ISPAD Clinical Practice Consensus Guidelines 2018 Definition, epidemiology and classification of diabetes in children and adolescents

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What's New?

- Emerging evidence suggests that the incidence of type 1 diabetes varies markedly country-to-country and may be plateauing in certain areas across the globe.
- Recent genome wide association and whole genome/exome sequencing studies have increased clinical understanding of monogenic forms of diabetes that are distinct from the major classes of type 1 and type 2 diabetes.
- Based on key gene variants associated with type 1 diabetes, composite type 1 diabetes genetic risk scores have also been explored as novel tools to differentiate type 1 diabetes from monogenic diabetes and type 2 diabetes.

Recommendations

- Diagnostic criteria for all types of diabetes in children and adolescents are based on laboratory measurement of plasma glucose levels (BGL) and the presence or absence of symptoms **(E)**. Finger prick BGL testing should not be used to diagnose diabetes **(E).** A marked elevation of the BGL confirms the diagnosis of diabetes, including a random plasma glucose concentration ≥11.1 mmol/L (200 mg/dl) or fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl) in the presence of overt symptoms.
- If significant ketones are present in blood or urine, treatment is urgent, and the child should be referred to a diabetes specialist on the same day to avoid the development of ketoacidosis **(A)**.
- The diagnosis of diabetes should not be based on a single plasma BGL in the absence of overt symptoms. If the diagnosis is in doubt, continued observation with fasting and/or 2 hour post-prandial BGLs 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 post-prandial 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 (MODY)
    - age less than 12 months and especially in first 6 months of life (NDM-Neonatal Diabetes Mellitus)

- mild fasting hyperglycemia (5.5–8.5 mmol [100–150 mg/dL]), especially if young, nonobese and asymptomatic.
- A prolonged honeymoon period over 1 year or an unusually low requirement for insulin of ≤0.5U/kg/day after 1 year of diabetes
- 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; gluocorticoids or some anti-depressants) (1).

- The differentiation between type 1, type 2, monogenic and other forms of diabetes has 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 β-cell-specific zinc transporter 8 autoantibodies (ZnT8). The presence of one of more of these antibodies confirms the diagnosis of type 1 diabetes **(A).**
- Molecular genetic testing can help define the diagnosis and treatment of children with suspected monogenic diabetes and should be limited to those who on clinical grounds are likely to be positive **(E)**.

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 (2, 3).

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 primarily by deficiency of insulin secretion; or type 2 diabetes, which results from a combination of resistance to insulin action, as well as an inadequate compensatory insulin secretory response for the degree of insulin resistance. While type 1 diabetes remains the most common form of diabetes in young people in many populations, especially those of European background, type 2

diabetes has become an increasingly important public health concern globally among children in high risk ethnic populations as well as in those with severe obesity (4, 5), see ISPAD guideline on type 2 diabetes (6).

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 (2, 7). Different methods can be used to diagnose diabetes (Table 1) and in the absence of unequivocal hyperglycemia, diagnosis 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, behavioural disturbance including reduced school performance, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia.
- In its most severe form, ketoacidosis or (rarer) nonketotic hyperosmolar syndrome may develop and lead to stupor, coma and in the absence of effective treatment, death.
- If symptoms are present, measurement of glucose and ketones using a bedside glucometer, or urinary ‘dipstick’ testing for glycosuria and ketonuria (if the former are 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 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. See Table 1 for fasting versus non-fasting blood glucose 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-hour post-prandial BGL and/or an oral glucose tolerance test (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 post-prandial criteria, as excessive hyperglycemia can result from the test. 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 OGTT re-testing 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 (3, 8). Moreover, the validity of HbA1c as a measure of average glucose is complicated in the context of 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 are a critical consideration in areas of iron deficiency and anemia such as China, where diabetes prevalence estimates using HbA1c may result in underestimations among women with iron deficiency and overestimations in men with anemia (9). 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 employ glucose criteria exclusively (3). Add reference to CFRD chapter In at-risk cohort studies, however, a rise in HbA1c within the normal range is frequently observed among individuals who subsequently progress to type 1 diabetes (10).

Table 1. Criteria for the diagnosis of diabetes mellitus

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

or

2. Fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl). Fasting is defined as no caloric intake for at least 8 h*.

or

3. 2-hour post-load glucose ≥11.1 mmol/l (≥200 mg/dl) during an OGTT *.

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

or

4. HbA1c ≥ 6.5%**

The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay

*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.

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (3)

IGT and 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. IFG is a measure of disturbed carbohydrate metabolism in the basal state whilst 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 ‘‘pre-diabetes’’ indicating their relatively high risk for development of diabetes and cardiovascular disease, especially in the context of obesity (11). Diagnostic criteria for pre-diabetes and diabetes in children, including FPG, OGTT and HbA1c A1C 5.7–6.4% (39–47 mmol/mol), have not been rigorously evaluated as they have in adults (12).

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-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) but are considered core defects typically associated with type 2 diabetes pathogenesis.

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) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described in Table 1)

The corresponding categories for Impaired Glucose Tolerance (IGT) when the OGTT is used are as follows:

- 2 hour post-load plasma glucose <7.8 mmol/l (140 mg/dl) = normal glucose tolerance
- 2 hour post-load plasma glucose 7.8 — <11.1 mmol/l (140 – 200 mg/dl) = IGT

- 2 hour post-load plasma glucose ≥11.1 mmol/l (200 mg/dl) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).

The FPG cut-point for diagnosing IFG has been controversial. In 2003, the American Diabetes Association (ADA) guideline lowered the FGP cut-point from 6.11-6.94 mmol/L [110-125 mg/dL] to 5.55-6.94 mmol/L [100-125 mg/dL] to increase the sensitivity of testing to identify subjects at risk for development of type 2 diabetes (13). The lower cut-point has not been adopted internationally (14, 15). The lower cut-point increases the number of subjects labeled with IFG and shows unclear associations with clinical complications (16, 17). A meta-analysis that evaluated the risk of coronary CVD in association with different criterion of IFG found that the CVD risk was comparably elevated along with evidence that the CVD risk maybe confounded by the undetected impaired IGT or other cardiovascular risk factors (18). A glucose load (i.e. an OGTT) is recommended in the context of elevated FPG concentration to accurately assess their future risk for type 2 diabetes (19).

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 (20, 21) and the presence of diabetic ketoacidosis in some young people at diagnosis of type 2 diabetes (22, 23). 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 (24-27).

The etiological classification of diabetes is shown in Table 2, which is based on the American Diabetes Association classification (3). Using the etiologic approach to classification of diabetes types in youth based on the 1997 American Diabetes Association (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 nonautoimmune plus insulin resistance categories (15.9%) consistent with traditional descriptions of type 1 or type 2 diabetes (28). The remaining groups represented obesity superimposed on type 1 diabetes (autoimmune plus insulin resistance, 19.5%) or atypical forms of diabetes (nonautoimmune plus insulin sensitivity, 10.1%), which require further characterization, including genetic testing for specific monogenic defects (28). As the prevalence of childhood obesity continues to increase in the general population and in youth with diabetes, great care must be taken to correctly differentiate diabetes type in the setting of obesity (29), particularly with regards to youth with type 1 diabetes and antibody negative diabetes who show clinical signs of type 2 diabetes such as obesity and insulin resistance (30).

Some forms, including specific drug-, hormone-, or toxin-induced forms of diabetes, are uncommonly 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 fibro-calculous pancreatic disease (31, 32).

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. Diabetes associated autoantibodies are an important diagnostic tool. The presence of GAD, IA2, IAA and/or ZnT8 confirms the diagnosis of type 1 diabetes, since one and usually more of these autoantibodies are present in >90% of individuals when fasting hyperglycemia is initially

detected (33).

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 in 3 generations with onset before age 35 years.
- diabetes diagnosed in the first 12 months of life, especially the first 6 months (Neonatal Diabetes Mellitus NDM).
- mild fasting hyperglycemia (5.5–8.5 mmol [100–150 mg/dL]) i.e. IFG, especially if young, nonobese 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) (34) or cause insulin resistance (glucocorticoids and certain anti-depressants) (35-37).

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 and Monogenic diabetes are more completely discussed in the ISPAD guidelines on these conditions (6) (38).

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.

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 (IAA, GAD, IA-2, ZnT8)

Idiopathic

II. Type 2

Insulin resistance with relative insulin deficiency and subsequent hyperglycemia

III. Other specific types

A. Common forms of monogenic diabetes*

MODY

HNF4-A MODY

GCK-MODY

HNF1A-MODY

HNF1B-MODY

Neonatal diabetes

KCNJ11

INS

ABCC8

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

Haemochromatosis

Transfusion related iron overload

E. Drug- or chemical-induced

Insulin resistance and deficiency

Glucocorticoids

Nicotinic acid

Atypical antipsychotics

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

D. Endocrinopathies	H. Other genetic syndromes sometimes associated with diabetes
Acromegaly	Down syndrome
Cushing's syndrome	Klinefelter syndrome
Hyperthyroidism	Turner syndrome
Phaeochromocytoma	Friedreich's ataxia
Glucagonoma	Myotonic dystrophy
Somatostatinoma	Porphyria
	Prader-Willi syndrome

IV. Gestational diabetes mellitus (GDM)

Abbreviations: HNF: Hepatic nuclear factor; GCK: Glucokinase

*See also Monogenic Diabetes Chapter

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

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. New insights into youth at-risk for developing type 1 diabetes suggest that early disease is a continuum that progresses through distinct identifiable stages prior to clinical symptoms (39). Youth progress through three stages at variable rates: Stage 1 is characterized by the presence of β-cell autoimmunity with normoglycemia and a lack of clinical symptoms, which can last for months to many years, stage 2 is progresses to dysglycemia but remains asymptomatic, and stage 3 is defined as the onset of symptomatic disease (39). The phases of diabetes are discussed in Chapter 3 (add ref).

The etiology of type 1 diabetes 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 (33). The expression of these antibodies is age-dependent, with IAA and ZnT8 more commonly expressed in children aged < 10 years, while GAD and IA-2 are associated with older age and GAD with female gender (40). Autoantibodies can occur very early in life and the order of appearance has been related to *HLA-DR-DQ* genotype (41).

Susceptibility to type 1 diabetes mellitus is determined by multiple genes. HLA genotype confers approximately 30-50% of risk (39, 42, 43); in the Caucasian population, specific combinations of HLA DR and DQ alleles determine genetic susceptibility (44). 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 type 1 diabetes (45), however < 10% of those with HLA conferred diabetes susceptibility genes progress to clinical disease (46).

Haplotypes conferring protection from type 1 diabetes are DRB1*15:01-DQA1*01:02-DQB1*06:02, DRB1*14:01-DQA1*01:01-DQB*05:03, and DRB1*07:01-DQA1*02:01-DQB1*03:03 (45).

The rising incidence of type 1 diabetes (5, 47) parallels a decrease in the relative contribution from the highest risk HLA genotype (39, 48). In particular, high-risk HLA genotypes have become less frequent over time in youth with type 1 diabetes in the UK (49), in Finland (50), and in non-Hispanic white (NHW) and Hispanic origin youth with type 1 diabetes in the US (51),

The remaining genetic risk for type 1 diabetes can be attributed to the other non-HLA genes or loci identified that contribute model to small effects on disease risk (52). Genome-wide association studies (GWAS) have identified more than 60 risk loci (53). Of these, the highest non-HLA genetic contribution arises from the *INS*, *PTPN22*, *CTLA4*, and *IL2RA* genes, all of which are involved in, or contribute to, immune regulation in the pancreatic β-cell (52).

In general, 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 (54-58). Recent work has studied the use of a type 1 diabetes genetic risk score for distinguishing patients with type 1 diabetes versus other forms of monogenic diabetes (59). A risk score generated from approximately 30 common genetic variants associated with type 1 diabetes has been shown to effectively discriminate monogenic diabetes from type 1 diabetes (59). Similarly, risk scores have been used to predict adolescents who will require insulin therapy, a novel tool for classifying individuals with type 1 diabetes from those with type 2 diabetes when clinical features and autoimmune markers are equivocal (29).

The environmental triggers (infective, nutritional 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 (56, 60, 61). Enterovirus infection during pregnancy, infancy, childhood and adulthood has been associated with development of both islet autoimmunity and type 1 diabetes in many populations (62, 63), particularly when infection occurs early in childhood (64), and enteroviruses have been detected in the islets of individuals with diabetes (65-67). Congenital rubella syndrome has been linked to the subsequent development of type 1 diabetes (68). There is a paucity of data to support the role of other viruses, such as CMV, Mumps, Influenza, Rotavirus and HIN1 in the development of type 1 diabetes.

Epidemiology of type 1 diabetes

Overall, approximately 96,000 children under 15 years are estimated to develop type 1 diabetes

annually worldwide (69). 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 (70), while current guidelines define diabetes based on abnormal test results (as shown in Table 1).

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. However, the incidence of type 1 diabetes versus type 2 diabetes may be different across populations with different distribution of age and race/ethnicity (5, 71). For example, the highest prevalence of type 1 diabetes in the United States was found among white youth and lowest in American Indian youth, with prevalence rates of 2.55 per 1000 (95% CI, 2.48-2.62) versus 0.35 per 1000 (95% CI, 0.26-0.47), respectively (71). By contrast, the highest prevalence of type 2 diabetes has been reported among non-white youth, with prevalence rates of 1.20 per 1000 among American Indian youth (95% CI, 0.96-1.51); 1.06 per 1000 among black youth (95% CI, 0.93-1.22); 0.79 per 1000 among Hispanic youth (95% CI, 0.70-0.88) versus 0.17 per 1000 among white youth (95% CI, 0.15-0.20) (71). Interestingly, recent data on the incidence of childhood diabetes in the United States show while both types of diabetes are increasing, type 1 diabetes is increasing more rapidly among Hispanic youth compared to non-Hispanic white youth (4.2% vs. 1.2%) and type 2 diabetes is increasing most rapidly among non-Hispanic black, Asians or Pacific Islander, and Native American youth compared to non-Hispanic white youth (6.3%, 8.5%, and 8.9%, versus 0.6%, respectively).

Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations, with the highest incidence rates observed in Finland (72), Northern Europe (73-75) and Canada (76). There is an approximate 20-fold difference in the disease incidence among Caucasians living in Europe (46), and incidence rates are correlated with the frequency of HLA susceptibility genes in the general population (77, 78). Of the estimated ~ 500, 000 children living with type 1 diabetes worldwide, ~ 26% are from Europe, and 22% are from North America and the Caribbean region (69). In Asia, the incidence of type 1 diabetes is very low; Japan ~2 per 100,000 person-years (79); China (Shanghai) 3.1 per 100,000 (80); Taiwan ~5 per 100 000 (81) and the type 1 diabetes in these countries has a different and unique HLA association compared with Caucasians (82-85). 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 (86, 87).

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 (80) or variation from year to year (88-90). In addition, development of islet autoimmunity also demonstrates seasonal variation, as does the association between month of birth and risk of type 1 diabetes (91, 92).

In stark 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 persistent male gender bias across countries is generally observed in older adolescents and young adults (90, 93, 94),

An increase in incidence of type 1 diabetes has been observed globally in recent decades (5, 47, 95) (47, 72, 74, 80, 81, 88-90, 96-104) (105). For example, overall unadjusted estimated incidence rates of type 1 diabetes was reported to have increased in the US by 1.4% annually (from 19.5 cases per 100,000 youth per year in 2002–2003 to 21.7 cases per 100,000 youth per year in 2011–2012) (5). The incidence of type 1 diabetes in youth less than 15 years of age has increased by 4.36% between 1995 and 2010, increasing at an accelerated rate after 2006 (106). There are estimates of greater increase in developing countries or those undergoing economic transition in recent decades (47, 99). In some reports, there has been a disproportionately greater increase in those under the age of 5 years (47, 109), but not in others (5).

There is evidence for a plateau in incidence in some countries in recent years (72, 74, 100, 110, 111), as well as cyclical trends (112). Taken together, such marked variation in incidence trends is consistent with an etiologic understanding of type 1 diabetes as a disease that involves environmental triggers acting with genetic susceptibility to initiate autoimmune destruction of pancreatic β-cells. Interestingly, the rising incidence of type 1 diabetes is associated with an increased proportion of individuals with moderate or low risk HLA genotypes in some populations (113-115), suggesting an increasing role for environmental factors in the disease etiology (39).

Familial aggregation accounts for approximately 10% of cases of type 1 diabetes (116), but more than 20% when accounting for the extended family history (117); however there is no recognizable pattern of inheritance. The lifelong risk of diabetes to an identical twin of a patient with type 1 diabetes is < 40% (46, 118); for a sibling the risk is approximately 4% by age 20 years (119, 120) and 9.6% by age 60 years (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) (121). The risk is also higher in siblings of probands diagnosed at younger age, paternal young-onset diabetes, male sex and older parental age (119, 121, 122).

Type 1 diabetes is 2–3 times more common in the offspring of diabetic men (3.6 – 8.5%) compared with diabetic women (1.3 – 3.6%) (122-127). The cumulative risk for type 1 diabetes is ~4% for offspring of adult onset (15-39 years) type 1 diabetes (128), with a similar recurrence risk in the offspring of mothers and fathers.

Pathogenesis of Type 2 Diabetes

Type 2 diabetes mellitus (type 2 diabetes) is characterized by hyperglycemia caused by insulin resistance, and relative impairment in insulin secretion due to beta-cell dysfunction either as an 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 (4). 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 (129). 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 (129). 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 (3).

Epidemiology of type 2 diabetes

Type 2 diabetes is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at risk populations (6), but population based epidemiological data are more limited compared with type 1 diabetes. Variations in population characteristics and methodological dissimilarities between studies may also account for some of the variation in incidence trends (130). Youth who are obese, of certain ethnic and genetic backgrounds, and having a positive family history of type 2 diabetes are at the highest risk for type 2 diabetes.

Worldwide incidence and prevalence of type 2 diabetes in children and adolescents vary substantially among countries, age categories and ethnic groups (130), and the results of epidemiologic studies have shown the incidence of type 2 diabetes in children and adolescents to have a range of 1–51/1000 (4). The highest reported rate is for certain groups of 15–19 year-old North American Indians, where the prevalence of type 2 diabetes per 1000 was 50.9 for Pima Indians, (versus 4.5 for all US American Indians and 2.3 for Canadian Cree and Ojibway Indians in Manitoba) (131). Increasing incidence rates for type 2 diabetes in pediatric patients have been reported in the US, Canada, Japan, Austria, United Kingdom and Germany (132). As in adults, youth with type 2 diabetes are more likely to be from lower socioeconomic backgrounds, where the socio-demographic disparities in disease seem to parallel the disparities in obesity among youth (133).

Type 2 diabetes has increased dramatically in children and adolescents throughout the world in recent years (134) (135), particularly among youth of minority racial and ethnic groups (5, 131). The incidence of IFG and IGT have also increased, and are associated with age and degree of obesity among children (11). (See ISPAD Guidelines on Type 2 Diabetes.)

Monogenic diabetes

A familial form of mild, non-ketotic diabetes presenting during adolescence or early adulthood (136, 137), originally termed maturity-onset diabetes of the young (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 β-cells (137, 138). Despite the classical description of MODY as a disorder with onset before 25 years of age, autosomal dominant inheritance and nonketotic diabetes mellitus (138, 139), it is clear that there is considerable overlap in the presentations of type 1 diabetes, type 2 diabetes and monogenic diabetes, so that monogenic diabetes may be misdiagnosed and treated incorrectly. With the increased awareness of type 2 diabetes in young people, many such patients will meet all of the ‘classical’ criteria for monogenic diabetes, but initially may be misclassified as having type 2 diabetes (140). Certain clinical characteristics should alert the clinician to the possibility of monogenic diabetes, as outlined in Table 3.

It is now considered more appropriate to define monogenic diabetes by its genetic subgroups, as shown in Table 2. The most common form is associated with mutations in the transcription factor

hepatocyte nuclear factor (HNF)-1α (also known as HNF1-MODY). Mutations in the glucokinase gene (*GCK)* and *HNF4A* contribute to the majority of remaining cases, while rare forms result from mutations in other transcription factors, including *HNF-1B*, pancreatic-duodenal homeobox *(PDX-1)* and *NeuroD1* (138, 141); for further detail see ISPAD guideline on Monogenic diabetes (38).

Within the diagnostic groups of monogenic diabetes, there is great variation in the degree of hyperglycemia, need for insulin and risk for future complications; importantly, HNF4A-MODYand HNF1A-MODY can be successfully treated with oral sulfonylurea medication, at least initially, whereas GCK-MODY does not require active treatment except in the setting of pregnancy where an affected mother has an unaffected fetus and there is *in utero* evidence of macrosomia (142)

Thus, making a specific molecular diagnosis permits one to predict the expected clinical course of the disease, guide the most appropriate management for an individual, has important implications for family members, and enables genetic counseling for future offspring and extended genetic testing in other diabetic family members, whose diabetes may eventually be reclassified (143).

Table 3. Clinical characteristics of type 1 diabetes, type 2 diabetes and Monogenic diabetes in children and adolescents

Characteristic	**Type 1**	**Type 2**	**Monogenic**
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	**>**6-12months	Usually pubertal (or later)	Often post pubertal except for GCK-MODY2) and neonatal diabetes (onset < 6-12 months)
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (frequently incidental in GCK-MODY2
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Rare	Common in neonatal diabetes, rare in other forms
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually 90%+	Most countries <10% Japan 60-80%)	1-6%
Parent with diabetes	2-4%	80%	90%+*

*mutations may occur *de novo*

Neonatal diabetes

Type 1 diabetes rarely presents in the first year of life, particularly before age 6 months (144, 145), 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 (IPEX) syndrome (146). A monogenic form of diabetes in the first six months of life is known NDM, although cases may present as late 9-12 months of age (147-149). Further details of the genetic basis of NDM are provided in the ISPAD guideline on Monogenic Diabetes (38).

Mitochondrial diabetes

Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterized by progressive non-autoimmune β-cell failure (150, 151). Transmission of maternal mutated mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. The most common mutation occurs at position 3,243 in the tRNA leucine gene, leading to an A-to-G transition (152, 153). 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 (150), but can occur in children and adolescents, who have a lower prevalence of hearing loss compared with adults (154).

Cystic fibrosis related diabetes

Cystic Fibrosis related diabetes (CFRD) is the most common co-morbidity 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 (155). 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 (156), but may occur at any age including infancy. The presentation may be asymptomatic, insidious, associated with poor weight gain (157), or precipitated by insulin resistance associated with infection/use of glucocorticoids. Detection rates for CFRD vary with screening practices (158). 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 is associated with increased morbidity and mortality reported prior to implementation of routine screening for CFRD and early use of insulin therapy (159). Poorly controlled CFRD interferes with immune responses to infection and promotes protein catabolism (158, 160).

Annual screening for CFRD should commence by age 10 years in all CF patients who do not have CFRD. Screening should be performed using the 2-hour 75 g (1.75 g/kg) OGTT. A more comprehensive discussion on CFRD can be found in Chapter X (161).

Hemochromatosis and diabetes

Hemochromatosis is an inherited or secondary disorder caused by excessive iron storage leading to multiple organ damage (162). Primary hemochromatosis is an autosomal recessive disease presenting as liver cirrhosis, cardiac dysfunction, hypothyroidism, diabetes, and hypogonadism, while secondary hemochromatosis may develop in patients who have received multiple red blood cell transfusions (163). Diabetes associated with hemochromatosis is primarily due to loss of insulin secretory capacity by damaged beta cells with insulin resistance playing a secondary role (164). The prevalence of diabetes in this population is not well characterized and has likely been underestimated (164).

Diabetes induced by drugs and toxins

A range of pharmacological agents impair insulin secretion (eg propranolol), and/or action (eg glucocorticoids, antipsychotic agents), while others (eg pentamidine) can cause permanent β-cell damage (141, 165, 166).

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 (167). Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction (168). 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 pre-existing obesity (169-171).

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 3-fold increased risk of non-autoimmune diabetes, and the risk was significantly higher with increasing cumulative dose (172). Among Canadian youth with medication induced diabetes, risk factors for type 2 diabetes (family history of type 2 diabetes, obesity, non-caucasian ethnicity, acanthosis nigricans) were less commonly observed than in youth with type 2 diabetes (173).

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 degrees) (174-177). 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 (178).

The reported incidence of progression to overt diabetes varies from 0% to 32% (177, 179-184). Children with incidental hyperglycemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness (182). 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 (182). In children who have sustained severe burns, insulin resistance may persist for up to three years later (176).

Conclusion

The worldwide trends of type 1 diabetes incidence vary by sex, by race, by age group as well as by time period around the world, consistent with disease etiology that involves environmental triggers superimposed on genetic susceptibility. Recent evidence has elucidated that pre-symptomatic type 1 diabetes progresses through a continuum of three distinct identifiable stages prior to the onset of symptoms. Moreover, recent GWAS and whole genome/exome sequencing studies have increased clinical understanding of monogenic forms of diabetes that are distinct from the major classes of type 1 and type 2 diabetes. Composite type 1 diabetes genetic risk scores have also been explored as novel tools to differentiate type 1 diabetes from monogenic diabetes and type 2 diabetes. The worldwide incidence of type 2 diabetes is increasing and represents a public health concern among children and young adults. Pathogenesis of type 2 diabetes is complex and further complicated by heterogeneity in genetic versus environmental input, comorbid metabolic disease. Other forms of diabetes are explored in detail in other chapters.

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