Definition, epidemiology, and classification of diabetes in children and adolescents


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Executive summary and Recommendations

• Diagnostic criteria for diabetes are based on laboratory measurement of plasma glucose concentrations and the presence or absence of symptoms (E). Finger prick blood glucose level (BGL) testing should not be used to diagnose diabetes (E).

• A marked elevation of the blood glucose level confirms the diagnosis. If ketones are present in blood or urine, treatment is urgent, and the child should be referred the same day to avoid the development of ketoacidosis (A).

• The diagnosis of diabetes should not be based on a single plasma glucose concentration. If the diagnosis is in doubt, continued observation with fasting and/or 2 h postprandial blood glucose levels and/or an oral glucose tolerance test (OGTT) may be required (E). However, an OGTT is not needed and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria as excessive hyperglycemia can result (E).

• Hyperglycemia detected under conditions of stress, such as acute infection, trauma, surgery, respiratory distress, circulatory, or other stress may be transitory and requires treatment but should not in itself be regarded as diagnostic of diabetes (E).

• The possibility of other types of diabetes should be considered in the child who has negative diabetes-associated autoantibodies and (B):
  ◦ An autosomal dominant family history of diabetes.
  ◦ Diabetes diagnosed in the first 6 months of life.
  ◦ Mild fasting hyperglycemia [5.5–8.5 mmol (100–150 mg/dL)], which does not progress, especially if young, non-obese, and asymptomatic.
  ◦ Associated conditions such as deafness, optic atrophy, or syndromic features.
  ◦ A history of exposure to drugs known to be toxic to β cells or cause insulin resistance.

• The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important implications for both treatment and
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Diagnostic criteria for diabetes in childhood and adolescence

Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of symptoms (1, 4). Different methods can be used to diagnose diabetes (Table 1) and in the absence of unequivocal hyperglycemia, must be confirmed by repeat testing.

- Diabetes in young people usually presents with characteristic symptoms such as polyuria, polydipsia, nocturia, enuresis, weight loss—which may be accompanied by polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia.

- In its most severe form, ketoacidosis or less commonly non-ketotic hyperosmolar syndrome may develop and lead to stupor, coma and in the absence of effective treatment, death.

- If symptoms are present, urinary ‘dipstick’ testing for glycosuria and ketonuria, or measurement of glucose and ketones using a bedside glucometer, provides a simple and sensitive screening tool. If the blood glucose level is elevated, then prompt referral to a center with experience in managing children with diabetes is essential. Waiting another day specifically to confirm the hyperglycemia is unnecessary and if

<table>
<thead>
<tr>
<th>Table 1. Criteria for the diagnosis of diabetes mellitus (1, 2)</th>
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<tbody>
<tr>
<td>i Classic symptoms of diabetes or hyperglycemic crisis, with plasma glucose concentration ≥11.1 mmol/L (200 mg/dL) or</td>
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<tr>
<td>ii Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL). Fasting is defined as no caloric intake for at least 8 h* or</td>
</tr>
<tr>
<td>iii Two hour postload glucose ≥11.1 mmol/L (≥200 mg/dL) during an OGTT*.</td>
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<tr>
<td>iv HbA1c &gt;6.5%†</td>
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</table>

*In the absence of unequivocal hyperglycemia, the diagnosis of diabetes based on these criteria should be confirmed by repeat testing.
†A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. The role of HbA1c alone in diagnosing type 1 diabetes in children is unclear.

Definition and description

The term diabetes mellitus describes a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Inadequate insulin secretion and/or diminished tissue responses to insulin in the complex pathways of hormone action result in deficient insulin action on target tissues, which leads to abnormalities of carbohydrate, fat, and protein metabolism. Impaired insulin secretion and/or action may coexist in the same patient (1, 2).

While the etiology of diabetes is heterogeneous, most cases of diabetes can be classified into two broad etiopathogenetic categories (discussed in further detail below): type 1 diabetes, which is characterized by an absolute deficiency of insulin secretion; or type 2 diabetes, which results from a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. While type 1 diabetes remains the most common form of diabetes in young people in many populations, especially those of Caucasian background, type 2 diabetes has become an increasingly important public health concern globally, see the ISPAD guideline on type 2 diabetes (3).
ketones are present in blood or urine, treatment is urgent, because ketoacidosis can evolve rapidly.

- A formal plasma glucose measurement is required to confirm the diagnosis; this should be based on laboratory glucose oxidase estimation rather than a capillary blood glucose monitor.
- Scenarios where the diagnosis of diabetes may be unclear include:
  - Absence of symptoms, for example, hyperglycemia detected incidentally or in children participating in screening studies
  - Presence of mild/atypical symptoms of diabetes
  - Hyperglycemia detected under conditions of acute infective, traumatic, circulatory, or other stress, which may be transitory and should not be regarded as diagnostic of diabetes.

In these situations, the diagnosis of diabetes should not be based on a single plasma glucose concentration and continued observation with fasting and 2 h postprandial blood glucose levels and/or an OGTT may be required to confirm the diagnosis.

- An OGTT is not required and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria as excessive hyperglycemia can result. It is rarely indicated in making the diagnosis of type 1 diabetes in childhood and adolescence, but may be useful in diagnosing other forms such as type 2 diabetes, monogenic diabetes, or cystic fibrosis related diabetes (CFRD). If doubt remains, periodic retesting should be undertaken until the diagnosis is established.
- HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement (2, 5). However, in rapidly evolving diabetes, such as the development of type 1 diabetes in some children, HbA1c may not be significantly elevated despite classic symptoms of diabetes.

Impaired glucose tolerance and impaired fasting glucose

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes (2). IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation or different stages in the progression of dysglycemia. IFG is a measure of disturbed carbohydrate metabolism in the basal state while IGT is a dynamic measure of carbohydrate intolerance after a standardized glucose load. IFG and IGT are not clinical entities in their own right; patients with IFG and/or IGT are referred to as having ‘prediabetes’ indicating their relatively high risk for development of diabetes and cardiovascular disease.

IFG and IGT may be associated with the metabolic syndrome, the features of which include obesity (particularly abdominal or visceral obesity), dyslipidemia [high triglyceride and/or low-high-density lipoprotein (HDL)], and hypertension. IFG and IGT can be observed as intermediate stages in any of the disease processes listed in Table 2 (etiologic classification of diabetes).

Individuals who meet criteria for IGT or IFG may be euglycemic in their daily lives as shown by normal or near-normal HbA1c, and those with IGT may manifest hyperglycemia only when challenged with an OGTT.

Categories of fasting plasma glucose (FPG) are defined as follows:

- FPG <5.6 mmol/L (100 mg/dL) = normal fasting glucose.
- FPG 5.6–6.9 mmol/L (100–125 mg/dL) = IFG.
- FPG ≥7.0 mmol/L (126 mg/dL) = diagnosis of diabetes (the diagnosis must be confirmed, as described in Table 1).

The corresponding categories when the OGTT is used are as follows:

- Two hour postload glucose <7.8 mmol/L (140 mg/dL) = normal glucose tolerance.
- Two hour postload glucose 7.8–<11.1 mmol/L (140–200 mg/dL) = IGT.
- Two hour postload glucose ≥11.1 mmol/L (200 mg/dL) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).

Classification of diabetes and other categories of glucose regulation

The type of diabetes assigned to a young person at diagnosis is typically based on their characteristics at presentation, however, increasingly the ability to make a clinical diagnosis has been hampered by factors including the increasing prevalence of overweight in young people with type 1 diabetes (6, 7) and the presence of diabetic ketoacidosis (DKA) in some young people at diagnosis of type 2 diabetes (8, 9). In addition, the presentation of a familial form of mild diabetes during adolescence should raise the suspicion of monogenic diabetes, which accounts for 1–4% of pediatric diabetes cases (10–13).

The etiological classification of diabetes is shown in Table 2, which is based on the American Diabetes
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| I. Type 1 |  
| --- | --- |
| β-Cell destruction, usually leading to absolute insulin deficiency | |
| A. Immune mediated | |
| B. Idiopathic | |

<table>
<thead>
<tr>
<th>II. Type 2</th>
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<td>May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance</td>
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</table>

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<tr>
<th>III. Other specific types</th>
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</thead>
<tbody>
<tr>
<td>A. Genetic defects of β-cell function</td>
<td>E. Drug- or chemical-induced</td>
</tr>
<tr>
<td>1. Chromosome 12, HNF1A (MODY3)</td>
<td>1. Vacor</td>
</tr>
<tr>
<td>2. Chromosome 7, GCK (MODY2)</td>
<td>2. Pentamidine</td>
</tr>
<tr>
<td>3. Chromosome 20, HNF4B (MODY1)</td>
<td>3. Nicotinic acid</td>
</tr>
<tr>
<td>4. Other rare forms of MODY including:</td>
<td>4. Glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>5. Thyroid hormone</td>
</tr>
<tr>
<td></td>
<td>6. Diazoxide</td>
</tr>
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<td></td>
<td>7. β-Adrenergic agonists</td>
</tr>
<tr>
<td></td>
<td>8. Thiazides</td>
</tr>
<tr>
<td></td>
<td>9. Dilantin</td>
</tr>
<tr>
<td></td>
<td>10. α-Interferon</td>
</tr>
<tr>
<td></td>
<td>11. Others</td>
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</tbody>
</table>

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<tr>
<th>IV. Gestational diabetes mellitus (GDM)</th>
<th></th>
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<tbody>
<tr>
<td>CEL, carboxyl ester lipase; HNF, hepatocyte nuclear factor; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; IPF, insulin promoter factor; KLF11, Kruppel-like factor 11; MODY, maturity-onset diabetes of the young; PAX4, Paired Domain gene 4.</td>
<td></td>
</tr>
<tr>
<td>Individuals with any form of diabetes may or may not require insulin treatment at various stages of their disease. Such use of insulin does not, of itself, classify the diabetes type.</td>
<td></td>
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</tbody>
</table>

Association classification (2). Some forms, including specific drug-, hormone-, or toxin-induced forms of diabetes, are rarely observed in young people. In Africa and South Asia, atypical forms of diabetes may occur in older children, adolescents, and young adults. These include ketosis-prone atypical diabetes, malnutrition-related diabetes, and fibrocalculous pancreatic disease (14, 15).

The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important
implications for both therapeutic decisions and educational approaches. Diagnostic tools, which may assist in confirming the diabetes type, include:

- **Diabetes-associated autoantibodies**: the presence of GAD, IA2, IAA, and/or ZnT8 confirms the diagnosis of type 1 diabetes, as one and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected (16).
- **An elevated fasting C-peptide level** can distinguish young people with non-autoimmune, insulin resistant type 2 diabetes from type 1 diabetes (17). However, as there is considerable overlap in insulin or C-peptide measurements between type 1 and type 2 diabetes in the first year after diagnosis, C-peptide measurements are not recommended in the acute phase. If patients are insulin treated, measuring C-peptide when the glucose is sufficiently high (>8 mmol/L) to stimulate C peptide will detect if endogenous insulin secretion is still present. This is rare beyond the remission phase (2–3 yr) in children with type 1 diabetes.

The possibility of other types of diabetes should be considered in the child who has no autoantibodies and:

- an autosomal dominant family history of diabetes;
- diabetes diagnosed in the first 6 months of life;
- mild fasting hyperglycemia [5.5–8.5 mmol (100–150 mg/dL)], which does not progress, especially if young, non-obese, and asymptomatic;
- associated conditions such as deafness, optic atrophy, or syndromic features; and
- a history of exposure to drugs known to be toxic to β cells or cause insulin resistance.

Characteristic features of youth onset type 1 diabetes in comparison with type 2 diabetes and monogenic diabetes are shown in Table 3. Type 2 diabetes is more completely discussed in the ISPAD guidelines on type 2 diabetes (3) and monogenic diabetes (18).

Regardless of the type of diabetes, however, the child who presents with severe hyperglycemia, ketonemia, and metabolic derangements will require insulin therapy initially to reverse the metabolic abnormalities.

**Pathogenesis of type 1 diabetes**

Type 1 diabetes is characterized by chronic immune-mediated destruction of pancreatic β-cells, leading to partial, or in most cases, absolute insulin deficiency. The majority of cases (type 1A) result from autoimmune mediated pancreatic β-cell destruction, which occurs at a variable rate, and becomes clinically symptomatic when approximately 90% of pancreatic β-cells are destroyed. The etiology is multifactorial, however, the specific roles for genetic susceptibility, environmental factors, the immune system, and β-cells in the pathogenic processes underlying type 1 diabetes remain unclear.

Diabetes-associated autoantibodies, which are serological markers of β-cell autoimmunity, include GAD, IA2, IAA, and ZnT8 (16). The expression of these antibodies is age-dependent, with IAA and ZnT8 more commonly expressed in children aged <10 yr, while GAD and IA-2 are associated with older age and GAD with female gender (19).

Susceptibility to autoimmune type 1 diabetes is determined by multiple genes; with more than 60 risk loci identified by genome-wide association studies (20). Human leukocyte antigen (HLA) genotype confers approximately 50% of risk (21, 22); in the Caucasian population, specific combinations of HLA DR and DQ alleles determine genetic susceptibility (23). The highest-risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 using the former serological designation). Haplotypes conferring protection from type 1 diabetes are DRB1*15:01-DQA1*01:02-DQB1*06:02, DRB1*14:01-DQA1*01:01-DQB1*05:03, and DRB1*07:01-DQA1*02:01-DQB1*03:03 (24). For individuals who are heterozygotes for the two highest risk HLA haplotypes (DR3/4), the odds ratio is 30 for development of islet autoimmunity and type 1 diabetes (24), however, <10% of those with HLA conferred diabetes susceptibility genes progress to clinical disease (25).

Individuals at increased risk of developing type 1 diabetes can be identified by a combination of diabetes-associated autoantibodies, genetic markers, intravenous glucose tolerance test (IVGTT) and/or OGTT (26–30).

The environmental triggers (infective and/or chemical) which initiate pancreatic β-cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms (28, 31, 32). Enterovirus infection has been associated with development of both islet autoimmunity and type 1 diabetes in many populations (33, 34) and enteroviruses have been detected in the islets of individuals with diabetes (35–37).

When the clinical presentation is typical of type 1 diabetes but antibodies are absent, then the diabetes is classified as type 1B (idiopathic). Most cases are of African or Asian ancestry, however, other forms of diabetes, including type 2 and monogenic diabetes, should also be considered (as shown in Table 2). In geographical areas where type 1 diabetes occurs with lower incidence, there is a higher rate of DKA at presentation (38).
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<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Monogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Polygenic</td>
<td>Polygenic</td>
<td>Monogenic</td>
</tr>
<tr>
<td>Age of onset</td>
<td>6 months to young adulthood</td>
<td>Usually pubertal (or later)</td>
<td>Monogenic Usually postpubertal except GCK and NDM</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Most often acute, rapid</td>
<td>Variable; from slow, mild (often insidious) to severe</td>
<td>Variable (may be incidental in GCK)</td>
</tr>
<tr>
<td>Associations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ketosis</td>
<td>Common</td>
<td>Uncommon</td>
<td>Population frequency</td>
</tr>
<tr>
<td>Obesity</td>
<td>Population frequency</td>
<td>Increased frequency</td>
<td>Population frequency</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Frequency (% of all diabetes in young people)</td>
<td>Usually &gt;90%</td>
<td>Most countries &lt;10% (Japan 60–80%)</td>
<td>Population frequency</td>
</tr>
<tr>
<td>Parent with diabetes</td>
<td>2–4%</td>
<td>80%</td>
<td>90%</td>
</tr>
</tbody>
</table>

**Epidemiology of type 1 diabetes**

In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, while across the lifespan, type 1 diabetes accounts for 5–10% of individuals with diabetes. Overall, approximately 80 000 children under 15 yr are estimated to develop type 1 diabetes annually worldwide (39). Type 2 diabetes is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at-risk populations (3), but population-based epidemiological data are more limited compared with type 1 diabetes.

Older epidemiological incidence studies define the ‘onset of type 1 diabetes’ by the date of the first insulin injection because of the variable time between the onset of symptoms and diagnosis (40), while current guidelines define diabetes based on abnormal test results (as shown in Table 1).

Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations (Figure 1), with the highest incidence rates observed in Finland (41), Northern Europe (42–44), and Canada (45). There is an approximate 20-fold difference in the disease incidence among Caucasians living in Europe (25), and incidence rates are correlated with the frequency of HLA susceptibility genes in the general population (46, 47).

Of the estimated approximately 500 000 children living with type 1 diabetes, approximately 26% are from Europe, and 22% from North America and the Caribbean region (39). In Asia, the incidence of type 1 diabetes is very low, Japan approximately 2 per 100 000 person-years (48); China (Shanghai) 3.1 per 100 000 (49); Taiwan approximately 5 per 100 000 (50) and has a different and unique HLA association compared with Caucasians (51–54). In addition, there is a distinct slowly progressive form of type 1 diabetes in Japan, which represents approximately one third of cases of type 1 diabetes (55, 56). Mean annual incidence rates for childhood type 1 diabetes (<age 15 yr) comparing different countries globally are shown in Fig. 1.

A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months, whereas other reports demonstrate higher rates in warmer seasons (49) or variation from year to year (57–59). In addition, development of islet autoimmunity also demonstrates seasonal variation, as does the association between month of birth and risk of type 1 diabetes (60, 61).

In contrast to most autoimmune disorders, which disproportionately affect females, gender differences in the incidence of type 1 diabetes are found in some, but not all, populations. However, a male gender bias is generally observed in older adolescents and young adults (59, 62, 63).

A rise in type 1 diabetes incidence has been observed globally in recent decades (41, 43, 49, 50, 57–59, 64–72). In some reports there has been a disproportionately greater increase in those under the age of 5 yr (64, 73) and in developing countries or those undergoing economic transition in recent decades (64, 68). There is evidence for a plateau in incidence in some countries in recent years (41, 43, 69, 74, 75). The rising incidence of type 1 diabetes is associated with an increased proportion of individuals with low-risk HLA genotypes in some populations (76–78), suggesting an increasing role for environmental factors in the disease etiology.

Familial aggregation accounts for approximately 10% of cases of type 1 diabetes (79), but more than 20% when accounting for the extended family history (80), however, there is no recognizable pattern of inheritance. The risk of diabetes to an identical twin of a patient with type 1 diabetes is <40% (25, 81); for a sibling the risk is approximately 4% by age 20 yr (82, 83) and 9.6% by age 60 yr (49); compared with 0.5% for...
the general population. The cumulative risk of diabetes by age 15 is greater in HLA-identical DR3-DQ2/DR4-DQ8 siblings (17 vs. 6% in those sharing one haplotype or none) (84). The risk is also higher in siblings of probands diagnosed at younger age, paternal young-onset diabetes, male sex, and older parental age (82, 84, 85).

Type 1 diabetes is two to three times more common in the offspring of diabetic men (3.6–8.5%) compared with diabetic women (1.3–3.6%) (85–90). The cumulative risk of type 1 diabetes is approximately 4% for offspring of adult onset (15–39 yr) type 1 diabetes (91), with a similar recurrence risk in the offspring of mothers and fathers.

**Monogenic diabetes**

A familial form of mild, non-ketotic diabetes presenting during adolescence or early adulthood (92, 93),
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Neonatal diabetes

Type 1 diabetes rarely presents in the first year of life, particularly before age 6 months (98, 99), and in very young infants is most likely to be due to mutations in the transcription factor FOXP3 as part of the immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) syndrome (100). A monogenic form of diabetes in the first 6 months of life is known as NDM, although cases may present as late 9–12 months of age (101–103). An alternative term, ‘monogenic diabetes of infancy’ has therefore been suggested to account for the fact that many cases are diagnosed beyond the neonatal period (104), but NDM is still widely used.

This rare condition (approximately 1 in 100,000–400,000 births) may be associated with intrauterine growth retardation, a consequence of prenatal insulin deficiency (105, 106), as well as a range of associated extra-pancreatic clinical features.

Approximately half of NDM cases will require lifelong treatment to control hyperglycemia (permanent NDM (PNDM)). In the remaining cases, diabetes remits within weeks or months (transient NDM (TNDM)), although may relapse later in life.

Approximately two thirds of cases of TNDM are caused by abnormalities in an imprinted region on chromosome 6q24 (107, 108). The majority of remaining cases result from activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (K\textsubscript{ATP}) channel of the β-cell membrane (KCNJ11, encoding the Kir6.2 subunit, or ABCC8, encoding the SUR1 subunit) (109). Although diabetes is transient during infancy, permanent diabetes appears in 50–60% of patients later in life, typically around puberty (110).

PNDM is associated with activating mutations of KCNJ11 and ABCC8 (111, 112) and mutations in the insulin gene (INS) (113–117) and less commonly, GCK (118, 119) and the transcription factor for pancreatic development, PDX1 (120). In addition, a range of syndromic forms of diabetes may present during infancy. Further details of the genetic basis of NDM are provided in the chapter on The diagnosis and management of monogenic diabetes in children and adolescents (18).

Mitochondrial diabetes

Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterized by progressive non-autoimmune β-cell failure (121, 122). Maternal transmission of mutated mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition (123, 124).

Mitochondrial diabetes may present with variable phenotypes, ranging from acute onset with or without ketoacidosis, to a more gradual onset resembling type 2 diabetes. The disease typically presents in young adults (121), but can occur in children and adolescents, who have a lower prevalence of hearing loss compared with adults (125).

Cystic fibrosis and diabetes

CFRD is the most common comorbidity associated with cystic fibrosis (CF). The pathophysiology of CFRD is primarily due to insulin deficiency, along with glucagon deficiency and variable insulin resistance (particularly during acute illness, secondary to infections and medications such as bronchodilators and glucocorticoids). Other contributory factors include the need for high caloric intake, delayed
gastric emptying, altered intestinal motility, and liver disease (126).

CF is associated with a progressive deterioration in glucose tolerance as individuals grow older, including indeterminate glycemia followed by IGT and finally diabetes. Early CFRD is characterized by normal fasting glucose levels, but over time fasting hyperglycemia develops.

CFRD typically presents in adolescence and early adulthood (127), but may occur at any age including infancy. The presentation may be asymptomatic, insidious, associated with poor weight gain (128), or precipitated by insulin resistance associated with infection/use of glucocorticoids. Detection rates for CFRD vary with screening practices (129). The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates.

The onset of CFRD is a poor prognostic sign, and was associated with increased morbidity and mortality reported prior to implementation of routine screening for CFRD and early use of insulin therapy (130). Poorly controlled CFRD interferes with immune responses to infection and promotes protein catabolism (129, 131).

Annual screening for CFRD should commence by age 10 yr in all CF patients who do not have CFRD. Screening should be performed using the 2-h 75 g (1.75 g/kg) OGTT. A more comprehensive discussion can be found in the ISPAD guideline on CFRD (132).

**Diabetes induced by drugs and toxins**

A range of pharmacological agents impair insulin secretion (e.g., propranolol), and/or action (e.g., glucocorticoids, antipsychotic agents), while others (e.g., pentamidine) can cause permanent β-cell damage (2, 133, 134).

In neurosurgery, large doses of dexamethasone are frequently used to prevent cerebral edema. The additional stress of surgery may add to the drug-induced insulin resistance, and cause a relative insulin deficiency, sufficient to cause transient diabetes. Hyperglycemia may be exacerbated if large volumes of intravenous dextrose are given for management of diabetes insipidus. An intravenous insulin infusion is the optimal method to control the hyperglycemia, which is usually transient.

In oncology, protocols which employ L-asparaginase, high dose glucocorticoids, cyclosporin, or tacrolimus (FK506) may be associated with diabetes. L-Asparaginase usually causes a reversible form of diabetes (135). Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction (136). Often the diabetes is cyclical and associated with the chemotherapy cycles, especially if associated with large doses of glucocorticoids.

Following organ transplantation, diabetes most frequently occurs with the use of high dose glucocorticoids and tacrolimus; the risk is increased in patients with preexisting obesity (137–139).

Diabetes can also be induced by the use of atypical antipsychotics including olanzapine, risperidol, quetiapine, and ziprasidone, which may be associated with weight gain. In children and adolescents, use of antipsychotics was associated with a more than threefold increased risk of non-autoimmune diabetes, and the risk was significantly higher with increasing cumulative dose (140). Among Canadian youth with medication-induced diabetes, risk factors for type 2 diabetes (family history of type 2 diabetes, obesity, non-caucasian ethnicity, and acanthosis nigricans) were less commonly observed than in youth with type 2 diabetes (141).

**Stress hyperglycemia**

Stress hyperglycemia has been reported in up to 5% of children presenting to an emergency department, in association with acute illness/sepsis; traumatic injuries, febrile seizures, burns, and elevated body temperature (>39°C) (142–145). However, the incidence of severe hyperglycemia (≥16.7 mmol/L or 300 mg/dL) was <1% and almost two thirds of patients had received glucose-influencing interventions before evaluation, suggesting the etiology may at least in part be iatrogenic (146).

The reported incidence of progression to overt diabetes varies from 0 to 32% (145, 147–152). Children with incidental hyperglycemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness (150). As would be expected, testing for diabetes-associated autoantibodies had a high positive and negative predictive value for the development of type 1 diabetes in children with stress hyperglycemia (150). In children who have sustained severe burns, insulin resistance may persist for up to 3 yr later (144).

**Conflicts of interest**

The authors have declared no conflicts of interest.

**References**

35. Richardson SJ, Wilcox A, Bone AJ, Fouls AK, Morgan NG. The prevalence of enteroviral
64. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new


73. GYURUS EK, PATTERTON C, SOLTESZ G. Twenty-one years of prospective incidence of childhood type 1 diabetes in Hungary – the rising trend continues (or peaks and highlands?). Pediatr Diabetes 2012: 13: 21–25.


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