


# ISPAD Clinical Practice Consensus Guidelines 2022: Definition, epidemiology, and classification of diabetes in children and adolescents

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## 1 | INTRODUCTION

This chapter serves as an update and replaces the 2018 ISPAD consensus guideline on definition, epidemiology, and classification of diabetes in children and adolescents.<sup>1</sup> It provides an evidence-based summary of current recommendations for defining and classifying diabetes in youth, as well as a description of the current knowledge about the epidemiology of this disease, emphasizing its heterogeneity.

- Research has been conducted worldwide over the last several years combining genetic, clinical, and pathophysiological characteristics to better define the different types of diabetes in childhood and better understand the subtypes that are currently clustered into two most common types, type 1 diabetes (T1D) and type 2 diabetes (T2D).
- The goal of accurately defining the type of diabetes is to optimize personalized treatment approaches.
- Significant geographical variation in the incidence and prevalence of childhood T1D and T2D continues to be observed.

## 2 | WHAT IS NEW OR DIFFERENT

- Diabetes in youth is a heterogeneous disorder in which clinical presentation and disease progression may vary considerably.
- Classification is important for determining therapy, but some individuals cannot be clearly classified at the time of diagnosis.

## 3 | EXECUTIVE SUMMARY AND RECOMMENDATIONS

- Diagnostic criteria for all types of diabetes in children and adolescents are based on laboratory measurement of blood glucose levels

(BGL) and the presence or absence of symptoms. BGL testing with a glucometer should not be used to diagnose diabetes. **E**

- A marked elevation of the plasma glucose concentration confirms the diagnosis of diabetes, including a random plasma glucose  $\geq 11.1$  mmol/L (200 mg/dl) or fasting plasma glucose  $\geq 7.0$  mmol/L ( $\geq 126$  mg/dl) in the presence of overt symptoms. **B**
- If blood or urine ketone levels are significantly increased, treatment is urgent and the child should be referred to a diabetes specialist on the same day to avoid the development of diabetic ketoacidosis (DKA). **A**
- The diagnosis of diabetes should not be based on a single BGL in the absence of overt symptoms. If the diagnosis is in doubt, continued observation with fasting and/or 2-h postprandial plasma glucoses 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. **E**
- Hyperglycemia detected under conditions of stress, such as acute infection, trauma, surgery, respiratory distress, circulatory, rare metabolic conditions or other stress may be transitory and requires treatment but should not in itself be regarded as diagnostic of diabetes. **E**
- The differentiation between T1D, T2D, monogenic, and other forms of diabetes have important implications for both treatment and education. **E**
- Diagnostic tools, which may assist in confirming the diabetes type if the diagnosis is unclear, include:
  - diabetes-associated autoantibodies: glutamic acid decarboxylase 65 autoantibodies (GAD); tyrosine phosphatase-like insulinoma antigen 2 (IA2); insulin autoantibodies (IAA); and  $\beta$ -cell specific zinc transporter 8 autoantibodies (ZnT8). The presence of one of more of these antibodies confirms the diagnosis of T1D in children. **A**
- 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 (maturity onset diabetes of the young [MODY])
  - age less than 12 months and especially in first 6 months of life (neonatal diabetes mellitus [NDM])
  - mild-fasting hyperglycemia (5.5–8.5 mmol/L [100–150 mg/dl]), especially if young, non-obese, and asymptomatic (MODY)
  - a prolonged honeymoon period lasting more than 1 year or an unusually low requirement for insulin of  $\leq 0.5$  U/kg/day after 1 year of diabetes (MODY)
  - associated conditions such as deafness, optic atrophy, or syndromic features (mitochondrial disease)
  - a history of exposure to drugs known to be toxic to  $\beta$ -cells or cause insulin resistance (e.g., immunosuppressive drugs such as tacrolimus or cyclosporin; glucocorticoids or some antidepressants).
- Molecular genetic testing can help define the specific cause of diabetes and inform the appropriate treatment of children with suspected monogenic diabetes. **C** While certain clinical characteristics

should alert clinicians to the possibility of monogenic diabetes, the absence of these characteristics does not exclude monogenic diabetes.

## 4 | 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 result in deficient insulin action on target tissues, which leads to abnormalities of carbohydrate, fat, and protein metabolism. Impaired insulin secretion and deficient insulin action may coexist in the same individual.<sup>2,3</sup> While the etiology of diabetes is heterogeneous, most cases of diabetes can be classified into two broad etiopathogenetic categories (discussed later in further detail): T1D, characterized by the destruction of the  $\beta$ -cells, usually by an autoimmune process, resulting in loss of endogenous insulin production, or T2D, characterized by the lack of an adequate insulin response in the presence of increasing insulin resistance. While T1D remains the most common form of youth-onset diabetes in many populations, especially those of European ancestry, T2D is an increasingly important global public health concern among youth, in particular adolescents, in high-risk ethnic populations as well as in those with obesity<sup>4,5</sup> (See ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 diabetes in children and adolescents). In addition, it is now recognized that people with monogenic diabetes, an autosomal dominant diabetes pattern first termed MODY, may make up 1%–6% of autoantibody negative individuals who may, initially, be considered to have either T1D or T2D with decreased insulin secretion.<sup>6,7</sup>

## 5 | DIAGNOSTIC CRITERIA FOR DIABETES IN CHILDHOOD AND ADOLESCENCE

Diagnostic criteria for diabetes are based on BGL measurements and the presence or absence of symptoms.<sup>1–3</sup> Different strategies can be used to measure BGL, including using a fasting plasma glucose (FPG) value, the 2-h plasma glucose (2-h PG) value during an OGTT, or hemoglobin A1c (HbA1c) criteria (Table 1) and in the absence of unequivocal hyperglycemia, diagnosis must be confirmed by repeat testing.

- Youth-onset diabetes usually presents with characteristic symptoms such as polyuria, polydipsia, nocturia, enuresis, and weight loss—which may be accompanied by polyphagia, fatigue, behavioral disturbance, including reduced school performance, and blurred vision. Impairment of growth and susceptibility to perineal candidiasis may also accompany chronic hyperglycemia. However, this is not always the case, particularly in youth with T2D.
- In its most severe form, DKA or (rarer) non-ketotic hyperosmolar syndrome may develop and lead to stupor, coma and, in the absence of effective treatment, death.

**TABLE 1** Criteria for the diagnosis of diabetes mellitus

1. Classic symptoms of diabetes or hyperglycemic crisis with plasma glucose concentration  $\geq 11.1$  mmol/L (200 mg/dl).

Or

2. Fasting plasma glucose  $\geq 7.0$  mmol/L ( $\geq 126$  mg/dl). Fasting is defined as no caloric intake for at least 8 h.<sup>a</sup>

or

3. Two-hour postload glucose  $\geq 11.1$  mmol/L ( $\geq 200$  mg/dl) during an oral glucose tolerance test (OGTT).<sup>a</sup>

The OGTT should be performed using a glucose load containing the equivalent of 75 g of anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g.

Or

4. HbA1c  $\geq 6.5\%$ .<sup>b</sup>

The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardized Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

<sup>a</sup>In the absence of unequivocal hyperglycemia, the diagnosis of diabetes requires two abnormal test results from the same sample or in two separate test samples.

<sup>b</sup>A value less than 6.5% does not exclude diabetes diagnosed using glucose tests. The role of HbA1c alone in diagnosis of T1D in children is unclear.

- If symptoms are present, point-of-care measurement of BGL and ketones using a meter, or urinary “dipstick” testing for glycosuria and ketonuria (if the former is not available) provides a simple and sensitive screening tool. If the BGL is elevated, then prompt referral to a center or facility with experience in managing children with diabetes is essential. Waiting another day, specifically to confirm the hyperglycemia, is unnecessary and if ketones are present in blood or urine, treatment is urgent, because DKA can evolve rapidly.
- A formal plasma glucose measurement is required to confirm the diagnosis. This should be obtained in a laboratory using an analytic instrument rather than a capillary glucose monitor. See Table 1 for fasting versus non-fasting BGL diagnostic cut-points.
- 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 infectious, 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 BGL and/or an OGTT may be required to confirm the diagnosis.
- An OGTT is usually not required and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria. It is rarely indicated for making the diagnosis of T1D in childhood and adolescence but may be useful in diagnosing other

forms such as T2D, monogenic diabetes, or cystic fibrosis-related diabetes (CFRD). If doubt remains, periodic OGTT retesting should be undertaken until the diagnosis is established. It is important that people consume a mixed diet with at least 150 g of carbohydrate on the 3 days prior to oral glucose tolerance testing.<sup>3,8</sup> Fasting and carbohydrate restriction can falsely elevate BGL with an oral glucose challenge.

- HbA1c can be used as a diagnostic test for diabetes, in particular to test for prediabetes or T2D in youth<sup>4</sup>; 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.<sup>3,4</sup> Moreover, the validity of HbA1c as a measure of average BGLs is affected by hemoglobinopathies, certain forms of anemia, or any other condition that affects normal red blood cell turnover. These conditions may follow specific ethnic and geographic distributions and thus is a critical consideration in areas of iron deficiency and anemia. For conditions with abnormal red cell turnover, such as anemias from hemolysis and iron deficiency, as well as cystic fibrosis, the diagnosis of diabetes must exclusively employ BGL criteria.<sup>3</sup> See ISPAD 2022 Consensus Guidelines Chapter 5 on Management of Cystic Fibrosis-Related Diabetes in children and adolescents.

In at-risk cohort studies, however, a rise in HbA1c within the normal range is frequently observed among individuals who subsequently progress to T1D.<sup>9</sup> Data from four separate prospective studies of high-risk subjects <21 years of age (the Diabetes Prevention Trial-Type 1 (DPT-1), The Environmental Determinants of Diabetes in the Young (TEDDY), Trial to Reduce IDDM in the Genetically at Risk (TRIGR), and T1D TrialNet Natural History Study (HbA1C) measured within 90 days of a diagnostic OGTT or fasting PG  $\geq 126$  mg/dl) show that HbA1C  $\geq 6.5\%$  is a highly specific but not a sensitive early indicator of T1D diagnosed by OGTT or asymptomatic hyperglycemia.<sup>10</sup> HbA1c when monitored in individuals longitudinally, even if within the normal range, maybe have added value in T1D prediction.<sup>11</sup> Point-of-care assays for HbA1c are not recommended for diagnostic purposes.

## 6 | 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. IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation or different stages in the progression of dysglycemia.<sup>3</sup> IFG is a measure of disturbed carbohydrate metabolism in the basal state, whereas IGT is a dynamic measure of carbohydrate intolerance after a standardized glucose load. IFG and IGT are not clinical entities in their own right; individuals with IFG and/or IGT are referred to as having “prediabetes,” indicating their relatively high risk

for development of diabetes and cardiovascular disease, especially in the context of obesity.<sup>12</sup> Diagnostic criteria for prediabetes and diabetes in children, including FPG, OGTT, and HbA1c 5.7%–6.4% (39–47 mmol/mol) are the same for the pediatric and adult population (Table 1). These criteria are extrapolated from adults, and the epidemiological studies that formed the basis for these definitions did not include pediatric populations. Therefore, the exact relevance of these definitions for pediatric populations remains unclear until more data become available.<sup>4</sup> Individuals who meet criteria for IGT or IFG may be euglycemic in their daily lives as shown by normal or near-normal HbA1c levels, and those with IGT may manifest hyperglycemia only when challenged with an OGTT. Screening with fasting glucose, OGTT, or HbA1C is an acceptable approach but the interpretation of the results should be based on sound clinical judgment, recognition of the strengths and weaknesses of each test, and the facilities and resources available.

Each of the tests mentioned has some variability, so it is possible that a test yielding an abnormal result (i.e., above the diagnostic threshold), when repeated, will produce a value below the diagnostic cut point.<sup>3,13</sup> One of the possibilities could be that the BGL samples are kept at room temperature and not centrifuged promptly. Because of the potential for pre-analytic variability, it is critical that samples for plasma glucose be spun and separated immediately after they are drawn. If individuals have test results near the margins of the diagnostic threshold, the health care professional should discuss signs and symptoms with them and repeat the test in 3–6 months.

## 7 | STAGING OF TYPE 1 DIABETES

Characterization of the underlying pathophysiology of T1D from prospective studies around the world has given rise to what is described as the staging of type 1 diabetes. Three distinct stages of T1D can be identified and serve as a framework for future research and regulatory decision-making.<sup>14</sup> This staging is based on the presence of  $\beta$ -cell autoantibodies and dysglycemia as predictors of clinical diabetes (stage one characterized by multiple  $\beta$ -cell autoantibody positivity with normal glucose, stage 2 multiple  $\beta$ -cell autoantibody positivity with dysglycaemia, and stage 3 meeting criteria for clinical diagnosis of T1D) and is described in detail in the ISPAD 2022 Consensus guidelines Chapter 2 on Stages of Diabetes.

## 8 | CONFIRMING THE DIAGNOSIS

Unless there is a clear clinical diagnosis (e.g., symptomatic individuals with clear hyperglycemia) diagnosis requires two abnormal screening test results, either from the same sample (two different tests) or in two separate test samples.<sup>3</sup> If using two separate test samples, it is recommended that the second test, which may either be a repeat of the initial test or a different test, be performed without delay. If two different tests (such as HbA1c and FPG) are both above the diagnostic threshold when analyzed from the same

sample or in two different test samples, this also confirms the diagnosis. On the other hand, if an individual has discordant results from two different tests, then the test result that is above the diagnostic cut point should be repeated, with careful consideration of the possibility of HbA1c assay interference. The diagnosis is made based on the confirmatory screening test.

## 9 | CLASSIFICATION OF DIABETES AND OTHER CATEGORIES OF GLUCOSE REGULATION

It was at the end of the 1970s that the scientific community established formal diabetes classifications, which could be used to guide therapy. The first, introduced in 1976 by the United States National Diabetes Data Group<sup>15</sup> and endorsed by the World Health Organization Expert Committee on Diabetes Mellitus,<sup>16</sup> was based on the need for insulin therapy for survival. The juvenile onset, usually ketotic type, was renamed insulin dependent diabetes mellitus (IDDM), while the adult onset, usually non-ketotic type, was termed non-insulin dependent diabetes (NIDDM). The classification was revised in 1997 based upon pathophysiology rather than insulin requirements, facilitated by the distinction between the autoimmunity driving insulin deficiency in IDDM and insulin resistance contributing to NIDDM. Absolute insulin deficient states became known as T1D, with NIDDM, usually associated with insulin resistance, renamed T2D.

The current etiological classification of diabetes is shown in Table 2, which is based on the ADA classification.<sup>3</sup> Today, most people with diabetes are grouped into two main types: T1D, characterized by the destruction of the  $\beta$ -cells, usually by an autoimmune process resulting in loss of endogenous insulin production, or T2D, characterized by the lack of an adequate insulin response in the presence of increasing insulin resistance. 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 T1D<sup>17,18</sup> and the presence of DKA in some young people at diagnosis of T2D.<sup>19,20</sup> In addition, the presentation of a familial form of mild diabetes during adolescence should raise the suspicion of monogenic diabetes, which accounts for 1% to 6% of pediatric diabetes cases.<sup>6,7,21–23</sup>

Using the etiologic approach to classification of diabetes types in youth based on the 1997 ADA framework, the majority of youth in the US-based SEARCH for Diabetes in Youth Study fell into either the autoimmune plus insulin sensitivity (54.5%) or non-autoimmune plus insulin resistance categories (15.9%) consistent with traditional descriptions of type 1 or T2D.<sup>24</sup> The remaining groups represented obesity superimposed on T1D (autoimmune plus insulin resistance, 19.5%) or atypical forms of diabetes (non-autoimmune plus insulin sensitivity, 10.1%), which require further characterization, including genetic testing for specific monogenic defects.<sup>25</sup> As the prevalence of childhood obesity continues to increase in the general population and

**TABLE 2** Etiological classification of diabetes

I. Type 1
β-cell destruction, usually leading to absolute insulin deficiency
Immune mediated (characterized by presence of one or more autoimmune markers)
Idiopathic
II. Type 2
Insulin resistance with relative insulin deficiency and subsequent hyperglycemia
III. Other specific types
A. Common forms of monogenic diabetes <sup>a</sup>
MODY
• HNF4-A MODY
• GCK MODY
• HNF1A MODY
• HNF1B MODY
Neonatal diabetes
• KCNJ11
• INS
• ABCCB
• 6q24 (PLAGL1, HYMA1)
• GATA6
• EIF2AK3
• FOXP3
B. Genetic defects in insulin action
INSR
Congenital generalized lipodystrophy
Familial partial lipodystrophy
PIK3R1 (Short Syndrome)
C. Diseases of the exocrine pancreas
Pancreatitis
Trauma/pancreatectomy
Neoplasia
Cystic fibrosis-related diabetes
Hemochromatosis
Transfusion-related iron overload
D. Endocrinopathies
Acromegaly
Cushing's syndrome
Hyperthyroidism
Pheochromocytoma
Glucagonoma
Somatostatinoma
E. Drug- or chemical-induced
Insulin resistance and deficiency
• Glucocorticoids
• Nicotinic acid
• Atypical antipsychotics

**TABLE 2** (Continued)

• Protease inhibitors (first generation)
• Statins
Insulin deficiency
• β-blockers
• Calcineurin inhibitors
• Diazoxide
• Phenytoin
• L-asparaginase
• Pentamidine
• Thiazide diuretics
Insulin resistance
• β-adrenergic agonists
• Growth hormone
F. Infections
Congenital rubella
Enterovirus
Cytomegalovirus
G. Uncommon forms of immune-mediated diabetes
Anti-insulin receptor antibodies
Polyendocrine autoimmune deficiencies APS I and II
H. Other genetic syndromes sometimes associated with diabetes
Down syndrome
Klinefelter syndrome
Turner syndrome
Friedreich's ataxia
Myotonic dystrophia
Porphyria
Prader-Willi syndrome
IV. Gestational diabetes mellitus (GDM)

Abbreviations: HNF, hepatic nuclear factor; GCK, glucokinase.

<sup>a</sup>See also ISPAD 2022 Guideline on Monogenic Diabetes.

in youth with diabetes, great care must be taken to correctly differentiate diabetes type in the setting of obesity,<sup>26</sup> particularly with regards to youth with T1D and antibody negative diabetes who show clinical signs of T2D such as obesity and insulin resistance.<sup>27,28</sup>

After the initial step of diagnosing diabetes, the differentiation between type 1, type 2, monogenic, and other forms of diabetes has important implications for both therapeutic decisions and educational approaches. 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. Diabetes-associated autoantibodies are an important diagnostic tool. The presence of GAD, IA2, IAA, and/or ZnT8 confirms the diagnosis of T1D in children.<sup>28</sup> Measurements of autoimmune markers are useful in confirming T1D in those where presentation is not clear, in particular obese adolescents.

The possibility of other types of diabetes should be considered in the child who does not have diabetes-specific autoantibodies and:

- an autosomal dominant family history of diabetes in three generations with onset before age 35 years.
- diabetes diagnosed in the first 12 months of life, especially the first 6 months (NDM).
- mild-fasting hyperglycemia (5.5–8.5 mmol [100–150 mg/dl]); that is, IFG, especially if young, non-obese, and asymptomatic.
- associated conditions such as deafness, optic atrophy, or syndromic features (mitochondrial disease).
- a history of exposure to drugs known to be toxic to  $\beta$ -cells (cyclosporine or tacrolimus)<sup>29</sup> or cause insulin resistance (glucocorticoids and certain antidepressants).<sup>30,31</sup>

T2D and monogenic diabetes are more completely discussed in the ISPAD guidelines on these conditions. See the ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 diabetes in children and adolescents and Chapter 4 on The diagnosis and management of monogenic diabetes in children and adolescents. Regardless of the type of diabetes, however, the child who presents with severe hyperglycemia, ketonemia, and metabolic derangements will initially require insulin therapy to reverse the metabolic abnormalities.

Some forms, including specific drug-, hormone-, or toxin-induced forms of diabetes, are less commonly observed in young people. Atypical forms of diabetes may occur in older children, adolescents, and young adults including ketosis-prone atypical diabetes, malnutrition-related diabetes, and fibro-calculeous pancreatic disease.<sup>32,33</sup>

## 10 | PATHOGENESIS OF T1D

T1D is characterized by chronic immune-mediated destruction of pancreatic  $\beta$ -cells, leading to partial, or in most cases, absolute insulin deficiency. In the majority of cases, autoimmune-mediated pancreatic  $\beta$ -cell destruction occurs at a variable rate and is influenced by different factors, including genes, age, and ethnicity.<sup>34,35</sup> New insights into youth at risk for developing T1D suggest that early disease is a continuum that progresses through distinct identifiable stages prior to the appearance of clinical symptoms.<sup>14</sup> Youth progress through three stages at variable rates: stage 1, which can last for months to many years, is characterized by the presence of  $\beta$ -cell autoimmunity with normoglycemia and a lack of clinical symptoms; stage 2 progresses to dysglycemia but remains asymptomatic, and stage 3 is defined as the onset of symptomatic disease.<sup>14</sup> The phases of diabetes are discussed in ISPAD 2022 Consensus Guidelines Chapter 2 on Stages of Type 1 Diabetes in Children and Adolescents.

The etiology of T1D is multifactorial; however, the specific roles for genetic susceptibility, environmental factors, the immune system, and  $\beta$ -cells in the pathogenic processes underlying T1D remain unclear.

The overall risk of T1D in the general population is 0.4%. Relatives of persons with T1D have a higher risk. In siblings, the lifetime risk is 6%–7%; 1.3%–4% in children of a mother with T1D, and 6%–9% in those with a father with T1D.<sup>36,37</sup> While the risk of T1D in non-identical twins is similar to that of siblings, it exceeds 70% in identical twins with long-term follow-up.<sup>38,39</sup> Additional evidence for the

contribution of genetic factors to the etiology of T1D is the rare occurrence of autoimmune diabetes in association with mutations affecting key genes that regulate immune function. An example of this is the autoimmune polyglandular syndrome type 1 (APS1) caused by mutations in the autoimmune regulator (*AIRE*) gene, which is critical for the establishment of immunological self-tolerance.<sup>40,41</sup>

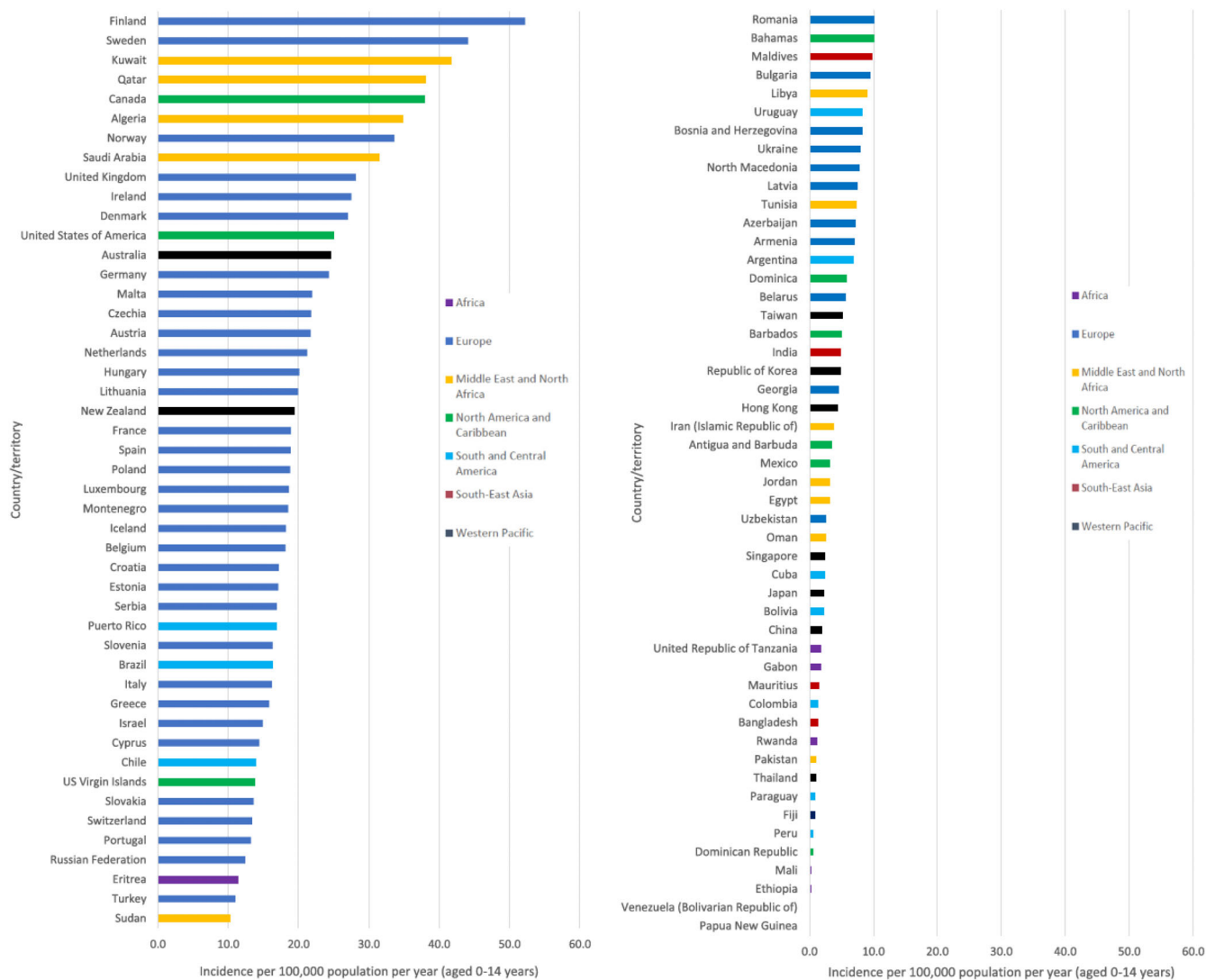
Studies predominantly from European ancestry populations have shown that susceptibility to T1D is determined by multiple genes. The HLA region on chromosome 6p21 accounts for approximately 30%–50% of the familial aggregation of T1D, and its association with T1D has been known for over 40 years.<sup>42,43</sup> The strongest association is with HLA DR and DQ. HLA DR and DQ are cell surface receptors that present antigens to T-lymphocytes. Both DR and DQ are alpha-beta heterodimers. The DR alpha chain is encoded by the *DRA* locus, and the DR beta chain is encoded by *DRB* loci. Similarly, *DQA1* and *DQB1* loci encode the alpha and beta chains, respectively, of the DQ molecule. The DR and DQ loci are highly linked to each other and, to a lesser degree, to other HLA loci.<sup>44,45</sup>

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). 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 T1D<sup>45</sup>; however, <10% of those with HLA-conferred diabetes susceptibility genes progress to clinical disease.<sup>46</sup> As the highest risk HLA allele combination is relatively rare (<5%) in European populations, the majority of T1D cases are associated with other combinations of these alleles that confer more moderate risk but in aggregate are more common than  $\frac{3}{4}$ .<sup>47</sup> For example, *DRB3*, *DRB4*, and *DRB5* alleles modify the risk conferred by *DRB1*.<sup>48</sup> Although the strength of the association is lower than with HLA DR and DQ, *HLA-DPB1* and *DPA1* are also associated to T1D.<sup>49</sup>

The remaining genetic risk for T1D can be attributed to the other non-HLA genes or loci identified that contribute smaller effects to disease risk. Genome-wide association studies (GWAS) have identified more than 60 risk loci.<sup>44</sup> Of these, the highest non-HLA genetic contribution arises from the insulin gene (*INS*) on chromosome 11p15,<sup>50,51</sup> protein tyrosine phosphatase, non-receptor type 22 (*PTPN22*), on chromosome 1p13,<sup>52</sup> cytotoxic T-lymphocyte associated protein (*CTLA-4*),<sup>53</sup> which is a negative regulator of cytotoxic T cells, and *IL2RA* genes,<sup>54</sup> all of which are involved in, or contribute to, immune regulation in various immune cell populations and/or the pancreatic  $\beta$ -cell.

Other genes not directly involved in immune function have been shown to possibly contribute to diabetogenesis in a subset of individuals with islet autoimmunity. Genetic variants in the transcription factor 7 like-2 (*TCF7L2*) locus are the strongest genetic factor in T2D.<sup>55</sup> Although this locus is not associated with T1D overall, persons with T1D with milder autoimmunity, as suggested by the expression of a single islet autoantibody and/or absence of high-risk HLA types, are more likely to carry the T2D-associated *TCF7L2* genetic variant compared to persons with T1D with stronger autoimmunity.<sup>56</sup>

One of the current challenges is how to integrate the wealth of knowledge about T1D genetics and apply it meaningfully for diagnosis



**FIGURE 1** Published age-standardized incidence of T1D reported in children aged 0–14 years.<sup>2</sup> Reprinted from Diabetes Research and Clinical Practice, Volume 183, Graham D. Ogle, Steven James, Dana Dabelea, Catherine Pihoker, Jannet Svennson, Jayanthi Maniam, Emma L. Klatman, Chris C. Patterson, *Global estimates of incidence of T1D in children and adolescents: Results from the International Diabetes Federation Atlas, 10th edition*, Copyright (2022) with permission from Elsevier (License Number: 5264490510252)].

and risk assessment. Recent work has studied the use of T1D genetic risk scores for distinguishing persons with T1D from other forms of diabetes<sup>57,58</sup> among them the DAISY Study,<sup>59–61</sup> the BABYDIAB study<sup>62,63</sup> and, more recently, the Exeter group have developed a T1D Genetic Score to identify individuals who became insulin dependent among young adults with diabetes<sup>25</sup> and discriminate T1D from monogenic diabetes.<sup>57</sup> This score was developed studying participants in the Wellcome Trust Case Control Consortium ( $n = 3887$ ), in which it was highly discriminative of T2D. This score was validated in the South West England Cohort, where it predicted insulin deficiency in a group of 20–40-year-old adults with diabetes ( $n = 223$ , excluded monogenic and secondary diabetes). A more recently developed T1D GRS2<sup>58</sup> has shown improved prediction of type 1 diabetes<sup>58,64</sup> and also demonstrated improved discrimination of type 1 from type 2 diabetes in USA youth self-reporting as either Black or Hispanic.<sup>65</sup>

As more genetic association data emerges from non-European ancestries,<sup>66</sup> there is an outstanding question as whether ancestry specific scores, or combined transancestry scores potentially with adjustable score thresholds per ancestry, will be the optimal method to aggregate genetic risk for clinical applications.

The environmental triggers (infectious, nutritional, obesity, changes in the microbiome, chemical) which are thought to be associated to T1D and pancreatic  $\beta$ -cell destruction remain largely unknown, but the process of  $\beta$ -cell destruction usually begins months to years before the manifestation of clinical symptoms.<sup>67–73</sup> Enterovirus infection during pregnancy, infancy, childhood, and adulthood has been associated with development of both islet autoimmunity and many populations,<sup>74,75</sup> particularly when infection occurs early in childhood,<sup>76</sup> and enteroviruses have been detected in the islets of persons with diabetes.<sup>77–79</sup> Congenital rubella syndrome has been

linked to the subsequent development of T1D.<sup>80</sup> There is a paucity of data to support the role of other viruses, such as CMV, mumps, Influenza, rotavirus, and H1N1 in the development of T1D.<sup>71</sup>

## 11 | EPIDEMIOLOGY OF TYPE 1 DIABETES

T1D is the most common form of diabetes in children and adolescents, accounting for >90% of childhood diabetes in most westernized countries, but other types of diabetes, including T2D and monogenic diabetes, also occur.<sup>81</sup> Worldwide, T1D is also one of the commonest chronic diseases of childhood. In 2021, there were an estimated 108,300 children and adolescents aged less than 15 years newly diagnosed with type 1 diabetes, and 651,700 children and adolescents living with the condition worldwide.<sup>82,83</sup>

Significant geographical variation in the incidence of childhood T1D continues to be observed (Figure 1),<sup>82–85</sup> ranging from 1.9 to 2.2 per 100,000 person years in China<sup>86</sup> and Japan,<sup>84,87</sup> respectively, to 52.2 per 100,000 in Finland,<sup>88</sup> where the highest incidence has been observed for several decades.<sup>89</sup> Notably, four of the top 10 countries with the highest incidence for childhood T1D listed in the latest edition of the International Diabetes Federation Global Atlas of Diabetes include the non-European populations of Kuwait, Qatar, Saudi Arabia, and Algeria.<sup>83</sup> While considering global patterns in childhood T1D, it is important to note that despite recent improvements in data availability from low-middle income countries,<sup>90,91</sup> most of the available global T1D incidence data is from highly developed countries,<sup>83</sup> and the relatively low incidence of T1D in low-middle income countries needs to be evaluated in the context of their higher mortality and lower case ascertainment rates.<sup>82,92</sup>

In addition to large differences in incidence between countries, significant geographic variation has also been observed within countries themselves.<sup>93–97</sup> Studies in heterogeneous populations have observed significant differences in incidence by race/ethnicity, which could contribute to geographical variation within and between countries. For example, in the United States SEARCH study, a higher incidence of T1D has been consistently observed in non-Hispanic white compared to Hispanic, Black, and American Indian youth aged <20 years.<sup>98,99</sup>

However, a study of genetically similar populations living in countries with different environments found that these populations had different incidence rates of childhood T1D<sup>93,100</sup> suggesting that a combination of both environmental and genetic differences are more likely to explain the geographical variation. Inconsistent findings have been reported on the association between higher childhood T1D incidence and environmental characteristics such as degree of urbanicity, population density, neighborhood socioeconomic status, higher latitude, or distance from the equator.<sup>94–97,100</sup> Factors underlying geographical differences in the incidence of childhood T1D remain poorly understood.<sup>101,102</sup>

Overall, there is no significant difference in the incidence of childhood T1D by sex,<sup>103–105</sup> although a slightly higher incidence has been reported in boys in some moderate-high incidence populations.<sup>90,106</sup> However, above the age of 15 years, there is a male preponderance in T1D incidence.<sup>107</sup>

The incidence of childhood T1D varies by age, with many populations reporting a peak age of onset in 10–14-year olds.<sup>91,92,105,106</sup> However, in Finland, the peak age of onset is 5–9 years, and in some countries, a decreasing peak age of incidence has been observed in recent years.<sup>82</sup>

Despite wide global variation in the incidence of childhood onset T1D, increasing trends in incidence have been observed in most populations, with incidence increasing by an average of 3%–4% per year.<sup>82,91,97,108</sup> However, more recently, a slowing of this increasing trend and a plateauing of incidence has been reported by several moderate-high incidence countries including Finland,<sup>88</sup> Austria,<sup>109</sup> Germany,<sup>110</sup> Ireland,<sup>106</sup> Australia,<sup>105</sup> New Zealand,<sup>111</sup> Sweden.<sup>107,108</sup> Intriguingly, a sinusoidal pattern with 4–6-year intervals between peak incidence years has been reported in some European countries and Australia,<sup>17,108,112,113</sup> with no explanation for this non-linear pattern. Of note, the cyclical pattern in incidence observed in these countries is distinct from the well-established seasonality of incidence of childhood T1D, with annual peaks in incidence having long been observed in the cooler autumn and winter months.<sup>106,114–117</sup>

Further analysis of temporal trends in the incidence of childhood T1D by sex, age group at diagnosis and race/ethnicity show additional complexity to the changing epidemiology of childhood T1D. In many populations a similar increasing trend has been observed in both boys and girls and across all age groups.<sup>82</sup> However, a higher rate of increase has been reported in girls compared to boys in Ireland, especially in 10–14-year olds, compared to younger age groups.<sup>106</sup> Since early reports in the late 1990s of a higher rate of increase being observed in those under 5 years old,<sup>118,119</sup> a decreasing incidence rate in the youngest age group has recently been reported in Finland,<sup>88</sup> Austria,<sup>109</sup> and Australia.<sup>105</sup> The decreasing incidence trend in 0–4-year olds has been suggested to account for the levelling off in the overall incidence of childhood T1D being observed in Finland<sup>88</sup> and Austria.<sup>109</sup> Interestingly, the United States SEARCH study, one of the few global studies to examine incidence rate trends of youth-onset T1D by race/ethnicity, recently showed that the rate of increase is highest in Black and Hispanic youth, compared to non-Hispanic White youth.<sup>99</sup> Differences in incidence by ethnicity have also been observed in New Zealand.<sup>111</sup>

The epidemiology of childhood T1D continues to change and evolve, with marked differences continuing to be observed between different countries and demographic groups within countries. The systematic, harmonized collection of robust, population-based data is vital for the ongoing monitoring of global patterns and trends in childhood T1D.

For example, recent epidemiological studies conducted during the COVID-19 pandemic have optimized the use of well-established robust data collection methods and enabled rapid reporting of contemporary changes in T1D epidemiology. An increased incidence of pediatric onset T1D occurring concurrent with the COVID-19 pandemic has been reported in Germany and the United States,<sup>120–122</sup> providing novel biologically plausible mechanistic insights into the etiology and/or clinical presentation of the condition.<sup>123</sup> It is possible that the increase in incidence might be due to concurrent illness



precipitating clinical diagnosis of T1D rather than a change in the risk of developing T1D as this often take years.

These data and analysis of incidence trends and patterns is essential for informing local health service planning and models of care in each country, and for providing contemporary population-specific clues to help further the understanding of potentially modifiable environmental determinants of childhood T1D and inform efforts to reduce its incidence. Recently, a new model, the Type 1 Diabetes Index, was developed based on available data to estimate T1D prevalence, incidence, associated mortality and life expectancy. Predictions for 2040, based on findings in 2021, include an increase in prevalent cases from 8.4 million individuals worldwide to 13.5–17.4 million, with the largest relative increase in low-income and lower-middle-income countries. This tool could play a critical role to support health delivery, advocacy, and funding decisions for T1D.<sup>124</sup>

Future research into the epidemiology of early life factors and their association with childhood T1D incidence<sup>125</sup> and the application of new methods and technologies<sup>126</sup> will provide novel knowledge and complement the ongoing surveillance of childhood T1D incidence.

## 12 | PATHOGENESIS OF T2D

T2D is characterized by hyperglycemia caused by insulin resistance, and relative impairment in insulin secretion due to  $\beta$ -cell dysfunction either as inborn genetic defect or acquired from glucose toxicity, lipotoxicity, or other mechanisms. The etiology includes contribution by genetic and physiologic components, lifestyle factors such as excess energy intake, insufficient physical activity, and increased sedentary behavior.<sup>4</sup> The pathogenesis of type 2 diabetes is variable between individuals and complicated by heterogeneity in the degree of insulin resistance and deficiency, genetic, and environmental influences, and comorbidities including hypertension, hyperlipidemia, and obesity.<sup>127</sup> Peripheral insulin resistance is a key feature that occurs early in the disease course, and initially is compensated by increased insulin secretion reflected in hyperinsulinemia.<sup>127</sup> Sustained hyperglycemia over time results in  $\beta$ -cell exhaustion and declining insulin secretion (glucose toxicity). Type 2 diabetes in youth is typically clinically characterized by insulin resistance, as well as other features of metabolic syndrome, which are commonly present, including hypertension, hyperlipidemia, acanthosis nigricans, fatty liver disease, and polycystic ovary disease.<sup>128</sup> Further details on the pathogenesis, and management are discussed in ISPAD 2022 Consensus Guidelines Chapter 3 on Type 2 Diabetes in Children and Adolescents.

## 13 | EPIDEMIOLOGY OF T2D

Once a rare disease in youth, T2D is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at-risk populations. Worldwide incidence and prevalence of T2D in children and adolescents vary substantially among countries, age categories and ethnic groups.<sup>129–134</sup> The incidence and

prevalence of T2D are highest among youth from a minority race/ethnicity,<sup>99</sup> likely because of many factors, including genetics, metabolic characteristics, cultural/environmental influences, and quality of and access to health care.<sup>135,136</sup>

## 14 | MONOGENIC DIABETES

A familial form of mild, non-ketotic diabetes presenting during adolescence or early adulthood<sup>137,138</sup> originally termed MODY, is now recognized as a group of disorders which result from dominantly acting heterozygous mutations in genes important for the development or function of  $\beta$ -cells.<sup>138,139</sup> Despite the classical description of MODY as a disorder with onset before 25 years of age, autosomal dominant inheritance, and non-ketotic diabetes mellitus,<sup>139,140</sup> it is clear that there is considerable overlap in the presentations of T1D, T2D, and monogenic diabetes. As a result, monogenic diabetes may be misdiagnosed and treated incorrectly. The etiology, diagnosis and management of monogenic diabetes are described in detail in the ISPAD 2022 Consensus Guidelines Chapter 5 on The diagnosis and management of monogenic diabetes in children and adolescents.

## 15 | NEONATAL DIABETES MELLITUS

T1D rarely presents in the first year of life, particularly before age 6 months.<sup>141,142</sup> In very young infants, under the age of 6 months, it is likely that over 80% have a monogenic cause,<sup>143</sup> with the most common one being  $\beta$  cell/potassium channel mutations. A small minority of NDM is accounted for by rare genetic mutations in immune system genes including mutations in the transcription factor FOXP3 as part of the immune-dysregulation poly-endocrinopathy enteropathy X-linked (IPEX) syndrome.<sup>144</sup> Genetic testing in those diagnosed under age 6 months is indicated, likely to find the cause, and may change treatment.<sup>144–147</sup> Further details of the genetic basis of NDM are provided in the ISPAD 2022 Consensus Guidelines Chapter 5 on The diagnosis and management of monogenic diabetes in children and adolescents.

## 16 | MITOCHONDRIAL DIABETES

Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterized by progressive non-autoimmune  $\beta$ -cell failure.<sup>148,149</sup> Transmission of maternal 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.<sup>150,151</sup> Mitochondrial diabetes may present with variable phenotypes, ranging from acute onset with or without DKA, to a more gradual onset resembling T2D. The disease typically presents in young adults, but can occur in children and adolescents, who have a lower prevalence of hearing loss compared with adults.<sup>152</sup>

## 17 | CYSTIC FIBROSIS-RELATED DIABETES

Cystic fibrosis-related 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.<sup>153</sup> 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 BGL, but over time fasting hyperglycemia develops. CFRD typically presents in adolescence and early adulthood<sup>154</sup> but may occur at any age. The presentation may be asymptomatic, insidious, associated with poor weight gain<sup>155</sup> or precipitated by insulin resistance associated with infection/use of glucocorticoids. Detection rates for CFRD vary with screening practices.<sup>156</sup> The onset of CFRD is defined as the date a person with CF first meets diagnostic criteria for diabetes, even if hyperglycemia subsequently abates. The onset of CFRD is a poor prognostic sign and is associated with increased morbidity and mortality reported prior to implementation of routine screening for CFRD and early use of insulin therapy.<sup>157</sup> Poorly controlled CFRD interferes with immune responses to infection and promotes protein catabolism.<sup>156,158</sup> Annual screening for CFRD should commence at least by age 10 years in all persons with CF who do not have CFRD. Screening should be performed using the 2-h 75 g (1.75 g/kg) OGTT.<sup>3</sup> A more comprehensive discussion on CFRD can be found in ISPAD 2022 Consensus guidelines Chapter 5 on Cystic Fibrosis Related Diabetes in Children and Adolescents.

## 18 | HEMOCHROMATOSIS AND DIABETES

Hemochromatosis is an inherited or secondary disorder caused by excessive iron storage leading to multiple organ damage.<sup>159</sup> Primary hemochromatosis is an autosomal recessive disease presenting as liver cirrhosis, cardiac dysfunction, hypothyroidism, diabetes, and hypogonadism. Secondary hemochromatosis may develop in individuals who have received multiple red blood cell transfusions.<sup>160</sup> Diabetes associated with hemochromatosis is primarily due to loss of insulin secretory capacity by damaged  $\beta$ -cells with insulin resistance playing a secondary role. The prevalence of diabetes in this population is not well characterized and has likely been underestimated.<sup>161</sup>

## 19 | 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., calcineurin inhibitors, pentamidine) can cause permanent  $\beta$ -cell damage.<sup>3,162-164</sup>

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 secondary or transient diabetes. L-asparaginase usually causes a reversible form of diabetes.<sup>165</sup> Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction.<sup>29</sup> Often the diabetes is cyclical and associated with the chemotherapy cycles, especially if associated with large doses of glucocorticoids. Immune checkpoint inhibitors can cause a special form of autoimmune diabetes characterized by a rapid loss of  $\beta$ -cell function.<sup>166</sup> Following organ transplantation, diabetes most frequently occurs with the use of high dose glucocorticoids and tacrolimus; the risk is increased in individuals with preexisting obesity.<sup>167-169</sup> Diabetes can also be induced by the use of atypical antipsychotics including olanzapine, risperidone, quetiapine, and ziprasidone, which may be associated with weight gain. In children and adolescents, use of antipsychotics was associated with a more than 3-fold increased risk of non-autoimmune diabetes, and the risk was significantly higher with increasing cumulative dose.<sup>170</sup> Among Canadian youth with medication-induced diabetes, risk factors for T2D (family history of T2D, obesity, non-Caucasian ethnicity, acanthosis nigricans) were less commonly observed than in youth with T2D.<sup>171</sup>

## 20 | STRESS HYPERGLYCEMIA

Hyperglycemia that occurs as a response to stress is transient in individuals without known diabetes. Stress hyperglycemia has been reported in up to 5% of children presenting to an emergency department, in association with acute illness or sepsis; traumatic injuries, febrile seizures, burns, and elevated body temperature ( $>39^{\circ}\text{C}$ ).<sup>172-175</sup>

However, the incidence of severe hyperglycemia ( $\geq 16.7$  mmol/L or 300 mg/dl) was  $<1\%$  and almost two-thirds of individuals had received interventions influencing glucose metabolism before evaluation, suggesting the etiology may at least in part be iatrogenic.<sup>176</sup>

The reported incidence of progression to overt diabetes varies from 0% to 32%.<sup>177-183</sup> Children with incidental hyperglycemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness.<sup>184</sup> As would be expected, testing for diabetes-associated autoantibodies had a high positive and negative predictive value for the development of T1D in children with stress hyperglycemia.<sup>181</sup> In children who have sustained severe burns, insulin resistance may persist for up to 3 years later.<sup>174</sup>

## 21 | CONCLUSION

Diabetes in youth is a heterogeneous disorder in which clinical presentation and disease progression may vary considerably. Classification is important for determining therapy, but in some individuals, overlapping clinical characteristics do not allow for diabetes type to be determined at the time of diagnosis. Progress has been made in understanding the pathophysiology as well as genetic characteristics of the different types of diabetes in childhood and markers are available to facilitate this task. Research has been conducted worldwide over the last several years combining genetic, clinical, and pathophysiological characteristics to better define the different types of diabetes in childhood, which is getting us closer to the goal of optimizing personalized treatment approaches. The challenge in the years ahead is to ensure that these advances reach all youth across the world.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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