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Definition, epidemiology and classification of diabetes in children and adolescents

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Definition

Diabetes mellitus is a group of metabolic diseases characterised by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The abnormalities in carbohydrate, fat, and protein metabolism that are found in diabetes are due to deficient action of insulin on target tissues. If ketones are present in blood or urine, treatment is urgent, because ketoacidosis can evolve rapidly.

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 (E) (4; 86). Three ways to diagnose diabetes are possible and each, in the absence of unequivocal hyperglycemia, must be confirmed, on a subsequent day, by any one of the three methods given in Table 1.

- Diabetes in children usually presents with characteristic symptoms such as polyuria, polydipsia, blurring of vision, and weight loss, in association with glycosuria and ketonuria.
- In its most severe form, ketoacidosis or rarely a non-ketotic hyperosmolar state may develop and lead to stupor, coma and in absence of effective treatment, death.
- The diagnosis is usually confirmed quickly by measurement of a marked elevation of the blood glucose level. In this situation if ketones are present in blood or urine, treatment is urgent. Waiting another day to confirm the hyperglycemia may be dangerous in allowing ketoacidosis to evolve rapidly.
- In the absence of symptoms or presence of mild symptoms of diabetes, hyperglycemia detected incidentally or under conditions of acute infective, traumatic, circulatory or other stress may be transitory and should not in itself be regarded as diagnostic of diabetes. The diagnosis of diabetes should not be based on a single plasma glucose concentration. Diagnosis may require continued observation with fasting and/or 2 hour post-prandial blood glucose levels and/or an oral glucose tolerance test (OGTT).
- An OGTT should not be performed if diabetes can be diagnosed using fasting, random or post-prandial criteria as excessive hyperglycemia can result. It is

Table 1. Criteria for the diagnosis of diabetes mellitus (4; 86) (E)

1. Symptoms of diabetes plus casual plasma glucose concentration ≥11.1 mmol/L (200 mg/dl)*. Casual is defined as any time of day without regard to time since last meal.
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 postload glucose ≥11.1 mmol/l (≥200 mg/dl) during an OGTT. The test should be performed as described by WHO (86), 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 (65).

*Corresponding values (mmol/L) are ≥10.0 for venous whole blood and ≥11.1 for capillary whole blood and
†≥6.3 for both venous and capillary whole blood

rarely indicated in making the diagnosis of type 1 diabetes in childhood and adolescence (E) (86).
- If doubt remains, periodic re-testing should be undertaken until the diagnosis is established.

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

- IGT and IFG are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes (E) (11; 65).
- IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation. IFG is a measure of disturbed carbohydrate metabolism in the basal state whilst IGT is a dynamic measure of carbohydrate intolerance after a standardised glucose load.
- Patients with IFG and/or IGT are now referred to as having ''pre-diabetes'' indicating the relatively high risk for development of diabetes in these patients (A) (33; 38).
- They can be observed as intermediate stages in any of the disease processes listed in Table 2.
- IFG and IGT may be associated with the metabolic syndrome, which includes obesity (especially abdominal or visceral obesity), dyslipidaemia of the high-triglyceride and/or low-HDL type, and hypertension.
- Individuals who meet criteria for IGT or IFG may be euglycemic in their daily lives as shown by normal or near–normal glycated haemoglobin levels, and those with IGT may manifest hyperglycemia only when challenged with an OGTT.

Categories of fasting plasma glucose 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 above under ''Diagnostic Criteria'')

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

- 2 hour postload glucose<7.8 mmol/l (140 mg/dl) = normal glucose tolerance
- 2 hour postload glucose 7.8—11.1 mmol/l (140–199 mg/dl) = IGT
- 2 hour postload glucose>11.1 mmol/l (200 mg/dl) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).

Pathogenesis of type 1 diabetes

- Individuals have an absolute deficiency of insulin secretion and are prone to ketoacidosis
- Most cases are primarily due to T-cell mediated pancreatic islet β-cell destruction, which occurs at a variable rate, and becomes clinically symptomatic when approximately 90% of pancreatic beta cells are destroyed (C) (25).
- Serological markers of an autoimmune pathologic process, including islet cell, GAD, IA-2, IA- 2β, or insulin autoantibodies, are present in 85-90% of individuals when fasting hyperglycemia is detected (B) (68; 82).
- Susceptibility to autoimmune type 1 diabetes is determined by multiple genes; in a recent meta-analysis more than 40 distinct genomic locations provided evidence for association with T1D (7). HLA genes having the strongest known association, there is linkage to specific combinations of alleles at the DRB1, DQA1 and DQB1 loci, with both susceptible or protective haplotypes (21; 45) (B).
- Individuals at increased risk of developing type 1 diabetes can often be identified by measurement of diabetes associated autoantibodies, genetic markers and intravenous glucose tolerance testing (B) (44; 51; 73; 81).
- The environmental triggers (chemical and/or viral) which initiate pancreatic beta cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms (B) (73; 81). Enterovirus infection has

Table 2. Aetiological classification of disorders of glycemia

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, HNF−1α (MODY3)
2. Chromosome 7, glucokinase (MODY2)
3. Chromosome 20, HNF−4α (MODY1)
4. Chromosome 13, insulin promoter factor- (IPF-1; MODY4)
5. Chromosome 17, HNF−1β (MODY5)
6. Chromosome 2, *NeuroD1* (MODY6)
7. Mitochondrial DNA mutation
8. Chromosome 7, KCNJ11 (Kir6.2)
9. 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. Haemochromatosis
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. Others

G. Uncommon forms of immune-mediated diabetes

1. ''Stiff-man'' syndrome
2. Anti-insulin receptor antibodies
3. Others
4. Polyendocrine autoimmune deficiencies APS I and II

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

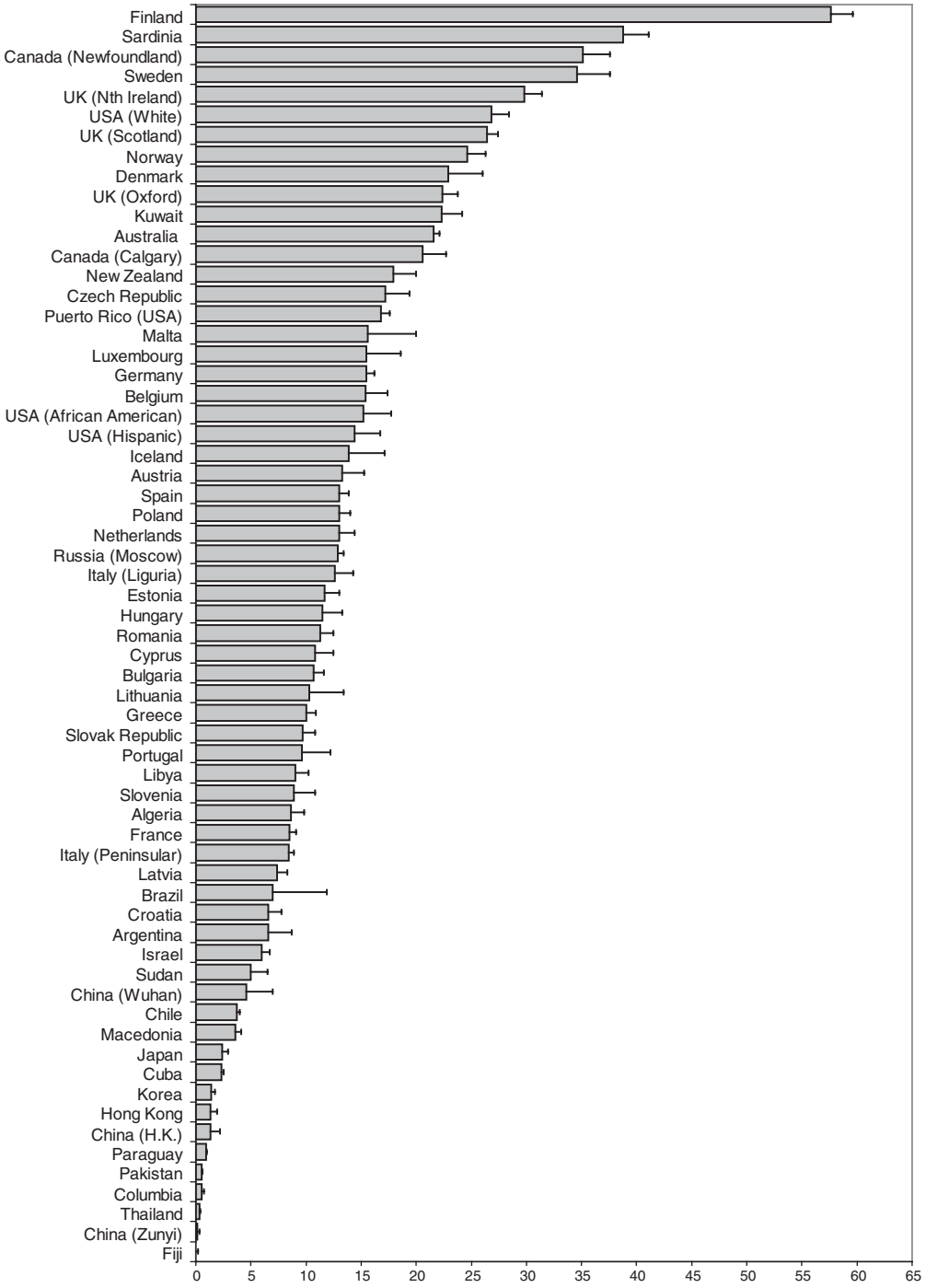

Fig. 1. Mean Annual Incidence Rates for Type 1 Diabetes (0–14 year age group) Comparing Different Countries in the World.

been associated with development of diabetes associated autoantibodies in some populations (48; 69) and enteroviruses have been detected in the islets of individuals with diabetes (16; 67; 88).

- In geographical areas where type 1 diabetes occurs with lower incidence, there is a higher rate of diabetic ketoacidosis (DKA) at presentation (18; 47).
- When the clinical presentation is typical of type 1 diabetes (often associated with DKA) but antibodies are absent, then the diabetes is classified as Type 1B (idiopathic). Most are of African or Asian ancestry, however other forms of diabetes should also be considered as shown in Table 2.

Epidemiology of type 1 diabetes

- In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes,

although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years (75; 79) (B). Type 2 diabetes is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at risk populations (B) (63).

- 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 (B) (3).
- Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations (B). Mean annual incidence rates for childhood type 1 diabetes (0–14 years age group) comparing different countries of the world are shown in Figure 1 (0.1 to 57.6 per 100,000) (3; 32; 41; 62)
- In Europe incidence rates show a close correlation with the frequency of HLA susceptibility genes in the general population (B) (14; 26; 40; 43).
- In Asia, the incidence of type 1 diabetes is extremely low: China 0.1 per 100 000 (3), Japan 2.4 per 100,000 (42); and has a different and unique HLA association compared with Caucasians (39). 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 (76).
- The rising incidence of type 1 diabetes is associated with an increased proportion of individuals with low risk HLA genotypes in some populations (23; 26)
- Gender differences in incidence are found in some, but not all, populations (B) (3; 10; 24; 85).
- A well documented rise in the incidence has been noted in many countries, and in some reports there has been a disproportionately greater increase in those under the age of 5 years (B) (3; 62).
- A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months (B) (29; 46; 85).
- Despite familial aggregation, which accounts for approximately 10% of cases of type 1 diabetes (34), there is no recognisable pattern of inheritance. The risk of diabetes to an identical twin of a patient with type 1 diabetes is about 36% (B) (60); for a sibling the risk is approximately 4% by age 20 years (B) (31; 74) and 9.6% by age 60 years (B) (49); compared with 0.5 % for the general population. The risk is higher in siblings of probands diagnosed at younger age (B) (27; 74).
- 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%) (B) (1; 15;20; 27; 50; 74; 84).

Classification

The aetiological classification recommended by the American Diabetes Association (E) (4) and the WHO expert committee on the classification and diagnosis of diabetes (E) (86) is shown in Table 2 with minor modification.

Classifying types of diabetes

The differentiation between type 1, type 2 and monogenic diabetes has important implications for both therapeutic decisions and educational approaches. Regardless of the type of diabetes, however, the child who presents with severe fasting hyperglycemia, metabolic derangements and ketonaemia, will require insulin therapy initially to reverse the metabolic abnormalities (72).

- Measurement of diabetes associated autoantibody markers, e.g. ICA, GAD, IA2, IAA and/or HbA1c may be helpful in some situations, however there is currently insufficient evidence to support the routine use of the haemoglobin A1c (A1C) for the diagnosis of diabetes (E) (4).
- Measurement of fasting insulin or C-peptide may be useful in the diagnosis of type 2 diabetes in children. Fasting insulin and C-peptide levels are usually normal or elevated, although not as elevated as might be expected for the degree of hyperglycemia (E) (2). 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 occurring. This is rare outside the honeymoon period (2–3 years) in children with Type 1 diabetes (E).

The possibility of other types of diabetes should be considered in the child who has:

- an autosomal dominant family history of diabetes.
- associated conditions such as deafness, optic atrophy or syndromic features.
- marked insulin resistance or require little or no insulin outside the partial remission phase.
- A history of exposure to drugs known to be toxic to beta 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 Chapter 3.

Monogenic diabetes

Genetic defects of β-cell function or insulin action, formerly termed 'Maturity onset diabetes of the young'

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 months to young adulthood	Usually pubertal (or later)	Often post pubertal except Glucokinase and neonatal diabetes
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (may be incidental in glucokinase)
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	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%)	?1-3%
Parent with diabetes	2-4%	80%	90%

(MODY) was originally described as a disorder with the following characteristics: onset before 25 years of age, autosomal dominant inheritance, nonketotic diabetes mellitus (22; 57; 61).

These classical definitions given to MODY are no longer very helpful as Type 2 diabetes occurs in children and will often meet all these criteria (B,C) (6). In addition, defining the molecular genetics has shown that there are marked differences between genetic subgroups within these old broad categories making it much more appropriate to use the genetic subgroups, an approach that has been supported by the ADA and WHO in their guidelines on classification (E) (Table 2). There is great variation in the degree of hyperglycemia, need for insulin and risk for future complications (B) (19), *see Monogenic diabetes chapter.*

Neonatal diabetes

Insulin-requiring hyperglycemia in the first three months of life is known as neonatal diabetes mellitus.

- This rare condition (1 in 400,000 births) may be associated with intrauterine growth retardation (C) (54; 83). Approximately half of the cases are transient and have been associated with paternal isodisomy and other imprinting defects of chromosome 6 (B, C) (35; 54) *see Monogenic diabetes chapter*. In patients with transient neonatal diabetes mellitus, permanent diabetes may appear later in life (C) (28).
- Permanent cases have been associated with pancreatic aplasia, activating mutations of KCNJ11, which is the gene encoding the ATP-Sensitive Potassium-Channel Subunit Kir6.2 (7p15-p13) (28; 53), mutations of the Insulin Promoter Factor-1 (chromosome 7) in which there is pancreatic aplasia, complete glucokinase deficiency (chromosome 7) (C) (58), mutations of the FOXP3 gene (T cell regulatory gene) as part of the IPEX syndrome (C) (8).

Mitochondrial diabetes

Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterised by progressive non-autoimmune beta-cell failure.

- Maternal transmission of mutated mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. Although several mutations have been implicated, the strongest evidence relates to a point substitution at nucleotide position 3243 (A to G) in the mitochondrial tRNA (leu(UUR)) gene (B) (66; 78).

Cystic fibrosis and diabetes

Cystic Fibrosis related diabetes (CFRD) is primarily due to insulin deficiency, but insulin resistance during acute illness, secondary to infections and medications (bronchodilators and glucocorticoids), may also contribute to impaired glucose tolerance and diabetes.

- CFRD tends to occur late in the disease, typically in adolescence and early adulthood. Cirrhosis, if present, may contribute to insulin resistance. The onset of CFRD is a poor prognostic sign, and is associated with increased morbidity and mortality (55). Poorly controlled diabetes will interfere with immune responses to infection and promote catabolism (E) (56; 87).

- Screening recommendations vary from testing a random blood glucose level annually in all children with cystic fibrosis ≥14 years old, to performing an oral glucose tolerance test annually in all those >10 years old (56; 87), but conventional measures such as FPG, OGTT and HbA1c may not be appropriate tools for the diagnosis of diabetes in patients with CF (B) (13).
- Insulin therapy initially may only be needed during respiratory infections due to acute or chronic infective episodes, but eventually insulin therapy is frequently necessary. Initially insulin doses are small (supplemental rather than total insulin replacement). In some patients, early insulin therapy prior to symptoms of hyperglycemia may provide metabolic effects beneficial to growth, weight and pulmonary function (12; 59) B. *See Chapter 5*.

Drug induced diabetes

- In neurosurgery, large doses of dexamethasone are frequently used to prevent cerebral oedema (eg dexamethasone 24 mg per day). The additional stress of the surgery may add to the drug-induced insulin resistance, and cause a relative insulin deficiency, sufficient to cause a transient form of diabetes. This will be exacerbated if large volumes of intravenous dextrose are given for diabetes insipidus. An intravenous insulin infusion is the optimal way 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 (B) (64). Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction (C) (17). Often the diabetes is cyclical and associated with the chemotherapy cycles, especially if associated with large doses of glucocorticoids.
- Following transplantation, diabetes most frequently occurs with the use of high dose steroids and tacrolimus; the risk is increased in patients with pre-existing obesity (B) (5; 52).
- Diabetes can also be induced by the use of atypical antipsychotics including olanzapine (Zyprexa), risperidol (Risperdal), quetiapine (Seroquel), and ziprasidone (Geodon), in association with weight gain (30).

Stress hyperglycemia

Stress hyperglycemia has been reported in up to 5% of children presenting to an emergency department. Acute illness or injury; traumatic injuries, febrile seizures and elevated body temperature (>39 degrees) were identified as the most common associated features (77).

- The reported incidence of progression to overt diabetes varies from 0% to 32% (B,C) (9; 36; 37; 70; 71; 80). Children with incidental hyperglycemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness (37). Islet cell antibodies and insulin autoantibody testing had a high positive and negative predictive value for type 1 diabetes in children with stress hyperglycemia (37).

Recommendations

- Severe hyperglycemia detected under conditions of acute infection, trauma, surgery, respiratory distress, circulatory or other stress may be transitory and require treatment but should not in itself be regarded as diagnostic of diabetes (E).
- Screening for diabetes associated antibodies may be useful in selected patients with stress hyperglycemia (E).

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