Type 2 diabetes in children and adolescents

Regular exercise, a healthy diet, and glycemic control are key to managing this complex metabolic disorder.

ABSTRACT: Type 2 diabetes mellitus is characterized by hyperglycemia secondary to insulin resistance as well as by impaired insulin secretion. Obesity is a major modifiable risk factor for type 2 diabetes and exacerbates insulin resistance. Given the current obesity epidemic, the incidence of type 2 diabetes is rising rapidly in young people and parallels the increasing frequency of the disease observed in the adult population. Treatment is dependent on mode of presentation, with initiation of insulin for metabolic decompensation. The mainstay of therapy is lifestyle modification focusing on healthy eating and regular physical activity. Implementation of such measures can be extremely challenging and should involve the entire family. Pharmacological agents such as metformin are often necessary for optimal glycemic control. Given that youth with type 2 diabetes have been found to develop earlier and more aggressive microvascular complications, yearly screening for retinopathy and nephropathy should begin at diagnosis.

Type 2 diabetes mellitus (T2D) in children and adolescents is a growing public health concern and reflects the increasing rates of obesity in our society. Reports from various centres in the United States suggest a ten- to thirtyfold increase in the number of children with T2D over the past 15 years. These studies focused primarily on children from ethnic groups at high risk for T2D, including children of African, Asian, Hispanic, Pacific Island, and American Indian heritage. However, there are currently no epidemiological data for Canadian children belonging to most of these ethnic groups, with the exception of First Nations children. The prevalence of T2D in Canadian aboriginal children and youth has been documented to be as high as 1%, with the highest prevalence in the Plains Cree people of Central Canada.

The Endocrinology and Diabetes Unit at BC’s Children’s Hospital currently follows over 100 children and youth with impaired glucose tolerance (IGT) and T2D; by contrast, in 1991 there were fewer than 5 patients with these conditions (C.P., unpublished data, 2004). This observation is consistent with reports in the literature that the proportion of children and adolescents newly diagnosed with T2D has increased from 9% to a maximum of 33% of diabetics. Given that 50% of children with T2D may be totally asymptomatic and are only diagnosed when screened for disorders related to obesity, health officials recognize that a large number of children and adolescents in the community may not yet be diagnosed. With increased screening, the number of youth with T2D and IGT is projected to grow exponentially.

Who should be tested?

The increase in type 2 diabetes among children appears to parallel the increase seen among adults in those ethnic populations that have the highest rates of disease. These high-risk ethnic populations include individuals of aboriginal, Hispanic, Asian/Pacific Island, and African descent. Other risk factors include overweight, a family history of T2D, intrauterine exposure to diabetes, acanthosis nigricans, hypertension, dyslipidemia, polycystic ovarian syndrome, and schizophrenia. The Canadian Diabetes Association’s recent recommendations suggest that screening for overweight children with at least two additional risk factors should be initiated at 10 years of age (or at the onset of...
puberty if puberty occurs at a younger age) by measuring fasting plasma glucose (see the [Table]). An oral glucose tolerance test ([OGTT] 1.75 g/kg, maximum 75 g) may also be used as a screening test for children and adolescents. The diagnostic criteria for diabetes in children are the same as for adults (fasting plasma glucose ≥7.0 mmol/L and/or a 2-hour post-OGTT plasma glucose ≥11.1 mmol/L).6

Pathophysiology

Type 2 diabetes is a complex metabolic disorder of heterogeneous etiology with environmental and behavioral risk factors unmasking the effects of genetic susceptibility.7 Hyperglycemia results from a combination of insulin resistance and increased hepatic glucose output, as well as a progressive decline in glucose-stimulated insulin secretion. In contrast with type 1 diabetes, in which there is an absolute deficiency of insulin secretion secondary to autoimmune destruction of pancreatic beta cells, type 2 diabetes involves some insulin secretory capacity but at levels inadequate to overcome the concomitant insulin resistance, leading to hyperglycemia. Although debate continues over whether insulin resistance or an insulin secretory deficiency is the primary defect in T2D, current evidence suggests that the initial abnormality is impaired insulin action (insulin resistance), compounded later by beta cell failure.7,9

Although insulin resistance appears to have a strong hereditary component, it is unlikely that the gene pool has changed sufficiently to account for the increasing rates of disease. Environmental factors, including obesity and physical inactivity, worsen insulin resistance, while weight loss and physical activity improve insulin sensitivity. Girls have been shown to be more insulin resistant than boys when data are controlled for body mass index (BMI).

Puberty also appears to play a major role in the development of T2D in children.7,9 During puberty, the insulin sensitivity of adolescents is, in general, approximately 30% lower than that of either preadolescents or adults, resulting in compensatory hyperinsulinemia in the presence of normal beta cell function. However, in those adolescents with a genetic predisposition for insulin resistance that is compounded by environmental risk factors, the additional insulin resistance from puberty may tip the balance from compensated hyperinsulinemia with normal glucose tolerance to inadequate insulin secretion with glucose intolerance. The hyperglycemia that ensues may then further induce abnormalities of insulin secretion and action, creating a vicious cycle allowing for the phenotypic expression of T2D that will then continue beyond puberty. This “glucose toxicity” (hyperglycemia begets more hyperglycemia)7 can be improved by correction of hyperglycemia.

| Table. Screening children and adolescents for type 2 diabetes. |
|-----------------------------|-------------------|
| **Age of initiation**       | ≥10 years of age or younger if puberty occurs at a younger age |
| **Risk factors**            | Overweight (BMI ≥85th percentile for age and sex, weight for height ≥85th percentile, or weight >120% of ideal for height) plus any two of the following risk factors: |
|                             | • Member of a high-risk ethnic group (aboriginal, Hispanic, Asian/Pacific Islander, or African) |
|                             | • Family history of type 2 diabetes (first- or second-degree relative with diabetes) |
|                             | • Intrauterine exposure to type 2 diabetes |
|                             | • Acanthosis nigricans |
|                             | • Polycystic ovarian syndrome |
|                             | • Hypertension |
|                             | • Dyslipidemia |
|                             | • Schizophrenia |

**Laboratory methods**

- Fasting plasma glucose preferred
- Oral glucose tolerance may also be used

**Frequency of screening**

- Every 2 years

*Based on American Diabetes Association7 and Canadian Diabetes Association6 Guidelines

Classification and diagnosis

In most children, the mode of presentation, clinical features, and subsequent course of the disease assist in classifying the type of diabetes.7,9,10 Type 2 diabetes usually has a more indolent presentation than type 1 diabetes. The classic symptoms of polyuria, polydipsia, and polyphagia may not be present. Some patients may be found to have glycosuria on routine urinalysis, while others may be completely asymptomatic and may be diagnosed because of screening based on risk factors. Acute metabolic decompensation in the form of diabetic ketoacidosis can occur but is rare. However, approximately 25% of patients presenting with T2D have ketonuria at diagnosis.

Approximately 95% of children with T2D are overweight at diagnosis, and many have a family history of T2D.7 Signs of insulin resistance or conditions associated with the metabolic syndrome and insulin resistance, including acanthosis nigricans, polycystic ovarian syndrome, dysli-
Type 2 diabetes in children and adolescents

demia (high LDL, elevated triglycerides, low HDL), and hypertension, may help in classification. Laboratory evaluation for the presence of autoantibodies to islet cells, glutamic acid decarboxylase (GAD), and insulin may be helpful, as patients with T2D should have no evidence of beta cell destruction. Fasting insulin and C-peptide levels, although expected to be normal or elevated, may be low at diagnosis because many patients present at a time of relative insulin deficiency. Finally, the clinical course of the patient after diagnosis may provide clues to the correct type of diabetes. Although patients with T2D may initially require insulin to correct hyperglycemia and to overcome glucose toxicity, most can achieve continued euglycemia with oral medications and lifestyle modification.

In families with a history of two, or preferably three, generations exhibiting early-onset hyperglycemia (<25 years of age) with good metabolic control on a low insulin dose, the clinician should consider the possibility of a genetic defect of beta cell function. In the past, the diagnosis of maturity-onset diabetes in the young (MODY) had been incorrectly thought to be synonymous with T2D. However, this form of diabetes is distinct from T2D and is characterized by a monogenic, autosomal-dominant mode of inheritance resulting in impaired insulin secretion with absence of severe ketosis. Several different gene mutations have been identified in patients with MODY, and management depends on the underlying genetic disorder. Commonly, children with MODY can initially be managed with lifestyle intervention or a sulfonylurea (depending on the specific gene defect), but many will require insulin treatment after several years. Currently, genetic testing can be performed only in research laboratories and requires blood samples from three generations.

**Treatment guidelines**

Guidelines for treatment of children and adolescents with type 2 diabetes have been extrapolated from adult studies. The United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that intensive treatment of adults with T2D results in improved metabolic control and decreased risk of microvascular complications. These children and their parents require education about this form of diabetes and its risks, and they must be taught the tools of diabetes management, including home blood glucose monitoring at least twice per day (before breakfast and 2 hours after dinner) and four times per day if insulin is being administered.

The cornerstone of therapy is lifestyle modification. Youth and their family members should be counseled to avoid smoking and, if necessary, provided with assistance for smoking cessation. Dietary changes and increased physical activity should be encouraged, while recognizing that implementation of such measures is extremely challenging and requires involvement of the entire family.

**Diet**

Dietary modifications are most effective when kept simple. We recommend, as a starting point, that patients switch from regular to diet pop, eliminate all juices, drink water when thirsty, and switch from whole milk to skim or 1%. We also suggest replacing “junk food” with healthful low-fat snacks and reviewing Canada’s Food Guide to Healthy Eating. Families

---

*Although patients with T2D may initially require insulin to correct hyperglycemia and to overcome glucose toxicity, most can achieve continued euglycemia with oral medications and lifestyle modification.*
Type 2 diabetes in children and adolescents

**Figure.** Treatment algorithm for children and adolescents diagnosed with type 2 diabetes.

**Diagnosis of type 2 diabetes**

**Metabolic decompensation?**

- **Yes**
  - FPG ≥15 mmol/L
  - Diabetic ketoacidosis
  - A1c ≥9%
  - Insulin + diet and exercise
  - Start metformin and attempt to wean patient off insulin after 3 – 6 months
  - Clinic visit every 3 months with A1c

- **Partial**
  - Mild symptoms: polyuria, polydipsia but no ketosis
  - 7% < A1c < 9%
  - Metformin + diet and exercise

- **No**
  - Asymptomatic
  - A1c ≤7%
  - Diet and exercise

- **A1c >7%**
  - Add sulfonylurea

**A1c >7%**

**A1c = glycosylated hemoglobin (HbA1c)**

**FPG = fasting plasma glucose**
should be given recommendations on appropriate portion sizes for the child’s age and every child should be encouraged to consume five to 10 servings of fruits and vegetables daily. Individualized meal plans should be reviewed at regular intervals (approximately every 3 months) by the diabetes dietician to ensure that the nutritional needs of the growing child are being met. Low-carbohydrate diets are not recommended.

Exercise
Exercise must be incorporated into the patient’s and family’s routine. Physical activity does not need to involve organized sports but can instead include walking to and from school, bicycling, performing household chores, and using the stairs instead of the elevator. We recommend that patients exercise for at least 30 minutes per day and that all family members adopt the same healthy eating patterns and exercise routines, whether they exercise together or individually. We recommend providing all families with Canada’s Physical Activity Guide for Children or Canada’s Physical Activity Guide for Youth, as appropriate, which suggests monthly milestones for gradually increasing the amount of physical activity over 5 months. All families should be encouraged to decrease inactive time (e.g., time spent playing video games or watching television) by 15 to 30 minutes per month, and to replace this with time spent in some form of moderate physical activity.

Pharmacotherapy
The majority of children will require medication to treat type 2 diabetes. In a placebo-controlled study of 82 children, only 8% met blood glucose goals with diet and exercise at 16 weeks. This finding is consistent with the finding in the UKPDS that only 3% of adults were able to achieve glycemic targets with lifestyle modification alone. Patients who have not achieved glycemic targets (HbA1c ≤7%) or whose blood glucose values have not improved after 3 months of lifestyle intervention should be prescribed an oral agent such as metformin. Metformin is the only oral agent that has been studied in children with T2D in a randomized controlled trial. Metformin improves glycemic control without increasing insulin secretion; it does this by reducing hepatic glucose production, increasing insulin sensitivity, and reducing intestinal glucose absorption. Hypoglycemia is not a side effect of this medication when taken alone. Jones and colleagues demonstrated that metformin (1000 mg b.i.d.) significantly improved glycemic control over a 16-week period in pediatric patients without a negative impact on body weight or lipids. Adverse effects, namely gastrointestinal upset, were similar to those reported in adults. The major risk associated with metformin is the potential for lactic acidosis, meaning this medication should be avoided in children with evidence of renal impairment, hepatic disease, or cardiac or respiratory insufficiency. As well, metformin should be stopped 24 hours before administration of radiographic contrast materials and for 48 hours afterwards. Youth should also be counseled about the interaction between alcohol and metformin. Specifically, alcohol is known to potentiate the effect of metformin on lactate metabolism, and could potentiate hypoglycemia.

If monotherapy with metformin is not successful after a trial of 3 to 6 months, a sulfonylurea may be added to the regimen. Currently, randomized controlled trials are underway to assess the newer thiazolidinediones, but until more is known about these agents their use in children should be limited. Finally, insulin may be added if treatment goals are not achieved using oral agents.

Insulin is also recommended as first-line therapy in those patients with severe metabolic decompensation at diagnosis, including diabetic ketoacidosis, high glycosylated hemoglobin levels (A1c ≥9%), or severe hyperglycemia (fasting blood glucose ≥15 mmol/L). Following improved metabolic control, metformin can be initiated and the patient can often be weaned from insulin after 3 to 6 months.

A treatment algorithm for children and adolescents newly diagnosed with T2D is provided here (see the Figure).

Complications and co-morbidities
Given the evidence that type 2 diabetes in youth is associated with early and severe microvascular complications, screening for retinopathy and nephropathy is recommended at diagnosis. For retinopathy, a dilated eye examination should be performed every 1 to 2 years after baseline assessment. For nephropathy, screening for microalbuminuria should occur yearly.

Monitoring for co-morbid features of the metabolic syndrome—including hypertension and hyperlipidemia—should also occur at diagnosis. Although there is no evidence to recommend specific interventions for dyslipidemia or hypertension in children or youth with T2D, these co-morbid conditions should be treated judiciously on a case-by-case basis with consideration of adult guidelines until further research data in the pediatric population is available.

Conclusions
Type 2 diabetes in children and adolescents is a growing public health
concern related to the increasing rates of obesity in our society. Current treatment guidelines are based primarily on adult studies. It is essential that controlled clinical trials of oral hypoglycemic agents be performed to assess the safety and efficacy of these agents for children and youth. Longitudinal studies will also increase our understanding of the natural history of T2D in children. Community- and school-based programs aimed at educating parents and children about the need for healthy eating and regular physical activity are critical for the primary prevention of T2D and its associated morbidities.

Competing interests
None declared.

References