Risk Factors for Kidney Disease in Type 1 Diabetes

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OBJECTIVE

In type 1 diabetes (T1D), the course of microalbuminuria is unpredictable and timing of glomerular filtration rate (GFR) loss is uncertain. Thus, there is a need to identify the risk factors associated with the development of more advanced stages of kidney disease through large, long-term systematic analysis.

RESEARCH DESIGN AND METHODS

Multivariable Cox proportional hazards models assessed the association of baseline and time-dependent glycemic and nonglycemic risk factors for incident macroalbuminuria and reduced estimated GFR (eGFR; defined as <60 mL/min/1.73 m^2) over a mean of 27 years in the Diabetes Control and Complications Trial (DCCT) cohort.

RESULTS

Higher mean HbA_{1c} (hazard ratio [HR] 1.969 per 1% higher level [95% CI 1.671–2.319]) and male sex (HR 2.767 [95% CI 1.951–3.923]) were the most significant factors independently associated with incident macroalbuminuria, whereas higher mean triglycerides, higher pulse, higher systolic blood pressure (BP), longer diabetes duration, higher current HbA_{1c}, and lower mean weight had lower magnitude associations. For incident reduced eGFR, higher mean HbA_{1c} (HR 1.952 per 1% higher level [95% CI 1.714–2.223]) followed by higher mean triglycerides, older age, and higher systolic BP were the most significant factors.

CONCLUSIONS

Although several risk factors associated with macroalbuminuria and reduced eGFR were identified, higher mean glycemic exposure was the strongest determinant of kidney disease among the modifiable risk factors. These findings may inform targeted clinical strategies for the frequency of screening, prevention, and treatment of kidney disease in T1D.

The lifetime risk of kidney disease in type 1 diabetes (T1D) has traditionally been estimated at ~50% but may exceed 70% (1). Diabetic kidney disease remains the leading cause of end-stage renal disease (ESRD) in North America (2) and is defined by the development of albuminuria or by loss in glomerular filtration rate (GFR). Levels of albuminuria >300 mg/24 h (termed macroalbuminuria) and estimated GFR <60 mL/min/1.73 m^2 (termed "reduced eGFR") are seen as clinically relevant advanced stages of kidney disease because of their strong association with subsequent ESRD, cardiovascular disease, and mortality (3).

The traditional concept of diabetic kidney disease holds that microalbuminuria (albumin excretion rate [AER] ≥30 mg/24 h) is the fundamental early prognostic variable that heralds macroalbuminuria (4–6), which, after long-term exposure, is

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followed by a decline in GFR that ultimately leads to ESRD (7). However, two key refinements to this concept have arisen. First, contrary to the traditional model, microalbuminuria has been proven to be a dynamic process that is more likely to remit to normal albumin excretion (termed "normoalbuminuria") than to progress (8,9). Second, a subset of individuals may experience decline in GFR prior to or during microalbuminuria regardless of the subsequent trajectory of progression or remission of microalbuminuria. Risk factors for the development of microalbuminuria, its progression, and its remission and for the development of early GFR loss have been well documented (10,11). In light of the dynamic process of microalbuminuria and the uncertain timing of the initiation of GFR loss, there is a need to identify risk factors associated with progression to advanced stages of kidney disease (macroalbuminuria and reduced eGFR) through systematic analysis in a large cohort of individuals with T1D followed longitudinally over many years.

The Diabetes Control and Complications Trial (DCCT) previously demonstrated the fundamental importance of reducing glycemic exposure to prevent or delay the development of early microvascular complications of T1D, including microalbuminuria, compared with conventional therapy (12–15). During the Epidemiology of Diabetes Interventions and Complications (EDIC) study, after 18 years of follow-up from the end of the DCCT, the risk of macroalbuminuria and reduced eGFR subsequently were reduced by 61% and 44%, respectively, in the original intensive therapy group as compared with conventional therapy (16). Although this work clearly proved a causal relationship between higher glycemic exposure in the development and progression of diabetic kidney disease, the relative importance of other risk factors such as hypertension, dyslipidemia, body weight, hyperlipidemia, and the presence of smoking could not be fully addressed.

We aimed to determine which established and putative clinical risk factors are of greatest importance for the incidence of macroalbuminuria and for the incidence of reduced eGFR in individuals with T1D after a mean follow-up of 27 years of the DCCT/EDIC cohort.

RESEARCH DESIGN AND METHODS

Study Design and Participants

The methods of the DCCT and EDIC study have been described in detail (17,18). In brief, the DCCT (1983–1993) was a randomized, controlled clinical trial that assigned 1,441 participants with T1D to either intensive therapy (n = 711) or conventional diabetes therapy (n = 730) to evaluate the impact of glycemia on the development and progression of diabetes complications. Intensive therapy was aimed at achieving glycemic control as close to the nondiabetic range as safely possible, whereas conventional therapy was aimed at preventing symptoms of hypo- or hyperglycemia without specific glucose targets. At DCCT baseline, the study cohort included a primary prevention cohort with 1–5 years diabetes duration, no retinopathy based on stereoscopic fundus photography, and $<$40 mg of albuminuria per 24 h and a secondary intervention cohort with 1–15 years duration, minimal to moderate nonproliferative retinopathy, and $<$200 mg of albuminuria per 24 h (17). Additional exclusion criteria included neuropathy sufficiently severe to require therapy, hypertension ($\geq$140/90 mmHg or use of antihypertensive medication), and hyperlipidemia (LDL $>$130 mg/dL or use of lipid-lowering medication). At the end of the DCCT, after an average follow-up of 6.5 years, all participants were taught intensive therapy and were referred to their health care providers for subsequent diabetes care. EDIC (1994 to present) enrolled 97% of the entire DCCT cohort, with 93% of the cohort survivors still actively participating after $>$20 years of additional follow-up. The DCCT and EDIC protocols were approved by the institutional review boards of all participating centers, and all participants provided written informed consent.

Risk Factors

Recognized and putative risk factors were assessed by standardized methods at periodic visits during DCCT and EDIC (2,3). Procedures for the measurement of blood pressure (BP) and antihypertensive use were described previously (15). In brief, during the DCCT, BP was measured every 3 months, and hypertension was a predefined outcome of interest. During the EDIC study, BP was measured and use and intended purpose of the antihypertensive medications was obtained at each annual visit. Incident hypertension was defined by the occurrence of systolic BP $\geq$140 and/or diastolic BP $\geq$90 mmHg on two consecutive annual visits. Pulse pressure was calculated as the difference between systolic and diastolic pressure. HbA_{1c} was measured with a high-performance liquid chromatography method quarterly during DCCT and annually during EDIC (19). Fasting lipid levels (cholesterol, triglycerides, HDL, and LDL) and albuminuria were measured annually during DCCT and every other year during EDIC. All laboratory measurements were performed in the DCCT/EDIC central biochemistry laboratory with standardized methods, and long-term quality control measures were in place to guard against any long-term measurement drift.

Similar to our previous work (20), candidate risk factors were grouped into the following 11 blocks (described in detail in Supplementary Table 1): design (treatment group and cohort from the original DCCT design), physical (sex, age, weight, and BMI), behavioral (smoking, drinking, and exercise), family history (family history of hypertension, myocardial infarction, T1D, and type 2 diabetes [T2D]), BP/pulse (systolic and diastolic BP, pulse pressure, and pulse rate), medication use (ACE inhibitors, angiotensin receptor blockade, β-adrenergic blockers, calcium channel blockers, and lipid-lowering agents), lipid levels (total cholesterol, triglycerides, LDL cholesterol [LDLc], and HDL cholesterol [HDLc]), diabetes specific (duration of diabetes at enrollment, stimulated C-peptide at DCCT baseline, and daily insulin dose), microvascular complications (eGFR, AER $\geq$300 mg/24 h, presence of proliferative diabetic retinopathy, presence of clinically significant macular edema, and presence of three-step progression on the Early Treatment Diabetic Retinopathy Study [ETDRS] scale), hypoglycemia events (coma, seizure, and/or episodes requiring assistance), and glycemia (HbA_{1c} at eligibility and HbA_{1c} during follow-up). A risk factor could be included in the model as a fixed or baseline covariate (labeled as B in Supplementary Table 1), as a time-dependent covariate using the most recent measurement (C), or as the updated mean of all follow-up values since randomization (M). For example, three

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HbA_{1c} measurements were analyzed: baseline HbA_{1c}, current HbA_{1c} (the most recent prior HbA_{1c} value that is used as a time-dependent covariate at each visit), and the updated mean HbA_{1c}, which is the weighted cumulative mean of the prior HbA_{1c} values up to each visit. To account for different measurement frequencies during DCCT (every 3 months) and EDIC (every 12 months), the updated mean was computed by weighting each value by the time interval since the last measurement.

Outcomes

AER was measured from 4-h urine samples by fluoroimmunoassay from DCCT baseline through EDIC year 18 (2012). After EDIC year 19, spot urine samples were collected, and AER was estimated using the ratio of urine albumin and creatinine concentrations (21). Serum creatinine was measured annually throughout. Serum creatinine levels, age, sex, and race were used to calculate the eGFR using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (15). ESRD was defined as the initiation of maintenance dialysis or kidney transplantation assessed yearly by questionnaire and adjudicated centrally. Macroalbuminuria was defined as AER $\geq$300 mg/24 h, and reduced eGFR was defined as eGFR $<$60 mL/min/1.73 m^2 on at least one occasion or progression to ESRD (9,13,15).

Statistical Analysis

To have adequate power to detect associations of interest and reduce the chance of false-positive findings, the multivariable risk modeling analyses presented herein were embargoed until accruing 100 conventional group outcome cases and conservatively estimating 150 cases (for which 192 were observed in final analysis) in the combined cohort. Allowing for an $R^2 = 0.35$ for the association of up to 10 adjusting covariates with a given risk factor of interest, and using a test at the 0.01 level (two sided), this number of events provided 83% power to detect a 30% risk reduction per SD change in a factor (22). For each outcome (macroalbuminuria and reduced eGFR), the analysis was based on the time to that outcome. The event-free (survival) probability (or its complement, the cumulative incidence) was obtained using the Kaplan-Meier method. Semiparametric Cox proportional hazards (PH) models assessed the association between fixed and time-dependent covariates and the risk of an outcome, and the proportionality assumption was tested (23). The follow-up was censored at the time of death for individuals who died before reaching the outcomes (n = 107 participants died before reaching macroalbuminuria, and n = 115 participants died before reaching reduced eGFR), and therefore the associations described by the Cox PH models are based on cause-specific hazard ratios (HRs). The functional form for the association between the weighted updated mean HbA_{1c} and the empirical log hazards of macroalbuminuria and reduced eGFR were investigated using smoothing splines (24).

Continuous variables were described using medians and first and third quartiles, and discrete variables using counts and percentages. The risk factor variable selection approach was previously described (20). In brief, both forward- and backward-selection approaches were used. The forward-selection procedure added variables into the Cox PH model one block at a time (see Supplementary Table 1 for block composition), and at each step, factors were eliminated using backward elimination to yield the best subset model based on the minimum (best) Akaike information criterion (AIC) (16) and a penalized likelihood (lasso method) (25). The next block of variables was then entered, and the process continued until a final model was reached. The backward-selection approach used the lasso and, separately, selected the model with the best (smallest) AIC, both starting with all the variables included in the model. Interaction terms with sex were used to investigate sex differences in the effect of covariates on risk of kidney disease.

Two types of models were considered. First, we identified nonrenal mechanistic models in which AER and eGFR were not included as predictors with the objective of identifying covariates that could reflect nonrenal processes that affect risk of nephropathy. Second, we identified clinical models that also included the current or updated mean AER as a predictor of macroalbuminuria and the current or mean level of eGFR as a predictor of reduced eGFR. These prediction models reflect the common use of periodic measurements of AER and eGFR in clinical practice for prediction of later-stage diabetic kidney disease. As any z statistic with absolute value of 3.89 or larger has $P < 0.0001$, and z values as high as 10–20 may be observed, the z value better represents the significance of the covariate effect in the model than does the designation "$P < 0.0001$." Thus, the z value is used to determine the relative magnitude of association for each variable.

RESULTS

With a mean follow-up of 27 years, there were a total of 192 macroalbuminuria cases (rate of 5 events per 1,000 person-years) and 189 reduced eGFR cases (rate of 4.9 events per 1,000 person-years). Supplementary Fig. 1 shows the number of subjects at risk and the event-free (survival) curves for macroalbuminuria and reduced eGFR over the 30 years of DCCT/EDIC. The event-free (survival) probability after 30 years of follow-up (Supplementary Fig. 1) declined to ~85% for both macroalbuminuria and reduced eGFR, although there was little decline (lower incidence) of reduced eGFR during the first 15 years of follow-up. Approximately 75% of the participants remained free from both macroalbuminuria and reduced eGFR after 30 years of follow-up. Macroalbuminuria cases and reduced eGFR cases were frequently not concordant. Of the 189 reduced eGFR cases, 98 (52%) had developed macroalbuminuria during follow-up, either before or after reaching reduced eGFR. Reduced eGFR without macroalbuminuria was reached in 91, whereas 94 had macroalbuminuria without reduced eGFR.

Baseline Characteristics

On enrollment in DCCT, 53% of the participants were males, with a median (first and third quartiles) age of 27 years (22, 32), duration of diabetes of 51 months (28, 109), and HbA_{1c} of 8.7% (7.8%, 9.9%), and 18% were smokers. Compared with participants without macroalbuminuria, those with incident macroalbuminuria were more likely to have been in the conventional therapy group and to have been adolescents ($<$18 years of age) at baseline, and to be male, older, and smokers (Table 1). They also had higher pulse and were more likely to have hypertension, higher triglycerides, lower HDLc, and higher

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Table 1—Baseline characteristics of DCCT/EDIC participants according to the presence or absence of incident macroalbuminuria

		Any macroalbuminuria				
	Overall	No	Yes	HR	95% CI	*P* value
Treatment group (% conventional)	51	48	67	2.211	1.636–2.989	**<0.0001**
Cohort (% secondary)	50	49	55	1.220	0.918–1.622	0.1702
Sex (% males)	53	50	68	2.014	1.488–2.726	**<0.0001**
Age (year)	27 (22, 32)	27 (22, 32)	27 (18, 32)	0.980	0.961–0.999	**0.0450**
Adult vs. adolescent*	86	88	78	0.515	0.367–0.724	**0.0001**
Weight males (kg)	75 (68, 82)	75 (68, 82)	74 (67, 82)	0.992	0.976–1.009	0.3609
Weight females (kg)	62 (56, 69)	62 (56, 69)	63 (57, 70)	1.010	0.983–1.038	0.4599
BMI males (kg/m^2)	24 (22, 25)	23 (22, 25)	24 (22, 26)	1.065	1.000–1.135	0.0515
BMI females (kg/m^2)	23 (21, 25)	23 (21, 25)	23 (22, 26)	1.072	0.986–1.165	0.1032
Smoking (%)	18	17	25	1.572	1.134–2.180	**0.0067**
Drinking (% occasional or regular)	29	28	34	1.314	0.976–1.770	0.0720
Exercise (% moderate or strenuous)	82	81	85	1.307	0.880–1.939	0.1846
Family history of hypertension (%)	56	56	60	1.225	0.917–1.636	0.1687
Family history of MI (%)	49	49	47	0.912	0.687–1.211	0.5255
Family history of T1D (%)	14	14	15	1.113	0.750–1.652	0.5952
Family history of T2D (%)	9	9	9	0.978	0.594–1.608	0.9287
Systolic BP (mmHg)	114 (108, 122)	114 (108, 122)	116 (110, 124)	1.012	1.000–1.025	0.0577
Diastolic BP (mmHg)	72 (68, 80)	72 (68, 80)	74 (70, 80)	1.015	0.998–1.033	0.0784
Pulse pressure (mmHg)	40 (36, 48)	40 (36, 48)	40 (35, 48)	1.005	0.990–1.020	0.4934
Pulse (bpm)	76 (68, 84)	76 (68, 82)	76 (72, 88)	1.024	1.012–1.036	**0.0001**
Hypertension (%)	3	2	5	2.098	1.074–4.097	**0.0300**
Total cholesterol (mg/dL)	174 (153, 196)	173 (152, 196)	180 (158, 197)	1.003	0.999, 1.007	0.1401
Triglycerides (mg/dL)	73 (55, 93)	71 (54, 91)	86 (61, 111)	1.171**	1.113–1.233**	**<0.0001**
HDLc (mg/dL)	49 (42, 58)	50 (42, 58)	44 (40, 55)	0.980	0.967–0.992	**0.0014**
LDLc (mg/dL)	107 (91, 127)	106 (89, 127)	111 (97, 130)	1.004	0.999–1.009	0.0888
Duration of T1D (months)	51 (28, 109)	50 (28, 109)	58 (31, 110)	1.001	0.998–1.004	0.3716
C-peptide among those with duration <5 years (nmol/L)	0.12 (0.04, 0.25)	0.12 (0.04, 0.24)	0.13 (0.04, 0.30)	2.490	0.598–10.358	0.2098
C-peptide among those with duration >5 years (nmol/L)	0.03 (0.03, 0.04)	0.03 (0.03, 0.04)	0.03 (0.03, 0.03)	0.056	0.000–32.985	0.3760
HbA_{1c} (%)	8.7 (7.8, 9.9)	8.5 (7.7, 9.6)	9.7 (8.5, 11.1)	1.429	1.324–1.541	**<0.0001**

Follow-up time was a mean of 27 years. Shown are the HRs for the association of each factor with the risk of macroalbuminuria in unadjusted Cox models. Data are medians (first quartile, third quartile) or %. With HR denoting the HR per 1 unit change in a quantitative risk factor (such as systolic BP), the HR per *x* units change in that risk factor is HR^*x*, where ^ denotes "to the power of." *P* values ≤0.05 are reported in boldface type. MI, myocardial infarction. *Adult vs. adolescent at baseline. The adolescent cohort (original *n* = 195) were those randomized into DCCT aged 13–17 years, and the adult cohort were those aged 18–40. **Per 20% increase.

baseline HbA_{1c}. Higher risk of reduced eGFR was associated with the conventional therapy group, older age, higher BMI in males, smoking, higher diastolic BP and pulse, and higher levels of total cholesterol, triglycerides, LDLc, AER, and baseline HbA_{1c} (Supplementary Table 2).

Unadjusted and Minimally Adjusted Time-Dependent Models

Similar patterns were also observed when risk factors were considered individually over the entire follow-up as time-dependent variables (Supplementary Table 3). When adjusted for age and updated mean HbA_{1c}, sex, BP, lipids (current LDLc, HDLc, and triglycerides and updated mean HDLc and triglycerides), daily insulin dose, and any three-step progression in retinopathy were highly correlated with the risk of macroalbuminuria (Supplementary Table 3), whereas BP, lipids (current total cholesterol, LDLc, HDLc, and triglycerides and updated mean total cholesterol, HDLc, and triglycerides), use of antihypertensive, use of lipid-lowering medication, duration of T1D, AER, retinopathy, and glycemia were associated with the risk of incident reduced eGFR (Supplementary Table 4).

Multivariable Models

Table 2 reports the final multivariable Cox models for incident macroalbuminuria and incident reduced eGFR, in which the variables have been listed from highest to lowest magnitude of association based on the *z* test value. In the nonrenal mechanistic model for macroalbuminuria (Table 2*A*), a higher updated mean HbA_{1c} and male sex were the most significant risk factors. Other significant factors associated with increased risk of macroalbuminuria were higher mean triglycerides, higher pulse, higher systolic BP, longer duration of diabetes, use of any β-blockers, any history of hypertension, current HbA_{1c}, and lower mean weight. In the clinical model for macroalbuminuria further adjusted for AER (Table 3*A*), higher AER, male sex, and higher updated mean HbA_{1c} were the most significant factors, whereas the use of β-adrenergic receptor antagonists was a weaker but statistically significant factor. Interaction terms with sex in the final multivariable models were not significant.

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Table 2—The nonrenal mechanistic multivariable Cox models for macroalbuminuria (*A*) and reduced eGFR (*B*)

	Variable type**	HR	95% CI	*z*	*P* value
A. Incident macroalbuminuria (AIC = 2,336.69, χ^2 = 405.46, df = 10)					
Updated mean HbA_{1c} (%)	M	1.969	1.671–2.319	8.1106	<0.0001
Sex (male)	B	2.767	1.951–3.923	5.7154	<0.0001
Mean triglycerides (mg/dL)*	M	1.113	1.047–1.183	3.4368	0.0005
Pulse (bpm)	C	1.023	1.009–1.036	3.4274	0.0006
Systolic BP (mmHg)	C	1.017	1.006–1.028	3.0789	0.0020
Duration of T1D (months)	B	1.004	1.001–1.007	2.6567	0.0078
Any β-blockers	C	2.247	1.223–4.128	2.6091	0.0090
Any hypertension	C	1.630	1.128–2.356	2.6057	0.0091
Current HbA_{1c} (%)	C	1.168	1.031–1.323	2.4509	0.0142
Mean weight (kg)	M	0.984	0.972–0.997	−2.3719	0.0177
B. Incident reduced eGFR (AIC = 2,163.84, χ^2 = 372.64, df = 10)					
Updated mean HbA_{1c} (%)	M	1.952	1.714–2.223	10.0896	<0.0001
Updated mean triglycerides (mg/dL)*	M	1.212	1.137–1.292	5.9207	<0.0001
Age (years)	C	1.062	1.040–1.086	5.5170	<0.0001
Calcium channel blockers	C	2.432	1.689–3.503	4.7777	<0.0001
Systolic BP (mmHg)	C	1.020	1.011–1.029	4.6318	<0.0001
Hypertension	C	2.677	1.708–4.194	4.2970	<0.0001
Insulin dose (units/kg/day)	C	0.333	0.186–0.597	−3.6888	0.0002
Hypoglycemia requiring assistance	C	1.046	1.011–1.083	2.5916	0.0095
Pulse (bpm)	C	1.015	1.002–1.028	2.3488	0.0188
Abstinence from alcohol	C	1.376	1.012–1.871	−2.0363	0.0417

AER is excluded from the model for macroalbuminuria, whereas eGFR is excluded from the model for reduced eGFR. With HR denoting the HR per 1 unit change in a quantitative risk factor (such as systolic BP), the HR per *x* units change in that risk factor is HR^*x*, where ^ denotes "to the power of." *Per 20% increase. **Model is shown as a function of fixed (baseline, B) and time-dependent covariates, the latter either the current value (C) or updated mean from baseline (M).

In the nonrenal mechanistic model for reduced eGFR (Table 2*B*), updated mean HbA_{1c} was the strongest risk factor, followed by triglycerides, age, any use of calcium channel blockers, systolic BP, and hypertension. Other significant risk factors associated with higher risk of reduced eGFR were lower total daily insulin dose, hypoglycemia requiring assistance, and higher pulse, whereas alcohol use was protective. In the clinical model further adjusted for eGFR and AER (Table 3*B*), lower eGFR, higher AER, and higher updated mean HbA_{1c} were the strongest risk factors, whereas higher pulse, higher systolic BP, older age, use of calcium channel blocker agents, and reported alcohol abstinence were more weakly associated, but statistically significant, factors. Interaction terms with sex in the final multivariable models were not significant.

The risk gradients for macroalbuminuria and reduced eGFR incidence according to updated mean HbA_{1c} were linear over a wide range of HbA_{1c} (Supplementary Fig. 2).

CONCLUSIONS

The DCCT/EDIC study previously demonstrated the causal and durable impact of hyperglycemia on the risk of albuminuria (12), reduction in the incidence of reduced eGFR (13,14), and reduction of the incidence of hypertension (13) and a beneficial effect on lipid profiles (26,27). However, by analyzing exposure according to assignment to intensive or conventional glycemic therapy, these prior analyses were not able to determine the relative quantitative impact of the levels of baseline, current, or cumulative weighted mean levels of glycemic exposure with nonglycemic risk factors. In this evaluation of demographic, traditional, and diabetes-related risk factors in these participants, we found that higher long-term cumulative glycemic exposure was the strongest independent factor associated with the incidence of macroalbuminuria and, likewise, with the incidence of reduced eGFR. Although lower in magnitude of association than glycemic control (HbA_{1c}), higher triglyceride levels and higher BP were also independent risk factors associated with both macroalbuminuria and reduced eGFR. Owing to the measurement of risk factors beginning early after the diagnosis of T1D in this study design, and to the extremely long-term and systematic follow-up of the cohort, these results indicate with a high level of confidence that greater glycemic exposure likely represents the greatest causal contributor to late-stage kidney disease in T1D, greater than any other modifiable risk factor such as hypertension, dyslipidemia, or smoking.

Traditionally, it has been believed that lower glycemic exposure may have a profound effect on reducing the incidence and progression of albuminuria, while not having a substantial impact on preservation of GFR or the prevention of reduced eGFR (28). In a large population database, such "uncoupling" of the clinical markers of later-stage diabetic kidney disease was observed (28). Specifically, the improvements in glycemic control that occurred from the 1990s to 2000s in T1D and in T2D in the U.S. were accompanied by substantial reduction in the prevalence of albuminuria, whereas there was a small-to-moderate increase in the prevalence of reduced eGFR over the same time period. Although there are confounding factors, studies that demonstrated reductions in glycemic exposure via use of insulin pump therapy, islet cell transplantation, or pancreas transplantation failed to demonstrate improvements in eGFR despite improvement in albuminuria and even despite improvement in the glomerular lesions seen by renal biopsy (29).

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Table 3—The clinical multivariable Cox models for macroalbuminuria (*A*) and reduced eGFR (*B*)

	Variable type**	HR	95% CI	*z*	*P* value
A. Incident macroalbuminuria (AIC = 1907.30, χ^2 = 836.85, df = 11)					
Time-dependent AER (mg/24 h)*	C	1.320	1.283–1.358	19.3112	**<0.0001**
Sex (male)	B	2.420	1.696–3.454	4.8721	**<0.0001**
Updated mean HbA_{1c} (%)	M	1.462	1.233–1.734	4.3738	**<0.0001**
Time-dependent β-adrenergic receptor antagonist use	C	1.943	1.047–3.607	2.1075	**0.0350**
B. Incident reduced eGFR (AIC = 1866.47, χ^2 = 774.35, df = 12)					
Lower eGFR (mL/min/1.73 m^2)	C	1.114	1.101–1.127	15.7785	**<0.0001**
AER (mg/24 h)*	C	1.054	1.037–1.072	6.2173	**<0.0001**
Updated mean HbA_{1c} (%)	M	1.412	1.220–1.634	4.6391	**<0.0001**
Pulse (bpm)	C	1.020	1.007–1.033	3.0332	**0.0024**
Time-dependent systolic BP (mmHg)	C	1.011	1.003–1.020	2.7156	**0.0066**
Age (years)	C	1.030	1.006–1.054	2.5121	**0.0119**
Time-dependent calcium channel blockers	C	1.564	1.067–2.294	2.2932	**0.0218**
Abstinence from alcohol	C	1.385	1.012–1.896	2.0368	**0.0416**
Lower insulin dose (units/kg/day)	C	1.664	0.932–2.970	1.7221	0.0850
Updated mean triglycerides (mg/dL)*	M	1.054	0.983–1.131	1.4989	0.1338
Hypoglycemia requiring assistance	C	1.026	0.977–1.077	1.0439	0.2965
Hypertension	C	1.252	0.781–2.007	0.9351	0.3497

With HR denoting the HR per 1 unit change in a quantitative risk factor (such as systolic BP), the HR per *x* units change in that risk factor is HR^*x*, where ^ denotes "to the power of." *P* values ≤0.05 are reported in boldface type. *Per 20% increase. **Model shown as a function of fixed (baseline, B) and time-dependent covariates, the latter either the current value (C) or mean from baseline (M). Neither AER nor eGFR were excluded from consideration in the models.

The failure to demonstrate the impact of lower glycemic exposure on the incidence of reduced eGFR in these previous studies may have been related to the longer duration of diabetes at study entry and the relatively shorter observation period for the outcome in those studies. In contrast, the DCCT/EDIC cohort had a much shorter duration of T1D (1–15 years) at baseline and a long interval of follow-up. These two factors in combination can explain why the cumulative, but not the current, level of glycemic exposure was associated with incident reduced eGFR. It is also noteworthy that there were independent effects of both the current level of glycemic exposure and the measure of cumulative glycemic exposure on the incidence of macroalbuminuria. This implies that glycemic exposure has both a more immediate impact on macroalbuminuria, as captured by the current HbA_{1c} value, and a compounding effect, captured by the cumulative updated mean HbA_{1c}, which may be induced by the multiple hemodynamic and nonhemodynamic (tubulo-interstitital) mechanisms invoked in the processes of GFR loss (30).

We observed strong relationships between the later-stage renal outcomes and the nonmodifiable risk factors of male sex (for macroalbuminuria) and age (for reduced eGFR). The mechanisms for a putative protection in females from the incidence of macroalbuminuria are not known (31), although sex-specific influences on renal hemodynamic function have been reported (32). These differences may be through estrogen-mediated effects on renin-angiotensin-aldosterone system activation or possibly from sex-specific adiposity factors (32,33). The age-related decline in eGFR is well established in health and in disease and remains a consistent risk factor for reduced eGFR for both males and females in studies with sufficient sample size and study duration (34).

Although most convincingly described in patients with T2D, the specific independent association of higher triglyceride exposure with both incident macroalbuminuria and incident reduced eGFR in T1D has been previously reported (27,35). Although not known with certainty, the relationship is likely causal, preceding later-stage loss of eGFR, and potentially associated with the generalized vascular endothelial damage that reduces functional lipoprotein lipase that is particularly prominent in the subset of individuals with T1D who develop features of the metabolic syndrome (36,37). Furthermore, the effect may be mediated through its specific negative impact on insulin sensitivity (37).

Similarly, the independent association of measures of hypertension with both incident macroalbuminuria and reduced eGFR observed in the current analysis speak to the known causal association of hypertension as a risk factor for renal disease. The use of β-adrenergic blockers and calcium channel blockers associated with the renal outcomes most likely reflects an indication bias. As an example, in sensitivity analyses, previous hypertension remained significantly associated with macroalbuminuria in the final model in the absence of β-blockers (HR 1.6835, *P* = 0.0052), and use of β-blockers remained significant in the final model without hypertension (HR 2.4344, *P* = 0.0041). These results were qualitatively similar to those in the full model that included both history of hypertension and use of β-adrenergic blockers.

Comparable longitudinal study for risk factors of macroalbuminuria and impaired GFR have not been studied as systematically or for as long a follow-up as the DCCT/EDIC study. However, recent reports of 2- and 9-year follow-up in the Prospective Cohort Study in Patients With Type 2 Diabetes Mellitus for Validation of Biomarkers (PROVALID) and the UK Prospective Diabetes Study Outcomes Model 2 and American College of Cardiology/American Heart Association Pooled Cohort Equations reveal a similar profile of risk factors in T2D as observed in the current analysis of T1D, including age, male sex, lipid parameters, albuminuria, BPs, BMI, and levels of eGFR (38–40). However, these risk factors were examined as baseline and not time-varying variables in these prior studies.

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The standardized assessments of established and putative risk factors, systematic evaluation of renal outcomes over nearly three decades, short duration of T1D and absence of significant complications at baseline, and exceptional follow-up (93%) of the surviving DCCT/EDIC cohort are clear strengths of this analysis. Limitations include aspects of participant selection, for which individuals with T1D with hypertension, dyslipidemia, or higher urinary albumin excretion were excluded at baseline. Our approach in identifying risk factors associated with development of more advanced stages of kidney disease was evaluated without a priori specified hypotheses.

In conclusion, we found that higher long-term cumulative glycemic exposure was the strongest independent factor associated with the incidence of macroalbuminuria and, likewise, with the incidence of reduced eGFR in this T1D cohort. Although lower in magnitude of association, higher triglyceride levels and higher BP were consistent independent risk factors for both later-stage renal outcomes. Consistent with risk reduction recommendations for retinal and cardiovascular complications in T1D, control of glycemia and these other metabolic factors should be aggressively pursued to reduce later-stage renal outcomes. In future analyses, these findings, particularly from the more extensive clinical prediction models, may inform more efficient and targeted clinical strategies to guide the frequency of screening for kidney disease in T1D.

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References

1. Costacou T, Orchard TJ. Cumulative kidney complication risk by 50 years of type 1 diabetes: the effects of sex, age, and calendar year at onset. Diabetes Care 2018;41:426–433
2. Saran R, Li Y, Robinson B, et al. US renal data system 2015 annual data report: epidemiology of kidney disease in the United States. Am J Kidney Dis 2016;67(Suppl. 1):S1–S305
3. Marshall SM. Diabetic nephropathy in type 1 diabetes: has the outlook improved since the 1980s? Diabetologia 2012;55:2301–2306
4. Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. Lancet 1982;1:1430–1432
5. Parving HH, Oxenbøll B, Svendsen PA, Christiansen JS, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy. A longitudinal study of urinary albumin excretion. Acta Endocrinol (Copenh) 1982; 100:550–555
6. Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med 1984;311:89–93
7. Williams ME. Diabetic nephropathy: the proteinuria hypothesis. Am J Nephrol 2005;25:77–94
8. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med 2003;348:2285–2293
9. de Boer IH, Rue TC, Cleary PA, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group. 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. Arch Intern Med 2011;171:412–420
10. Dunger DB. Banting Memorial Lecture 2016. Reducing lifetime risk of complications in adolescents with type 1 diabetes. Diabet Med 2017; 34:460–466
11. Krolewski AS, Gohda T, Niewczas MA. Progressive renal decline as the major feature of diabetic nephropathy in type 1 diabetes. Clin Exp Nephrol 2014;18:571–583
12. Nathan DM, Genuth S, Lachin J, et al.; Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–986
13. de Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care 2014;37:24–30
14. DCCT/EDIC Research Group. Effect of intensive diabetes treatment on albuminuria in type 1 diabetes: long-term follow-up of the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications study. Lancet Diabetes Endocrinol 2014;2:793–800
15. de Boer IH, Sun W, Cleary PA, et al.; DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. N Engl J Med 2011;365:2366–2376
16. Claeskens G, Hjort N. *Model Selection and Model Averaging*. Cambridge, UK, Cambridge University Press, 2008
17. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT). Design and methodologic considerations for the feasibility phase. Diabetes 1986;35:530–545
18. Epidemiology of Diabetes Interventions and Complications (EDIC) Research Group. Epidemiology of Diabetes Interventions and Complications (EDIC). Design, implementation, and preliminary results of a long-term follow-up of the Diabetes Control and Complications Trial cohort. Diabetes Care 1999;22:99–111
19. The DCCT Research Group. Feasibility of centralized measurements of glycated hemoglobin in the Diabetes Control and Complications Trial: a multicenter study. Clin Chem 1987;33: 2267–2271
20. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Research Group. Risk factors for cardiovascular disease in type 1 diabetes. Diabetes 2016;65:1370–1379
21. Younes N, Cleary PA, Steffes MW, et al.; DCCT/EDIC Research Group. Comparison of urinary albumin-creatinine ratio and albumin excretion rate in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Clin J Am Soc Nephrol 2010;5:1235–1242
22. Hsieh FY, Lavori PW. Sample-size calculations for the Cox proportional hazards regression model with nonbinary covariates. Control Clin Trials 2000;21:552–560
23. Lachin J. *Biostatistical Methods: The Assessment of Relative Risks*. 2nd ed. Hoboken, NJ, Wiley, 2011
24. Therneau TM, Grambsch PM. *Modeling Survival Data: Extending the Cox Model*. New York, Berlin, Springer, 2000
25. Tibshirani R. The lasso method for variable selection in the Cox model. Stat Med 1997;16: 385–395
26. Zhang Y, Jenkins AJ, Basu A, et al.; DCCT/EDIC Research Group. Associations between intensive diabetes therapy and NMR-determined lipoprotein subclass profiles in type 1 diabetes. J Lipid Res 2016;57:310–317
27. Jenkins AJ, Lyons TJ, Zheng D, et al.; DCCT/EDIC Research Group. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. Kidney Int 2003;64:817–828

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28. de Boer IH, Rue TC, Hall YN, Heagerty PJ, Weiss NS, Himmelfarb J. Temporal trends in the prevalence of diabetic kidney disease in the United States. JAMA 2011;305:2532–2539
29. Goel G, Perkins BA. Can improved glycemic control slow renal function decline at all stages of diabetic nephropathy? Semin Nephrol 2012; 32:423–431
30. Tonneijck L, Muskiet MH, Smits MM, et al. Glomerular hyperfiltration in diabetes: mechanisms, clinical significance, and treatment. J Am Soc Nephrol 2017;28:1023–1039
31. Raile K, Galler A, Hofer S, et al. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. Diabetes Care 2007; 30:2523–2528
32. Škrtić M, Lytvyn Y, Bjornstad P, et al. Influence of sex on hyperfiltration in patients with uncomplicated type 1 diabetes. Am J Physiol Renal Physiol 2017;312:F599–F606
33. Sibley SD, Thomas W, de Boer I, Brunzell JD, Steffes MW. Gender and elevated albumin excretion in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort: role of central obesity. Am J Kidney Dis 2006;47:223–232
34. Hommos MS, Glassock RJ, Rule AD. Structural and functional changes in human kidneys with healthy aging. J Am Soc Nephrol 2017;28: 2838–2844
35. Pacilli A, Viazzi F, Fioretto P, et al.; AMD-Annals Study Group. Epidemiology of diabetic kidney disease in adult patients with type 1 diabetes in Italy: the AMD-Annals initiative. Diabetes Metab Res Rev 2017;33:1–8
36. Hirano T. Abnormal lipoprotein metabolism in diabetic nephropathy. Clin Exp Nephrol 2014; 18:206–209
37. Chillarón JJ, Flores Le-Roux JA, Benaiges D, Pedro-Botet J. Type 1 diabetes, metabolic syndrome and cardiovascular risk. Metabolism 2014;63:181–187
38. Russo GT, De Cosmo S, Viazzi F, et al.; AMD-Annals Study Group. Plasma triglycerides and HDL-C levels predict the development of diabetic kidney disease in subjects with type 2 diabetes: the AMD annals initiative. Diabetes Care 2016; 39:2278–2287
39. Heinzel A, Kammer M, Mayer G, et al.; BEAt-DKD Consortium. Validation of plasma biomarker candidates for the prediction of eGFR decline in patients with type 2 diabetes. Diabetes Care 2018;41:1947–1954
40. Basu S, Sussman JB, Berkowitz SA, et al. Validation of Risk Equations for Complications of Type 2 Diabetes (RECODe) using individual participant data from diverse longitudinal cohorts in the U.S. Diabetes Care 2018;41: 586–595

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