

**The Natural History of Youth Onset Type 2 Diabetes Mellitus**

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## **Abstract**

Youth onset type 2 diabetes (T2DM) is a relatively new disease; therefore long-term outcome data is scant. Administrative data was anonymously linked to a clinical registry, to evaluate the validity of diabetes algorithms in youth. In addition, incident youth with T2DM (n=342) in Manitoba (1-18 years) from Jan.1986-2009 identified from the clinical registry were anonymously linked to healthcare records in order to evaluate complications; compared to youth with type 1 diabetes (T1DM) (n=1011) and non-diabetes (non-DM) controls (n=1710). Cox proportional-hazards models were constructed to analyze differences in risk of “any complication” as well as renal complications and the role of clinical risk factors. Kaplan Meier (KM) statistics were utilized to assess complication free and overall survival.

The algorithm including 1 or more hospitalizations or two or more outpatient claims over two years was the most valid. Youth with T2DM had a 47% increased risk of any complication. Age at diagnosis, HgA1c and ace inhibitor/angiotensin receptor blocker use (ACE/ARB) (which may be a marker of disease severity) were significant risk factors. Youth with T2DM also had a 2.29 fold increased risk of renal complication and a 4.03 fold increased risk of renal failure compared to youth with T1DM. Risk factors for renal complications included ACE/ARB use, albuminuria and diagnosis prior to 2000. Compared with non-DM controls, youth with T2DM had a 6.15 fold increased risk of vascular disease and a 16.13 fold increased risk of renal disease. Survival at 10 years was 91.4% in the T2DM group compared to 99.5% in the T1DM group and 100% in non-DM controls (p<0.0001).

Children with youth onset T2DM are at high risk of complications and death. Glycemic control and albuminuria are important potentially modifiable risk factors, and ACE/ARB use needs to be further evaluated in youth.

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## **Chapter 1: Introduction**

### **1.1 Epidemiology of youth onset type 2 diabetes mellitus**

Diabetes mellitus is a disease that affects an estimated 1.3 million Canadians and is projected to affect 2.4 million by 2016 (1). Overall, type 2 diabetes mellitus (T2DM) is the predominant form of diabetes and has been traditionally regarded as a disease of the middle-aged and elderly (2). However, it is now known to affect all age groups, including children and adolescents. In the 1980s it was first reported in First Nation (FN) children in Canada (3) and now has been described in children around the world including Japan, India, Australia, the United States and the United Kingdom (4-8). Definitions vary in the literature; however, for the purpose of this thesis, youth onset T2DM will be defined as T2DM diagnosed prior to 18 years of age. As youth onset T2DM is a relatively new disease, little is currently known about its epidemiology and natural history.

#### **1.1.1 Pathophysiology**

The pathophysiology of T2DM is complex and multifactorial. The increase in T2DM has paralleled the increase in overweight and obesity in high-risk populations (4) suggesting a causal link, although definitive studies proving this association in children do not exist (2). The disease is characterized by relative insulin insufficiency in the context of peripheral insulin resistance (9), which over time leads to pancreatic  $\beta$ -cell failure and expression of the disease. This transition often occurs at puberty, which is known to be associated with a decrease in insulin sensitivity (10). The diagnosis of diabetes as well as the determination of subtypes is based on clinical and biochemical criteria (see appendix 1.1).

### **1.1.2 Incidence and prevalence**

Worldwide, the incidence and prevalence of youth onset diabetes have been increasing over the last two decades (5,11,12). Type 1 diabetes (T1DM) remains the predominant form of diabetes in children; however, it has now been reported that 8-45% of new cases of diabetes in children are T2DM (9). The proportion of youth with T2DM varies by age group and ethnic background (12). In the 1990's, T2DM in Manitoba First Nation children was 7 times more prevalent than T1DM in the general pediatric population (13). In 2007, T2DM represented 36% of all new cases of diabetes in children in Manitoba (14).

The Pima Indians in central Arizona have the world's highest rates of T2DM, with approximately 50% of adults over the age of 35 years affected (15). This population has been systematically studied for over 30 years providing proof that this is a new disease in children and not simply improved case finding. In this population, the prevalence of T2DM in children increased from 0% of boys and 0.72% of girls aged 10-14 yrs from 1967-1976 to 1.4% of boys and 2.88% of girls from 1987-1996.

An epidemiologic study in the United States reported an incidence rate of 8.1/100,000 person years and 11.8 per 100,000 person-years in children aged 10-14 years and 15-19 years respectively (12). Lower rates of 0.53 per 100,000 children <17 years of age were reported in the United Kingdom (16).

In Canada, a recent National surveillance initiative estimated that the minimum incidence of T2DM in Canada is 1.54 cases per 100,000 youth less than 18 years of age. Sensitivity analyses suggest a maximum incidence of 40.5 cases per 100,000 children per year. The highest rates of T2DM in children were reported in Manitoba at 12.35 per 100,000 youth (17).

The prevalence is as high as 1% in First Nation children aged 4-19 years in some communities (18). In Manitoba, the minimum overall age specific point prevalence of T2DM in aboriginal youth aged 10-19 years increased from 0.1% (1/1000) to 0.22% (2.2/1000) from 1986 to 1998 (19).

### **1.1.3 Risk Factors**

In addition to obesity, multiple other risk factors for the development of T2DM have been proposed. Firstly, most affected children with youth onset T2DM belong to minority ethnic groups including Canadian First Nations, American Indian, Hispanic, African-American and Indo-asian (5). There is a strong hereditary component to T2DM, that is likely multigenic in most cases (20). A strong family history is almost universal, with 45-80% of children with T2DM having at least one parent affected and 70-100% having a first or second-degree relative affected with the disease (9,21). T2DM is distinct from a small percentage of cases of diabetes that have been explained by a single gene defect collectively known as maturity-onset diabetes of youth (MODY) (22).

A polymorphism in the HNF-1 $\alpha$  gene at codon 319 (HNF-1 $\alpha$  G319S) has been identified in Oji-Cree individuals lacking the characteristic features of insulin resistance, including

acanthosis nigricans and obesity and has been suggested to involve an insulin-secretory and/or –production defect (23). Homozygous individuals have a 4-fold increased risk of T2DM and heterozygous individuals have a 2-fold increased risk (24). This polymorphism may explain in part the high burden of disease in the Oji-Cree.

The intrauterine environment has been shown to significantly influence the future risk of T2DM in Pima Indians. There is a U-shaped relationship with birth weight, wherein both high and low extremes are associated with later development of T2DM. The lowest risk is in children who were between 3-3.5kg at birth, with significant increased risk in children less than 2.5 kg or greater than 4.0 kg even after adjusting for gestational diabetes, family history and socioeconomic status (25). The children of Canadian First Nation mothers with pre-gestational diabetes (OR 14.4; 95% C.I. 2.86-72.5) as well as those with gestational diabetes (OR 4.40; 95% C.I. 1.38-14.1) are also at increased risk of youth onset T2DM (26). Breastfeeding has been shown to be protective (26-29).

#### **1.1.4 Natural History**

The natural history and true burden of youth onset T2DM are still unknown. In adults, serious complications of T2DM are known to reach end stage 20 years after their onset (30). There is now evidence to suggest that complications occur at an earlier age with a shorter duration of diabetes in youth onset T2DM (31). Young people with T2DM also tend to be obese, and are therefore prone to additional cardiovascular risk factors such as hypertension and dyslipidemia (32,33). The earlier age of diagnosis raises concern regarding the resulting burden of disease because these children may begin to suffer the micro- and macrovascular complications of diabetes as young adults at the height of their

productivity, resulting in significant impact on quality of life as well as economic consequences. Chapter 2 reviews the current literature on youth onset T2DM associated complications.

## **1.2 Description of study region – Manitoba, Canada**

### **1.2.1 Geography and Demography**

Manitoba is the most eastern prairie province in Canada. It is bordered by Saskatchewan to the west and Ontario to the east, Nunavut to the north and the United States to the south. The province spans 649,950 km<sup>2</sup> in area. The majority of the land is in the subarctic zone and is covered by lakes, rivers and boreal forest. Agriculture dominates the province's economy (34).

The total population of Manitoba in 2006 was 1,148,401. The median age was 38.1 years. The pediatric population from 0 to 14 years was 224,065. The majority of the population lived in urban centers (72%) (35).

The predominant ethnic groups in addition to “Canadian” are English, German, Scottish, and Ukrainian (35). Also relevant to this thesis is a prominent Aboriginal population. In 2007, 124,410 registered First Nation people lived in Manitoba, with 59.8% under the age of 30 years. Geographic isolation of some of these communities has led to social and economical challenges: 61.8% of First Nations people lived on reserve in 2007. There are five First Nations linguistic groups in Manitoba: Cree, Ojibway, Dakota, Ojibway-Cree and Dene (36).

### **1.3 Description of data sources**

#### **1.3.1 Diabetes Education Resource for Children and Adolescents (DER-CA)**

The DER-CA provides integrated, interprofessional (physician, nurse educator, dietician, social worker and secretary) and specialized programming for youth with diabetes, predominantly in the outpatient setting. It is funded by Manitoba Health and is located in the Children's Hospital of Winnipeg, Health Sciences Centre, which is the only tertiary care pediatric referral centre for Manitoba. In addition to providing care for Manitoba children, it also offers services to children from Northwestern Ontario and Saskatchewan. The DER-CA is known to follow the vast majority of children in the province with type 1 diabetes mellitus (T1DM) (37). DER-CA also follows a large number of children and adolescents with T2DM, however the ascertainment rate has not yet been systematically evaluated.

All patients treated and followed in the DER-CA from January 1986 until present have been prospectively entered into a computerized diabetes registry. The registry contains personal health identification numbers (PHINs) and validated diagnostic data which distinguish the subtypes of diabetes.

#### **1.3.2 Manitoba Centre for Health Policy (MCHP)**

The Manitoba Health Services Insurance Plan (MHSIP) contains registration files, physician reimbursement claims, hospital discharge abstracts and records of prescriptions dispensed. Non-participation in the system is minimal since residents are not charged health care premiums. These data are stored in de-identified form in the Population

Health Research Data Repository (herein referred to as the Repository) housed at the Manitoba Centre for Health Policy (MCHP). 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 utilizing a unique, anonymized personal health identification number (PHIN).

The Repository includes records of physician reimbursement for each physician visit including a diagnostic code according to the International Classification of Diseases , 9<sup>th</sup> Revision, Clinical Modification (ICD-9CM), albeit at the 3 digit code level only, and a date of service. Discharge abstracts for hospital services also include date of admission and discharge and up to 16 diagnoses using ICD-9CM codes at the decimal level up until April 1, 2004 and up to 25 diagnoses using ICD-10 Canadian version (ICD-10CA) codes thereafter. The ICD-9CM code 250 (diabetes mellitus) and ICD-10-CA codes E10 (insulin dependent diabetes) and E11 (non-insulin dependent diabetes) were evaluated in this study.

All prescriptions dispensed by pharmacies are also available since 1995 in the pharmacy database which is a subset of the Drug Programs Information Network (DPIN) and includes information on date of dispensing, drug name, drug identification number (DIN), dosage form and quantity dispensed. DINs can be linked to Anatomic Therapeutic Chemical (ATC) codes in the Drug Product Directory which is maintained by Health Canada. A Master formulary is maintained by the MCHP which contains classification codes for drugs, generic product names and brand names. The ATC code A10 (drugs for

diabetes) was utilized for this study. At the time of this study data were available until the end of the fiscal year 2007 (March 31).

#### **1.4 Research objectives**

This thesis is organized into three individual publication-based documents (Chapters 3-5) aiming to meet the following research objectives:

1. To develop a validated case definition for youth onset T2DM utilizing administrative data.
2. To determine the natural history of youth onset T2DM with respect to microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular complications (cardiac, cerebrovascular and peripheral vascular disease) as well as overall survival as compared to children with youth onset T1DM and without diabetes.
3. To evaluate renal outcomes in youth with T2DM as compared to youth with T1DM and without diabetes and to determine clinical risk factors for progression of disease.

## **Appendix 1.1 Canadian Diabetes Association Criteria for the Diagnosis of Diabetes (38)**

Classical Symptoms of diabetes (polyuria, polydipsia and unexplained weight loss) plus:

1. Fasting (no caloric intake for at least 8 hours) plasma glucose  $\geq 7.0$  mmol/L or
2. Random plasma glucose  $\geq 11.1$  mmol/L or
3. Two-hour plasma glucose  $\geq 11.1$  mmol/L after a standard oral glucose tolerance test (75g anhydrous glucose dissolved in water).

If the child is asymptomatic a second confirmatory biochemical test is required.

Diagnosis of **Type 2 Diabetes**: based on clinical criteria including the presence of obesity, other evidence of insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome in females), family history of type 2 diabetes, intrauterine exposure to hyperglycemia and family heritage from a high-risk ethnic group (39). When available, the absence of diabetes-associated auto-antibodies is used to support the diagnosis of type 2 diabetes (40-41).

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## **Chapter 2: Complications in Youth Onset Type 2 Diabetes – A Review of the Literature**

Type 2 diabetes (T2DM) is associated with microvascular complications including retinopathy, nephropathy and neuropathy and macrovascular complications including cardiovascular, cerebrovascular and peripheral vascular disease. As youth onset T2DM is a relatively new disease, little is known about the natural history of the disease including its long-term complications. This chapter summarizes the current literature about each of the potential complications.

### **2.1 Nephropathy (Table 2.1)**

The first sign of diabetic nephropathy is microalbuminuria, which then either reverts or progresses to overt nephropathy and ultimately end stage renal disease (ESRD) requiring renal replacement therapy (1). Diabetic nephropathy accounts for only 0.2% of chronic renal disease in children (2), however it is the leading cause of ESRD in adults (1).

Microalbuminuria was present at diagnosis in 22% of Pima Indian children diagnosed with T2DM between the ages of 15 and 19 years (3), 14% of young Maori individuals less than 30 years at diagnosis (mean age 19.5; range 5-29 years) (4) and 7% of Australian children with T2DM diagnosed at <18 years of age (mean age 13.2; range 11.6-15 years) (5). The rate of progression also seems to be variable with microalbuminuria occurring in 9.6% of a Japanese cohort of early onset T2DM (mean age  $22.6 \pm 5.6$  years) at a mean follow-up of 6.8 years (6), and 40% of Latino and African-Americans with youth onset T2DM three years after diagnosis in a New York cohort

(mean age  $15 \pm 1.9$ ; range 11.8-18.1 years) (7). In the Pima Indians, the frequency of microalbuminuria increased to 58% at 10 years post diagnosis and macroalbuminuria was detected in 17% at a mean age of 26 years (3). Similarly, microalbuminuria increased to 62% in young Maori over 10 years (4).

Studies comparing microalbuminuria in individuals with type 1 diabetes mellitus (T1DM) and T2DM have shown the following: A Korean study of young people 8-28 years of age showed that 11.3% of 141 patients with T1DM and 18.2% of 22 patients with T2DM had microalbuminuria, despite a shorter disease duration. Glycemic control was poor in both of these groups (8). Similarly, a multicentre study across New Zealand of young people <26 years showed that 72% of 105 people with T2DM (mean age  $20 \pm 0.4$  years) and 17% of 662 with T1DM (age range 16-25 years) had microalbuminuria, despite shorter disease duration in those with T2DM (9). The Australian study of diabetes diagnosed < 18 years of age showed similar results with microalbuminuria in 28% of individuals with youth onset T2DM (mean age 13.2; range 11.6-15 years) compared with 6% with T1DM (mean age 8.1; range 4.8-10.8 years) (5).

In Japanese patients diagnosed with diabetes before age 30, the cumulative incidence of nephropathy after 30 years of postpubertal diabetes was significantly higher for patients with T2DM (44.4% vs. 20.2%). In this population, the incidence of T1DM associated nephropathy had decreased during the last two decades; however this had not occurred in patients with T2DM. The rate ratio for T2DM diagnosed between 1980 and 1984 relative to T1DM diagnosed in the same period was 2.74. Poor glycemic control and

hypertension were associated with the development of nephropathy in both T1DM and T2DM (10). These authors had previously reported a high risk subgroup of their cohort of 1065 patients with early-onset T2DM developing proliferative retinopathy prior to age 35. Of those with retinopathy (n= 135), 60% developed diabetic nephropathy at a mean age of 31 years, and 23% developed renal failure requiring dialysis at a mean age of 35 years (11).

In the Pima Indian population, individuals with T2DM who were <20 years of age at diagnosis had a 5-fold increased incidence of end-stage renal failure (age-sex-adjusted ESRD incidence of 25 cases per 1000 person-years) compared to nondiabetics and individuals with T2DM diagnosed between 20-55 years of age (5.4 cases per 1000 person-years). The younger age group also had increased mortality, with age-sex-adjusted death rates 3.0 times as high as in nondiabetic participants and 2.1 times as high as in individuals diagnosed with T2DM after the age of 20 (12). A subset analysis revealed that the differences were likely due to the longer duration of disease in the youngest cohort of patients in this study.

In 2002, a natural history study published by Dean and Flett identified 51 clinic graduates from Manitoba and northwestern Ontario with T2DM onset prior to age 17 years (18 to 33 years at the time of the study). There had been 7 deaths (mortality of 9%), including 2 sudden deaths on dialysis (females, aged 25 and 31 years). Three other females age 26, 28 and 29 years had been on dialysis for 2 months, 1 year and 6 years respectively (13).

The only study that has compared incidence of nephropathy, defined as a protein-to-creatinine ratio  $\geq 0.5$  g/g in patients with T2DM based on age of disease onset (<20 years vs. 20-39 years and >40 years) did not show a difference in risk of nephropathy over 25 years (14). These data are summarized in Table 2.1.

One major limitation in all of these studies is the lack of biopsy data confirming the diagnosis of diabetic nephropathy as the etiology of proteinuria in these patients. Recently, a small study reported the results of renal biopsy in 10 adolescents with youth onset T2DM and macroalbuminuria. These adolescents were all of Canadian First Nation descent. None of the patients had classic diabetic nephropathy and 9 out of 10 had immune complex disease or glomerulosclerosis (15). Although this study was small, it suggests renal biopsies may be warranted in cases of macroalbuminuria in individuals with youth onset T2DM in order to confirm the correct diagnosis.

## **2.2 Retinopathy (Table 2.2)**

Diabetes associated retinopathy is also a progressive disorder that affects the microvasculature of the retina. The mildest stage of disease is non-proliferative retinopathy, or background diabetic retinopathy (BDR). This can progress to pre-proliferative and ultimately proliferative diabetic retinopathy (PDR), which is associated with a high risk of visual loss. Few studies have been published on retinopathy associated with youth-onset T2DM. A Japanese study of 1065 patients with T2DM diagnosed prior to 30 years of age separated patients into those with (12.7%) and without proliferative retinopathy before the age of 35 years. In the proliferative retinopathy

group, 32 (24%) were blind by a mean of 35 years of age (11). Another subgroup of this cohort (n=394) which did not have proliferative retinopathy at diagnosis was evaluated in another study. 18.2% of this cohort had background retinopathy (BDR) at diagnosis and another 88 developed BDR during a mean follow-up period of 5.7 years. Of the 160 individuals with BDR, 50 (31.2%) developed proliferative retinopathy (PDR) after a mean of 7.1 years (16).

Other studies have shown a low risk of retinopathy in youth with T2DM. Krakoff et al. demonstrated a lower risk of retinopathy in youth onset T2DM in the Pima Indians, compared to adult onset disease. They also reported that it did not occur in any patients less than 20 years of age (14). Two other studies have compared youth onset T2DM to T1DM. Eppens et al. evaluated 1433 patients with T1DM and 68 with T2DM by seven-field stereoscopic retinal photography. Twenty percent of patients with T1DM had retinopathy compared with only 4% of the patients with T2DM, however the length of disease was shorter in the patients with T2DM by an average of 5.5 years (5). Scott et al. reported that 4% of 105 patients with T2DM with a mean age of  $20 \pm 0.4$  years had background retinopathy and 4% had sight-threatening retinopathy compared with 10% of patients with T1DM (9). The main risk factor for the development of diabetic retinopathy in adults is poor glycemic control (16-18).

Multifocal electroretinograms (mfERG) have been shown to identify focal retinal neuropathy in the absence of any clinically visible vascular damage. In youth aged 13 to 21 years with T2DM with diabetes for a mean of  $2.1 \pm 1.3$  years, mfERG's were

significantly delayed by 0.49 milliseconds. In addition, they were shown to have retinal thinning (10.3  $\mu\text{m}$ ) and significant venular dilation (16.2  $\mu\text{m}$ ) (20). In adult diabetic populations without retinopathy, a delayed mfERG implicit time is predictive of future development of retinopathy (19).

### **2.3 Neuropathy (Table 2.2)**

Diabetes associated neuropathy is a progressive disorder that affects both the autonomic and peripheral nervous systems. Limited information has been published about it in youth onset T2DM. Of 28 Maori with early onset T2DM, two had peripheral neuropathy (4). In an Australian cohort, rates of peripheral and autonomic neuropathy did not differ in adolescents younger than 18 years of age with T1DM and T2DM (27% and 61% vs. 21% and 57% respectively) (5). A recent study by Chuback et al. identified neuropathic symptoms in 12% of 110 subjects with youth onset T2DM at a mean age of  $15 \pm 3$  years (21). In another, more recent report, 4 out of 7 youth with T2DM had abnormal large and small nerve fibre function and 4 out of 7 had weak posterior tibial pulses (22).

### **2.4 Cardiovascular risk factors (Tables 2.3 and 2.4) and macrovascular disease (Table 2.5)**

Adults with T2DM have a high a rate of complications related to cardiovascular disease (23-25) and mortality rates are twice as high in adults with T2DM compared to people without the disease (24,25). Data on the long term cardiovascular outcomes of children and adolescents with youth onset T2DM is scant. However, several small studies have revealed a high rate of concomitant cardiovascular risk factors in this population.

The literature on the presence of dyslipidemia is mixed due to different definitions and reported abnormalities. However, all studies reveal high rates of dyslipidemia as summarized in Table 2.3 (3-5,26-31). Variable rates of hypertension have also been reported ranging from 10% to 73% (3,26,29,30,32-34) (Table 2.4).

Evidence of end organ damage has been reported by Korner et al. where 47% of 22 Hungarian children with T2DM had posterior and septal wall thickness above the reference range (35). Left ventricular hypertrophy has also been reported in 22% of adolescents with T2DM within 3 years of diagnosis (7). Gungor et al. did not find a difference in carotid intima media thickness between 20 youth with T2DM for  $1.7 \pm 0.4$  years and normal weight and obese controls but did show that they had a higher pulse wave velocity (36). In addition, 14 of 1065 patients in the Japanese early onset T2DM cohort developed atherosclerotic vascular disease by 36 years of age (11) (Table 2.5).

In one study of 7,844 patients with adult onset T2DM in the United States, after controlling for length of follow-up, younger adults with T2DM (< 45 years) were found to have an eightfold higher overall risk of developing any macrovascular disease relative to control subjects, compared with only a fourfold increased hazard in the usual onset T2DM group ( $\geq 45$  years at diagnosis) (37), suggesting the possibility that younger individuals with T2DM may do even worse than their older counterparts diagnosed in adulthood.

In summary, youth with T2DM have been shown to be at risk for all of the possible complications seen in adult onset diabetes to varying degrees. This raises concern that

they will have significant morbidity at young ages, at the height of their productivity. In order to better delineate this risk and possible modifying factors, more long-term outcome data are required.

**Table 2.1: Literature review of renal complications in youth onset type 2 diabetes mellitus**

	<b>Population</b>	<b>Patients (n)</b>	<b>Age of onset of diabetes (years)*</b>	<b>At presentation</b>	<b>At follow-up (years since diagnosis)*</b>
<b>Microalbuminuria:</b>					
Fagot-Campagna et al. (1998) (3)	Pima Indian	36	15-19	22%	58% (10)
Yokoyama et al. (1998) (6)	Japan	426	22.6 ± 5.6	-	9.6% (6-8)
McGrath et al. (1999) (4)	Maori	28	19.5 (5-29)	14%	62% (10)
Yoo et al. (2004) (8)	Korea	22	18.4 ± 4.3	-	18.2% (7.4 ± 3.9)
Ettinger et al. (2005) (7)	New York Latino and African American	26	15 ± 1.9	-	40% (<3)
Eppens et al. (2006) (5)	Australia	68	13.2 (11.6-15)	7%	28% (0.6-3)
Scott et al. (2006) (9)	New Zealand	105	16-25	-	72% (3 ± 0.3)
<b>Macroalbuminuria:</b>					
Fagot-Campagna et al. (1998) (3)	Pima Indian	36	15-19	0%	17% (10)
Yoo et al. (2004) (8)	Korea	22	8-28		4.5% (5.5 ± 3.9)
<b>Diabetic Nephropathy:</b>					
**Yokoyama et al. (2000) (10)	Japan	958	10-30	-	44.4% (95% CI 37.0 to 51.8%)
***Krakoff et al. (2003) (14)	Pima Indian	178	<20	-	20.2% (<5 to >25 years)
<b>End Stage Renal Disease:</b>					
Dean et al. (2002) (13)	Manitoba, Canada First Nation	51	<17	-	6.3%
Pavkov et al. (2006) (12)	Pima Indian	96	25.0 (25.0-48.7)	-	16% (8.3 (5.0-33.2))

\*Mean ± standard deviation or range ( )

\*\*Defined as persistent proteinuria, presence of diabetic retinopathy and absence of clinical or laboratory evidence of non-diabetic renal disease

\*\*\*Defined as protein-to-creatinine ratio ≥ 0.5 (g protein/g creatinine)

**Table 2.2: Literature review of presence of retinopathy and neuropathy in youth onset type 2 diabetes mellitus**

	Population	Patients (n)	Age of onset of diabetes (years)*	Percent affected	Comments
<b>Retinopathy:</b> Yokoyama et al. (1997) (11)	Japan	1065	< 30	12.7% PDR* (<35 years of age)	24% blind by mean of 35 years
Okudaira et al. (2000) (16)	Japan	394	22.6 ± 5.6	40.6% BDR** (18.2% at diagnosis) 12.6% PDR (mean follow-up 7.1 years)	Mean HgA1c and duration of diabetes predicted BDR Mean HgA1c and diastolic blood pressure predicted PDR
Krakoff et al. (2003) (14)	Pima Indian	178	< 20	17.4% (5-25 years with DM)	Lower incidence compared with older onset type 2 diabetes (p=0.007); did not occur <20 years of age
Eppens et al. (2006) (5)	Australia	68	13.2 (11.6-15)	4% (median 1.3 years DM; IQR 0.6-3.1)	Retinopathy more common in type 1 diabetes (20%; p=0.04) however duration of diabetes shorter (p<0.0001)
Scott et al. (2006) (9)	New Zealand	105	16-25	4% BDR 4% sight-threatening (DM for 3 years)	Compared with 10% in type 1 diabetes patients
Bronson-Castain et al. (2009) (20)	United States	15	16 ± 1.9	40% (8% controls)	6 or more abnormal mfERG implicit times; retina considered functionally abnormal
<b>Neuropathy:</b> McGrath et al. (1999) (4)	Maori	28	19.5 (5-29)	10.7% (mean duration DM 10 years)	1-erectile dysfunction 2-peripheral neuropathy
Eppens et al. (2006) (5)	Australia	68	13.2 (11.6-15)	21% peripheral neuropathy 57% autonomic neuropathy Mean 1.3 years DM (range 0.6-3.1)	
Chuback et al. (2007) (21)	Manitoba, Canada	110	Not available	12% neuropathic symptoms (DM duration 30 ± 20 months)	
Karabouta et al. (2008) (22)	United Kingdom	7	14.3 (9.8-17.2) (current age)	4/7 abnormal large and small nerve fiber function 4/7 weak posterior tibial pulse	Median duration of DM 1.8 years (0.8-3.0)

\*PDR = proliferative diabetic retinopathy

\*\*BDR = background retinopathy

**Table 2.3: Literature review of dyslipidemia in youth onset type 2 diabetes mellitus**

	Population	Patients (n)	Age of onset of diabetes (years)*	Percent affected (duration DM in years)	Definition
<b>Dyslipidemia:</b>					
Fagot-Campagna et al. (1998) (3)	Pima Indian	41	-	30% (5-10)	Total cholesterol
Hotu et al. (2004) (26)	New Zealand	18	15 (11-19)	85% (1.8)	Total /HDL >4.5 molar units
McGrath et al. (1999) (4)	Maori	28	19.4 (2-29)	62.5% (10)	Total cholesterol >5.04mmol/L
Wei et al. (2003) (27)	Taiwan	137	13.7	27.0% (at diagnosis)	Cholesterol >5.17mmol/L
Eppens et al. (2006) (5)	Australia	68	13.2 (11.6-15)	Chol 32% TG 53% (median 1.3 years DM; IQR 0.6-3.1)	Cholesterol >5.17mmol/L TG >1.69 mmol/L
Kershner et al. (2006) (28)	United States	283	>10	High: Tchol 33%; LDL 24%; TG 29%; Low: HDL 44% (at dx)	Tchol > 5.17mmol/L; LDL >3.36mmol/L ; TG >1.69 mmol/L; HDL < 1mmol/L
Rodriguez et al. (2006) (29)	United States	63	<20	High TG 65% Low HDL 60%	TG ≥ 110mg/dl; HDL ≤ 40mg/dl
Sellers et al. (2007) (30)	Manitoba, Canada First Nation	99	13.1 (9-17)	>75 <sup>th</sup> ile controls: - Tchol 75.8%; LDL 73.7%; apoB 72.3% <25 <sup>th</sup> ile controls: HDL 51.5%	Tchol > 4.68mmol/L; LDL >2.82mmol/L ; TG >1.5 mmol/L; HDL >0.9mmol/L
Newfield et al. (2008) (31)	Mexican American	52	13.6 ± 2.2	High: Tchol 55.8%; LDL 39.4%; TG 65.1%; Low: HDL 40% (at diagnosis)	Tchol > 5.17mmol/L; LDL >3.36mmol/L ; TG >1.68 mmol/L; HDL < 0.91 mmol/L

\*Mean ± standard deviation or range ( )

\*\*apoB = Apolipoprotein B; Tchol = total cholesterol; LDL=low density lipoprotein; HDL=high density lipoprotein; TG=triglyceride

**Table 2.4: Literature review of hypertension in youth onset type 2 diabetes mellitus**

	<b>Population</b>	<b>Patients (n)</b>	<b>Age of onset of diabetes (years)*</b>	<b>Percent affected (duration DM in years)</b>	<b>Comments</b>
<b>Hypertension:</b>					
Scott et al. (1997) (32)	Arkansas	50	13.9 ± 0.4	32% (at diagnosis)	
Fagot-Campagna et al. (1998) (3)	Pima Indians	100	15-19	18% (at diagnosis)	
Upchurch et al. (2003) (33)	Houston, TX	98	13.6 (8.7-18.4)	Systolic 49%; Diastolic 17% (at diagnosis)	
Hotu et al. (2004) (26)	New Zealand	18	15 (11-19)	28% (4 years)	
Zdravkovic et al. (2004) (34)	Toronto, ON	41	13.5 (8.8-17.5)	10% (at diagnosis)	
Rodriguez et al. (2006) (29)	United States	63	<20	73%	92% had ≥ 2 CVD risk factors
Sellers et al. (2007) (30)	Manitoba, Canada First Nation	99	13.1 (9-17)	12% male 14% female	31% males, 47% females smokers

\*Mean ± standard deviation or range ( )

**Table 2.5: Literature review of macrovascular disease in youth onset type 2 diabetes mellitus**

	<b>Population</b>	<b>Patients (n)</b>	<b>Age of onset of diabetes (years)*</b>	<b>Percent affected (duration DM in years)</b>	<b>Comments</b>
<b>Macrovascular disease:</b> Yokoyama et al. (1997) (11)	Japan	1065	<30	1.31%	Atherosclerotic vascular disease at mean age of 36 years.
Korner et al. (2002) (35)	Hungary	22	-	47%	Posterior and septal wall thickness > reference range 71% diminished nocturnal decline in blood pressure (non-dippers)
Gungor et al. (2005) (36)	United States (African American and Caucasian)	20	Not available (duration DM = 1.7 ± 0.4 years)	-	Carotid intima media thickness (IMT) not different but aortic pulse wave velocity (aPWV) higher than normal weight and obese controls
Ettinger et al. (2005) (7)	New York Latino and African American	24	15 ± 1.9	22% (<3)	Left ventricular hypertrophy

\*Mean ± standard deviation or range ( )

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## **Chapter 3: Validation of a Youth Onset Diabetes Definition Utilizing Administrative Data**

### **3.1 Abstract:**

Diabetes in youth is a rising health concern in Canada and its prevalence can be feasibly monitored on a longitudinal basis utilizing administrative data. Validation of definitions for pediatric age groups is required. **Methods:** Population-based administrative data from Manitoba, Canada for the years 2004-2006 were anonymously linked to a clinical youth onset diabetes registry to evaluate the validity of diabetes algorithms based on a combination of hospital, outpatient and drug utilization data over one to three years in youth 1-18 years of age. Agreement between data sources, sensitivity, specificity, negative (NPV) and positive predictive value (PPV) were evaluated for each algorithm. In addition, ascertainment rate of each source, prevalence and potential differences between subtypes of diabetes were evaluated. **Results:** Agreement between data sources was very good. The diabetes definition including one or more hospitalizations or two or more outpatient claims over two years provided a sensitivity of 94.2%, specificity of 99.9%, PPV of 81.6% and NPV of 99.9%. The addition of 1 or more prescription claims to the same definition over one year provided similar results. Case ascertainment rates of both sources were very good to excellent and the ascertainment-corrected prevalence for youth onset diabetes for the year 2006 was 2.4 per 1000. It was not possible to distinguish between subtypes of diabetes within the administrative database, however this limitation could be overcome with an anonymous linkage to the clinical registry. **Conclusions:** Administrative data are a valid data source for the evaluation of youth onset diabetes which can provide important information for health care planning and evaluation.

### **3.2 Background:**

Diabetes is a chronic disease that has a multi-factorial etiology and a prolonged clinical course (1). Similar to other chronic diseases, it has a profound impact on the Canadian population. The last Canadian Community Health Survey reported 1.3 million Canadians had been diagnosed with diabetes (2) and the prevalence has been projected to increase to 2 million in 2010 and 2.4 million by 2016 (3). Diabetes is the seventh leading cause of death in Canada, and accounted for 25,000 potential years of life lost in 1996 (4). The highest burden of diabetes is in the middle-aged and elderly (5), however the prevalence of diabetes continues to rise in all age groups, including children and adolescents (6-8). In adult populations, type 2 diabetes (T2DM) accounts for 90-95% of diabetes, however in youth populations, T2DM accounts for 8-45% of incident cases, depending on the ethnicity of the population evaluated (9).

In addition to being associated with an increased morbidity and mortality, diabetes also has a large economic impact, with estimated direct medical costs of 13.3 billion dollars in Canada in 1998 (10). Costs are even higher in individuals with diabetic complications such as chronic kidney disease (11). In order to describe the burden of disease and plan for and evaluate disease prevention and treatment strategies, reliable population based data are required on an ongoing basis (12). Vital statistics files, disease specific registries and population-based surveys are all potentially useful and adaptable to this purpose (13). Administrative data, which include hospital and physician records as well as drug utilization, are a valuable tool that have been utilized in a number of studies to evaluate the incidence and prevalence of adult onset diabetes nationally and internationally (14-

16) as well as locally in Manitoba (17-20). A number of studies have also evaluated the prevalence of youth onset diabetes utilizing administrative data (21-27). In addition, diabetes incidence and prevalence for children and adults (1 year of age and older) are monitored at the national level by Health Canada utilizing The National Diabetes Surveillance System (NDSS) which is a network that gathers anonymous administrative data for aggregate analysis from regional surveillance systems (28).

This type of data source is easily accessible on an ongoing basis and can thus provide cross-sectional and longitudinal information. It is not as costly and time consuming to establish and maintain as a population based registry and thus more feasible to study (13). As all data sources have potential limitations and the sensitivity and specificity of administrative databases have been reported to vary considerably according to the disease studied (29), validation of the data source for the given disease and population of interest is essential. Previous studies have systematically evaluated the relative validity of case definition algorithms for adult onset diabetes (13,20,30,31). The definition for diabetes utilized by the NDSS (1 hospitalization or 2 outpatient visits for diabetes (ICD-9 code 250) over a 2 year period) has also been validated in adults over 20 years of age and has been shown to have a sensitivity of 69-95%, specificity of over 95% and positive predictive value (PPV) of 78-80% depending on the comparative data source (32). It has also been shown that the addition of pharmaceutical data does not improve the validity of the definition (33).

The first study to assess the validity of the NDSS definition in youth was recently published by Guttman et al. (27). The authors assessed the sensitivity and specificity of the definition in youth less than 19 years of age as well as a number of other definitions utilizing hospital and outpatient claims over 1 or 2 years. Hospital chart audits from Ontario hospitals were utilized for validation. They found that the NDSS definition had a sensitivity of 100% and a specificity of 94.2% in this age group. These results have not yet been confirmed with other datasets, nor have the contribution of drug utilization data and the determination of differences between type 1 diabetes (T1DM) and T2DM been assessed in youth.

The specific research objectives of this study were to: 1) test the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of eighteen different pediatric diabetes case definition algorithms from administrative data; 2) test the agreement of each algorithm with confirmed cases from a clinical registry; 3) determine the case ascertainment rate of each data source utilizing the two source capture-recapture method; and 4) evaluate the ability to distinguish T1DM and T2DM in administrative data.

### **3.3 Methods:**

This study was conducted utilizing administrative, population-based data in Manitoba, Canada, which has a universal healthcare system and a population of 1.2 million people. Eighteen youth onset (1-18 years) diabetes case definition algorithms were evaluated utilizing different combinations of physician, hospital and drug utilization data over one,

two, and three years (Table 1). Validation of these algorithms was performed by comparing them to confirmed cases in a clinical registry, which was considered the ‘gold standard’ for diagnosis (full description below). Case ascertainment rates and evaluation of differences between T1DM and T2DM were also determined.

**Data Sources:**

1. **The Manitoba Health Services Insurance Plan (MHSIP)** contains registration files, physician reimbursement claims, hospital discharge abstracts and records of prescriptions dispensed. Non-participation in the system is minimal since residents are not charged health care premiums. These data are stored for research purposes in de-identified form in the Population Health Research Data Repository (herein referred to as the **Repository**) housed at the Manitoba Centre for Health Policy (MCHP) in the University of Manitoba’s Faculty of Medicine. Although de-identified, various files can be linked at the person-level for projects utilizing a unique, anonymized personal health identification number (PHIN), after receiving ethical approval from the University of Manitoba Research Ethics Board and from the provincial Health Information Privacy Committee.

The Repository includes records of physician reimbursement for each physician visit including a diagnostic code according to the International Classification of Diseases, 9<sup>th</sup> Revision, Clinical Modification (ICD-9CM) at the 3-digit code level, and a date of service. Discharge abstracts for hospital services also include date of admission and discharge and up to 16 diagnoses using ICD-9CM codes at the decimal level up until April 1, 2004 and up to 25 diagnoses using ICD-10 Canadian version (ICD-10CA) codes

thereafter. The ICD-9CM code 250 (diabetes mellitus) and ICD-10-CA codes E10 (insulin dependent diabetes) and E11 (non-insulin dependent diabetes) were evaluated in this study.

All prescriptions dispensed by pharmacies are also available since 1995 in the pharmacy database which is a subset of the Drug Programs Information Network (DPIN) and includes information on date of dispensing, drug name, drug identification number (DIN), dosage form and quantity dispensed. DINs can be linked to Anatomic Therapeutic Chemical (ATC) codes in the Drug Product Directory which is maintained by Health Canada. A Master Formulary is maintained by MCHP which contains classification codes for drugs, generic product names and brand names. The ATC code A10 (drugs for diabetes) was utilized for this study. At the time of this study, data were available until the end of the fiscal year 2007 (March 31). Therefore, as the last complete calendar year available was 2006, this year was utilized for evaluation of the algorithms.

## **2. The Manitoba Diabetes Education Resource for Children and Adolescents (DER-CA) Registry.**

The DER-CA provides integrated, interprofessional and specialized programming for youth with diabetes, predominantly in the outpatient setting. It is located in the only tertiary care pediatric referral centre for Manitoba and is known to follow the majority of children in the province with T1DM (26). The DER-CA also follows a large number of children and adolescents with T2DM, however the ascertainment rate has not yet been systematically evaluated.

All patients treated and followed in the DER-CA from January 1986 until present have been prospectively entered into a computerized diabetes registry. The registry contains PHIN codes and validated diagnostic data which distinguish the subtypes of diabetes. The diagnosis of diabetes was made according to the criteria of the Canadian Diabetes Association (34). Criteria include the classical symptoms of hyperglycemia plus a random plasma glucose  $\geq 11.1$  mmol/L or a fasting plasma glucose (FBG)  $\geq 7.0$  mmol/L or a two hour plasma glucose  $\geq 11.1$  mmol/L after a standard oral glucose tolerance test. If the child is asymptomatic, a second confirmatory biochemical test is required.

The classification of T2DM was based on clinical criteria including the presence of obesity, other evidence of insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome in females), family history of T2DM, intrauterine exposure to hyperglycemia and family heritage from a high-risk ethnic group (35). When available, the absence of diabetes-associated auto-antibodies was used to support the diagnosis of T2DM (36-37).

Utilizing de-identified PHIN codes and through the creation of a cross-walk file to the Repository, youth can be linked between data sources at the person level.

### **Sample**

The sample of youth evaluated in this study included all children and adolescents in Manitoba with prevalent diabetes and valid Manitoba PHIN codes between 1 and 18 years of age from January 1 to December 31, 2006. Individuals that did not have

coverage data available in the Repository for the full time period evaluated in each algorithm (i.e. 1, 2 or 3 years) were excluded from that particular analysis.

### **Description of the Diabetes Algorithms**

This study evaluated algorithms based on one (2006), two (2005-06) or three (2004-06) years of administrative data. The codes evaluated included the ICD-9CM code 250 for physician claim data and hospital separation data prior to April 1, 2004 and the ICD-10-CA codes E10 and E11 for hospital separation data after April 1, 2004. The ATC code A10 was evaluated for diabetes drug utilization. The algorithms varied in the number of occurrence of codes from each data source (Table 3.1). These algorithms were based on those previously studied in the literature (13,14,19,30,38).

### **Validation Methods and Analysis**

#### **Agreement between data sources**

The kappa statistic ( $\kappa$ ) was used to measure the agreement between the two data sources for the presence or absence of diabetes. A kappa of 0.80 to 1.00 was considered very good agreement.

#### **Sensitivity, Specificity, Negative and Positive Predictive Values**

A sensitivity and specificity analysis of each proposed algorithm was conducted, utilizing the DER-CA database as the “gold standard”. The sensitivity is defined as the percentage of true positives (TP) detected by each algorithm among all positive cases ( $TP/(TP+FN)$ ; FN = false negatives). The specificity is defined as the true negatives (TN) detected

among all the negative cases ( $TN/(FP + TN)$ ; FP=false positives). In addition, NPV and PPV were determined. The NPV is defined as the percentage of individuals with a negative result for an algorithm who do not have diabetes ( $TN/(TN+FN)$ ), and the PPV is defined as the percentage of individuals with a positive result for an algorithm amongst confirmed cases ( $TP/(TP+FP)$ ). The total mid-year population of children 1-18 years of age in Manitoba in 2006 was 268,120. This was considered the total population at risk for diabetes.

### **Ascertainment rate of the Repository and DER-CA**

The two-source capture, re-capture method was utilized to assess the ascertainment rate of the Repository and DER-CA for youth onset diabetes in Manitoba as well as to determine the ascertainment-corrected prevalence of diabetes in Manitoba for 2006. This method provides an accurate estimate of the total youth onset DM population (N) in Manitoba (19,37,38). The Repository was considered the first sample of cases (M) and the DER-CA was considered the second sample of cases (n). The population estimate was based on the number of cases “recaptured” by the second sample (m); that is the number of cases in common between the Repository and the DER-CA. The population estimate was calculated such that  $N = [(M+1)(n+1)/(m+1)] - 1$ . This population estimate was utilized to calculate the ascertainment-corrected prevalence of youth onset diabetes. Ascertainment rate was defined as the percentage of ascertainment-corrected cases (i.e. percentage of estimated population) identified by the Repository and DER-CA;  $[M/N \times 100]$  and  $[n/N \times 100]$  respectively.

### **Differences between subtypes of youth onset diabetes (T1DM and T2DM)**

Due to the fact that the ICD9-CM codes in the administrative physician visit data do not distinguish between the subtypes of diabetes, it was not possible to identify de novo the subtypes of diabetes in the Repository using any of the proposed algorithms.

However, as the clinical registry from the DER-CA contains validated diagnostic data which distinguish the subtypes of diabetes, it was utilized to determine the prevalence of each subtype of diabetes in Manitoba youth in 2006. Once individuals were identified as being either T1DM or T2DM from this data source they were then anonymously linked back to the Repository to determine what percentage of each subtype of diabetes was also present in the Repository data utilizing each of the eighteen algorithms. In addition, drug utilization (i.e. prescription of ATC code A10 drug over 3 years of data collection) was examined to determine if it would permit the differentiation of subtypes of youth onset diabetes within the Repository.

### **3.4 Results:**

#### **Validation of Diabetes Algorithms**

Table 3.2 contains the validation results for each youth onset diabetes algorithm. Overall the agreement between the two data sources was moderate to very good with kappa values of 0.57 to 0.89. The highest kappa value (0.89) was achieved in algorithm # 4, which included 1 or more hospital separation claims, or 2 or more physician claims or 1 or more DPIN records over a one-year period. Algorithm #2, 6 and 8 also had very high kappa values (0.87 - 0.88).

The sensitivity was very high for all algorithms (88.9% to 98.5%). Not surprisingly, the sensitivity was slightly higher if only 1 physician claim was required rather than 2 or more. However, these algorithms had much lower PPV's than those requiring 2 physician claims. The algorithm with the highest PPV was #2, which included at least 1 hospital claim or 2 physician claims over a one-year period. The addition of DPIN data to the algorithm including one year of data (algorithm #4) improved the sensitivity from 88.9 to 94.2% as compared to algorithm #2 while maintaining a relatively good PPV of 82.4%. In contrast, the addition of DPIN data to the algorithms including 2 or 3 years of data did not significantly improve the sensitivity of the algorithm and decreased the PPV. The specificity and NPV of all algorithms were between 99.7 and 99.9%.

The ascertainment rate of the Repository for youth onset diabetes was very good to excellent for all diabetes algorithms (88.9% to 98.5%). The ascertainment rate for the DER-CA had a wider range depending on the algorithm evaluated (41.4 to 86.1%). The Repository algorithms with the highest PPV were associated with the highest DER-CA ascertainment rates.

### **Prevalence of Youth Onset Diabetes**

The ascertainment-corrected prevalence of youth onset diabetes in 2006 ranged between 2.30 and 4.84 per 1000 children 1 to 18 years in Manitoba (Table 3.2).

### **Differences between T1DM and T2DM**

There were a total of 531 prevalent youth with diabetes identified from the DER-CA registry that had full coverage from January 1 to December 31, 2006 in the Repository (i.e. were alive and residents of Manitoba for the full time period). 420 youth had T1DM and 111 had T2DM. The prevalence of youth onset T1DM was therefore 1.57 per 1000 and the prevalence of youth onset T2DM was 0.41 per 1000. It was not possible to correct these estimates for ascertainment due to the lack of differentiation of the subtypes of diabetes in the Repository. These figures are probably underestimates (i.e. minimum prevalence rates).

Table 3 lists the percentage of children with each subtype of diabetes that was also captured by each diabetes algorithm in the Repository. The majority of the youth with T1DM were captured by all definitions (91.9 to 99.3%), however the percentage of youth with T2DM captured was more varied (77.5 to 95.5%). In general, the algorithms requiring 2 physician visits decreased the likelihood of a case being identified, indicating that many youth with T2DM only had one billed physician encounter in that calendar year.

The drug data were examined over 3 years (2004-06) and 409 youth with T1DM and 110 youth with T2DM identified from the DER-CA had full coverage in the Repository over this time period. The drug data revealed that 96.8% of youth with T1DM (n=396) and 63.6% of youth with T2DM (n=70) were dispensed a medication for diabetes (ATC code A10). The youth with T1DM were only dispensed insulin, however 42.7% (n=47) of the

youth with T2DM were dispensed only insulin, 13.6% were dispensed only an oral hypoglycemic agent (n= 15) and 7.3% (n=8) were dispensed both insulin and an oral hypoglycemic agent during that time period.

### **3.5 Discussion:**

#### **Youth Onset Diabetes Definition**

This study supports the use of population-based administrative data to evaluate diabetes prevalence in youth 1-18 years of age. The linkage of the Repository to a clinical youth onset diabetes registry (DER-CA) containing validated diagnostic data confirming the diagnosis of diabetes permitted the validation of administrative pediatric diabetes definitions. Agreement between the two data sources was very good (kappa greater than 0.80) for a number of different possible definitions including one, two or three years of administrative data. Several other generalizations about the algorithms can be made. Definitions that included three years of data were the most sensitive (97.9 to 98.5%), however had the worst PPV (40.0 to 77.4%) as more false positives were identified with the longer time period. The examination of two years of data rather than one year increased the sensitivity of the definition (94.2% vs. 88.9%), while sacrificing only slightly the PPV (81.6% vs. 86.1%). Algorithms that required at least two outpatient physician visits increased the PPV markedly over those that only required one as more “true” cases were being detected with the more restrictive definitions (86.1% vs. 62.2% and 81.6% vs. 48.9% for one and two years of data respectively). The addition of one or two prescription claims for a diabetes drug improved the sensitivity slightly (94.2% and

96.8% vs. 88.9%) for one year of data. Specificity and NPV were excellent at 99.7% - 99.9% for all definitions.

In balance, the overall best definitions for youth onset diabetes that should be considered for future studies are:

1. One year of data (#4): 1 or more hospitalizations or 2 or more physician claims or 1 or more prescription claims (kappa 0.89, sensitivity 94.2%, specificity 99.9%, PPV 82.4% and NPV 99.9%).
2. Two years of data (#8): 1 or more hospitalizations or 2 or more physician claims (kappa 0.87; sensitivity 94.2%, specificity 99.9%, PPV 81.6% and NPV 99.9%).

The second definition is identical to the one utilized by the NDSS (32) and thus supports its use in children. Guttman et al. also recently evaluated the validity of different algorithms for pediatric diabetes utilizing hospital chart audits in Ontario as the second data source (27). The NDSS definition in that study was found to have a sensitivity of 100% and a PPV of 97.6%, however the specificity was slightly lower at 94.2%. These authors also compared physician claim based algorithms with and without hospital claims data and found that the addition of hospital data increased the number of false positives identified, and thus decreased the specificity of the diabetes definition. This finding is difficult to interpret in the context of hospital chart review as the validation source. The most specific definition in their study was 4 outpatient visits over a 2 year period. However, 2 claims in a 2 year period had a higher sensitivity with only a marginal

difference in specificity (0.986 vs. 0.989). Pharmaceutical utilization was not assessed in this study.

Previous adult validation studies have revealed similar findings. Robinson et al. found that 3 years of data collection with one claim maximized the number of diabetes cases identified in administrative data. In addition, sensitivity decreased and kappa values decreased as additional diagnoses were required (30). In contrast, Rector et al. showed a maximum sensitivity of 0.91 and specificity of 0.93 for a definition that included 1 of any type of claim (inpatient or outpatient) or any pharmacy claim (31). In this study, requiring that the claim be a face-to-face encounter increased the specificity slightly, yet decreased the sensitivity of the algorithm. In keeping with other studies, increasing the number of years of claims data evaluated increased the sensitivity (0.90 to 0.95). Most recently, Lix et al. compared administrative data to survey data from the Canadian Community Health Survey (CCHS) (20). This study showed a good or very good agreement between the two data sources (kappa 0.65 to 0.83). Agreement was better in algorithms that required two-contact case definitions. This study also evaluated the utilization of physician only versus physician and hospital utilization and showed an improvement in agreement with the addition of hospital data, which is in contrast to the findings by Guttman et al. (27). The addition of pharmacy data also improved agreement. Specificity and negative predictive value (NPV) estimates were greater than 97% for all evaluated definitions (13).

A summary of the pediatric diabetes literature that has included administrative data to evaluate diabetes prevalence is provided in Table 3.4. Blanchard et al. utilized Manitoba

administrative data to evaluate the incidence and point prevalence of diabetes in 0-14 year olds utilizing the following case definition: five or more separate physician claims or minimum of three physician claims if registered with Manitoba Health for less than 2 years (26). Individuals with treaty status were excluded from the analysis in order to evaluate only children with T1DM in this study. Treaty status refers to individuals of Aboriginal descent included in the Indian Register, established by the Indian Act in 1876 (39). Incidence rates and prevalence were corrected for ascertainment utilizing two-source capture-recapture methodology (40,41) also utilizing the DER-CA clinical registry as the second data set. The administrative database was found to have a case ascertainment rate of 95%; however the case definition was not otherwise evaluated for validity.

Another pediatric study evaluated administrative coding for T2DM in youth, adolescents and young adults (42). The study evaluated the PPV of one inpatient or outpatient five-digit ICD-9CM code (250.X0/X2) that includes T2DM and “unspecified” diabetes compared with the PPV of T1DM codes (250.X1/X3, X=0-9) in a Boston Massachusetts database. The PPV was found to be only 16% for T2DM, but much higher for T1DM at 97%. One study evaluated encounter and pharmacy claims in privately insured children in the United States (43). Three other pediatric studies have utilized the Indian Health Service (IHS) Facility Database in the United States (US) (21,24,25) and two studies have evaluated prescription claim data in the UK (22) and US (23) to evaluate the prevalence of diabetes. The study by Dabelea et al. utilized a definition of 1 or more inpatient or outpatient records over 3 years to identify cases of DM, however reported

that only 50% of cases identified by the IHS were confirmed by chart audit, suggesting that the PPV of that definition was very low, which is in keeping with the results from the current study (21).

Administrative databases have been criticized for being incomplete or inaccurate (44). There has been concern that health care encounters may not be billed for, and thus not appear in the data. Alternatively, even though care may be billed for, the correct diagnosis may not be recorded (29,45,46). In addition, diagnoses listed may be a reflection of testing performed rather than diagnosis made (31). Despite these concerns, databases are extensively utilized in research. Database research offers the possibility of feasibly following individuals with chronic diseases such as diabetes cross-sectionally and longitudinally at a much reduced cost and improved feasibility as compared to other means, such as surveys (31). These concerns however highlight the importance of maximizing the performance of claims-based algorithms by assessing their validity, such as has been done in this study.

### **Ascertainment and Diabetes Prevalence**

The ascertainment of the Repository for the diagnosis of youth onset diabetes was very good for all evaluated algorithms (88.9% to 98.5%). This suggests that few cases are likely to be missed if this administrative database is utilized to evaluate youth onset diabetes prevalence. The ascertainment rate of the DER-CA was more variable (40.0% to 86.1%) depending on the diabetes algorithm evaluated. However, with the more valid algorithms described above, the ascertainment rates were very good (81.6% to 86.1%)

suggesting the majority of children and adolescents with confirmed diabetes in Manitoba are followed by the tertiary care referral centre, and thus captured in the clinical registry.

Once corrected for ascertainment, the two most favorable algorithms (#4 and #8) provided youth onset diabetes prevalence estimates of 2.40 and 2.43 per 1000 youth 1-18 years of age. This estimate is comparable to the crude prevalence of 1.82 per 1000 in the United States evaluated by a recent active surveillance initiative (47) and the Canadian prevalence of 3 per 1000 youth 1 to 19 years of age reported by the NDSS (28).

#### **Differences between T1DM and T2DM within administrative data**

The main limitation of administrative data in the evaluation of youth onset diabetes is the inability to identify the subtypes of diabetes with 3 digit ICD-9CM coding. This is less of an issue in adult populations where T2DM accounts for the vast majority of cases (5). In the past, T1DM could be assumed based on pediatric age, however with the development of T2DM in children, this is no longer the case (48). Depending on the population studied, the percentage of youth onset diabetes accounted for by T2DM is quite variable. In predominantly Caucasian populations, T1DM continues to predominate in youth (49), whereas T2DM is now more predominant in Aboriginal (6) and African American (50) populations. In addition, even if five-digit ICD-9CM coding is available, the PPV for the diagnosis of T2DM may be as low as 16% in children, adolescents and young adults populations (42). The current study evaluated drug utilization in both subtypes of diabetes as a potential means to differentiate T1DM from T2DM. However, lifestyle management is the mainstay of treatment in T2DM and is, of course, not

captured in the drug utilization database. Insulin remains the only approved pharmacologic agent for the treatment of diabetes in children in Canada and is the predominant form of recommended pharmacologic therapy for both T1DM and T2DM in youth (34,35). Thus, insulin use cannot be used as a reliable means to distinguish one subtype of diabetes from the other.

Possible mechanisms to overcome this limitation include linkages to clinical registries such as the DER-CA which contain diagnostic data differentiating the subtypes of diabetes or medical record reviews or audits.

### **3.6 Conclusions:**

This study supports the use of administrative data to determine the overall prevalence of diabetes in youth at a population level. This data source can feasibly provide cross-sectional and longitudinal data which are important in planning for healthcare utilization as well as evaluating disease prevention and treatment strategies. The identification of cases over a two-year period with either one hospitalization or two or more outpatient visits as utilized currently by the NDSS provides excellent sensitivity, specificity, NPV and PPV in youth age 1 to 18 years. The addition of drug utilization data to a one-year period of evaluation provides a definition with comparable validity. With the currently utilized ICD coding schema, in order to evaluate subtypes of diabetes, clinical correlation is required.

**Table 3.1: Algorithms Applied and Validated to Develop Case Definition for Youth Onset Diabetes using Manitoba Administrative Data**

<b>Years of Data Collection</b>	<b>Algorithm#</b>	<b>Hospital Separation OR</b>	<b>Physician Claims OR</b>	<b>DPIN Records</b>
1 (2006)	1	1 or more	1 or more	-
	2	1 or more	2 or more	-
	3	1 or more	1 or more	1 or more
	4	1 or more	2 or more	1 or more
	5	1 or more	1 or more	2 or more
	6	1 or more	2 or more	2 or more
2 (2005-06)	7	1 or more	1 or more	-
	8	1 or more	2 or more	-
	9	1 or more	1 or more	1 or more
	10	1 or more	2 or more	1 or more
	11	1 or more	1 or more	2 or more
	12	1 or more	2 or more	2 or more
3 (2004-06)	13	1 or more	1 or more	-
	14	1 or more	2 or more	-
	15	1 or more	1 or more	1 or more
	16	1 or more	2 or more	1 or more
	17	1 or more	1 or more	2 or more
	18	1 or more	2 or more	2 or more

**Table 3.2: Validation of pediatric diabetes algorithms compared to clinical DER-CA registry, ascertainment rates and ascertainment corrected prevalence of youth onset diabetes**

# Yrs	Alg. #	N (DER-CA)	N (MCHP)	Ascertainment Rate of DER-CA based on case definition	Ascertainment Rate of Repository for youth onset DM	Ascertainment Corrected Prevalence of Youth Onset DM (per 1000 youth)	K	MCHP Case Definition Algorithm			
								Sens	Spec	PPV	NPV
1	1	531	867	62.2%	95.4%	3.18	0.75	95.4	99.9	62.2	99.9
	2		579	86.1%	88.9%	2.30	0.87	88.9	99.9	86.1	99.9
	3		918	60.4%	96.8%	3.28	0.74	96.8	99.9	60.4	99.9
	4		662	82.4%	94.2%	2.40	0.89	94.2	99.9	82.4	99.9
	5		909	60.8%	96.8%	3.26	0.75	96.8	99.9	60.8	99.9
	6		651	83.1%	94.0%	2.38	0.88	94.0	99.9	83.1	99.9
2	7	531	1048	48.9%	96.4%	4.07	0.65	96.4	99.8	48.9	99.9
	8		613	81.6%	94.2%	2.43	0.87	94.2	99.9	81.6	99.9
	9		1096	47.4%	97.7%	4.19	0.64	97.7	99.8	47.4	99.9
	10		670	76.7%	96.8%	2.59	0.86	96.8	99.9	76.7	99.9
	11		1087	47.7%	97.7%	4.15	0.64	97.7	99.8	47.7	99.9
	12		661	77.8%	96.8%	2.55	0.86	96.8	99.9	77.8	99.9
3	13	519	1225	41.4%	97.9%	4.67	0.58	97.9	99.7	41.4	99.9
	14		650	77.4%	96.9%	2.50	0.86	96.9	99.9	77.4	99.9
	15		1279	40.0%	98.5%	4.84	0.57	98.5	99.7	40.0	99.9
	16		708	71.8%	97.9%	2.70	0.83	97.9	99.9	71.8	99.9
	17		1268	40.3%	98.4%	4.80	0.57	98.4	99.7	40.3	99.9
	18		697	72.9%	97.9%	2.66	0.84	97.9	99.9	72.9	99.9

sens = sensitivity; spec=specificity; PPV=positive predictive value; NPV=negative predictive value

**Table 3.3: Percentage of Youth with Diabetes Present in the Manitoba Centre for Health Policy Repository by Type and Algorithm.**

# Years	Algorithm #	N DER-CA T1DM <sup>1</sup>	% in MCHP	N DER-CA T2DM <sup>1</sup>	% in MCHP
1	1	420	96.2	111	92.8
	2		91.9		77.5
	3		97.9		92.8
	4		97.6		81.1
	5		97.9		92.8
	6		97.6		80.2
2	7	420	97.1	111	93.7
	8		95.7		88.3
	9		98.8		93.7
	10		98.8		89.2
	11		98.8		93.7
	12		98.8		89.2
3	13	409	98.5	110	95.5
	14		98.3		91.8
	15		99.3		95.5
	16		99.3		92.7
	17		99.3		95.5
	18		99.3		92.7

<sup>1</sup>Youth with diabetes identified in the DER-CA with coverage in the MCHP for full time period

**Table 3.4: Pediatric Studies Evaluating the Prevalence of Diabetes Utilizing Administrative Data**

Author	Data Source	Code and Algorithm	Age	Validation	Prevalence per 1000	Comments
Guttman 2009 (27)	-Ontario, Canada -Institute for Clinical Evaluative Sciences (ICES) -1994-2005	ICD-9CM 250.X; ICD 10 E10-14 Algorithms: 1+ hospital or 2+ outpatient visits over 2 years vs. 1-5 outpatient visits in 1 or 2 years ± hospital claim	<19 years	Hospital charts reviewed of random sample of 700 cases and 300 controls (no diabetes) at one of 5 study hospitals with pediatric wards  Calculated sensitivity and specificity –aimed to maximize specificity	<u>2002-03 by age and sex:</u> Females:      Males: 0-4: 0.54      0.61 5-9: 1.78      1.66 10-14: 3.10      3.02 15-19: 3.94      4.13 Overall: 2.42 (95% CI 2.36-2.47)	4 physician claims over 2 years: most specific (0.989) while maintaining sensitivity (0.828)  2 claims in 2 years: sensitivity 0.926 and specificity 0.989
Dabalea 2009 (21)	-United States -Indian Health Service (IHS) Facilities (inpatient and outpatient) -Navajo Youth -2001-2005	ICD-9CM 250.0-250.9  Algorithm: 1 or more outpatient visit or hospitalization over 3 years	<20 years	All cases validated using medical records  T1DM vs. T2DM determined	<u>2001 by age</u> 0-9: 0.11(95% CI 0.04-0.25) 10-14: 0.81 (95% CI 0.54-1.23) 15-19: 2.78 (95% CI 2.18-3.55) -Overall: T1DM 19.6% + T2DM 80.4%	50% of cases identified did not have diabetes (miscoded)
Hsia 2009 (22)	-United Kingdom -IMS Disease Analyzer (IMS DA) -Prescription records for antidiabetic drugs -1998-2005	ATC code A10  Algorithm: 1 or more prescription codes	0-18 years	“External validation using the General Practice Research Database”	<u>1998:</u> Insulin: 1.08 (95% CI 0.96-1.20) Oral meds: 0.006 (95% CI 0.0043- 0.025) <u>2005:</u> Insulin: 1.98 (95% CI 1.80-2.10) Oral meds: 0.05 (95% CI 0.025-0.080)	Validation not explained
Cox 2006 (23)	-St. Louis, MO, US -Scripts Inc. (commercial insurance) -Prescription claims for antidiabetic drugs -2002-2005	Antidiabetic drug  Algorithm: 1 or more prescription claim	5-19 years	None	2002: 1.85 2005: 2.66	
Kemper 2006 (43)	-United States -MarketScan: commercial claims and encounter database -Inpatient, outpatient and pharmacy data	ICD-9CM 250.XX  Algorithms: 1 or more code T1DM: 250.X1/X3 ± insulin T2DM: 250.X0/X2 ± no insulin	≤ 18 years	Compared ICD coding alone to ICD coding + insulin use to determine subtypes of diabetes utilizing kappa statistics  No validation of algorithms performed	2002: 2.28 (95% CI 2.08-2.28)	10% of T1DM identified with claims only did not use insulin
Moore 2003 (24)	-Montana and Wyoming, US -IHS Facilities (inpatient and outpatient) -1997-2001	ICD-9CM 250.0-250.9  Algorithm: 1 or more outpatient visit or hospitalization over 3 years	<20 years	All cases validated using medical records  T1DM vs. T2DM determined	2.4 (95% CI 1.8-3.2) T1DM: 0.7 (95%CI 0.4-1.1) T2DM: 1.3 (95% CI 0.9-1.8) Unknown: 0.3 (95% CI 0.1-0.7)	No comments made about miscoding
Acton 2002 (25)	-American Indian and Alaska Native, US -IHS outpatient database -1990-1998	ICD-9CM 250.0-250.9  Algorithm: 1 outpatient code	<35 years	None  Cited Wilson et al. (51) Sens 92% Spec 99%	Overall: 9.3 15-19yrs: 5.4	
Blanchard 1997 (26)	-Manitoba, Canada -Outpatient visits -1985-1993	ICD-9CM 250  Algorithm: 5 outpatient visits or 3-4 if < 2 years coverage	0-14 years	2 source capture-recapture to determine ascertainment = 95%	1993: 1.2	Excluded “Treaty status” in order to evaluate only T1DM

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## Chapter 4: The Natural History of Youth Onset Type 2 Diabetes Mellitus

### 4.1 Abstract:

Type 2 diabetes (T2DM) is a new disease in youth and natural history data are scant.

**Purpose:** To evaluate a) risk of any microvascular (nephropathy, retinopathy, neuropathy) or macrovascular (cardio, cerebro or peripheral vascular) complication b) risk factors for any complication and c) survival in youth onset T2DM. **Methods:**

Incident youth with T2DM (n=342) in Manitoba, Canada (1-18 years) from Jan.1986-2009 were identified from a clinical registry and anonymously linked to healthcare records housed at the Manitoba Centre for Health Policy in order to evaluate complications utilizing ICD codes, and compared to youth with T1DM (n=1011) and non-diabetic (non-DM) controls (n=1710). Cox proportional-hazards models were constructed to analyze risk of any complication and the role of clinical risk factors.

Kaplan Meier (KM) statistics were utilized to assess complication free and overall survival. **Results: T2 vs. T1DM:** Youth with T2DM had a 47% increased risk of any complication. Age at diagnosis, hemoglobin A1c (HgA1c) and ace inhibitor/angiotensin receptor blocker (ACE/ARB) use (which may be a marker of disease severity) were statistically significant risk factors. HNF-1 $\alpha$  polymorphism was protective in the T2DM cohort. KM analysis revealed a higher risk of nephropathy, neuropathy, peripheral vascular disease and major complication (dialysis, blindness or amputation) in T2DM. Risk of retinopathy was not different, and cardio and cerebrovascular diseases were rare in both groups. **T2 vs. non-DM:** Compared to non-DM controls, youth with T2DM had a 6.15 fold increased risk of vascular disease. **Survival:** Overall survival at 10 years was 91.4% (T2DM) vs. 99.5% (T1DM) vs. 100% (non-DM). **Conclusions:** Children with

youth onset T2DM are at high risk of complications and death. Glycemic control and age at diagnosis are significant risk factors. ACE/ARB's require further evaluation in youth onset diabetes.

## 4.2 Background

The worldwide prevalence of diabetes continues to increase, with an estimated 180 million cases in 2006, 90-95% of which accounted for by type 2 diabetes (T2DM) (1). This disease is associated with multiple morbidities, including both microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (cardiovascular, cerebrovascular and peripheral vascular disease) complications that have been well described in type 1 diabetes (T1DM) (2) and in adults with T2DM (3). Diabetes is also associated with a significant mortality risk, with death rates twice as high as in people without the disease (4,5), and even higher in high-risk groups with diabetes (6). In adults, significant complications typically manifest themselves 15-20 years after the diagnosis of diabetes (7). This disease thus impacts quality of life and life expectancy for the individual, causing lost productivity and triggering direct and indirect health care costs for society. It is estimated that direct health care costs associated with diabetes will exceed \$8 billion annually in Canada by 2016 (8).

Although T1DM remains the predominant form of pediatric diabetes, the prevalence of T2DM is increasing worldwide in youth, coincident with the rising obesity epidemic (9,10). T2DM now accounts for 8-45% of incident cases of diabetes in children (11). Since T2DM is a relatively new disease in children, first described in the 1980's, long-term outcome data are scant. The available literature does, however, suggest that the development of complications in youth with T2DM may be even more rapid than in adults, affecting individuals at a young age, at the height of their productivity (12).

A recent national surveillance study has estimated that the incidence of youth onset T2DM in Canada is a minimum of 1.54 cases per 100,000 youth less than 18 years of age. The highest incidence was reported in Manitoba (12.35/100,000) (13). Hepatic nuclear factor (HNF)-1 $\alpha$  is a transcription factor expressed in many tissues including the liver, intestine, pancreatic  $\beta$ -cell, and kidney. A polymorphism of this gene (HNF-1 $\alpha$  G319S) has been reported to occur in the Oji-Cree, which are an isolated First Nation population in North Central Canada, including Manitoba. This polymorphism has been associated with early onset T2DM in these populations (14-16). However its role in the natural history of this disease has not been studied.

The cohort of youth in Manitoba with T2DM has been systematically evaluated over the last twenty years and this study was designed to describe the natural history of this disease into adulthood, compared with youth with T1DM and non-DM controls. These data will add significantly to the current body of knowledge about this new disease in children and youth, and add insight into potentially modifiable risk factors for these high-risk individuals.

**Objectives:**

1. Determine the natural history of youth onset T2DM with respect to microvascular complications (nephropathy, retinopathy and neuropathy) and macrovascular complications (cardiac, cerebrovascular and peripheral vascular disease) in a cohort of Manitoba children and adolescents with T2DM, and to compare these outcomes with those in T1DM and matched non-DM controls.

2. Determine clinical risk factors associated with risk of complications in youth onset DM.
3. Evaluate overall survival rates of youth with T2DM compared with youth with T1DM and non-DM controls.

### **Hypotheses:**

1. Children with youth onset T2DM have higher rates of vascular complications, earlier in the course of their disease, compared with those with youth onset T1DM and non-DM controls.
2. Risk factors for the development of complications include poor glycemic control and hypertension. The use of ace inhibitors (ACE) and angiotensin receptor blockers (ARB) is protective.
3. Overall survival is decreased in youth onset T2DM compared with the other groups.

### **4.3 Methods:**

#### **Study Design:**

A cohort of youth with T2DM was retrospectively identified utilizing a clinical database from the Diabetes Education Resource for Children and Adolescents (DER-CA) in Manitoba, Canada, and compared to youth with T1DM (also identified through DER-CA) and without diabetes (age, sex and geographically matched utilizing forward sortation area (FSA) codes (ie. 1<sup>st</sup> three digits of the six digit postal code)). Using de-identified personal identifiers these children were anonymously linked to healthcare records and

vital statistics information in the Population Health Research Data Repository housed at the Manitoba Centre for Health Policy (MCHP) to evaluate complication rates. Clinical risk factors for the development of complications were also evaluated. Approvals were obtained from the Health Research Ethics Board in the Faculty of Medicine at the University of Manitoba, the DER-CA and the Manitoba Health Information Privacy Committee.

**Data sources:**

1. DER-CA registry: This registry has previously been described in detail in Chapter 1. In brief, the DER-CA is the only tertiary care pediatric diabetes referral centre for Manitoba, Canada. As shown in Chapter 3, it follows up to 86.1% of children in the province less than 18 years of age with diabetes. All patients followed in the DER-CA from January 1986 to present have been prospectively entered into the computerized diabetes registry that contains unique personal health identification numbers (PHINs) and clinical, genetic (HNF-1 $\alpha$  polymorphism) and laboratory data for all patients. Follow-up data are not available after 18 years of age within the registry therefore linkages utilizing scrambled PHIN codes to other administrative data sets housed at MCHP were established to generate longterm outcome data for the DER-CA cohorts.

2. The Manitoba Health Services Insurance Plan (MHSIP) has also previously been described in detail in Chapter 1. It contains registration files, physician reimbursement claims (based on International Classification of Diseases, 9<sup>th</sup> 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). Non-participation in the system is minimal since healthcare coverage is universal and residents are not charged healthcare premiums. These data are stored in de-identified form in the Population Health Research Data Repository (herein referred to as 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 (17). 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 T2DM: All incident cases of T2DM (1 to 18 years of age) with valid Manitoba PHIN codes diagnosed from January 1986 to January 2009 were identified through the DER-CA (n = 342).

Youth onset T1DM: All incident cases of T1DM (1 to 18 years of age) with valid Manitoba PHIN codes diagnosed from January 1986 to January 2009 were identified through the DER-CA (n=1011) and comprised the first control group.

Youth without DM: An age, sex and geographically matched (to T2DM cohort) second control group of children without diabetes was randomly selected from the Repository;

defined as no ICD-9CM or ICD-10CA code or pharmaceutical for diabetes. Control to case matching ratio was 5:1 (n=1710) in order to have adequate power. The index date for matching was the date of diagnosis of T2DM. Patients with secondary diabetes as defined by clinical criteria in the DER-CA database were excluded.

### **Variables:**

Predictor variables:

Clinical variables assessed for both groups of youth onset diabetes were age at diagnosis, sex, body mass index z-score (BMI z-score), hypertension (according to age, sex and height standardized normal values in children) (18), and hemoglobin A1c (H<sub>g</sub>A<sub>1c</sub>) at last follow-up, area-level socioeconomic status (SES) (defined as the lowest urban and rural income quintiles vs. other four quintiles), urban (Winnipeg and Brandon) vs. rural (all other) residence, presence of persistent albuminuria (defined as albumin: creatinine ratio (ACR) of  $\geq 3$  mg/mmol on a random urine sample or albumin excretion rate (AER) of  $\geq 30$  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). 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:

The children were followed post discharge from the DER-CA by means of healthcare utilization codes housed in the Repository to determine longterm outcomes. The codes utilized to assess for each possible diabetes complication are listed in Table 4.1.

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. 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).

### **Statistical Analysis:**

Descriptive statistics

Summary statistics were calculated and compared between groups using two-tailed student t-tests for normally distributed continuous variables, Mann-Whitney U tests for non-normally distributed continuous variables and the Chi-square test for categorical variables. Results are reported as mean  $\pm$  standard deviation (SD). P-values  $<0.05$  were considered statistically significant unless otherwise stated.

Analysis 1: T2DM vs. T1DM

All Manitoba children with diabetes treated in the DER-CA were included. Univariate and multivariate Cox proportional hazards models were constructed. All listed predictor variables were included in the univariate analysis. HNF-1 $\alpha$  polymorphism was evaluated

only in the univariate analysis, as it was not applicable to T1DM. The outcome measure evaluated was a composite outcome of having “any complication”, which included nephropathy, retinopathy, neuropathy, and cardiovascular, cerebrovascular or peripheral vascular disease. The statistically significant variables from the univariate analysis were entered into the multivariate model. 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: T2DM vs. non-DM

As clinical variables were not available for the non-DM controls, a separate analysis was conducted to compare this group with the T2DM population. This group was matched, therefore only a univariate analysis was performed. Each type of complication was evaluated separately. In addition, composite microvascular (nephropathy, 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 independent from each other, in order to prevent type 1 error, a p value  $<0.01$  was required to consider the results significant for these analyses. A Bonferroni correction factor was deemed to be too conservative as the outcomes were not independent from each other.

Additional analyses:

Kaplan-Meier analyses for each type of complication as well as for overall survival were conducted. All data manipulation and statistical analysis was conducted utilizing SAS version 9.1 software.

#### **4.4 Results:**

A total of 2174 adolescents were identified from the DER-CA database including 1412 with T1DM and 424 with T2DM. 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 T2DM cohort included 342 individuals, and the T1DM control group included 1011 individuals. 1710 non-DM controls were matched to the T2DM cohort from the Repository.

Compared to the T1DM group, the children with T2DM 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 hypertension at baseline. Sixteen (16%) of the children with T2DM had a mother with pre-gestational diabetes, compared with only 3% in the T1DM group. Half of the T2DM cohort was either a heterozygote (GS) or homozygote (SS) for the HNF-1 $\alpha$  polymorphism (Table 4.2).

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 as some of the individuals remained in the pediatric age group at the time of this study. The differences in BMI z-scores persisted, and 40-50% of individuals were hypertensive (Table 4.3). Glycemic control was on average suboptimal in both groups. The T2DM group had higher serum total cholesterol and triglyceride and lower HDL cholesterol levels, although absolute differences were small. Clinical practice guidelines prior to 2008 did not recommend lipid screening in T1DM and current guidelines do not recommend routine monitoring of lipids in youth less than 12 years of age with T1DM unless they have clinical risk factors (19,20), therefore only high risk children with T1DM had had screening done. This differential screening likely explains why absolute differences between groups were not as large as expected.

The mean follow-up time in the Repository was  $5.3 \pm 5.2$  years (range 0-27.4) for youth with T2DM,  $7.9 \pm 6.3$  years (range 0-28.2) for youth with T1DM and  $7.0 \pm 5.7$  years (range 0-29.9) for non-DM controls. Crude complication rates for all three groups are presented in Table 4.4 and percentage of each group with each number of complications is presented in Table 4.5. Overall, both groups with diabetes had higher microvascular and macrovascular disease rates than the non-DM control group. Differences in crude complication rates between the two diabetes cohorts were small, except for a higher percentage of youth with T2DM affected by renal complications. However, the Kaplan Meier analyses described below reveal a significant difference in time to complications between the two groups.

### Analysis 1 - T2DM vs. T1DM

The results of the univariate analysis are presented in Table 4.6. Of note, the HNF-1 $\alpha$  polymorphism was protective against future complications. 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, youth with T2DM had a 47% increased risk of a complication compared with T1DM (Table 4.7). Glycemic control was associated with future complications; each 1% increase of A1c was associated with a 6% increased risk of complication. An increased age at diagnosis was also associated with future complications. ACE/ARB use was associated with 1.75 times increased risk (Table 4.7). Tests for non-proportionality for all statistically significant variables were non-significant.

### Analysis 2 – T2DM vs. non-DM

Overall, youth with T2DM were at significantly higher risk of developing any “complication” (HR 6.15, 95% CI 4.26-8.87), and any microvascular (HR 6.26, 95% CI 4.32-9.10) or macrovascular disease (HR 4.44, 95% CI 1.71-11.52), compared to controls without diabetes (Table 4.8). In addition, when evaluated individually, the youth with T2DM also had an increased risk of ophthalmologic, renal and neurologic disease (Table 4.8). Likely due to low rates of macrovascular disease, when evaluated individually no differences between groups were found for cardiovascular and cerebrovascular outcomes. Despite low numbers, there was a statistically significant higher risk of peripheral vascular disease in the T2DM group (HR 6.25, 95% CI 1.68-23.28).

Kaplan Meier analyses

Figures 4.1-4.6 show event-free survival for each individual diabetic complication. Differences in renal and neurologic complications between the two groups begin to occur at 5 years post-diagnosis, whereas differences in ophthalmologic complications begin to occur at 10 years after the diagnosis of diabetes. Differences in ophthalmologic 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 T2DM cohort. Overall, major complications including blindness, amputation and renal failure requiring dialysis were rare in the T1DM cohort, but occurred in 1.1% of the T2DM cohort at 10 years, 26.0% at 15 years and 47.9% 20 years after diagnosis (Figure 4.7). Major complications occurred at a mean age of  $28.0 \pm 3.4$  years.

Overall survival at 10 years was 91.4% in the T2DM group compared with 99.5% in the T1DM group and 100% in the non-DM group. At 20 years, survival remained 100% in the non-DM group and 97.6% in the T1DM group, but decreased to 77.5% in the T2DM group (Figure 4.8).

#### **4.5 Discussion:**

This is the largest, most inclusive natural history study of youth onset T2DM compared with youth onset T1DM and non-DM controls. It expands upon the existing literature which has suggested a significant disease burden associated with T2DM diagnosed in

youth and young adulthood (12). This study highlights the fact that youth is not protective against the multisystem effects of T2DM. The time course to complications echos that reported in adults (7). The devastating part of this disease is the fact that severe complications, which are associated with a considerable effect on quality of life, life expectancy and economic consequences, occur in young adulthood.

The renal complications associated with youth onset T2DM have been the most frequently studied diabetic complication in the literature to date (Table 2.1) and are associated with significant morbidity (21). The renal complications of this cohort are evaluated separately in more detail in Chapter 5. In brief, when compared with T1DM, T2DM was found to be associated with a 2.25-fold increased risk of renal complications after controlling for multiple confounders including age at diagnosis, sex, glycemic control, BMI z-score and SES. Youth with T2DM had a 16-fold increased risk of renal disease when compared with matched non-DM controls. Risk factors for the development of renal complication included poor glycemic control, the presence of persistent albuminuria in youth, and the use of renin-angiotensin system (RAAS) inhibitors; which may be a confounder by indication (marker of disease severity), however this requires further controlled studies.

In contrast to the literature which suggests a lower risk of retinopathy in youth with T2DM compared with those with T1DM (22,23) and adults with T2DM (23), this study reveals a similar burden of ophthalmologic complications in both subtypes of diabetes (13.8% T1DM vs. 11.7% T2DM,  $p=0.13$ ). Although the mean follow-up time for the

T2DM cohort was on average 2.6 years shorter than the T1DM group, the survival analysis also failed to show a difference between groups (Figure 4.2). Reported rates of retinopathy in youth onset T2DM vary considerably in the literature from 4 to 40% depending on the population studied and the means of evaluation (22-26) (Table 2.2). Our results are at the lower end of this spectrum. As this study is based on diagnostic billing codes, it is possible that asymptomatic background retinopathy rates were underestimated and thus true differences between subgroups were not discernible.

There has been very limited information published about the neuropathy associated with youth onset T2DM, however previously reported rates have ranged between 12 and 57% (22,27,28) (Table 2.2). Although the crude rate in this study was lower at 7.6%, individuals with longer follow-up times had much higher rates. This is also the first study to show higher rates of this complication in youth onset T2DM compared with T1DM; 13.7%, 27.0%, 31.9% in the T2DM cohort vs. 4.8%, 12.7%, and 17.4% in the T1DM cohort at 10, 15 and 20 years respectively ( $p < 0.0001$ ).

This study is consistent with previous literature which has suggested high rates of cardiovascular risk factors in youth with T2DM (Tables 2.3, 2.4). In this cohort 45.8% had hypertension, the mean BMI z-score was  $1.8 \pm 0.7$  and the T2DM group had higher triglyceride and lower HDL cholesterol levels than the T1DM group. Despite the high prevalence of cardiovascular risk factors, this present study reports low rates of cardiovascular and cerebrovascular disease. However, there was an increased risk of peripheral vascular disease in the T2DM group, affecting 12.9% of the T2DM cohort 20

years after diagnosis. As the mean follow-up period 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 of mild disease are not being due to a low index of suspicion in 20- and 30-year-old patients.

Overall, the risk of development of diabetic complications was 47% higher in youth with T2DM compared with T1DM after controlling for baseline differences between groups, including SES status, sex and BMI z-score. Glycemic control was an important risk factor, with a 1% increase in HgA1c associated with a 6% increased risk of complication. This result is in keeping with previous literature (2). An increased complication burden was also associated with an increased age at diagnosis. As this study evaluated only children within the 1-18 year age range at diagnosis, this finding may be explained by the higher likelihood of the individual being an adolescent, 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 (29).

The increased complication risk associated with ACE/ARB use is in contrast to multiple previous studies in adults showing a benefit in terms of diabetic nephropathy and retinopathy. We hypothesize that this risk is not causal, but rather a consequence of confounding by indication or severity of illness, as has been described in ASA trials (30). On the other hand, there are no randomized controlled trials utilizing these drugs in youth onset T1DM or T2DM, thus the possibility that these drugs behave differently in youth

cannot be excluded. Future studies are required to evaluate the safety and efficacy of these drugs in youth onset DM populations.

A novel finding in this study is the relative protection of the HNF-1 $\alpha$  genetic polymorphism with respect to diabetic complications; HR 0.58 (95% CI 0.34-0.99). This genetic polymorphism has been associated with early onset diabetes in the Oji-Cree population (14-16). However, despite its influence on the rapidity of onset of T2DM, it does not appear to be associated with an accelerated burden of complications following onset of frank diabetes.

There are several limitations of this study that merit discussion. First, the outcome data are based on diagnostic codes, which can be prone to error in several ways. Only one diagnostic code can be included for each outpatient physician encounter. Therefore, depending on the physician (generalist vs. specialist) evaluating the individual, a code of “diabetes mellitus” may be given rather than one describing a complication. In addition, if more than one complication is present, only one can be coded at each visit. Therefore, there may exist an ascertainment bias within this study, and the true complication burden in these youth may be underestimated. The magnitude of this effect however should be equal in both groups. Another limitation of this study is the lack of data on smoking, which is an important cardiovascular risk factor that could not be evaluated. In addition, SES was assessed as an area-level measure in this study. However, it has been shown in the past to approximate individual-level measures of SES (31). 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.

#### **4.6 Conclusions:**

In conclusion, individuals with youth onset T2DM have an increased risk of diabetic complications and death, as compared to individuals with youth onset T1DM and non-DM controls. Microvascular complications and cardiovascular risk factors are highly prevalent, whereas macrovascular complications are rare in young adulthood.

Hemoglobin A1c is an important modifiable risk factor, and thus optimal 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 practise.

Table 4.1 Healthcare utilization codes used to identify diabetic complications in youth onset diabetes mellitus				
Type of Complication	*ICD-9CM (Diagnostic codes)	ICD-9CM (Procedure codes)	**ICD-10CA (Diagnostic codes)	***CCI codes
<b>Renal</b>	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) 584 (acute renal failure) 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 (arteriovenostomy 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) IKY (fistula) IOT53 (PD catheter) IOK85 or IPC85 (renal transplant)
<b>Ophthalmologic</b>	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)	ICN59 (retinal surgery)
<b>Neurological</b>	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)	
<b>Macrovascular</b>	410-14 (ischemic heart disease) 430-38 (cerebrovascular disease) 250.7 (diabetes with peripheral circulatory disorders) 440-5 (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)	I1J (cardiovascular surgery) I1A-Q (vascular surgery) 1TM93, 1TV9, 1WE93, 1WJ93, 1WL93, 1WM93, 1VA93, 1VB, 1VC93, 1VF, 1VG93, 1VQ93 (amputations)

\*International Classification of Diseases 9<sup>th</sup> Revision, Clinical Modification \*\* Revision 10CA (Canadian) \*\*\*The Canadian Classification of Health Interventions

**Table 4.2 Baseline Demographics for Incident Youth Onset Diabetes Cohorts**

	No. T1DM/T2DM	Type 1 Diabetes	Type 2 Diabetes	p-value
Age (years)	1011/342	8.9 ± 4.3	13.5 ± 2.2	<0.0001
Sex (Male %)	1011/342	53.2	37.8	<0.0001
BMI z-scores	923/288	0.4 ± 1.0	1.9 ± 0.7	<0.0001
Urban (%)	1011/342	51.9	26.9	<0.0001
Low SES (%)	877/281	11.4	59.1	<0.0001
HNF 1α polymorphism (%)	-/146	N/A	32.2% GS† 18.5% SS††	-
Hypertension (%)	813/282	11.1	9.9	0.59
Albuminuria at dx (%)	178/236	13.5	27.1	0.0008
Mother with Pre-Gestational DM (%)	772/277	2.7	15.9	<0.0001

Continuous variables are reported as mean ± SD † Heterozygous and †† Homozygous for HNF1α variant

**Table 4.3 Clinical Features at Last \*DER-CA Follow-up for Youth Onset Diabetes Cohorts**

	No. T1DM/T2DM	Type 1 Diabetes	Type 2 Diabetes	p-value
Age (years)	1011/342	15.1 + 3.2	16.5 + 2.3	0.0006
BMI z-scores	928/288	0.66 + 0.8	1.8 + 0.7	<0.0001
Total cholesterol (mmol/L)	410/296	4.3 + 1.0	4.6 + 1.0	0.0001
LDL-chol. (mmol/L)	51/224	2.9 + 2.2	2.8 + 0.8	0.05
HDL-chol. (mmol/L)	28/182	1.5 + 0.4	1.28 + 0.3	0.002
Triglycerides (mmol/L)	411/296	1.3 + 0.9	2.2 + 2.2	<0.0001
**ApoB (mmol/L)	11/215	0.9 + 0.4	0.8 + 0.2	0.60
Hypertension (%)	816/284	39.8	45.8	0.08
HemoglobinA1c (%)	977/305	9.2 + 2.3	8.9 + 3.0	0.04
Albuminuria (%)	727/280	19.8	38.6	<0.0001

Continuous variables reported as mean ± SD \*Diabetes Education Resource for Children and Adolescents

\*\*Apolipoprotein B

**Table 4.4 Crude Complication Rates in Youth Onset Diabetes Cohorts and Rates of Comparable Disease in Non-DM controls**

	<b>No Diabetes No. (%) Mean Age (yrs)</b>	<b>Type 1 Diabetes No. (%) Mean Age (yrs) Mean DM duration (yrs)</b>	<b>Type 2 Diabetes No. (%) Mean Age (yrs) Mean DM duration (yrs)</b>
<b>Any Complication</b>	87 (5.1) 20.8 ± 5.0	189 (18.7) 16.2 ± 5.2 7.2 ± 5.2	71 (20.8) 18.3 ± 4.3 5.0 ± 4.3
<b>Major Complication</b>	7 (0.4) 20.4 ± 5.8	* 13.4 ± 3.2 5.5 ± 5.2	11 (3.2) 28.0 ± 3.4 14.7 ± 4.0
<b>Microvascular Complication</b>	79 (4.6) 21.0 ± 5.2	178 (17.6) 16.6 ± 5.2 7.5 ± 5.4	69 (20.2) 18.4 ± 4.6 5.22 ± 4.7
<b>Macrovascular Complication</b>	10 (0.6) 19.3 ± 3.3	19 (1.9) 14.7 ± 5.7 6.4 ± 4.3	8 (2.3) 22.8 ± 6.4 10.1 ± 7.2
<b>Renal complication</b>	11 (0.6) 21.9 ± 6.5	27 (2.7) 18.7 ± 5.4 9.9 ± 6.3	30 (8.9) 20.3 ± 5.8 7.5 ± 5.7
<b>Renal failure</b>	* 18.7 ± 4.36	14 (1.4) 18.1 ± 5.8 9.3 ± 5.5	23 (6.7) 21.9 ± 5.9 9.1 ± 6.0
<b>Dialysis</b>	* 20.9 ± 5.12	0 N/A N/A	8 (2.3) 29.1 ± 3.6 16.1 ± 3.6
<b>Neuropathy</b>	61(3.6) 21.2 ± 5.1	50 (5.0) 18.7 ± 6.1 9.8 ± 4.9	26 (7.6) 20.1 ± 5.5 6.5 ± 5.6
<b>Blindness</b>	*	*	*
<b>Retinopathy</b>	13 (0.8) 21.3 ± 6.6	139(13.8) 16.9 ± 5.2 7.9 ± 5.8	40 (11.7) 20.5 ± 5.6 7.4 ± 5.9
<b>Cardiovascular Disease</b>	*	*	*
<b>Peripheral Vascular Disease</b>	* 19.5 ± 5.1	6(0.6) 17.1 ± 3.9 8.0 ± 3.9	* 26.6 ± 6.7 13.9 ± 7.0
<b>Cerebrovascular Disease</b>	* 20.6 ± 3.1	10(1.0) 12.9 ± 5.7 5.3 ± 4.3	* 20.2 ± 4.5 7.5 ± 6.5

\*≤5 individuals – suppressed to maintain patient anonymity. Continuous variables are reported as mean ± SD

**Table 4.5 Number of \*Complications in Youth Onset Diabetes Cohorts and Comparable Microvascular and Macrovascular Diseases in Non-Diabetes controls**

<b>Number of Diabetic Complications or Comparable Vascular Diseases</b>	<b>No Diabetes (%)</b>	<b>Type 1 Diabetes (%)</b>	<b>Type 2 Diabetes (%)</b>
<b>None</b>	94.9	81.3	79.2
<b>1</b>	4.6	14.9	14.9
<b>2</b>	0.5	3.0	2.9
<b>3</b>	0	0.7	2.0
<b>4</b>	0	0.1	0.6

\*Complications include microvascular (nephropathy, retinopathy, neuropathy) and macrovascular (cardiovascular, cerebrovascular, and peripheral vascular) diseases

**Table 4.6 Univariate Analysis Results of Risk Factors for the Development of any Microvascular or Macrovascular Complication in Youth Onset Diabetes Cohorts**

	No.	*HR	95% Confidence Intervals	p-value
<b>T2DM vs. T1DM</b>	1353	1.92	1.46-2.55	<b>&lt;0.0001</b>
<b>Age at Diagnosis</b>	1353	1.09	1.06-1.12	<b>&lt;0.0001</b>
<b>Male Sex</b>	1353	0.73	0.57-0.94	<b>0.01</b>
<b>Urban residence</b>	1353	0.92	0.72-1.17	0.48
<b>Hemoglobin A1c</b>	1282	1.09	1.05-1.14	<b>&lt;0.0001</b>
<b>Hypertension</b>	1100	0.86	0.64-1.15	0.30
<b>BMI z-score</b>	1216	1.21	1.03-1.42	<b>0.02</b>
<b>Diagnosis prior to 2000</b>	1353	0.94	0.67-1.34	0.94
<b>**ACE/ARB use</b>	1353	2.24	1.73-2.92	<b>&lt;0.0001</b>
<b>Pre-gestational DM in mother</b>	1049	1.49	0.65-3.37	0.37
<b>Lowest SES quintile</b>	1158	1.48	1.12-1.95	<b>0.007</b>
<b>Albuminuria</b>	1007	1.29	0.95-1.73	0.10
<b>HNF-1<math>\alpha</math> polymorphism (T2DM only)</b>	146	0.58	0.34-0.99	<b>0.04</b>

\*Hazard Ratio \*\* Ace inhibitor or angiotensin receptor blocker use

**Table 4.7 Risk Factors for the Development of any Microvascular or Macrovascular Complication in Youth Onset Diabetes as Determined by Final Multivariate Model**

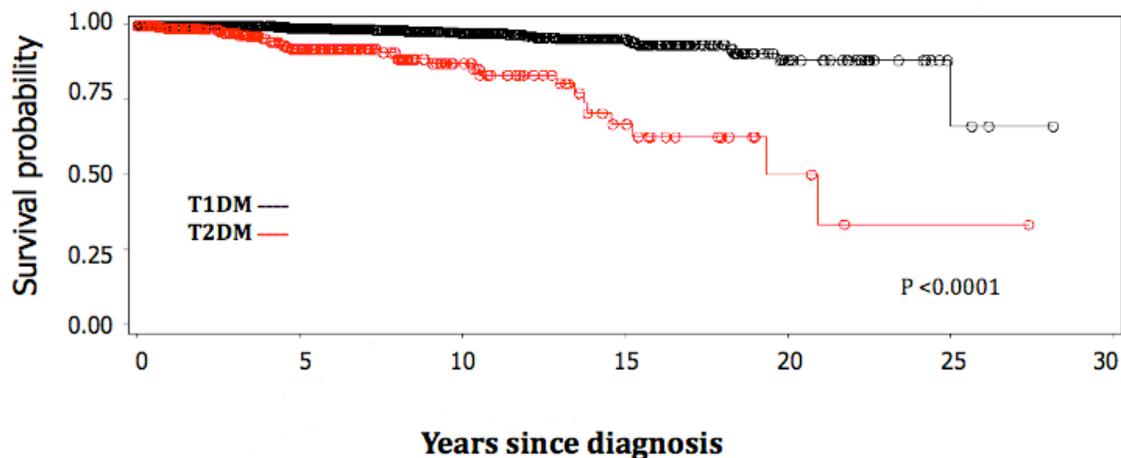
	X <sup>2</sup>	*HR	95% Confidence Intervals	p-value
<b>T2DM vs. T1DM</b>	4.17	1.47	1.02-2.12	<b>0.04</b>
<b>Age at Diagnosis</b>	14.09	1.08	1.04-1.12	<b>0.002</b>
<b>Hemoglobin A1c</b>	6.10	1.06	1.01-1.12	<b>0.01</b>
<b>**ACE/ARB use</b>	11.77	1.75	1.27-2.41	<b>0.0006</b>

\*Hazard Ratio \*\*Ace inhibitor or angiotensin receptor blocker use

**Table 4.8 Analysis of Risk of Development of Vascular Disease in Youth Onset Type 2 Diabetes Compared with Non-Diabetes Controls**

	# Events non-DM/ T2DM	X <sup>2</sup>	**HR	95% Confidence Intervals	***p-value
<b>Any Vascular Disease</b>	68/84	94.55	6.15	4.26-8.87	<0.0001
<b>Major Vascular Disease (blindness, dialysis, amputation)</b>	6/11	19.07	10.56	3.67-30.42	<0.0001
<b>Microvascular Disease</b>	66/78	93.03	6.26	4.32-9.10	<0.0001
<b>Macrovascular Disease</b>	10/8	9.42	4.44	1.71-11.52	<0.002
<b>Retinopathy</b>	12/40	70.50	19.49	9.75-39.00	<0.0001
<b>Blindness</b>	*/*	3.89	5.00	1.01-24.78	0.05
<b>Renal Diagnosis</b>	11/30	53.48	16.13	7.66-33.99	<0.0001
<b>Renal Failure</b>	6/23	40.18	22.83	8.68-60.1	<0.0001
<b>Dialysis</b>	*/8	11.94	39.10	4.89-312.69	0.0005
<b>Neuropathy</b>	61/26	18.34	2.93	1.79-4.80	<0.0001
<b>Cardiovascular Disease</b>	*/*	0.56	2.50	0.23-27.57	0.45
<b>Cerebrovascular Disease</b>	*/*	4.99	4.86	1.21-19.46	0.03
<b>Peripheral Vascular Disease</b>	*/*	7.46	6.25	1.68-23.28	0.006

\* ≤5 individuals – suppressed to maintained patient anonymity \*\* Hazard Ratio \*\*\* p-value <0.01 considered significant



**Figure 4.1 Renal Complication Free Survival in Youth Onset Diabetes Cohorts**

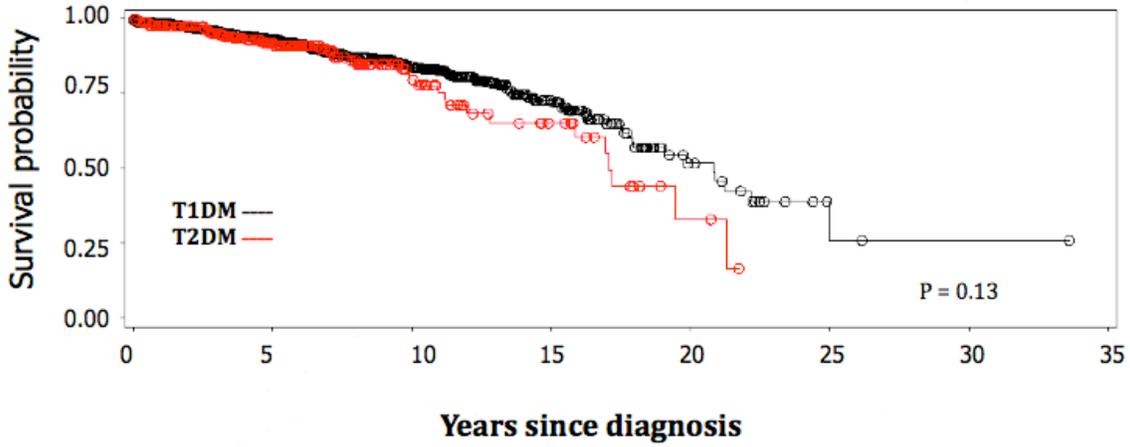


Figure 4.2 Ophthalmologic Complication Free Survival in Youth Onset Diabetes Cohorts

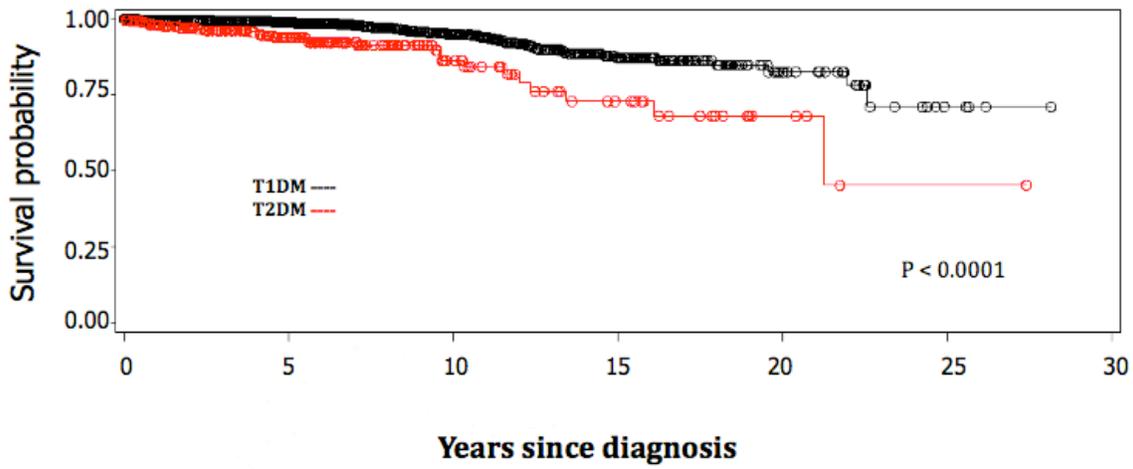


Figure 4.3 Neurologic Complication Free Survival in Youth Onset Diabetes Cohorts

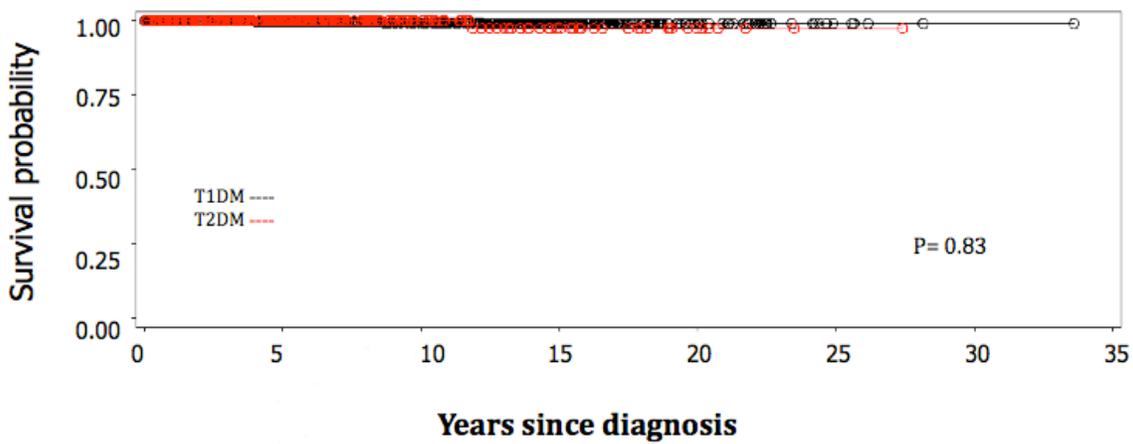


Figure 4.4 Cardiovascular Complication Free Survival in Youth Onset Diabetes Cohorts

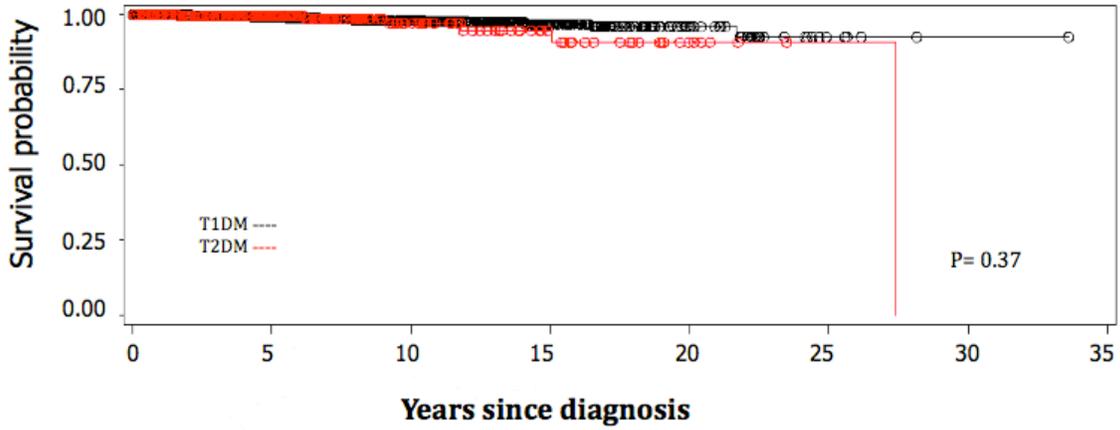


Figure 4.5 Cerebrovascular Complication Free Survival in Youth Onset Diabetes Cohorts

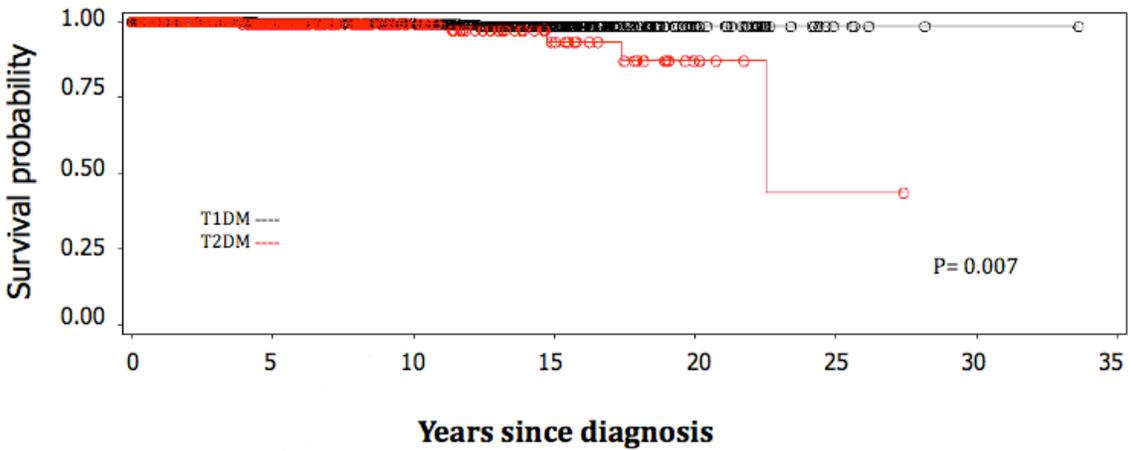


Figure 4.6 Peripheral Vascular Complication Free Survival in Youth Onset Diabetes Cohorts

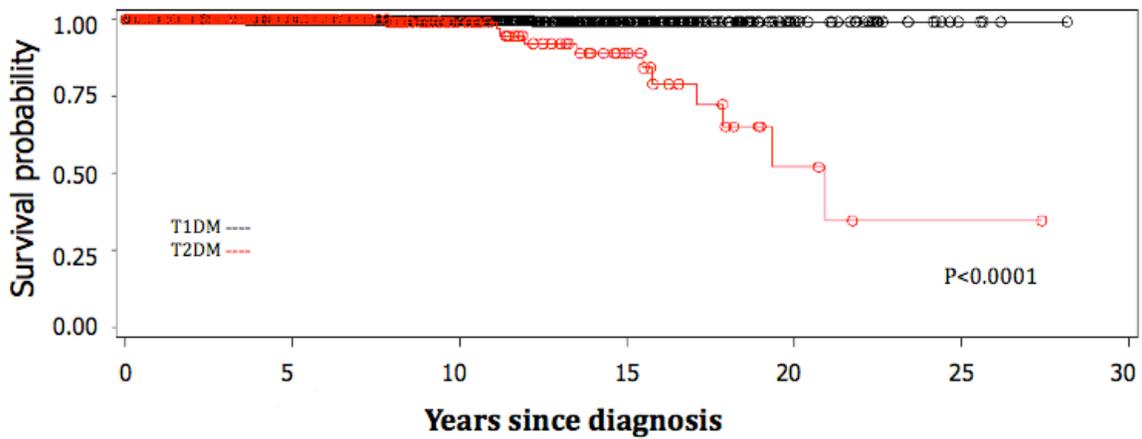


Figure 4.7 Major Complication (Blindness, Amputation or Dialysis) Free Survival in Youth Onset Diabetes Cohorts

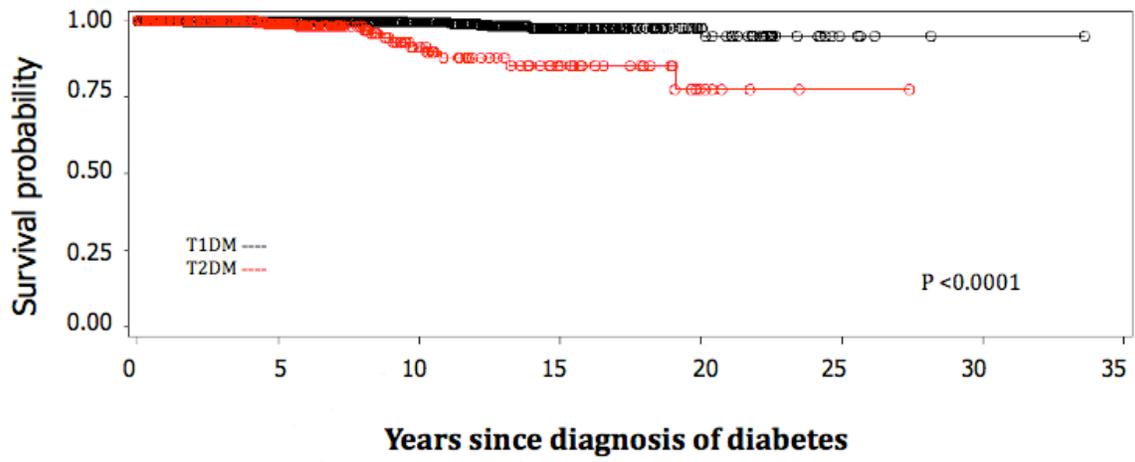


Figure 4.8 Overall Survival in Youth Onset Diabetes Cohorts

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## Chapter 5: High Burden of Renal Complications in Youth Onset Type 2 Diabetes

### 5.1 Abstract:

Type 2 diabetes (T2DM) is a new disease in youth (1-18 yrs) and renal outcome data is scant. **Objectives:** To evaluate a) risk of renal complication (RC) and renal failure (RF) b) survival c) risk factors for poor outcomes in youth with T2DM (n=342) vs. type 1 diabetes (T1DM) (n=1011) vs. non-DM controls (n=1710). **Methods:** All incident youth with diabetes in Manitoba from Jan.1986-2009 were anonymously linked to healthcare records housed at the Manitoba Centre for Health Policy. Renal outcomes were evaluated using ICD codes. Cox proportional-hazard models were constructed. Survival was assessed by Kaplan-Meier statistics (KM). **Results: T2 vs. T1DM:** Youth with T2DM had an increased risk of RC (HR 2.29, 95% CI 1.05-5.00) and RF (HR 4.03, 95% CI 1.64-9.95) vs. T1DM. Risk factors for RC were ace inhibitor (ACE) or angiotensin receptor blocker (ARB) use (HR 8.58, 95% CI 4.14-17.7), albuminuria (HR 3.17, 95% CI 1.54-6.54), and diagnosis prior to the year 2000 (HR 2.69, 95% CI 1.10-6.60). Similarly, ACE/ARB use (HR 15.82, 95% CI 5.29-47.27) and albuminuria (HR 3.88, 95% CI 1.50-10.0) were associated with an increased risk of RF. **T2 vs. non-DM:** Compared to controls (age, sex and postal code matched), those with T2DM had an increased risk of RC (HR16.13, 95% CI 7.66-33.99), RF (HR 22.83, 95% CI 8.68-60.1) and dialysis (HR 39.10, 95% CI 4.89-312.69). **Survival:** Survival at 10 years was 91.4% (T2DM) vs. 99.5% (T1DM) vs. 100% (non-DM). Renal survival was 100% at 10 years in the DM groups and 99.9% in the non-DM group. It decreased to 92.0% at 15 years and 55.0% at 20 years in the T2DM group but remained stable in the others. **Conclusions:** Children with youth onset T2DM are at high

risk of adverse renal outcomes and death. Albuminuria and ACE/ARB use, which may be a marker of severity of disease, are associated with poor outcomes in early adulthood.

## **5.2 Background:**

The worldwide prevalence of diabetes has increased from 30 million in 1985 to greater than 180 million people in 2006, with 90-95% of cases accounted for by type 2 diabetes (T2DM). The highest burden of T2DM is in the middle-aged and elderly (1), but it is now known to afflict children and adolescents. First reported in the 1980s in First Nation (FN) children in Canada (2), T2DM has now been described in children around the world including Japan, India, Australia, the United States and the United Kingdom (3-7). Although Type 1 diabetes (T1DM) remains the predominant form of diabetes in children, between 8-45% of incident cases of diabetes in children are T2DM (8).

Diabetes is associated with a high burden of disease related complications, especially diabetic kidney disease (diabetic nephropathy, DN) which begins with microalbuminuria but frequently progresses to end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) (9). DN now accounts for 30 to 40% of ESRD in North America (10,11). ESRD secondary to diabetes is associated with as low as a 34% 5-year survival rate (11). Studies of type 1 diabetes (T1DM) suggest that 25 to 45% of individuals develop clinical renal disease (12-14) and 4 to 17% develop ESRD 20 years from diagnosis (15-17). The time to progress from microalbuminuria to ESRD has been estimated at 15-20 years (9). Associated treatment costs, particularly for advanced disease, are high: RRT, for example, costs of \$30,000 to \$60,000 per year (18). Indirect costs may be even higher since RRT is associated with poor health status, downward trends in SES, unemployment and lost productivity. Rigorous glycemic control and treatment of hypertension, as well as the use of angiotensin converting enzyme inhibitors (ACE) and angiotensin receptor blockers

(ARB) have been shown to abrogate progression of disease (9). Although certain subgroups (19) may be at higher risk, the adult literature suggests that the renal risk associated with adult onset T2DM is comparable to that seen in T1DM (20,21).

Childhood onset of T2DM is concerning because affected children may begin to develop complications of diabetes as young adults at the height of their productivity, resulting in significant impact on quality of life as well as economic productivity. T2DM diagnosed in childhood is a relatively new disease, and therefore the natural history is still largely unknown. Evidence suggests that complications may occur at an earlier age with a shorter duration of diabetes (22). Cross-sectional studies have consistently shown a higher prevalence of albuminuria in youth with T2DM compared with youth with T1DM at various disease time points (23-25). The only study comparing long-term outcomes in T1DM to T2DM is based on a cohort of 1065 Japanese adults less than 30 years of age and revealed a significantly higher cumulative incidence of nephropathy in T2DM compared with T1DM (44.4 vs. 20.2%;  $p < 0.0001$ ). The majority of individuals (70%) in this study were 20-29 years of age at the time of diagnosis. Poor glycemic control and hypertension were associated with the development of nephropathy in this cohort (26). These authors also reported that in a high risk subgroup of their cohort developing proliferative retinopathy prior to age 35 ( $n=135$ ), 60% developed diabetic nephropathy at a mean age of 31 years and 23% developed renal failure requiring dialysis at a mean age of 35 years (27). ESRD has also been previously reported to occur before the age of 30 in Canadian FN young adults who had type 2 diabetes diagnosed in adolescence (28). These five

individuals are included as part of this study cohort. It is currently unknown if these findings are generalizable to other youth onset T2DM populations.

In Canada, a recent National surveillance study estimated the minimum incidence of T2DM in children under age 18 years to be 1.54 cases per 100,000 children per year. Manitoba had the highest estimated incidence (12.35/100,000 children) (29). The prevalence of T2DM may be as high as 1% in First Nation children in some communities (30).

The causes of childhood T2DM are incompletely defined. Environmental and genetic factors play a role. The increasing prevalence of childhood obesity appears to be a major contributor (3). In addition, a polymorphism in the HNF-1 $\alpha$  gene at codon 319 (HNF-1 $\alpha$  G319S) has been associated with T2DM in Oji-Cree individuals. Homozygous individuals have a four-fold increased risk of T2DM and heterozygous individuals have a two-fold increased risk (31). This polymorphism may explain in part the high burden of disease in the Oji-Cree of northeastern Manitoba and northwestern Ontario (32-34).

Given the high burden of diabetes among Manitoba youth, the potential for this disease to shorten life and to diminish quality of life and productivity during the most productive period of life, it is important to have robust estimates of long-term patient and kidney outcomes associated with childhood T2DM. These data are currently lacking. The present study, therefore, was designed to describe the long-term renal complications and survival associated with youth onset diabetes mellitus in Manitoba, and to identify potentially modifiable disease progression factors in this population.

**Objectives:**

The objectives of this study were to:

1. Evaluate the natural history of diabetic complications and renal failure (RF) in a cohort of Manitoba children and adolescents with T2DM compared with those with T1DM and matched non-DM controls.
2. Assess renal and overall survival in these groups.
3. Determine clinical risk factors associated with poor renal outcomes.

**Hypotheses:**

1. Children with youth onset T2DM have higher rates of renal complications, earlier in the course of their disease compared with those with youth onset T1DM and youth without diabetes.
2. Renal and overall survival is worse in the children with T2DM compared with T1DM and non-DM controls.
3. Risk factors for the development of renal complications include poor glycemic control and hypertension. The use of ace inhibitors (ACE) and angiotensin receptor blockers (ARB) is protective.

**5.3 Methods:****Study Design:**

A cohort of youth with T2DM was retrospectively identified utilizing a clinical database from the Diabetes Education Resource for Children and Adolescents (DER-CA) in Manitoba, Canada, and compared to 1) youth with T1DM identified in the DER-CA and 2)

youth without diabetes (age, sex and geographically matched to T2DM) identified in the Repository housed at the Manitoba Centre for Health Policy (MCHP) (see below). These children were anonymously linked via scrambled identifiers to healthcare records housed at the MCHP in order to track renal outcomes. Clinical risk factors for the development of poor renal outcomes were also evaluated. Approvals were obtained from the Health Research Ethics Board in the Faculty of Medicine at the University of Manitoba and the Manitoba Health Information Privacy Committee.

**Data sources:**

1. DER-CA registry. The Manitoba DER-CA provides integrated, interprofessional and specialized programming for youth with diabetes, predominantly in the outpatient setting and has been described in detail in Chapter 1. It is located within the only tertiary care pediatric referral centre for Manitoba and is known to follow at least 86.1% of children in the province with diabetes (Chapter 3). It also follows some children from southeastern Saskatchewan and northwestern Ontario, however these children are not included in this study. Children are followed in this clinic until their 18<sup>th</sup> birthday, and are then referred to adult care.

All patients treated and followed in the DER-CA from January 1986 until present have been prospectively entered into a computerized diabetes registry. This registry includes patient personal health identification numbers (PHIN codes), validated diagnostic data identifying the classification of diabetes (35,36), and comprehensive clinical and laboratory data including 24 hour urine collections and urine albumin-to-creatinine ratios, blood

pressures, heights, weights and body mass indexes, as well as genetic (HNF-1 $\alpha$  G319S polymorphism) information. Because the database lacks long-term follow-up data beyond 18 years of age, linkages via scrambled PHIN to other administrative data sets described below were used to generate long-term outcome data for the DER-CA cohorts.

2. The Manitoba Health Services Insurance Plan (MHSIP) has also previously been described in detail in Chapter 1. It contains registration files, physician reimbursement claims (based on International Classification of Diseases, 9<sup>th</sup> 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). Non-participation in the system is minimal since healthcare coverage is universal and residents are not charged healthcare premiums. These data are stored in de-identified form in the Population Health Research Data Repository (herein referred to as the Repository) housed at the MCHP. Physician billing codes, vital statistics and census data are also available. The Repository data has been previously shown to be accurate (37). 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 T2DM: All incident cases of T2DM (1 to 18 years of age) with valid Manitoba PHIN codes diagnosed from January 1986 to January 2009 were identified through the DER-CA (n = 342).

Youth onset T1DM: All incident cases of T1DM (1 to 18 years of age) with valid Manitoba PHIN codes diagnosed from January 1986 to January 2009 were identified through the DER-CA (n=1011) and comprised the first control group.

Youth without DM: An age, sex and geographically matched (to T2DM cohort) second control group of children without diabetes was randomly selected from the Repository; defined as no ICD-9CM or ICD-10CA code or pharmaceutical for diabetes. Geographical matching was done utilizing forward sortation area (FSA) codes (ie. 1<sup>st</sup> three digits of the six-digit postal code). 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 T2DM. Patients with secondary diabetes as defined by clinical criteria in the DER-CA database were excluded.

**Variables:**

Predictor variables:

The continuous predictor variables that were examined for the study cohort and the T1DM control group included age and body mass index z-score (BMI z-score) at diagnosis and the last hemoglobin A1c (HgA1c) available in the database, which is a measure of their most

recent glycemic control. Categorical variables included sex, hypertension at last follow-up (according to age, sex and height standardized normal values in children) (38), socioeconomic status (SES) (defined as the lowest urban and rural income quintiles vs. other four quintiles), urban (Winnipeg and Brandon) vs. rural (all other) residence, presence of persistent albuminuria (defined as albumin: creatinine ratio (ACR) of  $\geq 3$  mg/mmol or albumin excretion rate (AER) of  $\geq 30$  mg/24 hours on at least 2 out of 3 measurements  $>1$  month apart) and the (ever) use of ace inhibitors or angiotensin receptor blockers (ACE/ARB) from fiscal years 1995-2007 (utilizing DPIN data). 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 renal outcomes.

Utilizing the Repository, all children with diabetes were linked to their mother's records to determine if the mother had a pregestational (prior to pregnancy) diagnosis of diabetes.

#### Outcome data:

The children were followed post discharge from the DER-CA by means of the healthcare utilization codes housed in the Repository up until the end of the fiscal year 2007 (March 31) in order to determine long term outcomes. Patients in the DER-CA database with T1DM and T2DM not residing in Manitoba, and thus not having a valid Manitoba PHIN code, were excluded as they could not be linked to outcome data in the Repository.

The healthcare utilization codes used to evaluate both the children with T2DM and T1DM as well as the non-DM controls for any renal complication, renal failure and ESRD are listed in Table 5.1. In addition, the following billing codes were also used to identify

individuals with ESRD: 9798, 9799, 9805, 9807, 9801, 9802, 9806, 9819, 9821, 9610, 9820 (dialysis), and 5883 (renal transplant).

### **Statistical Analysis:**

#### Descriptive statistics

Summary statistics were calculated and compared between groups using student t-tests for Gaussian continuous variables, Mann-Whitney U test for non-Gaussian continuous variables, and the Chi-square test for categorical variables. Results are reported as mean  $\pm$  standard deviation (SD) therefore 95% of the sample will most likely have results within 2 standard deviations of the mean. P values  $<0.05$  were considered statistically significant.

#### Analysis 1: T2DM vs. T1DM

All Manitoba children with diabetes treated in the DER-CA were included in order to achieve the highest possible power. Univariate and multivariate Cox proportional hazards models were constructed. All possible confounders (as listed in the predictor variable section above) were tested in the univariate analysis. Statistically significant variables at the  $p<0.05$  level from the univariate analyses were entered into the multivariate model in the order of statistical significance and were removed from the model if they did not explain any additional variability. 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.

Two different composite outcomes were evaluated. The first analysis included all possible renal outcomes (any renal complication). The second analysis included only renal failure and ESRD outcomes (renal failure). HNF-1 $\alpha$  polymorphism was evaluated only in the univariate analysis, as it was not applicable to T1DM.

#### Sensitivity analysis

A second multivariate model was conducted 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 ACE/ARB use for both composite outcomes.

#### Analysis 2: T2DM vs. non-DM

As clinical variables were not available for the non-DM controls, a separate analysis was conducted to evaluate this group in comparison to the T2DM population. This group was matched, therefore only a univariate analysis was performed.

#### Additional analyses:

Kaplan-Meier analyses for renal and overall patient survival were also conducted. All data manipulation and statistical analysis was conducted utilizing SAS version 9.1 software.

### **5.4 Results:**

The cohorts have previously been presented in Chapter 4 but will be reviewed here. A total of 2174 adolescents were identified from the DER-CA database including 1412 with T1DM

and 424 with T2DM. 806 did not have valid PHIN numbers, generally because they were not Manitoba residents 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 T2DM cohort included 342 individuals, and the T1DM control group included 1011 individuals. 1710 non-DM controls were matched to the T2DM cohort from the Repository.

Compared to children with T1DM, the children with T2DM 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 hypertension at baseline. 16% of the children with T2DM had a mother with pre-gestational diabetes, compared with only 3% in T1DM group and half of the T2DM cohort was either a heterozygote (GS) or homozygote (SS) for the HNF-1 $\alpha$  polymorphism (Table 5.2).

At the time of the last available appointment in the DER-CA, the youth with diabetes were on average between 15 and 16 years of age as some individuals remained in the pediatric age group at the time of the study. The differences in BMI z-scores persisted, and 40-50% of individuals were hypertensive. Glycemic control was on average suboptimal in both groups. The T2DM group had higher total cholesterols and triglycerides and lower HDL cholesterols, although absolute differences were small (Table 5.3). Clinical practice guidelines prior to 2008 did not recommend lipid screening in T1DM and current guidelines do not recommend routine monitoring of lipids in youth <12 years of age with

T1DM unless they have clinical risk factors (35,39), therefore only high risk children with T1DM had had screening done. This differential screening may explain why absolute differences between groups were not as large as expected.

The T2DM cohort had considerably more persistent albuminuria (31.6%), although 14.3% of the T1DM group also had persistent albuminuria by the last follow-up in the DER-CA. An additional 17.9% of the T1DM group and 12.3% of the T2DM group had transient proteinuria documented only on a single urine sample (Table 5.4). Not all children were screened for albuminuria, due to the young age in the T1DM group (only recommended 5 years after diagnosis) (35), and poor adherence with recommendations in some adolescents. Therefore these rates may be underestimated. The presence of albuminuria in youth was highly predictive of the future risk of renal failure in both groups. Overall, 9.13% of individuals with diabetes who had persistent albuminuria in youth developed renal failure in young adulthood, compared with 1.06% without albuminuria ( $p < 0.001$ ).

Overall, only 32.1% of youth with diabetes that had persistent albuminuria prior to the last follow-up in the DER-CA were prescribed an ACE or ARB during the follow-up period. There were more youth with T2DM and persistent albuminuria that were treated (34/144; 43.5%) compared with T1DM youth with albuminuria (47/108; 23.6%).

Crude renal complication rates are displayed in Table 5.5. The mean follow-up time in the Repository was  $5.3 \pm 5.2$  years (range 0-27.4) for youth with T2DM,  $7.9 \pm 6.3$  years (range 0-28.2) for youth with T1DM and  $7.0 \pm 5.7$  years (0-29.9) for non-DM controls.

### Analysis 1a: Any Renal Complication

The results of the univariate analysis are displayed in Table 5.6. In the final multivariate model (Table 5.7), youth with T2DM had a 2.25 fold increased risk of a renal complication during the follow-up period compared with youth with T1DM. This increased risk persisted after controlling for age at diagnosis, sex, HgA1c, BMI z-score and socioeconomic status. The presence of persistent albuminuria prior to the last follow-up in the DER-CA increased the risk of a future renal complication 3-fold, and the (ever) use of an ACE or ARB was associated with a 8-fold increase in renal diagnoses. An interaction term between the variables albuminuria and ACE/ARB use was added to the model to determine if ACE/ARB use modulated the risk associated with albuminuria, however the result was not statistically significant (data not shown). Children diagnosed with diabetes prior to the year 2000 had a higher relative hazard of renal complication as compared with those diagnosed after the year 1999. This may have been a reflection of improvements in diabetes care that were not directly evaluated in this study such as improved insulin regimens and diabetes education.

The presence of hypertension at the last follow-up in the DER-CA, urban vs. rural residence, the presence of pre-gestational diabetes in the youth's mother and the HNF-1 $\alpha$  polymorphism were not predictive of future renal complications in this study (Table 5.6).

The sensitivity analysis, in which albuminuria and the use of ACE/ARB were excluded from the variable pool, revealed a HR of 7.14 (95% CI 3.78-13.49;  $p < 0.0001$ ) for T2DM and HR of 1.13 (95% CI 1.04-1.23;  $p = 0.003$ ) for HgA1c after controlling for age at diagnosis, BMI z-score, sex, diagnosis prior to 2000, and low SES.

### Analysis 1b: Renal Failure

The results of the univariate analysis are displayed in Table 5.8. In the final multivariate model (Table 5.9) youth with T2DM had a 4-fold increased risk of renal failure compared with those with T1DM, after controlling for age at diagnosis, HgA1c, BMI z-score and era of diagnosis. Albuminuria and ACE/ARB use were again strongly associated with an increased risk of renal failure. An interaction between the two variables was not statistically significant. In this analysis, sex, urban vs. rural, hypertension, pre-gestational diabetes, low SES and HNF-1 $\alpha$  polymorphism were not significantly associated with poor renal outcomes.

When albuminuria and the use of ACE/ARB were excluded in the sensitivity analysis, the hazard ratios for RF were 5.37 (95% CI 2.12-13.58; p=0.0004) for T2DM, 1.20 (95% CI 1.04-1.39; p=0.01) for HgA1c and 5.04 (95% CI 1.08-3.24; p=0.03) for BMI z-score, after adjusting for age at diagnosis and diagnosis prior to 2000.

### Analysis 2: T2DM vs. non-DM

Youth with T2DM had a 16 fold increased risk of a renal complication, 23 fold increased risk of renal failure, and a 39 fold increased risk of ESRD when compared with age, sex, and geographically matched controls (Table 5.10).

## Kaplan Meier analyses

Renal survival was 100% at 10 years in the T1DM and T2DM groups and 99.9% in the no DM group. It remained stable in the no DM and T1DM groups, however decreased to 92.0% at 15 years and 55.0% at 20 years in the T2DM group (Figures 5.1 and 5.3). Overall survival at 10 years was 91.4% in the T2DM group compared with 99.5% in the T1DM group and 100% in the no DM group. At 20 years, survival remained 100% in the no DM group and 97.6% in the T1DM group, however decreased to 77.5% in the T2DM group (Figure 5.2 and 5.4).

## **5.5 Discussion:**

This is the largest long term follow-up study comparing renal outcomes and overall survival in children and adolescents with T2DM to those with T1DM and healthy, matched controls. 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 new questions about the effectiveness of renin-angiotensin system (RAS) blockade in the treatment of youth onset diabetes.

At the time of diagnosis, 27.1% of children with T2DM already had microalbuminuria. Previous literature has reported microalbuminuria at diagnosis in 22% of Pima Indian children diagnosed with T2DM between the ages of 15 and 19 years (40), 14% of young Maori individuals less than 30 years at diagnosis (mean age 19.5; range 5-29 years) (41) and in 7% of Australian children with T2DM diagnosed less than 18 years of age (mean age 13.2; range 11.6-15 years) (42). In this study, during the time youth with T2DM were

followed in the DER-CA, 32.9% children progressed to persistent microalbuminuria, and 5.7% progressed to persistent macroalbuminuria (overt nephropathy), at a mean age of 16.5 years and duration of disease of 1.9 years. This is consistent with previously reported microalbuminuria rates of 28-42% in children with youth onset T2DM of <5 years duration (42-44). Macroalbuminuria rates have been reported as high as 17-27% at 5-10 years duration (40,41) although most of these other studies did not evaluate persistence of albuminuria (see Table 2.1).

Studies comparing microalbuminuria in patients with T1DM and T2DM have shown findings congruent with our study. A Korean study of young people 8-28 years of age reported microalbuminuria in 11.3% of 141 patients with T1DM and 18.2% of 22 patients with T2DM despite a shorter disease duration. Glycemic control was poor in both of these groups (23). Similarly, a multicentre study across New Zealand of young people <26 years reported that 72% of 105 people with T2DM (mean age 20) and 17% of 662 with T1DM (age range 16-25 years) had microalbuminuria despite shorter disease duration in those with T2DM (24). An Australian study of diabetes diagnosed less than 18 years of age showed similar results with microalbuminuria in 28% of individuals with youth onset T2DM (mean age 13.2; range 11.6-15 years) compared with 6% with T1DM (mean age 8.1; range 4.8-10.8 years)(42). None of these studies evaluated risk of development of renal failure or requirement of dialysis, however.

A 5-fold increased incidence of ESRD in middle aged individuals who were <20 years of age at diagnosis (n=96) (age-sex-adjusted ESRD incidence of 25 cases per 1000 person-

years) compared to individuals with T2DM diagnosed between 20-55 years of age (n=1760) (5.4 cases per 1000 person years) has been reported in the Pima Indian population. The younger age group also had increased mortality, with age-sex-adjusted death rates 3.0 fold higher than in nondiabetic participants and 2.1 fold higher than in individuals diagnosed with diabetes mellitus after the age of 20. In a multivariate analysis, the age at onset of T2DM was not associated with ESRD, but rather the incidence of ESRD and mortality increased with age and with duration of T2DM. The increased incidence of ESRD in middle age was largely driven by the longer duration of disease (45). The only study that has compared incidence of nephropathy, defined as a protein-to-creatinine ratio  $\geq$  0.5 g/g in patients with T2DM based on age of disease onset (<20 years vs. 20-39 years and >40 years) did not show a difference in risk of nephropathy over 25 years (46). This was also observed in the present study, as time to dialysis was on average 16.1 years from diagnosis in the T2DM group, in keeping with the adult literature.

This study does, however, show a distinct difference in renal outcome in the T2DM compared with T1DM group. The youth onset T2DM group were 2.25 times more likely to develop a renal complication and 4.03 times more likely to develop renal failure than those with T1DM after controlling for multiple possible confounders. Although the children with T2DM exhibited key differences from those with T1DM at baseline; including older age at diagnosis, female predominance, higher BMI z-scores and lower SES, these factors were not independently predictive of adverse renal outcomes in the multivariate analysis. This suggests that there is an inherent difference in renal risk associated with T2DM in youth.

In addition, this study showed a survival disadvantage in terms of renal and overall survival in the T2DM group.

One possible explanation for these differences in outcome is race. Certain racial groups in the adult literature are at higher risk of diabetic renal disease, such as African Americans and North American Indians (47,48). Although race data were not available for analysis directly in this study, measures of lower socioeconomic status were included in the analysis which are more frequent in minority groups, and controls were matched for geographical location at the FSA (1<sup>st</sup> 3 digits of the postal code) level, in order to account for the higher percentage of minority youth with T2DM residing in northern communities and urban lower-SES neighborhoods. In addition, the genetic HNF-1 $\alpha$  polymorphism which is present in the Aboriginal Oji-Cree population was evaluated amongst individuals with youth onset T2DM, and was not associated with an increased renal risk.

Another study done in Japan supports this finding, as it showed a higher incidence density of nephropathy in early onset T2DM compared with T1DM, although this study did not evaluate risk of progression to renal failure. The authors also showed that although the incidence of nephropathy in T1DM had declined during past decades, this was not the case for T2DM (26).

A number of large longitudinal studies have evaluated disease modifying clinical variables in adults. The most predictive risk factor has been shown to be intensity of treatment and glycemic control. The Diabetes Control and Complication Trial (DCCT study) (49)

confirmed that HgA1c was closely related to microalbuminuria development, with reductions in risk of 10-55% when intensified treatment was compared with conventional therapy in youth with T1DM. HgA1c has also been shown to be associated with poor outcomes in adult onset T2DM and youth onset T1 and T2DM (9,25,50). The sensitivity analysis in this study showed a 13% increased risk of renal complication and 20% increased risk of renal failure for every increase of 1% in the HgA1c.

Both systolic and diastolic hypertension have been shown to accelerate the loss of glomerular filtration rate (GFR) associated with diabetic nephropathy and treatment of hypertension has been shown to improve life expectancy (51). Similarly, hypertension has been associated with diabetic nephropathy in two studies of early-onset T2DM (43,50). Hypertension, evaluated at the last follow-up in the DER-CA was not shown to be a significant risk factor in this study. Other implicated factors have included smoking, puberty, hyperlipidemia, and renal hyperfiltration (52).

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.

We observed 8.2 fold increased risk of renal complication and 15.8 fold increased risk of renal failure in individuals that had ever filled a prescription for an ace inhibitor or angiotensin receptor blocker (ACE/ARB). 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 ASA in population studies (53). Certainly these results are at variance with those of multiple placebo controlled trials of ACE or ARB's showing a benefit in delaying the progression of diabetic nephropathy. On the other hand, recent literature re-analyzing the published studies has raised concerns regarding RAS blockade associated acute renal failure, calling for increased caution in utilizing ACE/ARB's (54). Moreover, there has also yet to be a randomized controlled trial in any youth onset diabetes group less than 18 years of age and therefore the true effect of these medications in youth is unknown (55). Therefore, we cannot exclude the possibility that the adverse risk associated with ACE/ARB in our study represents a true causation. Further study of these drugs in this at risk population are warranted.

Our study has several limitations that bear discussion. First, several outcomes in this study were based upon diagnostic codes in outpatient physician billing records. 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 mellitus" 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. Second, our data sets lacked drug

information before 1995, and we could measure only prescription. We could not measure actual timing of drug initiation, exact duration of therapy, or adherence to therapy. Third, SES was assessed as an area-level measure in this study. It has however been shown in the past to approximate individual-level measures of SES (56). Finally, biopsy data confirming the diagnosis of diabetic nephropathy as the etiology of proteinuria in these patients was lacking in most cases. This is of relevance because a small biopsy study in a Canadian First Nation cohort comprising 10 adolescents with youth onset T2DM with macroalbuminuria revealed that none of the children studied had evidence of classical diabetic renal disease (57). The predominant findings were immune complex deposition and secondary focal segmental glomerulosclerosis. Although this study was small, it questions whether the renal complications observed in T2DM are causally related to the diabetes. Nevertheless, the observation that childhood T2DM status is highly associated with adverse renal and patient survival remains an important finding, irrespective of possible mechanisms. Future renal biopsy studies in T2DM patients with abnormal urinary sediment are warranted to better define the renal pathology in this condition.

## **5.6 Conclusions:**

In conclusion, this study demonstrates the 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 also raises concern about the use of ACE/ARB's in youth onset DM. Prior to changing clinical practice, a large randomized controlled study in youth is required to further evaluate this issue. Glycemic control remains an important modifiable risk factor

for these youth, and may be the most important factor in delaying progression of renal associated complications.

**Table 5.1 Healthcare utilization codes used to identify diabetic renal complications in youth onset diabetes mellitus**

<b>Type of Complication</b>	<b>*ICD-9CM (Diagnostic codes)</b>	<b>ICD-9CM (Procedure codes)</b>	<b>**ICD-10CA (Diagnostic codes)</b>	<b>***CCI codes</b>
<b>End Stage Renal Disease</b>	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 (arteriovenostomy for renal dialysis) 39.42 (revision of arteriovenous shunt for renal dialysis)	Z49 (care involving dialysis)	KR53 (implantation of internal device for short-term dialysis) 1KY (fistula) 1OT53 (PD catheter) 1OK85 or 1PC85 (renal transplant)
<b>Renal Failure (All above codes +)</b>	584 (acute renal failure) 585 (chronic kidney disease) 586 (renal failure, unspecified)		N17 (acute renal failure) N18 (chronic renal failure) N19 (unspecified renal failure)	
<b>Any Renal Complication (All above codes +)</b>	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)		N08.3 (diabetic nephropathy) N04 (nephrotic syndrome) E10.2 (insulin dependent DM with renal complications) E11.2 (non-insulin dependent DM with renal complications)	

\*International Classification of Diseases 9<sup>th</sup> Revision, Clinical Modification \*\* Revision 10CA (Canadian) \*\*\*The Canadian Classification of Health Interventions

**Table 5.2 Baseline Demographics for Incident Youth Onset Diabetes Cohorts**

	No. T1DM/T2DM	Type 1 Diabetes	Type 2 Diabetes	p-value
Age (years)	1011/342	8.9 ± 4.3	13.5 ± 2.2	<0.0001
Male Sex (%)	1011/342	53.2	37.8	<0.0001
BMI z-scores	923/288	0.4 ± 1.0	1.9 ± 0.7	<0.0001
Urban (%)	1011/342	51.9	26.9	<0.0001
Low SES (%)	877/281	11.4	59.1	<0.0001
HNF 1α polymorphism (%)	-/146	N/A	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 pre-gestational diabetes (%)	772/277	2.7	15.9	<0.0001

Continuous variables reported as mean ± SD † Heterozygous and †† Homozygous for HNF1α variant

**Table 5.3 Clinical Features for Youth Onset Diabetes Cohorts at Last \*DER-CA Follow-up**

	No. T1DM/T2DM	Type 1 Diabetes	Type 2 Diabetes	p-value
Age (years)	1011/342	15.1 ± 3.2	16.5 ± 2.3	0.0006
BMI z-score	928/288	0.66 ± 0.8	1.8 ± 0.7	<0.0001
Total cholesterol (mmol/L)	410/296	4.3 ± 1.0	4.6 ± 1.0	0.0001
LDL-cholesterol (mmol/L)	51/224	2.9 ± 2.2	2.8 ± 0.8	0.05
HDL-cholesterol (mmol/L)	28/182	1.5 ± 0.4	1.28 ± 0.3	0.002
Triglycerides (mmol/L)	411/296	1.3 ± 0.9	2.2 ± 2.2	<0.0001
**ApoB (mmol/L)	11/215	0.9 ± 0.4	0.8 ± 0.2	0.60
Hypertension (%)	816/284	39.8	45.8	0.08
HemoglobinA1c (%)	977/305	9.2 ± 2.3	8.9 ± 3.0	0.04
Albuminuria (%)	727/280	19.8	38.6	<0.0001

Continuous variables reported as mean ± SD \*Diabetes Education Resource for Children and Adolescents

\*\*Apolipoprotein B

**Table 5.4: Albuminuria in Youth Onset Diabetes Cohorts Prior to Last Follow-up in the \*DER-CA**

	Type 1 Diabetes No. (%)	Type 2 Diabetes No. (%)
No sample available	284 (28.0%)	62 (18.1%)
No albuminuria	402 (39.8%)	130 (38.0%)
Albuminuria in only 1 sample (transient)	181 (17.9%)	42 (12.3%)
**Microalbuminuria in $\geq 2$ samples	128 (12.7%)	92 (26.9%)
***Macroalbuminuria in $\geq 2$ samples	16 (1.6%)	16 (4.7%)
Mean diabetes duration (years)	6.4 $\pm$ 5.5	1.9 $\pm$ 4.1
Total No.	1011	342

\*Diabetes Education Resource for Children and Adolescents \*\*Microalbuminuria - defined as urine albumin:creatinine ratio  $\geq 3$  mg/mmol or albumin excretion rate 30-300 mg/24 hrs \*\*\*Macroalbuminuria – defined as urine albumin:creatinine ratio  $> 28$ mg/mmol or albumin excretion rate  $> 300$  mg/24hours

**Table 5.5: Long Term Crude Renal Complication Rates in Youth Onset Diabetes Cohorts, Mean age and Duration of Diabetes at time of Renal Complication**

	No Diabetes N (%) Mean age (yrs)	Type 1 Diabetes N (%) Mean age (yrs) Mean DM duration (yrs)	Type 2 Diabetes N (%) Mean age (yrs) Mean DM duration (yrs)
Renal complication	11 (0.6) 21.9 $\pm$ 6.5	27 (2.7) 18.8 $\pm$ 5.4 9.9 $\pm$ 6.3	30 (8.9) 20.3 $\pm$ 5.8 7.5 $\pm$ 5.6
Renal failure	* 18.7 $\pm$ 4.36	14 (1.4) 18.1 $\pm$ 5.8 9.3 $\pm$ 5.5	23 (6.7) 21.9 $\pm$ 5.9 9.1 $\pm$ 6.0
Dialysis	* 20.9 $\pm$ 5.12	0 N/A N/A	8 (2.3) 29.1 $\pm$ 3.6 16.1 $\pm$ 3.6

\* $\leq 5$  individuals – suppressed to maintained patient anonymity

**Table 5.6: Univariate Analysis Results of Risk Factors for the Development of any Renal Complication in Youth Onset Diabetes Cohorts**

	<b>*HR</b>	<b>95% Confidence Intervals</b>	<b>p-value</b>
<b>T2DM vs T1DM</b>	6.11	3.60-10.37	<b>&lt;0.0001</b>
<b>Age at Diagnosis</b>	1.17	1.09-1.25	<b>&lt;0.0001</b>
<b>Male Sex</b>	0.55	0.32-0.95	<b>0.02</b>
<b>Urban vs. Rural</b>	0.70	0.38-1.28	0.24
<b>HgA1c at last visit</b>	1.14	1.06-1.23	<b>0.001</b>
<b>Hypertension</b>	0.74	0.37-1.49	0.40
<b>BMI z-score</b>	1.90	1.29-2.79	<b>0.0008</b>
<b>Diagnosis prior to year 2000</b>	2.76	1.30-8.88	<b>0.009</b>
<b>**Ace/Arb use</b>	12.29	6.70-22.60	<b>&lt;0.0001</b>
<b>Pre-gestational DM</b>	2.96	0.90-9.70	0.07
<b>Low SES</b>	1.76	1.02-3.06	<b>0.04</b>
<b>Albuminuria</b>	6.42	3.44-11.95	<b>&lt;0.0001</b>
<b>HNF-1alpha polymorphism (T2DM only)</b>	0.94	0.44-2.02	0.87

\*Hazard Ratio \*\*Ace inhibitor or angiotensin receptor blocker use

**Table 5.7: Risk Factors for the Development of any Renal Complication in Youth Onset Diabetes as Determined by Final Multivariate Model N= 838 Events = 43**

	<b>X<sup>2</sup></b>	<b>*HR</b>	<b>95% Confidence Intervals</b>	<b>p-value</b>
<b>T2DM vs. T1DM</b>	4.10	2.25	1.0-4.92	0.043
<b>Albuminuria</b>	9.77	3.17	1.54-6.54	0.0018
<b>**ACE/ARB use</b>	32.31	8.24	3.98-17.04	<0.0001
<b>Diagnosis prior to year 2000</b>	5.01	2.87	1.14-7.23	0.025

\*Hazard Ratio \*\*Ace inhibitor or angiotensin receptor blocker use

**Table 5.8: Univariate Analysis Results of Risk Factors for the Development of Renal Failure in Youth Onset Diabetes Cohorts**

	<b>*HR</b>	<b>95% Confidence Intervals</b>	<b>p-value</b>
<b>T2DM vs. T1DM</b>	9.17	4.68-17.90	<b>&lt;0.0001</b>
<b>Age at Diagnosis</b>	1.20	1.10-1.31	<b>&lt;0.0001</b>
<b>Male Sex</b>	0.55	0.28-1.08	0.07
<b>Urban vs. Rural</b>	0.55	0.26-1.05	0.07
<b>HgA1c at last visit</b>	1.16	1.06-1.28	<b>0.003</b>
<b>Hypertension</b>	0.89	0.41-1.96	0.77
<b>BMI z-score</b>	2.71	1.65-4.47	<b>&lt;0.0001</b>
<b>Diagnosis prior to 2000</b>	3.31	1.27-8.65	<b>0.02</b>
<b>*Ace/Arb use</b>	31.9	11.27-90.31	<b>&lt;0.0001</b>
<b>Pre-gestational DM</b>	2.11	0.28-15.99	0.52
<b>Low SES</b>	1.63	0.82-3.26	0.18
<b>Albuminuria</b>	9.47	4.01-22.33	<b>&lt;0.0001</b>
<b>HNF-1alpha polymorphism (T2DM only)</b>	0.89	0.36-2.13	0.77

\*Hazard Ratio \*\* Ace inhibitor or angiotensin receptor blocker use

**Table 5.9: Risk Factors for the Development of Renal Failure in Youth Onset Diabetes as Determined by Final Multivariate N=880 Events = 27**

	<b>X<sup>2</sup></b>	<b>*HR</b>	<b>95% Confidence Intervals</b>	<b>p-value</b>
<b>T2DM vs. T1DM</b>	9.167	4.03	1.64-9.95	0.0025
<b>ACE/ARB use</b>	24.43	15.82	5.29-47.27	<b>&lt;0.0001</b>
<b>Albuminuria</b>	7.85	3.88	1.50-10.0	0.0051

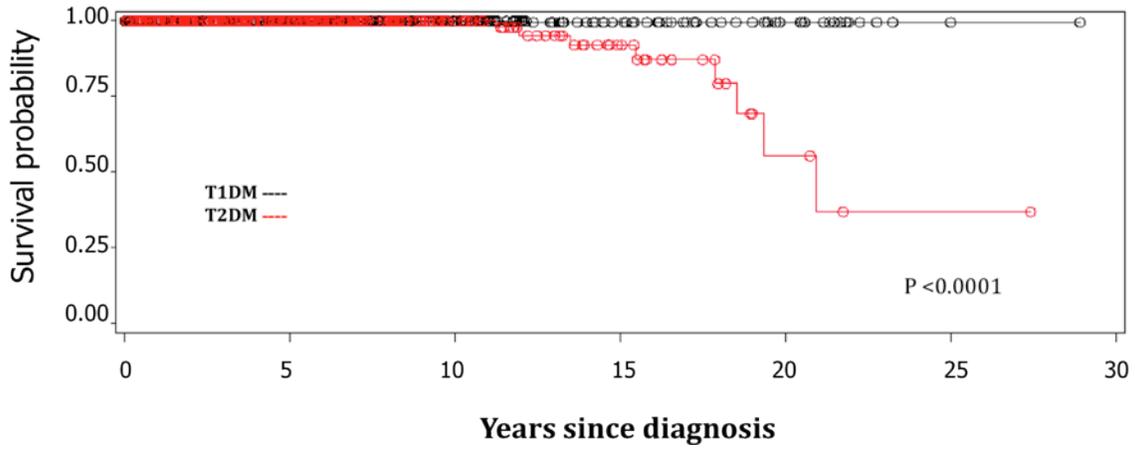
\*Hazard Ratio \*\* Ace inhibitor or angiotensin receptor blocker use

**Table 5.10: Analysis of Risk of Development of Renal Complications in Youth Onset Type 2 Diabetes Compared with Non-DM controls**

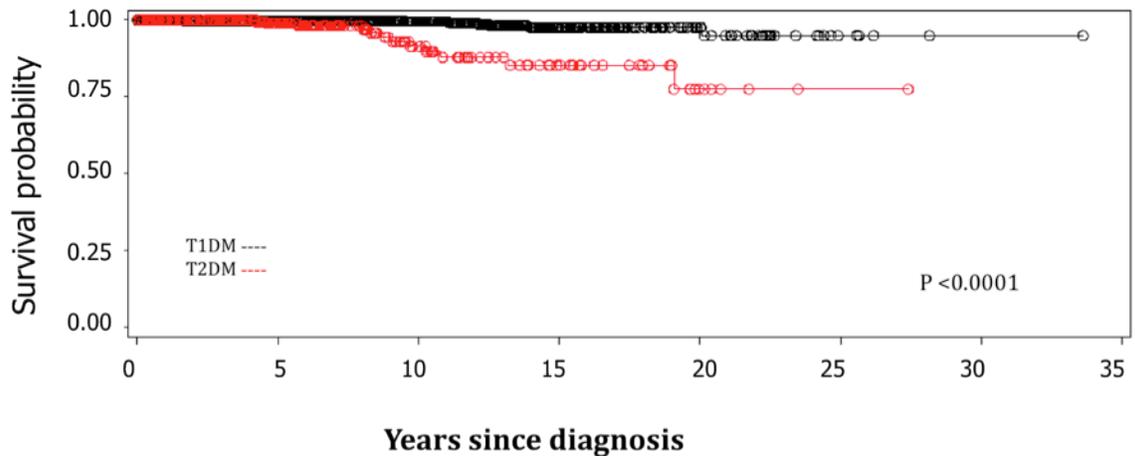
<b>Outcome analyzed</b>	<b># Events (%) (T2DM/non-DM)</b>	<b>X<sup>2</sup></b>	<b>**HR</b>	<b>95% Confidence Intervals</b>	<b>p-value</b>
<b>Renal Complication</b>	30(8.8)/11(0.64)	53.48	16.13	7.66-33.99	<b>&lt;0.0001</b>
<b>Renal Failure</b>	23(6.7)/*	40.18	22.83	8.68-60.1	<b>&lt;0.0001</b>
<b>Dialysis</b>	8(2.3)/*	11.94	39.10	4.89-312.69	0.0005

\*≤5 individuals – suppressed to maintained patient anonymity \*\*Hazard Ratios

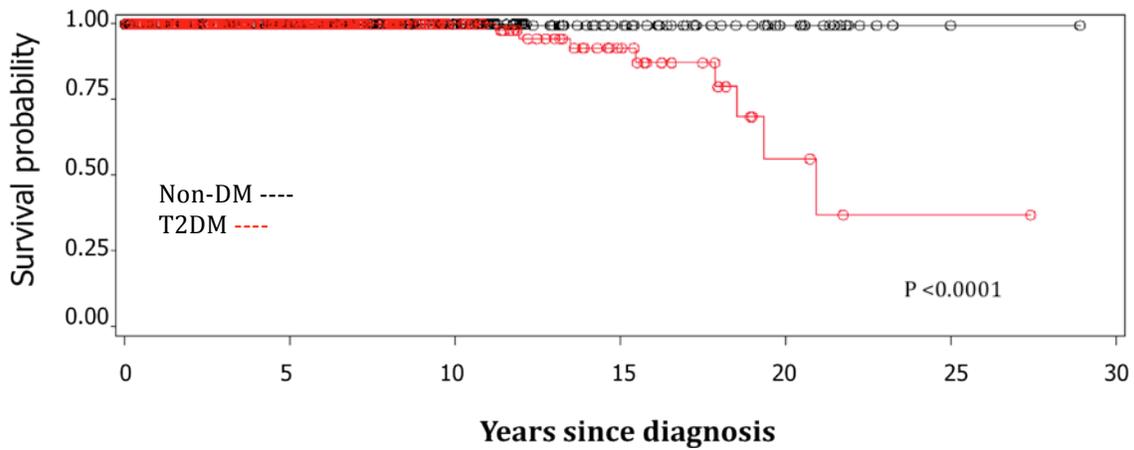
**Figure 5.1 Renal Survival in Youth Onset Diabetes Cohorts**



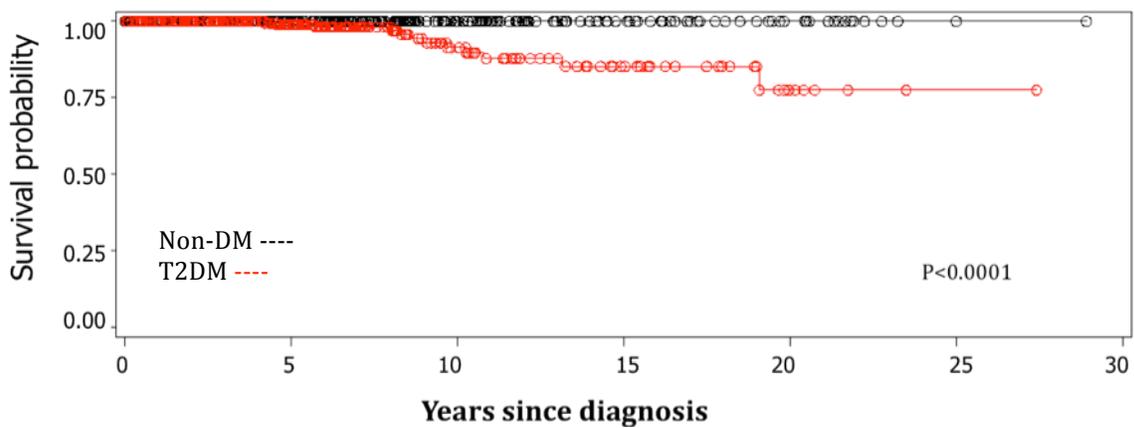
**Figure 5.2 Overall Survival in Youth Onset Diabetes Cohorts**



**Figure 5.3: Renal Survival in Youth Onset Type 2 Diabetes Cohort and Non-DM controls**



**Figure 5.4: Overall Survival in Youth Onset Type 2 Diabetes Cohort and Non-DM controls**



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## **Chapter 6: Summary and implications of research**

### **6.1 Summary**

This study utilized the combination of a clinical registry (Diabetes Education Resource for Children and Adolescents (DER-CA) in Manitoba, Canada) and administrative data housed at the Manitoba Centre for Health Policy (MCHP) to describe the natural history of youth onset T2DM into young adulthood compared with youth onset T1DM and non-DM controls.

First, this study determined that the ascertainment rate of the DER-CA for youth onset diabetes (both T1DM and T2DM) is as high as 86.1%, indicating that the study sample is representative of the population with youth onset diabetes in Manitoba. In addition, the following algorithms to identify prevalent individuals with youth onset diabetes utilizing administrative data were validated: 1. one or more hospitalizations or two or more outpatient claims over two years (sensitivity 94.2%, specificity 99.9%, positive predictive value (PPV) 81.6% and negative predictive value (NPV) 99.9% and 2. one or more hospitalizations or two or more outpatient claims or one or more prescription claims over one year (sensitivity 94.2%, specificity 99.9%, PPV 82.4% and NPV 99.9%). This study thus supports the use of administrative data for the longitudinal evaluation of the prevalence of youth onset diabetes, which is important for healthcare planning and evaluation.

Most importantly, this study has shown that youth onset T2DM is associated with a higher morbidity and mortality than youth onset T1DM. This cohort of youth with T2DM had a

47% increased risk of any complication, compared with youth with T1DM and a 6.15 fold increased risk of vascular disease than non-DM controls. In addition, they specifically had a higher risk of nephropathy, neuropathy, peripheral vascular disease, major complications (dialysis, blindness or amputation) and death. Mortality was 9.6% at 10 years in the T2DM group compared with 0.5% in the T1DM group and 0% in the controls ( $p < 0.001$ ). They did not have a higher risk of retinopathy or cardio or cerebrovascular disease during the follow-up period (T2M: mean  $5.3 \pm 5.2$  years (range 0-27.4), T1DM: mean  $7.9 \pm 6.3$  years (range 0-28.2), and non-DM: mean  $7.0 \pm 5.7$  years (range 0-29.9)).

Renal complications are associated with significant morbidity in T2DM populations, and this study has shown a significant burden of renal disease in youth onset T2DM. Albuminuria, indicative of incipient nephropathy was highly prevalent early in the course of disease.

Youth with T2DM had a 2.29 fold increased risk of any renal complication (RC) and a 4.03 fold increased risk of renal failure (RF) when compared with T1DM and a 16.13 and 22.83 fold increased risk of RC and RF when compared with non-DM controls. Identified risk factors for poor renal outcomes included albuminuria, diagnosis prior to the year 2000 and ace inhibitor (ACE) or angiotensin receptor blocker (ARB) use, which may be a marker of disease severity. These results highlight the significant health burden associated with the diagnosis of youth onset T2DM and the need for further research on this high risk population.

## **6.2 Policy recommendations**

### **1. Ongoing monitoring of youth onset diabetes prevalence**

Although not specifically evaluated in this study, the literature suggests that rates are increasing for both T1DM and T2DM over time (1-3). This study has confirmed the significant morbidity and mortality associated with youth onset T2DM diabetes, which are associated with significant direct and indirect healthcare costs. Administrative data, which is currently utilized by the National Diabetes Surveillance System (NDSS) (4), is a feasible means for longitudinal analysis of disease trends. This study has validated the current diabetes definition utilized by the NDSS (one or more hospitalizations or two or more outpatient claims over two years), and thus supports its ongoing use. Longitudinal prevalence data is important for planning healthcare utilization as well as evaluating disease prevention and treatment strategies.

### **2. Increase physician awareness and referrals to pediatric subspecialty care**

As youth onset T2DM is a relatively new disease, the natural history of the disease is just being described. This study reveals that the disease has significant associated complications affecting individuals in early adulthood; therefore care must be optimized as early as possible in the disease course. First, primary care physicians need to have a high index of suspicion to identify asymptomatic, affected individuals. Second, secondary prevention may play an important role in the natural history of the disease as potentially modifiable risk factors have been identified. These include poor glycemic control and the presence of albuminuria early in the course of disease (prior to 18 years of age). Because

obtaining optimal glycemic control is a challenge in youth, it is imperative that multidisciplinary specialty teams in pediatric diabetes care become involved in the care of these high-risk youth such that risk reduction can be optimized. In addition, screening for albuminuria should be performed at the time of diagnosis and referrals made to pediatric kidney specialists for prompt assessment and treatment.

### **3. Prevention strategies**

T2DM is associated with multiple risk factors (Chapter 1), however obesity has been shown to play a major associative role (5). Overweight and obesity continues to increase worldwide. In order to prevent the morbidity associated with T2DM itself, ideally the disease would be prevented in the first place. Therefore, prevention strategies for the development of overweight and obesity should be prioritized, especially in high-risk groups such as Canadian First Nations.

## **6.3 Future research**

### **1. Validation of complication algorithms**

This study has validated pediatric diabetes algorithms utilizing administrative data. Administrative data was also utilized to assess complication rates, however these outcomes have not yet been validated. Future research should be conducted to assess the validity of administrative data for each outcome measure as its validity has been shown to vary according to the disease studied (6). A priority would be the evaluation of renal outcome measures. The assessment of algorithms could be performed in the same manner as was conducted in this study. A comparable pediatric renal database does not exist in Manitoba

to act as the second data set, however chart audits could be performed. Alternatively, an adult renal database, such as the Manitoba Renal Program database could be utilized, as most renal outcomes occur once the affected youth are over 18 years of age.

## **2. Ace inhibitors and Angiotensin receptor blockers in the treatment of diabetic nephropathy**

This study identified the “ever” use of ace inhibitors (ACE) and angiotensin receptor blockers (ARB) as risk factors for adverse renal outcomes, as well as any diabetic complication. This was a surprising finding, as previous literature has shown these drugs to be effective treatments for the progression of diabetic renal disease (7). This association may be non-causal, resulting from the fact that physicians may prescribe ACE/ARB in more severe disease (i.e. confounding by indication). Nevertheless, the possibility that it is a true finding must be investigated, as these drugs have not been previously evaluated in adequately powered randomized studies in children. In order to evaluate this finding further, as a first step, the pharmaceutical data in the Repository housed at the MCHP could be evaluated more in depth with respect to the timing, dose, and length of treatment with ACE/ARBs to see if the risk associated with these drugs persists. In addition, a clinical trial in both youth onset T1DM and T2DM should be conducted to prospectively evaluate the effect of these drugs in a rigorous, blinded and randomized fashion.

## **3. Pathologic evaluation of renal complications**

This retrospective analysis of prospectively collected data revealed an increased risk of renal diagnoses, including renal failure in youth onset T2DM. A small study on a subset of

the same cohort of patients which included biopsy data, showed that classical diabetic nephropathy was not the etiology of albuminuria (8). Therefore, future clinical studies in youth onset T2DM should include renal biopsies in order to confirm the etiology of adverse renal outcomes in these youth. This information is of course important in guiding treatment decisions that could impact on individual outcomes.

#### **4. Evaluation of cardiovascular risk**

This study revealed a high prevalence of cardiovascular risk factors in youth onset T2DM, however did not show a high burden of cardiovascular events in early adulthood in these patients. There was however an increased risk of peripheral vascular disease. More study is required in this area, perhaps evaluating early markers of cardiovascular disease such as carotid intima-media thickness and measures of arterial stiffness and endothelium-dependant relaxation. Alternatively, longer follow-up of these patients may be required to capture cardiovascular events.

This study has clearly shown that youth onset T2DM is a disease associated with significant morbidity and mortality and thus research to identify treatable risk factors for the development of T2DM and its comorbidities should be a priority in the future.

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