SCREENING FOR TYPE 2 DIABETES

KRISTEN NADEAU, MD, MS

PROFESSOR, PEDIATRIC ENDOCRINOLOGY

CU ANSCHUTZ MEDICAL CAMPUS

CONFLICTS

- Dr. Nadeau has no conflicts to disclose

AMERICAN DIABETES ASSOCIATION (ADA) RECOMMENDATIONS FOR SCREENING FOR TYPE 2 DIABETES (T2D) IN YOUTH

- Risk-based screening for prediabetes and/or T2D should be considered after the onset of puberty or ≥10 years of age, whichever occurs earlier, in youth with overweight (BMI ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more additional risk factors for T2D
- If screening is normal, repeat screening at a minimum of 3-year intervals, or more frequently if BMI is increasing.
- Fasting plasma glucose (FPG), or 2-h plasma glucose during a 75-g oral glucose tolerance test (OGTT), or HbA1c can be used to test for prediabetes or type 2 diabetes in children and adolescents.

ADA DEFINITION OF DIABETES WHEN SCREENING FOR T2D IN YOUTH

- Recommended criteria for the diagnosis of diabetes include symptoms of hyperglycemia (increased thirst, urination, nocturia, fatigue) and at least one of the following laboratory values.
  - HbA1c ≥ 6.5% (48 mmol/mol)
  - FPG ≥ 126 mg/dL (7.0 mmoL/L)
  - Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)
  - 2-hour plasma glucose on an OGTT ≥ 200 mg/dL (11.1 mmoL/L); OGTT: 1.75 g/kg (max 75 g) anhydrous glucose dissolved in water.
- In the absence of unequivocal hyperglycemia symptoms (including polyuria, polydipsia, nocturia, unexplained weight loss and general fatigue), utilize TWO of the criteria above or confirmatory testing on a different day.

CAVEAT TO ADA-RECOMMENDED RANGES FOR DIABETES IN DIAGNOSING T2D IN YOUTH

- Diabetes diagnostic criteria are based on long-term health outcomes (i.e. retinopathy) in adults, and validations are not yet available in youth for any criteria
- An analysis of National Health and Nutrition Examination Survey (NHANES) data concluded that using HbA1c for screening of high-risk youth as the most practical.
- The ADA acknowledges the limited data supporting HbA1c for diagnosing T2D in youth. Although HbA1c is not recommended for diagnosis of diabetes in children with cystic fibrosis or symptoms suggestive of acute onset of type 1 diabetes (T1D), and only HbA1c assays without interference are appropriate for children with hemoglobinopathies, the ADA continues to recommend HbA1c for diagnosis of T2D in youth.

CLINICAL DIAGNOSIS OF T2D AND T1D IN YOUTH

- A clinical diagnosis of T2D is supported by the following, but each have caveats
  - BMI ≥85th percentile
  - Metabolic co-morbidities associated with insulin resistance*, i.e. metabolic syndrome characteristics (high triglycerides, low HDL-cholesterol, metabolic dysfunction-associated steatotic liver disease [MASLD] including elevated ALT, hypertension*, polycystic ovary syndrome [PCOS]*, obstructive sleep apnea)
  - Family history of T2D
  - Pubertal Tanner Stage 2 or greater, due to the physiological insulin resistance characteristic of puberty
  - Absence of diabetic ketoacidosis at presentation (DKA) or cerebral edema
  - Absence of pancreatic autoantibodies
- A clinical diagnosis of T1D is supported by the following, but each have caveats
  - BMI <85th percentile
  - Age of diabetes onset of <10 years of age
  - Pre-pubertal at diabetes onset
  - Absence of risk factors and clinical features of type 2 diabetes
  - DKA or cerebral edema at presentation
  - Presence of pancreatic autoantibodies

CLINICAL DIAGNOSIS OF MODY IN YOUTH

- There is also clinical overlap with monogenic diabetes (MODY) when diabetes is diagnosed in the teenage years.
- A clinical diagnosis of MODY is supported by the following, but each have caveats
  - BMI < 85th percentile
  - Family history of diabetes in one parent and first-degree relatives of that affected parent*
  - Absence of other risk factors and clinical features of T2D
  - Absence of pancreatic autoantibodies
  - Features such as genitourinary tract abnormalities, renal cysts, pancreatic atrophy, hyperuricemia or gout (HNF1B MODY)
  - Stable isolated fasting hyperglycemia in the range of 100-150mg/dL (5.5-8.5 mmol/L) (GCK MODY)
  - History of neonatal diabetes.
  - *However, family history of diabetes can be very strong in youth with T2D, which increases the challenge of distinguishing MODY from T2D, particularly with obesity and a milder presentation (e.g. elevated HbA1c on routine screening)
- In addition, there are rare and atypical diabetes cases that represent a challenge for classification

OVERVIEW OF TYPICAL CHARACTERISTICS OF DIABETES

	Classical type 1 diabetes	Classical type 2 diabetes	Monogenic diabetes
Age at presentation	Two peaks: age 4–6 years and 10–14 years	Onset after puberty	Onset before age 25 years
Weight	Usually normal weight, can be overweight or obese	>90% are overweight or obese	Usually normal weight, can be overweight or obese
Autoantibodies	Present	Absent	Absent
Insulin resistance	Present, but lack metabolic syndrome characteristics	Present, with metabolic syndrome chararacteritics	Absent?
Risk of DKA	High	Low	Low
C-peptide after diagnosis	Low	Detectable	Detectable
Family history of diabetes	Infrequent (10–15%)	Frequent (90%)	Frequent, usually in multiple generations
Associated Conditions	Autoimmune Conditions	Polycystic Ovary Syndrome, Metabolic dysfunction-associated steatotic liver disease, Dyslipidemia and Hypertension	Neonatal diabetes, genitourinary tract abnormalities, renal cysts, pancreatic atrophy, hyperuricemia or gout

ADA-RECOMMENDATIONS FOR DETERMINING DIABETES TYPE IN YOUTH WITH OVERWEIGHT/OBESITY

- Because of rising rates of obesity in the general population, including in youth with T1D, and because T1D currently remains the most common type of diabetes in youth. Thus, it is important to exclude the diagnosis of type 1 diabetes in adolescent youth, regardless of their clinical phenotype. youth with overweight or obesity with newly diagnosed diabetes should have a panel of pancreatic autoantibodies tested to exclude the possibility of autoimmune T1D
- Testing should include glutamic acid decarboxylase-65 (GAD-65), islet antigen-2 (IA-2), zinc transporter 8 (ZnT8) and insulin antibody (IAA), the latter in those who have not yet been treated with insulin.
- Why? Up to 12% of youth with clinical diagnosis of T2D in one study had a pancreatic antibody, and in the US TODAY study, provider diagnosis by a pediatric endocrinologist of T2D was incorrect in 9.8% of those screened for participation.

CHARACTERISTICS OF YOUTH WITH T2D

- Approximately 40% of pediatric cases of T2D occur between 10 and 14 years of age; the majority are ages 14-18 years, with average age of onset of age 16 years, except in non-Hispanic black youth where average age on onset is age 13 years.
- With the worldwide epidemic of childhood obesity on the rise, there are increasing reports of type 2 diabetes occurring in prepubertal children with extreme obesity and high T2D risk factors
- Girls present on average at least a year earlier with T2D, since puberty starts at a younger age in them
- In the US, youth-onset T2D is almost twice as common in girls as in boys; no sex difference is reported in China, and several Middle Eastern countries (UAE and Kuait) have a male predominance in both obesity and T2D
- There is significant seasonal variation in the onset of T2D in children and young people in the United States; diagnoses increase in August. Possible explanations for an August peak include weight gain during the summer vacation and an increase in physical exams for school athletic programs that may detect asymptomatic hyperglycemia

INSULIN RESISTANCE AND ECTOPIC FAT

- BMI and ectopic fat are lower in youth with T2D from South Asian populations
- In Taiwan, obesity was present in 37.9% and 39.5% respectively for school aged boys and girls with type 2 diabetes.
- Japanese children with youth-onset T2D are also thinner than non-Hispanic White youth with youth-onset T2D.
- Non-Hispanic Black youth have less visceral fat and hepatic fat than expected for their BMI or degree of insulin resistance, yet high rates of T2D
- Youth with T1D are more insulin resistant than youth without diabetes of the same Tanner Stage with obesity, and youth with T1D and obesity are almost as insulin resistant as youth with T2D
- However, youth with T1D generally lack the typical features of insulin resistance (the metabolic syndrome), likely implicating a different cause of insulin resistance than in T2D

CHALLENGES WITH DETERMINING DIABETES TYPE

- Determining diabetes type in youth is complex due to the overlapping characteristics between youth presenting with T1D and T2D, particularly given the rising background prevalence of obesity, and high background prevalence of GAD antibodies
- Youth with a clinical phenotype of T2D and single antibody positivity have been shown to have early insulin requirement, although data regarding the clinical course and most ideal treatment in patients with a clinical and single antibody positivity are limited
- The classical signs at the onset of diabetes - polydipsia and polyuria - are observed in about two-thirds of youth at the diagnosis of T2D. Only about 1/3 are diagnosed through routine screening of asymptomatic youth with obesity
- Presentation in ketosis and DKA among youth with T2D is not uncommon (5.5% and 6.6% in the SEARCH study and the Young Age at Onset in India study), and hyperglycemic hyperosmolar state is present at diagnosis in 2% of youth with T2D, often confused with DKA

SEARCH CATEGORIZATION OF YOUTH WITH DIABETES

- The SEARCH study operationalized the ADA classification framework using *autoimmunity* and *estimated insulin sensitivity* (estimated by HbA1c, triglycerides and waist circumference)
- Most SEARCH participants aligned with traditional T1D (*autoimmune and "insulin sensitive*"; 54.5%) and T2D (*non-autoimmune and "insulin resistant*"; 15.9%)
- The group classified as *autoimmune and "insulin resistant"* likely mainly represents individuals with autoimmune T1D and obesity, not a distinct diabetes etiology.
- The group with *non-autoimmune and "insulin sensitive"* (~10%) was deemed to require additional testing, including genetic testing for MODY

FUTURE DIRECTIONS

- The best approach to youth with obesity plus diabetes may be a personalized approach depending on degree of insulin resistance, BMI, residual beta-cell function and co-morbidities, rather than a focus on type of diabetes

QUESTIONS?

- Thanks!