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Kidney disease in children with type 2 diabetes

RESOURCES

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What is the prevalence and natural history of type 2 diabetes in children?

The prevalence of childhood-onset type 2 diabetes mellitus (T2DM) is increasing worldwide, paralleling that of overweight and obesity.[1] A recent Canadian Paediatric Surveillance Program (CPSP) study revealed a *minimum* incidence of T2DM in children under age 18 years in Canada 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.[2] In this study, 95% of children with T2DM were obese and 37% had at least one co-morbidity at diagnosis.[2] Children 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 children with type 1 diabetes of a similar age.[3-5]

The natural history and true burden of T2DM diagnosed in childhood are still largely unknown. However, current evidence suggests that complications may occur at an earlier age with a shorter duration of diabetes in childhood-onset T2DM compared to adult-onset disease.[3]

Is the risk for diabetic nephropathy similar for everyone?

Diabetic nephropathy is one of the most common complications of diabetes and is the leading cause of end-stage renal failure (ESRF) in adults.[6] People with diabetes of Native American, Canadian First Nations, Hispanic and African American heritage are at higher risk for the development of diabetic nephropathy.[6] In Canada, First Nations adults with diabetes are seven times more likely to develop diabetic ESRF than non-First Nations Canadian adults with diabetes.[7] The first sign of diabetic nephropathy is microalbuminuria, which may progress to macroalbuminuria and ultimately ESRF requiring renal replacement therapy.[6] Albuminuria is also a marker of significant increased cardiovascular morbidity and mortality for individuals with diabetes.[6] It is imperative to identify albuminuria early as progression can be prevented or delayed, with early interventions having the greatest impact.[8-10]

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Is albuminuria in children with T2DM associated with a different prognosis?

The natural history of albuminuria in children with T2DM is not well understood. In the recent CPSP non-type 1 diabetes mellitus study, 14 % of the children with T2DM had micro or macroalbuminuria at diagnosis.[2] Data on the persistence of the reported albuminuria is not available from this study. In the Pima Indians of the southwestern US, childhood-onset T2DM is associated with an increased incidence ESRF and mortality in middle age compared to those diagnosed in adulthood.[11] In a report from Manitoba, persistent macroalbuminuria was seen in 14/90 (16%) youth with T2DM within eight years of diagnosis of diabetes.[12] In some, albuminuria was present at diagnosis. ESRF has been reported before the age of 30 years in Canadian First Nations young adults who had T2DM diagnosed in childhood.[13] The associated clinical risk factors for albuminuria in this population have not been well described. While our understanding of albuminuria in childhood-onset T2DM is still evolving, these reports raise concern about the potential for ESRF in early adult years in this population.

Can other diseases cause albuminuria in children with youth-onset T2DM?

A complicating factor in assessing kidney disease in youth with T2DM is that many of the population groups at highest risk for childhood-onset T2DM are also at increased risk for non-diabetic congenital or acquired renal disease.[14,15] This includes children of Canadian First Nations heritage.[14] The relative contribution of non-diabetic renal disease to the development of albuminuria in children with T2DM is not fully understood. In a recent report of Canadian First Nations youth with T2DM, biopsy results of 10 individuals with macroalbuminuria revealed immune complex disease or glomerulosclerosis in nine, mild diabetes-related lesions in two, and focal segmental glomerulosclerosis (an obesity-related comorbidity) in seven.[12] The clinical features associated with albuminuria that distinguish diabetic from non-diabetic renal disease are not known.

What is the best screening test for persistent albuminuria?

Screening for renal disease in children with T2DM should begin at diagnosis and annually thereafter.[16] The recommended screening test is a first-morning or random urine for albumin to creatinine ratio. Careful laboratory documentation of persistent albuminuria is critical as transient albuminuria can be caused by a febrile illness, acute hyperglycemia, exercise, urinary tract infection, menstruation, heart failure and hypertension. In addition, benign orthostatic proteinuria is common in adolescents.[16] It is therefore important to demonstrate persistent albuminuria over a three- to six-month period. Persistent albuminuria is defined as an elevated urine albumin to creatinine ratio in two of three urine samples taken over three to six months. Given the high prevalence of orthostatic proteinuria in youth, a first-morning sample and/or overnight timed collection should be done to confirm the presence of albuminuria.

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Microalbuminuria

- Defined as urine albumin/creatinine ratio (ACR) 2.0–20.0 mg/mmol (male) or 2.8–28.0 mg/mmol (female).
- Persistent defined as two out of three positive samples over a three- to six-month period.
- Samples should be at least one month apart.
- Must be confirmed with either a first-morning urine sample or overnight timed urine collection for ACR.

Macroalbuminuria

- Defined as urine ACR >20.0 mg/mmol (male) or 28.0 mg/mmol (female).
- Persistent defined as two out of three positive samples over a three- to six-month period.
- Samples should be at least one month apart.
- Confirmation with either first-morning urine sample or overnight timed urine collection for ACR.

Why is it important to make the diagnosis of persistent albuminuria in youth with T2DM?

The earlier age of diagnosis of T2DM raises concern regarding the resulting burden of disease, as these children may begin to develop 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. In addition, persistent albuminuria in a child with T2DM should not be presumed to be related to diabetic nephropathy. Renal biopsy may be necessary to determine the underlying cause(s) in order that therapy be appropriately directed.

Why is surveillance for persistent albuminuria in children with T2DM necessary/important?

At present, the prevalence of persistent albuminuria, an early marker of renal disease, in children with T2DM is unknown. This information is necessary to define the spectrum and extent of the problem and is important for predicting burden of illness, and for planning screening and intervention programs.

RESOURCES

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Quiz

1. **Transient causes of albuminuria include:**

   a) Exercise
   b) Fever
   c) Menstruation
   d) Urinary tract infection
   e) All of the above

2. **How can you distinguish between orthostatic proteinuria and albuminuria that suggests pathology?**

   a) First-morning urine albumin/creatinine ratio (ACR)
   b) Serum creatinine
   c) Timed overnight urine collection
   d) All of the above
   e) a + c

3. **When do you begin screening for diabetic nephropathy in youth with type 2 diabetes (T2DM)?**

   a) Five years after diagnosis
   b) Age 12 years and five years after diagnosis
   c) At diagnosis
   d) Age 17 years
   e) One year after diagnosis

4. **A random urine ACR is found to be elevated in a patient with T2DM. What do you do next?**

   a) Repeat first-morning urine ACR one week later
   b) Repeat first-morning urine at least one month later
   c) 24-hour timed urine collection for albumin excretion rate
   d) Overnight timed urine collection
   e) None of the above

5. **Persistent albuminuria is defined as:**

   a) Two out of three positive samples in a one-month period
   b) Three out of five positive samples in a six-month period
   c) Two out of three positive samples in a three- to six-month period
   d) Confirmation with a first-morning urine sample or overnight timed urine collection
   e) c + d

Answers: 1-e, 2-e, 3-c, 4-b, 5-e