

High Burden of Kidney Disease in Youth-Onset Type 2 Diabetes

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OBJECTIVE—To evaluate renal outcomes and survival in youth with type 2 diabetes (T2DM) versus type 1 diabetes (T1DM) versus nondiabetic control subjects.

RESEARCH DESIGN AND METHODS—In total, 342 prevalent youth (aged 1–18 years) with T2DM, 1,011 youth with T1DM, and 1,710 control subjects identified from 1986 to 2007 were anonymously linked to health care records housed at the Manitoba Centre for Health Policy to assess long-term outcomes using ICD codes.

RESULTS—Youth with T2DM were found to have a fourfold increased risk of renal failure versus youth with T1DM. Risk factors associated with renal failure were renin angiotensin aldosterone system inhibitor use and albuminuria in adolescence. Compared with control subjects (age, sex, and postal code matched), youth with T2DM had a 23-fold increased risk of renal failure and a 39-fold increased risk of dialysis. Kaplan-Meier survival at 10 years was 91.4% in the type 2 diabetic group versus 99.5% in the type 1 diabetic group ($P < 0.0001$). Renal survival was 100% at 10 years in both groups. It decreased to 92.0% at 15 years and 55.0% at 20 years in the type 2 diabetic group but remained stable in the type 1 diabetic group ($P < 0.0001$).

CONCLUSIONS—Youth with T2DM are at high risk of adverse renal outcomes and death. Albuminuria and angiotensin aldosterone system inhibitor use, which may be a marker of severity of disease, are associated with poor outcomes in early adulthood.

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The prevalence of type 2 diabetes (T2DM) in youth continues to increase and now accounts for 8–45% of incident cases of diabetes in children (1). In adults, diabetes accounts for 30–40% of end-stage kidney disease (ESKD) in North America and is associated with a 5-year survival rate as low as 34% (2). The time to progress from microalbuminuria to ESKD has been estimated at 15–20 years (3).

T2DM diagnosed in childhood is a relatively new disease, and the natural history is still largely unknown. Evidence suggests that complications may occur at an earlier age with a shorter duration of diabetes (4). Cross-sectional studies show a higher prevalence of albuminuria in youth with T2DM compared with

youth with type 1 diabetes (T1DM) at various disease time points (5–7), and data from the Pima Indian population have shown a fivefold increased risk of ESKD in middle age in individuals diagnosed with T2DM before 20 years of age (8). The only study comparing long-term outcomes in T1DM with early onset T2DM is based on a cohort of Japanese young adults <30 years of age at diagnosis and reveals a significantly higher cumulative incidence of nephropathy in T2DM compared with T1DM (44.4 vs. 20.2%; $P < 0.0001$) (9). These authors also reported diabetic nephropathy in 60% (mean age 31 years) and renal failure requiring dialysis in 23% (mean age 35 years) of a subgroup of their cohort with proliferative

retinopathy ($n = 135$) (10). Graduates from our pediatric clinic also have previously been reported to develop ESKD before 30 years of age (11).

In adults with T2DM, rigorous glycemic control and treatment of hypertension, as well as the use of renin angiotensin aldosterone system (RAAS) inhibitors (including ACE and angiotensin II receptor antagonists), have been shown to abrogate progression of renal disease (3). Observational studies suggest that poor glycemic control may be an important modifiable risk factor in youth with T2DM (6,12); however, studies evaluating the role of other risk factors for progression, including hypertension, are conflicting (6,13,14), and RAAS inhibitors have never been formally evaluated in a published randomized controlled trial in youth.

Manitoba has an incidence of youth-onset T2DM that is 12.5-fold higher than any other province in Canada (15). A genetic single nucleotide polymorphism (hepatocyte nuclear factor [HNF]-1 α G319S), which is present in one of the aboriginal Oji-Cree language groups in Manitoba, has been shown to increase the risk of T2DM and may contribute to the high disease prevalence (16). As a result of the high burden of youth-onset T2DM in Manitoba, this study was designed to describe the long-term renal complications and survival and to identify potentially modifiable, pediatric specific, disease progression factors in this population.

RESEARCH DESIGN AND METHODS

A cohort of youth with T2DM was identified using a prospectively collected clinical database and compared with 1) youth with T1DM and 2) youth without diabetes (non-DM; age, sex, and geographically matched). These children were anonymously linked via scrambled identifiers to administrative health care records housed at the Manitoba Centre for Health Policy (MCHP) to track renal outcomes. Clinical risk factors were also evaluated. Approvals were obtained from the Health Research Ethics Board, Faculty of Medicine, University of Manitoba, and the Manitoba Health Information Privacy Committee.

Data sources

Diabetes Education Resource for Children and Adolescents. The Diabetes Education Resource for Children and Adolescents

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A slide set summarizing this article is available online.

The results and conclusions are those of the authors, and no official endorsement by the MCHP, Manitoba Health, or other data providers is intended or should be inferred.

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Kidney disease and youth-onset T2DM

(DER-CA) provides specialized integrated, interprofessional (physician, nurse educator, dietitian, and social worker) programming for youth <18 years of age with diabetes. It is located within the only tertiary care pediatric referral center in Manitoba, Canada, and is known to follow the majority of youth with diabetes in the province, as well as children from northwestern Ontario and Saskatchewan (17). All patients seen in the DER-CA from January 1986 onward have been prospectively entered into a computerized clinical diabetes database. The database was initially created as a quality improvement tool; therefore, consent was implied by patients participating in the clinic. This database includes personal health identification numbers (PHINs), validated diagnostic data identifying the type of diabetes at the time of diagnosis (see below) (18), and comprehensive clinical and laboratory data entered by clinic staff at each clinical encounter until the time of discharge from the clinic. This database was sent to Manitoba Health

to be de-identified. The DER-CA database was subsequently sent to the MCHP containing anonymized PHIN codes, where a crosswalk file was created to link data between data sources.

Manitoba Health Services Insurance Plan. The Manitoba Health Services Insurance Plan is housed at the MCHP and contains registration files, physician reimbursement claims (based on ICD-9CM codes), hospital discharge abstracts (ICD-9CM codes until 31 March 2004 and Canadian version 10 [ICD-10CA] codes thereafter), and records of prescriptions dispensed (subset of Drug Programs Information Network, available since 1995). Nonparticipation in the system is minimal since health care coverage is universal and residents are not charged health care premiums. Physician billing codes, vital statistics, and census data are also available. Records were available until the end of fiscal year 2007 at the time of the study. Although de-identified, various files

can be linked at the person level for projects receiving ethical approval from the University of Manitoba Research Ethics Board and from the provincial Health Information Privacy Committee using a unique, anonymized de-identified PHIN. Diagnostic and procedure codes used in this study are listed in Table 1.

Cohort definitions

Youth-onset diabetic cohorts. All incident cases of T2DM (cases) and T1DM (control group 1) seen between January 1986 and 2007 in the DER-CA and aged 1–18 years were included. Canadian Diabetes Association criteria (19) for the diagnosis of diabetes were used to confirm the diagnosis of diabetes, which is similar to the American Diabetes Association criteria (20). The diagnosis of T2DM was based on clinical criteria, including the presence of obesity, other evidence of insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, and polycystic ovarian

Table 1—Health care use codes used to identify kidney complications in youth-onset diabetes

Type of complication	ICD-9CM (Diagnostic codes)	ICD-9CM (Procedure codes)	ICD-10CA (Diagnostic codes)	CCI codes*
ESKD	V45.1 (renal dialysis status)	39.95 (hemodialysis)	Z49 (care involving dialysis)	KR53 (implantation of internal device for short-term dialysis)
	V56 (encounter for dialysis and dialysis catheter care)	54.98 (peritoneal dialysis)		1KY (fistula)
	V58.8 (fitting and adjustment of vascular catheter)	38.95 (venous catheterization for renal dialysis)		1OT53 (peritoneal dialysis catheter)
	996.56 (complications specific to peritoneal dialysis catheter)	39.27 (arteriovenostomy for renal dialysis)		1OK85 or 1PC85 (renal transplant)
		39.42 (revision of arteriovenous shunt for renal dialysis)		
Renal failure (all above codes plus)	585 (chronic kidney disease)		N18 (chronic renal failure)	
	586 (renal failure, unspecified)		N19 (unspecified renal failure)	
Any renal complication (all above codes plus)	250.4 (diabetes with renal manifestation)		N08.3 (diabetic nephropathy)	
	581 (nephrotic syndrome; includes intercapillary glomerulosclerosis and Kimmelstiel-Wilson syndrome)		N04 (nephrotic syndrome)	
	583 (nephritis and nephropathy, not specified as acute or chronic)		E10.2 (T1DM with renal complications)	
			E11.2 (T2DM with renal complications)	

*Canadian Classification of Health Interventions.

syndrome in females), family history of T2DM, intrauterine exposure to hyperglycemia, and family heritage from a high-risk ethnic group (18). When available, the absence of diabetes-associated autoantibodies was used to support the diagnosis of T2DM (21).

Non-DM youth (control group 2). An age-, sex-, and geographically matched (to T2DM cohort) group without diabetes was randomly selected from the MCHP database, defined as no ICD code or pharmaceutical for diabetes. Geographical matching was done using the first 3 digits of the 6-digit postal code. Control-to-case matching ratio was 5:1 ($n = 1,710$) to maximize power. The index date for matching was the date of diagnosis of T2DM.

Exclusions. Patients without a valid Manitoba PHIN code were excluded because they could not be linked to outcome data in the MCHP. Cases of secondary diabetes were also excluded.

Variables

Predictor variables. Continuous variables were age, BMI z score at diagnosis, and last hemoglobin A1C (HgA_{1c}). Categorical variables included sex, systolic hypertension at last follow-up (age, sex, and height standardized) (22), socioeconomic status (SES; lowest urban and rural income quintiles vs. other four quintiles), urban (Winnipeg or Brandon) versus rural residence, presence of persistent albuminuria (albumin-to-creatinine ratio ≥ 3 mg/mmol or albumin excretion rate ≥ 30 mg/24 h on two out of three measurements >1 month apart), the (ever) use of RAAS inhibitor (Drug Programs Information Network data), treatment-era effect (diagnosis prior to year 2000), and the presence of maternal pregestational (prior to pregnancy) diagnosis of diabetes identified from administrative data.

Outcome data. The children were followed postdischarge from the DER-CA by means of the health care use codes (Table 1). Billing codes were also used to identify individuals with ESKD: 9798, 9799, 9805, 9807, 9801, 9802, 9806, 9819, 9821, 9610, 9820 (dialysis), and 5883 (renal transplant). Outcomes were separated into 1) any renal complication pertinent to diabetes, 2) renal failure, and 3) ESKD (Table 1). To maximize power, renal failure was a composite outcome including all chronic kidney disease codes and ESKD, and any renal complication included both renal failure codes and ESKD codes.

Statistical analysis

Student t tests, Mann-Whitney U tests, and χ^2 tests were used where appropriate to

evaluate differences between groups. Results are reported as mean \pm SD. $P < 0.05$ was considered statistically significant. If data were missing for an outcome variable for a study participant, that particular individual was excluded from the associated analysis.

Analysis 1: T2DM versus T1DM. To control for variable follow-up times in this retrospective study, survival analyses were used. Both univariate and multivariate Cox proportional hazards models were constructed. Renal failure (as above) was the composite outcome used in this analysis. Possible confounders (listed above) were tested in the univariate analysis. Statistically significant variables at the $P < 0.05$ level were then entered into the multivariate model. Tests for proportionality of each significant variable in the final model were conducted. End of follow-up in the Population Health Research Data Repository was used as the censoring time. HNF-1 α polymorphism was evaluated only in the univariate analysis because it was not applicable to T1DM.

Sensitivity analysis. As a sensitivity analysis, a second multivariate model was constructed to further evaluate the effects of predictor variables, excluding the presence of albuminuria, which could be interpreted as an outcome variable rather than a predictor variable, and RAAS inhibitor use, which could be a confounder by indication (marker of disease severity). All other variables were included in the model as above.

Analysis 2: T2DM versus non-DM. Because clinical variables were not available for the non-DM control subjects, a separate analysis was conducted to evaluate this group in comparison with the T2DM

population. Since these groups were matched, only a univariate analysis was performed. The outcomes renal complication, renal failure, and ESKD were evaluated separately.

Additional analyses. Kaplan-Meier analyses for overall and renal survival comparing T2DM with T1DM were also conducted. All data manipulation and statistical analysis was conducted using SAS version 9.1 software.

RESULTS—A total of 2,174 incident adolescents with diabetes were identified from the DER-CA. Of these, 821 individuals were excluded: 806 were excluded owing to lack of a valid PHIN number because they were from out of province, and 15 did not meet the age criteria. The final T2DM cohort included 342 individuals, and the T1DM control group included 1,011 individuals. The 1,710 non-DM control subjects were age, sex, and postal code matched to the T2DM cohort. Table 2 lists the baseline characteristics of the study population. Compared with the T1DM group, the youth with T2DM were older at the time of diagnosis, were predominantly female, and had higher BMI z scores. They more often lived in a rural area and had a low SES. Both groups had similar rates of hypertension. Half of the T2DM cohort tested for the HNF-1 α polymorphism was either a heterozygote or homozygote for the polymorphism, and significantly more youth with T2DM had a mother with pregestational diabetes.

Crude renal outcomes

The T2DM cohort had more persistent microalbuminuria (26.9 vs. 12.7%; $P < 0.001$)

Table 2—Baseline demographics for incident youth-onset diabetic cohorts

	T1DM/ T2DM (n/n)	T1DM	T2DM	P value
Age (years)	1,011/342	8.9 \pm 4.3	13.5 \pm 2.2	<0.0001
Male sex (%)	1,011/342	53.2	37.8	<0.0001
BMI z scores	923/288	0.4 \pm 1.0	1.9 \pm 0.7	<0.0001
Urban (%)	1,011/342	51.9	26.9	<0.0001
Low SES (%)	877/281	11.4	59.1	<0.0001
HNF-1 α polymorphism (%)	NA/146	NA	32.2 GS† 18.5 SS††	—
Hypertension (%)	813/282	11.1	9.9	0.59
Albuminuria at diagnosis (%)	178/236	13.5	27.1	0.0008
Mother with pregestational diabetes (%)	772/277	2.7	15.9	<0.0001

Continuous variables are mean \pm SD. GS, glycine (wild type)/serine (serine substitution), i.e., heterozygous mutation for HNF-1 α polymorphism; SS, serine/serine (serine substitution), i.e., homozygous mutation for HNF-1 α polymorphism. †Heterozygous for HNF-1 α polymorphism. ††Homozygous for HNF-1 α polymorphism.

and persistent macroalbuminuria (4.7 vs. 1.6%; $P = 0.001$) than the T1DM group. The mean age of development of albuminuria was 15.3 ± 1.5 years in the T1DM group, with a mean disease duration of 6.3 ± 3.9 years (median = 6.0 years). The mean age in the T2DM group was 14.9 ± 2.1 years, with a mean disease duration of only 1.6 ± 1.5 years (median = 1.2 years). The rates may be underestimated because not all children were screened (28% of T1DM group and 18.1% of T2DM group) as a result of the young age in the T1DM group (screened only after age 12) (18), menses, and poor adherence with recommendations in some cases. The presence of albuminuria in youth was highly predictive of the future risk of renal failure in both groups. Of individuals with diabetes who had persistent albuminuria in youth, 9.1% developed renal failure in young adulthood compared with 1.1% without albuminuria ($P < 0.001$).

In the T1DM group, 2.7% of individuals developed a renal complication (mean age 18.8 ± 5.4 years; 9.9 ± 6.3 years of T1DM), 1.4% developed renal failure (mean age 18.1 ± 5.8 years; 9.3 ± 5.5 years of T1DM), and none had ESKD at the end of the study period. In contrast, 8.9% of the T2DM group had a renal complication (mean age 20.3 ± 5.8 years; 7.5 ± 5.6 years of T2DM), 6.7% had renal failure (mean age 21.9 ± 5.9 years; 9.1 ± 6.0 years of T2DM), and 2.3% developed ESKD (mean age 29.1 ± 3.6 years; 16.1 ± 3.6 years T2DM). In the age-, sex-, and geographically matched non-DM control group, only 0.6% ($n = 11$) had a renal diagnosis, and $\leq 0.3\%$ ($n \leq 5$) had either renal failure or ESKD. The mean follow-up time was 5.3 ± 5.2 years in the T2DM group, 7.9 ± 6.3 years in the T1DM group, and 7.0 ± 5.7 years in the non-DM control group.

Survival analyses

Analysis 1. Complete data were available for 880 individuals for the final multivariate model. Youth with T2DM had a four-fold increased risk of renal failure compared with those with T1DM (hazard ratio 4.03 [95% CI 1.64–9.95]; $P = 0.003$), after controlling for age at diagnosis, HgA_{1c}, BMI z score, and era of diagnosis (statistically significant variables from the univariate analysis). Albuminuria (3.88 [1.50–10.0]; $P = 0.005$) and RAAS inhibitor use (15.82 [5.29–47.27]; $P < 0.0001$) were strongly associated with an increased risk of renal failure. An interaction between

the two variables was not statistically significant, suggesting that RAAS inhibitor use did not modulate the risk associated with albuminuria (data not shown).

Analysis 2. Youth with T2DM had a 16.13-fold (95% CI 7.66–33.99; $P < 0.001$) increased risk of a renal diagnosis, 23.83-fold (8.69–60.1; $P < 0.0001$) increased risk of renal failure, and a 39.10-fold (4.89–312.69; $P = 0.0005$) increased risk of ESKD when compared with age-, sex-, and geographically matched control subjects.

Sensitivity analysis

When albuminuria and the use of RAAS inhibitors were excluded from the multivariate model (analysis 1), glycemic control and obesity remained statistically significant risk factors for renal failure, in addition to T2DM, with hazard ratios 5.37 (95% CI 2.12–13.58; $P = 0.0004$) for T2DM versus T1DM, 1.20 (1.04–1.39; $P = 0.01$) for HgA_{1c}, and 5.04 (1.08–3.24; $P = 0.03$) for BMI z score.

Kaplan-Meier analyses

Renal survival was 100% at 10 years in both diabetic cohorts. It remained stable in the T1DM group; however, it decreased to 92.0% at 15 years and 55.0% at 20 years in the T2DM group ($P < 0.0001$) (Fig. 1).

One individual in the non-DM control group, 12 individuals in the T2DM group, and 9 individuals in the T1DM group died during the follow-up period ($P = 0.0007$). Overall survival at 10 and 20 years was 91.4 and 77.5%, respectively, in the T2DM group compared with 99.5 and 97.6% in the T1DM group ($P < 0.0001$) (Fig. 2).

CONCLUSIONS—This is the largest long-term follow-up study evaluating renal outcomes and overall survival in youth-onset T2DM. This study confirms results from smaller cross-sectional and epidemiologic studies and offers new insights into the severe disease burden associated with youth-onset T2DM. It also raises important questions about the effectiveness of RAAS blockade in the treatment of renal disease in youth-onset diabetes.

In this study, 26.9% of youth with T2DM had persistent microalbuminuria, and 4.7% had persistent macroalbuminuria, at a mean age of 14.9 years and duration of disease of 1.6 years. This is in keeping with previously reported microalbuminuria rates of 22–42% in children with youth-onset T2DM of <5 years' duration (7,13,23,24). Macroalbuminuria rates have been reported as high as 17–27% at 5–10 years' duration (25,26), although most of these other studies did not

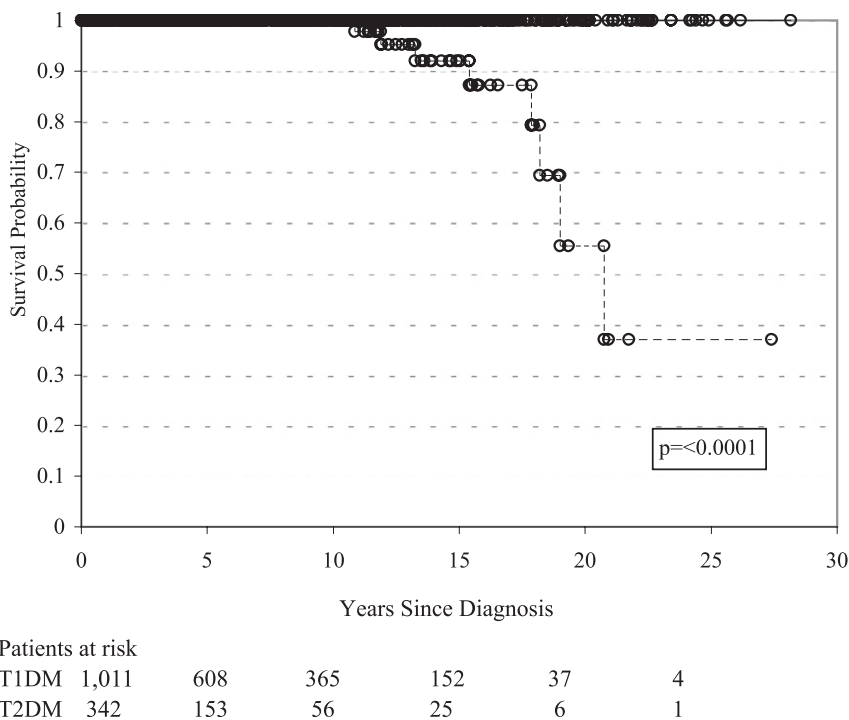
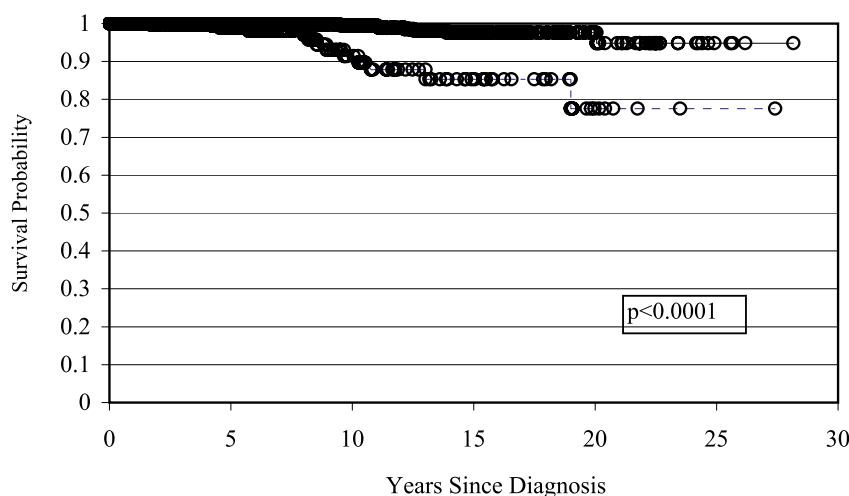


Figure 1—Renal survival in youth-onset diabetic cohorts. Patients at risk are the number of patients in each group with follow-up to that time period. T1DM, —; T2DM, - - -.



Patients at risk						
T1DM	1,011	608	365	152	37	4
T2DM	342	153	56	25	6	1

Figure 2—Overall survival in youth-onset diabetic cohorts. Patients at risk are the number of patients in each group with follow-up to that time period. T1DM, —; T2DM, - - -. (A high-quality color representation of this figure is available in the online issue.)

evaluate persistence of albuminuria and, therefore, may be overestimates.

This study also shows a distinct difference in risk of developing renal failure in youth-onset T2DM compared with T1DM. Youth with T2DM were four times more likely to develop renal failure than those with T1DM. Although the children with T2DM exhibited key differences from those with T1DM at baseline, including older age at diagnosis, female predominance, and lower SES, these factors were not independently predictive of adverse renal outcomes in the multivariate analysis. Obesity and other unmeasured factors inherent to T2DM, such as insulin resistance, may be involved in the pathophysiology of nephropathy in this group. Although the mechanisms have yet to be elucidated, there is an inherent difference in renal risk associated with T2DM in youth.

One possible explanation for this difference is ethnicity, for certain groups have been shown to have an increased risk of diabetic renal disease (27). Although not directly assessed, SES was included in the analysis, and control subjects were matched by postal code to account for youth residing in northern communities and urban lower-SES neighborhoods. In addition, the unique genetic HNF-1 α polymorphism, which is present in the Oji-Cree-speaking population and in 50% of the youth with T2DM tested in this study, was not associated with an increased renal risk.

This study supports the role of glycaemic control in the progression of renal disease in youth-onset T2DM, in keeping with the Diabetes Control and Complications Trial study in T1DM (28,29). In contrast, despite the adult literature consistently showing both systolic and diastolic hypertension accelerate the loss of glomerular filtration rate associated with diabetic nephropathy (3), systolic hypertension was not shown to be a significant risk factor in this study. Future studies should use more accurate blood pressure measurements, including ambulatory blood pressure monitoring, to more robustly assess this risk factor.

The lack of significance of SES and geography in this study was surprising. One possible explanation for this may be that individuals of lower SES and rural residence are not seeking medical care as often because of decreased access to medical services and, thus, are not being diagnosed with diabetes complications. Alternatively, although low SES may increase the risk of diabetes, once affected, the risk of complications of the disease may be the same.

We observed a 15.8-fold increased risk of renal failure in individuals that had ever filled a prescription for an RAAS inhibitor. It is possible that this observed association is not causal but a manifestation of confounding by indication or illness severity, as has been described for acetylsalicylic acid in population studies (30).

These results are certainly at variance with those of multiple placebo-controlled trials in adults of RAAS inhibitors showing a benefit in delaying the progression of diabetic nephropathy. On the other hand, recent literature reanalyzing published studies raises concerns regarding RAAS blockade-associated acute renal failure, calling for increased caution with these drugs (31). Moreover, there has yet to be a published randomized controlled trial in any youth-onset diabetes group aged <18 years and, therefore, the true effect of these medications in youth is unknown (32). Therefore, we cannot exclude the possibility that the adverse risk associated with RAAS inhibitors in our study represents a true causation. Further study of these drugs in this at-risk population is warranted.

Our study has several limitations that warrant discussion. First, a number of outcomes in this study were based on diagnostic codes in outpatient physician billing records. Although renal outcomes are based on laboratory data, the coding of diagnoses in administrative data are nonstandardized and may depend on the frequency of assessment and changes in definitions of renal failure and interpretation over time (i.e., introduction of estimated glomerular filtration rate reporting) (33). In addition, for billing purposes, only one diagnostic code can be used for each patient encounter. Those individuals followed mainly by their primary care physician or endocrinologist would more likely be given a diagnosis of diabetes rather than chronic kidney disease for their visit, independent of their renal health status. This may result in an unmeasured ascertainment bias for outpatient health system interactions. It is difficult to predict the magnitude and direction of this effect; however, it would likely be the same for both groups. Second, SES was assessed as an area-level measure in this study. However, this has been shown to approximate individual-level measures of SES (34). Third, biopsy data confirming the diagnosis of diabetic nephropathy was lacking in most cases. This is important because a previous report from our group highlights the lack of classical diabetic nephropathy on biopsy in youth with T2DM and macroalbuminuria (35). Nevertheless, the observation that youth-onset T2DM is associated with adverse renal and patient survival remains an important finding, irrespective of possible mechanisms. Renal biopsy studies are warranted in adolescents and young adults with T2DM to better define the

renal pathology. Finally, the number of patients with >10 years of follow-up in the T2DM group is small. However, differences exist between groups early in the course of disease when numbers are more robust, and despite the small numbers at long-term follow-up, our results are highly statistically significant and highlight the critical need for more investigation into these very high-risk patients.

In conclusion, this study demonstrates a high burden of renal complications and poor renal and overall survival associated with youth-onset T2DM. Albuminuria early in the course of the disease is highly prevalent and associated with poor outcomes in early adulthood. This study supports the importance of glycemic control and targeting obesity in the management of youth-onset T2DM. It also raises concerns about the use of RAAS inhibitors in youth-onset diabetes. Randomized controlled studies in youth are required to further evaluate these drugs.

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A.B.D. developed the study proposal, performed the analysis, and wrote the manuscript. E.A.S., P.J.M., C.R., M.D.B., and H.J.D. contributed to study design and interpretation of results and reviewed and edited the manuscript. A.B.D. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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