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

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Diagnostic criteria for diabetes are based on laboratory measurement of plasma glucose concentrations and the presence or absence of symptoms (E). Finger prick blood glucose level (BGL) testing should not be used to diagnose diabetes (E).
- A marked elevation of the blood glucose level confirms the diagnosis. If ketones are present in blood or urine, treatment is urgent, and the child should be referred the same day to avoid the development of ketoacidosis (A).
- The diagnosis of diabetes should not be based on a single plasma glucose concentration. If the diagnosis is in doubt, continued observation with fasting and/or 2 h postprandial blood glucose levels and/or an oral glucose tolerance test (OGTT) may be required (E). However, an OGTT is not needed and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria as excessive hyperglycemia can result (E).
- Hyperglycemia detected under conditions of stress, such as acute infection, trauma, surgery, respiratory distress, circulatory, or other stress may be transitory and requires treatment but should not in itself be regarded as diagnostic of diabetes (E).
- The possibility of other types of diabetes should be considered in the child who has negative diabetes-associated autoantibodies and (B):
  - An autosomal dominant family history of diabetes.
  - Diabetes diagnosed in the first 6 months of life.
  - Mild fasting hyperglycemia [5.5–8.5 mmol (100–150 mg/dL)], which does not progress, especially if young, non-obese, and asymptomatic.
  - Associated conditions such as deafness, optic atrophy, or syndromic features.
  - A history of exposure to drugs known to be toxic to β cells or cause insulin resistance.
- The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important implications for both treatment and

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).
  - OGTT (A).
  - Haemoglobin A1c (HbA1c) (B).

- Molecular genetic testing can help define the diagnosis and treatment of children with suspected monogenic diabetes. All patients diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of neonatal diabetes mellitus (NDM), as type 1 diabetes is extremely rare in this subgroup (B). Beyond the age of 6 months, genetic testing should be limited to those with negative autoantibodies (particularly if measured at diagnosis), who have clinical features suggestive of monogenic diabetes 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 (1, 2).

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

Diagnostic criteria for diabetes in childhood and adolescence

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

- Diabetes in young people usually presents with characteristic symptoms such as polyuria, polydipsia, nocturia, enuresis, weight loss – which may be accompanied by polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia.
- In its most severe form, ketoacidosis or less commonly non-ketotic hyperosmolar syndrome may develop and lead to stupor, coma and in the absence of effective treatment, death.
- If symptoms are present, urinary 'dipstick' testing for glycosuria and ketonuria, or measurement of glucose and ketones using a bedside glucometer, provides a simple and sensitive screening tool. If the blood glucose level is elevated, then prompt referral to a center with experience in managing children with diabetes is essential. Waiting another day specifically to confirm the hyperglycemia is unnecessary and if

Table 1. Criteria for the diagnosis of diabetes mellitus (1, 2)

i	Classic symptoms of diabetes or hyperglycemic crisis, with plasma glucose concentration ≥11.1 mmol/L (200 mg/dL) or
ii	Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL). Fasting is defined as no caloric intake for at least 8 h* or
iii	Two hour postload 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
iv	HbA1c >6.5%†
	• The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay

HbA1c, hemoglobin A1c; OGTT, oral glucose tolerance test
*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.

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

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

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

Impaired glucose tolerance and impaired fasting glucose

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

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

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

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

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

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

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

Classification of diabetes and other categories of glucose regulation

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

The etiological classification of diabetes is shown in Table 2, which is based on the American Diabetes

Table 2. Etiological classification of diabetes

I. **Type 1**
β-Cell destruction, usually leading to absolute insulin deficiency
A. Immune mediated
B. Idiopathic

II. **Type 2**
May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance

III. **Other specific types**

A. **Genetic defects of β-cell function**
1. Chromosome 12, *HNF1A* (MODY3)
2. Chromosome 7, *GCK* (MODY2)
3. Chromosome 20, *HNF4B* (MODY1)
4. Other rare forms of MODY including:
   Chromosome 13, *IPF-1* (MODY4);
   Chromosome 17, *HNF1B* (MODY5);
   Chromosome 2, *NEUROD1* (MODY6);
   Chromosome 2, *KLF11* (MODY7);
   Chromosome 9, *CEL* (MODY8);
   Chromosome 7, *PAX4* (MODY9)
5. TNDM (most commonly *PLAGL1/HYMAI* imprinting defect on 6q24)
6. PNDM (most commonly *KCNJ11* gene encoding Kir6.2 subunit of beta-cell KATP channel)
7. Mitochondrial DNA mutation
8. Others

B. **Genetic defects in insulin action**
1. Type A insulin resistance
2. Leprechaunism
3. Rabson–Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

C. **Diseases of the exocrine pancreas**
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others

D. **Endocrinopathies**
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Phaeochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others

E. **Drug- or chemical-induced**
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β-Adrenergic agonists
8. Thiazides
9. Dilantin
10. α-Interferon
11. Others

F. **Infections**
1. Congenital rubella
2. Cytomegalovirus
3. Enterovirus
4. Others

G. **Uncommon forms of immune-mediated diabetes**
1. 'Stiff-man' syndrome
2. Anti-insulin receptor antibodies
3. Autoimmune polyendocrine syndrome (APS) types I and II
4. IPEX
5. Others

H. **Other genetic syndromes sometimes associated with diabetes**
1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence–Moon–Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader–Willi syndrome
11. Others

IV. **Gestational diabetes mellitus (GDM)**

CEL, carboxyl ester lipase; HNF, hepatocyte nuclear factor; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; IPF, insulin promoter factor; *KLF11*, Kruppel-like factor 11; MODY, maturity-onset diabetes of the young; *PAX4*, Paired Domain gene 4.
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.

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

The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important

implications for both therapeutic decisions and educational approaches. Diagnostic tools, which may assist in confirming the diabetes type, include:

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

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

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

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

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

Pathogenesis of type 1 diabetes

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

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

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

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

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

When the clinical presentation is typical of type 1 diabetes but antibodies are absent, then the diabetes is classified as type 1B (idiopathic). Most cases are of African or Asian ancestry, however, other forms of diabetes, including type 2 and monogenic diabetes, should also be considered (as shown in Table 2). In geographical areas where type 1 diabetes occurs with lower incidence, there is a higher rate of DKA at presentation (38).

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

Characteristic	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	6 months to young adulthood	Usually pubertal (or later)	Often postpubertal except *GCK* and NDM
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (may be incidental in *GCK*)
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in NDM, 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%)	1–4%
Parent with diabetes	2–4%	80%	90%

Epidemiology of type 1 diabetes

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

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

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

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

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

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

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

Familial aggregation accounts for approximately 10% of cases of type 1 diabetes (79), but more than 20% when accounting for the extended family history (80), however, there is no recognizable pattern of inheritance. The risk of diabetes to an identical twin of a patient with type 1 diabetes is <40% (25, 81); for a sibling the risk is approximately 4% by age 20 yr (82, 83) and 9.6% by age 60 yr (49); compared with 0.5% for

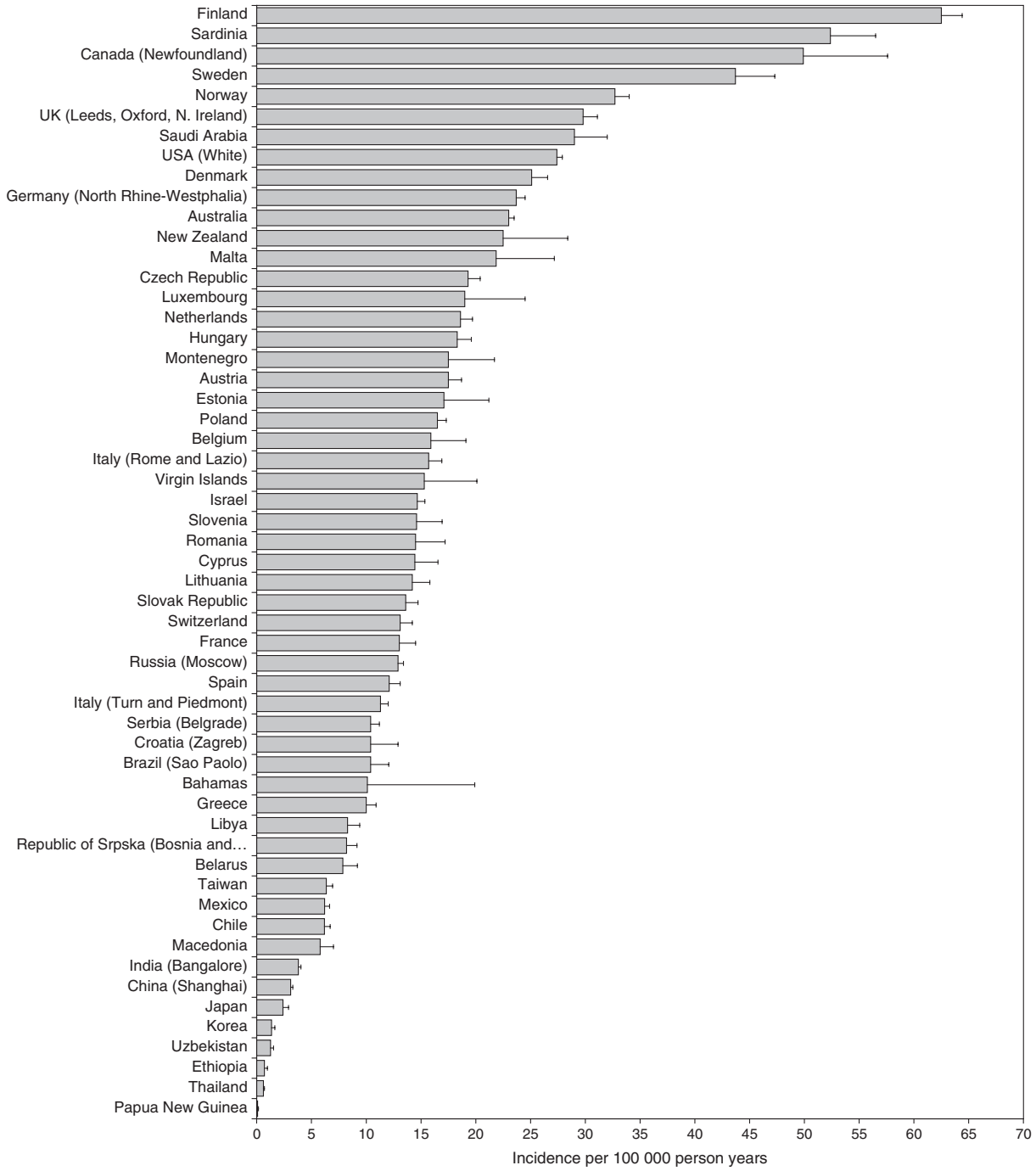

Fig. 1. Global mean annual incidence rates of type 1 diabetes in children and adolescents aged 0–14 yr. Only countries in which the study period included data from 2000 onwards are shown [adapted from the International Federation atlas (39)].

the general population. The cumulative risk of diabetes by age 15 is greater in HLA-identical DR3-DQ2/DR4-DQ8 siblings (17 vs. 6% in those sharing one haplotype or none) (84). The risk is also higher in siblings of probands diagnosed at younger age, paternal young-onset diabetes, male sex, and older parental age (82, 84, 85).

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

Monogenic diabetes

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

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 (93, 94). Despite the classical description of MODY as a disorder with onset before 25 yr of age, autosomal dominant inheritance and non-ketotic diabetes mellitus (94, 95), it is clear that there is considerable overlap in the presentation of type 1, type 2, and monogenic diabetes. With the increased recognition of type 2 diabetes in young people, many will meet all of the 'classical' criteria for monogenic diabetes, but may initially be classified as having type 2 diabetes (96). 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-1α (*HNF1A*, also known as MODY3). 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 *HNF1B*, insulin promoter factor (*IPF*)-*1*, and *NeuroD1* (Table 2) (2, 94); for further detail see The ISPAD guideline on Monogenic Diabetes (18).

Within the diagnostic groups of monogenic diabetes, there is great variation in the degree of hyperglycemia, need for insulin, and risk for future complications.

Making a specific molecular diagnosis helps predict the expected clinical course of the disease, guide the most appropriate management for an individual, and has important implications for family members, enabling genetic counseling and extended genetic testing in other diabetic family members, whose diabetes may eventually be reclassified (97).

Neonatal diabetes

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

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

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

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

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

Mitochondrial diabetes

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

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

Cystic fibrosis and diabetes

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

gastric emptying, altered intestinal motility, and liver disease (126).

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

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

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

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

Diabetes induced by drugs and toxins

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

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

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

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

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

Stress hyperglycemia

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

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

Conflicts of interest

The authors have declared no conflicts of interest.

References

1. World Health Organisation. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation. Geneva, Switzerland: World Health Organisation, 2006.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014: 37 (Suppl. 1): S81–S90.
3. Zeitler P, Fu J, Tandon N et al. Type 2 diabetes in the child and adolescent. Pediatr Diabetes 2014: 15 (Suppl. 20): 26–46.

4. American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care 2014: 37 (Suppl. 1): S14–S80.
5. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Geneva, Switzerland: World Health Organization, 2011.
6. Islam ST, Abraham A, Donaghue KC et al. Plateau of adiposity in Australian children diagnosed with type 1 diabetes: a 20-year study. Diabet Med 2014: 31: 686–690.
7. Kapellen TM, Gausche R, Dost A et al. Children and adolescents with type 1 diabetes in Germany are more overweight than healthy controls: results comparing DPV database and CrescNet database. J Pediatr Endocrinol Metab 2014: 27: 209–214.
8. Rewers A, Klingensmith G, Davis C et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics 2008: 121: e1258–e1266.
9. Dabelea D, Rewers A, Stafford JM et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics 2014: 133: e938–e945.
10. Fendler W, Borowiec M, Baranowska-Jazwiecka A et al. Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. Diabetologia 2012: 55: 2631–2635.
11. Irgens HU, Molnes J, Johansson BB et al. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. Diabetologia 2013: 56: 1512–1519.
12. Pihoker C, Gilliam LK, Ellard S et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013: 98: 4055–4062.
13. Galler A, Stange T, Muller G et al. Incidence of childhood diabetes in children aged less than 15 years and its clinical and metabolic characteristics at the time of diagnosis: data from the Childhood Diabetes Registry of Saxony, Germany. Horm Res Paediatr 2010: 74: 285–291.
14. Gill GV, Mbanya JC, Ramaiya KL, Tesfaye S. A sub-Saharan African perspective of diabetes. Diabetologia 2009: 52: 8–16.
15. Barman KK, Premalatha G, Mohan V. Tropical chronic pancreatitis. Postgrad Med J 2003: 79: 606–615.
16. Watkins RA, Evans-Molina C, Blum JS, Dimeglio LA. Established and emerging biomarkers for the prediction of type 1 diabetes: a systematic review. Transl Res 2014: 164: 110–121.
17. Dabelea D, Pihoker C, Talton JW et al. Etiological approach to characterization of diabetes type: the SEARCH for Diabetes in Youth Study. Diabetes Care 2011: 34: 1628–1633.
18. Rubio-Cabezas O, Hattersley A, Njolstad P et al. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2014: 15 (Suppl. 20): 47–64.
19. Howson JM, Stevens H, Smyth DJ et al. Evidence that HLA class I and II associations with type 1 diabetes, autoantibodies to GAD and autoantibodies to IA-2, are distinct. Diabetes 2011: 60: 2635–2644.
20. Barrett JC, Clayton DG, Concannon P et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat Genet 2009: 41: 703–707.
21. Noble JA, Valdes AM, Cook M, Klitz W, Thomson G, Erlich HA. The role of HLA class II genes in insulin-dependent diabetes mellitus: molecular analysis of 180 Caucasian, multiplex families. Am J Hum Genet 1996: 59: 1134–1148.
22. Lambert AP, Gillespie KM, Thomson G et al. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. J Clin Endocrinol Metab 2004: 89: 4037–4043.
23. Nguyen C, Varney MD, Harrison LC, Morahan G. Definition of high-risk type 1 diabetes HLA-DR and HLA-DQ types using only three single nucleotide polymorphisms. Diabetes 2013: 62: 2135–2140.
24. Erlich H, Valdes AM, Noble J et al. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes genetics consortium families. Diabetes 2008: 57: 1084–1092.
25. Knip M. Pathogenesis of type 1 diabetes: implications for incidence trends. Horm Res Paediatr 2011: 76 (Suppl. 1): 57–64.
26. Aly TA, Ide A, Jahromi MM et al. Extreme genetic risk for type 1A diabetes. Proc Natl Acad Sci U S A 2006: 103: 14074–14079.
27. Steck AK, Wong R, Wagner B et al. Effects of non-HLA gene polymorphisms on development of islet autoimmunity and type 1 diabetes in a population with high-risk HLA-DR, DQ genotypes. Diabetes 2012: 61: 753–758.
28. Ziegler AG, Rewers M, Simell O et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013: 309: 2473–2479.
29. Bonifacio E, Krumsiek J, Winkler C, Theis FJ, Ziegler AG. A strategy to find gene combinations that identify children who progress rapidly to type 1 diabetes after islet autoantibody seroconversion. Acta Diabetol 2014: 51: 403–411.
30. DPT-1 Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. N Engl J Med 2002: 346: 1685–1691.
31. Verge CF, Gianani R, Kawasaki E et al. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. Diabetes 1996: 45: 926–933.
32. Skyler JS, Krischer JP, Wolfsdorf J et al. Effects of oral insulin in relatives of patients with type 1 diabetes: the diabetes prevention trial – type 1. Diabetes Care 2005: 28: 1068–1076.
33. Yeung G, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus – a systematic review of molecular studies. BMJ 2011: 342: d35.
34. Laitinen OH, Honkanen H, Pakkanen O et al. Coxsackievirus B1 is associated with induction of beta-cell autoimmunity that portends type 1 diabetes. Diabetes 2014: 63: 446–455.
35. Richardson SJ, Willcox A, Bone AJ, Foulis AK, Morgan NG. The prevalence of enteroviral

capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes. Diabetologia 2009: 52: 1143–1151.
36. Dotta F, Censini S, van Halteren AG et al. Coxsackie B4 virus infection of beta cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. Proc Natl Acad Sci U S A 2007: 104: 5115–5120.
37. Richardson SJ, Leete P, Bone AJ, Foulis AK, Morgan NG. Expression of the enteroviral capsid protein VP1 in the islet cells of patients with type 1 diabetes is associated with induction of protein kinase R and downregulation of Mcl-1. Diabetologia 2013: 56: 185–193.
38. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ 2011: 343: d4092.
39. International Diabetes F. IDF Diabetes Atlas. 6th edn. Brussels, Belgium: International Diabetes F, 2013.
40. Diamond Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med 2006: 23: 857–866.
41. Harjutsalo V, Sund R, Knip M, Groop PH. Incidence of type 1 diabetes in Finland. JAMA 2013: 310: 427–428.
42. Berhan Y, Waernbaum I, Lind T, Mollsten A, Dahlquist G, Swedish Childhood Diabetes Study Group. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. Diabetes 2011: 60: 577–581.
43. Skrivarhaug T, Stene LC, Drivvoll AK, Strom H, Joner G, Norwegian Childhood Diabetes Study Group. Incidence of type 1 diabetes in Norway among children aged 0-14 years between 1989 and 2012: has the incidence stopped rising? Results from the Norwegian Childhood Diabetes Registry. Diabetologia 2014: 57: 57–62.
44. Rawshani A, Landin-Olsson M, Svensson AM et al. The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. Diabetologia 2014: 57: 1375–1381.
45. Newhook LA, Penney S, Fiander J, Dowden J. Recent incidence of type 1 diabetes mellitus in children 0-14 years in Newfoundland and Labrador, Canada climbs to over 45/100,000: a retrospective time trend study. BMC Res Notes 2012: 5: 628.
46. Ilonen J, Reijonen H, Green A et al. Geographical differences within finland in the frequency of HLA-DQ genotypes associated with type 1 diabetes susceptibility. Eur J Immunogenet 2000: 27: 225–230.
47. Kukko M, Virtanen SM, Toivonen A et al. Geographical variation in risk HLA-DQB1 genotypes for type 1 diabetes and signs of beta-cell autoimmunity in a high-incidence country. Diabetes Care 2004: 27: 676–681.
48. Tajima N, Morimoto A. Epidemiology of childhood diabetes mellitus in Japan. Pediatr Endocrinol Rev 2012: 10 (Suppl. 1): 44–50.
49. Zhao Z, Sun C, Wang C et al. Rapidly rising incidence of childhood type 1 diabetes in Chinese population: epidemiology in Shanghai during 1997-2011. Acta Diabetol 2014: Apr 29. [Epub ahead of print] (PMID: 24777734).
50. Lin WH, Wang MC, Wang WM et al. Incidence of and mortality from type I diabetes in Taiwan from 1999 through 2010: a nationwide cohort study. PLoS One 2014: 9: e86172.
51. Park Y. Why is type 1 diabetes uncommon in Asia? Ann N Y Acad Sci 2006: 1079: 31–40.
52. Park YS, Wang CY, Ko KW et al. Combinations of HLA DR and DQ molecules determine the susceptibility to insulin-dependent diabetes mellitus in Koreans. Hum Immunol 1998: 59: 794–801.
53. Ikegami H, Fujisawa T, Kawabata Y, Noso S, Ogihara T. Genetics of type 1 diabetes: similarities and differences between Asian and Caucasian populations. Ann N Y Acad Sci 2006: 1079: 51–59.
54. Sugihara S. Genetic susceptibility of childhood type 1 diabetes mellitus in Japan. Pediatr Endocrinol Rev 2012: 10 (Suppl. 1): 62–71.
55. Urakami T, Suzuki J, Yoshida A, Saito H, Mugishima H. Incidence of children with slowly progressive form of type 1 diabetes detected by the urine glucose screening at schools in the Tokyo metropolitan area. Diabetes Res Clin Pract 2008: 80: 473–476.
56. Urakami T, Yoshida A, Suzuki J et al. Differences in prevalence of antibodies to GAD and IA-2 and their titers at diagnosis in children with slowly and rapidly progressive forms of type 1 diabetes. Diabetes Res Clin Pract 2009: 83: 89–93.
57. Imkampe AK, Gulliford MC. Trends in type 1 diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991-2008. Diabet Med 2011: 28: 811–814.
58. Jarosz-Chobot P, Polanska J, Szadkowska A et al. Rapid increase in the incidence of type 1 diabetes in Polish children from 1989 to 2004, and predictions for 2010 to 2025. Diabetologia 2011: 54: 508–515.
59. Skordis N, Efstathiou E, Kyriakides TC et al. Epidemiology of type 1 diabetes mellitus in Cyprus: rising incidence at the dawn of the 21st century. Hormones (Athens) 2012: 11: 86–93.
60. Laron Z, Lewy H, Wilderman I et al. Seasonality of month of birth of children and adolescents with type 1 diabetes mellitus in homogenous and heterogeneous populations. Isr Med Assoc J 2005: 7: 381–384.
61. Kahn HS, Morgan TM, Case LD et al. Association of type 1 diabetes with month of birth among U.S. youth: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009: 32: 2010–2015.
62. Weets I, Kaufman L, Van der Auwera B et al. Seasonality in clinical onset of type 1 diabetes in Belgian patients above the age of 10 is restricted to HLA-DQ2/DQ8-negative males, which explains the male to female excess in incidence. Diabetologia 2004: 47: 614–621.
63. Wandell PE, Carlsson AC. Time trends and gender differences in incidence and prevalence of type 1 diabetes in Sweden. Curr Diabetes Rev 2013: 9: 342–349.
64. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new

cases 2005-20: a multicentre prospective registration study. Lancet 2009: 373: 2027–2033.
65. Schober E, Waldhoer T, Rami B, Hofer S. Incidence and time trend of type 1 and type 2 diabetes in Austrian children 1999-2007. J Pediatr 2009: 155: 190-3 e1.
66. Haynes A, Bulsara MK, Bower C, Jones TW, Davis EA. Cyclical variation in the incidence of childhood type 1 diabetes in Western Australia (1985-2010). Diabetes Care 2012: 35: 2300–2302.
67. Derraik JG, Reed PW, Jefferies C, Cutfield SW, Hofman PL, Cutfield WS. Increasing incidence and age at diagnosis among children with type 1 diabetes mellitus over a 20-year period in Auckland (New Zealand). PLoS One 2012: 7: e32640.
68. Sipetic S, Maksimovic J, Vlajinac H et al. Rising incidence of type 1 diabetes in Belgrade children aged 0-14 years in the period from 1982 to 2005. J Endocrinol Invest 2013: 36: 307–312.
69. Bruno G, Maule M, Biggeri A et al. More than 20 years of registration of type 1 diabetes in Sardinian children: temporal variations of incidence with age, period of diagnosis, and year of birth. Diabetes 2013: 62: 3542–3546.
70. Lipman TH, Levitt Katz LE, Ratcliffe SJ et al. Increasing incidence of type 1 diabetes in youth: twenty years of the Philadelphia Pediatric Diabetes Registry. Diabetes Care 2013: 36: 1597–1603.
71. Tran F, Stone M, Huang CY et al. Population-based incidence of diabetes in Australian youth aged 10-18 yr: increase in type 1 diabetes but not type 2 diabetes. Pediatr Diabetes 2014: Mar 17. doi: 10.1111/pedi.12131. [Epub ahead of print].
72. Lawrence JM, Imperatore G, Dabelea D et al. Trends in incidence of type 1 diabetes among non-Hispanic White youth in the United States, 2002-2009. Diabetes 2014: Jun 4. pii: DB_131891. [Epub ahead of print].
73. Gyurus EK, Patterson C, Soltesz G. Twenty-one years of prospective incidence of childhood type 1 diabetes in Hungary – the rising trend continues (or peaks and highlands?). Pediatr Diabetes 2012: 13: 21–25.
74. Cinek O, Kulich M, Sumnik Z. The incidence of type 1 diabetes in young Czech children stopped rising. Pediatr Diabetes 2012: 13: 559–563.
75. Kraan JA, Claessen FMAP, Elliott KD et al. Population based incidence of type 1 diabetes in New South Wales Australia 1990-2010 - have we reached a plateau? (Oral Abstract). Pediatr Diabetes 2011: 12 (Suppl. 15): 25.
76. Hermann R, Knip M, Veijola R et al. Temporal changes in the frequencies of HLA genotypes in patients with type 1 diabetes – indication of an increased environmental pressure? Diabetologia 2003: 46: 420–425.
77. Gillespie KM, Bain SC, Barnett AH et al. The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. Lancet 2004: 364: 1699–1700.
78. Fourlanos S, Varney MD, Tait BD et al. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes. Diabetes Care 2008: 31: 1546–1549.
79. Hemminki K, Li X, Sundquist J, Sundquist K. Familial association between type 1 diabetes and other autoimmune and related diseases. Diabetologia 2009: 52: 1820–1828.
80. Parkkola A, Harkonen T, Ryhanen SJ, Ilonen J, Knip M. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. Diabetes Care 2012: 36: 348–354.
81. Olmos P, A'Hern R, Heaton DA et al. The significance of the concordance rate for type 1 (insulin-dependent) diabetes in identical twins. Diabetologia 1988: 31: 747–750.
82. Harjutsalo V, Podar T, Tuomilehto J. Cumulative incidence of type 1 diabetes in 10,168 siblings of Finnish young-onset type 1 diabetic patients. Diabetes 2005: 54: 563–569.
83. Steck AK, Barriga KJ, Emery LM, Fiallo-Scharer RV, Gottlieb PA, Rewers MJ. Secondary attack rate of type 1 diabetes in Colorado families. Diabetes Care 2005: 28: 296–300.
84. Gillespie KM, Aitken RJ, Wilson I, Williams AJ, Bingley PJ. Early onset of diabetes in the proband is the major determinant of risk in HLA DR3-DQ2/DR4-DQ8 siblings. Diabetes 2014: 63: 1041–1047.
85. Gillespie KM, Gale EA, Bingley PJ. High familial risk and genetic susceptibility in early onset childhood diabetes. Diabetes 2002: 51: 210–214.
86. Green A, Schober E, Christov V et al. Familial risk of type 1 diabetes in European children. Diabetologia 1998: 41: 1151–1156.
87. Dorman JS, Steenkiste AR, O'Leary LA, McCarthy BJ, Lorenzen T, Foley TP. Type 1 diabetes in offspring of parents with type 1 diabetes: the tip of an autoimmune iceberg? Pediatr Diabetes 2000: 1: 17–22.
88. El Hashimy M, Angelico MC, Martin BC, Krolewski AS, Warram JH. Factors modifying the risk of IDDM in offspring of an IDDM parent. Diabetes 1995: 44: 295–299.
89. Lorenzen T, Pociot F, Stilgren L et al. Predictors of IDDM recurrence risk in offspring of Danish IDDM patients. Danish IDDM Epidemiology and Genetics Group. Diabetologia 1998: 41: 666–673.
90. Warram JH, Krolewski AS, Gottlieb MS, Kahn CR. Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. N Engl J Med 1984: 311: 149–152.
91. Harjutsalo V, Lammi N, Karvonen M, Groop PH. Age at onset of type 1 diabetes in parents and recurrence risk in offspring. Diabetes 2010: 59: 210–214.
92. Tattersall R. Maturity-onset diabetes of the young: a clinical history. Diabet Med 1998: 15: 11–14.
93. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. Diabetes Care 2011: 34: 1878–1884.
94. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. N Engl J Med 2001: 345: 971–980.
95. Tattersall RB, Fajans SS. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. Diabetes 1975: 24: 44–53.

96. Awa WL, Schober E, Wiegand S et al. Reclassification of diabetes type in pediatric patients initially classified as type 2 diabetes mellitus: 15 years follow-up using routine data from the German/Austrian DPV database. Diabetes Res Clin Pract 2011: 94: 463–467.
97. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab 2008: 4: 200–213.
98. Edghill EL, Dix RJ, Flanagan SE et al. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. Diabetes 2006: 55: 1895–1898.
99. Iafusco D, Stazi MA, Cotichini R et al. Permanent diabetes mellitus in the first year of life. Diabetologia 2002: 45: 798–804.
100. Rubio-Cabezas O, Minton JA, Caswell R et al. Clinical heterogeneity in patients with FOXP3 mutations presenting with permanent neonatal diabetes. Diabetes Care 2009: 32: 111–116.
101. Rubio-Cabezas O, Flanagan SE, Damhuis A, Hattersley AT, Ellard S. KATP channel mutations in infants with permanent diabetes diagnosed after 6 months of life. Pediatr Diabetes 2012: 13: 322–325.
102. Rubio-Cabezas O, Edghill EL, Argente J, Hattersley AT. Testing for monogenic diabetes among children and adolescents with antibody-negative clinically defined Type 1 diabetes. Diabet Med 2009: 26: 1070–1074.
103. Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, Plotnick LP. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of KCNJ11 mutation testing in neonatal DM. Pediatr Diabetes 2010: 11: 203–207.
104. Massa O, Iafusco D, D'Amato E et al. KCNJ11 activating mutations in Italian patients with permanent neonatal diabetes. Hum Mutat 2005: 25: 22–27.
105. Iafusco D, Massa O, Pasquino B et al. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births. Acta Diabetol 2012: 49: 405–408.
106. von Muhlendahl KE, Herkenhoff H. Long-term course of neonatal diabetes. N Engl J Med 1995: 333: 704–708.
107. Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, Shield JP. Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. Diabetes 2000: 49: 1359–1366.
108. Gardner RJ, Mackay DJ, Mungall AJ et al. An imprinted locus associated with transient neonatal diabetes mellitus. Hum Mol Genet 2000: 9: 589–596.
109. Flanagan SE, Patch AM, Mackay DJ et al. Mutations in ATP-sensitive K+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. Diabetes 2007: 56: 1930–1937.
110. Temple IK, Shield JP. 6q24 transient neonatal diabetes. Rev Endocr Metab Disord 2010: 11: 199–204.
111. Gloyn AL, Cummings EA, Edghill EL et al. Permanent neonatal diabetes due to paternal germline mosaicism for an activating mutation of the KCNJ11 Gene encoding the Kir6.2 subunit of the beta-cell potassium adenosine triphosphate channel. J Clin Endocrinol Metab 2004: 89: 3932–3935.
112. Massa O, Iafusco D, D'Amato E et al. KCNJ11 activating mutations in Italian patients with permanent neonatal diabetes. Hum Mutat 2005: 25: 22–27.
113. Colombo C, Porzio O, Liu M et al. Seven mutations in the human insulin gene linked to permanent neonatal/infancy-onset diabetes mellitus. J Clin Invest 2008: 118: 2148–2156.
114. Edghill EL, Flanagan SE, Patch AM et al. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. Diabetes 2008: 57: 1034–1042.
115. Polak M, Dechaume A, Cave H et al. Heterozygous missense mutations in the insulin gene are linked to permanent diabetes appearing in the neonatal period or in early infancy: a report from the French ND (Neonatal Diabetes) Study Group. Diabetes 2008: 57: 1115–1119.
116. Støy J, Edghill EL, Flanagan SE et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci U S A 2007: 104: 15040–15044.
117. Garin I, Edghill EL, Akerman I et al. Recessive mutations in the INS gene result in neonatal diabetes through reduced insulin biosynthesis. Proc Natl Acad Sci U S A 2010: 107: 3105–3110.
118. Njolstad PR, Sovik O, Cuesta-Munoz A et al. Neonatal diabetes mellitus due to complete glucokinase deficiency. N Engl J Med 2001: 344: 1588–1592.
119. Rubio-Cabezas O, Ellard S. Diabetes mellitus in neonates and infants: genetic heterogeneity, clinical approach to diagnosis, and therapeutic options. Horm Res Paediatr 2013: 80: 137–146.
120. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet 1997: 15: 106–110.
121. Guillausseau PJ, Dubois-Laforgue D, Massin P et al. Heterogeneity of diabetes phenotype in patients with 3243 bp mutation of mitochondrial DNA (maternally inherited diabetes and deafness or MIDD). Diabetes Metab 2004: 30: 181–186.
122. Laloi-Michelin M, Meas T, Ambonville C et al. The clinical variability of maternally inherited diabetes and deafness is associated with the degree of heteroplasmy in blood leukocytes. J Clin Endocrinol Metab 2009: 94: 3025–3030.
123. Reardon W, Ross RJ, Sweeney MG et al. Diabetes mellitus associated with a pathogenic point mutation in mitochondrial DNA. Lancet 1992: 340: 1376–1379.
124. van den Ouweland JM, Lemkes HH, Ruitenbeek W et al. Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. Nat Genet 1992: 1: 368–371.
125. Mazzaccara C, Iafusco D, Liguori R et al. Mitochondrial diabetes in children: seek and you will find it. PLoS One 2012: 7: e34956.
126. Rana M, Munns CF, Selvadurai H, Donaghue KC, Craig ME. Cystic fibrosis-related diabetes in children-gaps in the evidence? Nat Rev Endocrinol 2010: 6: 371–378.

127. Rana M, Munns CF, Selvadurai HC, et al. Increased detection of cystic-fibrosis-related diabetes in Australia. Arch Dis Child 2011: 96: 823–826.
128. Hameed S, Morton JR, Jaffe A et al. Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. Diabetes Care 2010: 33: 221–226.
129. Waugh N, Royle P, Craigie I et al. Screening for cystic fibrosis-related diabetes: a systematic review. Health Technol Assess 2012: 16 iii–iv, 1–179.
130. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009: 32: 1626–1631.
131. Moran A, Milla C, Ducret R, Nair KS. Protein metabolism in clinically stable adult cystic fibrosis patients with abnormal glucose tolerance. Diabetes 2001: 50: 1336–1343.
132. Moran A, Pillay K, Becker D, Acerini CL. Management of cystic fibrosis related diabetes in children and adolescents. Pediatr Diabetes 2014: 15 (Suppl. 20): 65–76.
133. Berne C, Pollare T, Lithell H. Effects of antihypertensive treatment on insulin sensitivity with special reference to ACE inhibitors. Diabetes Care 1991: 14 (Suppl. 4): 39–47.
134. Vestri HS, Maianu L, Moellering DR, Garvey WT. Atypical antipsychotic drugs directly impair insulin action in adipocytes: effects on glucose transport, lipogenesis, and antilipolysis. Neuropsychopharmacology 2007: 32: 765–772.
135. Pui CH, Burghen GA, Bowman WP, Aur RJ. Risk factors for hyperglycemia in children with leukemia receiving L-asparaginase and prednisone. J Pediatr 1981: 99: 46–50.
136. Drachenberg CB, Klassen DK, Weir MR et al. Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. Transplantation 1999: 68: 396–402.
137. Al Uzri A, Stablein DM, Cohn A. Posttransplant diabetes mellitus in pediatric renal transplant recipients: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Transplantation 2001: 72: 1020–1024.
138. Maes BD, Kuypers D, Messiaen T et al. Posttransplantation diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. Transplantation 2001: 72: 1655–1661.
139. First MR, Gerber DA, Hariharan S, Kaufman DB, Shapiro R. Posttransplant diabetes mellitus in kidney allograft recipients: incidence, risk factors, and management. Transplantation 2002: 73: 379–386.
140. Bobo WV, Cooper WO, Stein CM et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry 2013: 70: 1067–1075.
141. Amed S, Dean H, Sellers EA et al. Risk factors for medication-induced diabetes and type 2 diabetes. J Pediatr 2011: 159: 291–296.
142. Bhisitkul DM, Morrow AL, Vinik AI, Shults J, Layland JC, Rohn R. Prevalence of stress hyperglycemia among patients attending a pediatric emergency department. J Pediatr 1994: 124: 547–551.
143. Valerio G, Franzese A, Carlin E, Pecile P, Perini R, Tenore A. High prevalence of stress hyperglycaemia in children with febrile seizures and traumatic injuries. Acta Paediatr 2001: 90: 618–622.
144. Gauglitz GG, Herndon DN, Kulp GA, Meyer WJ III, Jeschke MG. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. J Clin Endocrinol Metab 2009: 94: 1656–1664.
145. Saz EU, Ozen S, Simsek Goksen D, Darcan S. Stress hyperglycemia in febrile children: relationship to prediabetes. Minerva Endocrinol 2011: 36: 99–105.
146. Weiss SL, Alexander J, Agus MS. Extreme stress hyperglycemia during acute illness in a pediatric emergency department. Pediatr Emerg Care 2010: 26: 626–632.
147. Herskowitz RD, Wolfsdorf JI, Ricker AT et al. Transient hyperglycemia in childhood: identification of a subgroup with imminent diabetes mellitus. Diabetes Res 1988: 9: 161–167.
148. Schatz DA, Kowa H, Winter WE, Riley WJ. Natural history of incidental hyperglycemia and glycosuria of childhood. J Pediatr 1989: 115: 676–680.
149. Vardi P, Shehade N, Etzioni A et al. Stress hyperglycemia in childhood: a very high risk group for the development of type I diabetes. J Pediatr 1990: 117: 75–77.
150. Herskowitz-Dumont R, Wolfsdorf JI, Jackson RA, Eisenbarth GS. Distinction between transient hyperglycemia and early insulin-dependent diabetes mellitus in childhood: a prospective study of incidence and prognostic factors. J Pediatr 1993: 123: 347–354.
151. Bhisitkul DM, Vinik AI, Morrow AL et al. Prediabetic markers in children with stress hyperglycemia. Arch Pediatr Adolesc Med 1996: 150: 936–941.
152. Shehadeh N, On A, Kessel I et al. Stress hyperglycemia and the risk for the development of type 1 diabetes. J Pediatr Endocrinol Metab 1997: 10: 283–286.