CPSP
CANADIAN PAEDIATRIC SURVEILLANCE PROGRAM

PROTOCOLS

Incidence trends of type 2 diabetes, medication-induced diabetes, and monogenic diabetes in Canadian children

A comparison Canadian Paediatric Surveillance Program study one decade later

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Background

Type 2 diabetes (T2D) in children is an emerging disease that was not described before the 1980s. However, today it accounts for 20 to 50% of new-onset childhood diabetes.[1] A Canadian Paediatric Surveillance Program (CPSP) study from 2006 to 2008 reported a minimum incidence of T2D in Canadian children less than18 years of age to be 1.54 cases per 100,000 children per year, with a sensitivity analysis suggesting a conservative incidence of 11.3 cases per 100,000 children per year.[2] National data on the incidence of childhood-onset T2D have not been collected since this sentinel Canadian CPSP study; however, in Manitoba, the annual incidence of T2D in youth doubled from 2006 to 2011 (from 9.03 to 20.55 cases per100,000 youth per year).[3]

One decade later, with access to Canadian baseline data on T2D incidence in children, there is an opportunity to re-examine national incidence trends in a new group of children with childhood-onset T2D. By largely replicating the first CPSP study on non-type 1 diabetes mellitus (NT1DM), this subsequent study can describe whether the 'face' of childhood-onset T2D is changing related to demographics, clinical

presentation, and severity; information that is critical to designing prevention and treatment programs that meet the specific needs of the populations affected.

Among Canadian children with newly diagnosed T2D, 95% had a body mass index (BMI) greater than the 95th percentile for age and sex and 37% already had at least one complication (e.g., microalbuminuria, hypertension, dyslipidemia) at diagnosis, at an average age of only 13.7 years.[2] This finding led to a recent CPSP surveillance study that reported the prevalence of persistent albuminuria in children with T2D to be 5.1% with the diagnosis of albuminuria occurring within the first year of T2D diagnosis.[4] Evidence from the TODAY trial in the United States demonstrated that almost half of children with T2D fail treatment with oral diabetes medications (and require insulin therapy) within four years of their diabetes diagnosis.[5] Over this same time period, rates of hypertension increased from 1 in 10 to 1 in 3 children and microalbuminuria almost tripled from 6.3% to 16.6%.[6] A recent study from Manitoba, utilizing administrative data, demonstrated rates of end-stage renal disease (ESRD) in childhood-onset T2D of 8% and 45% at 10 and 20 year follow-up respectively. These rates of ESRD are greater than those for childhood-onset type 1 diabetes (T1D) of 0.5% and 2.4% at 10 and 20 year follow-up respectively.[7] A significant difference in overall mortality was also described with a mortality rate of 22.5% at 20 year follow-up observed in childhood-onset T2D compared to 2.4% in childhood-onset T1D.[8] Clearly, T2D in children is a significant public health concern as it will pose an added burden in the short- and long-term to the Canadian healthcare system.

Collecting national data on the incidence of childhood-onset T2D is critically important. Although rates of childhood-onset T2D are on the rise, its incidence is relatively low (i.e., less than 500 cases per year) requiring national ascertainment to accurately assess epidemiological trends. The majority of Canadian data continue to originate from Manitoba, where most cases occur in First Nations children. A national study will provide a more accurate representation of incidence trends in childhood-onset T2D based on Canada's unique ethnic, cultural, and geographic characteristics.

This second surveillance study will also capture new cases of medication-induced diabetes (MID), neonatal diabetes, and monogenic diabetes. The initial CPSP study was the first in the world to report incidence rates of MID[2] and this follow-up study will provide an opportunity to document incidence trends and further characterize the disease. In our first study we showed that children with MID do not have similar risk factors to children diagnosed with T2D[9] as was thought to be the case. This next study will help to further characterize MID and inform guidelines for its screening and prevention. Similarly, diagnoses of monogenic diabetes may be on the rise with increased recognition of genetic causes of childhood diabetes. In particular, over the past decade, diabetes onset in neonates or infants less than 6 months of age are virtually all due to monogenic/genetic causes and have the potential to be treated with oral diabetes medications, so these cases will also be included in this surveillance.[10]

Methods

Through the established methodology of the CPSP, over 2500 paediatricians and paediatric subspecialists will be actively surveyed on a monthly basis for cases of NT1DM over a 24-month period. A detailed questionnaire will be sent for each new case identified.

Using the CPSP NT1DM (2006 to 2008) surveillance study as a stepping stone, the study team will provide the opportunity to health care providers, through consent, to recruit their newly diagnosed patients less than18 years of age with NT1DM to

participate in a study where additional clinical information can be obtained including blood samples for pancreatic autoantibody levels. This study will be separate from the CPSP surveillance study.

The research team will also use data from the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) for the same period that the CPSP study will occur to identify incident and prevalent cases of diabetes in children and youth less than18 years of age. The inclusion of these cases will optimize the ascertainment of cases of new-onset type 2 diabetes in children and youth over the CPSP study period. CPCSSN is a Canadian electronic medical record (EMR)-based surveillance system that includes 10 primary care practice-based research networks in eight provinces and territories across Canada. Over 1000 sentinels provide data on almost 1.3 million patients. Consenting primary care providers contribute anonymized EMR data that is first put in a regional repository and subsequently aggregated into a single national database.

Case definition

Report any new or revised* diagnosis of non-type 1 diabetes (NT1DM) in a patient less than 18 years of age with clinical features that are **not** consistent with classic type 1 diabetes (defined as a child with symptomatic acute hyperglycemia).

*A revised diagnosis occurs when a child previously diagnosed with type 1 diabetes mellitus receives a "revised" diagnosis of non-type 1 diabetes based on clinical progression and/or results of investigations.

Diabetes is defined based on the Canadian Diabetes Association Guidelines:

- Fasting plasma glucose (FPG) ≥ 7.0 mmol/L[†] or
- Random plasma glucose ≥ 11.1 mmol/L[†] or
- Two-hour plasma glucose ≥ 11.1 mmol/L[†] after a standard oral glucose tolerance test

[†] Requires a second, confirmatory test if child is asymptomatic

Clinical features suggestive of non-type 1 diabetes mellitus are listed below:

a) Obesity (body mass index >95th percentile for age and gender)
b) Family history of type 2 diabetes in a first- or second-degree relative(s)
c) Belonging to a high-risk ethnic group (e.g., Aboriginal, Black, Latin American, South-Asian)
d) A history of exposure to diabetes *in utero* (diagnosed before or during pregnancy)
e) *Acanthosis nigricans*
f) Polycystic ovarian syndrome
g) Diabetes in a person with a syndrome often associated with type 2 diabetes (Prader-Willi syndrome)
h) Diabetes in a non-obese patient with at least one first-degree relative with diabetes
i) Diabetes diagnosed in a neonate/infant less than 6 months of age
j) Minimal or no insulin requirement with a normal or near normal A1c level (4–6%) one year after diagnosis
k) A diagnosis of diabetes while on medical therapy with a known diabetogenic medication (e.g., glucocorticoids, L-asparaginase, cyclosporine, tacrolimus, atypical antipsychotic, anticonvulsant)

Exclusion criteria

Do not report patients with cystic fibrosis-related diabetes, pregnant teenagers with gestational diabetes, and patients in critical care settings requiring **short-term** insulin therapy for stress hyperglycemia.

Objectives

The objectives of this study are to determine in children and youth less than 18 years of age:

1) The incidence of NT1DM and its sub-types (T2D, MID, monogenic diabetes) in 2017–2019
2) Incidence trends of NT1DM sub-types (T2D, MID, and monogenic diabetes) from 2006–08 (baseline data) to 2017–2019(follow-up data).
3) Rates of and risk factors for diabetes-related complications in children with T2D.
4) Differences in the demographic and clinical features (e.g., age at diagnosis, ethnicity, BMI) of Canadian children diagnosed with T2D and MID compared to 10 years ago.
5) Differences in treatment approaches for T2D in children compared to 10 years ago and variation across provinces/territories.

Duration

June 2017 to May 2019

Expected number of cases

In the initial CPSP surveillance study for NT1DM, a total of 345 cases of NT1DM were reported over two years: 227 were T2D, 56 were MID, and 31were monogenic diabetes, respectively. The remaining 31 cases were classified as indeterminate where the research team could not ascertain the diabetes type. Assuming a 25% increase in T2D and constant rates of MID and monogenic diabetes, we expect the following number of cases:

- T2D – 145 cases per year
- MID – 30 cases per year
- Monogenic diabetes – 15 cases per year

Ethical approval

Health Canada and the Public Health Agency of Canada's Research Ethics Board
UBC Children and Women's Research Ethics Board
University of Manitoba Research Ethics Board

Analysis and publication

The minimum incidence rate will be calculated as the number of total new cases of NT1DM per year reported per 100,000 children aged 0 to 17.9 years. The incidence of all subgroups of NT1DM (i.e., T2D, monogenic diabetes, and medication induced diabetes) will also be determined and reported per 100,000 children aged 0 to 17.9 years of age. Descriptive statistics and tests of significance will be used to illustrate demographics and clinical features of NT1DM in Canadian children, and specifically to evaluate clinical features and coexisting morbidity of T2DM at diagnosis.

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The results of this research will be shared with key stakeholder groups through presentations at national conferences (e.g., the Canadian Diabetes Association, the Canadian Paediatric Society, the Canadian Pediatric Endocrine Group) and publication in high-impact peer-reviewed journals (e.g., *Diabetes Care*, *Journal of Pediatrics*). A final report and executive summary of the results will also be shared widely in Canada to decision makers at the national (Public Health Agency of Canada) and provincial levels. The results of the study will be published by CPSP and circulated to all paediatricians. CPCSSN will communicate study results to family physicians.

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