Earlier onset of complications in youth with type 2 diabetes

Submission to: Diabetes Care

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Abstract:

**Objective:** To evaluate the risk of complications in youth with type 2 diabetes. **Research Design and Methods:** Population based cohorts of 342 prevalent youth (1-18 yrs) with type 2 diabetes, 1011 youth with type 1 diabetes and 1710 non-diabetes controls identified between 1986-2007 from a clinical registry and were linked to healthcare records to assess long-term outcomes utilizing ICD codes. **Results:** Youth with type 2 diabetes had an increased risk of any complication (HR 1.47; 95% CI 1.02-2.12). Significant adverse clinical factors included age at diagnosis (HR 1.08; 95% CI 1.02-2.12), HbA1c (HR 1.06; 95% CI 1.01-1.12) and, surprisingly, renin angiotensin aldosterone system (RAAS) inhibitor use (HR 1.75; 95% CI 1.27-2.41). HNF-1α G319S polymorphism was protective in the type 2 diabetes cohort (HR 0.58; 95% CI 0.34-0.99). Kaplan Meier statistics revealed an earlier diagnosis of renal and neurological 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 non-diabetes controls, 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.
The prevalence of type 2 diabetes is increasing worldwide in youth, coincident with the rising obesity epidemic (1,2). It now accounts for greater than 50% of cases in some countries and ethnic groups (3). The incidence of youth onset type 2 diabetes in Canada now varies from 1.54 cases per 100,000 (4) to 20.55 per 100,000 youth less than 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 themselves 15-20 years after the diagnosis of diabetes (8). Since type 2 diabetes is a relatively new disease in children, first described in the 1980’s, long-term outcome data on complications are scant, and risk factors for their development 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). There is a clear need to better understand the evolution and risk factors for diabetes related complications in youth onset type 2 diabetes.

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 HNF-1α polymorphism has on the risk of complications associated with diabetes.
The main objective of the present study, therefore, was to describe the time course and risk factors for microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular complications (cardiac, cerebrovascular and peripheral vascular disease) in a large cohort of youth which has been carefully followed over 20 years, and to compare this evolution with that of youth with type 1 diabetes. We also sought to compare vascular complications in the youth with type 2 diabetes with non-diabetes controls. Finally, we sought to address 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).

Methods:
The cohort of youth with type 2 diabetes was identified utilizing a prospectively collected clinical registry from the Diabetes Education Resource for Children and Adolescents (DER-CA) in Manitoba, Canada, and was compared to youth with type 1 diabetes and without diabetes (age, sex and geographically matched) (online Figure 1). Using de-identified personal identifiers these children were linked to healthcare 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:
1. DER-CA registry: This registry has been previously described in detail (13,14).
   In brief, it is the only tertiary care pediatric diabetes referral centre for Manitoba, Canada as well as Northwestern Ontario and part of Saskatchewan. 86.1% of youth in the province of Manitoba less than 18 years of age with diabetes are followed by the DER-CA (14). All patients followed from January 1986 to present have been prospectively entered into the computerized diabetes registry that contains unique personal health identification numbers (PHIN) and clinical, genetic (HNF-1α polymorphism) and laboratory data. Data are not available in this registry after 18 years of age therefore linkages utilizing scrambled PHIN codes to other administrative data sets in the Repository were established to generate longterm outcome data for the DER-CA cohorts.

2. The Manitoba Health Services Insurance Plan (MHSIP) contains registration files, physician reimbursement claims (based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) codes), hospital discharge abstracts (ICD-9CM codes until March 31, 2004 and Canadian version 10 (ICD-10CA) codes thereafter) and records of prescriptions dispensed (subset of Drug Programs Information Network (DPIN); available since 1995). Outpatient physician utilization was assessed using the ICD-9CM diagnostic codes at the 3 digits level. Hospital utilization was assessed using ICD-9CM and ICD-10CA codes at the decimal level. Non-participation in the system is minimal since healthcare coverage is universal in Canada and residents are not charged healthcare premiums. These data are stored in de-identified 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). Records were available until the end of the fiscal year 2007 (March 31) at the time of the
study. All data manipulation and analysis was performed in the MCHP data laboratory itself, which is highly secured in order 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, age 1 to 18 years were included. Canadian Diabetes Association criteria (16) for the diagnosis of diabetes were utilized to confirm the diagnosis of diabetes which are similar to the 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 auto-antibodies 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 mis-classification of diabetes type in First Nation children was uncommon.

**Youth without Diabetes (noDM):** An age, sex and geographically matched (to type 2 diabetes cohort) second control group of children without diabetes was randomly selected from the Repository; defined as no ICD code or pharmaceutical for diabetes. Control to case matching ratio was 5:1 (n=1710) in order to maximize power. The index date for matching was the date of diagnosis of type 2 diabetes. Clinical data was not available for this group.
**Exclusions:** Patients without a valid Manitoba PHIN code were excluded as 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, body mass index z-score (BMIz), elevated blood pressure (according to age, sex and height standardized normal values in children) (19), and hemoglobin A1c (HbA1c) at last follow-up, area-level socioeconomic status (SES) (defined as the lowest urban and rural area level income quintiles vs. other four quintiles), HNF-1α polymorphism status (homozygous (SS) or heterozygous (GS) vs. wildtype (GG)), urban (Winnipeg and Brandon) vs. rural (all other) residence, presence of persistent albuminuria (defined as albumin: creatinine ratio (ACR) of ≥ 3 mg/mmol on a random urine sample or albumin excretion rate (AER) of ≥ 30 mg/24 hours on at least 2 out of 3 measurements > 1 month apart), the (ever) use of ace inhibitors or angiotensin receptor blockers (ACE/ARB) from fiscal years 1995-2007 (utilizing DPIN data), and the presence of pre-gestational diabetes in the youth’s mother (diagnosed prior to pregnancy) as determined in the Repository as an ICD code for diabetes prior to the pregnancy of interest. An era effect variable was also included to determine if standards of diabetes care that were not directly measured in this study prior to and after the year 2000 affected outcomes.

Outcome data:
All outcomes were determined by means of healthcare utilization codes from the Repository. The codes utilized to assess for each diabetes complication are listed in online Table 1. ICD-9CM procedure codes and Canadian Classification of Health Intervention (CCI) codes were also evaluated. In addition, billing codes were used to assess for dialysis utilization (9798, 9799, 9805, 9807, 9801, 9802, 9806, 9819, 9821, 9610, 9820) and renal transplant (5883). In order to maintain consistency, the same codes were utilized to determine outcomes for all three groups. In order to maximize power a composite outcome of “any complication” was utilized which included renal, ophthalmologic, and neurologic complications, and cardiovascular, cerebrovascular and peripheral vascular disease in order 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-tests, Mann-Whitney U and the Chi-square tests where appropriate. Results are reported as mean ± standard deviation (SD) or median and range if data is not normally distributed. P-values <0.05 were considered statistically significant unless otherwise stated.

Analysis 1: Type 2 vs. 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, as 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 values <0.05 were considered statistically significant.

Analysis 2: Type 2 diabetes vs. no diabetes

As clinical variables were not available for the no diabetes controls, a separate analysis was conducted to evaluate this group in comparison to the type 2 diabetes population. 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. As multiple outcomes were evaluated that were not totally independent from each other, in order to prevent type 1 error, a Bonferroni Correction factor at p value <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 analysis was conducted utilizing SAS version 9.1 software.
Results:

A total of 2174 adolescents were identified from the DER-CA database including 1412 with type 1 and 424 with type 2 diabetes (online Figure 1). 806 did not have valid PHINs, generally because they were not Manitoba residents, thus prohibiting long-term follow-up in the Repository and were therefore excluded. Fourteen infants less than one year of age and one nineteen year old were excluded, as they did not meet the age criteria. The final type 2 diabetes cohort included 342 individuals, and the type 1 diabetes control group included 1011 individuals. 1710 no diabetes controls were matched to the type 2 diabetes cohort from the Repository (online figure 1).

Compared to the type 1 diabetes group, the children with type 2 diabetes were on average older at the time of diagnosis and were more likely to be female. They were more likely to have a higher BMI z-score, 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 pre-gestational diabetes, compared with only 3% in the T1DM group and half of the type 2 diabetes cohort was either a heterozygote (GS) or homozygote (SS) for the HNF-1α polymorphism (Table 1).

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-scores persisted, and 40-50% of individuals 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 and lower HDL cholesterol levels, although absolute differences were small.
The median follow-up times in the Repository were 4.4 years (range 0-27.4) for youth with type 2 diabetes, 6.7 years (range 0-28.2) for youth with T1DM and 6.0 years (range 0-29.9) for non-diabetes controls. Crude complication rates for all three groups are presented in Table 3. Overall, both groups with diabetes had higher vascular disease rates than the non-diabetes 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 vs. type 1 diabetes

The statistically significant clinical factors in the univariate analysis associated with the composite outcome included type 2 vs. type 1 diabetes (Hazard Ratio (HR) 1.92 95% CI 1.46-2.55; p<0.0001), age at diagnosis (HR 1.09 95% CI 1.06-1.12; p<0.0001), male sex (HR 0.73 95% CI 0.57-0.94; p=0.01), HbA1c (HR 1.09 95% CI 1.05-1.14; p<0.0001), BMIz score (HR 1.21 95% CI 1.03-1.42; p=0.02), RAAS inhibitor use (HR 2.24 95% CI 1.73-2.92; p<0.0001), low SES (HR 1.48 95% CI 1.12-1.95; p=0.007) and HNF-1α polymorphism (HR 0.58 95% CI 0.34-0.99; p=0.04). Urban residence, elevated blood pressure, diagnosis prior to 2000, pre-gestational diabetes in the mother, and albuminuria were not significant.

The final multivariate model had a sample size of 1018 and there were 212 events. After controlling for low SES, sex and BMI z-score, the risk associated with type 2 vs. type 1 diabetes for risk of any complication was a HR of 1.47; (95% CI 1.02-2.12; p=0.04). Age at diagnosis was associated with a HR of 1.08 (95% CI 1.01-1.12; p=0.002), HbA1c was associated with a HR of 1.06 (95% CI 1.01-1.12; p=0.01), and RAAS inhibitor use was
associated with a HR of 1.75 (95% CI 1.27-2.41; p=0.0006). Tests for proportionality for all statistically significant variables were non-significant. 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 vs. no diabetes

Crude outcomes rates are in Table 3. In the univariate analysis, youth with type 2 diabetes were at significantly higher risk of developing any vascular disease (HR 6.15, 95% CI 4.26-8.87; p=<0.0001), and any microvascular (HR 6.26, 95% CI 4.32-9.10; p=<0.0001) or macrovascular disease (HR 4.44, 95% CI 1.71-11.52; p=<0.0001) compared to controls without diabetes. In addition, the youth with type 2 diabetes also had an increased risk of opthalmologic (HR 19.49, 95% CI 9.75-39.00; p=<0.0001), renal (HR 16.13 95% CI 7.66-33.99; p=<0.0001) and neurologic disease (HR 2.93, 95% CI 1.79-4.80; p=<0.001). There were few cardiovascular, cerebrovascular and peripheral vascular disease (PVD) events in all groups (≤ 5 events per group). Despite this, there was still a statistically significant higher risk of peripheral vascular disease (PVD) in the type 2 diabetes group (HR 6.25, 95% CI 1.68-23.28; p=0.006).

Kaplan Meier analyses

Figures 1A through C show event-free survival for each of the microvascular complications. Differences in renal and neurologic complications between the two groups began to occur prior to 5 years post diagnosis, whereas differences in opthalmologic complications began to occur 10 years after the diagnosis of diabetes. Differences in opthalmologic complications however were not statistically significant.
Both cardiovascular and cerebrovascular complications were rare in both groups, however peripheral vascular complications began to occur fifteen years after diagnosis in the type 2 diabetes cohort (data not shown). Overall, major complications were rare in the type 1 diabetes cohort; however, they occurred in 1.1% of the type 2 diabetes cohort at 10 years, 26.0% at 15 years and 47.9% 20 years after diagnosis (p<0.001) (Figure 2).

Discussion:

This is the largest natural history study of youth onset type 2 diabetes published to date. We have shown that youth with type 2 diabetes have a higher risk of any complication than youth with type 1 diabetes and non-diabetes controls. Clinical factors associated with complications include 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 neurological complications was significantly shorter in youth with type 2 diabetes than controls, whereas differences were not significant with respect to ophthalmologic and cardiovascular complications between cohorts. This study therefore highlights the fact 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 rates of end-stage-renal disease (ESRD) of up to 50% in youth with 20 years of follow-up (13). This study further highlights the accelerated rate
of renal complications in youth with type 2 diabetes early after diagnosis. This stresses the importance of screening for albuminuria in these patients, rather than waiting for a longer disease duration as is the routine practise in adults (25). Biopsy data of youth with type 2 diabetes suggests that pathophysiological mechanisms are different from traditional diabetic nephropathy. In fact, nine out of ten children biopsied from this population with macroalbuminuria have previously been shown to have either glomerulosclerosis or immune mediated disease (26). Recent National data supports this finding, which showed that glomerulonephritis was the most common cause of ESRD in Aboriginal children and young adults < 40 years old, whereas diabetes started to predominate only after 40 years of age (27). As 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 their higher risk of chronic kidney disease in this population, likely potentiated by diabetes.

This is the first study to compare neurological 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 this study was lower at 7.6%, individuals 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). This study relies on ICD coding which will likely include the most symptomatic individuals, however the validity of these codes have yet to be properly evaluated. Studies including 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 ophthalmologic complications are in contrast to the previous literature, which showed a lower risk of retinopathy in youth with type 2 diabetes as compared to type 1 diabetes (22,24) and adult onset type 2 diabetes (31). This study reveals instead a similar burden of diagnosed ophthalmologic complications in both subtypes of youth onset diabetes. Reported rates of retinopathy in youth onset type 2 diabetes vary considerably in the literature from 4 to 40% depending on the population studied and the means of evaluation (22,24,31-35). Our results are at the lower end of this spectrum. As this study is based on diagnostic coding it is likely that background retinopathy rates are underestimated due to its asymptomatic nature and thus actual differences between subgroups may not be evident early in the course of disease. Importantly, rates after ten years of disease began to steeply increase 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.

This study is consistent with previous 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. As the median follow-up time in this study 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. It is also possible that diagnoses are not being made of mild disease due to a low index of suspicion in 20- and 30-year-old patients.

The evaluation of clinically important factors associated with complications in this study yielded several important findings. First, glycemic control was an important clinical risk factor for any complication. This is in keeping with the type 1 diabetes literature (6) and
other cross sectional studies of youth with type 2 diabetes (34). An increased complication burden was also associated with an increased age at diagnosis. This finding may be explained by non-adherence in the adolescents, which is a high risk time regarding adherence to therapy. Alternatively, there is some evidence to suggest that pre-pubertal diagnosis of diabetes is associated with a better long-term risk profile, therefore younger children may be relatively protected (36). Pubertal status was unfortunately not available in this study. In addition, the relative protection of the HNF-1α genetic polymorphism with respect to diabetic 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 was surprising, as this result is in contrast to multiple clinical trials in adults showing a benefit in terms of diabetic nephropathy and retinopathy (37). The most reasonable interpretation is that this finding represents confounding by indication or illness severity, as has been described in ASA trials (38), rather than a causal association indicating harm. On the other hand, it should be noted that there are no randomized controlled trials of RAAS inhibitors in youth onset type 1 or type 2 diabetes and an assessment of the interaction of RAAS use and albuminuria was not significant, suggesting RAAS use did not abrogate the effect of established albuminuria. The possibility that these drugs behave differently in youth cannot be excluded.

This study has many clinical and research implications. Since 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 been manifest clinically in this study. Finally, the risk associated with RAAS inhibitors in this study is concerning as these medications are used routinely in clinical practise. 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 characterises 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, there may exist an ascertainment bias 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 does negate the possibility that one complication be “masked” by the coding of another. Due to the retrospective nature of this study, and changes in clinical practice guidelines over time, another concern is the fact that not all clinical variables were available for all patients. While this concern must be acknowledged, it does not affect the outcome rates, which are measured only utilizing administrative data in the Repository.
Another limitation is the fact that SES was assessed as an area-level measure in this study. However, it has been shown in the past that area-level approximate individual-level measures of SES (39). Finally, 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 due to decreased access to medical services, and thus not being diagnosed with diabetic 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.

Conclusions:

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. HbA1c is an important modifiable risk factor, and thus optimizing glycemic control should remain an important goal of therapy. In addition, age at diagnosis may alter future risk, and renin-angiotensin system inhibitors need to be evaluated with a randomized controlled study in youth with diabetes prior to changing clinical practice. As this is a unique population in Manitoba, the external validity of these findings must be evaluated in other populations.
Authors Contributions

A.D. developed the study proposal, performed the analysis and wrote the manuscript. All other authors (P.M., C.R, M.B., H.D., E.S.) contributed to the study design and interpretation of the results, and reviewed/edited the manuscript.

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Competing Financial Interests: none.
References


Table 1 Baseline Demographics of Youth Onset Diabetes Cohorts

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<th></th>
<th>Type 1 Diabetes (n=1710)</th>
<th>Type 2 Diabetes (n=342)</th>
<th>p-value</th>
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<td>Age (years)</td>
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<td>13.5 ± 2.2</td>
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<td>Sex (Male %)</td>
<td>53.2</td>
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<td>BMI z-scores</td>
<td>0.4 ± 1.0</td>
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<td>Urban (%)</td>
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<td>Low SES (%)</td>
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<td>HNF 1α polymorphism (%)</td>
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<tr>
<td></td>
<td></td>
<td>18.5% SS††</td>
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<tr>
<td>Elevated blood pressure (%)</td>
<td>11.1</td>
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<td>Albuminuria at diagnosis (%)</td>
<td>13.5</td>
<td>27.1</td>
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<td>Mother with pre-gestational diabetes (%)</td>
<td>2.7</td>
<td>15.9</td>
<td>&lt;0.0001</td>
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Continuous variables are reported as mean + SD † Heterozygous ††Homozygous for HNF1 α polymorphism
Table 2 Clinical Features at Last *DER-CA Follow-up for Youth Onset Diabetes Cohorts

<table>
<thead>
<tr>
<th></th>
<th>Type 1 Diabetes (N=1710)</th>
<th>Type 2 Diabetes (N=342)</th>
<th>p-value</th>
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<td>Age (years)</td>
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<td>BMI z-scores</td>
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<td>Total cholesterol (mmol/L)</td>
<td>4.3 ± 1.0</td>
<td>4.6 ± 1.0</td>
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<td>LDL-chol. (mmol/L)</td>
<td>2.9 ± 2.2</td>
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<td>HDL-chol. (mmol/L)</td>
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<td>Triglycerides (mmol/L)</td>
<td>1.3 ± 0.9</td>
<td>2.2 ± 2.2</td>
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<td>**ApoB (mmol/L)</td>
<td>0.9 ± 0.4</td>
<td>0.8 ± 0.2</td>
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<td>Elevated blood pressure (%)</td>
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<td>HemoglobinA1c (%) (mmol/mol)</td>
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<td></td>
<td>77 ± 25.1</td>
<td>74 ± 32.8</td>
<td></td>
</tr>
<tr>
<td>Albuminuria (%)</td>
<td>19.8</td>
<td>38.6</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Continuous variables reported as mean + SD *Diabetes Education Resource for Children and Adolescents *Apolipoprotein B
Table 3 Crude Complication Rates in Youth Onset Diabetes Cohorts and Rates of Comparable Disease in non-Diabetes Controls

<table>
<thead>
<tr>
<th></th>
<th>No Diabetes</th>
<th>Type 1 Diabetes</th>
<th>Type 2 Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=1710</td>
<td>N=1011</td>
<td>N=342</td>
</tr>
<tr>
<td>No. (%)</td>
<td>Mean Age (yrs)</td>
<td>Mean DM duration (yrs)</td>
<td>Mean DM duration (yrs)</td>
</tr>
<tr>
<td>Any Complication</td>
<td>87 (5.1)</td>
<td>189 (18.7)</td>
<td>71 (20.8)</td>
</tr>
<tr>
<td></td>
<td>20.8 ± 5.0</td>
<td>7.2 ± 5.2</td>
<td>5.0 ± 4.3</td>
</tr>
<tr>
<td>Renal complication</td>
<td>11 (0.6)</td>
<td>27 (2.7)</td>
<td>30 (8.9)</td>
</tr>
<tr>
<td></td>
<td>21.9 ± 6.5</td>
<td>9.9 ± 6.3</td>
<td>7.5 ± 5.7</td>
</tr>
<tr>
<td>Renal failure</td>
<td>*</td>
<td>14 (1.4)</td>
<td>23 (6.7)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9.3 ± 5.5</td>
<td>9.1 ± 6.0</td>
</tr>
<tr>
<td>Dialysis</td>
<td>*</td>
<td>0 N/A</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16.1 ± 3.6</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>61 (3.6)</td>
<td>50 (5.0)</td>
<td>26 (7.6)</td>
</tr>
<tr>
<td></td>
<td>21.2 ± 5.1</td>
<td>9.8 ± 4.9</td>
<td>6.5 ± 5.6</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>13 (0.8)</td>
<td>139 (13.8)</td>
<td>40 (11.7)</td>
</tr>
<tr>
<td></td>
<td>21.3 ± 6.6</td>
<td>7.9 ± 5.8</td>
<td>7.4 ± 5.9</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Peripheral Vascular</td>
<td>*</td>
<td>6 (0.6)</td>
<td>*</td>
</tr>
<tr>
<td>Disease</td>
<td></td>
<td>8.0 ± 3.9</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular Disease</td>
<td>*</td>
<td>10 (1.0)</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.3 ± 4.3</td>
<td></td>
</tr>
</tbody>
</table>

*<5 individuals – number suppressed in the table to maintain patient anonymity.
Continuous variables are reported as mean ± SD

Figure 1 Complication free survival in youth onset diabetes cohorts.

A – Retinopathy free survival B- Neuropathy free survival C-Nephropathy free survival of youth onset diabetes cohorts D - Major complication (dialysis, blindness, amputation) free survival Legend: Type 1 Diabetes (black line) ; Type 2 Diabetes (hatched line).
Survival probabilities

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 Patients at risk
T1DM  1011       608       365       152       37       4
T2DM  342       153        56       25        6       1

P < 0.13

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P < 0.001

---

P < 0.0001
Online Appendix
Online Figure 1: Study flow diagram

Assessed for eligibility in Diabetes Endocrine Resource for Children and Adolescents Database (n=2174)

Excluded (n=821)
No valid PHIN code (n=806)
Did not meet age criteria (n=15)

Included (n=13532052)

Type 2 Diabetes Group (n=342)
- Median Follow-up 4.4 years
- Mean Age 13.5 ± 2.2 years
- Male = 37.8%

Type 1 Diabetes Group (n=1011)
- Median Follow-up 6.7 years
- Mean Age 8.9 ± 4.3 years
- Male % = 53.2%

Non Diabetes Group (n=1710) (matched 5:1)
- Median Follow-up 6.0 years
- Mean Age 13.5 ± 2.3 years
- Male = 37.9%
<table>
<thead>
<tr>
<th>Type of Complication</th>
<th>*ICD-9CM (Diagnostic codes)</th>
<th>ICD-9CM (Procedure codes)</th>
<th>**ICD-10CA (Diagnostic codes)</th>
<th>***CCI codes</th>
</tr>
</thead>
</table>
| **Renal**            | 250.4 (diabetes with renal manifestation)  
581 (nephrotic syndrome; includes intercapillary glomerulosclerosis and Kimmelstiel-Wilson syndrome)  
583 (nephritis and nephropathy, not specified as acute or chronic)  
585 (chronic kidney disease)  
586 (renal failure, unspecified)  
V45.1 (renal dialysis status)  
V56 (encounter for dialysis and dialysis catheter care)  
V58.8 (fitting and adjustment of vascular catheter)  
996.56 (complications specific to peritoneal dialysis catheter) | 39.95 (hemodialysis)  
54.98 (peritoneal dialysis)  
38.95 (venous catheterization for renal dialysis)  
39.27 (arteriovenous fistula for renal dialysis)  
39.42 (revision of arteriovenous shunt for renal dialysis) | N08.3 (diabetic nephropathy)  
N04 (nephrotic syndrome)  
E10.2 (insulin dependent DM with renal complications)  
E11.2 (non-insulin dependent DM with renal complications)  
N17 (acute renal failure)  
N18 (chronic renal failure)  
N19 (unspecified renal failure)  
Z49 (care involving dialysis) | KR53 (implantation of internal device for short-term dialysis)  
1KY (fistula)  
1OT53 (PD catheter)  
1OK85 or 1PC85 (renal transplant) |
| **Ophthalmologic**   | 250.5 (diabetes with ophthalmic manifestations)  
362 (macular edema, retinal edema or retinopathy)  
365 (glaucoma)  
366 (cataract)  
369 (blindness) | 14 (laser eye therapy) | N10.3, N11.3 (diabetic retinopathy)  
H54 (blindness)  
H28 (cataract)  
H35 (macular edema)  
H36 (retinopathy)  
H40 (glaucoma) | 1CN59 (retinal surgery) |
| **Neurological**     | 250.6 (diabetes with neurologic manifestation)  
337 (peripheral autonomic neuropathy)  
353.3 (amyotrophy)  
354-5 (mononeuropathy)  
357 (polyneuropathy)  
536.3 (gastroparesis/paralysis)  
713 (neurogenic arthropathy) | E10.4, E11.4 (diabetic neuropathy)  
G59.0 (mononeuropathy)  
G63.2 (diabetic polyneuropathy)  
G73.0 (amyotrophy)  
G99.0 (autonomic neuropathy)  
K31.8 (gastroparesis)  
M14.2 (diabetic arthropathy) | E10.4, E11.4 (diabetic neuropathy)  
G59.0 (mononeuropathy)  
G63.2 (diabetic polyneuropathy)  
G73.0 (amyotrophy)  
G99.0 (autonomic neuropathy)  
K31.8 (gastroparesis)  
M14.2 (diabetic arthropathy) |
| **Macrovascular**     | 410-14 (ischemic heart disease)  
430-38 (cerebrovascular disease)  
250.7 (diabetes with peripheral circulatory disorders)  
440-8 (disease of the arteries)  
785.4 (gangrene) | 84 (amputation)  
36 (operations on vessels of heart) | I20-25 (ischemic heart diseases)  
I60-6, I67.2, I68 (cerebrovascular diseases)  
E10.5, E11.5 (diabetes with peripheral circulatory disorders)  
I70-77 (diseases of the arteries)  
I79.2 (peripheral angiopathy)  
A48, R02 (gangrene) | 1I6 (cardiovascular surgery)  
1IA-Q (vascular surgery)  
1TM93, 1TV9, 1WE93, 1WJ93, 1WL93, 1WM93, 1VA93, 1VB, 1VC93, 1VF, 1VG93, 1VQ93 (amputations) |

*International Classification of Disease 9th Revision, Clinical Modification ** Revision 10CA (Canadian) *** The Canadian Classification of Health Interventions