Earlier Onset of Complications in Youth With Type 2 Diabetes

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OBJECTIVE

To evaluate the risk of complications in youth with type 2 diabetes.

RESEARCH DESIGN AND METHODS

Population-based cohorts of 342 youth (1–18 years of age) with prevalent type 2 diabetes, 1,011 youth with type 1 diabetes, and 1,710 nondiabetic control youth were identified between 1986 and 2007 from a clinical registry and linked to health care records to assess long-term outcomes using ICD-9CM and ICD-10CA codes.

RESULTS

Youth with type 2 diabetes had an increased risk of any complication (hazard ratio 1.47 [95% CI 1.02–2.12]). Significant adverse clinical factors included age at diagnosis (1.08 [1.02–2.12]), HbA_{1c} (1.06 [1.01–1.12]), and, surprisingly, renin-angiotensin-aldosterone system (RAAS) inhibitor use (1.75 [1.27–2.41]). HNF-1α G319S polymorphism was protective in the type 2 diabetes cohort (0.58 [0.34–0.99]). Kaplan-Meier statistics revealed an earlier diagnosis of renal and neurologic complications in the type 2 diabetes cohort, manifesting within 5 years of diagnosis. No difference in retinopathy was seen. Cardiovascular and cerebrovascular diseases were rare; however, major complications (dialysis, blindness, or amputation) started to manifest 10 years after diagnosis in the type 2 diabetes cohort. Youth with type 2 diabetes had higher rates of all outcomes than nondiabetic control youth and an overall 6.15-fold increased risk of any vascular disease.

CONCLUSIONS

Youth with type 2 diabetes exhibit complications sooner than youth with type 1 diabetes. Younger age at diagnosis is potentially protective, and glycemic control is an important modifiable risk factor. The unexpected adverse association between RAAS inhibitor use and outcome is likely a confounder by indication; however, further evaluation in young people is warranted.

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The prevalence of type 2 diabetes in youth is increasing worldwide, coinciding with the rising obesity epidemic (1,2). It now accounts for >50% of cases in some countries and ethnic groups (3). The incidence of youth-onset type 2 diabetes in Canada is now between 1.54 (4) and 20.55 per 100,000 youth <18 years of age. The highest incidence is in the province of Manitoba (5).

Diabetes is associated with both microvascular and macrovascular complications. The evolution of these complications has been well described in type 1 diabetes (6) and in adult type 2 diabetes (7), wherein significant complications typically manifest 15–20 years after diagnosis (8). Because type 2 diabetes is a relatively new disease in children (first described in the 1980s), long-term outcome data on complications are scant, and risk factors for the development of complications are incompletely understood. The available literature suggests that development of complications in youth with type 2 diabetes may be more rapid than in adults, thus afflicting individuals at the height of their individual and social productivity (9). The evolution and risk factors for diabetes-related complications in youth-onset type 2 diabetes needs to be better understood.

A small but notable proportion of type 2 diabetes is associated with a polymorphism of hepatic nuclear factor (HNF)-1α, a transcription factor expressed in many tissues, including liver, intestine, pancreatic β-cell, and kidney. The HNF-1α G319S polymorphism, associated with an insulin secretory defect (10–12), occurs in First Nation populations of central Canada in whom it is associated with early onset type 2 diabetes. It is not yet known what effect the HNF-1α polymorphism has on the risk of complications associated with diabetes.

The main objective of the current study was to describe the time course and risk factors for microvascular complications (nephropathy, retinopathy, and neuropathy) and macrovascular complications (cardiac, cerebrovascular, and peripheral vascular diseases) in a large cohort of youth who have been carefully followed for >20 years and to compare this evolution with that of youth with type 1 diabetes. We also compared vascular complications in the youth with type 2 diabetes with nondiabetic control youth. Finally, we addressed the impact of HNF-1α G319S on the evolution of complications in young patients with type 2 diabetes. A detailed evaluation of renal outcomes and survival in youth with type 2 diabetes in Manitoba has been previously published (13).

RESEARCH DESIGN AND METHODS

The cohort of youth with type 2 diabetes was identified through a prospectively collected clinical registry from the Diabetes Education Resource for Children and Adolescents (DER-CA) in Manitoba, Canada, and was compared with youth with type 1 diabetes and without diabetes (by age, sex, and geography) (Supplementary Fig. 1). Through deidentified personal identifiers, these children were linked to health-care records in the Population Health Research Data Repository (herein referred to as the repository) housed at the Manitoba Centre for Health Policy (MCHP) to assess for complications. Clinical risk factors for the development of complications were also evaluated. Approvals were obtained from the Health Research Ethics Board, University of Manitoba, and the Manitoba Health Information Privacy Committee.

Data Sources

DER-CA Registry

This registry has been previously described in detail (13,14). In brief, it is the only tertiary-care pediatric diabetes referral center for Manitoba, Canada, as well as northwestern Ontario and part of Saskatchewan. In the province of Manitoba, the DER-CA follows 86.1% of youth with diabetes who are <18 years of age (14). All patients followed from January 1986 to present have been prospectively entered into the computerized registry, which contains unique personal health identification numbers (PHINs) and clinical, genetic (HNF-1α polymorphism), and laboratory data. Data are not available in this registry after 18 years of age; therefore, linkages using scrambled PHIN codes to other administrative datasets in the repository were established to generate long-term outcome data for the DER-CA cohorts.

The Manitoba Health Services Insurance Plan

This plan contains registration files, physician reimbursement claims (based on ICD-9 Clinical Modification [CM] codes), hospital discharge abstracts (ICD-9CM codes until 31 March 2004 and Canadian version 10 [ICD-10CA] codes thereafter), and records of prescriptions dispensed (a subset of the Drug Programs Information Network available since 1995). Outpatient physician visits were assessed with ICD-9CM diagnostic codes at the three-digit level. Hospitalization was assessed with ICD-9CM and ICD-10CA codes at the decimal level. Nonparticipation in the system is minimal because health-care coverage is universal in Canada, and residents are not charged health-care premiums. These data are stored in a deidentified form in the repository housed at the MCHP. Physician billing codes, vital statistics, and census data are also available. The repository data have been previously shown to be accurate (15). At the time of the study, records were available until the end of fiscal year 2007 (31 March 2007). All data manipulation and analysis were performed in the MCHP data laboratory, which is highly secured to protect patient anonymity.

Cohort Definitions

Youth-Onset Diabetes Cohorts

All prevalent cases of type 2 diabetes and type 1 diabetes (control group 1) seen between January 1986 and March 2007 in the DER-CA for youth aged 1–18 years were included. Canadian Diabetes Association criteria (16) for the diagnosis of diabetes were used, which are similar to American Diabetes Association criteria (17). The diagnosis of type 2 diabetes was based on clinical criteria, including the presence of obesity, other evidence of insulin resistance, family history of type 2 diabetes, intrauterine exposure to hyperglycemia, and family heritage from a high-risk ethnic group, such as First Nation status (16). When available, the absence of diabetes-associated autoantibodies was used to support the diagnosis of type 2 diabetes if clinical

equipoise existed about the diagnosis (18). Type 1 diabetes is exceptionally rare in First Nation populations; therefore, misclassification of diabetes type in First Nation children was uncommon.

Youth Without Diabetes

An age, sex, and geographically matched second control group of youth without diabetes was randomly selected from the repository and defined as no ICD code or pharmaceutical for diabetes. The ratio of control youth to case youth was 5:1 (n = 1,710) to maximize power. The index date for matching was the date of diagnosis of type 2 diabetes. Clinical data were not available for this group.

Exclusions

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

Variables

Predictor Variables

Clinical variables assessed for both groups of youth-onset diabetes were age at diagnosis, sex, BMI z score (BMIz), elevated blood pressure (according to age-, sex-, and height-standardized normal values in children) (19), hemoglobin A_{1c} (HbA_{1c}) at last follow-up, area-level socioeconomic status (SES) (defined as the lowest urban and rural area–level income quintiles vs. the other four quintiles), HNF-1α polymorphism status (homozygous [SS] or heterozygous [GS] vs. wild type [GG]), urban (Winnipeg and Brandon) versus rural (all other) residence, presence of persistent albuminuria (defined as albumin:creatinine ratio $\geq$3 mg/mmol on a random urine sample or albumin excretion rate $\geq$30 mg/24 h on at least two of three measurements $>$1 month apart), the (ever) use of ACE inhibitors or angiotensin receptor blocker from fiscal years 1995–2007 (from Drug Programs Information Network data), and the presence of pregestational diabetes in the youths' mothers (diagnosed before pregnancy) as determined in the repository as an ICD code for diabetes before the pregnancy of interest. An era effect variable was also included to determine whether standards of diabetes care not directly measured in this study before and after the year 2000 affected outcomes.

Outcome Data

All outcomes were determined by means of health-care utilization codes from the repository. The codes used to assess each diabetes complication are listed in Supplementary Table 1. ICD-9CM procedure codes and Canadian Classification of Health Intervention codes were also evaluated. In addition, billing codes were used to assess for dialysis (9798, 9799, 9805, 9807, 9801, 9802, 9806, 9819, 9821, 9610, 9820) and renal transplant (5883). To maintain consistency, the same codes were used to determine outcomes for all three groups. To maximize power, a composite outcome of any complication was used, which included renal, ophthalmologic, and neurologic complications and cardiovascular, cerebrovascular, and peripheral vascular diseases to evaluate overall risk in these cohorts.

Statistical Analysis

Descriptive Statistics

Summary statistics were calculated for each complication and compared between groups using two-tailed Student t, Mann-Whitney U, and χ^2 tests where appropriate. Results are reported as mean $\pm$ SD or median and range if data were not normally distributed. $P < 0.05$ was considered statistically significant unless otherwise stated.

Analysis 1: Type 2 Diabetes Versus Type 1 Diabetes

Univariate and multivariate Cox proportional hazards models were constructed for the composite outcome any complication. All listed predictor variables were included in the univariate analysis. The statistically significant variables in this analysis were entered into the multivariate model. HNF-1α polymorphism was evaluated only in the univariate analysis because it was not applicable to type 1 diabetes. Tests for proportionality of each significant variable in the final model were conducted. End of follow-up in the repository was used as the censoring time. $P < 0.05$ was considered statistically significant.

Analysis 2: Type 2 Diabetes Versus No Diabetes.

Because clinical variables were not available for the nondiabetic control youth, a separate analysis was conducted to evaluate this group compared with the type 2 diabetes group. This group was matched; therefore, only a univariate analysis was performed. Each type of complication was evaluated separately for this analysis to evaluate background outcome rates in a comparable population. In addition, composite microvascular (renal complication, retinopathy, or neuropathy), macrovascular (cardiovascular, cerebrovascular, or peripheral vascular disease), and major (blindness, dialysis, or amputation) complications were evaluated. Because multiple outcomes that were not totally independent from one another were evaluated, to prevent type I error, a Bonferroni correction factor at $P < 0.01$ was required to consider the results significant for these analyses.

Additional Analyses.

Kaplan-Meier analyses for each type of complication were conducted for the diabetes cohorts. All data manipulation and statistical analyses were performed with SAS version 9.1 (SAS Institute Inc.) software.

RESULTS

A total of 2,174 adolescents were identified from the DER-CA database, including 1,412 with type 1 and 424 with type 2 diabetes (Supplementary Fig. 1). Excluded were 806 who did not have valid PHINs generally because they were not Manitoba residents, thus prohibiting long-term follow-up in the repository. Fourteen infants $<$1 year of age and one 19-year-old were excluded because they did not meet the age criteria. The final type 2 diabetes cohort included 342 youth, and the type 1 diabetes control group included 1,011. The no diabetes control cohort comprised 1,710 youth matched to the type 2 diabetes cohort from the repository (Supplementary Fig. 1).

Compared with the youth with type 1 diabetes, the youth with type 2 diabetes were, on average, older at the time of diagnosis and more likely to be female. They were more likely to have a higher

BMIz, live in a rural area, have a low SES, and have albuminuria at diagnosis. There was no difference in elevated blood pressure at baseline. Sixteen percent of the children with type 2 diabetes had a mother with pregestational diabetes compared with only 3% in the type 1 diabetes group, and one-half of the type 2 diabetes group was either a heterozygote (GS) or a homozygote (SS) for the HNF-1α polymorphism (Table 1).

Table 1—Baseline demographics of youth-onset diabetes cohorts

	Type 1 diabetes (n = 1,710)	Type 2 diabetes (n = 342)	P value
Age (years)	8.9 ± 4.3	13.5 ± 2.2	<0.0001
Male sex	53.2	37.8	<0.0001
BMIz	0.4 ± 1.0	1.9 ± 0.7	<0.0001
Urban	51.9	26.9	<0.0001
Low SES	11.4	59.1	<0.0001
HNF-1α polymorphism			
GS†	N/A	32.2	—
SS††	N/A	18.5	—
Elevated blood pressure	11.1	9.9	0.59
Albuminuria at diagnosis	13.5	27.1	0.0008
Mother with pregestational diabetes	2.7	15.9	<0.0001

Data are mean ± SD or %. N/A, not applicable. †Heterozygous for HNF-1α polymorphism. ††Homozygous for HNF-1α polymorphism.

At the time of the last available follow-up in the DER-CA, the youth with diabetes were, on average, between 15 and 16 years of age. The differences in BMIz persisted, and 40–50% had an elevated blood pressure (Table 2). Glycemic control was, on average, suboptimal in both groups. The type 2 diabetes group had higher serum total cholesterol and triglyceride levels and lower HDL cholesterol levels, although absolute differences were small.

The median follow-up times in the repository were 4.4 (range 0–27.4) years for youth with type 2 diabetes, 6.7 (0–28.2) years for youth with type 1 diabetes, and 6.0 (0–29.9) years for nondiabetic control youth. Crude complication rates for all three groups are presented in Table 3. Overall, both groups with diabetes had higher vascular disease rates than the nondiabetes control group. Differences in crude complication rates between the two diabetes cohorts were small, except for a higher percentage of youth with type 2 diabetes affected by renal complications.

Analysis 1: Type 2 Diabetes Versus Type 1 Diabetes

The statistically significant clinical factors in the univariate analysis associated with the composite outcome included type 2 versus type 1 diabetes (hazard radio [HR] 1.92 [95% CI 1.46–2.55], $P < 0.0001$), age at diagnosis (1.09 [1.06–1.12], $P < 0.0001$), male sex (0.73 [0.57–0.94], $P = 0.01$), HbA_{1c} (1.09 [1.05–1.14], $P < 0.0001$), BMIz (1.21 [1.03–1.42], $P = 0.02$), renin-angiotensin-aldosterone system (RAAS) inhibitor use (2.24 [1.73–2.92], $P < 0.0001$), low SES (1.48 [1.12–1.95], $P = 0.007$), and HNF-1α polymorphism (0.58 [0.34–0.99], $P = 0.04$). Urban residence, elevated blood pressure, diagnosis before 2000, pregestational diabetes in the mother, and albuminuria were not significant.

The final multivariate model had a sample size of 1,018, and there were 212 events. After controlling for low SES, sex, and BMIz, the risk associated with type 2 versus type 1 diabetes of any complication was an HR of 1.47 (1.02–2.12, $P = 0.04$). Age at diagnosis was associated with an HR of 1.08 (1.01–1.12, $P = 0.002$), HbA_{1c} was associated with an HR of 1.06 (1.01–1.12, $P = 0.01$), and RAAS inhibitor use was associated with an HR of 1.75 (1.27–2.41, $P = 0.0006$). Tests for proportionality for all statistically significant variables were nonsignificant. In addition, a sensitivity analysis, including an evaluation of the interaction between RAAS inhibitor use and albuminuria, was not significant.

Analysis 2: Type 2 Diabetes Versus No Diabetes

Crude outcomes rates are shown in Table 3. In the univariate analysis, youth with type 2 diabetes were at significantly higher risk of developing any vascular (HR 6.15 [4.26–8.87], $P < 0.0001$), microvascular (6.26 [4.32–9.10], $P < 0.0001$), or macrovascular (4.44 [1.71–11.52], $P < 0.0001$) disease compared with control youth without diabetes. In addition, the youth with type 2 diabetes had an increased risk of opthalmologic (19.49 [9.75–39.00], $P < 0.0001$), renal (16.13 [7.66–33.99], $P < 0.0001$), and neurologic (2.93 [1.79–4.80], $P \leq 0.001$) disease. There were few cardiovascular, cerebrovascular,

Table 2—Clinical features at last DER-CA follow-up for youth-onset diabetes cohorts

	Type 1 diabetes (n = 1,710)	Type 2 diabetes (n = 342)	P value
Age (years)	15.1 ± 3.2	16.5 ± 2.3	0.0006
BMI z-scores	0.66 ± 0.8	1.8 ± 0.7	<0.0001
Total cholesterol (mmol/L)	4.3 ± 1.0	4.6 ± 1.0	0.0001
LDL cholesterol (mmol/L)	2.9 ± 2.2	2.8 ± 0.8	0.05
HDL cholesterol (mmol/L)	1.5 ± 0.4	1.28 ± 0.3	0.002
Triglycerides (mmol/L)	1.3 ± 0.9	2.2 ± 2.2	<0.0001
ApoB (mmol/L)	0.9 ± 0.4	0.8 ± 0.2	0.60
Elevated blood pressure (%)	39.8	45.8	0.08
HbA_{1c} (%)	9.2 ± 2.3	8.9 ± 3.0	0.04
HbA_{1c} (mmol/mol)	77 ± 25.1	74 ± 32.8	
Albuminuria (%)	19.8	38.6	<0.0001

Data are mean ± SD. apoB, apolipoprotein B.

Table 3—Crude complication rates in youth-onset diabetes cohorts and rates of comparable disease in nondiabetic control youth

	No diabetes (n = 1,710)		Type 1 diabetes (n = 1,011)		Type 2 diabetes (n = 342)	
	n (%)	Age (years)	n (%)	Diabetes duration (years)	n (%)	Diabetes duration (years)
Any complication	87 (5.1)	20.8 ± 5.0	189 (18.7)	7.2 ± 5.2	71 (20.8)	5.0 ± 4.3
Renal complication	11 (0.6)	21.9 ± 6.5	27 (2.7)	9.9 ± 6.3	30 (8.9)	7.5 ± 5.7
Renal failure	*	—	14 (1.4)	9.3 ± 5.5	23 (6.7)	9.1 ± 6.0
Dialysis	*	—	0	N/A	8 (2.3)	16.1 ± 3.6
Neuropathy	61 (3.6)	21.2 ± 5.1	50 (5.0)	9.8 ± 4.9	26 (7.6)	6.5 ± 5.6
Retinopathy	13 (0.8)	21.3 ± 6.6	139 (13.8)	7.9 ± 5.8	40 (11.7)	7.4 ± 5.9
Cardiovascular disease	*	—	*	—	*	—
Peripheral vascular disease	*	—	6 (0.6)	8.0 ± 3.9	*	—
Cerebrovascular disease	*	—	10 (1.0)	5.3 ± 4.3	*	—

Data are mean ± SD unless otherwise indicated. N/A, not applicable. *Five or fewer individuals; therefore, number suppressed in the table to maintain patient anonymity.

and peripheral vascular disease events in all groups (five or fewer events per group). Despite this, there was still a statistically significant higher risk of peripheral vascular disease in the type 2 diabetes group (6.25 [1.68–23.28], P = 0.006).

Kaplan-Meier Analyses

Figure 1*A–C* shows event-free survival for each microvascular complication. Differences in renal and neurologic complications between the two diabetes groups began to occur before 5 years postdiagnosis, whereas differences in ophthalmologic complications began 10 years postdiagnosis. Differences in ophthalmologic complications, however, were not statistically significant. Both cardiovascular and cerebrovascular complications were rare in both groups, but peripheral vascular complications began to occur 15 years after diagnosis in the type 2 diabetes group (data not shown). Overall, major complications were rare in the type 1 diabetes group, but they occurred in 1.1% of the type 2 diabetes cohort at 10 years, in 26.0% at 15 years, and in 47.9% at 20 years after diagnosis ($P < 0.001$) (Fig. 1*D*).

CONCLUSIONS

To our knowledge, this natural history study of youth-onset type 2 diabetes is the largest published to date. We show that youth with type 2 diabetes have a higher risk of any complication than youth with type 1 diabetes and nondiabetic control youth. Clinical factors associated with complications are age at diagnosis, glycemic control, and RAAS inhibitor use. The presence of HNF-1α G319S polymorphism in youth with type 2 diabetes was found to be protective of complications. The time to both renal and neurologic complications was significantly shorter in youth with type 2 diabetes than in control youth, whereas differences were not significant with respect to opthalmologic and cardiovascular complications between cohorts. This study, therefore, highlights that youth is not protective against the multisystem effects of type 2 diabetes, and although not directly evaluated, the time course to complications parallels that seen in adults (8).

The renal disease associated with youth-onset type 2 diabetes has been the most frequently described complication in the literature to date (20–23) and has been shown to be associated with significant morbidity (24). We have previously described high rates of albuminuria in adolescents and end-stage renal disease of up to 50% in youth with 20 years of follow-up (13). The current study further highlights the accelerated rate of renal complications in youth with type 2 diabetes early after diagnosis, stressing the importance of screening for albuminuria in these patients rather than waiting for a longer disease duration, as is the routine practice in adults (25). Biopsy data in youth with type 2 diabetes suggest that pathophysiological mechanisms are different from traditional diabetic nephropathy. In fact, 9 of 10 children from this population with macroalbuminuria were shown to have either glomerulosclerosis or immune-mediated disease on kidney biopsy (26). Recent national data support this finding, which showed that glomerulonephritis was the most common cause of end-stage renal disease in aboriginal children and adults <40 years old, whereas diabetes started to predominate only after 40 years of age (27). Because the majority of youth with type 2 diabetes in Manitoba are of self-declared aboriginal heritage (5), the high background rate of immune-mediated disease can be hypothesized to play an important role in the higher risk of chronic kidney disease in this population, likely potentiated by diabetes.

To our knowledge, this study is the first to compare neurologic outcomes in youth-onset type 2 diabetes with a type 1 diabetes cohort. The previously reported rates of neuropathy from small cross-sectional studies have ranged between 12 and 57% (24,28,29). Although the crude rate in the current study was lower at 7.6%, youth with longer follow-up times had much higher rates. Limitations in most of these studies include variability in the diagnostic criteria to define neuropathy and the reliance on insensitive clinical symptoms, such as numbness or tingling (30). The current study relied on ICD coding, which likely included the most symptomatic individuals; however, the validity of these codes have yet to be properly evaluated. Studies including

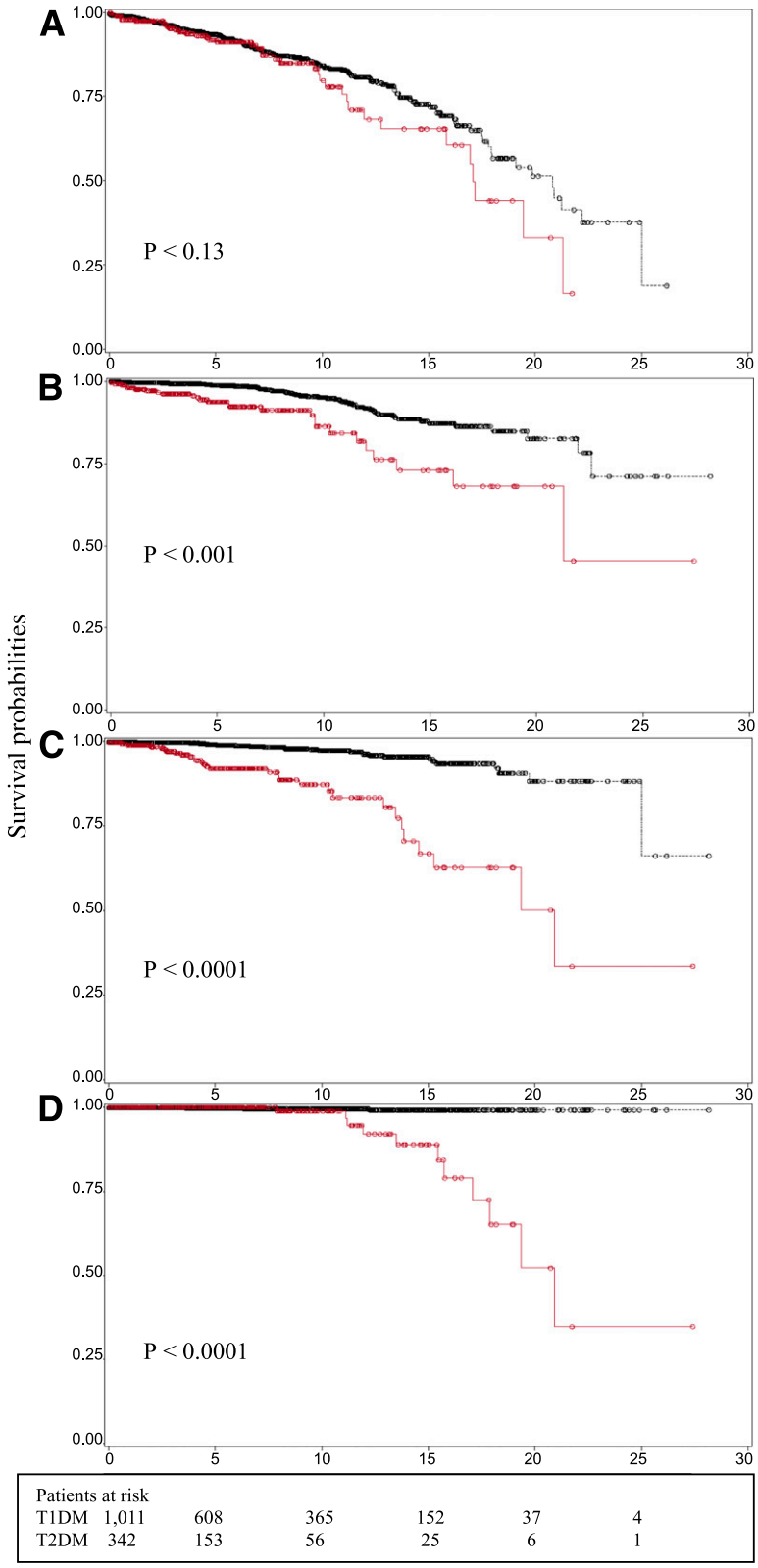

Figure 1—Complication-free survival in youth-onset diabetes cohorts. *A*: Retinopathy-free survival. *B*: Neuropathy-free survival. *C*: Nephropathy-free survival. *D*: Major complication (dialysis, blindness, and amputation)-free survival. Type 1 diabetes (T1DM) is indicated by the black line, and type 2 diabetes (T2DM) is indicated by the red line. The bottom box indicates the number of patients with follow-up at each time point.

validated testing and diagnostic criteria are required to adequately assess the burden of neuropathy in this population.

The results of this study with respect to opthalmologic complications contrast with the literature, which has shown a lower risk of retinopathy in youth with type 2 diabetes than in youth with type 1 diabetes (22,24) and in adult-onset type 2 diabetes (31). The current study reveals instead a similar burden of diagnosed opthalmologic complications in both subtypes of youth-onset diabetes. Reported rates of retinopathy in youth-onset type 2 diabetes vary considerably in the literature (4–40%), depending on the population studied and the means of evaluation (22,24,31–35). The current results are at the lower end of this spectrum. Because this study is based on diagnostic coding, it is likely that background retinopathy rates are underestimated because of their asymptomatic nature; thus, actual differences between subgroups may not be evident early in the course of disease. Of note, rates after 10 years of disease began to increase steeply, and by 20 years, almost 75% of patients had received the diagnosis, likely reflecting the manifestation of more symptomatic disease and the potential importance of early screening.

The current study is consistent with the literature, which has shown high rates of cardiovascular risk factors in youth with type 2 diabetes. However, despite the high prevalence of risk, this study reports low rates of clinical events. Because the median follow-up time was between 5 and 8 years, it is possible that a longer follow-up period would be required to correctly evaluate macrovascular outcomes in young adults. Also possible is that diagnoses of mild disease are not being made because of a low index of suspicion in 20- and 30-year-old patients.

The evaluation of clinically important factors associated with complications in this study yields several important findings. First, glycemic control is an important clinical risk factor for any complication, which is in keeping with the type 1 diabetes literature (6) and other cross-sectional studies in youth

with type 2 diabetes (34). An increased complication burden also is associated with an increased age at diagnosis. This finding may be explained by nonadherence to therapy in adolescence, which is a high-risk time. Alternatively, some evidence suggests that prepubertal diagnosis of diabetes is associated with a better long-term risk profile; therefore, younger children may be relatively protected (36). Pubertal status, unfortunately, was not available in the current study. In addition, the relative protection of the HNF-1α genetic polymorphism with respect to diabetes complications is a novel finding. Despite its influence on the rapidity of onset of disease (10), it does not appear to be associated with an accelerated burden of complications.

The increased risk associated with RAAS inhibitor use is surprising because this result contrasts multiple clinical trials showing a benefit in terms of diabetic nephropathy and retinopathy in adults (37). The most reasonable interpretation is that this finding represents confounding by indication or illness severity, as has been described in aspirin trials (38), rather than a causal association indicating harm. On the other hand, it should be noted that no randomized controlled trials of RAAS inhibitors in youth-onset type 1 or type 2 diabetes exist and that an assessment of the interaction of RAAS use and albuminuria is not significant, suggesting that RAAS use does not abrogate the effect of established albuminuria. The possibility that these drugs behave differently in youth cannot be excluded.

The current study has many clinical and research implications. Because nephropathy and neuropathy manifest early after diagnosis, it seems prudent to recommend active screening for these complications, starting at the time of diagnosis. The importance of glycemic control as an adverse risk factor suggests that achieving optimal glycemic control may be of major importance, despite the challenges that exist in this regard. Future randomized clinical trials should focus on these questions. In addition, more needs to be learned about the cardiovascular risk associated with the identified high-risk metabolic profiles in these youth. In particular, prospective observational studies are needed to evaluate subclinical signs of early cardiovascular disease, which may not yet have manifested clinically in this study. Finally, the risk associated with RAAS inhibitors in this study is concerning because these medications are used routinely in clinical practice. Future studies are required to evaluate the safety and efficacy of these drugs in youth-onset diabetes populations.

The major strength of this study is that it characterizes the natural history of youth-onset type 2 diabetes in a large, well-described cohort. There are a few limitations that merit discussion. The outcome data are based on diagnostic codes, which can be inaccurate. Only one diagnostic code can be included for each outpatient physician encounter. Therefore, depending on the physician (generalist vs. specialist), a code of "diabetes" may be given rather than one describing a complication. Therefore, an ascertainment bias may exist within this study. The magnitude of this effect, however, should be equal in both groups. In addition, the choice of an aggregate any complication outcome negates the possibility that one complication is masked by the coding of another. Because of the retrospective nature of this study and changes in clinical practice guidelines over time, another concern is that not all clinical variables were available for all patients. Although this concern must be acknowledged, it does not affect the outcome rates, which were measured only through administrative data in the repository. Another limitation is that SES was assessed as an area-level measure. However, it has been shown in the past that area-level measures approximate individual-level measures of SES (39). Finally, the lack of significance of SES and geography was surprising. One possible explanation 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 receiving diagnoses of diabetes complications. It is possible that longer follow-up would reveal an exponential increase of hospital diagnoses for these individuals as their disease progresses, thus necessitating acute care treatment.

In conclusion, youth with type 2 diabetes have an increased risk of complications early in the course of their disease. Microvascular complications and cardiovascular risk factors are highly prevalent, whereas macrovascular complications are rare in young adulthood. HbA_{1c} is an important modifiable risk factor; thus, optimizing glycemic control should remain an important goal of therapy. In addition, age at diagnosis may alter future risk, and RAAS inhibitors need to be evaluated with a randomized controlled study in youth with diabetes before changing clinical practice. Because this is a unique population in Manitoba, the external validity of these findings must be evaluated in other populations.

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