Epidemiology, presentation, and diagnosis of type 1 diabetes mellitus in children and adolescents

AUTHORS: Lynne L Levitsky, MD, Madhusmita Misra, MD, MPH
SECTION EDITOR: Joseph I Wolfsdorf, MD, BCh
DEPUTY EDITOR: Jessica Kremen

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INTRODUCTION

Type 1 diabetes mellitus (T1DM), one of the most common chronic diseases in childhood, is caused by insulin deficiency following destruction of the insulin-producing pancreatic beta cells. It most commonly presents in childhood, but one-fourth of cases are diagnosed in adults. T1DM remains the most common form of diabetes in childhood, despite the increasing rate of type 2 diabetes mellitus (T2DM) [1,2].

The epidemiology, presentation, and diagnosis of T1DM in children and adolescents are presented here. The pathogenesis of T1DM and the management and complications of childhood T1DM are discussed separately:

- (See "Pathogenesis of type 1 diabetes mellitus".)
- (See "Overview of the management of type 1 diabetes mellitus in children and adolescents".)
- (See "Insulin therapy for children and adolescents with type 1 diabetes mellitus".)
- (See "Hypoglycemia in children and adolescents with type 1 diabetes mellitus".)
- (See "Diabetic ketoacidosis in children: Clinical features and diagnosis".)
- (See "Diabetic ketoacidosis in children: Treatment and complications".)
- (See "Complications and screening in children and adolescents with type 1 diabetes mellitus".)

The assessment and management of individuals presenting during infancy with hyperglycemia also are discussed separately. (See "Neonatal hyperglycemia".)

EPIDEMIOLOGY

The incidence of childhood T1DM varies based upon geography, age, sex, family history, and ethnicity.

- **Geographical variation** – The incidence of childhood T1DM varies worldwide [3]. The highest reported incidences of T1DM occur in Finland and Sardinia (45 to 65 per 100,000 children younger than the age of 15 years) [3-5]. In the United States, the annual incidence of T1DM in children and adolescents is 22.3 per 100,000 overall, with substantial differences between race/ethnic groups (27.3 per 100,000 in non-Hispanic White youth, 20.8 per 100,000 in Black youth, and 16.3 per 100,000 in Hispanic youth) [6].

- **Age and sex** – The age of presentation of childhood-onset T1DM has a bimodal distribution, with one peak at four to six years of age and a second in early puberty (10 to 14 years of age) (figure 1) [7-9]. Overall, approximately 45 percent of children present before 10 years of age [10]. T1DM accounts for almost all cases of diabetes before 10 years of age, 90 percent of cases in children 10 to 14 years, and 80 percent in youth 15 to 19 years [2].

  Although most autoimmune diseases are more common in females, there appears to be no sex difference in the overall incidence of childhood T1DM [1,2]. However, in some studies, T1DM occurs more frequently in males. Globally, the ratio of males to females diagnosed with T1DM in young adulthood is approximately 1.5:1 [11]. The same male to female ratio also was reported in children younger than six years of age in an observational study from Massachusetts [12].

- **Time trends** – Several reports suggest that the incidence of childhood T1DM is rising worldwide, with increases of 2 to 5 percent per year in Europe, the Middle East, and Australia [4,13-16]. In the United States, the incidence has been rising at approximately 2 percent per year (from 19.5 per 100,000 in 2002-2003 to 22.3 in 2014-2015) (figure 2) [6]. The prevalence rose from 1.48 per 1000 to 2.15 per 1000 over a similar time period [2]. The reasons for this trend remain unknown.

  The time trends within age groups vary among populations. A report using data from 17 European countries between 1989 and 2003 revealed a greater annual increase among younger children compared with adolescents [15]. By contrast, in the United States

between 2001 and 2017, the annual change in prevalence slightly decreased for young children, while increasing for older children [2]. Similar decreases in trends among younger children born after 2000 were seen in studies from Sweden [17] and New Zealand [18].

RISK FACTORS

Both genetic and environmental factors contribute to the risk of developing T1DM. (See "Pathogenesis of type 1 diabetes mellitus".)

Genetic susceptibility — The lifetime risk of developing T1DM is significantly increased in close relatives of a patient with T1DM [3,19-21]:

- No family history – 0.4 percent
- Offspring of an affected mother – 1 to 4 percent
- Offspring of an affected father – 3 to 8 percent
- Offspring with both parents affected – Reported as high as 30 percent [22,23]
- Non-twin sibling of affected patient – 3 to 6 percent by age 20 years [20] and 10 percent by 60 years [24]
- Dizygotic twin – 8 percent
- Monozygotic twin – 30 percent within 10 years of diagnosis of the first twin [25] and 65 percent concordance by age 60 years [26]

In the United States, there also are ethnic differences in incidence of T1DM [2]. In a study that sampled several large multiethnic populations in 2017, the highest prevalence (per 1000 children <19 years) was seen in non-Hispanic White youth (2.79), followed by Black (2.18), Hispanic (1.56), Asian or Pacific Islander (0.76), and Native American youth (0.56) (figure 3) [2].

These observations of familial and ethnic risk factors are most likely the consequences of gene polymorphisms in the major histocompatibility complex or other genetic susceptibility regions. Details regarding genetic susceptibility and the genes that increase the risk of T1DM are presented elsewhere. (See "Pathogenesis of type 1 diabetes mellitus", section on 'Genetic susceptibility'.)

Other possible risk factors — In genetically susceptible individuals, exposure to one or more environmental agents (eg, viruses or foods) appears to trigger an immune response that ultimately causes destruction of the insulin-producing pancreatic beta cells. Identification of these factors should lead to a better understanding of the pathogenesis of the disease and aid

in developing strategies to prevent T1DM [3]. (See "Type 1 diabetes mellitus: Prevention and disease-modifying therapy" and "Pathogenesis of type 1 diabetes mellitus".)

A more complete description of environmental factors and their potential link to T1DM is discussed separately. (See "Pathogenesis of type 1 diabetes mellitus", section on 'Environmental factors'.)

CLINICAL PRESENTATION

For clinical purposes, T1DM has three initial presentations [27]:

- Classic new onset of polydipsia, polyuria, and weight loss with hyperglycemia and ketonemia (or ketonuria)
- Diabetic ketoacidosis (DKA)
- Silent (asymptomatic) incidental discovery

T1DM is now recognized to have four stages [28,29]:

- Stage 1 – Beta cell autoimmunity (≥2 islet autoantibodies), normal blood glucose; no symptoms
- Stage 2 – Beta cell autoimmunity (≥2 islet autoantibodies) and abnormal glucose tolerance; usually with no symptoms
- Stage 3 – Beta cell autoimmunity and raised blood glucose above diagnostic thresholds; usually with symptoms
- Stage 4 – Established/longstanding T1DM

Progression between the stages of T1DM is discussed in more detail separately. (See "Type 1 diabetes mellitus: Disease prediction and screening".)

Classic new onset — Hyperglycemia without acidosis is the most common presentation of childhood T1DM in most populations. Patients typically present with the following symptoms:

- Polyuria – Polyuria occurs when the serum glucose concentration rises significantly above 180 mg/dL (10 mmol/L), exceeding the renal threshold for glucose, which leads to increased urinary glucose excretion. Glycosuria causes osmotic diuresis (ie, polyuria) and hypovolemia. Polyuria may present as nocturia, bedwetting, or daytime incontinence in a previously continent child. In children who are not toilet trained, caregivers may note an increased frequency of wet diapers and/or diapers that are unusually heavy (wet).

- Polydipsia – Polydipsia is due to enhanced thirst because of increased serum osmolality from hyperglycemia and hypovolemia. Despite the hypovolemia, patients may not have the classic signs of dry mucus membranes or decreased skin turgor.

- Weight loss – Weight loss is a result of hypovolemia and increased catabolism. Insulin deficiency in diabetic children impairs glucose utilization in skeletal muscle and increases fat and muscle breakdown. Initially, appetite is increased, but over time, children are more thirsty than hungry and ketosis leads to nausea and anorexia, contributing to weight loss.

Patients with these symptoms usually present in the ambulatory setting appearing slightly ill, with vague complaints such as weight loss and lethargy [12]. In a study from Ireland, the mean duration of symptoms before presentation was 10 days [30]. The classic symptoms of polyuria and polydipsia are present in more than 90 percent of patients, but these are not always the initial complaints and may become apparent only after asking specifically about nocturia and bedwetting, increased frequency and/or unusually wet diapers, and persistent thirst. Weight loss is a presenting symptom in approximately one-half of children.

Other presentations include:

- Perineal candidiasis – This is a relatively common presenting symptom in young children and in girls [12].

- Acute visual disturbances – These are common because of alterations in the osmotic milieu of the lens and, to a lesser extent, the aqueous and vitreous humors, leading to changes in refractive index [31].

- Cataracts – Cataracts occasionally develop in children with longstanding hyperglycemia and may be a presenting feature [32-34]. In a large multicenter study in individuals 0.5 to 21 years old, cataracts were noted in 0.25 percent of children and adolescents with T1DM; they were more common in females and patients with higher hemoglobin A1c (A1C) and older age at diabetes onset [34]. (See "Cataract in children".)

Diabetic ketoacidosis — DKA (hyperglycemia and ketoacidosis) is the second most common form of presentation for T1DM in most populations. Symptoms are similar but usually more severe than those of patients without acidosis. In addition to polyuria, polydipsia, and weight loss, patients with ketoacidosis may present with a fruity-smelling breath and neurologic findings, including drowsiness and lethargy. DKA can be misinterpreted as an acute vomiting illness because classic pediatric symptoms of dehydration (decreased urination) are masked by the polyuria that is associated with glycosuria. (See "Diabetic ketoacidosis in children: Clinical features and diagnosis", section on 'Signs and symptoms'.)

The reported frequency of DKA as the initial presentation for childhood T1DM is approximately 30 percent but varies from 15 to 70 percent [35-37]. Young children (<6 years of age) or those from an adverse socioeconomic background are more likely to have DKA as their initial presentation of T1DM. Among children younger than age three years, more than one-half had DKA as their initial presentation of T1DM [38]. (See "Diabetic ketoacidosis in children: Clinical features and diagnosis", section on 'Epidemiology'.)

Children with DKA require hospitalization, rehydration, and insulin replacement therapy. (See "Diabetic ketoacidosis in children: Treatment and complications".)

Silent presentation — Some children will be diagnosed with T1DM before the onset of clinical symptoms. This presentation is least common and typically occurs in children who have another close family member with T1DM and are being closely monitored. The diagnosis often is made by either a family member or clinician with a high index of suspicion. Children with affected close relatives also may undergo pancreatic autoantibody screening to assess risk for the disease [39], although this is not a clinical care recommendation (see "Type 1 diabetes mellitus: Disease prediction and screening"). These children may be classified as having stage 1 or stage 2 diabetes, using International Society for Pediatric and Adolescent Diabetes guidelines [29]. The diagnosis of stage 2 diabetes is made based upon an elevated blood glucose concentration using the criteria outlined below. (See 'Approach to diagnosis' below.)

Special populations

Infants — A variety of disorders can cause hyperglycemia during infancy. Although autoimmune classic T1DM can occur in the first year of life, neonatal diabetes is uncommonly, if ever, autoimmune in nature. Neonatal diabetes is a rare disorder caused by one of several genetic defects in pancreatic development or beta cell function. (See 'Differential diagnosis' below and "Neonatal hyperglycemia", section on 'Neonatal diabetes mellitus'.)

Young children — Young children (eg, <6 years of age) are more vulnerable to dehydration compared with older children because they are less able to compensate for pathologic processes by seeking fluids and increasing fluid intake (to replace ongoing urinary losses) [12]. In addition, young children are more likely to present with DKA because health care personnel and families less often suspect diabetes in this age group. This leads to a prolonged duration of illness and more severe metabolic decompensation before diagnosis [12,30,38,40,41].

Children in this age group also have polydipsia and polyuria, but these symptoms are difficult to detect if the child is still in diapers or is nonverbal and unable to communicate thirst. Therefore, it is often difficult to recognize these symptoms of hyperglycemia in young children, especially those younger than two years of age [12]. The history or presence of prolonged or recurrent

candidal infection (usually in the diaper area) is an important clue that should raise suspicion about the possibility of diabetes mellitus in young children. Candidal infection was present at diagnosis in a significant proportion of children younger than six years with T1DM and especially in those younger than two years of age [12].

These patients often have been seen by a clinician for nonspecific complaints before the diagnosis [12]. In this vulnerable age group, a high index of suspicion is required for early diagnosis. When a young child presents for evaluation of dehydration, abdominal pain, or fatigue, the clinician should include diabetes in the differential diagnosis and consider measuring serum glucose and testing for glucosuria.

APPROACH TO DIAGNOSIS

T1DM is one of several different types of diabetes mellitus. The initial step is to diagnose diabetes. The second step is to differentiate T1DM from other causes of diabetes, based upon the clinical presentation of the patient and laboratory studies. (See 'Distinguishing type 1 from type 2 diabetes' below and 'Other causes of diabetes' below.)

Diagnostic criteria for diabetes — Diabetes mellitus is diagnosed based upon one of the following four signs of abnormal glucose metabolism (table 1) [3,42,43]:

- Fasting plasma glucose ≥126 mg/dL (7 mmol/L) on more than one occasion. Fasting is defined as no caloric intake for at least eight hours.
- Random venous plasma glucose ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia.
- Plasma glucose ≥200 mg/dL (11.1 mmol/L) measured two hours after a glucose load of 1.75 g/kg (maximum dose of 75 g) in an oral glucose tolerance test. Most children and adolescents are symptomatic and have plasma glucose concentrations well above ≥200 mg/dL (11.1 mmol/L); thus, an oral glucose tolerance test is seldom necessary to diagnose T1DM.
- Glycated hemoglobin (A1C) ≥6.5 percent (using an assay that is certified by the National Glycohemoglobin Standardization Program). This criterion should be confirmed by another measure of hyperglycemia.

Unless unequivocal symptomatic hyperglycemia is present, the diagnosis should be confirmed by repeat testing.

In the absence of continuous glucose monitoring, A1C is a valuable method to monitor glycemic control. A1C measures the percent of hemoglobin A bound to glucose via non-enzymatic glycation and is a useful index of mean glycemic control for 10 to 12 weeks before the time of measurement. In one study from Germany, all children with symptomatic new-onset T1DM had an A1C ≥6.35 percent, whereas those with transient hyperglycemia had A1C values ranging from 4.5 to 6.1 percent [44]. Individuals with abnormal hemoglobins or rapid destruction of red blood cells may have a measured A1C value that does not accurately reflect their average blood sugar values. The accuracy of measurements in individuals with abnormal hemoglobins will improve with the use of improved techniques for assessing A1C and with standardization of A1C measurements. For example, hemoglobin variants and derivatives interfere very minimally with the commercially available boronate affinity chromatography technique [45]. However, rapid turnover of hemoglobin will still affect the reported A1C level. (See "Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults", section on 'A1C'.)

Distinguishing type 1 from type 2 diabetes — Once a diagnosis of diabetes is made, the next step is to distinguish T1DM from type 2 diabetes mellitus (T2DM). T1DM is characterized primarily by insulin deficiency, whereas T2DM is characterized primarily by insulin resistance with relative insulin deficiency. As the prevalence of obesity and the incidence of T2DM increase in children and adolescents, it becomes increasingly important to consider both types. (See "Classification of diabetes mellitus and genetic diabetic syndromes".)

No set of criteria or diagnostic test can consistently distinguish between T1DM and T2DM. Therefore, differentiating between the two types is based upon a combination of the clinical presentation and history, often supported by laboratory studies (table 2).

Clinical characteristics

- Body habitus – Patients with T2DM usually have obesity (body mass index ≥95th percentile for age and sex). In contrast, children with T1DM are less likely to have excess body weight and often have a recent history of weight loss, although up to 25 percent are overweight (body mass index ≥85th to 95th percentile) [46]. Patients with new-onset T2DM may also have a history of recent weight loss.

- Age – Patients with T2DM generally present after the onset of puberty, whereas those with T1DM often present at an earlier age. Approximately 45 percent of children with T1DM present before 10 years of age [10]. By contrast, almost all cases of T2DM present after 10 years of age (figure 1). (See 'Epidemiology' above.)

- Insulin resistance – Patients with T2DM frequently have acanthosis nigricans (a sign of insulin resistance), hypertension, dyslipidemia, and polycystic ovary syndrome (in girls).

These findings are less likely in children with T1DM. As an example, in studies in the United States, 50 to 90 percent of youth diagnosed with T2DM have acanthosis nigricans [47,48]. Among those clinically diagnosed with T1DM, up to 25 percent have biochemical evidence of insulin resistance and approximately 12 percent have acanthosis nigricans [48].

- Family history – Up to 10 percent of patients with T1DM have an affected close relative, whereas 75 to 90 percent of those with T2DM have an affected close relative [47,49].

Laboratory testing — We suggest including the following laboratory tests in the evaluation, to help distinguish between type 1 and type 2 diabetes:

- **Pancreatic autoantibodies** – Measure autoantibodies against GAD65 (glutamic acid decarboxylase 65), IA2 (the 40K fragment of tyrosine phosphatase), insulin, and ZnT8 (zinc transporter 8) [3]. This panel of tests should be performed at the time of presentation, before or soon after starting insulin therapy. Insulin antibodies may develop approximately 10 to 14 days after exposure to exogenous insulin.

  Most patients with T1DM have one or more of the above pancreatic autoantibodies, indicating autoimmune destruction of pancreatic beta cells; this is sometimes referred to as type 1A diabetes (figure 4) [48]. A minority of patients with clinical features of T1DM have no detectable autoantibodies and are categorized as having type 1B diabetes. In these patients, there is no evidence of autoimmune beta cell destruction and no other cause has been identified. Conversely, up to 30 percent of individuals with clinical characteristics of T2DM have positive autoantibodies and may have a slowly progressive type of autoimmune diabetes [50]. (See "Classification of diabetes mellitus and genetic diabetic syndromes" and "Pathogenesis of type 1 diabetes mellitus".)

- **Insulin and C-peptide levels** – We measure these levels for children with clinical characteristics that raise the possibility of T2DM. In a newly diagnosed patient, these tests should be performed after the child has recovered from the initial hyperglycemic stress because insulin and C-peptide levels may be suppressed by severe hyperglycemia (glucose toxicity) and acute illness.

  In children with T1DM, levels of fasting insulin and C-peptide are inappropriately low relative to the concomitant plasma glucose concentration (ie, low or in the normal range despite hyperglycemia). By contrast, high fasting insulin and C-peptide levels suggest T2DM.

Some patients may have mixed features and are difficult to classify, highlighting the heterogeneity of diabetes. As an example, in a registry study in the United States, pediatric

diabetes was classified based upon the presence or absence of beta cell autoimmunity and the presence or absence of insulin sensitivity [48]. More than 70 percent of patients fell into traditional categories of autoimmune and insulin-sensitive T1DM (55 percent) or nonautoimmune and insulin-resistant T2DM (16 percent). An additional 20 percent had both autoimmunity and insulin resistance, a pattern typical for patients with obesity and T1DM. The remaining 10 percent of patients were insulin sensitive in the absence of islet cell autoimmunity, most of whom were clinically categorized as T1DM (ie, type 1B diabetes) and the remainder as T2DM (suggesting that these patients need additional evaluation for the possibility of monogenic diabetes, formerly referred to as maturity-onset diabetes of the young [MODY]). (See "Classification of diabetes mellitus and genetic diabetic syndromes", section on 'Distinguishing type 1 from type 2 diabetes' and 'Other causes of diabetes' below.)

DIFFERENTIAL DIAGNOSIS

Other causes of hyperglycemia — In the previously healthy child, diabetes mellitus is by far the most common cause of clinically significant hyperglycemia. Other considerations include:

- Critically ill patients – Patients with septic shock or other critical illnesses often have abnormalities in glycemic control, leading to either hypoglycemia or hyperglycemia. (See "Sepsis and septic shock in children in resource-abundant settings: Ongoing management after resuscitation", section on 'Manage glucose abnormalities'.)

- Medication – Children receiving intravenous infusions containing glucose, or those who receive acute sympathomimetic agents or high-dose glucocorticoids, may display elevations in blood glucose that revert to normal after treatment is complete.

- Neonatal hyperglycemia – Causes of hyperglycemia in a neonate include excessive glucose infusion, prematurity, stress, sepsis, drugs, and transient or permanent neonatal diabetes mellitus. (See "Neonatal hyperglycemia".)

Other causes of diabetes — T1DM is distinguished from other diseases that cause diabetes by patient characteristics, history, and laboratory studies. This approach is similar to that used to differentiate type 1 from type 2 diabetes, as discussed above. (See 'Distinguishing type 1 from type 2 diabetes' above.)

The following diseases that cause diabetes are discussed in greater detail separately. (See "Classification of diabetes mellitus and genetic diabetic syndromes".)

- **Monogenic diabetes** – Monogenic diabetes (formerly referred to as maturity-onset diabetes of the young [MODY]) is a clinically heterogeneous disorder characterized by noninsulin-dependent diabetes presenting at a young age, with autosomal dominant transmission and lack of autoantibodies. Many different genetic abnormalities have been identified, each leading to a different type of disease. Monogenic diabetes should be suspected in a patient presenting with noninsulin-dependent diabetes at a young age (<25 years), with autosomal dominant transmission across three generations, lack of islet autoantibodies, and lack of acanthosis nigricans. The diagnosis of monogenic diabetes is made by performing diagnostic genetic testing through direct sequencing of the gene. (See "Classification of diabetes mellitus and genetic diabetic syndromes", section on 'Monogenic diabetes (formerly called maturity onset diabetes of the young)'.)

- **Diseases affecting the exocrine pancreas** – Cystic fibrosis, hereditary hemochromatosis, and chronic pancreatitis. (See "Classification of diabetes mellitus and genetic diabetic syndromes", section on 'Diseases of the exocrine pancreas'.)

- **Endocrine abnormalities in glucose regulation** – Cushing syndrome, growth hormone excess, glucagon-secreting tumors, catecholamine excess in pheochromocytoma. With the exception of Cushing syndrome, these are all extremely rare. This possibility should be evaluated in patients presenting with Cushingoid features (such as central obesity, facial plethora, dorsocervical fat pad, and delayed linear growth). This is usually best accomplished by measuring 24-hour urinary cortisol excretion or salivary cortisol at 11:00 PM or midnight two or more times or an overnight low-dose dexamethasone suppression test; additional testing may be required. Two of these three tests need to be positive for a diagnosis of Cushing syndrome. It is important to recognize that children with Cushing syndrome may not manifest the classic features seen in adults. However, a deceleration of growth velocity despite increasing weight should raise concern for Cushing syndrome in a growing child. It is very rare for a child with Cushing syndrome to present with hyperglycemia, although it is relatively common in adults. (See "Epidemiology and clinical manifestations of Cushing syndrome", section on 'Glucose intolerance'.)

- **Drug-induced diabetes** – A number of drugs (eg, glucocorticoids, human immunodeficiency virus [HIV] protease inhibitors, cyclosporine, L-asparaginase, and tacrolimus) and atypical antipsychotic agents can impair glucose tolerance by inhibiting insulin secretion, increasing hepatic glucose production, or causing insulin resistance (table 3). In addition, newer immune checkpoint inhibitors used in the treatment of melanoma and other malignancies have been associated with the development of insulin-deficient diabetes [51]. (See "Pathogenesis of type 2 diabetes mellitus", section on 'Drug-

induced hyperglycemia' and "Pathogenesis of type 1 diabetes mellitus", section on 'Treatment with checkpoint inhibitor immunotherapy'.)

- **Neonatal diabetes mellitus** – Neonatal diabetes is a rare cause of hyperglycemia in infants. It can be transient or permanent and usually is caused by mutations in one of several genes that encode proteins that affect the function of the pancreatic beta cell (eg, proteins that are subunits of the ATP-sensitive potassium channel). Most of the infants are small for gestational age, and they present with weight loss, volume depletion, hyperglycemia, and glucosuria with or without ketonuria and ketoacidosis. The natural history and management of diabetes in these infants depends on the genetic defect, as discussed in a separate topic review. (See "Neonatal hyperglycemia", section on 'Neonatal diabetes mellitus'.)

Glycosuria without hyperglycemia — Patients with renal glucosuria or Fanconi syndrome will present with glycosuria but have normal plasma glucose concentrations.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Diabetes mellitus in children".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Type 1 diabetes (The Basics)" and "Patient education: Helping your child manage type 1 diabetes (The Basics)" and "Patient education: Giving your child insulin (The Basics)")

- Beyond the Basics topic (see "Patient education: Type 1 diabetes: Overview (Beyond the Basics)")

SUMMARY

- **Epidemiology** – Type 1 diabetes mellitus (T1DM) is one of the most common chronic diseases of childhood. In the United States, T1DM accounts for almost all cases of diabetes among children <10 years and approximately 80 percent of cases in children 10 to 19 years (figure 1).

  - The incidence of childhood T1DM varies worldwide, ranging from 0.1 to 65 per 100,000 children younger than the age of 15 years. The age of presentation has a bimodal distribution, with peaks at four to six years of age and between 10 and 14 years of age. In the United States, the incidence of T1DM is 22.3 per 100,000 annually, with the highest rates in non-Hispanic White children and adolescents (figure 3). (See 'Epidemiology' above.)

  - Although there appears to be no overall sex difference in the incidence of childhood T1DM, in select populations (eg, European adolescents), there seems to be an increased risk for males (3:2 male-to-female ratio). (See 'Epidemiology' above.)

- **Risk factors**

  - The risk of T1DM is moderately increased in children with an affected close relative, which is most likely due to gene polymorphisms in the major histocompatibility complex and other susceptibility areas. (See 'Genetic susceptibility' above.)

  - Although exposure to an environmental agent(s) in genetically susceptible individuals appears to trigger the destruction of the insulin-producing pancreatic beta cell, no factor(s) has been definitively identified. (See 'Risk factors' above and "Pathogenesis of type 1 diabetes mellitus".)

- **Clinical presentation** – Childhood T1DM usually presents with the classic signs and symptoms resulting from hyperglycemia, including polyuria, polydipsia, weight loss, and lethargy. Diabetic ketoacidosis (DKA) is often the initial presentation for T1DM, especially in children younger than six years of age and in children of all ages with poor access to

health care. Children also may be identified by screening for the disease before the onset of symptoms. (See 'Clinical presentation' above and "Type 1 diabetes mellitus: Disease prediction and screening".)

In young children, the diagnosis of T1DM is often missed because it may be difficult to recognize the symptoms of hyperglycemia in this age group. Children younger than two years of age are particularly likely to have a delay in diagnosis. In these patients, a history or presence of prolonged candidal infection should prompt consideration of diabetes mellitus and measurement of blood and urine glucose concentrations. (See 'Young children' above.)

- **Diagnosis** – The diagnosis of diabetes is based upon any one of four detected abnormalities of glucose metabolism (table 1) (see 'Diagnostic criteria for diabetes' above and "Clinical presentation, diagnosis, and initial evaluation of diabetes mellitus in adults"):
  - Fasting plasma glucose ≥126 mg/dL (7 mmol/L) on at least two occasions
  - Symptoms of hyperglycemia and a plasma glucose ≥200 mg/dL (11.1 mmol/L)
  - Plasma glucose ≥200 mg/dL (11.1 mmol/L) measured two hours after a standard glucose load in an oral glucose tolerance test
  - Glycated hemoglobin (A1C) ≥6.5 percent – This criterion should be confirmed in children by another measure of hyperglycemia
- **Differential diagnosis** – T1DM often can be distinguished from other causes of diabetes (such as T2DM) by clinical presentation and laboratory studies (table 2). Although no one diagnostic test can distinguish between the two types of diabetes, T1DM is suggested by the presence of serum autoantibodies against islet cells and by inappropriately low fasting C-peptide and insulin levels with concomitant hyperglycemia. (See 'Distinguishing type 1 from type 2 diabetes' above and 'Other causes of diabetes' above.)

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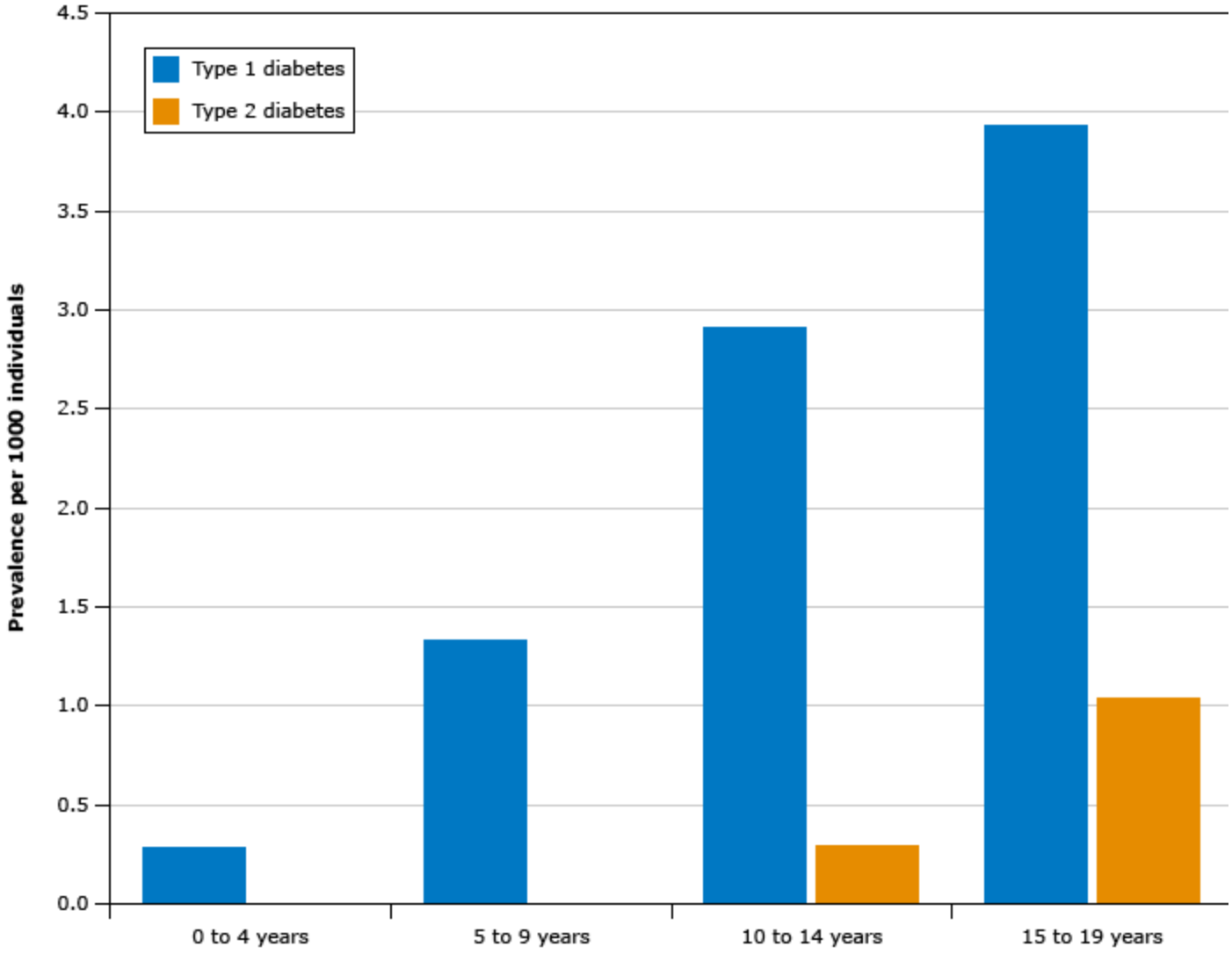
Topic 5816 Version 38.0

GRAPHICS

Prevalence of diabetes mellitus in youth by age group

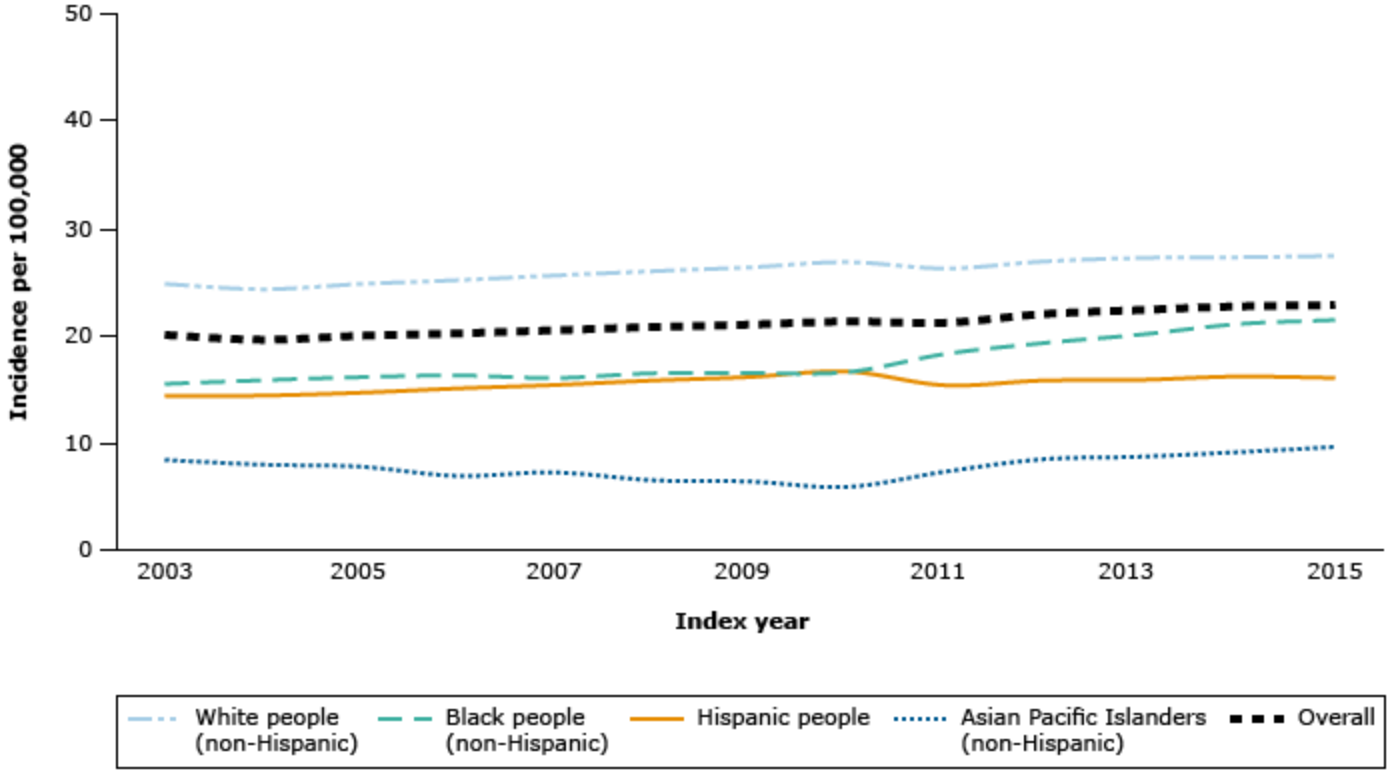


Prevalence of type 1 and type 2 diabetes mellitus in youth in the United States, from the SEARCH for Diabetes in Youth study group, 2001 to 2017. For type 1 diabetes, there are 2 peaks in incidence: in mid-childhood and early puberty. This bimodal distribution is not evident from the age categories used for this figure. For type 2 diabetes, there were no data for children <10 years.

Data from: Lawrence JM, Divers J, Isom S, et al. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001-2017. JAMA 2021; 326:717.

Graphic 88297 Version 4.0

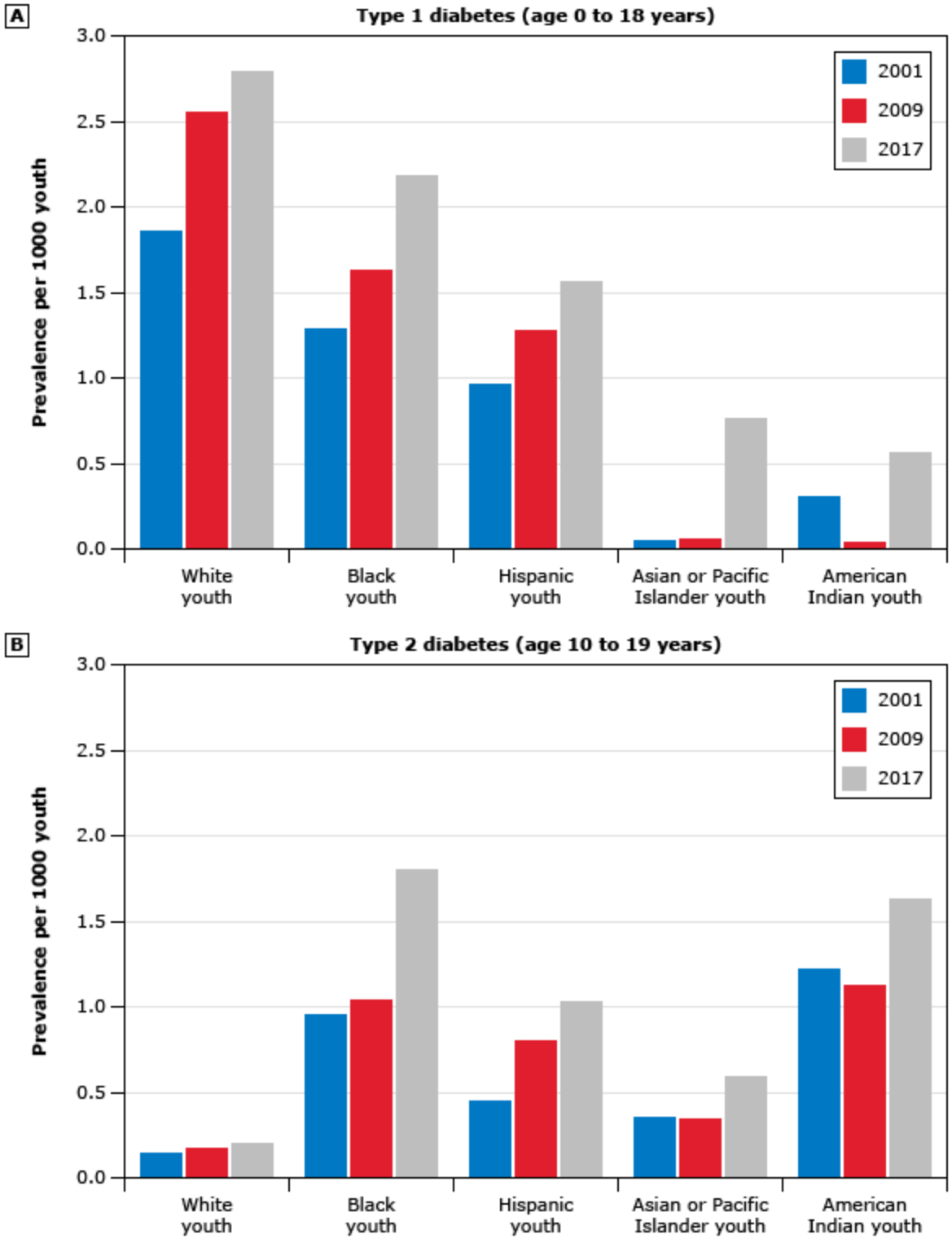
Trends in incidence of type 1 diabetes in United States children (0 to 19 years)



Reproduced from: National Diabetes Statistics Report 2020: Estimates of Diabetes and Its Burden in the United States. US Centers for Disease Control and Prevention. Available at: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf (Accessed on September 17, 2021).

Graphic 132714 Version 2.0

Prevalence of type 1 and type 2 diabetes in children and adolescents in the United States, 2001 and 2009



Data from: Lawrence JM, Divers J, Isom S, et al. Trends in prevalence of type 1 and type 2 diabetes in children and adolescents in the US, 2001-2017. JAMA 2021; 326:717.

Graphic 95197 Version 3.0

American Diabetes Association criteria for the diagnosis of diabetes

1. A1C ≥6.5%. The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*   **OR**
2. FPG ≥126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least 8 hours.*   **OR**
3. 2-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the World Health Organization, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*   **OR**
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

A1C: glycated hemoglobin; DCCT: Diabetes Control and Complications Trial; FPG: fasting plasma glucose; NGSP: National Glycohemoglobin Standardization Program; OGTT: oral glucose tolerance test.

* In the absence of unequivocal hyperglycemia, diagnosis requires 2 abnormal test results from the same sample or in 2 separate test samples.

Graphic 61853 Version 19.0

Characteristics of type 1 and type 2 diabetes mellitus in children and adolescents

	Type 1 diabetes	Type 2 diabetes
Prevalence	Common, increasing	Increasing
Age at presentation	Throughout childhood	Puberty
Onset	Typically acute severe	Insidious to severe
Ketosis at onset	Common	5 to 10%*
Affected relative	5 to 10%	75 to 90%
Female:male	1:1	Approximately 2:1
Inheritance	Polygenic	Polygenic
HLA-DR3/4	Strong association	No association
Ethnicity	Most common in non-Hispanic White people	All¶
Insulin secretion	Decreased/absent	Variable
Insulin sensitivity	Normal when controlled	Decreased
Insulin dependence	Permanent	Variable
Obese or overweight	20 to 25% overweightΔ	>80% obese
Acanthosis nigricans	12%◇	50 to 90%◇
Pancreatic antibodies	Yes§	No¥

T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus; IAA: autoantibodies to insulin; ICA: islet cell cytoplasm; GAD: glutamic acid decarboxylase; IA: tyrosine phosphatase (insulinoma-associated) antibody; ZnT8: zinc channel antibody.

* Reported frequency of ketonuria or ketoacidosis at time of diagnosis of T2DM varies widely.

¶ In North America, T2DM predominates in Native American, African American, Hispanic, Canadian First Nation, Pacific Islander, and Asian American youth[1].

Δ With increased prevalence of childhood overweight, 20 to 25% of newly diagnosed children with T1DM are overweight, which is higher than the prevalence of *overweight* in a similar population without T1DM. However, the prevalence of *obesity* is not increased among children and adolescents with T1DM[2,3]. Recent weight loss is common at presentation of children with T1DM, including among those who are overweight or obese.

◇ These frequencies of acanthosis nigricans are based on a registry study in the United States. Populations with lower rates of obesity or different ethnic mixes may have different results[4].

§ IAA, ICA, GAD, IA-2 and IA-2-beta, or ZnT8 are present at diagnosis in 85 to 98% of patients with T1DM[4,5].

¥ One study reported that 9.8% of youth with phenotypic T2DM have pancreatic antibodies to IA-2 and/or GAD[6].

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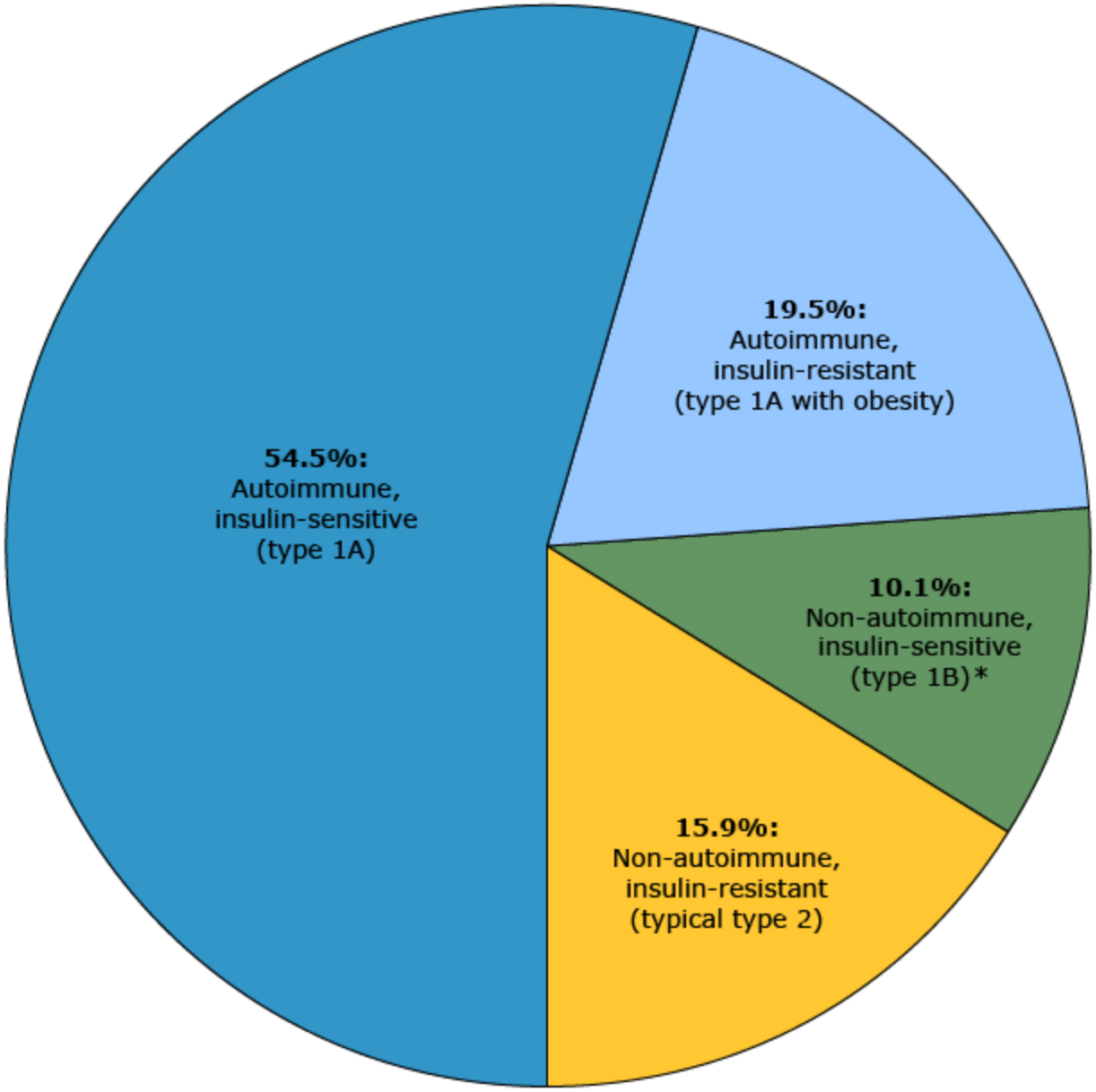
Modified from: Rosenbloom AL, Joe JR, Young RS, Winter WE. Emerging epidemic of type 2 diabetes in youth. Diabetes care 1999; 22:345-354.

Graphic 59370 Version 20.0

Relative prevalence of diabetes phenotypes in American youth



Relative prevalence of four diabetes phenotypes in individuals <20 years of age in the United States, from the SEARCH for Diabetes in Youth study, 2011.

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* Probably undetected autoimmunity, but may include some cases with monogenic diabetes.

Data from: Dabelea D, Pihoker C, Talton JW, et al. Etiological approach to characterization of diabetes type: the SEARCH for Diabetes in Youth Study. Diabetes Care 2011; 34:1628.

Graphic 129475 Version 1.0

Drugs that can impair glucose tolerance or cause overt diabetes mellitus

Category	Agents	Mechanism*
Anti-infectives		
Fluoroquinolones	Gatifloxacin¶ (not available in United States), moxifloxacin	Altered insulin secretion. Association with moxifloxacin is rare.
HIV antiretrovirals	Protease inhibitors Nucleoside reverse transcriptase inhibitors (NRTIs)	Increased peripheral insulin resistance. Part of antiretroviral-associated metabolic syndrome.
Other anti-infectives	Pentamidine	Altered pancreatic beta cell function. Following initial hypoglycemic effect, beta cell destruction can occur.
Antipsychotics		
First-generation	Chlorpromazine¶, perphenazine, other phenothiazines	Mechanism not established. Appears to involve increased insulin resistance and diminished insulin secretion.
Second-generation	Clozapine¶, iloperidone, olanzapine¶, paliperidone, quetiapine, risperidone	Mechanism not established. Appears to involve increased insulin resistance and diminished insulin secretion.
Cardiovascular		
Beta blockers	Atenolol, metoprolol, propranolol[1]	Decreased insulin sensitivity (moderate effect). Carvedilol does not appear to impair glucose tolerance. Refer to UpToDate topic on treatment of hypertension in patients with diabetes mellitus.
Hypolipidemic	Niacin (nicotinic acid)¶, statins	Niacin – Altered hepatic glucose metabolism, probably greater with extended-release form. Statins – Evidence of impaired glucose tolerance due to statins is conflicting, and overall risk appears low.

Thiazide diuretics	Hydrochlorothiazide, chlorthalidone, chlorothiazide, indapamide	Reduced total-body potassium, decreased insulin secretion, and increased insulin resistance[2]. Infrequent with low dosages (ie, hydrochlorothiazide ≤25 mg or equivalent). Potassium supplementation may decrease thiazide-associated glucose intolerance.
Vasodilators	Diazoxide	Reduced insulin secretion and sensitivity, increased hepatic glucose production.
Vasopressors	Epinephrine¶, norepinephrine[3]	Activation of glycogenolysis, increased hepatic gluconeogenesis, stimulation of glucagon and cortisol, inhibition of insulin secretion.
Gonadotropin-releasing hormone agonists	Class effect in males receiving androgen deprivation therapy for metastatic prostate cancer	Refer to UpToDate topic on side effects of androgen deprivation therapy.
Glucocorticoids, systemic* NOTE: Glucocorticoids are a particularly common cause of clinically significant drug-induced hyperglycemia	Class effect	Multifactorial, including increase hepatic glucose production, increased insulin resistance, increased expression of peroxisome proliferator activated gamma receptors (PPAR-gamma) Refer to UpToDate topic on majo side effects of systemic glucocorticoids.
Hormones, growth	Somatropin, tesamorelin	Increased counterregulatory responses. Refer to UpToDate topics on treatment of growth hormone deficiency and treatment of HIV-associated lipodystrophy.
Immune checkpoint inhibitors		
Programmed cell death receptor 1 (PD-1) inhibitors	Nivolumab, pembrolizumab, cemiplimab	PD-1 and PD-L1 inhibitors overcome immune suppression of cytotoxic T cells in the tumor milieu; CTLA-4 inhibitors overcome immune suppression
Programmed cell death ligand 1 (PD-L1) inhibitors	Atezolizumab, avelumab, durvalumab	

		of cytotoxic T cells in secondary lymphoid tissues. Immune checkpoint inhibitors promote activation of cytotoxic T cells that act "off target" to attack and destroy islet cells.
Cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitors	Iipilimumab, tremelimumab	
Immunosuppressants	Cyclosporine (cyclosporin), sirolimus, tacrolimus	Decreased insulin synthesis and release. Refer to UpToDate topic on new-onset diabetes after transplant ir kidney transplant recipients.

* Degree or incidence of hyperglycemia is generally related to dose.

¶ Among agents listed, these have been more frequently associated with hyperglycemia and/or diabetes mellitus.

Data from:

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Graphic 67257 Version 15.0

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Lynne L Levitsky, MD No relevant financial relationship(s) with ineligible companies to disclose. **Madhusmita Misra, MD, MPH** Consultant/Advisory Boards: Abbvie [Puberty suppression]. Other Financial Interest: Lumos Pharmaceuticals key opinion leader [Growth hormone secretagogue]; Tonix Pharmaceuticals study drug donation [Oxytocin- potential bone anabolic agent]. All of the relevant financial relationships listed have been mitigated. **Joseph I Wolfsdorf, MD, BCh** Consultant/Advisory Boards: Ultragenyx [Gene therapy trial in type 1A glycogen storage disease]. All of the relevant financial relationships listed have been mitigated. **Jessica Kremen** No relevant financial relationship(s) with ineligible companies to disclose.

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Conflict of interest policy

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