Endocrinology Rounds™

November 2003
Volume 3, Issue 9

As presented in the Rounds of the Division of Endocrinology and Metabolism, St. Michael's Hospital

www.endocrinologyrounds.ca

Type 2 Diabetes Mellitus in Youth: An emerging epidemic

By Amish Parikh, MD

Type 2 diabetes mellitus (DM) is now a worldwide epidemic. As a consequence, its prevention is one of the most important contemporary public health concerns. It is estimated that, worldwide, 225 million cases of Type 2 DM will be diagnosed by the end of the present decade and as many as 300 million cases by the year 2025.[1,2] This is double the current worldwide prevalence, which is estimated to be 150 million. The major part of this increase will occur in developing countries. Several factors are thought to account for this steep rise, but one of the most important is the marked rise in obesity. Obesity increases insulin resistance, which is the hallmark of Type 2 DM. Type 2 DM, via chronic hyperglycemia, exerts its deleterious effects through the development of both microvascular and macrovascular long-term complications that lead to substantial morbidity, mortality, and healthcare expenditures. Type 2 DM was traditionally considered to be an adult disease. However, an alarming trend in the growing epidemic of Type 2 DM is the number of new cases being diagnosed in children and in youth. Many argue that this rise can be explained by the growing prevalence of obesity amongst children and adolescents. This issue of *Endocrinology Rounds* reviews the epidemiology, screening, diagnosis, and treatment of Type 2 DM in youth.

Epidemiology

Obesity is the single most prevalent nutritional disease affecting children and adolescents in the United States.[3] It has significant negative psychosocial and disease-related consequences. Recent estimates (1999-2000) from the United States National Health and Nutrition Examination Study reveal that 15.5% of adolescents aged 12-19 years have a body mass index (BMI) above the 95th percentile for age and gender. Furthermore, 15.3% of 6-11-year-olds and 10.4% of 2-5-year-olds also have a BMI above the 95th percentile.[4] These values all represent a marked increase in the prevalence of obesity as compared to the previous decade. Canadian statistics indicate that the prevalence of obesity (body weight > 95th percentile) in Canadian children aged 7 to 13 more than doubled between 1981 and 1996, from 5% to 13.5% for boys and 11.8% for girls.[5] The prevalence of being overweight (>85th percentile) among boys increased from 15% to 28.8% and among girls from 15% to 23.6% during this same time interval.

Although obesity crosses all ethnic backgrounds, Strauss identified certain racial groups that are particularly affected, namely Hispanic and African-American populations.[6] Children from these racial backgrounds have also been found to be more insulin-resistant than Caucasian children.[7] In addition, the fact that Native American adolescents, specifically Pima Indians, have a high prevalence of Type 2 DM has been known for several decades.[8] Approximately 50% of Pima Indian adults >35 years have Type 2 DM and in Pima Indian youth, the prevalence has been increasing steadily over the past 3 decades.[9] Type 2 DM is now a major public health problem amongst American Indian children and Alaska natives.[10] With respect to trends in increasing body weight over time, the Diabetes Incidence Study

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Endocrinology Rounds is made possible by an unrestricted educational grant.

Table 1: Testing for Type 2 diabetes in children

Criteria*

Overweight (BMI >85th percentile for age and sex, weight for height >85th percentile, or weight >120% of ideal for height)

Plus

Any 2 of the following risk factors:

– Family history of type 2 diabetes in first- or second-degree relative
– Race/ethnicity (American Indian, African-American, Hispanic, Asian/Pacific Islander)
– Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)

Age of initiation: age 10 years or at onset of puberty if puberty occurs at a younger age

Frequency of screening: every 2 years

Test: fasting plasma glucose preferred

* Clinical judgment should be used to test for diabetes in high-risk patients who do not meet these criteria.

Table 2: Diagnosis of diabetes mellitus

A confirmatory test must be done on another day in all cases *in the absence of unequivocal hyperglycemia accompanied by acute metabolic decompensation.* This must be based on laboratory measurements of venous plasma glucose.

- Symptoms of diabetes plus a casual plasma glucose value ≥ 11.1 mmol/L*

OR

- A fasting plasma glucose (FPG) ≥ 7.0 mmol/L†

OR

- A plasma glucose value in the 2-h sample (2hPG) of the oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L

* The classic symptoms of diabetes include fatigue, polyuria, polydipsia and unexplained weight loss. Casual is defined as any time of the day, without regard to the interval, since the last meal.
† Fasting is defined as no caloric intake for at least 8 h.

in Sweden found that the BMI in young adults at the time of diagnosis increased substantially over the 17-year period from 1983-1999. This was true in both Type 1 and Type 2 DM.[11]

In some geographic regions, Type 2 DM is surpassing Type 1 DM as the most common form of diabetes in children. Wei recently reported that in a mass screening program of almost 3 million children aged 6- to 18-years in Taiwan, 54.2% of new DM cases were Type 2 versus 9.5% for Type 1.[12] The rate of newly identified diabetes was approximately 12.0 per 100 000. In this study, girls had a higher risk of Type 2 DM compared to boys. In this cohort, it was also concluded that obesity, age, hypercholesterolemia, blood pressure >85th percentile, and a positive family history of diabetes were significantly associated with Type 2 DM.

In a review of medical records from 1999 to 2001, Moore and colleagues found that the incidence of Type 2 DM was approximately 4 times the incidence of Type 1 DM among American Indian youth in Montana and Wyoming.[13] A recent population-based study from the greater Cincinnati area found a 10-fold increase in the incidence of Type 2 DM in youth over a 13-year period from 1982-1995.[14] Of this adolescent cohort, a substantial proportion was obese (mean BMI = 37.7 kg/m^2) and 92% had a BMI > 90% percentile. The rise in Type 2 DM in youth is not a phenomenon isolated to North America. Several studies have noted a rise in the prevalence of Type 2 DM in youth around the world, including Japan, Libya, Bangladesh, Australia, and the United Kingdom.[15-17]

The interplay between genetic and environmental factors that contribute to the development of Type 2 DM in youth is complex and not completely understood. In addition to obesity, other factors such as a sedentary lifestyle and a diet high in fat and low in fibre are related to an increased incidence of Type 2 DM in youth.[18]

Before the overt development of Type 2 DM, individuals often have a period of impaired glucose tolerance. Sinha studied 55 obese children (aged 4- to 10-years, mean BMI for males = 32 kg/m^2, females = 30 kg/m^2) and 112 obese adolescents (age 11- to 18-years, mean BMI for males = 37 kg/m^2, females = 34 kg/m^2) in a multi-ethnic cohort, and found that 25% of the children and 21% of the adolescents had impaired glucose tolerance.[19] Asymptomatic Type 2 DM was diagnosed in 4% of adolescents.

The exact prevalence and incidence of Type 2 DM is difficult to ascertain. One reason for this difficulty is the possibility that a substantial proportion of individuals with Type 2 DM may be misclassified, undiagnosed, or under-reported.[20]

Screening

In March 2000, the American Diabetes Association published guidelines and screening recommendations for Type 2 DM in children and adolescents (Table 1).[17] Screening with a fasting plasma glucose is recommended for individuals who are overweight and also have 2 of several risk factors.

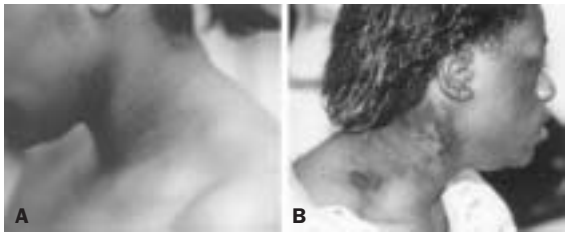
Diagnosis

The diagnostic criteria for diabetes are the same for children and youth as they are for adults, both in Type 1 and Type 2 DM (Table 2).[21]

The classic presentation of Type 1 DM is well-known to healthcare practitioners. These individuals are usually

Figure 1: Acanthosis nigricans. The skin is brown and thickened and has a papillomatous surface.[27]

Figure 2: Acanthosis nigricans[28]



A. Moderate acanthosis nigricans (darkening and thickening of skin) at the lateral lower fold of the neck.

B. Severe acanthosis nigricans in another patient with severe insulin resistance

not overweight and typically present with weight loss, polyuria, polydipsia, and up to 30%-40% may have ketoacidosis. Insulin is necessary for stabilization and for ongoing therapy.

The average age of onset of Type 2 DM in children is between 12 and 14 years, which coincides with the beginning of puberty. It is well-known that there is a relative degree of physiological insulin resistance at this stage of development.[22] Scott studied 50 youth with newly diagnosed Type 2 DM and 50 youth with newly diagnosed Type 1 DM in an attempt to delineate characteristics that would help to separate these 2 groups at the time of diagnosis.[23] Symptoms such as abdominal pain, headache, nocturia, polydipsia, polyphagia, polyuria, dizziness, and visual disturbances were reported in similar frequencies between the 2 groups. The only symptom found to be different was weight loss, which was more common in newly diagnosed youth with Type 1 DM. At all ages of presentation, the youth with newly diagnosed Type 2 DM were found to be obese. Furthermore, there was an upward trend in BMI in this study as the age of diagnosis increased. Hypertension and acanthosis nigricans were found in a substantially greater proportion of youth with newly diagnosed Type 2 DM. With respect to biochemical parameters, HbA_{1c} was similar in both groups. As would be expected, the Type 1 DM group had higher blood glucose values, lower insulin levels, lower C-peptide levels, and more urine ketones.

The presence of diabetic ketoacidosis (DKA) in youth does not necessarily imply a diagnosis of Type 1 DM. Several studies have reported that obese adolescents may initially present in ketoacidosis, even though the underlying diagnosis is ultimately Type 2, and not Type 1 DM.[24,25] These adolescents are often of African-American descent. Sellers studied 120 Canadian aboriginal youth with Type 2 DM and found that 4.2% had DKA at the time of diabetes diagnosis, but the overall incidence of DKA was 10.8% over the 14-year study period.[26] In some of these individuals, it is possible to withdraw insulin and treat with oral hypoglycemic agents after initially treating the DKA.

Clinically, there are several features that may suggest Type 2 DM. In addition to obesity, the cutaneous finding of acanthosis nigricans strongly suggests a diagnosis of Type 2 DM. Acanthosis nigricans can be described as velvety, dark, rough skin usually found on the back of the neck, but is also seen in the axillae, antecubical fossa, skin folds and thighs (Figure 1[27] and Figure 2[28]). It is characterized histologically by papillomatosis and hyperkeratosis. The thickness of the keratin-containing superficial epithelium gives skin the characteristic dark colour. The presence of acanthosis nigricans is associated with obesity, higher plasma insulin concentrations, and risk for the development of Type 2 DM. Acanthosis nigricans is also a clinical marker that is advocated as a surrogate for laboratory-determined hyperinsulinemia.[29] In a study of 675 New Mexico middle-school students, Mukhtar found that acanthosis nigricans and obesity were independently and positively associated with hyperinsulinemia and that acanthosis nigricans screening is an easily performed, noninvasive method for identifying adolescents at risk for Type 2 diabetes.[30]

Often, antibodies are used as a means of determining whether an individual has Type 1 versus Type 2 DM. In a study comparing 48 children and adolescents with Type 2 DM (mean age 14.05 years at diagnosis) versus 39 children with Type 1 DM (mean age 9.73 years at diagnosis), Hathout sought to determine if autoimmune characteristics (eg, islet cell antibodies [ICA], glutamic acid decarboxylase antibodies [GAD], insulin autoantibodies) could clearly separate the 2 groups at the time of diagnosis.[31] Thirty-three percent of the patients with Type 2 DM presented in diabetic ketoacidosis compared with 53.5% of patients with Type 1 DM (not statistically significant). The mean HbA_{1c} in both groups, the blood glucose at diagnosis, and C-peptide at diagnosis were not different

at the time of diagnosis. The incidence of diabetic antibody markers was significantly lower in the group with Type 2 DM:

- 8.1% had positive ICA
- 30.3% had positive GAD antibodies
- 34.8% had positive insulin autoantibodies.

In those with Type 1 DM, the incidence of diabetic markers was higher:

- 71.1% had positive ICA
- 75.7% had positive GAD antibodies
- 75.5% had positive insulin autoantibodies.

The conclusion of this study was that the absence of diabetes autoimmune markers is not a prerequisite for the diagnosis of Type 2 DM in children and adolescents.

Another interesting study examined a cohort of 97 young patients (aged 15-34 years) who were initially diagnosed with either Type 2 DM or an unclassifiable form of diabetes (the patients were not considered to have Type 1 DM at the time of diagnosis). Littorin et al examined the predictive value of ICA and GAD65 antibodies with respect to the need for insulin treatment 6 years after the initial diagnosis.[32] He found that the sensitivity for insulin treatment was highest (74%) in the presence of either ICA or GAD antibodies and the specificity was 100% for the combination of ICA and GAD antibodies. The positive predictive value for ICA alone was 98%; for GAD it was 95%; and for both it was 100%. They concluded that measurement of these antibodies at diagnosis could improve the classification of diabetes and predict the future need for insulin in young adults.

Treatment

The initial treatment for Type 2 DM in youth varies depending on the clinical presentation at the time of diagnosis. This can range anywhere from asymptomatic hyperglycemia to life-threatening ketoacidosis. Given that Type 2 DM in children is so strongly associated with obesity and sedentary lifestyle, interventions that target these 2 issues are first line approaches,[33] assuming that the patient is not acutely ill at the time of diagnosis. Non-pharmacologic interventions must include nutrition counseling (often for the entire family), along with the re-institution of physical education, especially in schools. Several studies have reported that there is a decrease in physical activity levels during adolescence. Kimm studied 1213 black girls and 1166 white girls and, through the use of a validated questionnaire, found that there were substantial declines in physical activity during adolescence.[34] This was more pronounced for black girls than for white girls. Pregnancy was associated with a decline in activity among black girls, while cigarette smoking was associated with a decline in activity among white girls.

Insulin is the mainstay of treatment for young people with Type 2 DM who present in diabetic ketoacidosis. The amount of insulin required to achieve normoglycemia is usually much greater in Type 2 DM than in Type 1 DM. When the distinction between Type 1 and Type 2 DM cannot be made at the outset, insulin is usually the initial therapy. It can be subsequently withdrawn very carefully and under cautious supervision in those individuals who are ultimately thought to have Type 2 DM. With respect to oral hypoglycemic agents, their use has not been well-studied in the pediatric population; however, the American Diabetes Association recommends that metformin be the oral agent that is used first in children and teens. Regardless of the initial treatment modality, these children need constant diabetes education, monitoring, and re-evaluation of their medical and pharmacological therapy.

The diagnosis of Type 2 DM in youth is often made when individuals are asymptomatic and lack the usual hyperglycemic symptoms of polyuria, polydipsia, and weight loss. For these reasons, treatment may be difficult, as the newly diagnosed youth may still feel generally well.

At the time of the diagnosis of Type 2 DM, individuals should be screened for both diabetic retinopathy and nephropathy. Other comorbid cardiovascular risk factors such as hypertension and dyslipidemia are also important to look for and treat. Young females with newly diagnosed Type 2 DM may also have concerns about irregular menses, anovulation, and hirsutism, which may lead to a concurrent diagnosis of the polycystic ovary syndrome.

Prevention of type 2 DM in youth

Attempts to prevent Type 2 DM in youth should follow the same pattern as those for preventing Type 2 DM in adults.[17] Some initiatives have sought to deal specifically with Type 2 DM in youth. Recently, the American Academy of Pediatrics Committee on Native American Child Health released a statement on the prevention and treatment of Type 2 DM in children, with a special emphasis on American Indian and Alaska Native children.[35] Their recommendations included general community health promotion (multidisciplinary activities in the area of public

health, nutrition, nursing, health education, advocacy) and clinical activities (with respect to glycemic control, complication surveillance, and monitoring for other cardiovascular risk factors). Other initiatives that are feasible in preventing Type 2 DM in high risk children and adolescents include dietary counseling and physical activity education and modification;[36,37] however, long-term outcomes are not yet well-defined. Children and adolescents with impaired glucose tolerance or impaired fasting glucose, but who have not yet been diagnosed with Type 2 DM, represent a higher risk group and need closer surveillance.

Conclusions

All healthcare providers should be aware of and vigilant for the rising incidence of Type 2 DM in youth. The most important contributing factors to this epidemic are obesity and sedentary lifestyle. It is important to screen those who are at higher risk in order to prevent long-term morbidity and mortality. The future population burden from Type 2 DM in youth will be from the premature development of devastating chronic microvascular and macrovascular complications. Another important issue, but one that this review has not addressed, is the future increase in the incidence of Type 2 DM during pregnancy and the maternal and fetal health consequences related to this condition. However, in all cases of Type 2 DM, healthy lifestyle practices including regular exercise, proper nutrition, smoking cessation (as required), and education (regarding compliance with medication, home blood sugar monitoring) must be encouraged for both primary and secondary prevention.

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Abstract of interest

Diabetic autoimmune markers in children and adolescents with type 2 diabetes

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BACKGROUND: There is an increase in the incidence of type 2 diabetes in children and adolescents. Absence of known diabetes autoimmune markers is sometimes required to confirm the diagnosis.

OBJECTIVE: To identify clinical and autoimmune characteristics of type 2 diabetes in a pediatric population.

METHOD: We report an analysis of 48 children and adolescents with type 2 diabetes, compared with 39 randomly selected children with type 1 diabetes, diagnosed and followed at the Loma Linda University Pediatric Diabetes Center. Ethnic, familial, seasonal, and autoimmune marker characteristics are outlined. To determine the reliability of antibody testing in confirming the type of diabetes at diagnosis, we studied the incidence of positive islet cell antibodies (ICAs), glutamic acid decarboxylase antibodies (GADs), and insulin autoantibodies (IAAs) at diagnosis in both groups. ICA512, GADs, and IAAs were measured by radioimmunoassay.

RESULTS: The cohort with type 2 diabetes had a similar gender distribution as the group with type 1 diabetes but a significantly higher age at diagnosis. Ethnic background was significantly different between the 2 groups, predominantly Hispanic in type 2 and white in type 1. Body mass index was significantly higher in type 2 diabetes (mean = 31.24 kg/m^2). Among the patients with type 2 diabetes, 33% presented in diabetic ketoacidosis, random blood glucose at diagnosis ranged from 11.4 to 22.25 mmol/L (228-445 mg/dL), fasting C-peptide levels ranged from 0.89 to 2.7 nmol/L (2.7-8.2 ng/mL; normal: <1.36 nmol/L), and hemoglobin A_{1C} was 10.8 +/- 3.5% (normal: <6.6%). None of these parameters was significantly different from the type 1 diabetes group. Although the incidence of diabetes antibody markers was significantly lower in type 2 versus type 1 diabetes, 8.1% of patients with type 2 diabetes had positive ICAs, 30.3% had positive GADs, and 34.8% had positive IAAs without ever being treated with insulin. In the type 2 diabetes group, none of the Hispanic patients had ICAs. However, there was no significant correlation between any of the diabetes antibodies and obesity, presence of acanthosis nigricans, or family history of diabetes. The frequency of thyroid antibodies was not significantly different from the group with type 1 diabetes. Daily insulin requirements 1 year after diagnosis were significantly lower in type 2 diabetes, ranging from 0 to 1.2 U/kg with a mean of 0.33.

CONCLUSION: Absence of diabetes autoimmune markers is not a prerequisite for the diagnosis of type 2 diabetes in children and adolescents.

Pediatrics 2001;107(6):E102.

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This publication is made possible by an educational grant from
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