ISPAD Clinical Practice Consensus Guidelines 2006–2007

Introduction

With this issue of Pediatric Diabetes, the first chapters of the Clinical Practice Consensus Guidelines 2006–2007 of the International Society for Pediatric and Adolescent Diabetes (ISPAD) are published. Sequential chapters will be published in subsequent issues of Pediatric Diabetes. Finally, the complete set of these guidelines will be published as a future compendium.

In 2003, the total child population of the world (0–14 yr) was estimated to be 1.8 billion, of whom 0.024% have diabetes. This means that 430 000 children around the world have diabetes, with 65 000 new cases diagnosed each year (1). This very large number of children need help with injections of insulin in order to survive and live a full life without restrictions or disabling complications and without being stigmatized for their diabetes.

In 1993, members of ISPAD formulated the Declaration of Kos, proclaiming their commitment to ‘promote optimal health, social welfare, and quality of life for all children with diabetes around the world by the year 2000’. Although all the aims and ideals of the Declaration of Kos were not reached by 2000, we believe that slowly, by small steps, the worldwide care of children with diabetes mellitus is improving.

ISPAD published its first set of guidelines in 1995 (2) and its second in 2000 (3). Since then, the acceptance of intensive therapy for children, even for very young children, has increased worldwide. Insulin pump usage has risen in all age groups in countries where this treatment modality can be afforded. However, intensive therapy requires an investment in better and more comprehensive education for the caregivers in order for it to be successful.

The ISPAD Consensus Guidelines 2000 have been translated into 11 languages, indicating the need for a truly international document. In 2003–2005, national guidelines for childhood diabetes were released: the Australian Clinical Practice Guidelines from the National Health and Medical Research Council (writing committee chair, Martin Silink)(4) and in the United Kingdom, the National Institute for Clinical Excellence Clinical Guidelines (group leader, Stephen Greene) (5). Both these publications are truly evidence-based in that they deal with the body of evidence in a systematic approach, grading each reference, and building the case for each recommendation. In 2003, the Canadian Diabetes Association published Clinical Practice Guidelines with chapters both on type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) in children and adolescents (6). In 2005, the American Diabetes Association (ADA) published their statement on the care of children and adolescents with T1DM (7).

This third edition of ISPAD’s Consensus Guidelines, now entitled ‘Clinical Practice Consensus Guidelines’, is much larger and has been enriched by reference to and resources in the above-mentioned national guidelines. In the Introduction to previous ISPAD Guidelines, the acknowledged intention was for the next version of our guidelines to be referenced. We have used the ADA system for grading evidences (Table 1) (8). Whenever possible, the reference for a statement or recommendation has been included, but as readers will note, a vast majority of the recommendations and suggestions will have the grade E (expert consensus or clinical experience).

The 2006–2007 Guidelines are based on a wide consensus of clinical practice. They were drafted by international writing teams, modified by experts in different specialties from many countries, debated at the annual ISPAD meeting in 2005 by the members, and reviewed by members via the internet and the ISPAD website. As far as possible, significant input by individuals has been acknowledged. Many thanks to those numerous individuals who have contributed but whose names could not be included.

As was the same in the 2000 Guidelines, the 2006–2007 edition places education at the center of clinical management. Education is the vehicle for optimal self-management, the key to success. New chapters have been added on T2DM in children and adolescents, monogenic diabetes, and exercise.

We hope, therefore, that the Guidelines will be widely consulted and will be used to

- improve awareness among governments, state healthcare providers, and the general public of the serious long-term implications of poorly managed diabetes and of the essential resources needed for optimal care
- assist individual caregivers in managing children and adolescents with diabetes in a prompt, safe, consistent, equitable, and standardized manner in accordance with the current views of experts in the field.
As in 2000, ‘these Guidelines are not strict protocols nor are they the final word’. Individual clinical judgment and decision making also require the family’s values and expectations to be considered, with the best outcomes being reached by consensus.

Ragnar Hanas, Kim Donaghue, Georgeanna Klingensmith, Peter GF Swift
Editors of the ISPAD Clinical Practice Consensus Guidelines 2006–2007
Ragnar Hanas, MD, PhD
Department of Pediatrics
Uddevala Hospital
S-45180 Uddevalla, Sweden
ragnar.hanas@vgregion.se

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

Authors: Maria E. Craig, University of NSW, University of Sydney, The Children’s Hospital at Westmead, Australia
Andrew Hattersley, Institute of Biomedical and Clinical Sciences, Peninsula Medical School, Exeter, UK
Kim Donaghue, University of Sydney, The Children’s Hospital at Westmead, NSW, Australia
e-mail KimD@chw.edu.au
Acknowledgements: Denis Daneman, Zvi Laron, Shin Amemiya, Shigetaka Sugihara, Tatsuhiko Urakami, Gun Forsander
Editors: Kim Donaghue, Ragnar Hanas, Georgeanna Klingensmith, Peter Swift

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.
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-2β, 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).
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).

### Table 2. Aetiological classification of disorders of glycaemia

<table>
<thead>
<tr>
<th>I. Type 1</th>
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<tbody>
<tr>
<td>β-cell destruction, usually leading to absolute insulin deficiency</td>
</tr>
<tr>
<td>A. Autoimmune</td>
</tr>
<tr>
<td>B. Idiopathic</td>
</tr>
</tbody>
</table>

| 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 | 
| 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, NeuroD1 (MODY6) | 
| Mitochondrial DNA mutation | 
| Chromosome 11, KCNJ11 (KIR6.2), ABC28 [sulphonylurea receptor 1 (SUR1)] | 
| Others | 
| B. Genetic defects in insulin action | 
| Type A insulin resistance | 
| Leprechaunism | 
| Rabson–Mendenhall syndrome | 
| Lipoatrophic diabetes | 
| Others | 
| C. Diseases of the exocrine pancreas | 
| Pancreatitis | 
| Trauma/pancreatectomy | 
| Neoplasia | 
| Cystic fibrosis | 
| Haemochromatosis | 
| Fibrocalculous pancreatopathy | 
| Others | 
| D. Endocrinopathies | 
| Acromegaly | 
| Cushing syndrome | 
| Glucagonoma | 
| Phaeochromocytoma | 
| Hyperthyroidism | 
| Somatostatinoma | 
| Aldosteronoma | 
| Others | 
| E. Drug or chemical induced | 
| Vacor | 
| Pentamidine | 
| Nicotinic acid | 
| Glucocorticoids | 
| Thyroid hormone | 
| Diazoxide | 
| β-adrenergic agonists | 
| Thiazides | 
| Dilantin | 
| α-Interferon | 
| Others | 
| F. Infections | 
| Congenital rubella | 
| Cytomegalovirus | 
| Coxsackie B4 | 
| Others | 
| G. Uncommon forms of immune-mediated diabetes | 
| ‘Stiff-man’ syndrome | 
| Anti-insulin receptor antibodies | 
| Autoimmune polyendocrine syndrome deficiencies I and II | 
| Others | 
| H. Other genetic syndromes sometimes associated with diabetes | 
| 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.
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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>T1DM</th>
<th>T2DM</th>
<th>Monogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetics</td>
<td>Polygenic</td>
<td>Polygenic</td>
<td>Monogenic</td>
</tr>
<tr>
<td>Age</td>
<td>Throughout childhood</td>
<td>Usually pubertal (or later)</td>
<td>Often postpubertal except MODY2 and neonatal diabetes</td>
</tr>
<tr>
<td>Onset</td>
<td>Most often acute, rapid</td>
<td>Variable; from slow, mild (often insidious) to severe</td>
<td>Variable</td>
</tr>
<tr>
<td>Associations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autoimmunity</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Ketosis</td>
<td>Common</td>
<td>Rare</td>
<td>Rare in MODY, common in neonatal diabetes</td>
</tr>
<tr>
<td>Obesity</td>
<td>Reflects the background risk</td>
<td>Very common</td>
<td>Reflects the background risk</td>
</tr>
<tr>
<td>Acanthosis nigricans</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Frequency (% of all diabetes in young people)</td>
<td>Usually 90%+</td>
<td>Most countries &lt;10%</td>
<td>91–3%</td>
</tr>
<tr>
<td>Parent with diabetes</td>
<td>2–4%</td>
<td>80%</td>
<td>90%</td>
</tr>
</tbody>
</table>

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 Alc (HbAlc) 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°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, IAAas 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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ISPAD Clinical Practice Consensus Guidelines 2006–2007

Phases of diabetes


Jennifer Couper*
Kim Donaghueb

aUniversity of Adelaide, South Australia, Australia
bUniversity of Sydney, The Children's Hospital at Westmead, NSW, Australia

Corresponding author:
Kim Donaghue, The Children's Hospital at Westmead,
Locked Bag 4001, Westmead, NSW 2145, Australia
Tel: 61 2 9845 3172;
e-mail: KimD@chw.edu.au

Acknowledgments: Denis Daneman, Desmond Schatz

Editors of the ISPAD Clinical Practice Consensus Guidelines 2006–2007; Kim Donaghue, Ragnar Hanas, Georgeanna Klingensmith, Peter Swift

Type 1 diabetes mellitus (T1DM) is characterized by

- Preclinical diabetes.
- Presentation of diabetes.
- Partial remission or honeymoon phase.
- Chronic phase of lifelong dependency on administered insulin.

Preclinical diabetes

Preclinical diabetes refers to the months or years preceding the clinical presentation of T1DM when antibodies can be detected as markers of beta-cell autoimmunity:

- Islet cell autoantibodies.
- Glutamic acid decarboxylase autoantibodies (65K isof orm).
- IA2 (also known as ICA512 or tyrosine phosphatase) autoantibodies.
- Insulin autoantibodies.

In addition to these immunological and genetic markers [human leukocyte antigen (HLA) genotype and INS genotype], the risk of T1DM can be further refined by measurement of insulin release in response to an intravenous glucose load [intravenous glucose tolerance test (IVGTT)].

Risks of progression to diabetes

Genetic markers conferring increased or decreased risk include:

a) HLA DR3-DQA1*0501-DQB1* 0201 (susceptible genotype).

b) HLA DR4-DQA1*0301-DQB1* 0302 (susceptible genotype).

c) HLA DR2-DQA1*0102-DQB1* 0602 (protective genotype).

Islet autoimmunity can be transient and one raised islet antibody alone has little prognostic value (1–3). If an individual is under 45 yr and does not have HLA DR2-DQA1*0102-DQB1* 0602 then:

- Impaired first phase insulin release on IVGTT (defined as an insulin response less than the 10th percentile for age and sex-matched controls) confers a 60% risk over the next 5 yr (4).
- Two or more islet antibodies raised without impaired first phase insulin release confer a 25–50% risk over the next 5 yr (5, 6).

Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined clinical studies (7).

Individuals who screen positive for genetic or immunological markers of T1DM should have access to appropriate counselling and to centres participating in intervention and other defined studies.

Intervention studies should be registered as part of an international network of investigation and information about ongoing studies should be readily available (7, 8).

The one proven environmental trigger of T1DM is congenital rubella (9, 10). Other potential environmental triggers are enteroviral infections (11), casein (12), and cereals (gluten or non gluten) (13, 14). Low levels of intercurrent infection and improved hygiene may be associated with increased risk (15). The hypothesis of acceleration (rather than triggering) of beta-cell...
destruction because of overload of the beta-cell with risk factors such as rapid growth and weight gain in early life can explain the increasing incidence of childhood diabetes and the younger age of onset (16). International networks following children at increased genetic risk from birth are investigating potential trigger and protective factors (8).

**Presentation of T1DM**

Prospective follow-up of high-risk subjects shows that diagnosis of T1DM can be made in asymptomatic individuals in the majority of cases (4). In the Diabetes Prevention Trial – Type 1 (DPT-1), when high-risk individuals were followed, 73% of participants who were diagnosed with diabetes were asymptomatic (4).

A child presenting with a classical history of increasing polyuria, polydipsia, and weight loss over 2–6 wk presents a straightforward diagnosis. However, failure to consider the possibility of diabetes or atypical presentations may result in late diagnosis.

Some children have a rapid onset of symptoms and present within days in diabetic ketoacidosis (DKA); others have a slow onset over several months.

Urinary ‘dipstick’ testing for glycosuria and ketonuria provides a simple and sensitive tool for excluding diabetes with less typical presentation. A blood glucose measurement (plasma glucose >11.1 mmol/L) confirms the diagnosis. The blood glucose measurement should be a laboratory estimation rather than a home glucose monitor or bedside reading.

- Clinical presentation of diabetes can vary from non-emergency presentations (e.g., polydipsia, polyuria, weight loss, enuresis) to severe dehydration, shock and DKA (17, 18) (E).

**Non-emergency presentations**

Non-emergency presentations of diabetes include:

- Recent onset of enuresis in a previously toilet-trained child, which may be misdiagnosed as a urinary tract infection or the result of excessive fluid ingestion.
- Vaginal candidiasis, especially in prepubertal girls.
- Vomiting, which may be misdiagnosed as gastroenteritis.
- Chronic weight loss or failure to gain weight in a growing child.
- Irritability and decreasing school performance.
- Recurrent skin infections.

**Emergency presentations**

The usual emergency presentation of DKA in a child or adolescent includes:

- Severe dehydration.
- Frequent vomiting.
- Continuing polyuria despite the presence of dehydration.
- Weight loss because of fluid loss and loss of muscle and fat.
- Flushed cheeks because of the ketoacidosis.
- Acetone detected on the breath.
- Hyperventilation of DKA (Kussmaul respiration) is characterized by a high respiratory rate and large tidal volume of each breath, which gives it a sighing quality.
- Disordered sensorium (disoriented, semicomatose or rarely comatose).
- Shock (rapid pulse rate, poor peripheral circulation with peripheral cyanosis).
- Hypotension (a late sign and rare in children with DKA).

**Diagnostic difficulties leading to late diagnosis**

The following situations may result in a late diagnosis of DKA:

- Very young children may present in severe ketoacidosis because of a more rapid onset of severe insulin deficiency (19) and because the diagnosis was not considered early.
- Hyperventilation of ketoacidosis may be misdiagnosed as pneumonia or asthma (cough and breathlessness distinguish these conditions from DKA).
- Abdominal pain associated with ketoacidosis may simulate an acute abdomen and lead to referral to a surgeon.
- Polyuria and enuresis may be misdiagnosed as a urinary tract infection.
- Polydipsia may be thought to be psychogenic.
- Vomiting may be misdiagnosed as gastroenteritis or sepsis.

If a child is diagnosed with diabetes in the presence of symptoms immediate referral to a centre with expertise in the care of such children is mandatory, because prompt diagnosis of diabetes in children is important in preventing rapid deterioration into ketoacidosis. Severe ketoacidosis, if untreated, is fatal. Therapy is urgent and referral to specialized services is essential (E).

**Differentiating between T1DM and type 2 diabetes mellitus (T2DM) at diagnosis**

Features suggesting the diagnosis of type 2 diabetes mellitus (T2DM) rather than T1DM at diagnosis are (20, 21):

- Obesity.
- Age greater than 10 yr.
- Strong family history of T2DM.
- Acanthosis nigricans.
- High-risk racial or ethnic group.
- Undetectable pancreatic autoantibodies.
- Normal to high C-Peptide levels.
Partial remission or honeymoon phase in T1DM

In approximately 80 percent of children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment (22).

The definition of the partial remission phase has been uncertain but a recent definition is when the patient requires less than 0.5 units of insulin per kg of body weight per day and has an HbA1c <7% (22).

The partial remission phase commences within days or weeks of the start of insulin therapy and may last for weeks to months. During this phase blood glucose levels are frequently stable within the normal range, despite fluctuations in diet and exercise. It is important for the families to be advised of the transient nature of the partial remission phase so as to avoid the false hope that the diabetes is spontaneously disappearing.

Several studies have shown intensive therapy preserves c-peptide, leads to better control (measured by A1c), and often a decrease in insulin dose (18, 23).

Intervention trials from diagnosis are in progress as part of an international network of intervention trials to preserve beta-cell function either in the preclinical phase or from diagnosis (8).

In a few children and adolescents, requirements for insulin may decrease to the point of being able to temporarily withdraw insulin therapy and may last for weeks to months. During this phase blood glucose levels are frequently stable within the normal range, despite fluctuations in diet and exercise. It is important for the families to be advised of the transient nature of the partial remission phase as to avoid the false hope that the diabetes is spontaneously disappearing.

Ketoacidosis at presentation (17) and young age (14) reduce the likelihood of a remission phase.

- Parents and children with T1DM should be informed that the remission phase of diabetes is transient and does not indicate total remission of diabetes (18) (E).

Chronic phase of lifelong dependence on insulin

The progression from the partial remission phase into the chronic phase of lifelong dependence on insulin is usually a gradual decrease in residual beta-cell function but clinically seems to be accelerated by an intercurrent illness.

At present, exogenous insulin replacement remains the only form of replacement therapy for children and adolescents with T1DM, although some other experimental treatments are under investigation.

Transplantation

Islet transplantation has become more successful since the introduction of less beta-cell toxic immunosuppressive agents and refined techniques to harvest adequate numbers of viable beta-cells (24). The numbers of subjects who remain insulin-independent fall with follow-up and several donor pancreases are required for adequate beta-cell numbers in the transplant (25).

The Edmonton protocol, which is a glucocorticoid-free immunosuppressant regimen, has been used in several centres with good clinical outcomes in those with full and partial graft function, namely, protection from severe hyperglycaemia and less labile blood glucose levels (26).

The induction of immunologic tolerance without the need for chronic immunosuppressive therapy is a major goal and the potential use of haematopoietic stem cell therapy for induction of tolerance and islet cell regeneration in vivo and neogenesis in vitro are rapidly expanding research directions.

Pancreas transplantation provides high rates of graft survival at 1 yr but there are significant surgical risks and the requirement for long-term immunosuppression precludes its use in children and adolescents (26, 27).

Prevention of diabetes – the evidence

The evidence on intervention trials to delay or prevent the onset of T1DM is listed in:

- European Nicotinamide Diabetes Intervention Trial, a multinational quasirandomized placebo-controlled, double-blinded intervention study, demonstrated that nicotinamide did not delay or prevent the onset of T1DM in high-risk, first-degree relatives (27, 28) (A).
- The National Institutes of Health DPT-1 demonstrated in a randomized controlled trial that low dose subcutaneous insulin therapy did not delay or prevent the onset of clinical diabetes in high-risk, first-degree relatives (4) (A).

Prevention – recommendations and principles

- Health care professionals should be aware that there are no interventions shown to delay or prevent the onset of T1DM.
- Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined clinical studies (7) (E).

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.

The evidence grading system used in the ISPAD Guidelines is the same as that used by the American

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Phases of diabetes
ISPAD Clinical Practice Consensus Guidelines 2006–2007
The diagnosis and management of monogenic diabetes in children

Authors: Andrew Hattersley, Institute of Biomedical and Clinical Sciences, Peninsula Medical School, Exeter, UK
Jan Bruining, Sophia Children’s Hospital, Rotterdam, the Netherlands
Julian Shield, Department of Child Health, University of Bristol, Bristol, UK
Pal Njolstad, Department of Child Health, University of Bergen, Bergen, Norway
Kim Donaghe, The Children’s Hospital at Westmead, University of Sydney, NSW, Australia
e-mail KimD@chw.edu.au
Editors: Kim Donaghe, Ragnar Hanas, Georgeanna Klingensmith, Peter Swift

Definition
Monogenic diabetes results from the inheritance of mutation or mutations in a single gene. It may be dominantly or recessively inherited or may be a \textit{de novo} mutation and, hence, a spontaneous case. In children, almost all monogenic diabetes results from mutations in genes that regulate $\beta$-cell function, although diabetes can rarely occur from mutations resulting in very severe insulin resistance (C) (1).

Diagnosis
Why diagnose monogenic diabetes?
The majority of patients with genetically proven monogenic diabetes are initially incorrectly diagnosed as having type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) (2) (C). It is important to correctly diagnose monogenic diabetes as it can predict the clinical course of the patient, explain other associated clinical features, and, very important, guide the most appropriate treatment. In addition, making a diagnosis will have implications for other family members often correcting the diagnosis and treatment for other diabetic family members, as well as allowing appropriate genetic counseling.

Clinical presentation of monogenic diabetes
Clinical presentations in children when a diagnosis of monogenic diabetes should be considered are discussed below and include the following:

(i) Neonatal diabetes and diabetes diagnosed within the first 6 months of life.
(ii) Familial diabetes with an affected parent.
(iii) Mild (5.5–8.5 mmol/L) fasting hyperglycemia, especially if young or familial.
(iv) Diabetes associated with extra pancreatic features.

When to suspect a diagnosis of T1DM in children may not be correct?
Features in children initially thought to have T1DM that should suggest a possible diagnosis of monogenic diabetes are shown below. None of these are absolute and should be considered as together, rather than in isolation (C) (3).

(i) A diagnosis of diabetes before 6 months (B) [in T1DM: <1% (4)].
(ii) Family history of diabetes with a parent affected (C) [in T1DM: 2–4% (5)].
(iii) Evidence of endogenous insulin production outside the ‘honeymoon’ phase (after 3 yr of diabetes), with detectable C-peptide (>200 nmol/L) when glucose level is >8 mmol/L (E) (in T1DM: 1–5%).
(iv) When pancreatic islet autoantibodies are absent, especially if measured at diagnosis (C) [in T1DM: 3–30% (6–8)]. The great variation in antibody prevalence in series probably represents differences in assays and means it is hard to apply published series directly into clinical practice. Absent antibodies should lead to other investigation/consideration rather than leading directly to genetic tests (E).

When to suspect a diagnosis of T2DM in children may not be correct?
Features in children initially thought to have T2DM that should suggest a possible diagnosis of monogenic diabetes are shown below. It should be noted that most T2DM in youth will meet the former classification for maturity-onset diabetes of the young (MODY) [diagnosed <25, autosomal dominant inheritance and non-insulin dependent (C) (9–12)].

(i) Not markedly obese or diabetic family members who are of normal weight [in T2DM: 20% (12)].
Making a diagnosis of monogenic diabetes

As well as having clinical features that are unusual for T1DM and T2DM, a patient on whom a diagnosis of monogenic diabetes is made should also have the features of a specific genetic subtype of monogenic diabetes (E). The features of the more common monogenic diabetes are given below.

While in T1DM and T2DM diabetes there is no single diagnostic test, this is not the case in monogenic diabetes where in >80% of cases, a molecular genetic diagnosis can be made by DNA testing (C). Molecular genetic testing is offered in most European countries and the USA, but many labs will test patients from other countries (for example, www.diabetesgenes.org and www.mody.no). These tests are expensive (up to €500/$600) but can have a big impact on management of the proband and other family members, for whom it will be cheaper, as the mutation is known (€100/$120). Some recently described monogenic diabetes genes like Kir6.2 testing in patients diagnosed less than 6 months may be available as research tests for no charge (see www.diabetesgenes.org). Approval from the patient’s insurance company should be sought prior to sending DNA when applicable.

Given the limited resources available, it is vital that these tests are used in situations where they are likely to be positive and will alter clinical care. This will involve careful clinical selection and performing physiological tests like C-peptide and autoantibody measurement, as well as testing other family members before performing molecular genetic tests (E).

Specific subtypes of monogenic diabetes and their management

Neonatal diabetes and diabetes diagnosed within the first 6 months of life

There is good evidence that diabetes diagnosed in the first 6 months is not T1DM, as autoantibodies are rare and human leukocyte antigen (HLA) genotyping shows HLA haplotypes actually protective for T1DM in these patients (B) (4). Neonatal diabetes is another area which has rapidly moved from a clinical to a molecular genetic classification (13, 14). Neonatal diabetes is insulin-requiring diabetes, which is usually diagnosed in the first 3 months of life. Clinically, two subgroups have been recognized: transient neonatal diabetes mellitus (TNDM) that resolved at a median of 12 wk and then did not require any treatment, although as many as 50% of cases would ultimately relapse (B) (15, 16); in contrast to permanent neonatal diabetes mellitus (PNDM), which required continual insulin treatment from diagnosis onward. For most patients with both types of neonatal diabetes, the molecular etiology can now be defined. The majority of patients with TNDM have an abnormality of imprinting of the ZAC and HYMAI genes on chromosome 6q (B) (14, 15), while the most common known cause of PNDM are mutations in the KCNJ11 gene encoding the Kir6.2 subunit of the β-cell KATP channel (B) (17, 18). However, TNDM and PNDM are found with activating mutations in KCNJ11 (Kir 6.2) and ABCCS [sulfonylurea receptor (SUR) 1]; some of these are amenable to treatment with sulfonylurea drugs which stimulate endogenous insulin secretion (19). If both parents are glucose intolerant, homozygous or compound heterozygous mutations in glucokinase are most frequent (20, 21).

Differential diagnosis. When diabetes is diagnosed in the neonatal period, it is difficult to tell if it is likely to be transient or permanent, although the features in Table 1 can help differentiate the possible different subtypes and can be used to guide molecular genetic testing.

TNDM from imprinting anomalies on 6q24. Imprinted anomalies of the 6q24 locus involving the ZAC and HYMAI genes are the most common cause of neonatal diabetes and result in TNDM (B) (14, 15, 22). The commonest 6q24 anomalies are inherited paternal duplications or paternal uniparental disomy, although methylation anomalies are being more frequently identified (E) (16). Diabetes associated with this is typically diagnosed within the first week and resolves around 12 wk (B) (15). In approximately 50% of cases, diabetes will recur during the pediatric age range (B) (15). Apart from macroglossia, seen in 23%, there are no nonpancreatic features (B) (15).

Initial glucose values can be very high (range: 12–57 mmol/L) and, therefore, insulin is used initially, although the dose can rapidly be reduced. Once patients have relapsed, they should remain under annual follow up due to the risk of diabetes relapsing. On relapse, patients are not insulin dependent and can be treated with diet initially, although subsequently, they often need insulin (E) (14). The response to oral treatments such as sulfonylureas or metformin is uncertain.

PNDM, TNDM and diabetes diagnosed in the first 6 months of life due to Kir6.2 mutations. Kir6.2 mutations are the second most common cause of
Table 1. Characteristics of diabetes presenting in the first 6 months of life [modified from reference (13)]

<table>
<thead>
<tr>
<th>Gene, clinical syndrome, inheritance</th>
<th>PNDM/TNDM</th>
<th>Number of cases described (% in consanguineous or isolated populations)</th>
<th>Median birth weight in grams (SDS)</th>
<th>Age of diagnosis in weeks, median (range)</th>
<th>Pancreatic appearance</th>
<th>Other features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZAC/HYAMI, imprinting defect on 6q24</td>
<td>TNDM</td>
<td>≥150, rare</td>
<td>2100 (−2.94)</td>
<td>0.5 (0–4)</td>
<td>Normal</td>
<td>Macroglossia (23%)</td>
</tr>
<tr>
<td>Kir6.2 (KCNJ11), spontaneous dominant (10%)</td>
<td>PNDM, TNDM (10%)</td>
<td>≥100, rare</td>
<td>2.580 (−1.73)</td>
<td>6 (0–260)</td>
<td>Normal</td>
<td>Developmental delay (20%), epilepsy (6%), DKA (30%)</td>
</tr>
<tr>
<td>EIF2AK3, Wolcott–Rallison syndrome, recessive</td>
<td>PNDM</td>
<td>30 (90)</td>
<td>?</td>
<td>13 (6–65)</td>
<td>Atrophy of pancreas (?), exocrine dysfunction (25%)</td>
<td>Epiphyseal dysplasia (90%), osteopenia (50%), acute liver failure (75%), developmental delay (80%), hypothyroidism (25%)</td>
</tr>
<tr>
<td>FOXP3, IPEX syndrome, X linked</td>
<td>PNDM</td>
<td>14, rare</td>
<td>2860 (−1.2)</td>
<td>6 (0–30)</td>
<td>?</td>
<td>Only boys affected, chronic diarrhea with villous atrophy (95%); pancreatic and thyroid autoantibodies (75%), thyroiditis (20%), eczema (50%); anemia (30%) and often die young (1 yr)</td>
</tr>
<tr>
<td>GCK (glucokinase), recessive</td>
<td>PNDM</td>
<td>6 (85)</td>
<td>1720 (−2.75)</td>
<td>Normal</td>
<td>Parents have fasting hyperglycemia, as heterozygotes</td>
<td></td>
</tr>
<tr>
<td>IPF1, recessive</td>
<td>PNDM</td>
<td>2 (50)</td>
<td>2140 (−2.97)</td>
<td>Absent</td>
<td>Parents may have early-onset diabetes, as heterozygotes</td>
<td></td>
</tr>
<tr>
<td>HNF-ββ, dominant (60%) spontaneous</td>
<td>TNDM</td>
<td>2, rare</td>
<td>1900 (−3.21)</td>
<td>Atrophy</td>
<td>Renal developmental disorders</td>
<td></td>
</tr>
<tr>
<td>PTF1A, recessive</td>
<td>PNDM</td>
<td>3 (100)</td>
<td>1390 (−3.8)</td>
<td>Atrophy</td>
<td>Severe neurological dysfunction and cerebellar hypoplasia</td>
<td></td>
</tr>
</tbody>
</table>

DKA, diabetic ketoacidosis; HNF, hepatocyte nuclear factor; IPEX, immunodysregulation, polyendocrinopathy, enteropathy, X-linked; IPF1, insulin promoter factor 1; PNDM, permanent neonatal diabetes mellitus; SDS, standard deviation score; TNDM, transient neonatal diabetes mellitus.
mutations in patients with diabetes diagnosed in the first 6 months of life (B) (17, 18). While some (10%) have a remitting form of diabetes that may later relapse, the majority have PNDM (C) (23). Most patients have isolated diabetes, although neurological features are seen in 20% of patients. Despite being a heterozygous mutation, most have no family history, as 90% of cases are spontaneous mutations. The most severe defect is very marked developmental delay of motor and social function and generalized epilepsy often with hypsarrhythmia, as seen in West syndrome (C) (17). This has been called the developmental delay, epilepsy, and neonatal diabetes (DEND) syndrome (18). More common is the intermediate DEND syndrome where patients have less severe developmental delay and do not have epilepsy (18).

Patients with Kir6.2 mutations have all the clinical features of insulin dependency, as 30% of them present with ketoacidosis, and they usually do not have detectable C-peptide and, thus, are treated with insulin (C) (18). It has recently been shown that these patients can not only be successfully treated with oral sulfonylureas but can also get better glycemic control without an increase in hypoglycemia. The doses needed are high when calculated on a per kg body weight basis compared with adults, with patients typically needing 0.5 mg/kg/glibenclamide/d, although some may need as much as 1 mg/kg/d (C) (24–29). With time, many patients have been able to reduce their doses of sulfonylureas but maintain excellent glycemic control (E).

Wolcott–Rallison syndrome. Wolcott–Rallison syndrome is a rare autosomal recessive condition characterized by early-onset diabetes, epiphyseal dysplasia, renal impairment, acute hepatic failure, and developmental delay (B) (30, 31). It is associated with mutations in EIF2AK3 (32). Diabetes usually presents in infancy but may appear later. It is associated with β-cell loss, leading to insulin deficiency without autoimmune pathology. Insulin treatment is required. Wolcott–Rallison syndrome should be considered in any patient with diabetes in the first 3 yr who has epiphyseal dysplasia or acute severe hepatic failure (C, E) (30).

Other causes of neonatal diabetes. In Table 1, the clinical features of other causes of neonatal diabetes are outlined. Scanning the pancreas to assess if it is present and its size, checking for exocrine pancreatic function and pancreatic autoantibodies [found in the immunodysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) syndrome] are the most useful diagnostic tests before proceeding to molecular genetic testing (E). All other causes need to be treated with insulin. Some pediatricians consider that these patients are easiest to manage on subcutaneous insulin pumps. In patients with pancreatic aplasia, exocrine pancreatic supplements will be required.

Familial diabetes

The most common causes of familial diabetes or familial hyperglycemia are shown in Table 2.

Children and young adults with diabetes and a strong family history of diabetes: hepatocyte nuclear factor 1 alpha gene mutations (MODY3). The possibility of monogenic diabetes should be considered whenever a parent has diabetes, even if he/she is thought to have T1DM or T2DM (E). The most common form of monogenic diabetes which results in familial diabetes (known in the past as MODY) are hepatocyte nuclear

Table 2. Characteristics of common forms of monogenic diabetes and hyperglycemia

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Number of families identified in UK</th>
<th>Typical age of presentation in pediatric clinic (range)</th>
<th>Typical glucose level at presentation (range) mmol/L</th>
<th>Other clinical features</th>
</tr>
</thead>
<tbody>
<tr>
<td>HNF-1α (MODY3)</td>
<td>Dominant 197</td>
<td>14 (4–18)</td>
<td>17 (11–26)</td>
<td>Large increment in an OGTT (at 2–0 h usually &gt;5 mmol/L), low renal threshold, progressive hyperglycemia with age, sensitive to sulfonylureas</td>
</tr>
<tr>
<td>HNF-4α (MODY1)</td>
<td>Dominant 22</td>
<td>17 (5–18)</td>
<td>15 (9–20)</td>
<td>Similar to HNF-1α but renal threshold normal</td>
</tr>
<tr>
<td>Glucokinase (MODY2)</td>
<td>Dominant 152</td>
<td>10 (0–18)</td>
<td>11 (5.5–16)</td>
<td>Usually incidental finding at diagnosis, fasting glucose in the range of 5.5–8 mmol/L, small increment in an OGTT (at 2–0 h usually &lt;3.5 mmol/L), little deterioration in glycemia with age</td>
</tr>
</tbody>
</table>

HNF, hepatocyte nuclear factor; MODY, maturity-onset diabetes of the young; OGTT, oral glucose tolerance test.
factor (HNF)-1α mutations (B) (33). The clinical characteristics of patients with HNF-1α mutations are as follows:

(i) Young-onset diabetes that shows characteristics of not being insulin dependent, e.g., not developing ketoacidosis in the absence of insulin, good glycemic control on a small dose of insulin, or detectable C-peptide measured when on insulin, with glucose >8 mmol/L outside a normally expected honeymoon period (3 yr) (E).

(ii) Family history of diabetes. This may be treated with insulin and considered to be ‘T1DM’. This would typically be diagnosed in the age of 20, 30, or 40 yr. There may also be an affected grandparent although often they are diagnosed after 45 yr (C).

(iii) Oral glucose tolerance tests (OGTTs) in early stages tend to show a very large glucose increment, usually >5 mmol/L (34). Some subjects may have a normal fasting value but still rise into the diabetic range at 2 h (34) (B).

(iv) Glycosuria at relatively normal blood glucose levels is often seen, as these patients have a low renal threshold (B) (34).

(v) Marked sensitivity to sulfonylureas resulting in hypoglycemia, despite poor glycemic control before starting sulfonylureas (C) (35, 36).

Treatment. Patients with HNF-1α gene mutations can initially be treated with diet although they will have marked postprandial hyperglycemia following a high carbohydrate meal, as the β-cell defect results in insufficient increase in insulin secretion with hyperglycemia (37).

Most patients will need pharmacological treatment, as they show progressive deterioration in glycemic control throughout life and are at risk of considerable microvascular and macrovascular complications (B,C) (38). The first treatment to be used in children who are not controlled on insulin should be low-dose sulfonylureas, which results in a four-fold greater lowering of glucose than metformin (A) (39). These patients are extremely sensitive to sulfonylureas, and as long as they do not have problems with hypoglycemia, they can be maintained on these for many decades (C) (35). Glycemic control by sulfonylureas is often better than that achieved by insulin, especially in children and young adults (40). The dose of sulfonylureas should initially be low (one-quarter of the normal starting dose in adults) to avoid hypoglycemia (E). If there is hypoglycemia despite dose titration of a once- or twice-daily sulfonylurea preparation such as gliclazide, a slow-release preparation or meal time doses with a short-acting agent like nateglinide may be considered (C) (41).

Children and young adults with diabetes and a strong family history of diabetes: HNF-4α gene mutations (MODY1). Diabetes due to mutations of the HNF-4α gene are considerably less common (Table 2) than diabetes due to mutations of the HNF-1α gene but has similar characteristics, except that there is no low renal threshold and the age of diagnosis may be later (C) (42). HNF-4α mutations should be considered when HNF-1α sequencing is negative but the clinical features were strongly suggestive of HNF-1α (42). Patients are often sensitive to sulfonylureas (C) (43).

Other causes of familial diabetes. A handful of families with autosomal dominant non-insulin-dependent diabetes have been described with mutations in insulin promoter factor 1 (IPF1) (MODY4) (44), NeuroD1 (MODY6) (45, 46) and, recently, the carboxyl ester lipase (CEL) gene (MODY7) (47), but these are so unusual, they do not need to be tested for in children with diabetes except in a research setting (E) or when there are additional phenotypes, such as pancreatic exocrine dysfunction (47).

Mild fasting hyperglycemia: due to glucokinase mutations (MODY2)

The finding of raised fasting blood glucose in the range of 5.5–8.5 mmol/L is unusual in children and young adults. This always raises concern that they may be about to develop T1DM or that the patient has T2DM. However, a considerable proportion of these patients with persistent mild fasting hyperglycemia will have a heterozygous mutation in the glucokinase gene. The phenotype associated with glucokinase mutations is remarkably similar for all mutations. The following features suggest a diagnosis of a glucokinase mutation:

(i) The fasting hyperglycemia is persistent and stable over a period of months or years (34).

(ii) Hemoglobin A1c is typically just below or just above the upper limit of normal range (5.5–5.7%).

(iii) In an OGTT, the increment (2-h glucose – fasting glucose) is small (typically <3.5 mmol/L), although because of the variability of the OGTT, this should not be considered an absolute criterion (34).

(iv) Parents may have ‘T2DM’ or may not be diabetic. On testing, one parent will have a mildly raised fasting blood glucose, in the range of 5.5–8.5 mmol/L, as this is an autosomal dominant condition (C) (34). Testing of apparently unaffected parents’ fasting glucose is important when considering a diagnosis of a glucokinase mutation (E).

Treatment. The fasting hyperglycemia does not deteriorate significantly and the glucose is regulated at the higher set point (34). This is rarely associated with
any microvascular or macrovascular complications even when no treatment is given throughout life (C) (48).

An important point is that these patients do not need treating in the pediatric age range. There is very little, if any, response to either oral hypoglycemic agents or insulin (E). Exogenous insulin results in reduction of endogenous insulin secretion and so the degree of glycemia will be maintained, explaining why these children can be treated with insulin without significant hypoglycemia.

Genetic syndromes associated with diabetes

When diabetes in a child is associated with other multi-system disease, the possibility of a monogenic syndrome that explains all features should be considered.

The Online Mendelian Inheritance in Man (OMIM) website [access via the National Center for Biotechnology Information (NCBI) website, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi] can help with clinical features and enables one to know if the gene has been defined and, hence, molecular genetic testing is available. For described and previously undescribed syndromes, assistance can be obtained through the International Society for Pediatric and Adolescent Diabetes (ISPAD) rare diabetes collection (access via the link on the ISPAD web page or through www.diabetesgenes.org). The most common genetic syndromes which include diabetes are listed below:

Diabetes insipidus, diabetes mellitus, optic atrophy, deafness syndrome (Wolfgram syndrome). Wolfram syndrome is an autosomal recessive syndrome in which the association of diabetes with progressive optic atrophy under 16 yr of age is diagnostic (49). The syndrome is more common in countries where consanguineous marriages are frequent. Other features are bilateral sensorineural deafness, diabetes insipidus, dilated renal tracts, and truncal ataxia or more protean neurological signs, with the complete phenotype seen in 75% of patients, with increasing prevalence with age. The order of appearance of the neurological symptoms may vary even within families. The median age of death in Wolfram syndrome is 30 yr (49). Mutations in the gene for Wolfram syndrome (WFS1) are present in at least 90% of patients with clinical Wolfram syndrome (50–52).

The diabetes is non-autoimmune, insulin deficient, and presents at a mean age of 6 yr (49). Patients require insulin treatment from the time of diagnosis, but autoantibodies are not present (C) (49).

Thiamine-responsive megaloblastic anemia (Roger’s syndrome). Thiamine-responsive megaloblastic anemia is a rare, recessive genetic syndrome of early-onset megaloblastic anemia (which responds to thiamine), and it is associated with diabetes and sensorineural deafness. This results from mutations in the gene SLC19A2 (53).

The diabetes, which is insulin deficient in nature, is responsive to thiamine in some patients, although all seem to develop an insulin requirement in the long term (C) (54). Deafness is unresponsive to thiamine.

Renal cysts and diabetes syndrome due to a HNF-1β mutation. Although initially described as a subgroup of familial diabetes (MODY5), it is now clear that patients with mutations in HNF-1β rarely present with isolated diabetes (55). Renal developmental disorders, especially renal cysts and renal dysplasia, are present in almost all patients with mutations or gene deletions (56). They may be diagnosed in utero and precede the diagnosis of diabetes (B). Other features which may be present in children include uterine and genitalia developmental anomalies, hyperuricemia, gout, and abnormal liver function tests (55). A diagnosis of HNF-1β should be considered in any child with diabetes who also has non-diabetic renal disease.

Patients with HNF-1β mutations, unlike patients with HNF-1α mutations, are not sensitive to sulfonylureas and, therefore, usually require insulin treatment (57). Pancreatic size is reduced, reflecting a reduction in both the endocrine and exocrine pancreas, and subclinical exocrine deficiency is present in most patients (58), but it is uncertain if this should be treated if it is asymptomatic.

Mitochondrial diabetes. Maternal transmission of mutated or deleted mitochondrial DNA can result in maternally inherited diabetes, although they are not usually in the pediatric age range. Despite that several mutations and deletions have been implicated, the strongest evidence relates to a point substitution at nucleotide position 3243 (A→G) in the mitochondrial tRNA [leu (UUR)] gene (B) (59). An identical mutation occurs in the mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like syndrome, and there may be some overlap between these syndromes in family members. Mitochondrial diabetes is commonly associated with sensorineural deafness and short stature. The diabetes is characterized by progressive non-autoimmune β-cell failure and may progress to needing insulin treatment rapidly.

Insulin-resistance syndromes: type A insulin resistance, leprechaunism, Rabson–Mendenhall syndrome and lipodystrophy. The key features of all insulin-resistance syndromes are acanthosis nigricans, androgen excess, and massively raised insulin concentrations in the absence of obesity (1). The more severe the insulin resistance and the earlier the onset, the more likely is diabetes (C) (1). A summary of some of the key clinical features is shown below [adapted from Musso et al. (1)] in Table 3.

Treatment of severe insulin resistance is very difficult. Most patients with diabetes have poor glycemic control and frequently develop long-term
complications (C) (1). Approaches used include the use of the insulin sensitizers, metformin, and glitazones, but their impact is limited when the insulin resistance is very severe. Insulin is the mainstay of treatment, and 500 U insulin and insulin pumps are usually required (1). In partial lipodystrophy, metformin may have benefit and insulin is not required in the early stages (C) (60). In total lipodystrophy, the response of diabetes to recombinant lipodystrophy (61) can be dramatic but is only available on a research basis.

Recommendations

Advances in molecular genetics have led to the identification of the genes associated with many clinically identified subgroups of diabetes. The identification of genes has explained clinical heterogeneity in conditions defined on the basis of when they were diagnosed, e.g., neonatal diabetes and MODY. Now molecular genetics is being used as a diagnostic test which can help define the diagnosis and treatment of children with diabetes. As these tests are expensive, genetic testing should be limited to those who on clinical grounds are likely to be positive (E).

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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ISPAD Clinical Practice Consensus Guidelines 2006–2007

Diabetes education


Peter GF Swift

Corresponding author:
Peter GF Swift, Childrens Hospital, Leicester Royal Infirmary, Leicester, UK.
Tel: +44 776 970 6320;
e-mail: peter.swift3@ntlworld.com

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Education is the keystone of diabetes care and structured self-management education is the key to a successful outcome. Adapted from ISPAD Consensus Guidelines 2000 (1).

National pediatric guidelines emphasize the importance of education but do not include specific chapters on education and educational principles (2–5).

Publications that provide useful guidelines on education in diabetes include National Standards for Diabetes Self-management Education (6), Position Statement on Structured Education (7), Guidance on the Use of Patient-Education Models for Diabetes (8), and the International Curriculum for Diabetes Health Professional Education (9).

A definition of Diabetes Education has been proposed:

‘The process of providing the person with the knowledge and skills needed to perform diabetes self-care, manage crises and to make lifestyle changes to successfully manage the disease.’ (10)

Education may be seen as an interface between clinical practice and research. Research into diabetes and educational methods is important in improving clinical practice (2, 5, 6, 10, 11), and this should be the responsibility of each nation/state and be a national priority (7, 12).

Educational programs must be carefully planned and have specific aims and learning objectives, which are shared with people with diabetes, carers, and their families (8).

It has remained contentious whether educational interventions per se are beneficial in diabetes care, particularly in children and adolescents because ‘educational, psychosocial and psychotherapeutic interventions are frequently combined for the purpose of improving knowledge, skills and self-efficacy across various aspects of diabetes self-management’ (13).

Nevertheless, systematic reviews of psychoeducational interventions conclude that they have small to medium beneficial effects on glycemic control (13, 14) and somewhat greater effect on psychological outcomes (15). The effects are greater for children than for adults (15) and are most effective when integrated into routine care, when parents are involved, empowerment principles are involved, and problem solving, goal setting, and self-efficacy are promoted (14, 16).

The Diabetes Control and Complications Trial provided unequivocal evidence that intensification of management reduces microvascular complications and that intensification requires effective diabetes self-management. Most importantly, effective self-management requires frequent and high levels of educational input and continuing support (6, 10, 11, 17, 18). Related to this is evidence that health care professionals engaged in education who are perceived by young people as being ‘motivating’ may encourage greater adherence to therapy (19). This high level of motivation and enthusiasm in educational intervention is likely to improve biomedical outcomes by itself and makes interpretation of educational research a complex science (20).

In contrast, those people who do not receive education or do not continue to have educational contacts are more likely to suffer diabetes-related complications (6, 18, 21, 22). It is a concern, however, that parents and adolescents often express satisfaction about services received (5) even when there may be large gaps in education, psychological support, and self-management techniques accounting for relatively unsatisfactory and variable metabolic control (23).
**Universal principles**

Every young person has a right to comprehensive expert structured education which should empower them and their families to take control of their diabetes. (1, 5, 7)

- Children and adolescents, their parents, and other care providers should all have easy access to and be included in the educational process (5).
- Diabetes education should be delivered by health care professionals with a clear understanding of the special and changing needs of young people and their families as they grow through the different stages of life (1).
- Diabetes education needs to be adaptable and personalized so that it is appropriate to each individual's age, stage of diabetes, maturity, and lifestyle; culturally sensitive; and at a pace to suit individual needs (1, 2, 4, 5).
- The priorities for health care professionals in diabetes education may not match those of the child and family. Thus, diabetes education should be based on a thorough assessment of the person's attitudes, beliefs, learning style, ability and readiness to learn, existing knowledge, and goals (1).
- Educators (doctors, nurses, dieticians, and other health care providers) should have access to continuing specialized training in diabetes education and educational methods (2, 6, 7, 9, 10).
- Diabetes education needs to be a continuous process and repeated for it to be effective (2, 4, 5, 8–10).

**Content and organization of education program**

It is widely accepted that diabetes cannot be successfully managed without behavioral modification (24, 25). Health professionals need to understand that education per se with acquisition of knowledge is unlikely to alter behavior, particularly in those individuals where diabetes appears to be overwhelmingly difficult. There is, therefore, a need for training the diabetes team not only in the principles of teaching and structured education but also in behavioral change management, including counselling techniques (24–26).

The importance of structured education (7) programs is considered in a variety of contexts, and there is evidence, mainly from adult diabetes, that it is more effective than informal unstructured education in improving metabolic control (11, 13–16, 27, 28). In pediatric diabetes, structured educational programs have been less well publicized, and because of the nature of the problems, have focused more on psychosocial interventions. The evidence for efficacy of these interventions, nearly all from North America, has been extensively reviewed in various texts (13–16) but some others are in an early stage of development (29).

There are four key criteria that characterize a structured educational program (7):

(i) has a structured, agreed, written curriculum;
(ii) uses trained educators;
(iii) is quality assured;
(iv) is audited.

To put this into practice, it has been recommended that (1–8):

- Structured education should be available to all people with diabetes at the time of initial diagnosis, or when it is appropriate for them, and then as required on an ongoing basis, based on a formal, regular individual assessment of need.
- Education should be provided by an appropriately trained interdisciplinary team: the team should have a sound understanding of the principles governing teaching and learning.
- Interdisciplinary teams providing education should include, as a minimum, a diabetes specialist nurse and a dietician.
- Sessions should be held in a location accessible to individuals and families, whether in the community or in the inpatient center.
- Educational programs should use a variety of teaching techniques, adapted wherever possible to meet the different needs, personal choices, learning styles of young people with diabetes and parents, as well as local models of care.

The principles of education in children (Table 1) have been adapted from discussions with teachers and reference (29).

Moreover, the principles that govern quality in teaching should be recognized by diabetes educators (Table 2) (29, 30).

Specifically in diabetes care, the following guidelines (1) may act as a template on which to develop an appropriate educational curriculum and, indeed, they have been quoted extensively elsewhere (2, 4, 5).

**Primary (level 1) education**

*At diagnosis: survival skills*

(i) Explanation of how the diagnosis has been made and reasons for symptoms;
(ii) Simple explanation of the uncertain cause of diabetes. No cause for blame;
(iii) The need for immediate insulin and how it will work;
(iv) What is glucose? Normal blood glucose (BG) levels and glucose targets;
Table 1. Principles and practice of education in children

| 1. Motivation | The learner needs to and/or have a desire to learn |
| 2. Context | Where is the learner now? |
| 3. Environment | Where does the learner want to be later? |
| 4. Significance | Learner centered, comfortable, trusting |
| 5. Concepts | Enjoyable/entertaining/interesting/open |
| 6. Activity | Meaningful, important, links or joins up |
| 7. Reinforcement | Reward or gain |
| 8. Reassess, evaluate, audit | Simple to complex in gentle steps (short attention span) |
| 9. Move forward (continuing education) | Constantly interactive |
|  | Practical (fitting into real life) |
|  | Goal setting and problem solving |
|  | Repetition, review, summarize |

Secondary (level 2) continuing educational curriculum

Continuing curriculum

(i) Pathophysiology, epidemiology, classification, and metabolism;
(ii) Insulin secretion, action, and physiology;
(iii) Insulin injections, types, absorption, action profiles, variability, and adjustments;
(iv) Nutrition: food plans; qualitative and quantitative advice on intake of carbohydrate, fat, proteins and fiber; coping with special events and eating out; growth and weight gain; ’diabetic foods’; sweeteners and drinks;
(v) Monitoring, including glycated hemoglobin and clear (agreed) targets of control;
(vi) Hypoglycemia and its prevention, recognition, and management including glucagon;
(vii) Intercurrent illness, hyperglycemia, ketosis, and prevention of ketoacidosis;
(viii) Problem solving and adjustments to treatment;
(ix) Goal setting;
(x) Micro- and macrovascular complications and their prevention. The need for regular assessment;
(xi) Exercise, holiday planning, and travel, including educational holidays and camps;
(xii) Smoking, alcohol, and drugs;
(xii) School, college, employment, and driving vehicles;

Table 2. Qualities looked for by the UK Office for Standards in Education, OFSTED (29, 30)

| Lessons should be purposeful with high expectations conveyed |
| Learners should be given some opportunities to organize their own work (overdirection by teachers needs to be guarded against) |
| Lessons should elicit and sustain learners’ interest and be perceived by pupils to be relevant and challenging |
| The work should be well matched to the learners’ abilities and learning needs |
| Learners’ language should be developed and extended (teachers’ questioning skills play a part here) |
| A variety of learning activities should be used |
| Good order and control should be largely based on skillful management of learner’s involvement in the lesson and mutual respect |

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Continuing education will take place most often in an ambulatory (outpatient, domiciliary, community) setting (2, 4, 5, 33). Where staffing levels, expertise, and local circumstances do not permit this, educational programs may be carried out in the hospital environment, either by individual teaching or in groups and, whenever possible, in a protected environment conducive to learning (33, 34).

The educational program should utilize appropriate patient-centered, interactive teaching methods for all people involved in the management of diabetes, particularly the affected child or adolescent (33).

Higher levels of diabetes education should be grounded in a realistic understanding of self-management as both educational and psychosocial issues are important determinants of success (13, 29, 33).

Newer technology may be attractive to young people including videos, CDs, computer games, text messaging for information (35), telephone reminders and support (36) but is used most effectively in interactive modes (5, 8, 13, 16).

Group education may be more cost-effective and enhanced by peer group (27, 28, 33) or school friendships (29), although there is evidence that education directed at individual needs is equally effective as group education (5, 8, 37).

There is anecdotal evidence that benefit may be gained from participation in organized Diabetes Association meetings and in holiday or camping experiences (38, 39).

Evidence from group discussions with young people suggest that education using these newer technologies is attractive, but there is little scientific evidence to support its widespread use (5). In contrast, traditional, intensive, individualized outpatient education in specialized clinics has been shown in some situations to produce excellent results in terms of glycemic control (40, 41).

When education is viewed as an important factor in empowerment, both for parents and adolescents, it should enable young people to use knowledge and practical skills in problem solving and self-care to be in control of goal setting for better care and to have influence over their own lives in making informed decisions about their diabetes (31, 32, 42, 43).

Matching and adjusting insulin profiles to quantified food intake and exercise levels have become an important part of modern intensified management with multiple injection treatment, the availability of analogue insulins, and infusion pumps. Higher levels of education and understanding are required for these interventions to be successful and require more time, skill, and greater resources from the educational team (41, 44, 45).

Changing insulin regimens per se does not improve metabolic control (11, 23). In contrast, by addressing the total management package utilizing comprehensive structured education, there is more likelihood of success (6, 7, 13–18, 27, 28, 46), especially if the educators are highly motivated (20).

### Education and age group

Diabetes education needs to be adaptable and appropriate to each individual’s age and maturity (1, 47).

#### Infants and toddlers

- Total dependence on parents and care providers for injections, food, and monitoring and the requirement of a trusting attachment between infant and caregivers (48);
- Mothers may feel increased stress, diminished bonding, and depressive feelings (48, 49), but this applies to many chronic diseases (50);
- Unpredictable erratic eating and activity levels;
- Difficulties in distinguishing normal infant behavior from diabetes-related mood swings (49);
- Hypoglycemia is more common. Severe hypoglycemia may be more harmful (see chapter on Hypoglycemia). Education on prevention, recognition, and management is therefore a priority. Age-specific targets for BG should be discussed (see chapter on Monitoring).

There is conflicting evidence on the behavioral characteristics of preschool children with diabetes (48, 51) and whether diabetes outcomes depend on education per se. But parents report the importance of education and nonjudgmental support from a team (49, 52).

#### School-age children

- Adjusting to the change from home to school, developing self-esteem, and peer relationships (47, 53);
- Learning to help with and developing skills in injections and monitoring;
- Progressive recognition and awareness of hypoglycemic symptoms (54);
- Increasing understanding and self-management;
- Adapting diabetes to school programs, school meals, exercise, and sport (53);
- Including monitoring of BG levels and injections in the school setting;
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Advising parents on the gradual development of the child’s independence, with progressive stepwise hand over of appropriate responsibilities (1, 47).

School-age children have expressed dissatisfaction that health professionals talk to parents and not to them (5). There is some evidence that focused age-appropriate educational interventions are effective in children and families (5, 13, 14, 16, 47, 55).

Adolescents

(See chapter on Adolescence for references)

- Accepting the critical role of continued parental involvement and yet promoting independent, responsible self-management appropriate to the level of maturity and understanding;
- Understanding that knowledge about diabetes in adolescents is predictive of better self-care and (metabolic) control, but the association is modest;
- Discussing emotional and peer group conflicts;
- Teaching problem-solving strategies for dealing with dietary indiscretions, illness, hypoglycemia, sports, smoking, alcohol, drugs, and sexual health;
- Negotiating targets, goals, and priorities and ensuring that the tasks taken on by the adolescent are understood, accepted, and achievable;
- Understanding that omission of insulin is not uncommon. The opportunity should be grasped for nonjudgmental discussion about this;
- Developing strategies to manage transition to adult services.

Summary and recommendations

- Education is the key to successful management of diabetes (1–10). (E)
- There is evidence that educational interventions in childhood and adolescent diabetes have a modestly beneficial effect on glycemic control and a stronger effect on psychosocial outcomes (13–16). (A)
- To maximize the effectiveness of both conventional diabetes treatment and the advances in diabetes management and technology (especially self-monitoring of BG, analogue insulins, and insulin pumps), it is advisable that quality-assured structured education is available to all young people with diabetes and their caregivers (2, 4, 5, 7). (E)
- Health care professionals require appropriate specialized training in the principles and practice of teaching and education (24, 26, 29, 30) to implement successfully behavioral approaches to education designed to empower young people and caregivers in promoting self-management (24, 31, 32). (E,C)
- The content and delivery of structured education need regular review to enable it to evolve to suit individuals, local practice, and the changes in diabetes management and technology (2, 6, 7, 10, 16). (E)
- Educational interventions that have been shown to be most effective are most likely to be based on clear theoretical psychoeducational principles (13–16) (A) be integrated into routine clinical care (e.g., as an adjunct to intensive insulin management) (13, 14, 16, 44, 45) (A,C) involve the continuing responsibility of parents and other caregivers throughout adolescence (4, 5, 29, 33, 55) (B) make use of cognitive behavioral techniques most often related to problem solving, goal setting, communication skills, family conflict resolution, coping skills, and stress management (13–16) (A) utilize new technologies in diabetes care as one of the vehicles for educational motivation (13, 16, 35, 36) (A).
- Evaluation of educational programs is essential and should focus on outcomes such as the patient’s achievement of self-selected diabetes care goals, improved psychosocial adaptation, and enhanced self-efficacy in addition to glycemic control (13–16) (E).

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.

The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See the Introduction of the ISPAD Clinical Practice Consensus Guidelines. Pediatric Diabetes 2006: 7: 341–342.

References


Appendix Resource

In addition to the references in the text, several other sources of further reading and information may be useful

1. IDF Diabetes Education modules. To view or order free book and CD-ROM with teaching slides, www.idf.org


3. Diabetes Education Study Group of the European Association for the Study of Diabetes (EASD). See Basic Curriculum for Health Professionals on Diabetes Therapeutic Education, http://www.des-g.org/article/articlestatic/50/1/10/


8. A valuable resource for families and professionals: www.childrenwithdiabetes.com

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Insulin treatment

Insulin therapy started in 1922 using regular insulin before each main meal and one injection at night, usually at 1 AM. With the development of intermediate- and long-acting insulin, most patients moved to one or two injections per day after 1935. By 1960, a study showed that patients who were diagnosed between 1935 and 1945 and using one or two injections per day had a much higher risk of retinopathy after 15 yr of diabetes compared with those diagnosed before 1935 using multiple daily injections (MDI) (61 vs. 9%) (1) (C). There are no randomized controlled studies comparing the longer term outcomes of using older more traditional insulins with newer regimens when both groups receive equal educational input. But the fact that the traditional insulins have certain clinical limitations has led to the development of new analogues, rapid and long acting. These insulins represent some improvement in the care of diabetes, but the extent of benefit in a clinical long-term setting is not fully established.

There are no randomized controlled studies comparing the longer term outcomes of using older more traditional insulins with newer regimens when both groups receive equal educational input. But the fact that the traditional insulins have certain clinical limitations has led to the development of new analogues, rapid and long acting. These insulins represent some improvement in the care of diabetes, but the extent of benefit in a clinical long-term setting is not fully established.

Data in adults are not readily transferable to pediatric patients of different age-groups (2), but in children and adolescents, as in adults (3) (A), rapid-acting insulin (aspart) is rapidly absorbed and eliminated (4). Higher maximum insulin concentrations in adolescents vs. children were reported both for insulin aspart and for human regular insulin (5) (A) but not with glulisine (6) (A). The results from one study (5) are in-line with the relatively impaired insulin sensitivity and higher insulin concentrations reported in healthy adolescents (7, 8) (B). Such findings highlight the necessity to study the effects of these new insulins in all age-groups separately.

The different rapid-acting analogues have different chemical properties, but no significant difference in time of action and duration has been reported (9). Their advantages compared with regular (soluble) insulin are still under debate. The Cochrane review from 2006 stated that in patients with type 1 diabetes mellitus (T1DM), the weighted mean difference (WMD) of hemoglobin A1c (HbA1c) was −0.1% in favor of insulin analogue [−0.2% when using continuous subcutaneous insulin infusion (CSII)] (10) (A). In children and adolescents, blood glucose control has not been shown to be significantly improved with these analogues (10–14) (A).

A reduction in hypoglycemia has been reported, both for lispro (11, 12, 15) (A) (16) (B) and for aspart (17, 18) (A). In the Cochrane review, the WMD of the overall mean hypoglycemic episodes per patient per month was −0.2 (95% confidence interval: −1.1 to 0.7) (10) in favor of rapid-acting insulin analogues. In adolescents, a significantly reduced rate was found with analogues (14), but no difference was found in prepubertal children (11, 13). The median incidence of severe hypoglycemia for adults was 26.8 episodes/100 patient years vs. 46.1 for regular insulin (10) (A). In the
included pediatric studies, there was no difference found in prepubertal children (10, 11) or adolescents (14).

The basal insulin analogues have different modes of action. Insulin glargine is a clear insulin, which precipitates in situ after injection, whereas insulin detemir is acylated insulin bound to albumin. These analogues have reduced day-to-day variability in absorption compared with neutral protamine Hagedorn (NPH) insulin, with detemir having the lowest within-subject variability in one study (19) (A). So far, the reduction in hypoglycemia but not in HbA1c is the most prominent feature (20) (A), both for glargine (21–24) (A) (25) (B) (26, 27) (C) and for detemir (28, 29) (A) (30) (B) (31) (C). Parental fear of severe hypoglycemia, especially at nighttime, is an impediment to achieving morning blood glucose control. Lower body mass index (z-score) has been reported for detemir (29) (C).

In randomized trials, better blood glucose control has been obtained using MDI and pumps compared with a twice daily treatment (32, 33). The Diabetes Control and Complications Trial (DCCT) proved convincingly that intensive insulin therapy, including a heavy multidisciplinary approach in adolescents with multiple injections or pumps, resulted in a lower rate of long-term complications (33) (A). A further analysis showed that even when comparing patients with the same HbA1c levels, intensive insulin therapy with MDIs or CSII resulted in fewer complications, especially at higher levels of HbA1c (34) (A). Although this has not been studied in the same way in younger children, there is reason to believe that the results apply also to them, limited only by the risk of increasing the risk of severe hypoglycemia (E).

However, in a cross-sectional clinical setting, HbA1c, hypoglycemia, and diabetic ketoacidosis (DKA) were not associated with the number of injections per day in pediatric populations (35) (B).

Insulin pump therapy is at present the best way to imitate the physiological insulin profile. Insulin is infused subcutaneously at a preprogrammed basal rate and boluses are added to counterbalance the intake of carbohydrates. CSII has mostly been compared with MDI with NPH as the long-acting insulin (36, 37) (A) (38–40) (B) (41–46) (C). A reduction in hypoglycemia and improved blood glucose control has been reported. One randomized study has recently confirmed these findings when glargine was the basal insulin in use (47) (B). Several studies have compared the use of analogues and regular insulin in pumps (48) (A) (12) (B). Insulin pumps from the onset have been found to result in superior metabolic control when compared with one to two injections per day (32) (A) but not with MDI (49) (C). However, in the study comparing MDI with CSII, diabetes treatment satisfaction was higher with CSII (50) (C).

Unequivocal evidence for the benefit of MDI, the analogues, and CSII treatment in children is lacking. Carefully structured randomized studies are needed. The fact that these modalities are more expensive than conventional treatment has been an obstacle to the implementation of the use of them in many countries. This implies that the new practical recommendations of the International Society for Pediatric and Adolescent Diabetes (ISPAD) have to be applicable for the total diabetes community worldwide.

The DCCT study and its follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) study confirmed that an improvement in long-term glucose control, as obtained with intensified insulin therapy, including heavy support and education, can reduce the incidence of complications and delay the progression of existing complications in T1DM, also in pediatric patients (33, 50, 51) (A). A rapidly increasing numbers of centers around the world are introducing the basal-bolus concept of intensive insulin treatment already from the onset of diabetes.

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**Insulin availability**

- Children and adolescents with T1DM are dependent on insulin for survival and should have access to adequate amounts of at least regular and NPH insulin.
- ISPAD and the International Diabetes Federation are working towards making insulin available for all children and adolescents with diabetes and promoting universal insulin labeling.

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**Insulin formulation and species**

- Many formulations of insulin are available; most have some role in the management of T1DM (Table 1).
- Currently, children are prescribed human insulins instead of porcine or bovine insulin because of low immunogenicity, but in many countries, these are being superceded by analogues.
Porcine or bovine preparations may be cheaper and more readily available in some parts of the world. They are not inferior in clinical efficacy to human insulins (52) (A). Some locally manufactured preparations have greater immunogenicity, and high titer antibodies may alter pharmacodynamics by acting as insulin-binding proteins. This is particularly relevant when using older bovine insulins. However, animal species insulins are being withdrawn from the market, and major manufacturers are moving towards production of analogue insulins only. At the same time, the production of zinc-containing insulin (lente) is about to be terminated by the largest insulin-producing companies.

The time action of most insulins is dose dependent in that a smaller dose has a shorter duration of effect and earlier peak (53, 54) (C) and (E). There is some evidence that lispro (55) and aspart (56) (C) have the same time action irrespective of dose. The results of these studies are obtained from a relatively small number of adult subjects, and the results in children may result in different profiles of action.

Regular insulin (short acting)

Regular soluble insulin (usually identical to human insulin) is still used as an essential component of most daily replacement regimens in many parts of the world either combined with:

- intermediate-acting insulin in twice daily regimen or
- as premeal bolus injections in basal-bolus regimens (given 20–30 min before meals) together with intermediate-acting insulin twice daily or a basal analogue given once or twice daily.

Rapid-acting insulin analogues

Several novel insulin analogues have been developed. Three rapid-acting types are currently available for children (aspart, glulisine, and lispro). They have a rapid onset and shorter duration of action than regular insulin (Table 1). The rapid-acting analogues:

- Can be given immediately before meals because there is evidence that the rapid action not only reduces postprandial hyperglycemia but nocturnal hypoglycemia may also be reduced (11, 12, 15) (A) (16) (B).
- Offer the useful option of being given after food when needed (e.g., infants and toddlers who are reluctant to eat) (57) (B).
- Give a quicker effect than regular insulin when treating hyperglycemia, with or without ketosis, including sick days (E).
- Are most often used as prandial or snack boluses in combination with longer acting insulins (see basal-bolus regimens).
- Are most often used in insulin pumps.

Intravenous insulin

Regular insulins are best suited for intravenous (i.v.) therapy and are used in the following crisis situations:

- DKA.
- Control of diabetes during surgical procedures.

Rapid-acting insulin can also be given i.v. (58) (C). However, the effect is not superior to that of regular insulin and it is more expensive.

All children should have rapid-acting or regular insulin available for crisis management.

Intermediate-acting insulins

The action profiles of these insulins make them suitable for twice daily regimens and for prebed dosage in basal-bolus regimens.

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**Table 1. Types of insulin preparations and suggested action profiles according to the manufacturers**

<table>
<thead>
<tr>
<th>Insulin type</th>
<th>Onset of action (h)</th>
<th>Peak of action (h)</th>
<th>Duration of action (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid-acting analogues</td>
<td>0.15-0.35</td>
<td>1–3</td>
<td>3–5</td>
</tr>
<tr>
<td>(aspart, glulisine, and lispro)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular/soluble (short-acting)</td>
<td>0.5–1</td>
<td>2–4</td>
<td>5–8</td>
</tr>
<tr>
<td>Intermediate-acting analogues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Semilente (pork)</td>
<td>1–2</td>
<td>4–10</td>
<td>8–16</td>
</tr>
<tr>
<td>NPH</td>
<td>2–4</td>
<td>4–12</td>
<td>12–24</td>
</tr>
<tr>
<td>IZS lente type</td>
<td>3–4</td>
<td>6–15</td>
<td>18–24</td>
</tr>
<tr>
<td>Basal analogues</td>
<td></td>
<td></td>
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<tr>
<td>Glargine</td>
<td>2–4</td>
<td>None</td>
<td>24*</td>
</tr>
<tr>
<td>Detemir</td>
<td>1–2</td>
<td>6–12</td>
<td>20–24</td>
</tr>
<tr>
<td>Long-acting analogues</td>
<td>4–8</td>
<td>12–24</td>
<td>20–30</td>
</tr>
<tr>
<td>Ultralente type</td>
<td></td>
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</tbody>
</table>

IZS, insulin zinc suspension; NPH, neutral protamine Hagedorn insulin.

*The duration of action may be shorter than 24 h (65) (A).
Two principal preparations exist:

- Isophane NPH insulins.
- Crystalline zinc acetate insulin (IZS or lente insulins).

Isophane insulins are mostly used in children, mainly because of their suitability for mixing with regular insulin in the same syringe, vial, or cartridge without interaction.

Note: When regular insulin is mixed with lente preparations, it reacts with excess zinc, blunting its short-acting properties (59) (B).

Basal insulin analogues

The new basal insulin analogues are glargine and detemir.

- They show a more predictable insulin effect with less day-to-day variation compared with NPH insulin. (60) (A) (61) (B).
- In most countries, the two basal analogues have not been formally approved for children younger than 6 yr. However, there is a report on successful use of glargine in children aged from <1 to 5 yr (62) (C).
- Basal analogues are more expensive (approximately +50 to 100%).

Glargine

- Lack of an accumulation effect of glargine given on consecutive days has been shown in one study (63) (C).
- The effect of glargine lasts for up to 24 h; however, a waning effect can be seen approximately 20 h after injection (64) (A).
- Some children report a burning sensation when injecting glargine because of the acid pH (65) (C).

Detemir

- A study with detemir in adults found the time of action to be between 6 and 23 h when doses between 0.1 and 0.8 U/kg were given (66) (A). In a pediatric study, 70% of the patients used detemir twice or three times daily (29) (A).
- In adults, studies with detemir have shown weight reduction or less weight gain (31) (C), which has been observed also in children and adolescents (29) (C).

Traditional long-acting insulins

- Ultralente™ and Ultratard™ insulins were designed to have duration of more than 24 h to meet basal insulin requirements and, therefore, could be used in basal-bolus injection regimens.

Their action profile in children appears to be extremely variable (53), with dose accumulation effect (E). If available, basal insulin analogues are superior to traditional long-acting insulins (E).

Premixed insulin preparations

Premixed insulins (fixed ratio mixtures of premeal and basal insulins) are popular in some countries, particularly for prepubertal children on twice daily regimens. Although they reduce potential errors in drawing up insulin, they remove the flexibility offered by separate adjustment of the two types. Such flexibility is especially useful for children with variable food intake. Recently, premixed insulins have also become available with rapid-acting analogues. Biphasic insulin aspart 30 (30% aspart and 70% aspart bound to NPH) given for three main meals combined with NPH at bedtime was equally efficient as premixed human insulin (70% NPH), given for morning and bedtime with regular insulin for lunch and dinner (67).

- There is no clear evidence that premixed insulins in young children are less effective but some evidence of poorer metabolic control when used in adolescents (35).
- Premixed insulins with regular (or rapid-acting) insulin:NPH in different ratios, e.g., 10:90, 15:85, 20:80, 25:75, 30:70, 40:60, 50:50 are available in various countries from different manufacturers.
- Premixed insulins are suitable for use in pen injector devices.
- Premixed insulins may be useful to reduce the number of injections when compliance (or adherence) with the regimen is a problem.

Inhaled insulin

- This new form of insulin therapy has been investigated in children older than 12 yr as part of a study in adults (68) (B) but is not approved for clinical use in children.

Insulin concentrations

- The most widely available insulin concentration is 100 IU/mL (U100).
- Treatment with U40 (40 IU/mL), U50 or other concentrations such as U500 are also acceptable subject to availability and special needs.
- Care must be taken to ensure that the same concentration is supplied each time new supplies are received.
- Very young children occasionally require insulin diluted with diluent obtained from the manufacturer, but special care is needed in dilution and drawing up the insulin into the syringe. Rapid-acting insulin can be diluted to U10 or U50 with sterile NPH diluent and stored for 1 month (69, 70) (C) for use in pumps for infants or very young children.
Storage of insulin

Regulatory requirements state that the insulin product must retain at least 95% of its labeled potency at the expiration date (71). At room temperature (77°F), insulin will lose <1.0% of its potency over 30 d. In contrast, insulin stored in a refrigerator will lose <0.1% of its potency over 30 d (71) (C). Storage recommendations are more often based on regulatory requirements regarding sterility than loss of potency (71). The individual manufacturer’s storage recommendations and expiration dates must be adhered to. These usually recommend that:

- Insulin must never be frozen.
- Direct sunlight or warming (in hot climates) damages insulin.
- Patients should not use insulin that has changed in appearance (clumping, frosting, precipitation, or discoloration).
- Unused insulin should be stored in a refrigerator (4–8°C).
- After first usage, an insulin vial should be discarded after 3 months if kept at 2–8°C or 4 wk if kept at room temperature. However, for some insulin preparations, manufacturers recommend only 10–14 d of use in room temperature (71) (E).
- In hot climates where refrigeration is not available, cooling jars, earthenware pitcher (matka) (72) (C), or a cool wet cloth around the insulin will help to preserve insulin activity.
- In children on small doses of insulin, 3-mL cartridges instead of 10-mL vials should be chosen to avoid wasting of insulin.

It is essential that a small supply of spare insulin should be readily available to all children and adolescents so that the supply remains uninterrupted.

Problems with injections

- **Local hypersensitivity** reactions to insulin injections are uncommon but when they do occur, formal identification of the insulin (or, more rarely, preservative) responsible may be possible with help from the manufacturers. A trial of an alternative insulin preparation may solve the problem. If true allergy is suspected, desensitization can be performed using protocols available from the manufacturers. Adding a small amount of corticosteroids to the insulin may help (74) (C).
- **Lipohypertrophy** with the accumulation of fat in lumps underneath the skin are common in children (75).
- **Lipoatrophy** is now uncommon since the introduction of highly purified insulins but has been described also with the newer analogues (76, 77) (C).
- **Painful injections** are a common problem in children. Check angle, length of the needle, and depth of injection to ensure that injections are not being given intramuscularly and that the needle is sharp. Reused needles can cause more pain (78) (A). Indwelling catheters (Insuflon®) can decrease injection pain (79) (A).
- **Leakage of insulin** is common and cannot be totally avoided. Encourage slower withdrawal of needle from skin, stretching of the skin after the needle is withdrawn, or pressure with clean finger over the injection site.
- **Bruising and bleeding** are more common after intramuscular injection or tight squeezing of the skin. Use of thinner needles has shown significantly less bleeding at the injection site (80) (B).
- **Bubbles in insulin** should be removed whenever possible. If the bubble is not big enough to alter the dose of insulin, it should not cause problems. When using insulin pens, air in the cartridge can cause drops of insulin appearing on the tip of the pen needle if withdrawn too quickly (81) (C).

Insulin absorption

- Insulin activity profiles show substantial variability both day to day in the same individuals and between individuals, particularly in children (5, 53).
- The onset, peak effect, and duration of action depend on many factors that significantly affect the speed and consistency of absorption.

Injection sites

The usual injection sites are given below:

- Abdomen (the preferred site when faster absorption is required and it may be less affected by muscle activity or exercise);
- Front of thigh/lateral thigh (the preferred site for slower absorption of longer acting insulins);
- Buttocks (upper outer quadrant – may be useful in small children);
- Lateral aspect of the arm (in small children with little subcutaneous fat, intramuscular injection is more likely and it may cause unsightly bruising).

Cleaning or disinfection of skin is not necessary unless hygiene is a real problem. Infection at injection sites is rare (73) (C).
Young people and care providers should know the factors that influence insulin absorption such as:

- **Age** (young children, less subcutaneous fat—faster absorption) (E)
- **Fat mass** (large subcutaneous fat thickness (82) (B) and lipohypertrophy (83) (B)—slower absorption).
- **Dose of injection** (larger dose—slower absorption) (53) (C).
- **Site and depth of subcutaneous injection** (abdomen faster than thigh (84) (A); no good data exist on absorption from thigh vs. buttock).
- **Subcutaneous vs. intramuscular injection** (intramuscular injection—faster absorption in thigh), also with rapid-acting analogues (85) (B). Accidental intramuscular injections can cause variable glucose control (E).
- **Exercise** (leg injection and leg exercise—faster absorption) (86) (B).
- **Insulin concentration, type, and formulation** (lower concentration—faster absorption) (87) (B).
- **Ambient and body temperature** (higher temperatures—faster absorption) (82) (B).

In general, the absorption speed of rapid-acting analogues is less affected by the above-mentioned factors (88–90) (B, B, A).

There is no significant difference in the absorption of glargine from abdomen or thigh (91) (B). Exercise does not influence glargine absorption (92) (A).

There is a risk of hypoglycemia if injecting glargine intramuscularly, particularly in young and lean individuals (93) (C).

Note: Faster absorption usually results in shorter duration of action (see page 90).

**Administration of insulin**

**Devices for insulin delivery**

*Insulin syringes.*

- Plastic fixed-needle syringes with small dead space are preferable to glass syringes.
- Syringes are available in a variety of sizes in different countries, ensuring accurate dose delivery, but it is desirable to have small syringes with 1 U per mark (e.g., 0.3 mL) available for small children.
- Plastic fixed-needle syringes are designed for single use. However, many persons with diabetes successfully reuse them without significant increase in risk of infection (94) (B). Reuse should be discouraged if there is concern about hygiene or injection pain, as they become less sharp when reused (78) (A).
- Insulin syringes must have a measuring scale consistent with the insulin concentration (e.g., U100 syringes).

*Syringes must never be shared with another person because of the risk of acquiring blood-borne infection (e.g., hepatitis, HIV).*

It is advisable that all children and adolescents with diabetes should know how to administer insulin by syringe because other injection devices may malfunction.

**Insulin must be administered by syringes (or other injection devices) calibrated to the concentration of insulin being used.**

**Disposal of syringes.**

- Appropriate disposal procedures are mandatory.
  - Specifically designed and labeled ‘sharps containers’ may be available from pharmacies and diabetes centers.
  - Special needle clippers (e.g., Safeclip®) may be available to remove the needle and make it unusable.
  - Without a ‘sharps container’, syringes with needles removed may be stored and disposed of in opaque plastic containers or tins for garbage collection.

*Pen injector devices.*

- Pen injector devices containing insulin in prefilled cartridges have been designed to make injections easier and more flexible. They eliminate the need for drawing up from an insulin vial, the dose is dialed up on a scale, and they may be particularly useful for insulin administration away from home, at school or on holidays.
- Special pen injection needles of small size (5–6 mm) and diameter are available and may cause less discomfort on injection (80) (B).
- Pen injectors of various sizes and types are available from the pharmaceutical companies. Some pens can be set to ½ unit increments. Availability is a problem in some countries and although pen injectors may improve convenience and flexibility, they are a more expensive method of administering insulin.
- Pen injector devices are useful in children on multiple injection regimens or fixed mixtures of insulin but are less acceptable when free mixing of insulins is used in a two- or three-dose regimen (E).

**Needle length.**

- The traditional needle length of 12–13 mm (27 G) has been replaced by thinner needles that are 5–8 mm long (30–31 G). A two-finger pinch technique is recommended for all types of injections to ensure a strict subcutaneous injection, avoiding intramuscular injection (95) (C).
High-pressure jet injection of insulin into the subcutaneous tissue has been designed to avoid the use of needle injection. Jet injectors may have a role in cases of needle phobia. The use of jet injectors has resulted in metabolic control similar to both conventional injections (103) and CSII (104), but problems with have included a variable depth of penetration, delayed pain, and bruising (105) (B).

**Subcutaneous indwelling catheters.**

Such catheters (e.g., Insuflon) inserted using topical local anesthetic cream may be useful to overcome problems with injection pain at the onset of diabetes (79) (A).

Insuflon is used in an increasing number of centers for introduction of MDI. The use of Insuflon does not affect metabolic control negatively (100) (B). In children with injection problems, HbA1c has been lowered by using Insuflon (99) (B).

The use of a basal analogue and a short- or rapid-acting insulin at the same injection time in an Insuflon is not advisable in case of possible interaction of the two insulins (for mixing with glargine, see page 95).

Insuflons should be replaced every 2–4 d to prevent scarring and a negative effect on insulin absorption (100) (B) (101) (C).

**Automatic injection devices.**

Automatic injection devices are useful for children who have a fear of needles. Usually, a loaded syringe is placed within the device, locked into place, and inserted automatically into the skin by a spring-loaded system.

The benefits of these devices are that the needle is hidden from view and the needle is inserted through the skin rapidly.

Automatic injection devices for specific insulin pen injectors are available (102) (B).

**Jet injectors.**

High-pressure jet injection of insulin into the subcutaneous tissue has been designed to avoid the use of needle injection. Jet injectors may have a role in cases of needle phobia. The use of jet injectors has resulted in metabolic control similar to both conventional injections (103) and CSII (104), but problems with have included a variable depth of penetration, delayed pain, and bruising (105) (B).

**Subcutaneous insulin infusion pumps.**

The use of external pumps is increasing and is proving to be acceptable and successful (36, 37) (A) (38, 40–46) (C) (39) (E), even in young infants (42) (C). Randomized studies in the preschool group have failed to show better glycemic control (36, 106) (A).

The positive effects on glycemic control and hypoglycemia in non-randomized observational studies have probably been influenced by the patient selection in these studies, such as good compliance and/or poor metabolic control. Pump therapy has also been found effective in recurrent ketoacidosis (107, 108). This highlights the importance of individualizing the decision of the method of therapy for every situation.

An insulin pump is an alternative to treatment with MDI (including basal analogues) if HbA1c is persistently above the individual goal, hypoglycemia is a major problem, or quality of life needs be improved (109) (E).

Insulin pump use is increasing in the younger agegroup, as clinicians become more comfortable with CSII as a more physiological insulin replacement therapy (E).

The newer generation of ‘smart’ pumps that automatically calculate meal- or correction-boluses based on insulin-to-carbohydrate ratios and insulin sensitivity factors have enabled alternate providers, such as grandparents, nannies, and daycare workers, to participate in diabetes management tasks (E).

Insulin pump treatment may be hazardous when education and adherence to therapy is inadequate because of the smaller depot of subcutaneous insulin and the sudden rise in ketones when insulin supply is interrupted. Pump stops for 5 h in adult patients resulted in β-ketone (beta-hydroxybutyrate) levels of approximately 1–1.5 mmol/L but not in DKA (110) (B). Results in children and adolescents seem to be similar (111) (C).

Patients using insulin pumps, especially younger children, will benefit from being able to measure β-ketones (E).

For patients using insulin pump, and prone to ketosis, it may help to give a small dose of basal insulin before bedtime (E).

Patients must be instructed on treatment of hyperglycemia, giving insulin with a pen or syringe in case of suspected pump failure (hyperglycemia and elevated ketone levels).

Rapid-acting analogue insulins are used in most pumps (E), and a meta-analysis has shown a 0.26% lower HbA1c level when comparing with human regular insulin (24) (A). Regular insulin is less often used in pumps but works well if rapid-acting insulin is not available.
There is no difference in action effect (112), pump stops or catheter cloggings when using insulin lispro or aspart in pumps (113).

Lower percentage of basal insulin and more than seven daily boluses are an option for better metabolic control when using pumps (114) (C).

The use of pumps requires special education for users but does not need to be restricted to centers with 24 h access to pump expertise. The pump user or the family should be taught how to switch to multiple injections with pens or syringes in case of emergency.

Injection technique

- **Injections by syringe** are usually given into the deep subcutaneous tissue through a two-finger pinch of skin at a 45° angle. A 90° angle can be used if the s.c. fat is thick enough (see page 94).

- **Pen injector technique** requires a careful education including the need to ensure that no airlock or blockage forms in the needle. A wait of 15 s after pushing in the plunger helps to ensure complete expulsion of insulin through the needle (81) (B).

**Self-injection.**

- It should be emphasized that a proportion of people with diabetes have a severe long-lasting dislike of injections, which may influence their glycemic control (E). For these individuals, an injection aid, Insufilon (99) (B), or insulin pump therapy may improve compliance (E).

- There is great individual variation in the appropriate age for children to self-inject (115) (B).

- The appropriate age relates to developmental maturity rather than to chronological age.

- Most children older than 10 yr either give their own injections or help with them (115) (B)

- Younger children sharing injection responsibility with a parent or other care provider may help prepare the device or help push the plunger and, subsequently, under supervision, be able to perform the whole task successfully.

- Self-injection is sometimes triggered by an external event such as overnight stay with a friend, school excursion, or diabetes camp.

- Parents or care providers should not expect that self-injection will automatically continue and should accept phases of non-injection with the need for help from another person.

- Younger children on multiple injection regimens may need help to inject in sites difficult to reach (e.g., the buttocks) to avoid lipo hypertrophy.

- The choice of insulin regimen will depend on many factors including age, duration of diabetes, lifestyle (dietary patterns, exercise schedules, school, work commitments, etc.), targets of metabolic control, and, particularly, individual patient/family preferences.

**Regular checking of injection sites, injection technique, and skills remain a responsibility of parents, care providers, and health professionals.**

**Self-mixing of insulin.** When a mixture of two insulins is drawn up (e.g., regular mixed with NPH), it is most important that there is no contamination of one insulin with the other in the vials. To prevent this, the following principles apply:

- There is no uniformity of advice but most often it is taught that regular (clear insulin) is drawn up into the syringe before cloudy insulin (intermediate or long acting).

- Vials of cloudy insulin must always be gently rolled (not shaken) at least 10, preferably 20, times (116) (B) to mix the insulin suspension before carefully drawing it up into the clear insulin.

- If the cloudy insulin is of lente type, the mixture must be administered immediately, otherwise the regular component interacts with zinc, which blunts the action (59, 117) (C).

- Insulins from different manufacturers should be used together with caution, as there may be interaction between the buffering agents.

- NPH and lente insulins should never be mixed.

- Rapid-acting insulin analogues may be mixed in the same syringe as NPH immediately before injections (118) (B) (119) (C). Immediate injection of a mixture of Ultralente and Humalog has been found not to diminish the Humalog effect (120) (C).

- The manufacturer recommends that glargine should not be mixed with any other insulin before injection, but there is some evidence that it can be mixed with insulin lispro and aspart without affecting the blood-glucose-lowering effect (121) (B) or HbA1c (122) (C).

- The manufacturer recommends that detemir should not be mixed with any other insulin before injection. There are no available studies on this.

**Insulin regimens**

- No insulin injection regimen satisfactorily mimics normal physiology.
The basal-bolus concept (i.e., a pump or intermediate-acting insulin/long-acting insulin/basal analogue once or twice daily and rapid-acting or regular boluses with meals and snacks) has the best possibility of imitating the physiological insulin profile.

At least two injections of insulin per day (mixing short/rapid-acting and basal insulin) are advisable in most children.

Most regimens include a proportion of short- or rapid-acting insulin and intermediate-acting insulin, long-acting or basal analogue, but some children may, during the partial remission phase, maintain satisfactory metabolic control on intermediate- or long-acting insulins alone (i.e., an HbA1c close to the normal range).

Principles of insulin therapy

**Aim for appropriate insulin levels throughout the 24 h to cover basal requirements and higher levels of insulin in an attempt to match the glycemic effect of meals.**

**Frequently used regimens**

- **Two injections daily** of a mixture of short- or rapid- and intermediate-acting insulins (before breakfast and the main evening meal).
- **Three injections** daily using a mixture of short- or rapid- and intermediate-acting insulins before breakfast; rapid or regular insulin alone before afternoon snack or the main evening meal; intermediate-acting insulin before bed or variations of this.
- **Basal-bolus regimen**
  - of the total daily insulin requirements, 40–60% should be basal insulin, the rest preprandial rapid-acting or regular insulin.
  - injection of regular insulin 20–30 min before each main meal (breakfast, lunch; and the main evening meal); intermediate-acting insulin or basal/long-acting analogue at bedtime or twice daily (mornings and evenings).
  - injection of rapid-acting insulin analogue immediately before (or after) (11, 57) (A) each main meal (breakfast, lunch, and main evening meal); intermediate-acting insulin or basal/long-acting analogue at bedtime, probably before breakfast and occasionally at lunchtime or twice daily (mornings and evenings).

- **Insulin pump** regimens are regaining popularity with a fixed or a variable basal dose and bolus doses with meals.

Note: None of these regimens can be optimized without frequent assessment by blood glucose monitoring (BGM).

**Daily insulin dosage**

*Daily insulin dosage varies greatly between individuals and changes over time. It, therefore, requires regular review and reassessment.*

Dosage depends on many factors such as:

- Age;
- Weight;
- Stage of puberty;
- Duration and phase of diabetes;
- State of injection sites;
- Nutritional intake and distribution;
- Exercise patterns;
- Daily routine;
- Results of BGM (and glycated hemoglobin);
- Intercurrent illness.

Guidelines on dosage:

- During the partial remission phase, the total daily insulin dose is often <0.5 IU/kg/day.
- Prepubertal children (outside the partial remission phase) usually require insulin of 0.7−1.0 IU/kg/day.
- During puberty, requirements may rise substantially above 1 and even up to 2 U/kg/day.

The 'correct' dose of insulin is that which achieves the best attainable glycemic control for an individual child or adolescent without causing obvious hypoglycemia problems, and the harmonious growth according to weight and height children’s charts.

**Distribution of insulin dose**

The distribution of insulin dose across the day shows great individual variation. Regardless of mode of insulin therapy, doses should be adapted based on the daily pattern of blood glucose.

- Children on twice daily regimens often require more (perhaps 2/3) of their total daily insulin in the morning and less (perhaps 1/3) in the evening.
- On this regimen, approximately 1/3 of the insulin dose may be short-acting insulin and approximately 2/3 may be intermediate-acting insulin although these ratios change with greater age and maturity of the young person.
On basal-bolus regimens, the nighttime intermediate-acting insulin may represent between 30 (typical for regular insulin) and 50% (typical for rapid-acting insulin) of total daily insulin. Approximately 50% as rapid-acting or approximately 70% as regular insulin is divided up between three and four premeal boluses. When using rapid-acting insulin for premeal boluses, the proportion of basal insulin is usually higher, as short-acting regular insulin also provides some basal effect.

Glargine is often given once a day, but many children may need to be injected twice a day or combined with NPH to provide daytime basal insulin coverage (25, 123) (C).

Glargine can be given before breakfast, before dinner or at bedtime with equal effect, but nocturnal hypoglycemia occurs significantly less often after breakfast injection (64) (A, adult study).

When transferring to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycemia (123) (C). After that, the dose should be individually tailored.

Detemir is most commonly given twice daily in children (29) (A) and (E).

When transferring to detemir from NPH, the same doses can be used to start with (E).

**Insulin dose adjustments**

Soon after diagnosis:

- Frequent advice by members of the diabetes care team on how to make graduated alterations of insulin doses at this stage is of high educational value.
- Insulin adjustments should be made until target blood glucose levels and target HbA1c are achieved.
- If frequent BGM is not possible, urinary tests are useful, especially in the assessment of nocturnal control.

Later insulin adjustments:

- **On twice daily insulin regimens**, insulin dosage adjustments are usually based on recognition of daily patterns of blood glucose levels over the whole day or for a number of days or on recognition of glycemic responses to food intake or energy expenditure.
- **On basal-bolus regimens**, flexible or dynamic adjustments of insulin are made before meals and in response to frequent BGM. In addition, the daily blood glucose pattern should be taken into account. The rapid-acting analogues may require postprandial blood glucose tests approximately 2 h after meals to assess their efficacy. Frequently, insulin is dosed based on food consumption (carbohydrates) and on deviation from a target glucose. Many newer insulin pumps allow programming algorithms for these automatic adjustments for ambient blood glucose and carbohydrate intake.

**Health care professionals have the responsibility to advise parents, other care providers, and young people on adjusting insulin therapy safely and effectively. This training requires regular review, reassessment, and reinforcement.**

Advice for persistent deviations of blood glucose from target

- Elevated blood glucose level before breakfast—increase predinner or prebed intermediate- or long-acting insulin. (Blood glucose tests during the night are needed to ensure that this change does not result in nocturnal hypoglycemia.)
- Rise in blood glucose level after a meal—increase premeal rapid-acting/regular insulin.
- Elevated blood glucose level before lunch/dinner meal—increase prebreakfast basal insulin or increase dose of prebreakfast regular/rapid-acting insulin if on basal-bolus regimen. When using rapid-acting insulin for basal-bolus regimen, the dose or type of basal insulin may need to be adjusted in this situation.
- When using carbohydrate counting, persistent elevations of blood glucose may require adjustment in ratios for carbohydrate (insulin-to-carbohydrate ratio).
- Correction doses can be used according to the ‘1800 rule’, i.e., divide 1800 by total daily insulin dose to get the results in mg/dL that 1 U of rapid-insulin will lower the blood glucose. For the results in mmol/L, use the ‘100 rule’, i.e. divide 100 by total daily insulin dose (C) and (E). For regular insulin, a ‘1500 rule’ can be used for results in mg/dL and a ‘83-rule’ for results in mmol/L. However, correction doses should always be adjusted individually before administration, depending on other factors affecting insulin resistance, such as exercise.
- Rise in blood glucose level after evening meal— increase pre-evening meal regular/rapid-acting insulin.

In addition:

- Unexplained hypoglycemia requires re-evaluation of insulin therapy.
- Hyper- or hypoglycemia occurring in the presence of intercurrent illness requires a knowledge of ‘sick day management’.
- Day-to-day insulin adjustments may be necessary for variations in lifestyle routine, especially exercise or dietary changes.
Various levels of exercise require adjustment of diabetes management.

Special advice may be helpful when there are changes in routine, travel, school outings, educational holidays/diabetes camps, or other activities that may require adjustment of insulin doses.

During periods of regular change in consumption of food (e.g., Ramadan), the total amount of carbohydrate intake. However, if total calorie intake is reduced during Ramadan, the daily amount of bolus insulin for meals usually needs to be reduced, e.g., to 2/3 or 3/4 of the usual dose (E).

**Dawn phenomenon**

Blood glucose levels tend to rise in the hours of the morning (usually after 5 AM) prior to waking. This is called the dawn phenomenon. In individuals without diabetes, the mechanisms include increased nocturnal growth hormone secretion, increased resistance to insulin action, and increased hepatic glucose production. These mechanisms are more potent in puberty.

Pump studies (124) (B) (125) (C) have shown that younger children often need more basal insulin before midnight than after (reversed dawn phenomenon). With a basal-bolus analogue regimen, this can be achieved by giving regular instead of rapid-acting insulin for the last bolus of the day (nighttime blood glucose levels need to be checked) (E).

In individuals with TIDM, fasting hyperglycemia is predominantly caused by waning insulin levels, thus exaggerating the dawn phenomenon. Morning hyperglycemia can, in some cases, be preceded by nighttime hypoglycemia, being seen less often in pump therapy compared with MDI (126) (B).

Correction of fasting hyperglycemia is likely to require an adjustment of the insulin regimen to provide effective insulin levels throughout the night and the early morning by the use of:

- intermediate-acting insulin later in the evening or at bedtime;
- a longer acting evening insulin/basal insulin analogue;
- changeover to insulin pump treatment.

The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See the Introduction of the ISPAD Clinical Practice Consensus Guidelines in Pediatric Diabetes 2006: 7: 341–342.

**References**

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22. Murphy NP, Keane SM, Ong KK et al. Randomized cross-over trial of insulin glargine plus lispro or NPH insulin plus regular human insulin in adolescents with type 1 diabetes on intensive insulin regimens. Diabetes Care 2003: 26: 799–804.


Diabetic ketoacidosis (DKA) results from absolute or relative deficiency of circulating insulin and the combined effects of increased levels of the counter-regulatory hormones: catecholamines, glucagon, cortisol, and growth hormone (1, 2). Absolute insulin deficiency occurs in previously undiagnosed type 1 diabetes mellitus (T1DM) and when patients on treatment deliberately or inadvertently do not take insulin, especially the long-acting component of a basal-bolus regimen. Patients who use an insulin pump can rapidly develop DKA when insulin delivery fails for any reason. Relative insulin deficiency occurs when the concentrations of counter-regulatory hormones increase in response to stress in conditions such as sepsis, trauma, or gastrointestinal illness with diarrhea and vomiting. The pathophysiology of DKA in children is summarized in Fig. 1.

The combination of low serum insulin and high counter-regulatory hormone concentrations results in an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), impaired peripheral glucose utilization resulting in hyperglycemia and hyperosmolality, and increased lipolysis and ketogenesis, causing ketonemia and metabolic acidosis. Hyperglycemia that exceeds the renal threshold [approximately 10 mmol/L (180 mg/dL), although the range in normal and diabetic individuals is very wide] and hyperketonemia causes osmotic diuresis, dehydration, and obligatory loss of electrolytes, which often is aggravated by vomiting. These changes stimulate further stress hormone production, which induces more severe insulin resistance and worsening hyperglycemia and hyperketonemia. If this cycle is not interrupted with exogenous insulin and fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue. Ketoacidosis may be aggravated by lactic acidosis from poor tissue perfusion or sepsis.

DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid (ECF) compartments; the range of losses is shown in Table 1. Despite their dehydration, patients continue to maintain normal blood pressure and have considerable urine output until extreme volume depletion leads to a critical decrease in renal blood
flow and glomerular filtration. At presentation, the magnitude of specific deficits in an individual patient varies depending upon the duration and severity of illness, the extent to which the patient was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention. Consumption of fluids with a high-carbohydrate content (juices or sugar containing soft drinks) exacerbates the hyperglycemia (3).

Clinical manifestations of DKA

- Dehydration
- Rapid, deep, sighing (Kussmaul respiration)
- Nausea, vomiting, and abdominal pain mimicking an acute abdomen
- Progressive obtundation and loss of consciousness
- Increased leukocyte count with left shift
- Non-specific elevation of serum amylase
- Fever only when infection is present

Definition of DKA

The biochemical criteria for the diagnosis of DKA are (4):

- Hyperglycemia (blood glucose > 11 mmol/L [≈200 mg/dL])
- Venous pH < 7.3 or bicarbonate < 15 mmol/L
- Ketonemia and ketonuria

Partially treated children and children who have consumed little or no carbohydrates may have, on rare occasion, only modestly increased blood glucose concentrations (‘euglycemic ketoacidosis’) (5, 6).

Table 1. Losses of fluids and electrolytes in diabetic ketoacidosis (DKA) and maintenance requirements in normal children

<table>
<thead>
<tr>
<th></th>
<th>Average (range) losses per kg</th>
<th>24-h maintenance requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Water</td>
<td>70 mL (30–100)</td>
<td>*&lt;10 kg 100 mL/kg/24 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11–20 kg 1000 mL + 50 mL/kg/24 h for each kg from 11–20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;20 kg 1500 mL + 20 mL/kg/24 h for each kg &gt;20</td>
</tr>
<tr>
<td>Sodium</td>
<td>6 mmol (5–13)</td>
<td>2–4 mmol†</td>
</tr>
<tr>
<td>Potassium</td>
<td>5 mmol (3–6)</td>
<td>2–3 mmol</td>
</tr>
<tr>
<td>Chloride</td>
<td>4 mmol (3–9)</td>
<td>2–3 mmol</td>
</tr>
<tr>
<td>Phosphate</td>
<td>(0.5–2.5) mmol</td>
<td>1–2 mmol</td>
</tr>
</tbody>
</table>

Data are from measurements in only a few children and adolescents (41, 42, 80–82). In any individual patient, actual losses may be less or greater than the ranges shown in the Table (E).

Three methods for determining maintenance water requirements in children are commonly used: *the Holliday–Segar formula (143) (shown in this Table), a simplified Holliday–Segar formula† (see below), and a formula based on body surface area for children more than 10 kg (1500 mL/m²/24 h) (144).†Maintenance electrolyte requirements in children are per 100 mL of maintenance IV fluid (144, 145).

†Simplified method based on Holliday–Segar: *<10 kg 4 mL/kg/h; 11–20 kg 40 + 2 mL/kg/h for each kg between 11 and 20; >20 kg 60 + 1 mL/kg/h for each kg >20.
Type 2 diabetes mellitus (T2DM), associated with increased rates and severity of obesity, in some centers now accounts for as much as one half of newly diagnosed diabetes in children aged 10–21 yr, depending on the socioeconomic and ethnic composition of the population (7). Acute decompensation with DKA has been recognized to occur at the time of diagnosis in as many as 25% of children with T2DM (7). This is more likely in those of African-American descent, less so in Hispanic, and least in Canadian First Nation teenagers (8–13). The majority of new cases of diabetes in Japanese children and adolescents are detected in asymptomatic individuals by routine urine screening (14, 15); however, overall, approximately 5% of patients with T2DM have DKA at the time of diagnosis (16).

The severity of DKA is categorized by the degree of acidosis (17):

- **Mild**: venous pH < 7.3 or bicarbonate < 15 mmol/L
- **Moderate**: pH < 7.2, bicarbonate < 10 mmol/L
- **Severe**: pH < 7.1, bicarbonate < 5 mmol/L

**Hyperglycemic hyperosmolar state (HHS)** also may occur in young patients with T2DM (18, 19). The criteria for HHS include (2):

- Plasma glucose concentration > 33.3 mmol/L (600 mg/dL)
- Arterial pH > 7.30
- Serum bicarbonate > 15 mmol/L
- Small ketonuria, absent to mild ketonemia (serum β-hydroxybutyrate 1 ± 0.2 (SEM) mmol/L (2))
- Effective serum osmolality > 320 mOsm/kg
- Stupor or coma

It is important to recognize that overlap between the characteristic features of HHS and DKA may occur. Some patients with HHS, especially when there is very severe dehydration, have mild or moderate acidosis. Conversely, some children with T1DM may have features of HHS (severe hyperglycemia) if high-carbohydrate-containing beverages have been used to quench thirst and replace urinary losses prior to diagnosis (3). Therapy must be appropriately modified to address the pathophysiology and unique biochemical disturbances of each individual patient.

**Frequency of DKA**

At disease onset

There is wide geographic variation in the frequency of DKA at onset of diabetes; rates inversely correlate with the regional incidence of T1DM. Frequencies range from approximately 15% to 70% in Europe and North America (A) (20–24). DKA at diagnosis is more common in younger children (<5 yr of age), and in children whose families do not have ready access to medical care for social or economic reasons (A) (6, 24, 25).

In children with established diabetes (recurrent DKA)

The risk of DKA in established T1DM is 1–10% per patient per year (A, C) (26–29).

Risk is increased in (28):

- Children with poor metabolic control or previous episodes of DKA
- Peripubertal and adolescent girls
- Children with psychiatric disorders, including those with eating disorders
- Children with difficult or unstable family circumstances (e.g., parental abuse)
- Children who omit insulin (30) (C)
- Children with limited access to medical services
- Insulin pump therapy (as only rapid-acting or short-acting insulin is used in pumps, interruption of insulin delivery for any reason rapidly leads to insulin deficiency) (29) (C)

**Management of DKA**

Emergency assessment

- Perform a clinical evaluation to confirm the diagnosis and determine its cause. Carefully look for evidence of infection. In recurrent DKA, insulin omission or failure to follow sick day or pump failure management guidelines accounts for almost all episodes, except for those because of acute severe febrile or gastrointestinal illness.
- Weigh the patient. (If body surface area is used for fluid therapy calculations, measure height or length to determine surface area.) This weight should be used for calculations and not the weight from a previous office visit or hospital record.
- Assess clinical severity of dehydration.
- Clinical assessment of dehydration is imprecise, inaccurate, and generally shows only fair to moderate agreement among examiners. It should be based on a combination of physical signs. The three most useful individual signs for assessing dehydration in young children and predicting at least 5% dehydration and acidosis are:
  - prolonged capillary refill time (normal capillary refill is ≤1.5–2 s)
  - abnormal skin turgor (‘tenting’ or inelastic skin)
  - abnormal respiratory pattern (hyperpnea) (31)
- Other useful signs in assessing degree of dehydration include dry mucus membranes, sunken eyes, absent tears, weak pulses, and cool extremities. More signs of dehydration tend to be associated with more severe dehydration (31).
≥10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, and oliguria.

♦ Assess level of consciousness [Glasgow coma scale (GCS) – see Table 2] (32).
♦ Obtain a blood sample for laboratory measurement of serum or plasma glucose, electrolytes (including bicarbonate or total carbon dioxide), blood urea nitrogen, creatinine, osmolality, venous (or arterial in critically ill patient) pH, pCO₂, hemoglobin and hematocrit or complete blood count (an increased white blood cell count in response to stress is characteristic of DKA and is not indicative of infection (22). The white cell count need not be measured unless there is evidence of concurrent infection), calcium, phosphorus, and magnesium concentrations (if possible), HbA1c.
♦ Perform a urinalysis for ketones.
♦ Measurement of blood β-hydroxybutyrate concentration, if available, is useful to confirm ketoacidosis and may be used to monitor the response to treatment (33, 34).
♦ Obtain appropriate specimens for culture (blood, urine, throat), if there is evidence of infection.
♦ If laboratory measurement of serum potassium is delayed, perform an electrocardiogram (ECG) for baseline evaluation of potassium status (35, 36).
♦ In the child with established diabetes (recurrent DKA) and suspected insulin omission, it may be useful to obtain a blood sample for determination of serum free insulin concentration (even when children have been treated exclusively with biosynthetic human insulin, anti-insulin antibodies may be present in the serum and interfere with insulin immunoassays. Thus anti-insulin antibodies must be eliminated before the concentration of free (active) insulin is determined (27)) before insulin is administered because the history of recent insulin administration may not be available or accurate (37).

Supportive measures

♦ Secure the airway and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration in the unconscious or severely obtunded patient.
♦ A peripheral intravenous (IV) catheter should be placed for convenient and painless repetitive blood sampling. An arterial catheter may be necessary in some critically ill patients managed in an intensive care unit.
♦ A cardiac monitor should be used for continuous electrocardiographic monitoring to assess T waves for evidence of hyper- or hypokalemia (35, 36).
♦ Give oxygen to patients with severe circulatory impairment or shock.
♦ Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids.
♦ Catheterization of the bladder is usually not necessary, but if the child is unconscious or unable to void on demand (e.g., infants and very ill young children) the bladder should be catheterized.

Where should the child be managed? The child should receive care in a unit that has:

♦ Experienced nursing staff trained in monitoring and management
♦ Written guidelines for DKA management in children
♦ Access to laboratories for frequent and timely evaluation of biochemical variables
♦ A specialist/consultant pediatrician with training and expertise in the management of DKA should direct inpatient management.

Table 2. Glasgow coma scale or score. The GCS consists of three parameters and is scored between 3 and 15 (32); 3 being the worst and 15 the best. One of the components of the GCS is the best verbal response, which cannot be assessed in non-verbal young children. A modification of the GCS was created for children too young to talk.

<table>
<thead>
<tr>
<th>Best eye response</th>
<th>Best verbal response</th>
<th>Best verbal response (non-verbal children)</th>
<th>Best motor response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No eye opening</td>
<td>1. No verbal response</td>
<td>1. No response</td>
<td>1. No motor response</td>
</tr>
<tr>
<td>2. Eyes open to pain</td>
<td>2. No words, only incomprehensible</td>
<td>2. Inconsolable, irritable, restless, cries</td>
<td>2. Extension to pain (decerebrate posture)</td>
</tr>
<tr>
<td>3. Eyes open to verbal command</td>
<td>sounds; moaning and groaning</td>
<td>3. Inconsistently consolable and moans; makes vocal sounds</td>
<td>3. Flexion to pain (decorticate posture)</td>
</tr>
<tr>
<td>5. Oriented, normal conversation</td>
<td>4. Confused, disoriented conversation†</td>
<td>5. Oriented, normal conversation</td>
<td>5. Localizes pain</td>
</tr>
<tr>
<td>7. Interacts appropriately</td>
<td>and interacts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Inappropriate words, no sustained conversational exchange.
†Attention can be held; responds in a conversational manner, but shows some disorientation.
Immediate assessment

Clinical History
- Polyuria
- Polydipsia
- Weight loss (Weigh)
- Abdominal pain
- Tiredness
- Vomiting
- Confusion

Shock (reduced peripheral pulses)
Reduced conscious level/coma

Dehydration >5%
Not in shock
Acidotic (hyperventilation)
Vomiting

Biochemical Features & Investigations
- Ketones in urine
- Elevated blood glucose
- Acidemia
- Blood gases, urea, electrolytes
- Other investigations as indicated

Resuscitation
- Airway ± NG tube
- Breathing (100% oxygen)
- Circulation (0.9% saline 10-20 ml/kg over 1-2 h. & repeat until circulation is restored) but do not exceed 30 ml/kg

Acidosis not improving
Blood glucose 17 mmol/l
or
blood glucose falls >5 mmol/l/hour

Re-evaluate
- IV fluid calculations
- Insulin delivery system & dose
- Need for additional resuscitation
- Consider sepsis

Critical Observations
- Hourly blood glucose
- Hourly fluid input & output
- Neurological status at least hourly
- Electrolytes 2 hourly after start of IV therapy
- Monitor ECG for T-wave changes

IV Therapy
- Calculate fluid requirements
- Correct over 48 hours
- Saline 0.9%
- ECG for abnormal T-waves
- Add KCL 40 mmol per litre fluid

Continuous insulin infusion
0.1 unit/kg/hour

Transition to SC Insulin
- Start SC insulin then stop IV insulin after an appropriate interval

Acidosis not improving
Blood glucose 17 mmol/l
or
blood glucose falls >5 mmol/l/hour

No improvement

WARNING SIGNS:
- headache, slowing heart rate, irritability, decreased conscious level, incontinence, specific neurological signs

Exclude hypoglycaemia
- Is it cerebral edema?

Management
- Give mannitol 0.5-1 g/kg
- Restrict IV fluids by one-third
- Call senior staff
- Move to ICU
- Consider cranial imaging only after patient stabilised

Adapted from Dunger et al. Karger Pub. 1999. NG, nasogastric, SC, subcutaneous

Fig. 2. Algorithm for the immediate assessment and management of diabetic ketoacidosis (DKA).
Children with severe DKA (long duration of symptoms, compromised circulation, or depressed level of consciousness) or those who are at increased risk for cerebral edema (e.g., <5 yr of age, severe acidosis, low pCO2, high blood urea nitrogen) should be considered for immediate treatment in an intensive care unit (pediatric, if available) or in a unit that has equivalent resources and supervision, such as a child’s ward specializing in diabetes care (C,E) (4, 38).

In a child with established diabetes, whose parents have been trained in sick day management, hyperglycemia and ketosis without vomiting or severe dehydration can be managed at home or in an outpatient health care facility (e.g., emergency ward), provided an experienced diabetes team supervises the care (C,E) (17, 39, 40).

Clinical and biochemical monitoring

Successful management of DKA and HHS demands meticulous monitoring of the patient’s clinical and biochemical response to treatment so that timely adjustments in treatment can be made when indicated by the patient’s clinical or laboratory data (E).

There should be documentation on a flow chart of hour-by-hour clinical observations, IV and oral medications, fluids, and laboratory results. Monitoring should include the following:

- Hourly (or more frequently as indicated) vital signs (heart rate, respiratory rate, blood pressure)
- Hourly (or more frequently as indicated) neurological observations (Glasgow coma score) for warning signs and symptoms of cerebral edema (see below)
  - headache
  - inappropriate slowing of heart rate
  - recurrence of vomiting
  - change in neurological status (restlessness, irritability, increased drowsiness, incontinence) or specific neurologic signs (e.g., cranial nerve palsy, abnormal pupillary responses)
  - rising blood pressure
  - decreased oxygen saturation
- Amount of administered insulin
- Hourly (or more frequently as indicated) accurate fluid input (including all oral fluid) and output
- Capillary blood glucose should be measured hourly (but must be cross-checked against laboratory venous glucose, as capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis)
- Laboratory tests: serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphorus, hematocrit, and blood gases should be repeated 2–4 hourly, or more frequently, as clinically indicated, in more severe cases
- Urine ketones until cleared or blood β-hydroxybutyrate (BOHB) concentrations, if available, every 2 h (34)
- If the laboratory cannot provide timely results, a portable biochemical analyzer that measures plasma glucose, serum electrolytes and blood ketones on fingerstick blood samples at the bedside is a useful adjunct to laboratory-based determinations.

**Calculations:**

- **Anion gap = Na – (Cl + HCO₃):** normal is 12 ± 2 mmol/L
- **In DKA the anion gap is typically 20–30 mmol/L:** an anion gap >35 mmol/L suggests concomitant lactic acidosis (E)
- **Corrected sodium = measured Na + 2 × ([plasma glucose − 5.6]/5.6) mmol/L**
- **Effective osmolality = 2 × (Na + K) + plasma glucose mOsm/kg**

**Goals of therapy**

- Correct dehydration
- Correct acidosis and reverse ketosis
- Restore blood glucose to near normal
- Avoid complications of therapy
- Identify and treat any precipitating event

**Fluids and salt.** Patients with DKA have a deficit in ECF volume that usually is in the range 5–10% (C) (41, 42). Shock with hemodynamic compromise is rare in pediatric DKA. Clinical estimates of the volume deficit are subjective and inaccurate (43, 44); therefore, in moderate DKA use 5–7% and in severe DKA 7–10% dehydration.

The effective osmolality (formula above) is frequently in the range of 300–350 mmol/kg. Increased serum urea nitrogen and hematocrit may be useful markers of the severity of ECF contraction (40, 45). The serum sodium concentration is an unreliable measure of the degree of ECF contraction for two reasons: (1) glucose, largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space thereby inducing dilutional hyponatremia (46, 47), and (2) the low sodium content of the elevated lipid fraction of the serum in DKA. The latter is not a concern with most modern methods for measuring sodium. Therefore, it is important to calculate the corrected sodium (using the above formula) and monitor its changes throughout the course of therapy. As the plasma glucose concentration decreases after administering fluid and insulin, the measured serum sodium concentration should increase, but it is important to appreciate that this
does not indicate a worsening of the hypertonic state. A failure of measured serum sodium levels to rise or a further decline in serum sodium levels with therapy is thought to be a potentially ominous sign of impending cerebral edema (48–50).

The objectives of fluid and electrolyte replacement therapy are:

- Restoration of circulating volume
- Replacement of sodium and the ECF and intracellular fluid deficit of water
- Improved glomerular filtration with enhanced clearance of glucose and ketones from the blood
- Reduction of risk of cerebral edema

Principles of water and salt replacement

Despite much effort to find the cause of cerebral edema it remains a mystery. There is no convincing evidence of an association between the rate of fluid or sodium administration used in the treatment of DKA and the development of cerebral edema (51). No treatment strategy can be definitively recommended as being superior to another based on evidence. The principles described below were developed after a comprehensive review of the literature and were accepted and endorsed by a panel of expert physicians representing the Lawson Wilkins Pediatric Endocrine Society (LWPES), the European Society for Paediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) (4, 52).

**Begin with fluid replacement before insulin therapy. Volume expansion (resuscitation) is required only if needed to restore peripheral circulation. Subsequent fluid administration (including oral fluids) should rehydrate evenly over 48 h at a rate rarely in excess of 1.5–2 times the usual daily maintenance.**

- Water and salt deficits must be replaced (A).
- IV or oral fluids that may have been given in another facility before assessment should be factored into calculation of deficit and repair (E).
- *If needed to restore peripheral circulation, volume expansion (resuscitation) should begin immediately with 0.9% saline (E).*
  - The volume and rate of administration depends on circulatory status and, where it is clinically indicated, the volume administered typically is 10–20 mL/kg over 1–2 h, and may be repeated, if necessary (E).
  - Use crystalloid not colloid (E). There are no data to support the use of colloid in preference to crystalloid in the treatment of DKA.
- *Subsequent fluid management (deficit replacement) should be with 0.9% saline or Ringer’s acetate for at least 4–6 h (C,E) (45, 49, 53–55).*
  - Thereafter, deficit replacement should be with a solution that has a tonicity equal to or greater than 0.45% saline with added potassium chloride, potassium phosphate, or potassium acetate (see below under potassium replacement) (C,E) (45, 49, 53, 56, 57).
  - The rate of fluid (IV and oral) should be calculated to rehydrate evenly over 48 h (C, E) (4, 45).
  - As the severity of dehydration may be difficult to determine and frequently is under- or over-estimated (C) (44), infuse fluid each day at a rate rarely in excess of 1.5–2 times the usual daily maintenance requirement based on age, weight, or body surface area (E) (4). See Table 3 for examples of calculations.

- In addition to clinical assessment of dehydration, calculation of effective osmolality may be valuable to guide fluid and electrolyte therapy (E).
- Urinary losses should not routinely be added to the calculation of replacement fluid, but may be necessary in rare circumstances (E).
- The sodium content of the fluid may need to be increased if measured serum sodium is low and does not rise appropriately as the plasma glucose concentration falls (C) (48, 58).
- The use of large amounts of 0.9% saline has been associated with the development of hyperchloremic metabolic acidosis (59, 60).

**Insulin therapy**

DKA is caused by a decrease in effective circulating insulin associated with increases in counter-regulatory hormones (glucagon, catecholamines, growth hormone, cortisol). Although rehydration alone causes some decrease in blood glucose concentration (61, 62), insulin therapy is essential to normalize blood glucose and suppress lipolysis and ketogenesis (A) (63).

**DKA is caused by either relative or absolute insulin deficiency. Begin with 0.1 U/kg/h. 1–2 h AFTER starting fluid replacement therapy.**

Extensive evidence indicates that ‘low dose’ IV insulin administration should be the standard of care (A) (64).

- Start insulin infusion 1–2 h after starting fluid replacement therapy, i.e., after the patient has received initial volume expansion (E,C) (65).
- Correction of insulin deficiency
  - Dose: 0.1 unit/kg/h (for example, one method is to dilute 50 units regular [soluble] insulin in 50 mL normal saline, 1 unit = 1 mL) (64, 66)
Route of administration IV (A)

An IV bolus is unnecessary (67), may increase the risk of cerebral edema (65), and should not be used at the start of therapy (C).

The dose of insulin should usually remain at 0.1 unit/kg/h at least until resolution of DKA (pH > 7.30, bicarbonate > 15 mmol/L and/or closure of the anion gap), which invariably takes longer than normalization of blood glucose concentrations (B) (68).

If the patient demonstrates marked sensitivity to insulin (e.g., some young children with DKA, patients with HHS, and some older children with established diabetes), the dose may be decreased to 0.05 unit/kg/h, or less, provided that metabolic acidosis continues to resolve.

During initial volume expansion the plasma glucose concentration falls steeply (61) (C). Thereafter, and after commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L/h, depending on the timing and amount of glucose administration (C) (69–75).

To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% glucose should be added to the IV fluid (e.g., 5% glucose in 0.45% saline) when the plasma glucose falls to approximately 14–17 mmol/L (250–300 mg/dL), or sooner if the rate of fall is precipitous (B).

If blood glucose falls very rapidly (>5 mmol/L/h) after initial fluid expansion consider adding glucose even before plasma glucose has decreased to 17 mmol/L (E).

If biochemical parameters of DKA (pH, anion gap) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin; e.g., infection, errors in insulin preparation (E).

In circumstances where continuous IV administration is not possible, hourly, or 2-hourly subcutaneous (SC) or intramuscular (IM) administration of a short- or rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion (C) (70, 76–79), but should not be used in subjects whose peripheral circulation is impaired (E).

If the blood glucose concentration decreases too quickly or too low before DKA has resolved, increase the amount of glucose administered. Do not decrease the insulin infusion.

Table 3. Shows an alternative example of fluid volumes for the subsequent phase of rehydration

<table>
<thead>
<tr>
<th>Body weight kg</th>
<th>Maintenance mL/24 h</th>
<th>mL/24 h</th>
<th>mL/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>325</td>
<td>530</td>
<td>22</td>
</tr>
<tr>
<td>5</td>
<td>405</td>
<td>650</td>
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<td>6</td>
<td>485</td>
<td>790</td>
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<tr>
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<td>2690</td>
<td>5380</td>
<td>224</td>
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</tbody>
</table>

After initial resuscitation, and assuming 10% dehydra
tion, the total amount of fluid should be given over 48 h. The Table gives volumes for maintenance and rehydration per 24 h and per hour. If fluid has been given for resuscitation, the volume should not be subtracted from the amount shown in the Table. Fluids given orally (when patient has improved) should be subtracted from the amount in the table. The Table is based on maintenance volumes according to Darrow (146). For body weights >32 kg, the volumes have been adjusted so as not to exceed twice the maintenance rate of fluid administration.

- Route of administration IV (A)
- An IV bolus is unnecessary (67), may increase the risk of cerebral edema (65), and should not be used at the start of therapy (C).
- The dose of insulin should usually remain at 0.1 unit/kg/h at least until resolution of DKA (pH > 7.30, bicarbonate > 15 mmol/L and/or closure of the anion gap), which invariably takes longer than normalization of blood glucose concentrations (B) (68).
Potassium replacement

Children with DKA suffer total body potassium deficits of the order of 3–6 mmol/kg (41, 42, 80–82). The major loss of potassium is from the intracellular pool. Intracellular potassium is depleted because of transcellular shifts of this ion caused by hypertonicity (increased plasma osmolality causes solvent drag in which water and potassium are drawn out of cells) and glycogenolysis and proteolysis secondary to insulin deficiency cause potassium efflux from cells. Potassium is lost from the body from vomiting and as a consequence of osmotic diuresis. Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. Thus, total body depletion of potassium occurs, but at presentation serum potassium levels may be normal, increased, or decreased (83). Renal dysfunction, by enhancing hyperglycemia and reducing potassium excretion, contributes to hyperkalemia (83). Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels (84). The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias.

![Even with normal or high levels of serum potassium at presentation, there is always a total body deficit of potassium. Begin with 40 mmol potassium/L in the infusate or 20 mmol potassium/L in the hypokalemic patient receiving fluid at a rate >10 mL/kg/h.]

- Replacement therapy is required regardless of the serum potassium concentration (A) (85, 86).
- If the patient is hypokalemic, start potassium replacement at the time of initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium after initial volume expansion and concurrent with starting insulin therapy. If the patient is hyperkalemic, defer potassium replacement therapy until urine output is documented (E).
- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia (C) (35, 36). Flattening of the T wave, widening of the QT interval, and the appearance of U waves indicate hypokalemia. Tall, peaked, symmetrical, T waves and shortening of the QT interval are signs of hyperkalemia.
- The starting potassium concentration in the infusate should be 40 mmol/L. Subsequent potassium replacement therapy should be based on serum potassium measurements (E).
  - If potassium is given with the initial rapid volume expansion, a concentration of 20 mmol/L should be used.
- Potassium phosphate may be used together with potassium chloride or acetate; e.g., 20 mmol/L potassium chloride and 20 mmol/L potassium phosphate or 20 mmol/L potassium phosphate and 20 mmol/L potassium acetate (C,E).
- Potassium replacement should continue throughout IV fluid therapy (E).
- The maximum recommended rate of IV potassium replacement is usually 0.5 mmol/kg/h (E).
- If hypokalemia persists despite maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.

Phosphate

Depletion of intracellular phosphate occurs in DKA and phosphate is lost as a result of osmotic diuresis (41, 42, 80). Plasma phosphate levels fall after starting treatment and this is exacerbated by insulin, which promotes entry of phosphate into cells (87–89). Total body phosphate depletion has been associated with a variety of metabolic disturbances (90–92). Clinically significant hypophosphatemia may occur if IV therapy without food intake is prolonged beyond 24 h (41, 42, 80).

- Prospective studies have not shown clinical benefit from phosphate replacement (A) (93–98).
- Severe hypophosphatemia in conjunction with unexplained weakness should be treated (E) (99).
- Administration of phosphate may induce hypocalcemia (C) (100, 101).
- Potassium phosphate salts may be safely used as an alternative to or combined with potassium chloride or acetate, provided that careful monitoring of serum calcium is performed to avoid hypocalcemia (C) (100, 101).

Acidosis

Severe acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate (A). Treatment of hypovolemia improves tissue perfusion and renal function increasing the excretion of organic acids.

Controlled trials have shown no clinical benefit from bicarbonate administration (B,C) (102–105). Bicarbonate therapy may cause paradoxical CNS acidosis (106, 107); rapid correction of acidosis with bicarbonate causes hypokalemia (106, 108, 109), and failure to account for the sodium being administered and appropriately reducing the NaCl concentration of the fluids can result in increasing osmolality (106). Nevertheless, there may be selected patients who may benefit from cautious alkali therapy. These include: patients with severe acidemia (arterial pH < 6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion, and patients with life-threatening hyperkalemia (E) (110).
There is no evidence that bicarbonate is either necessary or safe in DKA.

- Bicarbonate administration is not recommended unless the acidosis is profound and likely to affect adversely the action of adrenaline/epinephrine during resuscitation (A).
- If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 min (E).

Complications of therapy
- Inadequate rehydration
- Hypoglycemia
- Hypokalemia
- Hyperchloremic acidosis
- Cerebral edema

Introduction of oral fluids and transition to SC insulin injections
- Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis/ketosis may still be present) (E).
- When oral fluid is tolerated, IV fluid should be reduced (E).
- When ketoacidosis has resolved, oral intake is tolerated, and the change to SC insulin is planned, the most convenient time to change to SC insulin is just before a mealtime (E).
- To prevent rebound hyperglycemia the first SC injection should be given 15–30 min (with rapid-acting insulin) or 1–2 h (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed (E). With intermediate- or long-acting insulin, the overlap should be longer and the IV insulin gradually lowered. For example, for patients on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the insulin infusion is stopped the next morning (E).
- The dose and type of SC insulin should be according to local preferences and circumstances.
- After transitioning to SC insulin, frequent blood glucose monitoring is required to avoid marked hyperglycemia and hypoglycemia (E).

Morbidity and mortality
In national population studies, the mortality rate from DKA in children is 0.15–0.30% (C,B) (111, 112). Cerebral edema accounts for 60–90% of all DKA deaths (C,B) (50, 113). From 10% to 25% of survivors of cerebral edema have significant residual morbidity (C,B) (50, 113, 114).

Other rare causes of morbidity and mortality include:
- Hypokalemia
- Hyperkalemia
- Severe hypophosphatemia
- Hypoglycemia
- Other central nervous system complications (disseminated intravascular coagulation, dural sinus thrombosis, basilar artery thrombosis)
- Peripheral venous thrombosis
- Sepsis
- Rhinocerebral or pulmonary mucormycosis
- Aspiration pneumonia
- Pulmonary edema
- Adult respiratory distress syndrome (ARDS)
- Pneumothorax, pneumomediastinum and SC emphysema
- Rhabdomyolysis
- Acute renal failure
- Acute pancreatitis (115)

Cerebral edema
The incidence of cerebral edema in national population studies is 0.5–0.9% and the mortality rate is 21–24% (50, 113, 114).

Demographic factors that have been associated with an increased risk of cerebral edema include:
- Younger age (C) (116)
- New onset diabetes (B) (112) (C) (116)
- Longer duration of symptoms (C) (117)

These risk associations may reflect the greater likelihood of severe DKA.

In addition, epidemiological studies have identified several potential risk factors at diagnosis or during treatment of DKA. These include:
- Greater hypocapnia at presentation after adjusting for degree of acidosis (C) (50, 118)
- Increased serum urea nitrogen at presentation (C) (50)
- More severe acidosis at presentation (C) (65, 119)
- Bicarbonate treatment for correction of acidosis (C) (50, 120)
- An attenuated rise in measured serum sodium concentrations during therapy (C) (48–50)
- Greater volumes of fluid given in the first 4 h (65)
- Administration of insulin in the first hour of fluid treatment (65)

Warning signs and symptoms of cerebral edema include:
- Headache & slowing of heart rate
- Change in neurological status (restlessness, irritability, increased drowsiness, incontinence)
- Specific neurological signs (e.g., cranial nerve palsies)
- Rising blood pressure
- Decreased O₂ saturation
Clinically significant cerebral edema usually develops 4–12 h after treatment has started, but can occur before treatment has begun (50, 114, 121–124) or, uncommonly, may develop as late as 24–48 h after the start of treatment (C,B) (50, 116, 125). Symptoms and signs are variable. A method of clinical diagnosis based on bedside evaluation of neurological state is shown below (C) (126):

**Diagnostic criteria.**
- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne-Stokes respiration, apneusis)

**Major criteria.**
- Altered mentation/fluctuating level of consciousness
- Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state
- Age-inappropriate incontinence

**Minor criteria.**
- Vomiting
- Headache
- Lethargy or not easily arousable
- Diastolic blood pressure > 90 mm Hg
- Age <5 yr

One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4%.

A chart with the reference ranges for blood pressure and heart rate, which vary depending on height, weight, and gender, should be readily available, either in the patient’s chart or at the bedside.

Have mannitol or hypertonic saline at the bedside and the dose to be given calculated beforehand. In case of profound neurological symptoms, mannitol should be given immediately.

### Treatment of cerebral edema
- Initiate treatment as soon as the condition is suspected.
- Give mannitol 0.5–1 g/kg IV over 20 min and repeat if there is no initial response in 30 min to 2 h (C,E) (127–129).
- Reduce the rate of fluid administration by one-third.
- Hypertonic saline (3%), 5–10 mL/kg over 30 min, may be an alternative to mannitol, especially if there is no initial response to mannitol (C) (130, 131).
  - Mannitol or hypertonic saline should be available at the bedside.
- Elevate the head of the bed.
- Intubation may be necessary for the patient with impending respiratory failure, but aggressive hyperventilation (to a pCO₂ < 2.9 kPa [22 mm Hg]) has been associated with poor outcome and is not recommended (C) (132).
- After treatment for cerebral edema has been started, a cranial CT scan should be obtained to rule out other possible intracerebral causes of neurologic deterioration (≈10% of cases), especially thrombosis (133–136) or hemorrhage, which may benefit from specific therapy.

### Prevention of recurrent DKA
Management of an episode of DKA is not complete until its cause has been identified and an attempt made to treat it.

**All cases of recurrent DKA are preventable**

- Insulin omission, either inadvertently or deliberately, is the cause in most cases (C, A) (28, 30).
- The most common cause of DKA in insulin pump users is failure to take extra insulin with a pen or syringe when hyperglycemia and hyperketonemia or ketonuria occur (E).
- Home measurement of blood BOHB concentrations, when compared with urine ketone testing, decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) by the early identification and treatment of ketosis (137). Blood BOHB measurements may be especially valuable to prevent DKA in patients who use a pump because interrupted insulin delivery rapidly leads to ketosis (E).
  - There may be dissociation between urine ketone and serum BOHB concentrations, which may be increased to levels consistent with DKA when a urine ketone test is negative or shows only trace or small ketonuria (138).
- There usually is an important psychosocial reason for insulin omission.
  - an attempt to lose weight in an adolescent girl with an eating disorder,
  - a means of escaping an intolerable or abusive home situation,
  - clinical depression or other reason for inability of the patient to manage the diabetes unassisted.
- An infection that is not associated with vomiting and diarrhea is seldom the cause when the patient/family is properly educated in diabetes management and is receiving appropriate follow-up care by
a diabetes team with a 24-h telephone helpline (B) (139–141).

- A psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to development of DKA (E).
- Insulin omission can be prevented by schemes that provide education, psychosocial evaluation and treatment combined with adult supervision of insulin administration (B) (142).
  - Parents and patients should learn how to recognize and treat impending DKA with additional rapid- or short-acting insulin and oral fluids (E)
  - Patients should have access to a 24-h telephone helpline for emergency advice and treatment (B) (139)
  - When a responsible adult administers insulin there may be as much as a tenfold reduction in frequency of recurrent DKA (B) (142).

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.

The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See the Introduction of the ISPAD Clinical Practice Consensus Guidelines in Pediatric Diabetes 2006: 7: 341–342.

References


ISPAD Clinical Practice Consensus Guidelines 2006–2007

Management of children with diabetes requiring surgery


Peter Betts, Stuart J Brink, Peter GF Swift, Martin Silink, Joseph Wolfsdorf, Ragnar Hanas

Royal Infirmary, Leicester LE1 5WW, UK; Institute of Endocrinology, The Children's Hospital at Westmead, Sydney, Australia; Division of Endocrinology, Children's Hospital, Boston, MA, USA; Department of Pediatrics, Uddevalla Hospital, Uddevalla, Sweden

Corresponding author: Ragnar Hanas, MD, PhD
Department of Pediatrics
Uddevalla Hospital
S-451 80 Uddevalla
Sweden
e-mail: ragnar.hanas@vgregion.se


When children with diabetes require surgery or other procedures requiring sedation or anesthesia, optimal management should maintain adequate hydration and near to normal glycemia, while minimizing the risk of hypoglycemia. The stress of surgery may cause acute hyperglycemia, which increases the risk of postoperative infection (1, 2) (B).

Evidence-based controlled studies of perioperative care in children have not been conducted, but a review of management has recently been published in the anesthesiology literature (3); our current guidelines are consistent with the recommendations in that reference. Perioperative management of type 1 diabetes in adults is reviewed in a separate reference (4).

The current revised guidelines are based on those of the ISPAD Consensus Guidelines 2000 with additions and amendments from the Australian Clinical Practice Guidelines: Type 1 Diabetes in Children and Adolescents (5), and the Canadian Diabetes Association: Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada (6). As there are few relevant scientific papers on management during surgery, the recommendations are mostly based on expert consensus.

Glycemic targets for surgery

In the past, adults with diabetes have had an increased risk of postoperative wound infections (approximately 10-fold in a study of 23 000 patients in 1973) (7) (C). However, when blood glucose (BG) is maintained between 6.8 and 9.3 mmol/L (122–168 mg/dL), there is no difference in the risk of postoperative wound infections after major vascular surgery (8) (B). Maintaining BG levels below 11 mmol/L (200 mg/dL) for the first two postoperative days decreased the risk of sternal wound infections after heart surgery from 2.4 to 1.5% (9) (C). Improved postoperative glycemic control [plasma glucose levels of 4.5–6.0 mmol/L (~80–110 mg/dL)] using continuous intravenous (IV) insulin infusion significantly decreased mortality and morbidity in patients who required postoperative intensive care and mechanical ventilation after major surgery (10) (A). With this degree of tight glycemic control, 5.2% of subjects experienced hypoglycemic episodes compared with 0.8% in the control group; however, none of the episodes was severe (11) (A).

The safe implementation of such intensive glycemic control with a continuous IV insulin infusion requires a written protocol and staff training to ensure effectiveness and to minimize the risk of hypoglycemia.

To achieve optimal glycemic control, insulin dosage may need to be increased on the day of major surgery and for approximately 2 d after surgery. This is best achieved by continuous IV insulin infusion even after the resumption of oral feeding (12) (C).
Appropriate perioperative glycemic targets for brief and minor surgical procedures are less clear. To date, no intervention studies have assessed the impact of different BG levels on morbidity or mortality in these circumstances. However, a few studies in adults that compared different methods of achieving glycemic control during minor and moderate surgery did not show any adverse effects of maintaining perioperative glycemic levels between 5 and 11 mmol/L (~90–200 mg/dL) (13, 14) (A) (15) (B).

Because the data in adults show adverse effects of hyperglycemia, and support tight perioperative control of glucose in patients undergoing major surgery, it seems reasonable to aim for BG levels between 5 and 10 mmol/L (90–180 mg/dL) during surgical procedures in children (E).

The benefits of tight glycemic control must be weighed against the risk of perioperative hypoglycemia, which may not be recognized during anesthesia; however, this risk can be mitigated by frequent capillary BG monitoring.

Children with type 1 diabetes or type 2 treated with insulin requiring a major surgical procedure

- Must be admitted to hospital for general anesthesia (GA).
- Need insulin, even if fasting, to avoid ketoacidosis.
- Should receive a glucose infusion when fasting for more than 2 h before an anesthetic to prevent hypoglycemia.
- Should be carefully monitored via capillary BG measurement for hyperglycemia as stress caused by surgery may cause hyperglycemia and increased insulin requirements. Anesthesia may cause vasodilation and drop the blood pressure (BP). If there is an unexpected acute event (bleeding, drop in BP), normal saline 0.9% (NS) or Ringer’s lactate must be infused rapidly. In this case, potassium-containing fluids must not be infused rapidly.

Recommendations

(i) Whenever possible, surgery on children and adolescents with diabetes should be performed in centers with appropriate personnel and facilities to care for children with diabetes (E).
(ii) To ensure the highest levels of safety, careful liaison is required between surgical, anesthetic, and children’s diabetes care teams before admission to hospital for elective surgery and as soon as possible after admission for emergency surgery (E).

(iii) The elective surgery should be scheduled as the first case on a surgical list, preferably in the morning (E).
(iv) Centers performing surgical procedures on children with diabetes should have available written protocols for postoperative management of diabetes on the wards where children are admitted (E).
(v) IV access, infusion of glucose, and frequent BG monitoring is essential in all situations when general anesthesia is given. Glucose 5% is usually sufficient; glucose 10% may be necessary when there is a risk of hypoglycemia (E).
(vi) Elevated blood ketone (beta-hydroxybutyrate, BOHB) and BG concentrations require extra insulin and possibly IV fluids for correction. Such correction also requires the consideration of delay and rescheduling of an elective surgical procedure. A bedside meter for BOHB levels works well in a hospital setting and may suffice for monitoring (16) (B, E).

It is helpful in the management of children with diabetes undergoing surgery to divide procedures into two categories:

(i) **Minor surgery or procedures** that require a brief GA (or heavy sedation), usually of less than 1-h duration, and that should not have a major impact on glycemic control. Examples include endoscopies, jejunal biopsy, adenotonsillectomy, grommet insertion, or repeated short procedures such as in oncology or burns wards. The child will usually be discharged from hospital on the day of procedure.

(ii) **Major surgery** that requires more prolonged general GA is associated with greater risks of metabolic decompensation, and the child is unlikely to be discharged from hospital on the day of procedure.

Although the majority of surgical procedures are elective, both types of procedure may occur as emergencies.

**Elective surgery**

This should be performed when the diabetes is under the best possible control.

If glycemic control is uncertain or poor;

- Consider admission to hospital prior to surgery for assessment and stabilization of glycemic control.
- If control remains problematic;
- Surgery should be cancelled and rescheduled.
Scheduling of surgery

- Procedures are preferably scheduled first on surgical lists, ideally in the morning.
- Admit to hospital in the afternoon prior to surgery for major operations, but in appropriate circumstances, it is possible to admit early on the day of surgery for both minor and major operations (E).

Evening prior to surgery

- Frequent BG monitoring is important especially before meals and snacks and at bedtime (measure blood β-hydroxybutyrate and/or urinary ketone concentration if BG is >15–20 mmol/L) (E).
- Give the usual evening or bedtime insulin(s) and bedtime snack.
- Ketosis or severe hyperglycemia will necessitate correction, preferably by overnight IV insulin infusion, and might delay surgery.

**Major elective surgery (that requires, at a minimum, overnight hospital stay postoperatively)**

- Procedures preferably should be first on the list, ideally, in the morning.
- No solid food for at least 6 h prior to surgery.
- Clear fluids (including breast milk) may be allowed up to 4 h before surgery (check with anesthetist).
- Omit the usual morning insulin dose.
- At least 2 h before surgery start, an IV insulin infusion with glucose 5% (10% if there is concern about hypoglycemia) (see Table 1) (4) (E). If BG is high (>14 mmol/L, 250 mg/dL), use 0.5 NS or NS without glucose and increase insulin supply, but add 5% dextrose when BG falls below 14 mmol/L (250 mg/dL).
- Monitor BG hourly before surgery and every 30–60 min during the operation and until the child awakens from anesthesia (E).
- Monitor BG hourly for 4 h after surgery or for as long as the patient is receiving IV insulin.
- Aim to maintain BG between 5 and 10 mmol/L (90–180 mg/dL) and use correction rates of IV insulin during surgery (E). With IV insulin, a suitable ratio of insulin to glucose for prepubertal children is typically 1 unit per 5 g of IV glucose and for adolescents 1 unit per 3 g of IV glucose (3) (E). The dose is adjusted based on BG response.
- Once the patient is awake, it should be possible to adjust the IV insulin to maintain BG in the ideal range, 4.5–8 mmol/L (80–160 mg/dL), without excessive risk of hypoglycemia (Table 1) (E).
- When oral intake is not possible, the IV infusion should continue for as long as necessary.

**Minor surgery (where discharge home usually occurs later in the day of surgery)**

- Procedures preferably should be first on a surgical list, ideally in the morning.
- Aim for BG 5–10 mmol/L (90–180 mg/dL) during and after surgery (E).

Algorithms for different types of insulin regimens are suggested below. For more detail, see Rhodes et al. (3).

- No solid food for at least 6 h prior to GA.
- Clear fluids (including breast milk) are allowed up to 4 h before anesthesia (check with anesthetist).

Patients treated with twice daily insulin regimens

**Morning operations scheduled 08.00 h to 09.00 h.**

- At 07.00 h, give 50% of the usual morning dose of intermediate-acting insulin (NPH, lente). Omit the short- or rapid-acting insulin unless needed to correct hyperglycemia. Commence IV fluids (use glucose 5–10%, as necessary, to prevent hypoglycemia).
- After surgery, start oral intake or continue IV glucose depending on the child’s condition. Give small doses of short- or rapid-acting insulin (based on the child’s usual correction factor), if needed, to reduce hyperglycemia or to balance food intake. The dinner or evening dose of insulin is given as usual.
- Alternatively, IV insulin infusion may be started at 07.00 h (see below).
- If IV insulin has been used, continue the insulin infusion until lunch and then give a small dose of short- or rapid-acting insulin to last until the dinner or evening insulin dose.
- If the child is fully recovered, it may be possible to discharge the child from hospital later in the day.

**Afternoon operations scheduled for 13.00 h to 14.00 h.**

- At 07.00 h, give 50% of the usual dose of intermediate-acting insulin (NPH, lente) and the usual dose of short- or rapid-acting insulin.
- Alternatively, give 30–40% of the usual morning insulin dose of short- or rapid-acting insulin (but no intermediate- or long-acting insulin) and use an IV insulin infusion beginning at least 2 hours before surgery (Table 1).
- Allow the child to eat a light breakfast. Clear fluids may be allowed up to 4 hours before anesthesia. Start IV fluids (and IV insulin infusion, if applicable) 2 hours before surgery or no later than midday (Table 1).
- Thereafter, proceed as for morning operations (above).
Patients on basal-bolus insulin regimens (17)

Morning operations scheduled for 08.00 h to 09.00 h.
- Children on basal–bolus regimens benefit from not discontinuing their basal insulin before minor surgical procedures as IV insulin will disrupt their usual basal insulin supply when restarting subcutaneous (SC) insulin injections. This is particularly relevant for children requiring repeated procedures.
- Consider the need for reduction (by 20–30%) of the preceding evening long-acting insulin if there is a pattern of low BG values in the morning.
- If the general anesthesia is short (<1 h), give 50% of the usual morning dose of intermediate-acting insulin dose (NPH, lente) or 75–100% of the dose if the patient takes long-acting insulin (glargine, detemir, ultratard) at 07.00 h and commence IV fluids containing glucose 5% (10% if risk of hypoglycemia). Do not give short- or rapid-acting insulin in the morning unless necessary to correct hyperglycemia.
- Alternatively, IV regular insulin infusion may be started at breakfast time (omitting all types of morning SC insulin).
- Perform BG measurements before, during, and immediately after GA (at least hourly) and, if necessary, increase glucose concentration of IV fluids to 10% to prevent hypoglycemia. Adjust glucose infusion and insulin (by SC injection of rapid-acting insulin or IV infusion) to maintain perioperative BG in the range 5–10 mmol/L (E).
- In the postoperative period, supplemental mid-morning short-/rapid-acting insulin may be given if required (10–25% of total daily dose) and, when tolerated, a light meal.
- Later in the day, the aim is to resume normal meals and premeal insulin doses as soon as the child is able to tolerate oral feeds.

Afternoon operations scheduled for 13.00 h to 14.00 h.
- The patient is usually allowed to eat breakfast and drink clear fluids until 4 h preoperatively.
- At breakfast, give the usual dose of rapid-acting or 50–60% of the usual short-acting insulin and usual dose of basal intermediate- or long-acting insulin (if usually given at this time).
- Commence IV fluids containing glucose 5% (10% if risk of hypoglycemia) at a maintenance rate approximately ≥2 h after breakfast.

Table 1. Infusion guide for surgical procedures

<table>
<thead>
<tr>
<th>Maintenance fluid guide</th>
<th>Body weight</th>
<th>Fluid requirement/24 h</th>
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<tbody>
<tr>
<td>Glucose</td>
<td>3–9 kg</td>
<td>100 mL/kg</td>
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<tr>
<td>5% glucose; 10% if there is concern about hypoglycemia. If BG is high (&gt;14 mmol/L, 250 mg/dL), use 0.5 normal saline or normal saline without glucose and increase insulin supply but add 5% dextrose when BG falls below 14 mmol/L (250 mg/dL).</td>
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<tr>
<td>Sodium</td>
<td>10–20 kg</td>
<td>Add an additional 50 mL/kg</td>
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<tr>
<td>Saline 0.18–0.25% (~20–40 mmol Na/L) with glucose is widely used. There is evidence that the risk of acute hyponatremia may be increased when using hypotonic maintenance solutions (i.e., &lt;0.9% NaCl) in hospitalized children (18) (C). Many centers, therefore, use saline 0.45–0.9% (77–154 mmol Na/L). A compromise would be to give 0.45% saline with 5% glucose, carefully monitor electrolytes, and change to 0.9% saline if plasma-Na is falling.</td>
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<tr>
<td>20 kg</td>
<td>Add an additional 20 mL/kg</td>
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<tr>
<td>Max 2000 mL female, 2500 mL male</td>
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<tr>
<td>Insulin infusion</td>
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<tr>
<td>Add soluble insulin 50 units to 50 mL normal saline 0.9%, making a solution of 1 unit insulin/mL; attach to syringe pump and label clearly</td>
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<tr>
<td>Start infusion at 0.025 mL/kg/h (i.e., 0.025 U/kg/h) if blood glucose is &lt;6–7 mmol/L, 0.05 mL/kg/h if 8–12 mmol/L, 0.075 mL/kg/h between 12 and 15 mmol/L and 0.1 U/kg/h if &gt;15 mmol/L.</td>
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<tr>
<td>Aim to maintain BG between 5 and 10 mmol/L, depending of the type of surgery, by adjusting insulin infusion hourly</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BG must be measured at least hourly when the patient is on IV insulin.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do not stop the insulin infusion if BG &lt; 5–6 mmol/L (90 mg/dL) as this will cause rebound hyperglycemia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reduce the rate of infusion.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>The insulin infusion may be stopped temporarily if BG &lt;4 mmol/L (55 mg/dL) but only for 10–15 min.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BG, blood glucose.
• Measure capillary BG hourly and, if necessary, adjust the glucose concentration of IV fluids to prevent hypoglycemia. Give supplemental IV insulin, if needed, to keep perioperative BG concentrations in the target range.
• After surgery, IV insulin or additional short-/rapid-acting insulin may be required until normal eating is resumed.
• Later, if tolerated, resume meals and the child’s usual insulin at the appropriate times.

Patients on insulin pumps

The diabetes team should determine the approach depending on the individual patient and procedure.

• When a child on continuous subcutaneous insulin infusion (CSII) goes to the operating theatre, it is important to secure the SC infusion site to prevent dislodgement and interruption of insulin supply during the procedure.
• If the general anesthesia is short (approximately <1 h), the pump can be continued at the basal rate, keeping IV glucose 5% infusion at the maintenance rate (see below). Do not give a morning/meal bolus dose unless necessary to correct hyperglycemia. Monitor BG levels hourly preoperatively and at least half hourly during GA.
• When necessary, correction doses can be given with the pump preoperatively and postoperatively. Alternatively, give extra IV insulin to keep perioperative BG within target.
• A meal bolus is given when the patient is ready to eat.
• Alternatively, CSII can be discontinued and a continuous IV insulin and glucose infusion commenced, as described above, until feeding has been satisfactorily established.

Minor procedures requiring fasting – simplified procedure

For short procedures (with or without sedation or anesthesia) and when rapid recovery is anticipated, a simplified protocol may be formulated by personnel experienced in the anesthesia for children with diabetes and may include the following alternatives:

• Early morning procedure (e.g., 08.00 h to 09.00 h): delay insulin and food until immediately after completion of the procedure.
  Twice daily insulin: give 50% of usual insulin dose (NPH/lente and short-/rapid-acting) or give repeated small doses of short-/rapid-acting insulin (20–50% of morning short-/rapid-acting dose).
• Basal/bolus or CSII: give usual basal insulin/continue basal rate in the morning and, if needed, add small doses of rapid-acting insulin. Give bolus dose and food when the child can eat again.

Emergency surgery

| Diabetic ketoacidosis may present as an ‘acute abdomen’. | Acute illness may precipitate diabetic ketoacidosis (with severe abdominal pain). |

• No fluid food or medication by mouth; in some emergency situations the stomach must be emptied by a nasogastric tube.
• Secure IV access.
• Check weight, measure serum electrolytes, BG, blood gases, and blood β-hydroxybutyrate or urinary ketones before anesthesia.
• If ketoacidosis is present, follow protocol for diabetic ketoacidosis and delay surgery until circulating volume and electrolyte deficits are corrected.
• If there is no ketoacidosis, start IV fluids and insulin infusions as for elective surgery.

Type 2 diabetes

For those individuals who have type 2 diabetes and are treated with insulin, follow the insulin guidelines as for elective surgery, depending on type of insulin regimen.

Patients on oral treatment

Metformin: discontinue 24 h before the procedure for elective surgery, if <24 h since the last dose for emergent surgery, it is essential to maintain hydration with IV fluids before, during, and after surgery. Sulfonylureas or thiazolidinediones: stop for the day of surgery.

Monitor BG hourly and if greater than 10 mmol/L (180 mg/dL) treat with IV insulin, as for elective surgery, to normalize levels, or SC insulin if it is a minor procedure.

References

Microvascular and macrovascular complications

The long-term vascular complications of diabetes include retinopathy, nephropathy, neuropathy, and macrovascular disease. The outcomes are the following:

- Visual impairment and blindness due to diabetic retinopathy.
- Renal failure and hypertension due to diabetic nephropathy.
- Pain, paresthesiae, muscle weakness, and autonomic dysfunction due to diabetic neuropathy.
- Cardiac disease, peripheral vascular disease, and stroke due to macrovascular disease.

Clinically evident diabetes-related vascular complications should be rare in childhood and adolescence. However, early functional and structural abnormalities may be present a few years after the onset of the disease.

There has been a declining incidence of complications reported in many areas with specialized clinics (1–3). This has occurred over a period of time during which there have been major changes in diabetes management, identification of putative risk factors, and the advent of regular screening for complications. There is no evidence that this is a worldwide occurrence: in areas where health care is not optimal, a greater risk of complications will remain.

Interventional studies of intensive glycemic control

The Diabetes Control and Complications Trial (DCCT) was a multicenter, randomized controlled clinical trial involving 1441 patients with type 1 diabetes conducted in North America from 1983 to 1993 (4). At recruitment, 195 were pubertal adolescents (aged 13–17 yr): there were no children (5). After completion of the DCCT (a median of 7.4 yr in the adolescent group) and hence the end of randomization to the two treatment groups (intensive and conventional treatments), the Epidemiology of Diabetes Interventions and Complications (EDIC) study continued to follow patients (6). After 4 yr, there was no significant difference in hemoglobin A1c (HbA1c) between the former intensive and conventional treatment groups.

The DCCT provided unequivocal evidence that intensive diabetes treatment and improved glycemic control conferred a significant risk reduction for microvascular complications compared with conventional treatment (5) (A).

The EDIC study has shown that this positive effect continued after randomization, i.e., there was a memory effect of the improved glycemic control. In addition, it showed a positive effect of intensive therapy for reduction in macrovascular disease (7) (A).
In the adolescent cohort, intensive treatment compared with conventional treatment reduced the risk and progression of background retinopathy by 53%, clinical neuropathy by 60%, and microalbuminuria by 54%. The difference in HbA1c was 8.1 vs. 9.8%. The benefits of intensive therapy persisted in the former adolescent cohort during the EDIC study: the previously intensively managed group had 74% less retinopathy, 48% less microalbuminuria, and 85% less albuminuria (6).

Cardiovascular events were reduced by 50% in the previously intensively treated group compared with that of the control group during a mean 17 yr follow-up (7).

The DCCT confirmed that improved glycemic control may initially worsen diabetic retinopathy. However, within 1.5–3 yr, the advantage of intensive treatment is evident (8–10). In the DCCT, the long-term benefits of intensive insulin treatment greatly outweighed the risk of early retinal deterioration.

Ophthalmological monitoring is recommended before initiation of intensive treatment and at 3-month intervals for 6–12 months thereafter for patients with long-standing poor glycemic control, particularly if

### Table 1. Screening, risk factors, and interventions for vascular complications: the levels of evidence for risk factors and interventions pertaining to adult studies, except for improved glycemic control. For clarity, references for these evidence levels are included in the text

<table>
<thead>
<tr>
<th>When to commence screening?</th>
<th>Screening methods</th>
<th>Risk factors</th>
<th>Potential intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>Annually from age 11 yr with 2 yr of diabetes duration and from 9 yr with 5 yr of duration (E)</td>
<td>Fundal photography or mydriatic ophthalmoscopy (less sensitive) (E)</td>
<td>Hyperglycemia (A), high blood pressure (B), lipid abnormalities (B), and higher BMI (C)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>Annually from age 11 yr with 2 yr of diabetes duration and from 9 yr with 5 yr of duration (E)</td>
<td>Urinary albumin/creatinine ratio or first morning albumin concentration (E)</td>
<td>High blood pressure (B), lipid abnormalities (B), and smoking (B)</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>Unclear History and physical examination</td>
<td>Hyperglycemia (A) and higher BMI (C)</td>
<td>Improved glycemic control (A)</td>
</tr>
<tr>
<td>Macrovascular disease</td>
<td>After the age of 12 yr (E)</td>
<td>Lipid profile every 5 yr and blood pressure annually (E)</td>
<td>Hyperglycemia (A), high blood pressure (B), lipid abnormalities (B), higher BMI (B), and smoking (B)</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitors; AIIRA, angiotensin II receptor antagonists; BMI, body mass index.

In the adolescent cohort, intensive treatment compared with conventional treatment reduced the risk and progression of background retinopathy by 53%, clinical neuropathy by 60%, and microalbuminuria by 54%. The difference in HbA1c was 8.1 vs. 9.8%. The benefits of intensive therapy persisted in the former adolescent cohort during the EDIC study: the previously intensively managed group had 74% less retinopathy, 48% less microalbuminuria, and 85% less albuminuria (6).

Compared with conventional treatment, intensive treatment in the total age group reduced the risk of clinical neuropathy by 60%.

### Table 2. Target levels for different parameters to reduce the risk of microvascular and cardiovascular diseases in children and adolescents with type 1 diabetes; the levels of evidence pertain to adult studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Target level</th>
<th>Evidence grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin A1c</td>
<td>≤7.5% without severe hypoglycemia</td>
<td>A</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol</td>
<td>&lt;2.6 mmol/L</td>
<td>A</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol</td>
<td>&gt;1.1 mmol/L</td>
<td>C</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>&lt;1.7 mmol/L</td>
<td>C</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;90th percentile by age, sex, and height</td>
<td>C/B</td>
</tr>
<tr>
<td>Body mass index</td>
<td>&lt;95th percentile (non-obese)</td>
<td>E</td>
</tr>
<tr>
<td>Smoking</td>
<td>None</td>
<td>A</td>
</tr>
<tr>
<td>Physical activity</td>
<td>&gt;1 h of moderate physical activity daily</td>
<td>B</td>
</tr>
<tr>
<td>Sedentary activities</td>
<td>&lt;2 h daily</td>
<td>B</td>
</tr>
<tr>
<td>Healthy diet</td>
<td>Caloric intake appropriate for age and normal growth</td>
<td>E</td>
</tr>
<tr>
<td></td>
<td>Fat &lt;30% of caloric intake and saturated fat &lt;10% of caloric intake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fiber intake 25–35 g daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased intake of fresh fruit and vegetables</td>
<td></td>
</tr>
</tbody>
</table>
retinopathy severity is at or past the moderate non-proliferative stage at the time of intensification (E).

**Other risk factors for the development of complications**

Longer duration of diabetes, older age, and puberty are risk factors for complications (11). The prepubertal years of diabetes duration have a significantly lesser impact especially further from the onset of gonadarche (12) (B). For the same diabetes duration, age and puberty increase the risk for retinopathy and elevated albumin excretion rate (AER) (13) (B).

Smoking is associated with an increased risk of developing persistent microalbuminuria or macroalbuminuria (4, 14). The evidence for the effect of smoking on retinopathy is less clear. Type 1 diabetes and smoking interact to produce excess cardiovascular morbidity and mortality (15) (B).

Hypertension has a greater impact on cardiovascular disease (CVD) in diabetic patients than in non-diabetic individuals (16). Blood pressure control (<140/80 mmHg in adults) is effective in decreasing cardiovascular morbidity and mortality in diabetes (17) (A).

Dyslipoproteinemia is associated with microalbuminuria and retinopathy developments in the DCCT/EDIC (18, 19). This included higher total and low-density lipoprotein (LDL) cholesterol and higher triglyceride levels for microalbuminuria, as well as larger LDL particle size and apoprotein B in men (B).

Family history of complications increases the risk for nephropathy (20) and retinopathy (21) (B).

Higher body mass index (BMI) is a risk factor for retinopathy (22), neuropathy (23), microalbuminuria (24), and CVD (25) (B).

Lifestyle issues – sedentary men with diabetes have higher mortality than active individuals (26) (B).

**Diabetic retinopathy**

Adolescents have a higher risk of progression to vision-threatening retinopathy compared with adult patients with diabetes (27, 28). The progression may be rapid, especially in those with poor glycemic control (29). Hence, adolescence is the time when efforts should be directed to screening for early signs of diabetic retinopathy and modifiable risk factors. Regression of retinopathy can also occur (27, 28, 30).

**Progression of retinopathy**

Background retinopathy is characterized by microaneurysms specific to diabetic retinopathy; hemorrhages both pre-retinal and intraretinal; soft and hard exudates involving microinfarction and protein and lipid leakages, respectively; intraretinal microvascular abnormalities and dilatation; and constriction and tortuosity of vessels. Background retinopathy is not vision threatening and does not invariably progress to proliferative retinopathy.

Preproliferative retinopathy is characterized by vascular obstruction, progressive intraretinal microvascular abnormalities and infarctions of the retinal nerve fibers causing cotton wool spots.

Proliferative retinopathy is characterized by neovascularization in the retina and/or vitreous posterior surface. The vessels may rupture or bleed into the vitreoretinal space which is vision threatening. Encasement in connective tissue results in adhesions, which can cause hemorrhage and retinal detachment. High-risk characteristics for visual loss are the location and extent of neovascularization and signs of vitreous or pre-retinal hemorrhage (31).

Maculopathy is characterized by decreased vascular competence and microaneurysm formation, which produce exudation and swelling in the central retina.

**Assessment of retinopathy**

The most sensitive detection methods for retinopathy are stereoscopic fundal photography and fluorescein angiography. Seven-field stereoscopic fundus photography provides greater sensitivity for detecting both background and proliferative retinopathies compared

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**Table 3. Recommended threshold values for different parameters for intervention and the primary prevention; the levels of evidence pertain to adult studies**

<table>
<thead>
<tr>
<th>Threshold value</th>
<th>Type of intervention</th>
<th>Evidence grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure &gt; 90th percentile for age, gender, and height</td>
<td>Lifestyle intervention</td>
<td>B</td>
</tr>
<tr>
<td>Blood pressure &gt; 90th percentile despite lifestyle intervention</td>
<td>ACEI</td>
<td>E</td>
</tr>
<tr>
<td>Blood pressure &gt; 95th percentile</td>
<td>Lifestyle intervention and ACEI</td>
<td>A</td>
</tr>
<tr>
<td>LDL cholesterol &gt; 2.6 mmol/L</td>
<td>Dietary intervention</td>
<td>A</td>
</tr>
<tr>
<td>LDL cholesterol &gt; 3.4 mmol/L and one or more cardiovascular disease risk factors</td>
<td>Statins</td>
<td>A</td>
</tr>
</tbody>
</table>

ACEI, angiotensin-converting enzyme inhibitors; LDL, low-density lipoprotein.
Laser treatment for retinopathy

Once sight-threatening retinopathy has been detected, the treatment options are limited. Panretinal photocoagulation, commonly known as ‘laser therapy’, consists of multiple discrete outer retinal burns throughout the mid and far peripheral areas but sparing the central macula. It has been proven to reduce the progression of visual loss by more than 50% in patients with proliferative retinopathy (31, 35) (A). However, photocoagulation is not indicated for eyes with mild or moderate non-proliferative retinopathy (36). Side effects of treatment are decreased night and peripheral visions and subtle changes in color perception. Complications of laser therapy are vitreal and choroidal hemorrhages or visual sequelae of misplaced burns.

Diabetic nephropathy

Diabetic nephropathy is defined as persistent proteinuria greater than 500 mg/24 h or albuminuria greater than 300 mg/24 h and is usually associated with hypertension and a diminishing glomerular filtration rate (37). End-stage renal failure may occur many years later and requires dialysis or kidney transplantation. Diabetic nephropathy is a major cause of morbidity and mortality among young adults with type 1 diabetes (38, 39).

Assessment of incipient nephropathy

The first clinical sign is microalbuminuria. This is defined (37) as any of those below:

- AER between 20 and 200 μg/min or AER 30–300 mg/24 h in 24-h urine collections.
- Albumin concentration (AC) 30–300 mg/L (in early morning urine sample).
- Albumin/creatinine ratio (ACR) 2.5–25 mg/mmol or 30–300 mg/g (spot urine) in males and 3.5–25 mg/mmol in females (because of lower creatinine excretion).

Other definitions have also been used in longitudinal studies.

Microalbuminuria is confirmed by finding two or all three samples abnormal over a period of 3–6 months.

Persistent microalbuminuria has been shown to predict the progression to end-stage renal failure (2, 30, 31, 40–42) and is associated with an increased risk of macrovascular disease (43, 44) (B).

An increase of AER within the microalbuminuric range identifies patients at risk of progression to renal damage (24, 45, 46) (B). Loss of nocturnal dipping on 24-h blood pressure monitoring is an early marker of diabetic renal disease preceding microalbuminuria (47). Microalbuminuria can also regress (48), especially in adolescents (24, 49). Progression to microalbuminuria is preceded by renal hypertrophy (50) (B).

Confounders – exercise increases the AER in non-diabetic individual and increases it more markedly during diabetes. Even moderate exercise may interfere with the interpretation of data (37). For interpretation of persistently elevated AER values, especially in children with short diabetes duration, it is essential to exclude other causes of albuminuria such as immunoglobulin A or other types of nephritis common in childhood.

In an incident cohort, after 6 yr of duration, early elevation of AER (greater than 7.5 μg/min) was detected in 5% of children younger than 11 yr and 5% of prepubertal children: no microalbuminuria was detected. This compared with early elevation of AER in 25% adolescents older than 11 yr and 26% of pubertal adolescents. (13). Screening from age 11 yr with 2 yr of diabetes duration or from 9 yr with 5 yr of duration will capture most retinopathy developing in children and adolescents (E).

Antihypertensive treatment for prevention of nephropathy

Effective antihypertensive therapy in patients with nephropathy prolongs the time to end-stage renal disease (51) (B). A recent prospective study has shown improved prognosis of renal function from 5 to 7 yr from onset of nephropathy to a median of 21.7 yr (52), predominantly due to aggressive antihypertensive treatment, with smaller contributions from improved glycemic control and smoking cessation (B).
Blood pressure values between the 90th and 95th percentiles are defined as prehypertension (53, 54). Protocols and reference values for 24-h ambulatory blood pressure monitoring in children have also been published (21, 47). Angiotensin-converting enzyme inhibitors (ACEI) are recommended for use in children and adolescents with hypertension (55). They have been effective and safe in children in short-term studies (28, 56). The clinical beneficial effect of angiotensin II receptor antagonists (AIIRA) in hypertension is similar to that observed with ACEI but have not been used extensively in children.

ACEI and AIIRA reduce progression from microalbuminuria to macroalbuminuria and increase the regression rate to normoalbuminuria (57) (A). For those with microalbuminuria, ACEI and AIIRA reduce the doubling of serum creatinine. While ACEI reduces all-cause mortality, AIIRA use was associated with higher all-cause mortality compared with placebo (A).

Despite the above evidence mainly in adults, there are still some concerns regarding the use of ACEI in protecting long-term renal function in young individuals without hypertension. In meta-analysis of individual patient data, the beneficial effects were more modest in those with the lowest levels of microalbuminuria (58) (A). Young people with microalbuminuria would potentially be taking ACEI for decades. Side effects include cough, hyperkalaemia, headache, and impotence (57). Furthermore, an increase in major congenital malformations has recently been reported after first-trimester exposure to ACEI but not with other antihypertensive agents in non-diabetic women (59).

**Diabetic neuropathy**

Diabetes can affect the somatic and autonomic nervous systems. The somatic neuropathies associated with diabetes fall into the following two broad categories:

- **Focal neuropathies** include mononeuropathies such as carpal tunnel syndrome, palsy of the peroneal nerve, palsy of the third cranial nerve, and proximal nerve conditions (e.g., diabetic amyotrophy).

- **Diabetic sensorimotor polyneuropathy** is the most common generalized neuropathy, and, for this reason, the simplified term “diabetic neuropathy” is commonly used. It is a polyneuropathy because of the diffuse damage to all peripheral nerve fibers – motor, sensory, and autonomic. Such damage occurs insidiously and progressively and is characterized at first by sensory loss and later by loss of motor function, in a stocking and glove distribution.

- **Autonomic neuropathy** can cause postural hypotension, vomiting, diarrhea, bladder paresis, impotence, sweating abnormalities, impaired light reflex, impotence, and retrograde ejaculation. Abnormal heart rate responses and prolonged QT intervals have been associated with increased risk of sudden death (60).

**Assessment of neuropathy**

Clinical assessment involves history taking – especially of numbness, persistent pain, or paresthesia – and physical examination of ankle reflexes and vibration and light touch sensations (by conventional neurological examination or by graduated monofilaments). Autonomic nerve tests include heart rate response to deep breathing, standing from a lying position, Valsalva maneuver, heart rate variation at rest, QT interval, postural changes in blood pressure, and pupillary responses to light and dark adaptation. Peripheral nerve tests include quantitating vibration and thermal discrimination thresholds and nerve conduction. These are mostly used in research settings. Age- and gender-specific normal ranges need to be applied where relevant when interpreting results.

Nerve function test abnormalities have not decreased in an adolescent population in which retinopathy and microalbuminuria have decreased over the same time: peripheral nerve abnormalities actually increased (3). This is probably due to the increasing BMI which has occurred over the same time (B).

**Macrovacular disease**

The mortality and morbidity of CVD are markedly increased in diabetic individuals compared with that in non-diabetic population (61) (B).

Hypertension has a greater impact on CVD in diabetic patients than in non-diabetic individuals (16). Blood pressure control (<140/80 mmHg in adults) reduces cardiovascular morbidity and mortality in diabetes (17) (A).

A family history of early CVD (before 55 yr of age), lipid disturbances, type 2 diabetes, hypertension (10), and smoking place the individual with diabetes at higher risk (B).

Atherosclerosis starts in childhood and adolescence as shown by intima-media thickness of the carotids and aorta (62) and silent coronary atherosclerosis measured by intravascular ultrasound in young adults with childhood-onset diabetes (9) (B). Silent coronary atherosclerosis (9) and cardiovascular events (7) are strongly associated with poor glycemic control (A).

Cholesterol plays an important role in the initiation and progression of atherosclerosis (53). Well-controlled type 1 diabetes is not associated with gross blood lipid disturbances, but more advanced lipoprotein subclass examinations reveal atherogenic profiles (18). Poor glycemic control was associated with a potentially more atherogenic lipoprotein profile (63).
Changes in lipids associated with increased cardiovascular risk are also associated with central obesity in type 1 diabetes (as well as type 2 diabetes) (64). Individuals with type 1 diabetes are as much at risk for hypercholesterolemia as the non-diabetic population. The prevalence approached 50% of young adults in one study (65). The prevalence of elevated non-high-density lipoprotein cholesterol was 25% in a study of individuals younger than 21 yr of age with type 1 diabetes (66).

In adults, statins are effective in the primary and secondary preventions of major cardiovascular events, stroke, and limb revascularization in patients with diabetes (67) (A). The Heart Protection Study was a 5-yr interventional study of 5963 patients with diabetes, in which 10% had type 1 diabetes. This effect was independent of glycemic control and cholesterol levels.

Short-term trials have shown that simvastatin, lovastatin, and pravastatin are effective and safe in children and adolescents (68–70). No significant side effects were observed in terms of growth, pubertal Tanner grading, testicular volume, menarche, endocrine function parameters, or liver or muscle enzymes. The efficacy and safety of statins in children with type 1 diabetes still need to be determined in randomized trials, as does the age at which treatment should be initiated. Special attention should be paid to symptoms associated with muscles and connective tissues, as there is an increased risk of rhabdomyolysis (71).

Screening for and prevention of complications

Screening for diabetes complications aims to detect subclinical complications, which may be treated to delay progression to clinical disease.

- Improvement in glycemic control will reduce the risk for onset and progression of diabetes vascular complications (A).
- Initial eye examination should occur shortly after diagnosis to detect cataracts or major refractive errors that require treatment for binocular vision (E).
- Screening for retinopathy and microalbuminuria should start from 11 yr with 2 yr of diabetes duration and from 9 yr with 5 yr of duration and after 2 yr of diabetes duration in an adolescent (13) (E).
- Minimum assessment for retinopathy should be by ophthalmoscopy through dilated pupils by an experienced observer (E).
- The frequency of retinopathy screening in general should occur annually but should be more frequently if there are high-risk features for visual loss. For those with duration less than 10 yr, minimal background retinopathy on fundal photography, and reasonable glycemic control, biennial assessment by fundal photography, can occur (27) (E).
- Laser treatment reduces the rate of visual loss for vision-threatening retinopathy (A).
- Annual screening for microalbuminuria should be undertaken by any of the methods below (13):
  - First morning urine samples (AC).
  - Spot urine: ACR.
  - Timed urine collections (AER). Timed overnight urine collections are generally easier for adolescents and are less subject to the effects of exercise and posture.
  - Because of biological variability, two of three consecutive collections should be used as evidence of microalbuminuria. Confounders are exercise and menstrual bleeding.
  - Abnormal screening tests should be repeated, as microalbuminuria may disappear and not be persistent.
  - When persistent microalbuminuria is confirmed, screening for retinopathy, neuropathy, and lipid abnormalities is also recommended (E).
  - ACEI are recommended for use in children with hypertension (55) (E). They have been effective and safe in children in short-term studies (28, 56) but are not safe during pregnancy.
  - ACEI or AIIRA agents should be used in patients with persistent microalbuminuria to prevent progression to proteinuria (E) in adolescents.
  - Blood pressure should be measured at least annually. (E) Confirmation of hypertension may be assisted by 24-h ambulatory blood pressure measurements (E).
  - Blood pressure values should be compared with age-appropriate centile charts (55). Blood pressure should be maintained at less than the 95th centile for age as in all children with hypertension (55) (E).
  - Screening for fasting blood lipids should be performed soon after diagnosis (when diabetes stabilized) in all children with type 1 diabetes older than 12 yr (E). If normal results are obtained, this should be repeated every 5 yr. If there is a family history of hypercholesterolemia, early CVD, or if the family history is unknown, screening should start at 2 yr of age (8) (E).
  - Target level for LDL cholesterol should be lower than 2.6 mmol/L. If interventions to improve metabolic control and dietary changes cannot help reach the target level, statins should be considered, although long-term safety is not established (55) (E).
  - Cessation of smoking/never initiating smoking will reduce progression of microalbuminuria and CVD (52) (B).

References


ISPAD Clinical Practice Consensus Guidelines 2006–2007

Other complications and associated conditions


Olga Kordonouri, Ann M Maguire, Mikael Knip, Edith Schober, Renata Lorini, Reinhard W Holl, and Kim C Donaghue

Impaired growth and development

Monitoring of growth and development and the use of percentile charts is a crucial element in the care of children and adolescents with diabetes.

Increased height at diagnosis of type 1 diabetes mellitus (T1DM) has been frequently reported (1–4). The precise mechanism for this and whether or not this increased height is maintained is unclear. Some studies report that poorly controlled patients show a decrease in height standard deviation score over the next few years, while better controlled patients maintain their height advantage (3, 4). Others have not shown this relationship with diabetic control (1).

In a recent study from Australia, children treated with modern regimens (diagnosed after 1990) maintained their increased height better than children diagnosed before 1991 (2). Although the median haemoglobin A1c (HbA1c) did not differ significantly, those diagnosed after 1990 had a significantly higher number of insulin injections per day.

Poor gain of height and weight, hepatomegaly (non-alcoholic steatosis hepatitis) and late pubertal development (Mauriac’s syndrome) have been reported in children with persistently poorly controlled diabetes. Insulin insufficiency, coeliac disease and other gastrointestinal disorders should be considered in this setting. Growth hormone (GH) levels are high in poorly controlled diabetes mellitus, but insulin-like growth factor (IGF)-1 levels are decreased. Thus, GH therapy is contraindicated in the children with poorly controlled T1DM. The possible uses of IGF-1 in T1DM are the subject of considerable investigation.

Once the child or adolescent has reached a satisfactory weight after diagnosis, excessive weight gain may indicate high energy intake, and this may be related to excessive exogenous insulin. Excessive weight gain is more common during and after puberty (5). The Diabetes Control and Complications Trial and other studies have reported increased weight gain as a side-effect of intensive insulin therapy with improved metabolic control (6–8). As obesity is a modifiable cardiovascular risk factor, careful monitoring and management of weight gain should be emphasized in diabetes care. Girls seem to be more at risk of being overweight and developing eating disorders as well. In association with increased weight is the risk of hyperandrogenism and polycystic ovarian syndrome (9).

It is important to remember to reduce the dose of insulin when pubertal development is completed because increased doses of insulin are required during the adolescent growth spurt.

Associated autoimmune conditions

Islet cell antibodies (ICA) as well as autoantibodies to insulin, the 65-kDa isoform of glutamic acid decarboxylase (GAD65) and/or the protein tyrosine phosphatase-related molecules islet antigen-2 (IA-2) (ICA512) and IA-2β (phogrin) are observed in the overwhelming majority of children en route to clinical T1DM (10, 11).

A higher proportion of children with T1DM also have other detectable organ-specific autoantibodies.
[e.g., thyroid, tissue transglutaminase (tTG), adrenal] than children from the general population.

Family members of children with diabetes are more likely to have autoantibodies and other manifestations of autoimmune disease than the general population (12, 13).

Hypothyroidism

Primary hypothyroidism caused by autoimmune thyroiditis occurs in approximately 3–8% (14) or 0.9 per 100 patient years (15) of children and adolescents with diabetes. Antithyroid antibodies have been shown to occur during the first years of diabetes in up to 25% of individuals with diabetes (16–20) and to be predictive for the development of clinical or compensated hypothyroidism (20). Thyroid antibodies are observed more frequently in girls than in boys, often emerging along with pubertal maturation (20).

Clinical features may include the presence of a painless goitre, increased weight gain, retarded growth, tiredness, lethargy, cold intolerance and bradycardia. Diabetic control may not be significantly affected.

Hypothyroidism is confirmed by demonstrating a low free thyroxine and a raised thyroid stimulating hormone (TSH) concentration. Compensated hypothyroidism may be detected in an asymptomatic individual with a normal thyroxine level and a modestly increased TSH.

The treatment is based on replacement with oral L-thyroxine (T4) sufficient to normalize TSH levels and usually this allows regression of the goitre if present.

Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism in association with diabetes (18, 21), but still more common than in the general population. It may be because of Grave’s disease or the hyperthyroid phase of Hashimoto’s thyroiditis.

Hyperthyroidism should be considered if there is unexplained difficulty in maintaining glycaemic control, weight loss without loss of appetite, agitation, tachycardia, tremor, heat intolerance, thyroid enlargement or characteristic eye signs.

Treatment of hyperthyroidism consists of antithyroid drugs such as carbimazole or propylthiouracil. Beta-adrenergic blocking drugs are helpful during the acute phase of thyrotoxicosis to control tachycardia and agitation. Treatment options for persistent or recurrent hyperthyroidism include surgery or radioactive iodine.

Coeliac disease

Coeliac disease occurs in 1–10% of children and adolescents with diabetes or 0.7 per 100 patient years (15, 22–30). Coeliac disease is often asymptomatic (26, 28, 31) and not necessarily associated with poor growth or poor diabetic control (although it should be excluded in such situations). Any child with gastrointestinal signs or symptoms including diarrhoea, abdominal pain, flatulence, dyspeptic symptoms, recurrent aphthous ulceration, unexplained poor growth or anaemia should be investigated. Undiagnosed coeliac disease has also been associated with increased frequency of hypoglycaemic episodes and a progressive reduction in insulin requirement over a 12-month period prior to diagnosis (32).

The screening for coeliac disease is based on the detection of immunoglobulin (Ig)A antiendomysial (EMA) antibodies and IgA antibodies against tTG. Although experience with a recently introduced assay for tTG antibodies suggests that tTG may be more sensitive than EMA (91 vs. 86%), the latter is slightly more specific for coeliac disease (100 vs. 96%) (33). Antigliadin antibodies might be more sensitive for coeliac disease than EMA and tTG antibodies in very young children (<2 yr), although their specificity remains modest.

IgA deficiency (which is present in 1:500 individuals) should be excluded when screening for coeliac disease by measuring the total IgA level. IgA antibodies may not be detected in IgA deficiency, resulting in a false-negative test. If the child is IgA deficient, then IgG antigliadin and IgG tTG antibodies should be used for screening (34). It is important to remember that coeliac disease is more common in those with IgA deficiency than in the general population (1.7% compared with 0.25%) (35).

In the presence of an elevated antibody level, a small bowel biopsy is needed to confirm the diagnosis of coeliac disease (Marsh classification) (36).

A gluten-free diet normalizes the bowel mucosa and frequently leads to disappearance of antibodies but may not necessarily lead to improved metabolic control (37).

In an asymptomatic child with proven coeliac disease, a gluten-free diet can be considered justified with the aim of reducing the risk of subsequent gastrointestinal malignancy and conditions associated with subclinical malabsorption (i.e., osteoporosis and iron deficiency). While this is a prudent recommendation, there is no literature documenting the long-term benefit of a gluten-free diet in asymptomatic children diagnosed with coeliac disease by routine screening. One paediatric case series has shown an increase in height for weight following the introduction of a gluten-free diet (31). Another demonstrated a non-significant increase in body mass index and a non-significant reduction in HbA1c (38). Some studies have demonstrated short-term benefits in other patient groups in terms of improved well-being and increased bone mineral density (39–41).
The risk of coeliac disease is negatively and independently associated with age at the onset of diabetes, with a threefold higher risk being seen in children aged < 4 yr than in those aged > 9 yr, and girls have a higher risk of having both diseases (42).

Children with proven coeliac disease should be referred to a paediatric gastroenterologist and receive support from a paediatric dietician with experience of gluten-free diets.

Vitiligo

Vitiligo is an acquired pigmented disorder characterized by a loss of melanocytes, resulting in white spots or leucoderma (43). It is a common autoimmune condition associated with T1DM and is present in about 6% of diabetic children (44). Treatment is difficult and multiple therapies have been tried with little success.

Primary adrenal insufficiency
(Addison’s disease)

Up to 2% of patients with T1DM have detectable antidiadrenal autoantibodies (16, 45, 46). Addison’s disease is occasionally associated with T1DM in the autoimmune polyglandular syndromes (APS I and II). APS I is associated with mucocutaneous candidiasis and hypoparathyroidism and is caused by a mutation in the autoimmune regulator gene on chromosome 21q22.3 (47, 48). APS II is more common in adults but is also seen in children in association with autoimmune thyroiditis (49).

The condition is suspected by the clinical picture of frequent hypoglycaemia, unexplained decrease in insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatraemia and hyperkalaemia.

The diagnosis is based on the demonstration of a low cortisol response to an adrenocorticotropic hormone (ACTH) test. Treatment with a glucocorticoid is urgent and lifelong. In some cases, the therapy has to be supplemented with a mineralocorticoid.

In asymptomatic children with positive adrenal antibodies detected on routine screening, a rising ACTH level suggests a failing adrenal cortex and the development of primary adrenal insufficiency.

The immunodysregulation polyendocrinopathy X-linked syndrome is another rare disorder associated with diabetes in early infancy, severe enteropathy and autoimmune symptoms because of a clear genetic defect (FOX-P3) (50).

Lipodystrophy (lipoatrophy and lipohypertrophy)

Lipoatrophy is now seen infrequently with the use of human insulin. Recent case reports have described lipoatrophy also occurring in patients on insulin pumps treated with lispro insulin, and in patients treated with Lantus (51–53), it is still a rare side-effect.

Lipohypertrophy is a frequent complication of insulin therapy. It has been found in up to 48% of those with T1DM and has associated with higher HbA1c, more injections and longer duration but not the needle length (54–56).

Non-rotation of injection sites has been consistently reported as an independent risk factor for lipohypertrophy (54, 56). Not only is it unsightly but insulin may also be absorbed erratically and unpredictably from these areas (57, 58).

Necrobiosis lipoidica diabeticum

These are well-circumscribed, raised, reddish lesions sometimes progressing to central ulceration, usually seen in the pretibial region. The reported prevalence in children varies from 0.06 to 10% (44, 59). The aetiology is not clearly understood. Necrobiosis lipoidica diabeticum has been associated with underlying microvascular complications (60, 61). A wide variety of treatments have been used over the years in adults including topical, systemic or intra-lesional steroids, aspirin, cyclosporin, mycophenolate, becaplermin, excision and grafting, laser surgery, hyperbaric oxygen, topical granulocyte–macrophage colony-stimulating factor and photochemotherapy with topical psoralen and ultraviolet-A radiation (62–69). None has been proven useful in controlled clinical trials, and many of these treatments have significant side-effects.

Limited joint mobility

Limited joint mobility (LJM) is the earliest clinically apparent long-term complication of T1DM in childhood. It is a bilateral painless, but obvious, contracture of the finger joints and large joints, associated with tight waxy skin. Following its initial description associated with short stature, and early microvascular complications, it was recognized to be a common feature of both T1DM and type 2 diabetes mellitus, with a wide range of limitation, affecting ~30% of youngsters and correlating with diminished stature (70, 71). Changes begin in the metacarpophalangeal and proximal interphalangeal joints of the fifth finger and extend radially with involvement of the distal interphalangeal joints as well. Involvement of larger joints includes not particularly the wrist and elbow but also the ankles and cervical and thoracolumbar spine. The limitation is only mildly disabling even when severe.

A simple examination method is to have the patient attempt to approximate palmar surfaces of the interphalangeal joints (72). Passive examination is
essential to confirm that inability to do so is because of LJM. With rare exception, LJM appears after the age of 10 yr. The interval between the detection of mild LJM and the progression to moderate or severe changes in those who progress beyond mild changes, ranges from a few months to 4 yr, following which stabilization occurs (71).

Skin biopsy specimens have shown active fibroblasts and extensive collagen polymerization in the rough endoplasmic reticulum (73). The biochemical basis for LJM is likely glycation of protein with the formation of advanced glycation end products. This results in increased stiffness of the periartricular and skin collagen with decreased range of motion. Fluorescence of skin collagen, reflecting the accumulation of stable end products of the glycation reaction, with increased cross-linking, dehydration and condensation of collagen, increases linearly with age but with abnormal rapidity in T1DM, correlating with the presence of retinopathy, nephropathy and LJM (74).

LJM is associated with a three- to fourfold risk for retinopathy, nephropathy and neuropathy (71, 75, 76). Although cross-sectional studies showed no relationship to diabetes control as measured by HbA1c, longitudinal study of average HbA1c from onset of diabetes showed that for every unit increase in average HbA1c, there was an approximately 46% increase in the risk of developing LJM (77).

There has been a more than fourfold reduction in frequency of LJM between the mid-1970s and the mid-1990s in children (78) and a lesser decline in adults (79), with a marked decrease in severity in the fewer children who are affected, most likely the result of improved glucose control during this era.

Oedema

Generalized oedema because of water retention is a rare complication of insulin therapy. Oedema may be seen during establishment of improved glycaemic control after prolonged periods of poor metabolic control, particularly if there has been significant omission of insulin (80, 81). The oedema spontaneously resolves over a period of days to weeks with continued good glycaemic control.

in the absence of thyroid autoantibodies. More frequent assessment is indicated otherwise (E).

Screening for coeliac disease should be carried out at the time of diagnosis and every second year thereafter. More frequent assessment is indicated if the clinical situation suggests the possibility of coeliac disease or the child has a first-degree relative with coeliac disease (E).

Children with T1DM detected to have coeliac disease on routine screening should be referred to a paediatric gastroenterologist and on confirmation of the diagnosis should receive support from a paediatric dietitian with experience of gluten-free diets (E).

Routine clinical examination should be undertaken for skin and joint changes. Regular screening by laboratory or radiological methods is not recommended. There is no established therapeutic inter- vention for lipodystrophy, necrobiosis lipoidica or LJM (E).

Recommendations

Monitoring of growth and physical development and the use of growth charts is an essential element in the continuous care of children and adolescents with T1DM (E).

Screening of thyroid function by analysing circulating TSH and antibodies is recommended at the diagnosis of diabetes and, thereafter, every second year in asymptomatic individuals without goitre or

References


