

ISPAD Clinical Practice Consensus Guidelines 2006–2007 Definition, epidemiology and classification

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Definition

Diabetes mellitus (DM) is a group of metabolic diseases characterized by chronic hyperglycaemia 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 the 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) (1, 2). Three ways to diagnose diabetes are possible and each, in the absence of unequivocal hyperglycaemia, 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 the blood or urine, treatment is urgent. Waiting another day to confirm the hyperglycaemia may be dangerous in allowing ketoacidosis to evolve rapidly.

- In the absence of symptoms or presence of mild symptoms of diabetes, hyperglycaemia 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-h postprandial 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 postprandial criteria, as excessive hyperglycaemia can result using a fasting OGTT in these circumstances. It is rarely indicated in making the diagnosis of type 1 DM (T1DM) in childhood and adolescence (E) (2).
- If doubt remains, periodic re-testing should be undertaken until the diagnosis is established or refuted.

Impaired glucose tolerance and impaired fasting glycaemia

- Impaired glucose tolerance (IGT) and impaired fasting glycaemia (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes (E) (3, 4).
- 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, while IGT is a dynamic measure of carbohydrate intolerance after a standardized 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) (5, 6).
- 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 (MS), which includes obesity (especially abdominal or visceral obesity), dyslipidaemia of the high-triglyceride and/or low-high density lipoprotein (HDL) type, and hypertension.

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

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 the last meal.
 or
 Fasting plasma glucose ≥ 7.0 mmol/L (≥ 126 mg/dL).[†] Fasting is defined as no caloric intake for at least 8 h.
 or
 2-h postload glucose ≥ 11.1 mmol/L (≥ 200 mg/dL) during an oral glucose tolerance test (OGTT). The test should be performed as described by the World Health Organization (WHO) (2), 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 (3).

^{*}Corresponding values (mmol/L) are ≥ 10.0 for venous whole blood and ≥ 11.1 for capillary whole blood.

[†]Corresponding values are ≥ 6.3 mg/dL for both venous and capillary whole blood.

- Individuals who meet the criteria for IGT or IFG may be euglycaemic in their daily lives as shown by normal or near-normal glycated haemoglobin levels, and those with IGT may manifest hyperglycaemia 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 above under ‘Diagnostic criteria’).

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

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

Pathogenesis of T1DM

- 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 β -cells are destroyed (C) (7).
- Serological markers of an autoimmune pathologic process, including islet cell, glutamic acid decarboxylase (GAD), islet antigen (IA)-2, IA-2 β , or insulin autoantibodies (IAAs), are present in 85–90% of individuals when fasting hyperglycaemia is detected (B) (8, 9).
- Susceptibility to autoimmune T1DM is determined by the interaction of multiple genes. Human leucocyte

antigen (HLA) genes having the strongest known association, with linkage to *DQA* and *DQB* genes, which can be either predisposing or protective (B) (10–12).

- Individuals at increased risk of developing T1DM can often be identified by measurement of diabetes-associated autoantibodies, genetic markers, and intravenous glucose tolerance testing (B) (13–16).
- The environmental triggers (chemical and/or viral) which initiate pancreatic β -cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms (B) (15, 16).
- In geographical areas where T1DM occurs with lower incidence, there is a higher rate of diabetic ketoacidosis (DKA) at presentation (17, 18)
- When the clinical presentation is typical of T1DM (often associated with DKA) but antibodies are absent, then the diabetes is classified as T1B (idiopathic). Other forms of diabetes should also be considered as shown in Table 2.

Epidemiology of T1DM

- More than half of individuals with T1DM are diagnosed before the age of 15 yr (B) (19). In most western countries, T1DM accounts for more than 90% of childhood and adolescent diabetes. Type 2 DM (T2DM) is becoming more common and accounts for a significant proportion of youth-onset diabetes in certain at-risk populations (B) (20).
- Epidemiological incidence studies define the ‘onset of T1DM’ by the date of the first insulin injection because of the variable time between the onset of symptoms and diagnosis (B) (21).
- The incidence of T1DM varies greatly between different countries, within countries, and between different ethnic populations (B). Annual incidence rates for childhood T1DM (0–14 yr age group) comparing different countries of the world are shown in Figure 1 (0.1–37.4 per 100 000) (21, 22).

Table 2. Aetiological classification of disorders of glycaemia

I. Type 1

β -cell destruction, usually leading to absolute insulin deficiency

- A. Autoimmune
- 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

- | | |
|---|--|
| <ul style="list-style-type: none"> A. Genetic defects of β-cell function <ul style="list-style-type: none"> Chromosome 12, HNF-1α (MODY3) Chromosome 7, glucokinase (MODY2) Chromosome 20, HNF-4α (MODY1) Chromosome 13, insulin promoter factor (IPF)-1 (MODY4) Chromosome 17, HNF-1β (MODY5) Chromosome 2, <i>NeuroD1</i> (MODY6) Mitochondrial DNA mutation Chromosome 11, <i>KCNJ11</i> (Kir6.2), <i>ABCC8</i> [sulphonylurea receptor 1 (SUR1)] Others B. Genetic defects in insulin action <ul style="list-style-type: none"> Type A insulin resistance Leprechaunism Rabson–Mendenhall syndrome Lipoatrophic diabetes Others C. Diseases of the exocrine pancreas <ul style="list-style-type: none"> Pancreatitis Trauma/pancreatectomy Neoplasia Cystic fibrosis Haemochromatosis Fibrocalculous pancreatopathy Others D. Endocrinopathies <ul style="list-style-type: none"> Acromegaly Cushing syndrome Glucagonoma Phaeochromocytoma Hyperthyroidism Somatostatinoma Aldosteronoma Others | <ul style="list-style-type: none"> E. Drug or chemical induced <ul style="list-style-type: none"> Vacor Pentamidine Nicotinic acid Glucocorticoids Thyroid hormone Diazoxide β-adrenergic agonists Thiazides Dilantin α-Interferon Others F. Infections <ul style="list-style-type: none"> Congenital rubella Cytomegalovirus Coxsackie B4 Others G. Uncommon forms of immune-mediated diabetes <ul style="list-style-type: none"> 'Stiff-man' syndrome Anti-insulin receptor antibodies Autoimmune polyendocrine syndrome deficiencies I and II Others H. Other genetic syndromes sometimes associated with diabetes <ul style="list-style-type: none"> Down's syndrome Klinefelter's syndrome Turner's syndrome Wolfram's syndrome Friedreich's ataxia Huntington's chorea Laurence–Moon–Biedl syndrome Myotonic dystrophy Porphyria Prader–Willi syndrome Others |
|---|--|

IV. Gestational diabetes

HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of the young.

- In Europe, incidence rates show a close correlation with the frequency of HLA susceptibility genes in the general population (B) (23–26).
- In Japan, the incidence of T1DM is extremely low at 1.5–2.0 per 100 000 and has a different and unique HLA association compared with Caucasians (27). In addition, a slowly progressive form of T1DM is common (28).
- Gender differences in incidence are found in some, but not all, populations (B) (21, 29–32).
- 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 younger than the age of 5 yr (B) (33–35).
- A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months (B) (32, 36, 37).
- Despite familial aggregation, there is no recognizable pattern of inheritance. The risk of diabetes to an identical twin of a patient with T1DM is about 36% (B) (38); for a sibling, the risk is approximately 4% by the age of 20 yr (B) (39, 40) and 9.6% by the age of 60 yr (B) (41), compared with 0.5% for the general population. The risk is higher in siblings of probands diagnosed at a younger age (B) (40, 42).

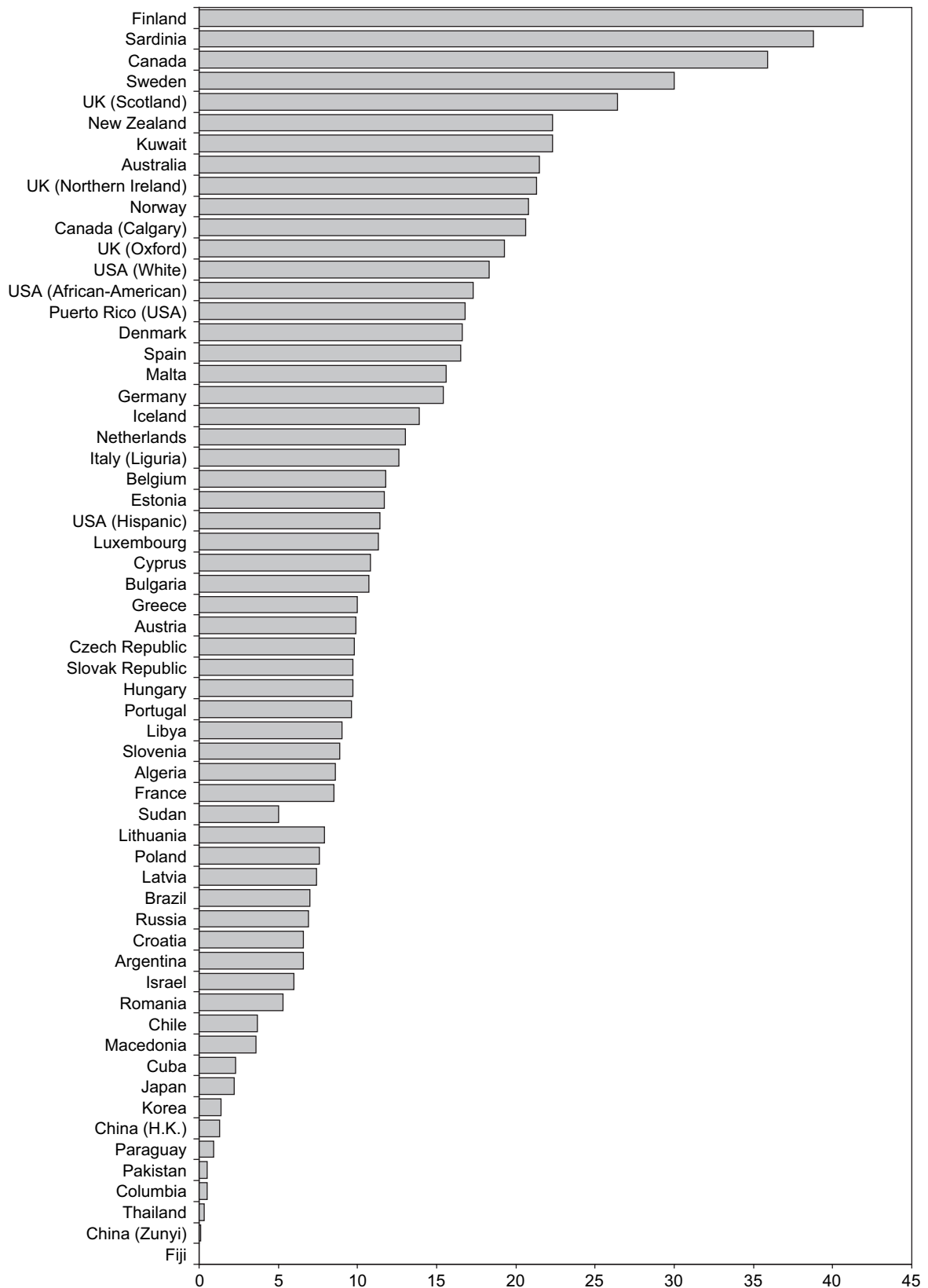


Fig. 1. Annual incidence rates for type 1 diabetes mellitus (T1DM) (0–14 yr age group) comparing different countries in the world [modified from the International Diabetes Federation Atlas (80)].

- T1DM 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%) (B) (40, 42–47).

Classification

The etiological classification recommended by the American Diabetes Association (ADA) (E) (1) and the World Health Organization (WHO) expert committee on the classification and diagnosis of diabetes (E) (2) is shown in Table 2 with minor modification.

Classifying types of diabetes

The differentiation between T1DM, T2DM, 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 hyperglycaemia, metabolic derangements, and ketonaemia will require insulin therapy initially to reverse the metabolic abnormalities (48).

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

- An autosomal dominant family history of diabetes.
- Associated conditions such as deafness, optic atrophy, or syndromic features.
- Marked insulin resistance or requires little or no insulin outside the partial remission phase.
- A history of exposure to drugs known to be toxic to β -cells or cause insulin resistance.

Measurement of fasting insulin or C-peptide is useful in the diagnosis of T2DM 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 hyperglycaemia (E) (49). If patients are treated with insulin, 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 yr) in children with T1DM (E). T2DM is more completely discussed in a later chapter.

Characteristic features of youth-onset T1DM in comparison with T2DM and monogenic diabetes are shown in Table 3.

Maturity-onset diabetes of the young

Maturity-onset diabetes of the young (MODY) was described as a disorder with the following characteristics: onset before 25 yr of age, autosomal dominant inheritance, non-ketotic DM (50, 51).

These classical definitions given to MODY are no longer very helpful, as T2DM occurs in children and will often meet all these criteria (B, C) (52). 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 hyperglycaemia, need for insulin, and risk for future complications (B) (53), see chapter, ‘The diagnosis and management of monogenic diabetes in children’.

Table 3. Clinical characteristics of T1DM, T2DM and monogenic diabetes in children and adolescents

	T1DM	T2DM	Monogenic
Characteristics			
Genetics	Polygenic	Polygenic	Monogenic
Age	Throughout childhood	Usually pubertal (or later)	Often postpubertal except MODY2 and neonatal diabetes
Onset	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Rare	Rare in MODY, common in neonatal diabetes
Obesity	Reflects the background risk	Very common	Reflects the background risk
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, maturity-onset diabetes of the young; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus.

Neonatal diabetes

Insulin-requiring hyperglycaemia in the first 3–6 months of life is known as neonatal DM.

- This rare condition (1 in 400 000 births) may be associated with intra-uterine growth retardation (C) (54, 55). Approximately half of the cases are transient and have been associated with paternal isodisomy and other imprinting defects of chromosome 6 (B, C) (55, 56), see chapter, 'The diagnosis and management of monogenic diabetes in children'. In patients with transient neonatal DM, permanent diabetes may appear later in life (C) (57).
- Permanent cases have been associated with pancreatic aplasia, activating mutations of *KCNJ11*, which is the gene encoding the adenosine-triphosphate-sensitive potassium channel subunit Kir6.2 (7p15-p13), as well as *ABCC8* [sulphonylurea receptor 1 (SUR1)], also in the same chromosome region (57, 58); mutations of the insulin promoter factor-1 (IPF-1) (chromosome 7) in which there is pancreatic aplasia; complete glucokinase deficiency (chromosome 7) (C) (59); mutations of the *FOXP3* gene (T-cell regulatory gene) as part of the IPEX syndrome (C) (60).

Mitochondrial diabetes

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

- Maternal transmission of mutated mitochondrial DNA 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) (61, 62).

Cystic fibrosis and diabetes

Cystic fibrosis (CF)-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 IGT 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. Poorly controlled diabetes will interfere with immune responses to infection and promote catabolism (E) (63, 64).

- Screening recommendations vary from testing a random blood glucose level annually in all children with cystic fibrosis ≥ 14 yr old to performing an OGTT annually in all those > 10 yr old (63, 64), but conventional measures such as FPG, OGTT, and haemoglobin A1c (HbA1c) may not be appropriate tools for the diagnosis of diabetes in patients with CF (B) (65).
- 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 hyperglycaemia may provide metabolic effects beneficial to growth, weight, and pulmonary function (66, 67) (B).

Drug-induced diabetes

- In neurosurgery, large doses of dexamethasone are frequently used to prevent cerebral oedema (e.g., dexamethasone 24 mg/d). 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 hyperglycaemia, which is usually transient.
- In oncology, protocols which use L-asparaginase, high-dose glucocorticoids, cyclosporin, or tacrolimus (FK506) may be associated with diabetes. L-Asparaginase usually causes a reversible form of diabetes (B) (68). Tacrolimus and cyclosporin may cause a permanent form of diabetes, possibly due to islet cell destruction (C) (69). 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) (70, 71).
- Diabetes can also be induced by the use of atypical antipsychotics including olanzapine, risperidol, quetiapine, and ziprasidone, in association with weight gain (72).

Stress hyperglycaemia

Stress hyperglycaemia 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 ($> 39^{\circ}\text{C}$) were identified as the most common associated features (73).

- The reported incidence of progression to overt diabetes varies from 0 to 32% (B, C) (74–79). Children with incidental hyperglycaemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness (77). Islet cell antibodies (ICAs) and IAAs testing had a high positive and negative predictive value for T1DM in children with stress hyperglycaemia (77).

Recommendations

- Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of symptoms (E) (1, 2).
- 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 the blood or urine, treatment is urgent. Waiting another day to confirm the hyperglycaemia may be dangerous in allowing ketoacidosis to evolve rapidly (E).
- An OGTT should not be performed if diabetes can be diagnosed using fasting, random or postprandial criteria, as excessive hyperglycaemia can result. It is rarely indicated in making the diagnosis of T1DM in childhood and adolescence (E) (2).
- Severe hyperglycaemia 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).
- Measurement of diabetes-associated autoantibody markers, e.g., ICAs, GAD, IA-2, IAAs and/or HbA1c may be helpful in some situations. There is currently insufficient evidence to support the routine use of the HbA1c for the diagnosis of diabetes (E) (1).
- Measurement of fasting insulin or C-peptide is useful in the diagnosis of T2DM 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 hyperglycaemia (E) (49).

This article is a Chapter in the ISPAD Clinical Practice Consensus Guidelines 2006–2007 of the International Society for Pediatric and Adolescent Diabetes (ISPAD, www.ispad.org). The complete set of these Guidelines will later be published as a compendium. Additional comments, clarifications or corrections should be directed to the Corresponding Author.

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