PROTOCOLS

Non-type 1 diabetes mellitus in Canadian children

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Background

Recently, diabetes mellitus (DM) in children has evolved from the most common diagnosis of type 1 diabetes mellitus (T1DM) to a more complex differential diagnosis comprising type 2 diabetes mellitus (T2DM), monogenic forms of diabetes, and secondary diabetes including medication-induced DM (e.g., steroids, L-asparaginase, tacrolimus, atypical antipsychotics). For the purpose of this study, these three causes of diabetes will be classified together as "non-type 1 diabetes" (NT1DM). The increasing prevalence of T2DM is associated with the rapidly increasing prevalence of childhood obesity.[1] Additionally, both monogenic diabetes and medication-induced diabetes may also be on the rise in childhood, mediated directly or indirectly by increased body weight, and can be difficult to distinguish from T2DM.

Obesity has been identified as a significant risk factor for the development of T2DM. It has become apparent, however, that not all obese individuals develop T2DM and additional risk factors may confer susceptibility. These include a positive family history of T2DM, specific ethnic backgrounds (Aboriginal, African/Caribbean, Hispanic and Asian), and insulin resistance evidenced by the presence of *acanthosis nigricans.*[2]

There is paucity of data in regards to diabetes mellitus secondary to medical therapy in childhood. Studies of post-renal transplant paediatric patients have shown medical therapy, most commonly associated with glucocorticoids, can result in severe hyperglycemia requiring insulin therapy.[3] Chemotherapeutic agents (e.g., L-asparaginase), and immunosuppressants (e.g., cyclosporine and tacrolimus), have also been implicated. Additionally, recognition of genetic forms of diabetes as an important cause of childhood DM has improved substantially over the last decade with the isolation of six causative gene mutations important in insulin and glucose regulation and pancreatic beta cell function.[4]

Epidemiology

Preliminary data specific to the Oji-Cree First Nations people of Canada estimate prevalence of T2DM as 1.1% in the 4- to19-year age group[5] rising to 3.5% in the 15- to 19-year age group (personal communication). In Nova Scotia, T2DM accounts for roughly 16-18% of new cases of diabetes in children less than 19 years of age.[6] Manitoba reports a minimum incidence of 35 to 45 new cases per year of T2DM, which recently represents 30% of new cases of diabetes in children in Manitoba annually.[7]

There is limited epidemiological data available on other forms of NT1DM. Secondary diabetes due to medical therapy has largely been studied in post-renal transplant patients with a reported 7% of paediatric patients affected with post-transplant diabetes mellitus (PTDM).[8] Fifty percent of these patients were obese and the most significant risk factor for the development of PTDM was a positive family history of T2DM.

It has been estimated that monogenic forms of diabetes account for 1-5% of all cases of diabetes.[9] A cross-sectional questionnaire survey in the U.K. reported a minimum prevalence for monogenic diabetes as 0.17/100,000 with 50% of the children being overweight or obese.[10]

Need for Canadian incidence data

Data on the incidence and prevalence of non-type 1 diabetes mellitus in Canadian children are limited. There is currently a global effort to conduct population incidence and prevalence studies in order to quantify the extent of the problem. It is imperative that Canadian data is obtained based on Canada's unique ethnic, cultural, geographic and behavioural characteristics in order to gain a better understanding of the magnitude, characteristics, and public health consequences of this disease.

Non-type 1 diabetes mellitus (continued)

This study will provide epidemiological and demographic data about Canadian children with NT1DM, and specifically, obesity-related T2DM. It will provide a foundation upon which health promotion and disease prevention programs can be established.

Methods

It is important to recognize that almost half of all family practitioners also evaluate children in their practice.[11] Furthermore, older adolescents may be referred to adult, rather than paediatric, endocrinology specialists. Therefore, in order to accurately ascertain the epidemiology of NT1DM in Canadian children, it is essential to include a representative sample of family practitioners and adult endocrinologists, in addition to paediatricians and paediatric subspecialists, in this surveillance study.

National surveillance will be conducted with the collaboration of the Canadian Paediatric Surveillance Program and the National Research System (NaReS); both well established health surveillance programs. All paediatricans in Canada will receive monthly surveillance questionnaires. An enriched sample of family practitioners will be generated from the NaReS database to identify family physicians and nurse practitioners with previously coded relevant practice interests (paediatrics, adolescent medicine, Aboriginal medicine, rural medicine, or inner-city medicine). The sample will be limited to those in practice in northern and core urban regions. Adult endocrinologists will be recruited from the Canadian Medical Directory. Following initial assessment of physician interest in participation, a sample of up to 300 family practitioners and 500 adult endocrinologists will be generated. Physicians involved will be required to fill out a questionnaire for each new or reclassified patient with NT1DM, or submit "nothing to report" if no new cases are identified.

Data analysis/statistical methods

The incidence rate will be calculated as the number of total new cases of NT1DM (T2DM, monogenic diabetes, and drug-induced diabetes) per year reported per 100,000 children aged 0 to 17.9 years. The calculated incidence rate will be expressed as a **minimum** incidence rate with the understanding that it will likely underestimate the true incidence rate. A **maximum** incidence rate will also be determined using sensitivity analysis.

Objectives

1. Determine the incidence of non-type 1 diabetes mellitus (NT1DM) amongst Canadian children.
2. Determine the incidence of type 2 diabetes mellitus (T2DM) amongst Canadian children.

3. Describe the clinical features of T2DM at diagnosis that aid in the differentiation of T2DM from type 1 diabetes mellitus (T1DM).
4. Identify co-existing morbidity associated with T2DM at diagnosis.

Case definition

Report any patient 0 to 17.9 years of age with a diagnosis of non-type 1 diabetes, either new or revised, with clinical features that are **not** consistent with classic type 1 diabetes (non-obese child with symptomatic acute hyperglycemia).

Canadian Diabetes Association's definition of diabetes

- 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 (75g) 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. If you are uncertain whether your patient has NT1DM, please report the case for study investigators to review and classify.

- Obesity (body mass index >95th percentile for age and gender)
- Family history of T2DM in a first or second degree relative(s)
- Belonging to a high-risk ethnic group (e.g., Aboriginal, African, Hispanic, South-Asian)
- A history of exposure to diabetes *in utero* (diagnosed before or during pregnancy)
- *Acanthosis nigricans*
- Polycystic ovarian syndrome
- Diabetes in a person with a syndrome often associated with type 2 diabetes (Prader-Willi syndrome)
- Diabetes in a non-obese patient with at least one first-degree relative and/or two second-degree relatives with diabetes
- Minimal or no insulin requirement with a normal or near normal A1c level (4-6%) one year after diagnosis
- A diagnosis of diabetes while on medical therapy with a known diabetogenic medication (e.g., glucocorticoid, L-asparaginase, cyclosporine, tacrolimus, atypical antipsychotic, anticonvulsant)

Exclusion criteria

Do not report any cystic fibrosis-related diabetes or patients in critical care settings requiring short-term insulin therapy for stress hyperglycemia.

Duration

April 2006 to March 2007 (renewable)

Expected number of cases

The expected number of new non-type 1 diabetes mellitus cases per year is ~200-250; secondary diabetes per year is ~50-75 and monogenic diabetes per year is ~100. (Estimates were obtained from recent assessment of clinic

Non-type 1 diabetes mellitus (continued)

diagnoses of new patients at the diabetes clinics of the Children's Hospital of Winnipeg in Manitoba, and the Hospital for Sick Children, Toronto, Ontario. An additional 10-30% of cases are expected from surveillance of family practitioners and adult endocrinologists.)

Ethical approval

Children's Hospital of Winnipeg, University of Manitoba
The Hospital for Sick Children, University of Toronto

Analysis and publication

The investigators will analyze the data promptly and report any significant findings to the CPSP/NaReS. Quarterly reports and an annual report will be distributed to all physicians (paediatricians, family doctors and adult endocrinologists) participating in this surveillance study. It will be presented as a scientific abstract at international paediatric and/or diabetes meetings in the spring of 2008 and submitted for publication to a peer-reviewed paediatric and/or diabetes journal. The results will be shared widely in Canada with colleagues in provincial and federal governments by circulation of a final report through the established networks in National Diabetes Surveillance System at Health Canada.

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