



Persistent albuminuria in the paediatric population with type 2 diabetes mellitus

Principal investigators

Elizabeth Sellers, MD, FRCPC, Section of Paediatric Endocrinology and Metabolism,
Children's Hospital, Winnipeg MB R3E 0Z2; tel.: 204-787-4351; fax: 204-787-1655;
esellers@exchange.hsc.mb.ca.

Stasia Hadjiyannakis, MD, FRCPC, Section of Paediatric Endocrinology, Children's Hospital
of Eastern Ontario, Ottawa ON K1HL8I; tel.: 613-737-7600, ext. 2179; fax: 613-738-4236;
shadjiyannakis@cheo.on.ca.

Co-investigators

Shazhan Amed, MD, FRCPC, University of British Columbia
Allison Dart, MD, FRCPC, University of Manitoba
Heather Dean, MD, FRCPC, University of Manitoba
Roland Dyck, MD, FRCPC, University of Saskatchewan
Jill Hamilton, MD, FRCPC, University of Toronto
Valerie Langlois, MD, FRCPC, University of Toronto
Constadina Panagiotopoulos, MD, FRCPC, University of British Columbia
Anne-Marie Ugnat, PhD, Public Health Agency of Canada

Background

The prevalence of childhood onset type 2 diabetes mellitus (T2DM) is increasing worldwide. In Canada, a recent CPSP study revealed a minimum incidence of T2DM mellitus in children under age 18 years of 1.54 cases per 100,000 children per year with a sensitivity analysis suggesting a maximum incidence of 40.5 cases per 100,000 children per year. Significant regional variation has been identified with the highest rates of T2DM observed in Manitoba, with a recently reported minimum incidence of 12.35 per 100,000 children.

In adults, serious end-stage complications of T2DM occur within 20 years. The natural history and true burden of T2DM diagnosed in childhood are still largely unknown. Adolescents with T2DM have a higher prevalence of other cardiovascular disease risk factors, including obesity, elevated blood pressure and dyslipidemia compared to youth without diabetes and higher rates of microalbuminuria when compared to adolescents with type 1 diabetes of a similar age. Evidence suggests that complications occur at an earlier age with a shorter duration of diabetes in youth-onset T2DM. Youth-onset T2DM is associated with an increased incidence of end-stage renal failure (ESRF) and mortality in



middle age in the Pima Indians of the southwestern United States. ESRF has been reported before the age of 30 years in Canadian First Nations young adults who had T2DM diagnosed in adolescence. The earlier age of diagnosis raises concern regarding the resulting burden of disease, as these children may begin to develop micro- and macrovascular complications of diabetes as young adults at the height of their productivity and childbearing years, resulting in significant impact on quality of life as well as economic consequences.

Diabetic nephropathy is the leading cause of end-stage renal failure in adults. The first sign of diabetic nephropathy is microalbuminuria, which may progress to macroalbuminuria and ultimately ESRF requiring renal replacement therapy. Albuminuria is also a marker of significant increased cardiovascular morbidity and mortality for individuals with diabetes. It is imperative to identify albuminuria early, as progression can be prevented, with early interventions having the greatest impact. In adults, improved control of blood glucose and blood pressure slows the rate of progression to ESRF. The natural history of albuminuria in children with T2DM is not known. Most reports come from clinic-based surveys and are cross-sectional but raise concern about the potential for ESRF in early adult years.

Careful laboratory documentation of albuminuria is critical, as transient albuminuria can be caused by a febrile illness, acute hyperglycemia, exercise, urinary tract infection, heart failure and hypertension. There is also some variability in day-to-day albumin secretion, and adolescents can have benign orthostatic proteinuria. It is therefore important to demonstrate persistent elevation in two out of three samples over a three- to six-month period. Samples must be at least one month apart, and at least one must be a first morning or overnight sample.

National surveillance for the prevalence of persistent albuminuria in children with T2DM is necessary to define the spectrum and extent of the problem. This is important for predicting burden of illness, and for planning screening programs and intervention programs. Study data will be relevant to paediatricians, family physicians, community health professionals, policy makers and program planners. Furthermore, this will provide a baseline prevalence estimate for future comparison. Identification of the population of children affected with T2DM and persistent albuminuria will facilitate research to understand the etiology and prevention of this significant complication.

Methods

New cases of persistent micro/macroalbuminuria in children and youth with T2DM will be reported through the CPSP. For each initial monthly report, participants will be asked to complete a detailed clinical questionnaire to ensure that the case definition is met.

Control population

Clinical features at diagnosis of T2DM in those who develop persistent micro/macro albuminuria will be compared to a population of youth with T2DM, reported in the recent CPSP non-T1DM incidence study, who had neither albuminuria at diagnosis or in follow-up (as determined by no report in this surveillance study). This will be done to determine if there are any clinical features that identify those most likely to develop albuminuria during the paediatric years.

Persistent albuminuria in the paediatric population with type 2 diabetes mellitus (continued)

Objectives

- 1) To determine the minimum prevalence of persistent microalbuminuria and macroalbuminuria in children less than 18 years of age in Canada with T2DM
- 2) To characterize the clinical risk features at diagnosis of diabetes associated with persistent microalbuminuria or macroalbuminuria in children less than 18 years of age in Canada with T2DM.
- 3) To determine clinical features that distinguish diabetic and non-diabetic renal disease in children less than 18 years of age in Canada with T2DM.

Case definition

Report any patient less than 18 years of age with type 2 diabetes mellitus (T2DM)

and

persistent microalbuminuria or macroalbuminuria, defined as two out of three positive samples at least one month apart over a three- to six-month period.

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 oral glucose tolerance test.

* Requires a second, confirmatory test if child is asymptomatic.

Diagnosis of T2DM will be based on the following clinical features:

- Obesity (body mass index $>95^{\text{th}}$ percentile for age and gender)
- Family history of T2DM in 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)
- Evidence of insulin resistance: acanthosis nigricans, polycystic ovarian syndrome, hypertension, dyslipidemia
- Absence of diabetes-associated autoantibodies when available

Definition of albuminuria

	Urine albumin to creatinine ratio (ACR)*	24-h urine collection for albumin
Microalbuminuria	2.0-20.0 mg/mmol (male) 2.8-28.0 mg/mmol (female)	30-300 mg/day (male or female)
Macroalbuminuria	>20.0 mg/mmol (male) >28.0 mg/mmol (female)	>300 mg/day (male or female)

* Confirmation with either first morning urine sample or overnight urine collection.

Inclusion criteria

Children less than 18 years of age with T2DM and **persistent** albuminuria (including those with renal disease confirmed prior to diagnosis of diabetes).



Duration

April 2010 to March 2012

Expected number of cases

The expected number of cases is approximately 16-20 per year.

Ethical approval

Research Ethics Board, Children's Hospital of Eastern Ontario, University of Ottawa
Research Ethics Board, University of Manitoba

Analysis and publication

Prevalence will be calculated and description of the demographic and clinical features will be done using descriptive statistics. Annual study results will be published by the CPSP and circulated to all participants. Results will also be presented in the form of a scientific abstract at national and international paediatric and/or diabetes meetings and submitted for publication in a peer reviewed paediatric and/or diabetes journal. The results will be shared widely in Canada with colleagues in provincial and federal governments and Aboriginal agencies.

Bibliography

- Amed S, Dean HJ, Panagiotopoulos C, Sellers EA, Hadjiyanakis S, Laubscher TA, Dannenbaum D, Shah BR, Booth GL, Hamilton JK. Type 2 diabetes, medication-induced diabetes and monogenic diabetes in Canadian children: a prospective national surveillance study. *Diabetes Care* (published online before print January 12, 2010, doi: 10.2337/dc09-1013)
- American Diabetes Association. Diabetic nephropathy. *Diabetes Care* 2002;25(Suppl 1):S85-9
- Dean H, Flett B. Natural history of type 2 diabetes diagnosed in childhood: long term follow-up in young adult years. *Diabetes* 2002;51(Suppl 2):A24
- Eppens MC, Craig ME, Cusumano J, et al. Prevalence of diabetes complications in adolescents with type 2 compared with type 1 diabetes. *Diabetes Care* 2006;29(6):1300-6
- Fagot-Campagna A, Pettitt DJ, Engelgau MM, et al. Type 2 diabetes among North American children and adolescents: an epidemiologic review and a public health perspective. *J Pediatr* 2000;136(5):664-72
- Maahs DM, Snively BM, Bell RA, et al. Higher prevalence of elevated albumin excretion in youth with type 2 than type 1 diabetes: the SEARCH for Diabetes in Youth study. *Diabetes Care* 2007;30(10):2593-8
- Pavkov ME, Bennett PH, Knowler WC, Krakoff J, Sievers ML, Nelson RG. Effect of youth-onset type 2 diabetes mellitus on incidence of end-stage renal disease and mortality in young and middle-aged Pima Indians. *JAMA* 2006;296(4):421-6
- Remuzzi G, Schieppati A, Ruggenenti P. Clinical practice. Nephropathy in patients with type 2 diabetes. *N Engl J Med* 2002;346(15):1145-51
- West NA, Hamman RF, Mayer-Davis EJ, et al. Cardiovascular risk factors among youth with and without type 2 diabetes: differences and possible mechanisms. *Diabetes Care* 2009; 32(1):175-80