the development of PMA over the clinical course of type 1 diabetes in our population, we first graphed the cumulative incidence of PMA by duration of diabetes in the full DCCT/

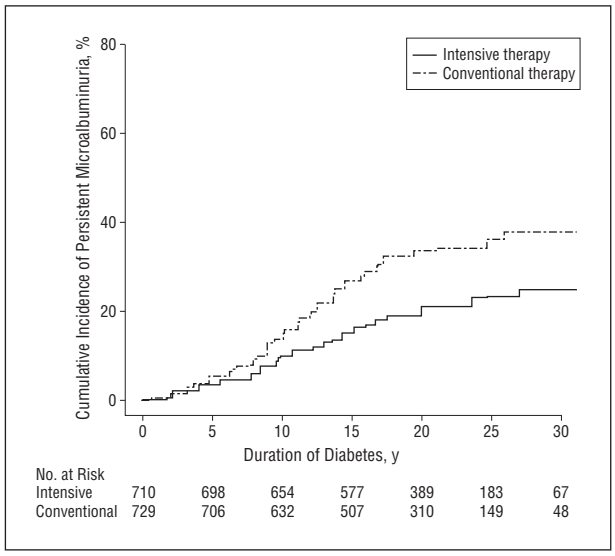

Figure 1. Cumulative incidence of persistent microalbuminuria in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study by duration of type 1 diabetes and by Diabetes Control and Complications Trial treatment assignment.

EDIC cohort. We used an estimator by Turnbull[20] for interval-censored observations to allow for left censoring of participants with prevalent PMA and right censoring of participants who did not develop PMA during the DCCT/EDIC observation period.

Among 325 participants who developed incident PMA, long-term renal outcomes were evaluated separately. Time at risk began at PMA diagnosis and extended to diagnosis of the renal outcome being analyzed or to each participant's penultimate AER measurement (for progression and regression of microalbuminuria), penultimate estimated GFR (for impaired GFR), or last study visit (for ESRD). Incidence rates were expressed in person-years. In prevalence analyses only, normoalbuminuria, microalbuminuria, and macroalbuminuria were assessed at 2-year intervals, and the mean AER was used if 2 AER measurements were available.

Risk factors for long-term renal outcomes after diagnosis of PMA were assessed using cumulative incidence plots and discrete Cox proportional hazards regression models.[21] We repeated all analyses using a Weibull model for interval censoring, with no substantial differences in results. Cox proportional hazards regression models assessed as exposures (1) characteristics at the time of PMA diagnosis and (2) characteristics at the time of follow-up examination (time-updated variables) and adjusted for age, sex, and duration of diabetes at the time of PMA diagnosis. Analyses were performed using commercially available statistical software (SAS version 9.1; SAS Institute, Cary, North Carolina).

RESULTS

INCIDENCE OF PMA

Among participants randomly assigned to DCCT conventional therapy, PMA developed most frequently during the second decade after diagnosis of diabetes (**Figure 1**). Cumulative incidences of PMA were 14%, 33%, and 38% at 10, 20, and 30 years' duration of diabetes, respectively, and the cumulative incidence seemed to plateau below 40%. Among participants assigned to intensive therapy, the cumulative incidence of PMA was reduced, and the development of PMA during the second decade after diagnosis of diabetes was particularly blunted. Cumulative incidences of PMA were 10%, 21%, and 25% at 10, 20, and 30 years' duration of diabetes, respectively, and the cumulative incidence seemed to plateau near 25%.

Table 1. Characteristics of 325 Participants in the DCCT/EDIC Study at the Time of Incident Persistent Microalbuminuria Diagnosis

Characteristic	Value
Demographic Data and Medical History	
Age, mean (SD), y	33.3 (10.0)
Female sex, No. (%)	132 (40.6)
White race/ethnicity, No. (%)	304 (93.5)
Duration of diabetes, mean (SD), y	14 (6)
DCCT cohort, No. (%)	
Primary prevention	140 (43.1)
Secondary prevention	185 (56.9)
DCCT treatment assignment, No. (%)	
Intensive therapy	115 (35.4)
Conventional therapy	210 (64.6)
Time of persistent microalbuminuria diagnosis, No. (%)	
During the DCCT	170 (52.3)
During the EDIC study	155 (47.7)
Retinopathy	231 (71.1)
Active smoking	99 (30.5)
RAAS inhibitor use	24 (7.4)
Lipid-lowering medication use	16 (4.9)
Physical Examination	
Body mass index, mean (SD)[a]	26.0 (4.1)
Blood pressure, mean (SD), mm Hg	
Systolic	122 (14)
Diastolic	78 (9)
Laboratory Data	
Glycated hemoglobin level, mean (SD), %	9.4 (1.8)
Albumin excretion rate, median (interquartile range), mg/24 h	48 (37-76)
Estimated GFR, mL/min/1.73 m^2	114 (30)
Total cholesterol concentration, mean (SD), mg/dL	190 (38)
High-density lipoprotein cholesterol concentration, mean (SD), mg/dL	51 (13)
Triglycerides concentration, mean (SD), mg/dL	108 (89)
Low-density lipoprotein cholesterol concentration, mean (SD), mg/dL	119 (32)

Abbreviations: DCCT/EDIC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study; GFR, glomerular filtration rate; RAAS, renin-angiotensin-aldosterone system.

SI conversion factors: To convert cholesterol concentration to millimoles per liter, multiply by 0.0259; glycated hemoglobin level to proportion of total hemoglobin, multiply by 0.01; triglycerides concentration to millimoles per liter, multiply by 0.0113.

[a] Calculated as weight in kilograms divided by height in meters squared.

CLINICAL CHARACTERISTICS

Of 325 participants who developed incident PMA, 40.6% were women, and 35.4% had been assigned to intensive diabetes therapy (**Table 1**). At the time of PMA diagnosis, the mean age was 33.3 years, the mean duration of diabetes was 14 years, 71.1% of participants had retinopathy, and 47.7% were in the EDIC phase of the study. The median AER was 48 mg/24 h, and the mean estimated GFR was 114 mL/min/1.73 m^2. Compared with participants assigned to DCCT conventional therapy who developed PMA,

Table 2. Incidence of Long-term Renal Outcomes After Diagnosis of Persistent Microalbuminuria Among 325 Participants in the DCCT/EDIC Study

Variable	Follow-up		Events				
	Median (Range), y	Person-years	No.	Incidence Rate[a]	Cumulative Incidence, %		
					5 y	10 y	15 y
Overall follow-up	13 (1-23)	4096	...	...	...	...	...
Normoalbuminuria	8 (2-21)	1302	117	9.1	23	40	48
Macroalbuminuria	8 (0-21)	2578	98	3.8	22	28	39
Impaired GFR	11 (0-22)	3416	60	1.8	10	15	19
ESRD	12 (1-23)	4026	21	0.5	1	4	7

Abbreviations: DCCT/EDIC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study; ellipsis, not applicable; ESRD, end-stage renal disease; GFR, glomerular filtration rate.
[a]Per 100 person-years.

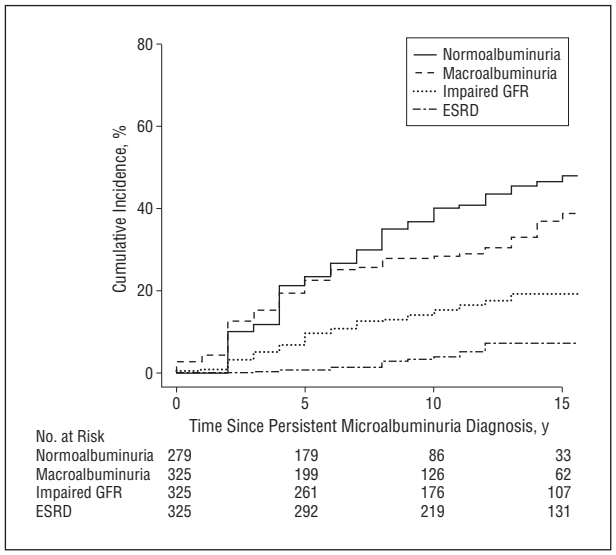

Figure 2. Cumulative incidence of long-term renal outcomes after the development of persistent microalbuminuria (time 0) among 325 participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. ESRD indicates end-stage renal disease; GFR, glomerular filtration rate.

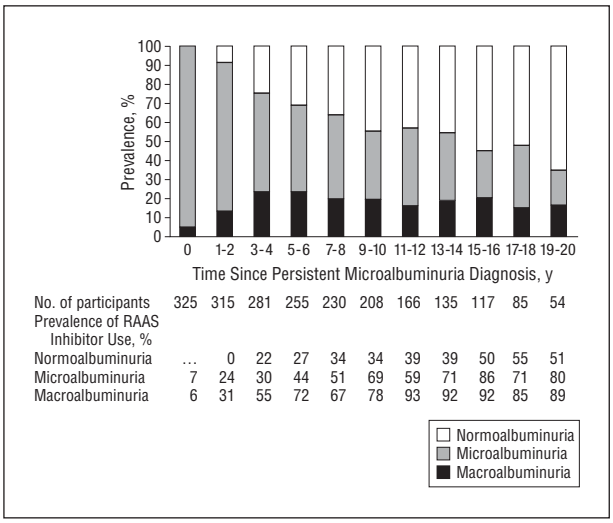

Figure 3. Prevalence of normoalbuminuria, microalbuminuria, and macroalbuminuria by time following the diagnosis of incident persistent microalbuminuria (time 0) among 325 participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Ellipsis indicates not applicable; RAAS, renin-angiotensin-aldosterone system.

participants assigned to intensive therapy who developed PMA did so at a slightly later duration of diabetes (15 vs 13 years), were slightly heavier (mean body mass index, 26.6 vs 25.0), had lower glycated hemoglobin levels (mean, 8.9% vs 9.6%), and were more likely to report the use of RAAS inhibitors (10.4% vs 5.7%) and lipid-lowering agents (7.8% vs 3.3%); other characteristics did not differ.

LONG-TERM RENAL OUTCOMES

The mean and median follow-up periods after diagnosis of PMA were 13 years, with a maximum follow-up period of 23 years (**Table 2**). Follow-up data for the AER and the estimated GFR were complete for 95.4% and 93.3% of study visits, respectively. Twenty-six of 325 participants (8.0%) with incident PMA died during the follow-up period. Ninety-eight participants progressed to macroalbuminuria, 60 developed impaired GFRs, 21 developed ESRD, and 117 regressed to normoalbuminuria; 26, 4, 0, and 44 of these events, respectively, occurred during the DCCT, with the remainder occurring during the EDIC follow-up period. Ten-year cumulative incidences of progression to macroalbuminuria, impaired GFR, ESRD, and regression to normoalbuminuria were 28%, 15%, 4%, and 40%, respectively (Table 2 and **Figure 2**). At the time of progression or regression, RAAS inhibitor use was reported by 36.7% of participants who progressed to macroalbuminuria, 70.7% of participants who developed impaired GFRs, and 24.6% of participants who regressed to normoalbuminuria.

Seventeen participants regressed to normoalbuminuria more than 10 years after the initial PMA diagnosis. At the time of regression to normoalbuminuria, the mean glycated hemoglobin level was 7.7%, and the mean blood pressure was 121/77 mm Hg. Prevalences of RAAS inhibitor and lipid-lowering medication use were 47.1% and 11.8%, respectively. Three of these late regressors developed sustained macroalbuminuria before regressing to normoalbuminuria, but none developed sustained impaired GFR before regressing.

Macroalbuminuria prevalence increased over the first 4 years following PMA diagnosis and then stabilized near

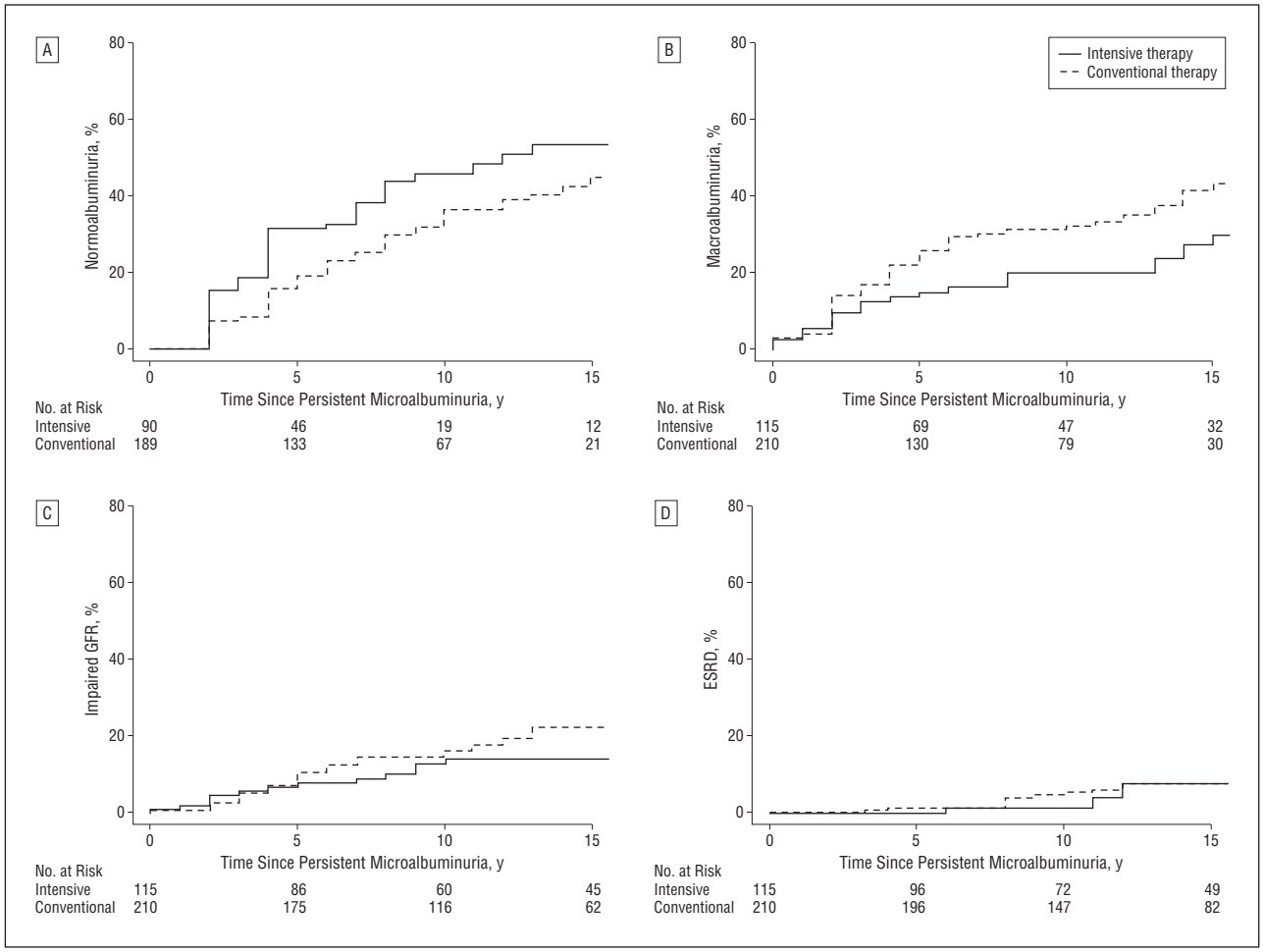

Figure 4. Cumulative incidence of long-term renal outcomes after the development of persistent microalbuminuria (time 0) among 325 participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study by Diabetes Control and Complications Trial treatment assignment. A, Regression to normoalbuminuria. B, Progression to macroalbuminuria. C, Impaired glomerular filtration rate (GFR). D, End-stage renal disease (ESRD).

20% (**Figure 3**). Further increases in macroalbuminuria may have been obscured by increasing prevalence of RAAS inhibitor use among participants with an AER measured in the microalbuminuria range (>50% at 7-8 years after PMA diagnosis). Normoalbuminuria became increasingly prevalent over the full follow-up period, exceeding 50% after 13 to 14 years. Fewer than 50% of participants who regressed to prevalent normoalbuminuria during the first 14 years after PMA diagnosis were using RAAS inhibitors.

INTENSIVE DIABETES THERAPY, GLYCEMIA, AND LONG-TERM RENAL OUTCOMES

Participants who were assigned to intensive diabetes therapy during the DCCT and developed PMA experienced more favorable long-term renal outcomes than those who were assigned to conventional diabetes therapy and developed PMA (**Figure 4**). Adjusting for age, sex, and duration of diabetes, the hazard ratios associated with intensive diabetes therapy were 0.64 (95% confidence interval [CI], 0.40-1.02) for progression to macroalbuminuria, 0.65 (95% CI, 0.36-1.16) for impaired GFR, and 1.92 (95% CI, 1.28-2.86) for regression to normoalbuminuria ($P<.05$ for regression to normoalbuminuria only) (**Table 3**). Further adjusting for body mass index and the use of RAAS inhibitors and lipid-lowering medications, the hazard ratios associated with intensive diabetes therapy were 0.61 (95% CI, 0.38-0.98) for progression to macroalbuminuria, 0.64 (95% CI, 0.35-1.17) for impaired GFR, and 2.16 (95% CI, 1.43-3.26) for regression to normoalbuminuria. Associations of intensive diabetes therapy with renal outcomes were stronger for participants diagnosed as having PMA during the DCCT compared with participants diagnosed as having PMA during the EDIC follow-up period, although these interactions were not statistically significant (data not shown). Lower glycated hemoglobin levels measured at PMA diagnosis or after PMA diagnosis were associated with decreased risk of progression to macroalbuminuria and of impaired GFR and with increased probability of regression to normoalbuminuria ($P<.05$ for all) (Table 3).

OTHER RISK FACTORS

Albuminuria outcomes were also more favorable (decreased risk of progression to macroalbuminuria and increased probability of regression to normoalbuminuria) with absence of retinopathy, female sex, lower blood pressure (at diagnosis or during the follow-up period), and

Table 3. Risk Factors for Long-term Renal Outcomes After Diagnosis of Persistent Microalbuminuria (PMA) Among 325 Participants in the DCCT/EDIC Study

	Macroalbuminuria		Impaired GFR		Normoalbuminuria	
Risk Factor	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Assessed at PMA Diagnosis						
Age, per y	1.00 (0.98-1.02)	.94	1.04 (1.01-1.07)	.01	1.00 (0.98-1.02)	.84
Female sex	0.52 (0.33-0.82)	.005	1.10 (0.65-1.87)	.73	2.53 (1.70-3.76)	<.001
Duration of diabetes, y						
<10	0.62 (0.38-1.02)	.06	0.54 (0.28-1.06)	.07	1.60 (1.04-2.45)	.03
10-19	1 [Reference]	. . .	1 [Reference]	. . .	1 [Reference]	. . .
≥20	0.27 (0.06-1.11)	.07	0.89 (0.31-2.59)	.84	1.38 (0.62-3.09)	.43
DCCT intensive therapy	0.64 (0.40-1.02)	.06	0.65 (0.36-1.16)	.14	1.92 (1.28-2.86)	.002
Retinopathy	3.15 (1.09-9.11)	.03	2.83 (0.64-12.50)	.17	0.46 (0.24-0.87)	.02
Active smoking	1.13 (0.73-1.75)	.57	1.04 (0.60-1.81)	.90	1.33 (0.87-2.03)	.19
RAAS inhibitor use	0.57 (0.17-1.94)	.37	1.17 (0.38-3.54)	.79	0.59 (0.14-2.57)	.49
Lipid-lowering medication use	2.16 (0.80-5.83)	.13	2.52 (0.84-7.55)	.10	1.04 (0.29-3.76)	.95
Body mass index, per kg/m^2	1.01 (0.96-1.07)	.64	0.95 (0.88-1.02)	.18	0.96 (0.91-1.01)	.13
Blood pressure, per 10 mm Hg						
Systolic	1.30 (1.10-1.54)	.003	1.06 (0.86-1.30)	.60	0.85 (0.72-0.99)	.04
Diastolic	1.38 (1.08-1.77)	.01	1.21 (0.89-1.65)	.23	0.71 (0.56-0.90)	.004
Glycated hemoglobin level, per %	1.25 (1.11-1.40)	<.001	1.33 (1.15-1.53)	<.001	0.76 (0.67-0.85)	<.001
Total cholesterol concentration, per 10 mg/dL	1.14 (1.05-1.23)	.001	1.07 (0.97-1.18)	.16	0.88 (0.82-0.94)	<.001
High-density lipoprotein cholesterol concentration, per 10 mg/dL	1.10 (0.85-1.42)	.48	1.21 (0.87-1.67)	.26	0.96 (0.78-1.18)	.69
Triglycerides concentration, per 10 mg/dL	1.06 (1.01-1.10)	.01	1.04 (0.98-1.10)	.15	0.93 (0.87-0.98)	.007
Low-density lipoprotein cholesterol concentration, per 10 mg/dL	1.12 (1.03-1.22)	.01	1.04 (0.93-1.16)	.52	0.88 (0.82-0.95)	.001
Albumin excretion rate, mg/24 h						
30-49	1 [Reference]	. . .	1 [Reference]	. . .	1 [Reference]	. . .
50-99	1.98 (1.23-3.18)	.005	1.42 (0.75-2.69)	.28	0.85 (0.54-1.36)	.50
≥100	3.33 (1.95-5.69)	<.001	3.17 (1.69-5.93)	<.001	0.70 (0.40-1.25)	.23
Time Updated						
Blood pressure, per 10 mm Hg						
Systolic	1.71 (1.49-1.97)	<.001	1.91 (1.65-2.21)	<.001	0.82 (0.70-0.95)	.008
Diastolic	2.03 (1.63-2.53)	<.001	2.17 (1.67-2.82)	<.001	0.68 (0.55-0.84)	<.001
Glycated hemoglobin level, per %	1.25 (1.10-1.42)	<.001	1.13 (0.95-1.33)	.16	0.79 (0.69-0.90)	<.001

Abbreviations: CI, confidence interval; DCCT/EDIC, Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study; ellipsis, not applicable; GFR, glomerular filtration rate; HR, hazard ratio; RAAS, renin-angiotensin-aldosterone system.

lower concentrations of low-density lipoprotein cholesterol and triglycerides (Table 3). Younger age, absence of retinopathy, and lower blood pressure (the latter during the follow-up period) were also associated with decreased risk of impaired GFR. RAAS inhibitor use was not associated with improved albuminuria or GFR outcomes, with or without adjustment for blood pressure. The AER at PMA diagnosis was strongly associated with progression to macroalbuminuria and development of impaired GFR but was only weakly associated with regression to normoalbuminuria.

COMMENT

This study characterizes long-term renal outcomes from the time of development of PMA in type 1 diabetes. Progression to macroalbuminuria, impaired GFR, and ESRD occurred at clinically important frequencies (cumulative incidences of 28%, 15%, and 4% at 10 years, respectively). However, regression to normoalbuminuria was the most common renal outcome, with a 10-year cumulative incidence of 40%. Therefore, the development of PMA does not necessarily represent the start of an inexorable downhill course for diabetic nephropathy. Among persons who develop microalbuminuria, lower levels of glycemia and the use of intensive insulin therapy remain associated with more favorable long-term renal outcomes, providing provocative evidence that glycemic control may help prevent progression of existing kidney disease in addition to the development of microalbuminuria. Other modifiable risk factors associated with long-term renal outcomes included blood pressure (for albuminuria and GFR outcomes) and lipid concentrations (for albuminuria outcomes only).

Progression of PMA to macroalbuminuria and impaired GFR was common in our study. This progression carries important implications, as it portends substantially increased risk of cardiovascular events and mortality.[7,22] Although progression to ESRD has been uncommon in the DCCT/EDIC cohort,[6] this study reinforces the adverse prognostic renal implications of microalbuminuria by noting substantial cumulative incidences of ESRD of 4% and 7% at 10 and 15 years after the development of PMA, respectively. Furthermore, ESRD incidence rates will likely increase with further EDIC follow-up.

Microalbuminuria was once viewed as the first step in a committed course of progressive diabetic kidney disease in type 1 diabetes, but it is now widely recognized that microalbuminuria may commonly regress to normoalbuminuria.[23] Although RAAS inhibitors reduce urine

albumin excretion and can induce regression, most regression to normoalbuminuria in our study was spontaneous, as previously observed in other studies.[23,24] Our results also document regression to normoalbuminuria after more than a decade of PMA, mostly without RAAS inhibitor use and generally in the setting of excellent control of glycemia and blood pressure.

We observed an incidence of regression to normoalbuminuria higher than that in some studies[11,12,23] and comparable to that in other studies.[25-27] Our high incidence rate is likely owing to our unique study design. Participants were longitudinally screened for the onset of PMA, as recommended for clinical care.[4] This approach yields a representative mix of persons with incident PMA, which is less likely to be selected for persistent and severe disease compared with populations having prevalent microalbuminuria. Rates of regression may also vary with the frequency of AER ascertainment. More frequent AER sampling is likely to detect microalbuminuria of shorter duration, which is more susceptible to regression, and more frequent AER sampling after microalbuminuria diagnosis is likely to increase the observed rate of regression, each contributing to higher observed rates of disease "regression." Our sampling interval (every 1-2 years) is consistent with current screening recommendations and actual clinical care.

The DCCT[5,6] and the United Kingdom Prospective Diabetes Study[28] demonstrated an important role for glycemic control in the prevention of early diabetic kidney disease. However, the role of glycemic control in preventing progression of established kidney disease remains controversial.[12] In particular, it has been suggested that glycemic control may improve metabolic and endothelial abnormalities that lead to microalbuminuria but not necessarily fibrotic processes that lead to macroalbuminuria, impaired GFR, and ESRD. In the DCCT, intensive diabetes therapy significantly reduced the incidence of macroalbuminuria, but it has been difficult to determine whether this was owing to the large effect of intensive diabetes therapy on preventing the development of microalbuminuria or to effects on progression of microalbuminuria to macroalbuminuria per se.[5] The present study identifies hyperglycemia as an important risk factor for progression of established microalbuminuria to macroalbuminuria and impaired GFR. Furthermore, our results suggest that intensive diabetes therapy may help prevent this progression, whether applied before, at, or after the time of PMA diagnosis. The latter results are not definitive because participants were not randomized to diabetes therapy at the time of PMA diagnosis. The direction and magnitude of resulting bias cannot be determined, but it is reasonable to speculate that the benefits of intensive diabetes therapy were underestimated in our study, as the outcomes of participants who developed PMA with conventional therapy were compared with the outcomes of participants who developed PMA despite intensive therapy. Therefore, our findings suggest that glycemic control remains important for preventing renal progression in type 1 diabetes even after microalbuminuria has developed.

Our results highlight the known importance of blood pressure control in the prevention of diabetic kidney disease and again note the associations of lipid concentrations with renal outcomes.[11,27,29,30] We confirm that men with type 1 diabetes have less favorable albuminuria outcomes.[7,11,13] Sex was not associated with the development of impaired GFR in our analyses, although this relationship may be biased by the inclusion of sex in the formula used to estimate GFR.[17] Our data cannot be validly used to assess the effect of RAAS inhibitors or lipid-lowering medications on disease progression, as the use of these medications in this observational study is subject to confounding by indication.[31] As a result, and given rigorous randomized clinical trials demonstrating that RAAS inhibitors prevent progression of kidney disease in patients with type 1 and type 2 diabetes,[32-35] our data should not discourage the use of RAAS inhibitors in the setting of microalbuminuria.

Although our study population is not an inception cohort, our observed PMA cumulative incidence (25%-40% at 30 years' duration of diabetes) and timing (largely during the second decade of diabetes duration) are similar to those in prior studies.[7,11] This concordance reinforces the prior observation that complication rates among the DCCT participants assigned to conventional diabetes therapy are similar to historical rates in a community-based cohort.[36]

The main strengths of this study derive from the careful longitudinal characterization of the DCCT/EDIC participants over a long duration of follow-up, allowing identification of PMA at or near its time of onset and accurate diagnosis of subsequent outcomes. By requiring persistence of microalbuminuria at diagnosis and persistence of normoalbuminuria, macroalbuminuria, and impaired GFR during the follow-up period, we are able to report changes in disease status with confidence. As a result, our findings offer relevant guidance to clinicians and patients who are newly diagnosed as having PMA.

This study also has limitations. We evaluated GFR only as a dichotomous outcome, although early renal function decline is also likely to have important clinical implications.[37] Few ESRD cases were observed. The incidence and outcomes of PMA may be changing over time with innovations in clinical care, including increased RAAS inhibitor use. We did not assess cardiovascular and mortality outcomes; however, because death has been uncommon in the DCCT/EDIC study relative to renal outcomes,[38] it is unlikely that the incidence of renal outcomes was substantially biased because of informative censoring.

In conclusion, progression and regression of kidney disease commonly occur after the development of PMA in type 1 diabetes, suggesting that PMA diagnosis represents a valuable occasion to assess and target renal interventions. In particular, intensive diabetes therapy seems to improve renal outcomes after the development of PMA in addition to preventing progression to microalbuminuria.

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