Persistent Albuminuria in Children with Type 2 Diabetes: A Canadian Paediatric Surveillance Program Study

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Objective To determine the prevalence and the clinical features associated with persistent albuminuria in Canadian children aged <18 years with type 2 diabetes.

Study design This national prospective surveillance study involved a network of pediatricians and pediatric endocrinologists. Cases of persistent albuminuria in children with type 2 diabetes were reported during a 24-month period from 2010 to 2012. Persistent albuminuria was defined as an elevated albumin-to-creatinine ratio in a minimum of 2 out of 3 urine samples obtained at least 1 month apart over 3-6 months and confirmed with a first morning sample. Descriptive statistics were used to illustrate demographic and clinical features of the population. The prevalence of persistent albumuria was estimated using data from a previous national surveillence study of type 2 diabetes in children.

Results Fifty cases were reported over the 24-month study period. The estimated prevalence of persistent albuminuria in children with type 2 diabetes in Canada was 5.1%. The median duration of diabetes at the time of diagnosis of albuminuria was 21 days (IQR, 0-241 days). Almost two-thirds (64%) were female, 80% were of Canadian First Nations heritage, and 76% were from Manitoba. Exposure to gestational or pregestational diabetes in utero occurred in 65%, and 48% had a family history of diabetes-related renal disease. Structural anomalies of the kidney were found in 37%.

Conclusion Persistent albuminuria occurs in youths with type 2 diabetes in the first year after diagnosis, demonstrates regional variation, and is associated with First Nations heritage and exposure to maternal diabetes during pregnancy. *(J Pediatr 2016;168:112-7)*.

The prevalence of childhood-onset type 2 diabetes is increasing worldwide.[1] In Canada, a recent Canadian Paediatric Surveillance Program (CPSP) study revealed a minimum annual incidence of type 2 diabetes mellitus of 1.55 per 100 000 children aged <18 years, with a sensitivity analysis suggesting a conservative incidence of 11.3 cases per 100 000 children per year.[2] Diabetic nephropathy is the leading cause of end-stage renal disease (ESRD) in adults.[3] The first sign of diabetic nephropathy is persistent microalbuminuria.[3] In adults, improved glycemic control and blood pressure control slows the rate of progression to ESRD.[3] Thus, it is imperative to identify albuminuria early in its course.

Evidence suggests that complications occur at an earlier age with a shorter duration of diabetes in childhood-onset type 2 diabetes.[4] Childhood-onset type 2 diabetes is associated with an increased incidence of ESRD and mortality in middle age in the Pima Indians of the southwestern US.[5] ESRD has been reported before age 30 years in Canadian First Nations young adults who had type 2 diabetes diagnosed in adolescence.[6] A study from the province of Manitoba demonstrated rates of ESRD in childhood-onset type 2 diabetes of 8% at 10-year follow-up and 45% at 20-year follow-up, which compare unfavorably with rates of 0.5% at 10 years and 2.4% at 20 years in childhood-onset type 1 diabetes.[7]

Little is known about the natural history of albuminuria in children with type 2 diabetes. Orthostatic proteinuria is common in adolescents, and thus first morning or overnight urine collections are required in this population.[8] Microalbuminuria was present at the diagnosis of type 2 diabetes in 22% of Pima Indian children,[9] 14% of young Maori,[10] and 7% of Australian children.[11] In the CPSP study of non–type 1 diabetes, 14% of the children with type 2 diabetes had microalbuminuria or macroalbuminuria at the time of diagnosis.[2] Similarly, in the SEARCH for Diabetes in Youth study, 22.2% of participants had albuminuria on a single first morning or overnight urine sample, but persistence was not demonstrated.[12] In the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY)

ACR	Albumin-to-creatinine ratio
CPSP	Canadian Paediatric Surveillance Program
ESRD	End-stage renal disease
HbA1c	Hemoglobin A1c
TODAY	Treatment Options for Type 2 Diabetes in Adolescents and Youth

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study, 6.3% of participants had albuminuria at study initiation on a random urine sample.[13] In Manitoba, we reported persistent macroalbuminuria in 14 of 90 children (16%) with type 2 diabetes. Of these 14 youth, macroalbuminuria resolved spontaneously in 1, and orthostatic albuminuria was confirmed in 3. The remaining 10 underwent renal biopsy, which demonstrated nondiabetic primary renal disease in 9, with coexisting diabetic changes in 2.[14] Of these, 3 had IgA nephropathy, 2 had changes consistent with lupus (both confirmed clinically), and 7 had secondary focal segmental glomerulosclereosis. Nine of 10 individuals were either overweight or obese. These findings suggest that albuminuria in youths with type 2 diabetes may be multifactorial, involving both diabetes-related and non–diabetes-related factors.

These reports raise concerns about the rates of albuminuria and renal disease in children with type 2 diabetes with the potential for progression to ESRD in early adult life. Consequently, we conducted a prospective, national surveillance study in Canadian children with type 2 diabetes to determine the prevalence of persistent albuminuria and the clinical features associated with persistent albuminuria in children with type 2 diabetes.

Methods

The CPSP is a partnership between the Canadian Paediatric Society and the Public Health Agency of Canada and has been successfully collecting data on rare disorders since 1996. We undertook a 2-year national surveillance initiative designed to estimate the prevalence and clinical features of persistent microalbuminuria and macroalbuminuria in Canadian children aged <18 years with type 2 diabetes. The prevalence of coexisting risk factors for nondiabetic renal disease was also determined. Surveillance was conducted through the CPSP, a network of more than 2500 pediatricians and pediatric subspecialists across Canada. The CPSP supports the study of rare disorders in Canada associated with significant morbidity and mortality in children, as well as serious or rare complications of more common disorders.[15] The Health Research Ethics Board of the Faculty of Medicine, University of Manitoba approved the study.

Participants were surveyed for 24 months between April 1, 2010, and March 30, 2012. An introductory protocol that included the case definition was mailed to all physicians. A monthly reporting form that required a "yes" or "no" answer to identification of a case of persistent albuminuria in a child with type 2 diabetes was sent out by mail or electronically. A detailed questionnaire was subsequently sent by mail to any physician reporting a case. Duplicate reports were identified in the follow-up period. Quarterly reminders were sent to physicians who had not responded for all 12 months of the year. Completed questionnaires were reviewed independently by 2 investigators to confirm that case definitions for both type 2 diabetes and persistent albuminuria were met.

Microalbuminuria was defined as a urine albumin-to-creatinine ratio (ACR) >2.0 mg/mmol in males and >2.8 mg/mmol in females. Macroalbuminuria was defined as a urine ACR >20 mg/mmol in males, 28 mg/mmol in females, or quantitatively as >300 mg albumin/24 hours. Persistent albuminuria was defined as 2 of 3 positive samples obtained at least 1 month apart over at least a 6-month period. Albuminuria had to be confirmed with either a first morning urine sample or overnight urine collection.[16]

The diagnosis of diabetes was made according to the criteria of the Canadian Diabetes Association.[17] The classification of type 2 diabetes was supported by clinical criteria, including the presence of obesity, other evidence of insulin resistance (eg, acanthosis nigricans, hypertension, nonalcoholic fatty liver disease, dyslipidemia, polycystic ovarian syndrome in females), family history of type 2 diabetes, intrauterine exposure to hyperglycemia, family heritage from a high-risk ethnic group, or use of an atypical antipsychotic.[17] When available, the absence of diabetes-associated autoantibodies was used to support the diagnosis of type 2 diabetes.[18] Children with known nondiabetic primary renal disease and type 2 diabetes were included (including those diagnosed before the diagnosis of diabetes). Children with other forms of diabetes were excluded, as were children receiving medications associated with hyperglycemia or nephrotoxicity.

Hypertension was defined as blood pressure >95th percentile for age, sex, and height percentile.[19] Nonalcoholic fatty liver disease was defined as alanine aminotransferase level more than 3 times the upper limit of normal.

Statistical Analyses

Descriptive statistics were used to describe the demographic and clinical features of youths with type 2 diabetes and persistent albuminuria. To generate an estimate of the prevalence of persistent albuminuria in youths with type 2 diabetes, the number of children aged <18 years with type 2 diabetes was estimated based on a previous CPSP conducted in 2006-2008.[2] Using the minimum incidence data reported in that surveillance study, an estimated 976 Canadian children aged <18 years had type 2 diabetes during the study period.

Results

A total of 62 cases of persistent albuminuria were reported during the 2-year study period. Of these, 3 were duplicate reports, and 9 were excluded because they did not meet the case definition. In all 9 excluded reports, albuminuria was detected by random ACR, but the reporting physicians were unable to obtain a first morning or overnight urine sample to rule out orthostatic albuminuria. Thus, 50 confirmed cases of persistent albuminuria in youths with type 2 diabetes were reported.

Almost two-thirds (64%) of the 50 confirmed cases were in females. The mean age at diagnosis of diabetes was 12.3 ± 2.1 years (range, 6.8-16.8 years). In 4 cases, the diagnosis of albuminuria preceded the diagnosis of diabetes. After excluding those 4 cases, the median duration of diabetes at diagnosis of albuminuria was 21 days (IQR, 0-241 days).