

GLOBAL IDF/ISPAD GUIDELINE FOR  
**DIABETES** IN **CHILDHOOD**  
AND **ADOLESCENCE**



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# Preface

In 2007, the total child population of the world (0-14 years) was estimated to be 1.8 billion, of whom 0.02% have diabetes. This means that approximately 440,000 children around the world have diabetes with 70,000 new cases diagnosed each year (1). This very large number of children needs help to survive with injections of insulin to live a full life without restrictions or disabling complications and without being stigmatised for their diabetes.

Even today, almost a century after the discovery of insulin, the most common cause of death in a child with diabetes from a global perspective is lack of access to insulin (2). Many children die before their diabetes is diagnosed. It is therefore of utmost importance that all forces unite to ensure that no child should die from diabetes. A promising initiative has been taken by IDF/Life for a Child ([www.lifeforachild.org](http://www.lifeforachild.org)) in collaboration with ISPAD and other organisations (Access to Essential Diabetes Medicines for Children in the Developing World and Changing Diabetes in Children). Several major companies that produce insulin and other diabetes supplies have pledged their support, and the numbers of children provided with insulin will according to plan increase to approximately 30,000 by 2015. ISPAD has pledged structural support and assistance in the training of paediatricians and healthcare professionals in childhood and adolescent diabetes through its membership network.

In 1993, members of International Society for Pediatric and Adolescent Diabetes (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 have not been reached by 2000, we feel that slowly, by small steps, the worldwide care of children with diabetes is improving.

ISPAD published its first set of guidelines in 1995 (3) and its second in 2000 (4). Since then, the acceptance of intensive therapy, also for very young children, has increased around the world. Insulin pump usage has risen in all age groups in countries where this treatment modality can be afforded. Intensive therapy requires better and more comprehensive education for it to be successful. The ISPAD Consensus Guidelines 2000 edition has been translated into 11 languages, indicating the need for a truly international document. The 3<sup>rd</sup> edition of ISPAD’s Consensus Guidelines, now called “Clinical Practice Consensus Guidelines” was released in 2009 (5).

The current guideline has been developed by ISPAD and the International Diabetes Federation. While there is

extensive evidence on the optimal management of type 1 diabetes, unfortunately such care is not reaching many people who could benefit.

Guidelines are one part of a process which seeks to address those problems. In 2005 the first IDF Global Guideline for Type 2 Diabetes was developed. This presented a unique challenge as we tried to develop a guideline that is sensitive to resource and cost-effectiveness issues. Many national guidelines address one group of people with diabetes in the context of one healthcare system, with one level of national and healthcare resources. This is not true in the global context where, although every healthcare system seems to be short of resources, the funding and expertise available for healthcare vary widely between countries and even between localities.

Despite the challenges, we feel that we found an approach which is at least partially successful in addressing this issue which we termed ‘Levels of care’ (see next page).

We hope the guidelines will be widely consulted and will be used to:

- ▶ improve awareness among governments, state health care 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 care givers in managing children and adolescents with diabetes in a prompt, safe, consistent, equitable, standardised manner in accordance with the current views of experts in the field.

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## Levels of care

All people with diabetes should have access to cost-effective evidence-based care. It is recognised that in many parts of the world the implementation of particular standards of care is limited by lack of resources. This guideline provides a practical approach in children and adolescents to promote the implementation of cost-effective evidence-based care in settings between which resources vary widely. The United Nations has defined childhood to include ages up until 18 years of age, and this is the age group that these guidelines cover.

The approach adopted has been to advise on three levels of care:

- › **Recommended care** is evidence-based care which is cost-effective in most nations with a well developed service base, and with healthcare funding systems consuming a significant part of national wealth.

Recommended care should be available to all people with diabetes and the aim of any healthcare system should be to achieve this level of care. However, in recognition of the considerable variations in resources throughout the world, other levels of care are described which acknowledge low and high resource situations.

- › **Limited care** is the lowest level of care that anyone with diabetes should receive. It acknowledges that standard medical resources and fully-trained health professionals are often unavailable in poorly funded healthcare systems. Nevertheless this level of care aims to achieve with limited and cost-effective resources a high proportion of what can be achieved by Recommended care. Only low cost or high cost-effectiveness interventions are included at this level.
- › **Comprehensive care** includes the most up-to-date and complete range of health technologies that can be offered to people with diabetes, with the aim of achieving best possible outcomes. However the evidence-base supporting the use of some of these expensive or new technologies is relatively weak.

### Summary of the Levels of Care structure

- › **Recommended care:** Evidence-based care, cost-effective in most nations with a well developed service base and with healthcare funding systems consuming a significant part of their national wealth.
- › **Limited care:** Care that seeks to achieve the major objectives of diabetes management, but is provided in healthcare settings with very limited resources - drugs, personnel, technologies and procedures.
- › **Comprehensive care:** Care with some evidence-base that is provided in healthcare settings with considerable resources.

# Methodology

The methodology used in the development of this guideline is not described in detail here, as it broadly follows the principles described in IDF Guide for Guidelines ([www.idf.org](http://www.idf.org)).

The development of this guideline was overseen by a Guideline Development Group of clinicians and researchers with expertise in the topic and guideline development. The evidence used in developing this guideline included reports from key meta-analyses, evidence-based reviews, clinical trials, cohort studies, epidemiological studies, animal and basic science studies, position statements and guidelines.

The guideline is based on the ISPAD Clinical Practice Consensus Guidelines Compendium 2009 (*Pediatr Diabetes* 2009; 10 [Suppl 12]: 1-210).

All chapters have been rewritten to fit the IDF Guidelines format by the head author of that group, with the assistance of the editors. Those drafts were then reviewed by the members of the group who originally worked on each section, and amendments made according to their suggestions.

The draft guideline was sent out for wider consultation to IDF member associations and ISPAD members. Each comment received was reviewed by the Guideline Development Group and changes were made where the evidence-base confirmed these to be appropriate.

The guideline is being made available in paper form, and on the IDF website. IDF will consider the need for review of this guideline after 3-5 years.

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## Duality of interest:

Members of the Guideline Development Group and consultants have declared dualities of interest in respect of medical conditions, and in relationships with commercial enterprises, governments, and non-governmental organisations. No fees were paid to Group members in connection with the preparation of this Guideline. No external funding was received for the preparation of this Guideline.

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# 01

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DEFINITION,  
EPIDEMIOLOGY  
AND CLASSIFICATION

## Recommendations

### Recommended care

1. The usual presenting symptoms of diabetes in children are: polyuria, polydipsia, blurring of vision, and weight loss, in association with glycosuria and ketonuria.
2. A marked elevation of the blood glucose level confirms the diagnosis. If ketones are present in blood or urine, treatment is urgent, and the child should be referred the same day to avoid the development of ketoacidosis.
3. The diagnosis of diabetes should not be based on a single plasma glucose concentration. Diagnosis may require continued observation with fasting and/or 2 hour post-prandial blood glucose levels and/or an OGTT.
4. An OGTT should not be performed if diabetes can be diagnosed using fasting, random or post-prandial criteria as excessive hyperglycaemia can result.
5. Once the diagnosis of diabetes has been made, it is safest to start the child on insulin to prevent progression to ketoacidosis especially if ketones are present in urine or blood. Subsequent diagnosis of the type of diabetes can be made after metabolic stability has been achieved.

### Type 1 diabetes

- › Individuals have an absolute deficiency of insulin secretion and are prone to ketoacidosis.
- › Most cases are primarily due to T-cell mediated pancreatic islet  $\beta$ -cell destruction, which occurs at a variable rate. There are usually serological markers of an autoimmune pathologic process, including islet cell antibodies (ICA), insulin autoantibodies (IAA), glutamic acid decarboxylase (GAD), the insulinoma-associated 2 molecule (IA-2) and zinc transporter 8 (ZnT-8).
- › The date of onset of type 1 diabetes is defined as the date of first insulin injection.

### *Classifying types of diabetes*

- › The differentiation between type 1, type 2 and monogenic diabetes has important implications for both therapeutic decisions and educational approaches.
- › The possibility of other types of diabetes should be considered in the child who has:
  - › An autosomal dominant family history of diabetes.
  - › Associated conditions such as deafness, optic atrophy or syndromic features.
  - › Marked insulin resistance or requiring little insulin outside the partial remission phase.
  - › A history of exposure to drugs known to be toxic to beta cells or cause insulin resistance.
  - › Genetic testing for neonatal diabetes (onset < 6 months of age) should be performed as transition from insulin to sulphonylurea treatment may be possible.

### Limited care

1. If blood glucose testing is unavailable, diabetes can be provisionally diagnosed by the finding of high levels of glucose and ketones in the urine.
2. The date of onset of diabetes is defined as the date of first insulin injection or when the clinical diagnosis is made.
3. In geographical areas where type 1 diabetes occurs with lower incidence, providers should be aware that there is a higher rate of diabetic ketoacidosis at presentation.

## Comprehensive care

1. The principles as for Recommended care.
2.  $\beta$ -cell autoantibodies and C-peptide should be performed at diagnosis. These investigations should also be considered in children presenting with stress hyperglycaemia.
3. When the clinical presentation is typical of type 1 diabetes (often associated with DKA) but antibodies are absent, then the diabetes is classified as Type 1B (idiopathic), particularly if the patient is of African or Asian ancestry. Other forms of diabetes should also be considered as shown in Table 3.
4. If monogenic diabetes is suspected, then genetic testing should be undertaken because it may influence management.

## Rationale

**Table 1. Criteria for the diagnosis of diabetes mellitus\***

1. Symptoms of diabetes plus casual plasma glucose concentration  $\geq 11.1$  mmol/l (200 mg/dl)\*.  
Casual is defined as any time of day without regard to time since last meal.
- or**
2. Fasting plasma glucose  $\geq 7.0$  mmol/l ( $\geq 126$  mg/dl) †.  
Fasting is defined as no caloric intake for at least 8 hours.
- or**
3. 2 hour postload glucose  $\geq 11.1$  mmol/l ( $\geq 200$  mg/dl) during an OGTT.  
The test should be performed as described by WHO (1), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g (2).
  4.  $HbA_{1c} \geq 6.5$ .  
However, there are difficulties with assay standardisation and individual variation in the relationship between blood glucose and  $HbA_{1c}$ , which may outweigh the convenience of this test.
- \* Corresponding values are  $\geq 10.0$  mmol/l for venous whole blood and  $\geq 11.1$  mmol/l for capillary whole blood and  
†  $\geq 6.3$  mmol/l for both venous and capillary whole blood

*Prediabetes includes Impaired Glucose Tolerance (IGT) and Impaired Fasting Glycaemia (IFG)*

- ▶ IGT: 2 hour postload plasma glucose 7.8-11.1 mmol/l (140-199 mg/dl)
- ▶ IFG: plasma glucose 5.6-6.9 mmol/l (100-125 mg/dl)

## Evidence-base

### *Epidemiology of diabetes*

In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, although less than half of individuals with type 1 diabetes are diagnosed before the age of 15 years (3,4). Type 2 diabetes is becoming more common in adolescents, particularly in the peripubertal period, and accounts for a significant proportion of youth onset diabetes in certain at risk populations (5,6).

Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations. Annual incidence rates for childhood type 1 diabetes show the highest incidence of 64 per 100,000/year in Finland (7) and the lowest of 0.1 per 100,000/year in China and Venezuela (8). A well documented rise in the incidence has been noted in many countries, and in some reports there has been a disproportionately greater increase in those under the age of 5 years (8,9). A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months (10,11).

Susceptibility to autoimmune type 1 diabetes is associated with multiple genetic loci. HLA genes having the strongest known association and account for approximately 40% of familial clustering of type 1 diabetes. Linkage to specific combinations of alleles at the DRB1, DQA1 and DQB1 loci, with both susceptible or protective haplotypes (12,13).

The environmental triggers (chemical and/or viral) which initiate pancreatic beta cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms (14,15). Enterovirus infection has been associated with development of diabetes associated autoantibodies in some populations (16,17) and enteroviruses have been detected in the islets of individuals with diabetes (18-20).

Despite familial aggregation, which accounts for approximately 10% of cases of type 1 diabetes (21), there is no recognisable pattern of inheritance. The risk of diabetes to an identical twin of a patient with type 1 diabetes is about 36% (22); for a sibling the risk is approximately 4% by age 20 years (23,24) and 9.6% by age 60 years (25); compared with 0.5% for the general population. Type 1 diabetes is 2-3 times more common in the offspring of diabetic men (3.6-8.5%) compared with diabetic women (1.3-3.6%) (24,26-31).

In Africa and South Asia, atypical forms of diabetes also occur in older children, adolescents, and young adults. These include ketosis-prone atypical diabetes, malnutrition-related diabetes, and fibrocalculous pancreatic disease (32,33).

#### *Cystic fibrosis and diabetes*

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

Poorly controlled diabetes will interfere with immune responses to infection and promote catabolism. Insulin therapy initially may only be needed during respiratory infections due to acute or chronic infective episodes, but eventually insulin therapy is usually necessary. Initially insulin doses are small (supplemental rather than total insulin replacement). Early insulin therapy prior to symptoms of hyperglycaemia may provide metabolic effects beneficial to growth, weight and pulmonary function (34,35).

#### *Drug induced diabetes*

In oncology, protocols which employ L-asparaginase, high dose glucocorticoids, cyclosporin or tacrolimus (FK506) may be associated with diabetes. L-asparaginase usually causes a reversible form of diabetes (36). Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction (37). 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 (38,39).

Diabetes can also be induced by the use of atypical antipsychotics including olanzapine (Zyprexa), risperidol (Risperdal), quetiapine (Seroquel), and ziprasidone (Geodon), in association with weight gain (40).

#### *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 (41). The reported incidence of progression to overt diabetes varies from 0% to 32% (42-47). Children with incidental hyperglycaemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness (45). Islet cell antibodies and insulin autoantibody testing had a high positive and negative predictive value for type 1 diabetes in children with stress hyperglycaemia (45).

## Consideration

Diabetes in childhood is a diagnostic specialty with a wide range of different types of diabetes, see Tables 2 and 3. The monogenic forms of diabetes have been traditionally numbered according to the order by which the responsible gene was identified. It is now preferred to describe monogenic diabetes by the gene responsible (e.g. HNF1B-MODY, rather than MODY 4).

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

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

**Table 3. Aetiological Classification of Disorders of Glycaemia (modified ADA and WHO)**

<b>I. Type 1</b> β-cell destruction, usually leading to absolute insulin deficiency a. Autoimmune b. Idiopathic	
<b>II. Type 2</b> May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance	
<b>III. Other specific types</b>	
<b>A. Monogenic defects of β-cell function</b> <ol style="list-style-type: none"> <li>1. HNF-1α MODY (MODY 3),</li> <li>2. Glucokinase MODY (MODY 2)</li> <li>3. HNF-4 α MODY (MODY 1),</li> <li>4. HNF-1β MODY (MODY 4)</li> <li>5. WFS1 Wolfram syndrome</li> <li>6. Neonatal diabetes</li> <li>7. Other MODY</li> </ol>	<b>F. Drug- or chemical-induced</b> <ol style="list-style-type: none"> <li>1. Glucocorticoids</li> <li>2. Vacor</li> <li>3. Pentamidine</li> <li>4. Nicotinic acid</li> <li>5. Thyroid hormone</li> <li>6. Diazoxide</li> <li>7. β-adrenergic agonists</li> <li>8. Thiazides</li> <li>9. Dilantin</li> <li>10. α-Interferon</li> <li>11. Others</li> </ol>
<b>B. Mitochondrial diabetes</b>	
<b>C. Genetic defects in insulin action</b> <ol style="list-style-type: none"> <li>1. Type A insulin resistance</li> <li>2. Leprechaunism</li> <li>3. Rabson-Mendenhall syndrome</li> <li>4. Lipotrophic diabetes</li> <li>5. Others</li> </ol>	<b>G. Infections</b> <ol style="list-style-type: none"> <li>1. Congenital rubella</li> <li>2. Cytomegalovirus</li> <li>3. Others</li> </ol>

<p><b>D. Diseases of the exocrine pancreas</b></p> <ol style="list-style-type: none"> <li>1. Fibrocalculous pancreatopathy</li> <li>2. Pancreatitis</li> <li>3. Trauma / pancreatectomy</li> <li>4. Neoplasia</li> <li>5. Cystic fibrosis</li> <li>6. Haemochromatosis</li> <li>7. Others</li> </ol>	<p><b>H. Uncommon forms of immune-mediated diabetes</b></p> <ol style="list-style-type: none"> <li>1. Insulin autoimmune syndrome (antibodies not insulin)</li> <li>2. Anti-insulin receptor antibodies</li> <li>3. "Stiff-man" syndrome</li> <li>4. Others</li> </ol>
<p><b>E. Endocrinopathies</b></p> <ol style="list-style-type: none"> <li>1. Acromegaly</li> <li>2. Cushing syndrome</li> <li>3. Glucagonoma</li> <li>4. Pheochromocytoma</li> <li>5. Hyperthyroidism</li> <li>6. Somatostatinoma</li> <li>7. Others</li> </ol>	<p><b>I. Other genetic syndromes sometimes associated with diabetes</b></p> <ol style="list-style-type: none"> <li>1. Down syndrome</li> <li>2. Klinefelter's syndrome</li> <li>3. Turner syndrome</li> <li>4. Friedreich's ataxia</li> <li>5. Huntington's chorea</li> <li>6. Laurence-Moon-Biedl syndrome</li> <li>7. Myotonic dystrophy</li> <li>8. Porphyria</li> <li>9. Prader-Willi syndrome</li> <li>10. Others</li> </ol>
<p><b>IV. Gestational diabetes</b></p>	

## Implementation

Insulin therapy should be instituted in most cases as soon as the diagnosis of diabetes is made to prevent development of life-threatening ketoacidosis. Classification of diabetes requires assessment of clinical characteristics and biochemical tests. Some forms need genetic testing.

## Evaluation

Regular monitoring of clinical course of diabetes and review of the classification is required for optimal management and outcomes.

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# 02

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PHASES  
OF TYPE 1  
DIABETES

## Recommendations

### Recommended care

#### 1. Preclinical type 1 diabetes

Preclinical diabetes refers to the months or years preceding the clinical presentation of type 1 diabetes when antibodies can be detected as markers of beta cell autoimmunity:

- › Islet cell autoantibodies (ICA).
- › Glutamic acid decarboxylase autoantibodies (65K GAD isoform).
- › IA2 (also known as ICA 512 or tyrosine phosphatase) autoantibodies.
- › Insulin autoantibodies (IAA).

#### 2. Presentation of type 1 diabetes

- › Clinical presentation of diabetes can vary from non-emergency presentations (e.g. polydipsia, polyuria, weight loss, enuresis) to severe dehydration, shock and diabetic ketoacidosis.
- › Prospective follow-up of high-risk subjects shows that diagnosis of type 1 diabetes can be made in asymptomatic individuals in the majority of cases.
- › Some children have a rapid onset of symptoms and present within days in diabetic ketoacidosis; others have a slow onset over several months.
- › 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. Hands should be washed since glucose from sweets or fruit can give a false high reading.

#### 3. 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.
- › Chronic weight loss or failure to gain weight in a growing child.
- › Irritability and decreasing school performance.
- › Recurrent skin infections.

#### 4. Emergency presentations

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

- › Severe dehydration.
- › Frequent vomiting.
- › Continuing polyuria despite the presence of dehydration.
- › Weight loss due to fluid loss and loss of muscle and fat.
- › Vomiting and abdominal pain, which may be misdiagnosed as gastroenteritis.
- › Flushed cheeks due to the ketoacidosis.
- › Acetone detected on the breath.
- › Hyperventilation of diabetic ketoacidosis (Kussmaul respiration) is characterised 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).
- › Decreased peripheral circulation with rapid pulse rate.
- › Hypotension and shock with peripheral cyanosis (a late sign and rare in children with diabetic ketoacidosis).

## 5. Diagnostic difficulties leading to late diagnosis

The following situations may result in a late diagnosis of diabetic ketoacidosis:

- 】 Very young children may present in severe ketoacidosis because of a more rapid onset of severe insulin deficiency 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 diabetic ketoacidosis).
- 】 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, since 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 specialised services is essential.

## 6. Partial remission or Honeymoon phase in type 1 diabetes

- 】 In many children and adolescents, insulin requirements decrease transiently following initiation of insulin treatment. This has been strictly defined as insulin requirements of less than 0.5 units per kg of body weight per day with an HbA<sub>1c</sub> < 7%.
- 】 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.
- 】 Ketoacidosis at presentation and young age reduce the likelihood of a remission phase.
- 】 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. They should be advised that as the child comes out of this phase an increasing amount of insulin is needed.

## 7. 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 may be accelerated by an intercurrent illness.

- 】 At present exogenous insulin replacement remains the only form of replacement therapy for children and adolescents with type 1 diabetes.

## Limited care

1. The principles as for Recommended care.
2. The child with newly diagnosed type 1 diabetes needs to be cared for in a centre with maximal expertise. At diagnosis, insulin treatment may need to be initiated prior to this transfer.
3. Patient meters can be used when suspecting diabetes, but a high blood glucose reading should be verified by a laboratory analysis when possible.

## Comprehensive care

1. Neither screening of any population nor intervention in the preclinical phase should occur outside the context of defined clinical studies.
2. Individuals who screen positive for genetic or immunological markers of type 1 diabetes should have access to appropriate counselling and to centres participating in intervention and other defined studies.
3. Intervention studies should be registered as part of an international network of investigation and information about ongoing studies should be readily available.

## Rationale

- › Health care professionals should be aware that there are no interventions shown to delay or prevent the onset of type 1 diabetes.
- › Past and current natural history studies have taught us more about the prediabetes phase. In addition to immunological and genetic markers, the risk of progression to type 1 diabetes can be further refined by measurement of insulin release in response to an intravenous glucose load (IVGTT).
- › After clinical diagnosis of diabetes, there is still some functioning pancreas or  $\beta$ -cell function. This remaining function results in the partial remission phase, during which exogenous insulin requirements can be reduced substantially.
- › Clinical diabetes intervention aims to preserve beta cell function. This can be measured by C-peptide production in response to stimuli, as C-peptide is secreted by the  $\beta$ -cell at the same time as insulin.

## Evidence-base

*Prediabetes: Risks of progression to type 1 diabetes*  
Genetic markers conferring increased or decreased risk include:

- a) HLA DR3 - DQA1\*0501 - DQB1\* 0201 (susceptible haplotype).
- b) HLA DR4 - DQA1\*0301 - DQB1\* 0302 (susceptible haplotype).
- c) HLA DR2 - DQA1\*0102 - DQB1\* 0602 (protective haplotype).

Islet autoimmunity can be transient and one raised islet antibody alone has little prognostic value.[1-3]. If an individual is under 45 years 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 years [4].

- › Two or more islet antibodies raised without impaired first phase insulin release confer a 25-50% risk over the next 5 years [5,6].

## Prevention of diabetes

There have been two major trials to delay or prevent diabetes which have not been successful. The European Nicotinamide Diabetes Intervention Trial (ENDIT), a multinational quasi-randomised placebo-controlled, double blinded intervention study, demonstrated that nicotinamide did not delay or prevent the onset of type 1 diabetes in high-risk first-degree relatives [7]. The second was the National Institute of Health Diabetes Prevention Trials (DPT) that demonstrated in randomised controlled trials that neither low dose subcutaneous nor oral insulin therapy delayed or prevented the onset of clinical diabetes in high-risk first-degree relatives [4, 8].

## Consideration

- › Diabetes should be considered when elevation of blood glucose by whatever measurement is found. Patient meters can be used when suspecting diabetes, but a high blood glucose reading should be verified by a laboratory analysis when possible.
- › There are no interventions shown to delay or prevent the onset of type 1 diabetes.

## Implementation

Neither screening nor intervention in the preclinical phase should occur outside the context of defined clinical studies.

## Evaluation

Families should be aware of the increased risk for diabetes in other family members so that treatment can be instituted early before ketoacidosis develops.

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03

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TYPE 2  
DIABETES

## Recommendations

### Recommended care

**Diagnosis: The clinical diagnosis of type 2 diabetes in an asymptomatic individual requires at least two abnormal glucose values, diagnostic of diabetes, on two separate days.**

1. In areas where, and age groups when, type 1 diabetes predominates diabetes auto-antibody testings should be considered:
  - 】 When the clinical diagnosis of type 2 diabetes is made, because islet cell autoimmunity may be present in otherwise “typical” type 2 diabetes:
    - 】 Antibodies will indicate an earlier need for insulin.
    - 】 Antibodies will indicate the need to check for thyroid autoimmunity and to consider other associated autoimmune disorders.
    - 】 Antibodies will alter disease prediction in other family members.
  - 】 Especially in overweight/obese children > 13 years of age with a clinical picture of type 1 diabetes (weight loss, ketosis/ketoacidosis), some of whom may have type 2 diabetes.
2. In regions where type 2 diabetes predominates diabetes autoantibody testing should be considered:
  - 】 In children of any age with a clinical picture of type 1 diabetes (weight loss, ketosis/ketoacidosis), some of whom will have autoimmune type 1 diabetes
3. C-peptide measurements, with or without diabetes autoantibody determination, should be considered in all children, especially those > 13 years of age with the initial clinical diagnosis of type 2 diabetes who have worsening levels of control on oral agents to confirm those requiring insulin therapy and to reconsider the diabetes classification.

### Initial medical treatment

4. Initial treatment is determined by symptoms, severity of hyperglycaemia, and presence or absence of ketosis/ketoacidosis. As in type 1 diabetes, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and appropriate treatment.
  - 】 Insulin may be required for initial metabolic stabilisation if significant hyperglycaemia and ketosis is present, even in the absence of ketoacidosis
5. After initial stabilisation, if insulin is not required or when insulin is eliminated, blood glucose testing may be decreased to twice a day, fasting and 2-3 hours after the largest meal.
6. Lifestyle changes in diet and exercise are essential to increase insulin sensitivity and should be recommended for all individuals with type 2 diabetes, other treatment may be added to this required treatment.
7. Metformin is the initial pharmacologic treatment of choice, if metabolically stable
  - 】 Begin with 250 mg daily for 3-4 days, if tolerated, increase to 250 mg twice a day, titrate in this manner over 3-4 weeks until the maximal dose of 1,000 mg twice a day is reached.
  - 】 If insulin was initially required, transition from insulin to metformin can usually be made over 2-6 weeks beginning when metabolic stability is reached, usually 1-2 weeks after diagnosis.
  - 】 Transition can usually be achieved safely by titration of the metformin as in number one above. Insulin may be decreased by 10-20% each time the metformin is increased with a goal of eliminating insulin therapy.
  - 】 If at any time during the insulin taper, the glucose values rise into the impaired range, the taper should be slowed until values become stable.



## Rationale

Type 2 diabetes in children and adolescents is becoming an increasingly important public health concern throughout the world (1-12). Because of the relatively recent recognition of the problem in this age group, many children with new onset type 2 diabetes may be misclassified as having type 1 diabetes. Conversely, as the population becomes heavier, overweight adolescents with autoimmune diabetes may be misdiagnosed as having type 2 diabetes. Type 2 diabetes is often associated with risk factors for CVD that may be present at the time of diagnosis, making normalisation of blood glucose levels and diagnosis and treatment of hypertension and dyslipidaemia important (13). Data from diverse populations suggest that preadolescent children are unlikely to have type 2 diabetes, even if obese (7), and that overweight adolescents from all ethnic/racial groups can have either type 1 diabetes or type 2 diabetes (4,7).

These considerations make thoughtful determination of diabetes classification and treatment essential (14).

## Evidence-base

### *Type 2 diabetes*

Type 2 diabetes occurs when insulin secretion is inadequate to meet the increased demand posed by insulin resistance (15). Thus, type 2 diabetes is commonly associated with other features of the insulin resistance syndrome (hyperlipidaemia, hypertension, acanthosis nigricans, ovarian hyperandrogenism, NAFLD) (16). Insulin secretion depends on disease status and duration, and can vary from delayed but markedly elevated in response to a glucose challenge, to absolutely diminished (15). Adults with symptoms have 50% reduction at the time of diagnosis, and may become insulin dependent within a few years (17).

Type 2 diabetes occurs in youth of all backgrounds, but is more common in those of black African descent, native North American, Central and South American, Asian, South Asian (Indian Peninsula), and Native Pacific islanders. In the US and the EU, type 2 diabetes makes up < 10-40% of diabetes in adolescents, except for Native Americans, where 76% of young onset diabetes is type 2 diabetes; in Hong Kong it is 37%, in Taiwan 50% and nearly 60% in Japan (7,8,11). In youth in North America and Europe, type 2 diabetes is associated with a BMI above 85th percentile for age and sex. In Japan, however, ~30% of type 2 diabetes are not obese (12), in Asian Indian urban children, half of those with type 2 diabetes had normal weight (< 120% ideal for height), and half of Taiwanese children with type 2 diabetes were not obese (8). As in type 1 diabetes, type 2 diabetes may present in asymptomatic individuals during medical, school, or

sports examinations (16), or with the classic symptoms of diabetes and ketosis/ketoacidosis (one third or more of newly diagnosed patients) (18). Occasionally severe dehydration (hyperosmolar hyperglycaemic coma, hypokalaemia) is present at presentation, which can be fatal (19).

It is important to remember that if hyperglycaemia (blood glucose > 11.1mmol/L, or > 200 mg/dl) is recognised in an asymptomatic individual, in the absence of unequivocal hyperglycaemia, the diagnosis of diabetes must be confirmed, with a second documentation of blood glucose > 11.1mmol/L on a subsequent day (20,21).

### *Uncertainties of diagnostic classification:*

**Distinguishing type 2 diabetes from type 1 diabetes and monogenic diabetes.** The clinician is obliged to weigh the evidence in each individual patient to distinguish between type 1 diabetes and type 2 diabetes, and less commonly, from monogenic diabetes. This difficulty occurs because with increasing obesity in childhood, as many as 15-25% of newly diagnosed type 1 diabetes (or monogenic diabetes) patients may be obese and misclassified as type 2 diabetes, and because of the significant number of paediatric patients with type 2 diabetes demonstrating ketonuria or ketoacidosis at diagnosis (18), an incorrect diagnosis of type 1 diabetes can be made. Type 2 diabetes is common in the general adult population, with a random family history of ~15% or greater in many populations, reducing the specificity of a positive family history for both type 2 diabetes and monogenic diabetes. In addition, there is considerable overlap in insulin or C-peptide measurements between type 1 diabetes, type 2 diabetes and MODY at onset of diabetes and over the first year or so. This overlap is due to the recovery phase of autoimmune-mediated type 1 diabetes (the honeymoon) and degree of glucotoxicity/lipotoxicity impairing insulin secretion at the time of testing in both type 1 diabetes and type 2 diabetes. Finally, the insulin resistance of obesity raises initial residual C-peptide levels in obese adolescents with type 1 diabetes. Such measurements are thus relatively valueless in the acute phase. The role of C-peptide is more helpful in established diabetes as persistent elevation of C-peptide above the level of normal would be unusual in type 1 diabetes after 12-24 months.

The correct classification of diabetes is important for treatment decisions and family counselling. Youth and adults in US and Europe who are clinically diagnosed with type 2 diabetes are found to have type 1 diabetes-associated auto-antibodies in 10-40% of cases, including many who are not receiving insulin one year after diagnosis (22, 23). B-cell function is significantly less in antibody positive individuals, the most dramatic difference being reported in younger adult patients (25-34 years), resulting in more rapid development of insulin dependence, usually by 3 years duration (22). Antibodies will also indicate the need

to monitor for thyroid autoimmunity and to consider other autoimmune disorders associated with type 1 diabetes. Family risk for diabetes will also differ for type 1 diabetes vs. type 2 diabetes. The presence of islet cell antibodies (ICA) and glutamic acid decarboxylase antibodies in adults with clinically typical type 2 diabetes has been referred to as latent autoimmune diabetes of adults. Neither the autoimmunity nor the diabetes is latent, however (24).

Diabetes autoantibody testing also should be considered in overweight/obese children > 13 years of age with a clinical picture of type 1 diabetes (weight loss, ketosis/ketoacidosis), some of whom may have type 2 diabetes.

**Monogenic diabetes (formerly referred to as maturity onset diabetes of the young or MODY)** may also be misdiagnosed as type 2 diabetes (25). It also occurs in families with multigenerational diabetes, but is not associated with obesity beyond that in the general population and it is not associated with insulin resistance .

#### *Treatment of type 2 diabetes*

**Caveat: Initial treatment modality is determined by symptoms, severity of hyperglycaemia, and presence or absence of ketosis/ketoacidosis. As in type 1 diabetes, those with symptoms, particularly vomiting, can deteriorate rapidly and need urgent assessment and treatment.**

The overall goals of treatment of type 2 diabetes are: weight loss, increase in exercise capacity, normalisation of glycaemia and control of co-morbidities, including hypertension, dyslipidaemia, nephropathy, and hepatic steatosis. Reduction in the rate of complications may require more stringent control in insulin resistant type 2 diabetes than in type 1 diabetes, and especially diligent attention to co-morbidities, as suggested by the United Kingdom Prospective Diabetes Study (17).

#### *Education*

Patient and family education for youth with type 2 diabetes is as important as it is in type 1 diabetes (see also chapter 5: Diabetes education). Initial and on-going education in type 2 diabetes will place a greater emphasis on behavioural, dietary and physical activity changes than is generally required for type 1 diabetes. Education in insulin therapy and hypoglycaemia will be required when hypoglycaemic agents, including insulin, are required. Education should be given by team members with special expertise and knowledge of the dietary, exercise, and psychological needs of youth with type 2 diabetes. Education should be provided in a culturally sensitive and age appropriate manner. The entire family will need education to understand the principles of treatment of type 2 diabetes and to understand the critical importance of the lifestyle changes required to manage type 2 diabetes.

For overweight or obese youth, the family and child should understand the medical implications of obesity and type 2 diabetes and the medical importance of decreasing the obesity. For these families, referral to a nutritionist/dietitian with knowledge and experience in nutritional management of children with DM is necessary. The family should be encouraged to make dietary changes consistent with healthy eating recommendations, including individualised counselling for weight reduction, reduced total and saturated fat intake, increased fibre intake, and increased physical activity (26). Specific, negotiated and enjoyable exercise prescriptions should be developed for each patient and family that are sensitive to family resources and environment, and should be provided to all caregivers. This should include daily efforts to be physically more active, such as using stairs instead of elevators, walking or bicycling to school and to shop, and doing house and yard work. Approaches aimed primarily at reducing sedentary time, such as turning off the TV and decreasing the time spent in computer related activities, may be the most effective initially (27). A family member or friend should be identified who is available to participate in physical activity with the patient. Pedometers may be motivating to patients and family members.

#### *Glycemic monitoring*

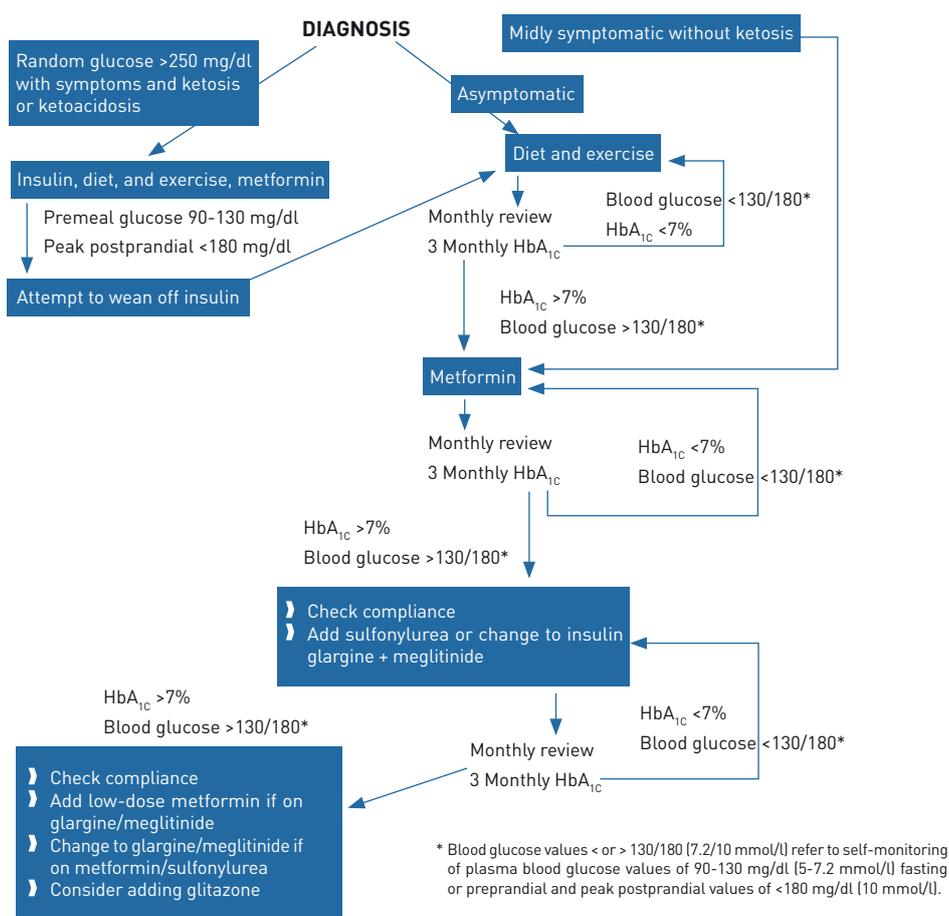
SMBG should be performed regularly. Frequency of SMBG should be individualised, and include a combination of fasting and postprandial glucose measurements. Once glycaemic goals have been achieved, several fasting values a week and daily post prandial values, taken after the biggest meal are satisfactory while the values remain within the target range. Patients on insulin or sulphonylureas need to monitor for asymptomatic hypoglycaemia. If values rise into the impaired glucose tolerance range, more frequent testing should be recommended for adjustment of therapy. During acute illness or when symptoms of hyperglycaemia or hypoglycaemia occur, patients should perform more frequent testing and be in contact with their diabetes care team for advice.

HbA<sub>1c</sub> concentration should be determined at least twice a year and quarterly if insulin is being used or metabolic control is unsatisfactory.

#### *Pharmacologic therapy*

Lifestyle change should be continued in addition to pharmacologic therapy (Fig. 1). The aim of pharmacologic therapy is to decrease insulin resistance, increase insulin secretion, or to slow postprandial glucose absorption. The first medication used should be metformin. It has the advantage over sulphonylureas of similar reduction in HbA<sub>1c</sub> without the risk of hypoglycaemia. Furthermore, weight is either decreased or remains stable, and LDL-C and triglyceride levels decrease during treatment.

Failure of monotherapy with metformin over 3 months indicates the need to add insulin alone or in combination with other agents (Fig. 1).

**Figure 1. Management of type 2 diabetes mellitus in children and adolescents**

**Patients at-risk for pregnancy should be counselled on the effects of diabetes and oral agents on conception and fetal development and increased risk for conception with metformin therapy.** Metformin and sulphonylureas may be continued during pregnancy, but for many youth, insulin will be required to maintain optimal glycaemia and decrease risk for early congenital malformations and fetal macrosomia. Other oral agents should not be used during pregnancy.

Only metformin and insulin are approved for use in children/adolescents in the majority of countries. Sulphonylureas are approved for use in children in some countries; other oral agents are described below with the understanding that some older adolescents may benefit from their use. Thiazolidinediones may be used in older adolescents but these are not approved in those under 18 years and should never be used in combination with insulin as this increases the risk for fluid retention and cardiac failure. Combination formulations may improve compliance.

*A review of currently available hypoglycaemic agents*  
**Biguanides.** Metformin acts on insulin receptors in liver, muscle, and fat tissue to increase insulin action (increase

insulin sensitivity), with a predominant action on the liver. Long-term use is associated with a 1-2% reduction in HbA<sub>1c</sub>. Intestinal side effects are transient abdominal pain, diarrhoea, nausea. The side effects may be decreased by slow titration of the dose and the use of extended release formulations. Metformin should not be given to patients with renal impairment, hepatic disease, cardiac or respiratory insufficiency, or who are receiving radiographic contrast materials or abuse alcohol. Metformin should be temporarily discontinued during a gastrointestinal illness.

Metformin may normalise ovulatory abnormalities in girls with PCOS and increase pregnancy risk.

**Insulin.** Despite hyperinsulinemia and insulin resistance, relatively small doses of supplemental insulin are often effective. If there is inadequate glycaemic control on oral agents, a long-acting insulin analogue without peak effects has been shown to provide satisfactory therapy without meal related therapy, NPH has also been used in the evening to improve fasting glucose values (28). Metformin should be continued to improve insulin sensitivity. Thiazolidinediones are not recommended in combination with insulin because of increased risk for fluid retention with the combination (Fig. 1).

### *Bariatric surgery*

Bariatric surgery may be considered for adolescents with obesity-related co-morbidities, including type 2 diabetes (31). Gastric bypass, the traditional surgical procedure for weight loss, can have significant complications including nutrient malabsorption and even death. Newer techniques, appear to be safer, including gastric banding and vagal nerve stimulators. A randomised controlled trial of gastric banding versus conventional treatment for recent onset type 2 diabetes in a small population of obese adults achieved a 73% remission rate which correlated with weight loss and lower baseline HbA<sub>1c</sub>, without serious complications (32).

- ▶ Although the morbidity and mortality rates in adults have decreased over the last 5 years, this treatment is still uncommon in children and should be undertaken only in centres with an established program designed to collect outcome data (31).

### *Type 2 diabetes and the insulin resistance syndrome*

Insulin resistance is an impaired response to the physiologic effects of insulin, including effects on glucose, lipid, and protein metabolism, and on vascular endothelial function. Insulin resistance occurs in most tissues including liver, muscle, and fat tissue and is influenced by sex, age, race/ethnicity, stage of sexual maturation, and total adiposity (15,19, 33-36).

Other associations important to evaluate in youth with type 2 diabetes include:

- (i) Obesity.
- (ii) Nephropathy: Albuminuria (either micro- or macro-), present at the time of diagnosis in some adolescents (10-15%) with type 2 diabetes and prevalence increases with duration of diabetes (18). Proteinuria and focal segmental glomerular sclerosis have also been reported in adolescents with severe obesity, in the absence of diabetes (37).
- (iii) Hypertension, present in 20-30% of youth at diabetes diagnosis, is estimated to account for 35-75% of diabetes complications, both microvascular and macrovascular.
- (iv) Dyslipidaemia with hypertriglyceridemia and decreased HDL-C are the hallmarks of type 2 diabetes dyslipidaemia and are found at onset in 20-25% and 50-65% of youth with type 2 diabetes respectively. (38, 39)
- (v) Ovarian hyperandrogenism and premature adrenarche are recognised as part of the insulin resistance syndrome. Decreasing insulin resistance may improve ovarian function and increase fertility.
- (vi) NAFLD: Hepatic steatosis is present in 25-45% of adolescents with type 2 diabetes and more advanced forms of NAFLD, such as non-alcoholic steatohepatitis, are increasingly common and associated with progression to cirrhosis (40).

Additional health problems related to obesity include obstructive sleep apnoea (OSA) with associated pulmonary hypertension, orthopaedic problems resulting in diminishing physical activity, pancreatitis, cholecystitis and pseudotumor cerebri.

In adults, there is a strong association between level of hyperglycaemia in diabetes and increased risk of macrovascular disease. Hyperglycaemia, dyslipidaemia, and hypertension are contributors to the acceleration of atherosclerosis in type 2 diabetes. Defective endothelium dependent vasodilatation is an additional factor accelerating atherosclerosis in type 2 diabetes (68,69). These findings suggest that type 2 diabetes in youth are at a high risk for coronary events and increased mortality in young adulthood. Aggressive treatment of hyperglycemia, hypertension and dyslipidaemia may reduce this risk.

### *Testing for co-morbidities and complications*

Co-morbidities characteristic of the insulin resistance syndrome are commonly seen at diagnosis or appear early in the course of type 2 diabetes and should be tested for sooner than in type 1 diabetes, where these disorders are complications of the diabetes rather than co-morbid conditions (38,40). A more complete discussion of testing for complications/co-morbidities is presented in chapter 17: Microvascular and macrovascular complications. Either microalbuminuria or macroalbuminuria, may be present at the time of diagnosis and albuminuria should be evaluated at diagnosis and annually thereafter (55,72). Likewise, hypertension may be present at, or prior to diagnosis of diabetes and each individual should be evaluated at every visit for hypertension. Dyslipidaemia is more common in type 2 diabetes and in family members, and should be screened for when metabolic stability is achieved.

### *Treatment of co-morbidities/complications*

Confirmed hypertension (BP > 95% for age, gender and height) or albuminuria should be treated with an ACE-inhibitor or, if not tolerated, an ARB. Combination therapy may be required if hypertension or albuminuria does not normalise on single agent treatment. Major congenital malformations have been reported with first trimester exposure to ACE-inhibitors but not with other antihypertensive agents in non-diabetic women (42). The goal of lipid lowering therapy is LDL-C < 2.6 mmol (100mg/dl) and triglycerides < 1.7mmol/l (68). Initial life style changes and dietary intervention to decrease total and saturated fat should be initiated, if the LDL-C and/or triglycerides remain elevated after 3-6 months of attempts to optimise blood glucose control and diet, pharmacotherapy is warranted (40). Statin therapy has been shown to be safe and effective in children as in adults and should be the first pharmacologic intervention (72) although long term safety data are not available. Special attention should be paid to symptoms associated with muscles and connective tissues, as there is an increased risk of rhabdomyolysis (43).

### Testing (case finding) for type 2 diabetes

Accumulated data indicate that screening to identify diabetes in asymptomatic youth, even in very high risk populations, has a low yield [35,44,45]. However, some clinicians in populations with high incidence of type 2 diabetes, if resources are available, may favour screening while awaiting more information on more optimal strategies for testing, including the frequency of testing [2]. Recent studies emphasise the limitation of fasting glucose determination for testing purposes in obese youngsters with a greater yield from a 2 hour post challenge glucose level. In most populations screening for type 2 diabetes outside of a research setting is not cost effective.

Because abnormal glucose tolerance may be present in 2-3% of high risk groups and additional findings of insulin resistance may be also be present prior to overt diabetes, a high index of suspicion should be maintained and at risk children should be advised on approaches to prevent type 2 diabetes (see subsequently). Several studies, including all ethnicities have also noted the high frequency of detection of non-glycaemic features of the insulin resistance syndrome in children and youth with BMI greater than 85<sup>th</sup> percentile, who may also be at increased risk for eventual type 2 diabetes [46].

Children at risk for type 2 diabetes and metabolic syndrome include:

- ▶ Children with BMI 85-95<sup>th</sup> percentile:
  - ▶ if there is an immediate family history of type 2 diabetes, early CVD, or
  - ▶ if there are signs of insulin resistance (acanthosis nigricans, dyslipidaemia, hypertension, PCOS)
- ▶ Asian children regardless of BMI, if history of abnormally low or high birth weight, or family history of diabetes.
- ▶ Children with BMI > 95<sup>th</sup> percentile, regardless of family history or associated features.

### Prevention of type 2 diabetes

Worldwide, obesity is increasing in all segments of the population. Prevention of type 2 diabetes requires prevention of obesity in those who are not overweight and treatment of obesity in those who have a BMI > 85<sup>th</sup> percentile (or even less in non-European populations). Intervention in adult populations reflects difficulty in altering lifestyle and dietary habits [47]. The societal changes required are of such magnitude that enormous community and governmental commitment is required.

- ▶ Primary prevention of type 2 diabetes is directed toward the obesity pandemic and involves reversing eating and entertainment trends in homes, schools, and communities that have resulted in excess caloric intake and decrease in energy expenditure; optimising the fetal environment in pregnancy; and the promotion of breastfeeding.
- ▶ Relatively minimal weight loss can decrease rate of diabetes in at risk populations [48,49].

## Consideration

Type 2 diabetes is increasing worldwide, including in adolescents, although less data exist on the optimal care of type 2 diabetes in adolescents. Therefore, guidelines for care of adolescents with type 2 diabetes are based on data extrapolated from adults with type 2 diabetes and short-term or cross-sectional studies in youth with type 2 diabetes. Consideration must be given to current uncertainties that exist with diagnostic classification and possible misclassification of type 2 diabetes with either type 1 diabetes or monogenic diabetes. Type 2 diabetes care in adolescents should emphasise family education as healthy diet and exercise are key components of therapy and a family history of type 2 diabetes is often present. Screening for and prevention of complications should be highlighted as earlier onset of type 2 diabetes could lead to onset of diabetic complications at a younger age.

## Implementation

Initial care of type 2 diabetes will depend on the severity of symptoms at presentation and insulin may be required for metabolic stabilisation and until diagnostic classification as type 2 diabetes. Once metabolically stable, metformin is the pharmacologic treatment of choice in addition to self-monitoring of blood glucose, healthy diet and exercise. Primary prevention of type 2 diabetes in adolescents focuses on prevention of obesity. Screening for diabetic complications should begin at diagnosis and continue per stated guidelines.

## Evaluation

Longitudinal data are needed on outcomes in adolescents with type 2 diabetes to better inform clinical care. Currently, self monitoring of blood glucose, HbA<sub>1c</sub>, and screening for diabetic complications and their risk factors (obesity, nephropathy, hypertension, dyslipidaemia, ovarian hyperandrogenism, and NAFLD) are used to monitor care and direct therapy. More effective methods to prevent obesity are required for the primary prevention of type 2 diabetes in adolescents.

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MONOGENIC  
DIABETES

## Recommendations

### Recommended care

1. Monogenic diabetes results from the inheritance of a mutation or mutations in a single gene (dominant or recessive inheritance or a de novo mutation).
2. Monogenic diabetes is confirmed by molecular genetic testing.
3. Some forms of monogenic diabetes are exquisitely sensitive to sulphonylureas, such as HNF-1 $\alpha$  MODY and HNF-4 $\alpha$  MODY and many cases of permanent neonatal diabetes (Kir6.2 mutations).
4. Mild fasting hyperglycaemia due to glucose kinase deficiency is not usually progressive during childhood, but may require insulin during pregnancy.
5. Transient neonatal diabetes is usually diagnosed within the first week and resolves around 12 weeks.

### Limited care

1. Genetic testing should be considered in all children presenting with diabetes before six months of age, as it is available free of charge and its diagnosis may have major effects on treatment (see Implementation).

### Comprehensive care

1. When monogenic diabetes is suspected, the child should be referred to a tertiary centre for diagnostic testing and review of treatment.

## Rationale

Now molecular genetics is being used as a diagnostic test which can help define the diagnosis and treatment of children with diabetes. It is important to correctly diagnose monogenic diabetes as it can predict the clinical course of the patient, explain other associated clinical features and importantly guide the most appropriate treatment (1). 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 counselling. The majority of patients with genetically proven monogenic diabetes are initially incorrectly diagnosed as type 1 or type 2 diabetes (2).

## Evidence-base

### Neonatal diabetes

Neonatal diabetes is insulin requiring diabetes which is usually diagnosed in the first three months of life. Clinically two subgroups are recognised: transient and permanent. Transient neonatal diabetes mellitus (TNDM) resolves at a median of 12 weeks but as many as 50% of cases will ultimately relapse (3,4). The majority of patients with TNDM have an abnormality of imprinting of the *ZAC* and *HYMAI* genes on chromosome 6q (3,5). Permanent neonatal diabetes mellitus (PNDM) requires

continuous insulin treatment from diagnosis. The commonest known cause of PNDM are mutations in the *KCNJ11* gene encoding the Kir6.2 subunit of the  $\beta$ -cell  $K_{ATP}$  channel (6,7).

### Familial diabetes

The commonest causes of familial diabetes or familial hyperglycaemia are:

#### Hepatocyte nuclear factor 1 alpha (HNF-1 $\alpha$ ) gene mutations (MODY3)

The most common form of monogenic diabetes which results in familial diabetes (known in the past as maturity-onset diabetes of the young [MODY]) are HNF-1 $\alpha$  mutations. The clinical characteristics of patients with HNF-1 $\alpha$  mutations are:

- i. Young-onset diabetes that shows characteristics of not being insulin-dependent e.g. not developing ketoacidosis in the absence of insulin, good glycaemic control on a small dose of insulin, or detectable C-peptide measured when on insulin with glucose > 8mmol/L outside a normally expected honeymoon period (3 years).
- ii. Family history of diabetes. This may be insulin treated and considered to be "type 1" diabetes. This would typically be diagnosed in the twenties, thirties or forties. There may also be an affected grandparent although often these are diagnosed after 45 years.

- iii. OGTTs in early stages tend to show a very large glucose increment usually > 5 mmol/l (11). Some subjects may have a normal fasting value but still rise into the diabetic range at 2 hours (11).
- iv. Glycosuria at relatively normal blood glucose levels are often seen as these patients have a low renal threshold (11).
- v. Marked sensitivity to sulphonylureas resulting in hypoglycaemia despite poor glycaemic control before starting sulphonylureas (12,13).

Patients with HNF-1 $\alpha$  gene mutations can initially be treated with diet although they will have marked post-prandial hyperglycaemia after high carbohydrate food as the  $\beta$ -cell defect results in insufficient increase in insulin secretion in response to hyperglycaemia (14).

Most patients will need pharmacological treatment as they show progressive deterioration in glycaemic control throughout life and are at risk of considerable microvascular and macrovascular complications (15).

**Table 1. Neonatal diabetes: characteristics of diabetes presenting in the first 6 months of life**

Gene	PNDM/ TNDM	% in consan- guineous or isolated populations	Median birth weight (SD)	Age of diagnosis in weeks. Me- dian (range)	Pancreatic appearance	Other features
ZAC/HYAMI Imprinting defect on 6q24	TNDM	Rare	2,100g [-2.7]	0.5 [0-4]	Normal	Macroglossia (23%)
Kir6.2 (KCNJ11) [8,9]	PNDM TNDM (10%)	Rare	2,580g [-1.73]	6 [0-260]	Normal	Developmental delay (20%) Epilepsy (6%) DKA (30%)
SUR1 (ABCC8) [10]	PNDM TNDM (78%)	Rare	2,600g [-1.7]	6 [0-17]	Normal	Developmental delay
EIF2AK3  Wolcott-Rallison syndrome  Recessive	PNDM	90%	3,000g [-1.0]	13 [6-65]	Exocrine dysfunction (25%)	Epiphyseal dysplasia (90%) Osteopenia (50%) Acute liver failure (75%) Developmental delay (80%) Hypothyroidism (25%)
FOXP3  IPEX syndrome  X linked	PNDM	Rare	2,860g [-1.2]	6 [0-30]	Normal	Only boys affected Chronic diarrhoea with villous atrophy (95%) Pancreatic and thyroid autoantibodies (75%) Thyroiditis (20%) Eczema (50%) Anaemia (30%) Often die young
INS	PNDM	Rare	2,600g [-1.7]	9 [0-26]	Normal	None
GCK (Glucokinase)  Recessive	PNDM	85%	2,050g [-2.6]		Normal	Parents have fasting hyperglycaemia as heterozygotes
IPF1  Recessive	PNDM	50%	2,140g [-2.97]		Absent	Parents may have early-onset diabetes as heterozygotes
HNF-1 $\beta$ dominant (60%)  Spontaneous	TNDM	Rare	1,900g [-3.0]		Atrophy	Renal developmental disorders
PTF1A  Recessive	PNDM	100%	1,390g [-3.8]		Absent	Severe neurological dysfunction and cerebellar hypoplasia

### *Hepatocyte nuclear factor 4 alpha (HNF-4a) gene mutations (MODY1)*

Diabetes due to mutations of the HNF-4a gene is considerably less common than diabetes due to mutations of the HNF-1a gene but has similar characteristics except there is not a low renal threshold and the age of diagnosis may be later (16). HNF-4a mutations should be considered when HNF-1a sequencing is negative but the clinical features were strongly suggestive of HNF-1a (16). Patients are often sensitive to sulphonylureas (17).

### *Mild fasting hyperglycaemia 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 type 1 diabetes or the patient has type 2 diabetes. However a considerable proportion of these patients with persistent mild fasting hyperglycaemia 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 hyperglycaemia is persistent and stable over a period of months or years (11).
- ii. HbA<sub>1c</sub> is typically just below or just above the upper limit of normal (5.5-5.7%).
- iii. In an OGTT the increment (2 hour 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 criteria (11).
- iv. Parents may have "type 2 diabetes" 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 (11). Testing fasting glucose of apparently unaffected parents is important when considering a diagnosis of a glucokinase mutation.

The fasting hyperglycaemia does not deteriorate significantly and the glucose is regulated at the higher set point (11). This is rarely associated with any microvascular or macrovascular complications even when no treatment is given throughout life (18).

### *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 through the NCBI website <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>) can help with clinical features and whether the gene has been defined and hence molecular genetic testing is available. For described and previously undescribed syndromes, help can

be obtained through the ISPAD rare diabetes collection (contact through link on the ISPAD web page or through [www.diabetesgenes.org](http://www.diabetesgenes.org)). The most common genetic syndromes which include diabetes are listed below:

### **Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness (DIDMOAD) syndrome (Wolfram syndrome)**

Wolfram syndrome is an autosomal recessive syndrome in which the association of diabetes with progressive optic atrophy under 16 years of age is diagnostic (19). The syndrome is more common in races 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 age. The order of appearance of the neurological symptoms may vary even within families. The median age of death in Wolfram syndrome is 30 years (19). Mutations in the gene for Wolfram syndrome (WFS1) are present in at least 90% of patients with clinical Wolfram syndrome (20-22).

The diabetes is non-autoimmune and insulin deficient and presents at a mean age of 6 years (19). Patients require insulin treatment from the time of diagnosis but autoantibodies are not present (19).

### **Thiamine responsive megaloblastic anaemia (Roger's syndrome)**

Thiamine responsive megaloblastic anaemia (TRMA) is a rare recessive, genetic syndrome of early onset megaloblastic anaemia (which responds to thiamine) is associated with diabetes and sensorineural deafness. This results from mutations in the gene SLC19A2 (23). 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 (24). Deafness is unresponsive to thiamine.

### **Renal cysts and diabetes syndrome due to a Hepatic Nuclear Factor 1-β 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 (25). Renal developmental disorders, especially renal cysts and renal dysplasia, are present in almost all patients with mutations or gene deletions (26), may be diagnosed in utero and precede the diagnosis of diabetes. Other features which may be present in children include uterine and genitalia developmental anomalies, hyperuricaemia, gout and abnormal liver function tests (25). 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 sulphonylureas and so usually require insulin treatment (27). Pancreatic

size is reduced reflecting a reduction in both the endocrine and exocrine pancreas and sub-clinical exocrine deficiency is present in most patients [28] but it is uncertain if this should be treated if it is asymptomatic.

### Mitochondrial diabetes

Maternal transmission of mutated or deleted mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. Mitochondrial diabetes is commonly associated with sensorineural deafness and short stature. The diabetes is characterised by progressive non-autoimmune  $\beta$ -cell failure and may rapidly progress to insulin requiring diabetes.

## Consideration

Making a diagnosis of monogenic diabetes will have implications for other family members often correcting the diagnosis and treatment for other diabetic family members as well as allowing appropriate genetic counselling. The majority of patients with genetically proven monogenic diabetes are initially incorrectly diagnosed as type 1 or type 2 diabetes [2].

It should be considered with these clinical presentations:

- ▶ Neonatal diabetes or diabetes diagnosed within the first 6 months of life.
- ▶ Familial diabetes with an affected parent.
- ▶ Mild (5.5-8.5 mmol/l) fasting hyperglycaemia especially if young or familial.
- ▶ Good glycaemic control on a small dose of insulin and not developing ketoacidosis in the absence of insulin.
- ▶ Diabetes associated with extra pancreatic features.

Laboratory evidence which supports the clinical suspicion:

- ▶ Detectable C-peptide when glucose > 8 mmol/l after 3 years of diabetes.
- ▶ Negative pancreatic autoantibodies.

The treatment of children with HNF-1 $\alpha$  or HNF-4 $\alpha$  should be low dose sulphonylureas which result in a four-fold greater lowering of glucose than metformin [29]. The dose of sulphonylureas should initially be low (one quarter of the normal starting dose in adults) to avoid hypoglycaemia. If there is hypoglycaemia despite dose titration of a once or twice daily sulphonylurea preparation such as gliclazide, a slow release preparation or meal time doses with a short-acting agent like nateglinide may be considered [30].

Children with glucokinase deficiency do not need treatment in the paediatric age range. There is very little if any response to either oral hypoglycaemic agents or insulin. Exogenous insulin results in suppression of endogenous insulin secretion and so the degree of glycaemia will

be maintained. This explains why these children can be treated with insulin without experiencing significant hypoglycaemia.

## Implementation

Molecular genetic testing is offered in most European countries, Australia and the USA but many labs will test patients from other countries (e.g. [www.diabetesgenes.org](http://www.diabetesgenes.org) and [www.mody.no](http://www.mody.no)). These tests are expensive (up to €500/US\$600) but can have a big impact on management of the proband and other family members whose samples will be cheaper to analyse after the mutation is known (€100/US\$120). Some recently described monogenic diabetes genes testing in patients diagnosed less than 6 months may be available as research tests for no charge (see [www.diabetesgenes.org](http://www.diabetesgenes.org)). 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.

## Evaluation

Once a diagnosis of monogenic diabetes has been made, it may be possible to transfer the patient to an oral hypoglycaemic agent and cease insulin. It is unclear how common monogenic diabetes may be, and is likely to vary across different populations.

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05

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DIABETES  
EDUCATION

## Recommendations

### Recommended care

1. Every young person with diabetes and their parents/carers have a right to accessible, planned diabetes self-management education.
2. This includes all elements described in limited care.
3. Diabetes education should be delivered by an interdisciplinary paediatric diabetes team (as a minimum a doctor, nurse and dietitian), acknowledging their different skills 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.
4. Diabetes education needs to be learner-centred and thus be adaptable to suit individual needs.
5. Diabetes management, facilitated by education, is unlikely to be successful without some degree of behavioural change in children, adolescents and their parents/carers.
6. The diabetes team should receive training in teaching and counselling techniques (see chapter 15: Psychological care).
7. Diabetes education needs to be a continuous process and repeated for it to be effective.

### Limited care

1. All children and adolescents with diabetes and their carers have the right to basic education and practical skills training to enable them to survive the onset of diabetes safely and successfully.
2. Initial learning, started as soon as possible after diagnosis, should include immediate knowledge-based education and practical survival skills (see Appendix). This should be followed by graduated levels of education reinforced whenever possible by diagrams, drawings, written guidelines, booklets and other visual media appropriate to the child's age, maturity and environmental circumstances.
3. Diabetes education must be given by someone with experience and expertise in paediatric diabetes management.
4. Appropriately adapted diabetes education at all ages must be centred on the needs and levels of understanding of both the child and parents/carers.
5. Diabetes education is most effective when based on self-management and is child and parent centred.

### Comprehensive care

1. A comprehensive educational programme should be:
  - › Structured, agreed and have a written curriculum.
  - › Using trained educators.
  - › Quality assured.
  - › Audited.
2. Structured education should be available to all young people with diabetes at the time of initial diagnosis; it should be appropriate to each individual's age, stage of diabetes, maturity and lifestyle, culturally sensitive and at a pace to suit individual needs or when it is appropriate for them; and then as required on an on-going basis, based on a formal, regular individual assessment of need.
3. Important aspects of intensified management (with multiple injection treatment, the availability of analogue insulins and infusion pumps) involve matching and adjusting insulin profiles to quantified food intake and exercise levels. Higher levels of education, understanding and self-management are required for these interventions to be successful and require more time, skill and greater resources from the educational team.

4. The diabetes team should have access to continuing specialised training in diabetes education, in the principles of teaching and structured education, and also in behavioural change management including empowerment techniques and motivational interviewing (see chapter 15: Psychological care).
5. Educational programs should use a variety of teaching techniques (including modern technology), 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.

## Rationale

Education is the keystone for diabetes care and structured diabetes self-management education (DSME) is the key to a successful outcome (1,2).

Education may be seen as an interface between clinical practice and research. Research into diabetes and educational methods is important in improving clinical practice and this should be the responsibility of each nation/state and be a national priority (3). People who do not receive education or do not continue to have educational contacts are more likely to suffer diabetes related complications (2).

Educational programmes are more likely to be successful when carefully planned, have specific aims and learning objectives, and which are shared with people with diabetes, their families and the healthcarers (1,2).

It is widely accepted that diabetes cannot be successfully managed without behavioural modification (4). Health professionals need to understand that education per se with acquisition of knowledge is unlikely to alter behaviour 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 behavioural change management including counselling techniques (1,2).

## Evidence-base

The DCCT 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 (2).

Structured education programmes are considered in a variety of contexts (2,3,5) and there is evidence, mainly from adult diabetes, that they are more effective than informal unstructured education in improving metabolic control (3,6). In paediatric diabetes, structured educational

programmes have been less well publicised and because of the nature of the problems have focussed more on psychosocial interventions. The evidence for efficacy of these interventions, nearly all from North America, has been extensively reviewed in various texts (4,6), but others have developed more recently (3,5).

It has remained contentious whether educational interventions per se are beneficial in diabetes care, particularly in children and adolescents. Nevertheless, systematic reviews of psycho-educational interventions conclude that they have small to medium beneficial effects on glycaemic control and somewhat greater effect on psychological outcomes (6). The effects are greater for children than adults, and are most effective when integrated into routine care (4,7), when education is learner-centred, parents are involved, empowerment principles are utilised, and self-management, problem-solving, goal setting and self-efficacy are promoted (1,2,6).

## Considerations

- ▶ In all clinical settings it is essential that one of the healthcare team takes responsibility for designing and implementing diabetes education for children and their parents.
- ▶ Any consideration of education in diabetes must take account of the child's age, maturity and level of understanding, and that of the parent(s) as well as the environmental circumstances.
- ▶ Successful education is more likely when the educator is perceived to be motivated.
- ▶ Unsuccessful education and communication is likely to be associated with deficiencies in understanding, motivation and metabolic control.

## Implementation

It is important that governmental, educational and public health authorities recognise that children and adolescents with diabetes not only require specialised training but time and facilities to implement structured self-management education.

## Evaluation

Regular audit and evaluation of knowledge and practical skills should be part of routine care of children and adolescents with type 1 diabetes and be recorded as part of clinic consultations.

## Appendix

### Primary (Level 1) education

#### At diagnosis: Survival skills

1. Explanation of how the diagnosis has been made and reasons for symptoms.
2. Simple explanation of the uncertain cause of diabetes. No cause for blame.
3. The need for immediate insulin and how it will work.
4. What is glucose? - normal blood glucose levels and glucose targets.
5. Practical skills -insulin injections.  
- blood and/or urine testing and reasons for monitoring.
6. Basic dietetic advice.
7. Simple explanation of hypoglycaemia.
8. Diabetes during illnesses. Advice not to omit insulin - prevent DKA.
9. Diabetes at home or at school including the effects of exercise.
10. Identity cards, necklets, bracelets and other equipment.
11. Membership of a Diabetes Association and other available support services.
12. Psychological adjustment to the diagnosis.
13. Details of emergency telephone contacts.

### Secondary (level 2) education

#### Continuing curriculum

1. Pathophysiology, epidemiology, classification and metabolism.
2. Insulin secretion, action and physiology.
3. Insulin injections, types, absorption, action profiles, variability and adjustments.
4. Nutrition - food plans; qualitative and quantitative advice on intake of carbohydrate, fat, proteins and fibre; coping with special events and eating out; growth and weight gain; "diabetic foods"; sweeteners and drinks.
5. Monitoring, including HbA<sub>1c</sub> and clear (agreed) targets of control.
6. Hypoglycaemia and its prevention, recognition and management including glucagon.
7. Intercurrent illness, hyperglycaemia, ketosis and prevention of ketoacidosis.

8. Problem solving and adjustments to treatment.
9. Goal setting.
10. Microvascular and macrovascular complications and their prevention. The need for regular assessment.
11. Exercise, holiday planning and travel, including educational holidays and camps.
12. Smoking, alcohol and drugs.
13. School, college, employment and driving vehicles.
14. Sexuality, contraception, pregnancy and childbirth
15. Updates on research.

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## Appendix resources

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

IDF Diabetes Education modules - to view or order free Book and CD-ROM with teaching slides [www.idf.org](http://www.idf.org)

Life for a Child education pages: [www.idf.org/lifeforachild/diabetes-education-resources](http://www.idf.org/lifeforachild/diabetes-education-resources)

Structured Patient Education - guidance booklet from the Patient Education Working Group [www.diabetes.org.uk](http://www.diabetes.org.uk)

Diabetes Education Study Group of EASD - see Basic Curriculum for Health Professionals on Diabetes Therapeutic Education. <http://www.desg.org/article/artic-lestatic/50/1/10/>

Psychology in Diabetes Care. 1st Edition; 2000. 2<sup>nd</sup> Edition; 2005. Editors: Snoek FJ, Skinner TC. Published by: John Wiley & Sons, Chichester, England. See chapters on Children; Adolescents; Behaviour change. [www.wiley.co.uk](http://www.wiley.co.uk)

Hanas R. Type 1 diabetes in children, adolescents and young adults - how to become an expert on your own diabetes. 4th UK Edition; 2010. Published by: Class Publishing, London. [www.class.co.uk](http://www.class.co.uk) or [www.betamed.se/eng](http://www.betamed.se/eng)

# 06

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STRUCTURES,  
PROCESSES AND  
OUTCOMES OF  
AMBULATORY  
DIABETES CARE

## Recommendations

### Recommended care

#### A. Structure of care

1. A team of specialists with expertise in diabetes and paediatrics should care for children with diabetes and their families.
  - › The team should consist of a paediatrician, a diabetes specialist nurse educator, a dietitian, a paediatric social worker and/or psychologist/psychiatrist.
  - › The family and child are an integral part of the care team. Their importance as members of the team should be emphasised.
2. General aims of the Diabetes Care Team should be to provide comprehensive diabetes medical care, initial and ongoing diabetes education, and psychosocial support of the family.
3. Specific aims of the Diabetes Care Team should be to provide:
  - › specialised hospital care including the diagnosis and initial treatment using established protocols for DKA;
  - › Comprehensive ambulatory care of diabetes and associated complications and co-morbid conditions, including advice on all aspects of the child's home/school care;
  - › thoughtful introduction of new therapies and technologies;
  - › Emergency access to advice for patients 24 hours a day.

#### B. Processes of care

4. Ambulatory diabetes care should include:
  - › A care visit every 3 months for a re-evaluation of diabetes management and review of home management records;
  - › An annual visit with greater attention to dietary assessment, educational assessment and updates, psychosocial needs and long-term complication and co-morbidities screening;
  - › Quarterly HbA<sub>1c</sub> determination, assessment of hypoglycaemia unawareness and a physical examination including height, weight, BMI and blood pressure;
  - › Planned transition to adult diabetes care to ensure continuity of care;
  - › Attention to minority children and children of recent immigrants to provide culturally sensitive communication and medical care with assistance in accessing care.

#### C. Outcomes of care

5. Outcomes monitoring should identify areas in structure and process of care to improve acute and chronic diabetes health outcomes, satisfaction with care, and quality of life (QOL) and to identify and rectify health care disparities.
6. Benchmark outcomes for the Team should be identified and tracked. Electronic or paper recording is important to develop clinic benchmarks to compare to regional and national/international benchmarks for improvement of care.

### Limited care

1. All possible Recommended care recommendations should be implemented.
2. The multidisciplinary team is very unlikely to be available in areas of low population density and where childhood diabetes rarely occurs. In these circumstances diabetes care is likely to be provided by a locally based paediatrician/physician or internist.
3. Since glucose control is more difficult in a limited care setting, screening for complications must be started earlier than for Recommended care.
4. Local practitioners should have access to facilities and advice provided by the Diabetes Care Team in regional centres of excellence as well as education and management materials to implement safe diabetes care.

5. Increasingly, these materials are available through the internet as well as by personal contact with Diabetes Care Teams at regional centres of excellence.

## Comprehensive care

1. The principles as for Recommended care.
2. Diabetes Care Teams can:
  - ▶ Provide expertise more widely, especially to areas of lower population density and regions of lower diabetes incidence.
  - ▶ Develop new strategies for care and provide research outcomes supporting the useful new strategies and technology in the care of children with diabetes.
3. Outpatient ambulatory management of children at the time of diagnosis is possible when members of the Diabetes Care Team are experienced in the outpatient initiation of insulin therapy and adequate reimbursement of Diabetes Team Care is available.
4. Outcomes should be compared to regional, national/international benchmarks to improve outcomes locally and in the larger diabetes community.
  - ▶ These results should be published to add to regional, national and international benchmark data.
5. Some comprehensive diabetes teams can collect and provide data on the cost of care and treatment to benefit outcomes data over the child's lifetime.

## Rationale

Diabetes is primarily managed in the outpatient/ambulatory setting (1). The importance of regular, ambulatory on-going diabetes care assessment for youth with diabetes is essential in maintaining optimal glucose control and to monitor for risk factors for acute and chronic complications. The components of medical care include structure, processes and outcomes. The ultimate goal is to provide care that results in normal growth and development, a high quality of life, and lowest possible risk of acute and long-term complications. This is best accomplished by helping youth and families become proficient in self-management, remain motivated throughout adolescence and encourage development into independent, healthy adults. These recommendations are primarily based on the ISPAD Clinical Consensus Guidelines for the delivery of ambulatory diabetes care: structures, processes, and outcomes of ambulatory diabetes care (1). Additional guidelines recommending specific diabetes care practices may be helpful for review (2-11).

Continuously improving the outcomes of care is essential to the optimal health of children with diabetes. This can best be accomplished by careful analysis of diabetes care outcomes. Outcomes to be evaluated can be divided into structure and processes of care outcomes and biological outcomes. Improvements in processes of care generally precede improvements in biological outcomes. The impact of changes in structures and processes of care on biological outcomes are less well studied in paediatric diabetes. Cost of care is an important part in the

evaluation of diabetes care although cost-effectiveness of care in paediatric diabetes is an area in which there are insufficient data and that requires additional study.

## Evidence-base

### *Structures of care*

A multidisciplinary paediatric diabetes team can provide cost effective care to children with diabetes resulting in improved metabolic outcomes and fewer hospitalisations for acute complications (12). The multidisciplinary team is very unlikely to be available in areas of low population density and where childhood diabetes rarely occurs. Nevertheless, local practitioners should have ready access to facilities and advice provided by the Diabetes Care Team in regional centres of excellence (13,14). Advice and support to physicians and/or health care professionals providing diabetes care in areas of low population density can be facilitated through telecommunications and the internet. In some areas, two-way telecommunication utilising video-computer technology and local medical staff to facilitate the telemedicine visit may allow more efficient and effective distant care (14,15). Appropriate resources or reimbursement must be available for these services in order for diabetes care teams to utilise these newer technologies.

### *Processes of care*

All care providers should have easy access (24 hour a day) to experienced paediatric emergency care and the diabetes team for rapid diagnosis and initiation of treatment with availability of accepted written protocols for

management of DKA and other presentations of childhood diabetes to decrease morbidity and mortality at the time of initial diabetes presentation (16). For initial education and skills training the importance of providing 'a good start' with confident, clear, positive messages, support, and advice cannot be overemphasised.

A diabetes care visit is recommended every 3-4 months for assessment of diabetes care, more often if particular difficulties in managing diabetes are recognised or the child is very young. This assessment should include a review of home monitoring records. The ability to download data from blood glucose meters, insulin pens, pumps, and continuous glucose sensing devices to view the actual data from the child/adolescent's home care at each clinic visit provides very valuable insight into home management. These data often allow the diabetes team to identify areas where adjustments need to be made in diabetes care plans and, more importantly, to identify areas where the young patient is in need of additional help or supervision from the family or a supportive adult. The patient and his/her family should be complimented for the blood testing they have been able to do, and the record should never be used to criticise the child or family for failing to reach glucose targets. The records are best used as a tool to identify patterns and trends, identify and solve problems, and teach improved diabetes self-management skills. It should be emphasised that blood glucose meter memories and clinic downloads of the monitor data are not substitutes for regular home review of blood glucose readings by the patient and his/her family. Appropriate education in how to interpret these data and make initial therapy adjustments is essential for optimal care.

An annual comprehensive evaluation is helpful to review care, growth and development, screen for co-morbidities and complication risks, and bring education up to date. At this visit, an annual assessment should be made for depression and disordered eating in children  $\geq 10$  years of age and an assessment of the youth's understanding of risks for complications and care plans to minimise these risks, and to provide age appropriate information on driving, employment, smoking, sex, pregnancy, drugs, and alcohol. An HbA<sub>1c</sub> at least annually, and ideally quarterly is recommended to monitor metabolic regulation. Determination of barriers to successful diabetes management, including needle fears may reveal ways to improve care. Assessment to determine if the diabetes care plan is optimally intensified to obtain the lowest possible HbA<sub>1c</sub> should be performed at least annually, taking the above assessments into consideration.

*Outcomes of care and quality improvement, including evaluation of structure and processes of care outcomes as well as biological outcomes*

Improvements in processes of care generally precede improvements in biological outcomes. The impact of

changes in the structure of care on biological outcomes is less well studied in paediatric diabetes. Information from quality improvement programs indicates that these programs can increase recommended processes of care such as frequency of HbA<sub>1c</sub> determinations and insulin injections as well as lead to improvement in meeting guidelines for ophthalmological and renal microalbumin excretion screening. The impact of quality improvement programs on HbA<sub>1c</sub> levels is less clear (17).

Recommendations for data collection for outcome assessments are given in Table 1. To collect outcome data required for assessment of quality improvement, either paper or computer records must be regularly used to collect the necessary quality 'benchmark' information. Analysis at 3-12 month intervals is useful to determine improvement or deterioration over time allowing changes in processes to be made when necessary. Adequate data management and statistical analysis capabilities are required to analyze outcome data for quality improvement assessment. However, small diabetes teams may be able to calculate key benchmark outcomes, e.g. mean HbA<sub>1c</sub>, acute complication rates, without this service.

Diabetes teams should compare their results to other regional, national and international centres and published benchmarks and guideline recommendations. Regional centres of excellence should publish their results and join consortiums, when possible, to publish combined results. Multicentre studies have published analyses of some processes of care that may affect biological outcomes, but additional studies are needed to fully define best care practices (12,18,19). However, these data sets will allow paediatric diabetes care teams to identify some processes of care that result in improvement in biological outcomes, improving quality of care for children throughout the world.

#### *Additional considerations for care*

##### **Care for minority children and children of recent immigrants**

Globalisation and migration are great challenges to the health care systems of the developed and, sometimes, the developing world. Barriers to treatment that affect the care of minority children and children of recent immigrants may be unfamiliar to the diabetes team but will negatively impact diabetes care in these children. Recognition of these barriers is necessary to optimise care, and novel ways to overcome these unfamiliar cultural barriers requires cooperation, communication, and the establishment of trust among all team and family members. Knowledge of a family's cultural and religious beliefs can be critical to providing care; in some cultures the stigma of a chronic disease may delay or prevent the family from providing urgent or necessary daily diabetes treatment (20). Perceived or actual access to health care by immigrant and minority

**Table 1. Examples of quality indicators reflecting the process and outcomes of diabetes care, relevant for paediatric diabetes [adapted from (31)]**

Treatment	Quality indicator
Normal growth	Percentage of patients with height < 3 <sup>rd</sup> percentile
Normal physical development	Average BMI in diabetic children compared with non-diabetic children Percentage of patients with BMI > 85 <sup>th</sup> percentile
Normal pubertal development	Mean age at menarche in girls with diabetes
Low rate of acute complications	Frequency of severe hypoglycaemia in all patients Frequency of severe hypoglycaemia in all patients younger than 5 years of age Frequency of admission because of diabetic ketoacidosis after onset of diabetes
Prevention of microvascular complications	Percentage of patients with eye exams during the past year Percentage of patients with urine albumin excretion rate determined during the past year Mean HbA <sub>1c</sub> achieved in all patients Mean HbA <sub>1c</sub> achieved in adolescent patients Percentage of patients beyond 5 years of diabetes with diabetic retinopathy Percentage of patients beyond 5 years of diabetes with diabetic nephropathy Percentage of patients with persistent microalbuminuria not receiving ACE-inhibitors (or other interventions for microalbuminuria)
Prevention of cardiovascular complications	Percentage of patients with lipid levels available during the past year Percentage of patients with blood pressure recordings available during the past year Percentage of patients with hypertension Percentage of patients with hyperlipidaemia Percentage of patients with hypertension not receiving antihypertensive therapy Percentage of patients with hyperlipidaemia not receiving lipid-lowering therapy Mean HbA <sub>1c</sub> achieved in all patients Mean HbA <sub>1c</sub> achieved in adolescent patients
Optimal social adjustment	Average number of days spent in hospital Average number of days where school was missed because of diabetes Percentage of patients on flexible insulin regimen (beyond remission) QOL in patients with diabetes QOL in parents of patients with diabetes Percentage of patients missing appointments
Number of visits annually	Percentage of patients with three or more, ambulatory visits annually Number of visits per patients per year and mean and median number of visits per patient per year

BMI, body mass index; HbA<sub>1c</sub>, glycated haemoglobin; QOL, quality of life.

families may be different than that of the country's majority inhabitants. Recognition of these perceptions and differences requires cultural sensitivity, establishment of trust among all team and family members, careful communication and inquiry, and understanding of the family's social circumstances. When necessary for clear communication, licensed interpreters are always best used if available. If a licensed interpreter is not available, a non-family interpreter is optimal, and the child or other family member should only be used as an interpreter if no other option is available.

#### **Children with diabetes in the school setting**

Children spend 40-50% of their waking hours in school. Diabetes care in school is an important part of their diabetes management plan. The child has the right to receive adult support for diabetes care from school personnel during school hours, outdoor school activities, when at school sponsored events away from school, and should natural disasters occur at school. School personnel must be trained to provide or supervise all diabetes care prescribed by the diabetes physician and/or the specialty team, including identification and treatment for hypoglycaemia, both mild-moderate and severe (21). Resources for schools are available on line (22,23) [www.diabetes.org/schooltraining](http://www.diabetes.org/schooltraining) and [www.diabeteskidsandteens.com.au](http://www.diabeteskidsandteens.com.au).

#### **Children with diabetes in organised camps**

Diabetes camps offer an estimated 15,000 to 20,000 children and adolescents worldwide the opportunity to enjoy a camping experience in a safe environment and to experience a setting where caring for diabetes is a shared experience with all or most of the campers also having diabetes (1,24). Camps specialising in children with diabetes should be staffed by professionals and volunteers trained in the management of children with diabetes including knowledge of insulin dose, recognition and treatment of hypoglycaemia as well as the identification and treatment of early ketosis and when referral to a medical facility should be initiated. Diabetes camps should have insulin and other diabetes supplies available including glucagon and ketone testing supplies (1). Professional staff should make insulin dose adjustments for the increased levels of activity that are usual at camps and at least one staff member should have knowledge of medical nutrition therapy and the principles of adjusting insulin doses for variable carbohydrate content of meals (25).

Most camps provide some education in diabetes management either in planned sessions or, more commonly, by taking advantage of helping campers 'learn by doing' and of 'teachable moments' to discuss one-on-one or in a group issues related to diabetes care and outcomes (26). Camp staff should recognise that the primary goal of camp is to provide an enjoyable recreational experience for each child in a safe environment.

Many national organisations have position statements or guidelines for the care of children with diabetes in a camp setting. These are valuable references and should be reviewed by camp medical directors to ensure adherence to national standards (24,27).

#### **Transition to adult clinics**

The transition to adult care is inevitable. This transition occurs at different ages in differing care settings, and there is no age when transition is smoothest. Lack of consistent care may follow transition in 30-40% of patients. Discussion about transition during the several visits before transition may help prepare for transition. Counselling on how care and care practices may differ in adult clinics may be helpful to teens (28).

#### **Overall analysis of diabetes health care costs and utilisation**

It has been well documented that in adults, diabetes imposes a large economic burden (29,30), however, there is very little information on the cost of diabetes in children and adolescents, especially for those with type 2 diabetes. Yet such information is critical when assessing the economic burden of disease and evaluating the economic efficiency of diabetes prevention and control programs in this population.

## **Consideration**

Costs of diabetes care have increased dramatically in the past 10 years with the introduction of analogue insulin, increased use of insulin pumps and recommendations for increased frequency of blood glucose testing. If continuous glucose sensor technology use increases, as it undoubtedly will, this will also add to the cost of daily care. Personal expenses for diabetes care vary widely around the world with costs prohibitive in some countries and completely paid for by the state in others. Regardless of the source of payment for care, cost effectiveness data is required to inform health care decisions.

The child with diabetes who receives limited care is more likely to have a lower quality of life and develop diabetes long-term complications at an earlier age. Improvement in quality of care determined by care practices that improve outcomes will decrease the overall lifetime cost of diabetes by decreasing acute and chronic complications of diabetes and will normalise life expectancy. More importantly, improving outcomes will improve quality of life for individuals with diabetes and their families.

## **Implementation**

Sufficient numbers of experienced paediatric diabetes specialists, including physicians, nurses, dietitians,

social workers and psychologists are required. Sufficient diabetes supplies (insulin, syringes, and blood glucose monitoring equipment) are required to ensure insulin can be administered as needed daily and glucose monitored frequently enough to guide insulin therapy and identify and guide treatment of acute complications. Emergency services to respond to acute diabetes emergencies also need to be in place.

Data collection processes and analysis is required in order to determine outcomes of care and compare benchmark outcomes across centres locally, nationally and internationally to improve outcomes around the world. Data on the most cost effective treatments are required to implement optimal treatment as often as possible. A high priority should be given to collecting and providing these data to, and with the help of, governments and health care agencies.

## Evaluation

Data collection processes and analysis are required in order to determine outcomes of care and compare benchmark outcomes across centres locally, nationally and internationally to improve outcomes around the world. Data on the most cost effective treatments are required to implement optimal treatment as often as possible. A high priority should be given to collecting and providing these data to, and with the help of, governments and health care agencies.

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ASSESSMENT  
AND MONITORING  
OF GLYCAEMIC  
CONTROL

## Recommendations

### Recommended care

1. Self-monitoring of blood glucose (SMBG) is an essential tool in the optimal management of childhood and adolescent diabetes and, when financially possible, should be made available for all children with diabetes.
2. SMBG should be prescribed at a frequency to optimise each child's diabetes control, usually four to six times a day, because frequency of SMBG correlates with glycaemic control.
3. Without accurate monitoring, the risks of acute crises and long-term microvascular and macrovascular complications are greatly increased.
4. The acute and chronic complications of diabetes lead increased health care costs and personal disability.
5. Ketone testing should be available and performed:
  - ▶ During illness with fever and/or vomiting.
  - ▶ When blood glucose value above 14 mmol/l (250 mg/dl) in an unwell child or when persistent blood glucose levels above 14 mmol/l (250 mg/dl) are present.
  - ▶ When there is persistent polyuria with elevated blood glucose, especially if abdominal pains or rapid breathing are present.
  - ▶ Blood ketone testing is preferred if available, especially for small children and patients on insulin pumps.
6. Glucose monitoring records should not be used as a judgment but as a vehicle for discussing the causes of variability and strategies for improving glycaemic control.
7. Frequent home review of records to identify patterns in glycaemic levels and subsequent adjustment in diabetes management are required for successful intensified diabetes management.
8. Facilities for the measurement of HbA<sub>1c</sub> should be available to all centres caring for young people with diabetes.
9. HbA<sub>1c</sub> should be monitored four to six times per year in younger children and three to four times per year in older children.
10. Adolescents with stable type 2 diabetes should have two to four HbA<sub>1c</sub> measurements per year because adolescents may become insulin requiring more rapidly than adults.
11. The target HbA<sub>1c</sub> for all age-groups is recommended to be less than 7.5% (58 mmol/mol).
12. There is evidence that intensive treatment, with a goal of lowering HbA<sub>1c</sub> as in the DCCT study, results in lower risk for long-term complications.
13. Targets for all age-groups include the requirement for minimal levels of severe hypoglycaemia and absence of hypoglycaemia unawareness.
14. When severe hypoglycaemia occurs or when hypoglycaemia unawareness is present, glycaemic targets must be increased until hypoglycaemia awareness is restored and severe hypoglycaemia no longer occurs.
15. When severe hypoglycaemia occurs or when hypoglycaemia unawareness is present, glycaemic targets must be increased until hypoglycaemia awareness is restored and severe hypoglycaemia no longer occurs.

### Limited care

1. The cost of blood glucose monitoring is very expensive and in many countries the cost relative to the cost of living may make this technology unavailable.
2. All centres caring for young people with diabetes should urge nations, states, and health care providers to ensure that children and adolescents with diabetes have adequate glucose monitoring supplies.
3. Testing three to four times a day several days a week may provide more information than a single daily measurement.

4. When urine glucose testing is used, as many urine tests as possible should show no glycosuria without the occurrence of frequent or severe hypoglycaemia.
5. Urine ketone test strips should be available and testing performed:
  - ▶ During illness with fever and/or vomiting.
  - ▶ When there is persistent polyuria with elevated blood glucose (above 14 mmol/l [250 mg/dl] if measured), especially if abdominal pains or rapid breathing are present.
6. Urine ketone, interpretation as for Recommended care.
7. Frequency of HbA<sub>1c</sub> measurement will depend on local facilities and availability, but every child should have a minimum of one measurement per year.
8. Adolescents with stable type 2 diabetes should have at least one HbA<sub>1c</sub> measurement per year and symptoms of uncontrolled diabetes reinforced frequently since adolescents may become insulin requiring more rapidly than adults.
9. The target HbA<sub>1c</sub> for all age-groups is recommended to be the same as for standard care, i.e. less than 7.5% (58 mmol/mol).

### Comprehensive care

1. Continuous glucose monitoring may allow near normalisation of blood glucose and HbA<sub>1c</sub> while decreasing risk of hypoglycaemia.
2. Continuous monitoring devices may particularly benefit those with hypoglycaemic unawareness.
3. In some instances, especially among teenagers, maintaining written monitoring records is difficult. If the family can upload the blood glucose monitoring data to a computer for frequent family review, this may substitute for a manual record, although details of daily management may be lost with this method.
4. Blood ketone measuring should be available for all paediatric patients with diabetes.

## Rationale

Monitoring of glycaemic control includes daily monitoring of glucose at home as well as periodic monitoring of overall glycaemia. The aims of monitoring glycaemic control are:

- ▶ To assess with accuracy and precision the level of glycaemic control achieved by each individual so that they may attain their most realistic glycaemic targets.
- ▶ To help in preventing both the acute complication of hypoglycaemia and the chronic complications of microvascular and macrovascular diseases.
- ▶ To minimise the effects of hypoglycaemia and hyperglycaemia on cognitive function.
- ▶ To collect data on glycaemic control from each diabetes centre for comparison with stated local, national, and international standards so that the performance and standards of the interdisciplinary Diabetes Care Teams may be improved.

Measurement of immediate glycaemic control is best determined by SMBG, as this provides immediate documentation

of hyperglycaemia and hypoglycaemia, allowing implementation of strategies to optimally treat, as well as to avoid, out of range glucose values. HbA<sub>1c</sub> is the only measure of chronic glycaemic control for which robust outcome data are available. Elevated HbA<sub>1c</sub> predicts long-term microvascular and macrovascular outcomes (1,2). However, HbA<sub>1c</sub> has limitations as a measure of glycaemic control, i.e. average blood glucose. In the Diabetes Control and Complications Trial (DCCT), although lower average HbA<sub>1c</sub> in the intensive treatment group conferred significantly lower risk of microvascular complications (2), the same group had significantly more hypoglycaemia (4) than the conventionally treated patients. Secondary analysis of the DCCT data has found that subjects in the DCCT with lower HbA<sub>1c</sub> levels had similar lower risk for retinopathy regardless of treatment group (3). A given HbA<sub>1c</sub> of 7.0% corresponded also to a higher average blood glucose [measured seven times a day] of 10.7 mmol/l (192 mg/dl) in the conventionally treated patients vs. 9.0 mmol/l (163 mg/dl) in the intensively treated patients (5). HbA<sub>1c</sub> is only one of the several measures of optimal glycaemic control, along with documented frequency of hypoglycaemia including severe hypoglycaemia, type of treatment, patient's age, and quality of life. The recommendations in this section are primarily derived from

the Assessment and monitoring of glycaemic control in children and adolescents with diabetes in ISPAD Clinical Practice Consensus Guidelines 2009 (6).

## Evidence-base

The DCCT, and similar studies, provide clear evidence in adults and adolescents that better metabolic control, as measured by a lower HbA<sub>1c</sub> level, is associated with fewer and delayed microvascular complications (1,2,7-10). Additional studies have shown that frequent and accurate blood glucose monitoring and concomitant optimal adjustment of insulin to carbohydrate intake and exercise (11,12) are required to attain and to maintain optimal metabolic control. Finally, follow-up data from the DCCT indicate that 5-7 years of poor glycaemic control, even during adolescence and young adulthood, results in an increased risk for microvascular and macrovascular complications in the subsequent 6-10 years (10,13). These data support trying to achieve for each individual an HbA<sub>1c</sub> as close to the normal range as possible.

Both hypoglycaemia and hyperglycaemia may result in central nervous system (CNS) alterations, both acutely and chronically. Brain imaging studies show that both hypoglycaemia and hyperglycaemia cause changes in the white and gray matter of developing brains (14). There is evidence for CNS changes in children with diabetes associated with hyperglycaemia as well as hypoglycaemia, although the cognitive functioning and brain imaging findings in children with diabetes as a whole are not significantly different from healthy control children (14,15). The CNS changes in association with hyperglycaemia are relatively new findings but are consistent with reported neurocognitive findings (16).

Experts agree that at present, the safest recommendation for improving glycaemic control generally in all children is to achieve the lowest HbA<sub>1c</sub> that can be sustained without disabling or severe hypoglycaemia while avoiding prolonged periods of significant hyperglycaemia (blood glucose levels > 15-20 mmol/l) (16,17) and episodes of DKA and that these goals can only be achieved by some form of frequent glucose monitoring.

**Self blood glucose monitoring.** The frequency of SMBG is associated with improved HbA<sub>1c</sub> in patients with type 1 diabetes (11,12,18,19). This is thought to be because of both better insulin adjustment for food consumed and an improved ability to quickly correct out-of-target glucose values. In addition, early detection of lower glucose values prior to symptomatic hypoglycaemia may allow correction with a decreased risk of overcorrection and resultant hyperglycaemia. The use of SMBG during exercise may also allow improved insulin management and a decreased risk for hypoglycaemia during and

following exercise (20). There are many types of excellent monitors for SMBG; however, significant inaccuracies may arise from operator-related errors (21). Health care professionals should choose and advise on a type that is robust, precise, accurate, and familiar to them as well as affordable to the patient.

SMBG is best measured at different times in the day to show levels of blood glucose after the overnight fast, during the night to detect unnoticed hypoglycaemia and hyperglycaemia, in response to the action profiles of insulin (at anticipated peaks and troughs of insulin action), and after food intake (1.5-2 hours after a meal), and in association with vigorous sport or exercise (during and several hours after) so that changes may be made in management to improve blood glucose profiles (19,20). SMBG is also important to confirm hypoglycaemia and to monitor recovery; and during intercurrent illness to prevent hyperglycaemic crises.

The number and regularity of SMBG should be individualised depending on the availability of equipment and the ability of the child to identify hypoglycaemia. Successful application of intensified diabetes management with multiple injection therapy or insulin infusion therapy requires frequent SMBG (four to six times a day) and regular, frequent review of the results to identify patterns requiring adjustment to the diabetes treatment plan.

**Blood glucose targets.** There is little age-related scientific evidence for strict, i.e. near normal, glucose targets (Table 1). However, each child should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycaemia as well as frequent mild to moderate hypoglycaemia. The targets in Table 1 are intended as guidelines.

**Urine glucose monitoring.** It is recognised that in many countries, urine glucose monitoring is the only monitoring method available and that it provides useful but different information from SMBG. Urinary glucose reflects glycaemic levels over the preceding several hours and is affected by the renal threshold for glucose, which in children is approximately 10-11 mmol/l (180-200 mg/dl). Periodic, quantitative, timed urine glucose determinations to include different times of the day, e.g. from dinner until bed, overnight until arising, etc., can allow determination of grams of glucose excreted during these times and may increase the usefulness of urine glucose determinations.

Limitations of urine glucose monitoring include: uncertain correlation with blood glucose levels; inability to detect hypoglycaemia or monitor response to treatment of hypoglycaemia; less valuable than blood glucose as an educational tool to identify glycaemic patterns; and unhelpful in hyperglycaemic crises because of the lag phase between recovery and changes in urine glucose.

Urine glucose oxidase strips that are relatively inexpensive, convenient, and safe and are recommended over non-specific reducing agent methods such as Clinitest tablets or Benedict's test. These non-specific reducing agents are less convenient to use and are also potentially dangerous if the chemical reagents come into contact with the skin, oesophagus, or gastrointestinal tract.

**Urine glucose target.** As many urine tests as possible should show no glycosuria without the occurrence of frequent or severe hypoglycaemia.

**Continuous glucose monitoring.** Intermittent blood glucose monitoring, SMBG, determines the capillary glucose level at the moment when the test is performed, generally two to six times a day. Minimally invasive

devices are available that measure interstitial fluid glucose every 1-20 minutes, i.e. 'continuous' measurement. Currently, these devices are expensive and may not be available in many countries. Insurance coverage is also limited. Over time, these devices are becoming more widely available and, with greater evidence of efficacy, may be covered by both national and private insurance. As continuous glucose monitoring becomes more widely available, it is anticipated that decreased blood glucose targets may be achieved more safely, allowing further decreases in target HbA<sub>1c</sub> levels and an improved outlook for children with diabetes (22). Some devices allow targets to be set so that an alarm will alert the wearer to a glucose value projected to fall below or above the target in 10-30 minutes, based on the rate of change of the interstitial glucose (23).

**Table 1. Target indicators of glycemic control**

Level of control	Ideal (non-diabetic)	Optimal	Suboptimal (action suggested)	High risk (action required)
Clinical assessment				
Raised BG	Not raised	No symptoms	Polyuria, polydipsia, and enuresis	Blurred vision, poor weight gain, poor growth, delayed puberty, poor school attendance, skin or genital infections, and signs of vascular complications
Low BG	Not low	Few mild and no severe hypoglycaemias	Episodes of severe hypoglycaemias (unconscious and/or convulsions)	
Biochemical assessment*				
SMBG Values in mmol/l (mg/dl)				
AM fasting or preprandial PG	3.6–5.6 (65–100)	5–8 (90–145)	>8 (>145)	>9 (>162)
Postprandial PG†	4.5–7.0 (80–126)	5–10 (90–180)	10–14 (180–250)	>14 (>250)
Bedtime PG†	4.0–5.6 (80–100)	6.7–10 (120–180)	<6.7 or 10–11 (<120–200)	<4.4 or >11 (<80 or >200)
Nocturnal PG†	3.6–5.6 (65–100)	4.5–9 (80–162)	<4.2 or >9 (<75 or >162)	<4.0 or >11 (<70 or >200)
HbA <sub>1c</sub> DCCT (%)				
(DCCT standardized)	<6.05	<7.5†	7.5–9.0†	>9.0‡
IFCC (mmol/mol)	< 43	< 58	58-75	>75

BG, blood glucose; DCCT, Diabetes Control and Complications Trial; HbA<sub>1c</sub>, hemoglobin A1c; PG, plasma glucose.

These targets are intended as guidelines, and each child should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycaemia as well as frequent mild to moderate hypoglycaemia.

\* These population-based target indicators must be adjusted according to individual circumstances. Different targets will be appropriate for various individuals such as those who have experienced severe hypoglycaemia or those with hypoglycemic unawareness.

† These figures are based on clinical studies and expert opinion, but no strict evidence-based recommendations are available. PG levels are given because BG meters are internally calibrated to reflect the plasma glucose level.

‡ DCCT conventional adult cohort had a mean HbA<sub>1c</sub> value of 8.9%, and both DCCT and EDIC have shown poor outcomes with this level; therefore, it seems prudent to recommend levels below this value.

Continuous sensor devices are available for single user continuous use and owned by the patient; or multiple users, intermittent use and provided by a diabetes care team for diagnostic and management advice. Both may guide real-time adjustments of insulin dosing and can identify times of consistent hyperglycaemia and times of increased risk for hypoglycaemia presenting a much more sophisticated approach to home SMBG [24,25]. These devices have been used in research settings to evaluate frequency of hypoglycaemia and develop strategies to decrease its occurrence, especially during and following exercise. Information gained in these studies has provided information that allows improved recommendations for insulin management for all individuals with diabetes [26,27] including those not using continuous sensing devices.

With short-term use of sensors, mean blood glucose values decrease and time spent in the hypoglycaemic range also decreases [24]. Studies in longer term use of sensors (6 months) have found advantages in improved glucose control with frequent use. These studies also documented that many adolescents are not willing to wear a device as often, or for as prolonged a period of time as is required to result in consistently improved glucose metabolism since the frequency of sensor use (average days per week over a month) predicts the HbA<sub>1c</sub> lowering effect of the sensor [28,29]. These results indicate additional technology is needed that is less intrusive in a teen's life as are new ways to help adolescents adapt to healthcare tasks required to maintain optimal near-normal glucose levels.

**Ketone monitoring.** Urine (acetoacetate) or blood (β-hydroxybutyrate) ketone measurement should be monitored during episodes of uncontrolled hyperglycaemia, insulin deficiency, intercurrent illness (sick days), and impending ketoacidosis. Blood ketone determination has been shown to be more helpful in avoiding emergency room visits and hospital admissions than urine ketone determinations [30], and can thus be very cost-effective. Because the blood ketone strips are expensive, many centres advise using the blood ketone testing for young children, in whom it is often more difficult to obtain a urine specimen, and for patients on insulin pumps. The routine use of blood ketone testing for all children with diabetes is increasing.

*Interpretation of ketone testing.* The presence of vomiting with hyperglycaemia and large urinary ketones must be assumed to be due to systemic acidosis and requires rapid, further evaluation [31]. Determination of blood ketone levels can more accurately guide management, e.g. > 3.0 mmol/l is usually accompanied by acidosis and urgent contact with diabetes provider or Emergency Department is needed. Blood ketone levels below 0.6 mmol/l are normal after an overnight fasting.

Blood glucose levels must be checked before administering insulin in patients with ketonuria or ketosis. Urine or blood ketones may be elevated in diabetic patients as a physiological metabolic response to fasting, low carbohydrate diets (e.g. Atkins diet), during prolonged exercise, or pregnancy as well as in gastroenteritis and in alcohol intoxication. Blood glucose levels are normal or low in these situations, and supplemental insulin is not indicated. See also chapter 12: Sick day management.

**Home record keeping of glycaemic control.** Ideally families should be taught to use their home glucose records to determine patterns of glycaemic control and how to make initial adjustments to insulin treatment. This is required for successful intensified diabetes management. The record book is useful at the time of consultation and should contain time and date of blood glucose levels; insulin dosage; note of special events affecting glycaemic control (e.g. illness, parties, exercise, menses, etc.); hypoglycaemic episodes, description of severity, and potential alterations in the usual routine to help explain the cause for the event; and episodes of ketonuria/ketonaemia.

**Glycated haemoglobin.** Glucose becomes irreversibly attached to the molecule of haemoglobin during the life cycle of the circulating red cell (which is approximately 120 days) forming HbA<sub>1c</sub>. HbA<sub>1c</sub> reflects levels of glycaemia over the preceding 4-12 weeks, weighted toward the most recent 4 weeks. However, the most recent week is not included because the most recent glycation is reversible [32]. HbA<sub>1c</sub> monitoring has been shown to be the most useful measure in evaluating metabolic control and is the only measure for which good data are available in terms of its relationship with later microvascular and macrovascular complications [1,2].

**Determination of glycated haemoglobin.** Facilities for the measurement of HbA<sub>1c</sub> should be available to all centres caring for young people with diabetes. Frequency of measurement will depend on local facilities and availability. Every child should have a minimum of one measurement per year, ideally three to six measurements per year depending on age and degree of glycaemic control. A normal reference range for non-diabetic children should be available.

HbA<sub>1c</sub> (called A1C in the US) is currently expressed as a percentage (%) and has been used as such in most current textbooks and patient literature, with reference to the DCCT study. The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) has produced a reference material which will be used for the calibration of all laboratory machines measuring HbA<sub>1c</sub> worldwide. The IFCC units will be expressed in mmol/mol instead of %. However, both numbers refer to the same thing, and in this manual, HbA<sub>1c</sub> of already published studies is expressed in %. The recommendation for laboratories and journals is to

report in both DCCT (%) and IFCC (mmol/mol) numbers, and conversion tables should be made easily accessible to the diabetes community [33].

IFCC values in mmol/mol which may be encountered in the literature can be converted to DCCT % values by using the equation [34,35]:

$$\text{HbA}_{1c} (\%) = 0.0915 \times \text{IFCC HbA}_{1c} (\text{mmol/mol}) + 2.15$$

**Table 2. DCCT and IFCC conversion tables of glycated haemoglobin values**

DCCT HbA <sub>1c</sub> (%)	IFCC HbA <sub>1c</sub> (mmol/mol)
6.0	42
6.5	48
7.0	53
7.5	58
8.0	64
8.5	69
9.0	75
9.5	80
10.0	86
11.0	97
12.0	108
13.0	119
14.0	129

For easy reference, the table shows equivalent values of % and mmol/mol.

There should be regular quality control comparisons with national and DCCT standards or the new IFCC standard. It is recommended that scientific papers also provide HbA<sub>1c</sub> in DCCT and IFCC numbers if the local analysis is not calibrated to report results in DCCT or IFCC numbers. It is preferable that a capillary method for collection of the child's blood is available and that the HbA<sub>1c</sub> result is available at the time of the medical visit so that immediate adjustments in management can be based on the HbA<sub>1c</sub> level. A rapid method using a prepared kit has been shown to provide comparable results to chromatographic methods [36].

Glycated haemoglobin targets. A target range for all age-groups of < 7.5% (58 mmol/mol) is recommended (Table 1). These targets are intended as guidelines. Each child should have their targets individually determined with the goal of achieving a value as close to normal as possible while avoiding severe hypoglycaemia as well as

frequent mild to moderate hypoglycaemia. The goal is to avoid the long-term microvascular and macrovascular complications of diabetes while also avoiding sequelae of acute hypoglycaemia and the CNS changes associated with both hypoglycaemia and hyperglycaemia.

Evidence for HbA<sub>1c</sub> target from the DCCT is available for adolescents, and recommendations for younger children can only be determined using these data and expert opinion. The intensively treated adolescent cohort of the DCCT achieved a mean HbA<sub>1c</sub> of 8.1%, while subjects in the corresponding adult cohort achieved a mean HbA<sub>1c</sub> of 7.1%. Subjects in the follow-up observational study, Epidemiology of Diabetes Interventions and Complications (EDIC), maintained an average HbA<sub>1c</sub> of 7.8-8.2% (regardless of DCCT randomisation) during the 12 years of follow-up reported to date. In addition, a proportion of children should expect to achieve an HbA<sub>1c</sub> within the normal reference range at some time in the first year after diagnosis (during the partial remission phase), generally between 1 and 6 months after diagnosis.

In many studies, there is evidence of an increased risk for hypoglycaemia as the HbA<sub>1c</sub> decreases [1,2,37,38], but this is not always the case [12,39]. Glycemic control and the risk of hypoglycaemia may be decreased by the choice of insulin regimens and the frequency of blood glucose monitoring. Targets for HbA<sub>1c</sub> are given with the expectation that careful attention will be taken to avoid severe hypoglycaemia. Because severe hypoglycaemia is more common when hypoglycaemia unawareness is present, HbA<sub>1c</sub> targets must be increased when hypoglycaemia unawareness occurs.

Hypoglycaemia unawareness is defined as neuroglycopenia occurring before autonomic activation and can be associated with reduced awareness of the onset of hypoglycaemia. It occurs when a single, or multiple, hypoglycaemic episode(s) lead to a significant decrease in neuro-hormonal counter-regulatory responses causing unawareness of hypoglycaemia [40]. Hypoglycaemia unawareness is more common in those who maintain generally lower blood glucose levels [40,41]. Continuous monitoring devices are becoming available that may particularly benefit those with hypoglycaemic unawareness, as the devices will alarm when glucose is below a specified range or with rapid rate of fall of glucose. Loss of awareness of hypoglycaemia can be reversed by avoiding hypoglycaemia for 2-3 weeks [42], although this may be difficult for very young patients.

Individuals and families should be instructed in the signs and symptoms of hypoglycaemia unawareness, and a history for hypoglycaemia unawareness should be taken at every diabetes care visit.

The youngest children (< 6 years old) are at increased risk for adverse neurologic outcomes from severe hypoglycaemia,

and because they are unable to self-identify hypoglycaemia, caution in achieving lower targets for younger children is appropriate. In reality, many paediatric centres find that the average HbA<sub>1c</sub> is in fact lowest in this youngest age-group, reflecting the more complete caregiver involvement at younger ages.

As teens approach adulthood, targets similar to those of the adult population should be approached (< 7%, 53 mmol/mol), recognising that the hormonal alterations and psychological adjustments of adolescence make achieving these targets difficult. Of all age-groups, adolescents are currently the farthest from achieving HbA<sub>1c</sub> < 7.5% (58 mmol/mol), reflecting the diabetes mismanagement that frequently accompanies the increased independence in diabetes care during the adolescent years, as well as the effect of psychological and hormonal challenges of adolescence. However, results from the DCCT and the follow-up EDIC studies document that poor control for 5-7 years that is similar to the duration of adolescence may have prolonged adverse effects (10,13). Although better insulins, insulin pumps, and glucose monitors are available today, compared with the DCCT era, adolescents at large may still be unable to achieve a lower HbA<sub>1c</sub> levels than the DCCT adolescent average without novel approaches to care in this age-group. Too ambitious goals may lead to an unwarranted sense of failure and alienation on part of many teenage patients.

Fructosamine and other glycosylated products. Fructosamine or glycosylated albumin may be useful in monitoring glucose control over time in individuals with abnormal red cell survival time. Fructosamine and other glycosylated products have not been evaluated in terms of later vascular risk.

## Consideration

Care providers should be aware that achieving an HbA<sub>1c</sub> consistently within the target range without extensive personal and national health care resources and outside of a clinical trial structure may be very difficult. As a benchmark, the most recent mean HbA<sub>1c</sub> is 7.8% in a well-educated, adult EDIC cohort that has excellent access to the newest diabetes technology and a mean age of 45 ± 7 years (43). Without access to newer insulins and frequent self-blood glucose monitoring, achieving target will be extremely difficult.

## Implementation

Achieving target glucose control will need to be a national and international priority to allow all children access to diabetes care and care supplies. Even in regions where supplies are available, achieving target control during adolescence will be difficult. As diabetes technology

improves, especially continuous glucose monitoring, improved glucose control may be possible and recommended target indicators for glycaemic control will likely decrease to reflect a new balance of benefits and risks.

## Evaluation

As the technology to measure blood glucose levels improves and becomes more available, the ability to achieve good glycaemic control will also improve. Assessment of the available tools to monitor glycaemic control and ketonaemia will be important to determine future standards for immediate and long-term monitoring.

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INSULIN  
TREATMENT

## Recommendations

### Recommended care

1. Insulin treatment must be started as soon as possible after diagnosis in all children with hyperglycaemia to prevent metabolic decompensation and diabetic ketoacidosis (for patients in ketoacidosis, see also chapter 10: Diabetic ketoacidosis as rehydration should be started before insulin is given).
2. The dynamic relationship between carbohydrate intake, physical activity and insulin should be stressed from the very first moment.
3. The insulin treatment modality should be as physiological as possible, but with consideration of the patient's and caregiver's preferences.
4. Good technical skill concerning syringes, insulin pens and pumps is important.
5. Rapid- and long-acting insulin analogues should generally be available, alongside with Regular (soluble) and NPH insulin.
6. Insulin storage
  - › Insulin must never be frozen.
  - › Direct sunlight or warming (in hot climates) damages insulin.
  - › Patients should not use insulins that have changed in appearance (clumping, frosting, precipitation, or discolouration).
  - › Unused insulin should be stored in a refrigerator (4-8oC).
  - › After first usage, an insulin vial should be discarded after 3 months if kept at 2-8oC or 4 weeks if kept at room temperature. However, for some insulin preparations, manufacturers recommend only 10-14 days of use in room temperature.

### Limited care

1. Insulin should be available in sufficient amounts, being consistent in quality and type.
2. Use syringes and vials for insulin administration (or pens, if available).
3. The principles of insulin use including professional support, are as for Recommended care, but a combination of NPH and Regular insulin may give acceptable blood glucose control.
4. Regular and NPH insulin may be mixed in the same syringe, given as pre-mixed insulin or given as separate injections.
5. A basal bolus regimen with Regular and NPH is preferred to pre-mixed insulin preparations. NPH insulin should be given twice daily in most cases, in addition, Regular insulin needs to be given 2-4 times daily to match carbohydrate intake.
6. Pre-mixed insulins may be convenient (i.e. few injections), but limit the individual tailoring of the insulin regimen, and can be difficult in cases where regular food supply is not available.
7. Insulin storage as for Recommended care.
8. In hot climates where refrigeration is not available, cooling jars, earthenware pitcher (matka) or a cool wet cloth around the insulin will help to preserve insulin activity.
9. In children on small doses of insulin, 3 ml cartridges instead of 10 ml vials should be chosen for use with syringes to avoid wastage of insulin.

### Comprehensive care

1. The principles of insulin use as for Recommended care.
2. Rapid- and long-acting insulin analogues should be available, alongside Regular and NPH insulin.
3. Insulin pump therapy should be available and considered.
4. Continuous Glucose Monitoring (CGM) should be available and considered as a tool for adjusting insulin doses.

## Rationale

Correct use of insulin should help to redress the balance between hyperglycaemia and hypoglycaemia, which themselves result in long-term and short-term complications. This implies availability and optimal use of insulin, tailoring the treatment according to the patient's/family's personality, preference and way of living. Education of patient/family and the health care professionals is equally important.

## Evidence-base

Treatment approaches depend on the etiology and phases of diabetes in children (1-5). The strong relationship between the level of HbA<sub>1c</sub> and long-term complications warrants good blood glucose control (6-10) early on from diagnosis. The basal-bolus concept, i.e. either multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII), has been shown to give the best results regarding this aspect, even in teenagers (11-14).

Insulin is only successful as part of a comprehensive diabetes management including nutritional management (15), physical activity (16), education (17), rules for sick days (18), surgery (19), and psychosocial support (20,21).

The necessity for a low HbA<sub>1c</sub> may increase the risk of severe hypoglycaemia. However, there is evidence that cognitive impairment is rather related to long-standing hyperglycaemia than to the rate of severe hypoglycaemia during intensive therapy (6,22).

Rapid-acting analogues can be given immediately before meals because there is evidence that the rapid action not only reduces postprandial hyperglycaemia but nocturnal hypoglycaemia may also be reduced (23). They offer the useful option of being given after food when needed (e.g. infants and toddlers who are reluctant to eat). The benefit of the rapid-acting insulin analogues in children is related to the reported reduction of hypoglycaemia. At the present time there is no evidence to show improvements in HbA<sub>1c</sub> using analogues (9,14).

Basal analogues show a more predictable insulin effect with less day to day variation compared to NPH insulin, with detemir having the lowest within-subject variability (24). While the effect of basal analogues on HbA<sub>1c</sub> improvement is controversial, there is evidence for a reduced rate of hypoglycaemia and a greater treatment satisfaction (9,14). Glargine has an effect up to 24 hours (25), while detemir has a time of action between 6 and 23 hours depending of the dose (26).

The use of external pumps (continuous subcutaneous insulin infusion, CSII) is increasing. It is acceptable and

successful even in young infants when adequate education and support is provided (18,27-29). Combining intensive insulin therapy with glucose sensors with real-time display are associated with a significant improvement of HbA<sub>1c</sub> compared to conventional blood glucose self monitoring when worn continuously (30).

Prevention of DKA during insulin treatment warrants special attention as it is associated with considerable mortality and morbidity (31-33). A potential increased risk of DKA when using CSII is still under debate as some studies have found an unchanged rate (34,35), while an increase was found in a population with a low incidence of DKA (36).

## Consideration

In spite of moderate improvements of HbA<sub>1c</sub> in some cohorts and evidence of reduced rates of long-term complications in children (37,38), the HbA<sub>1c</sub> levels presented from different centres are not satisfying (6,39). Insulin treatment during the day may lead to particular problems in the school and day care setting (40). Insulin needs to be stored according manufacturers recommendations. In a hot climate, storage in an earthenware pitcher (matka) has been used successfully (41,42).

Different target levels of HbA<sub>1c</sub> have been put forward. The trend is to achieve as low HbA<sub>1c</sub> as possible without increasing the risk of hypoglycaemia. The present ISPAD target is < 7.5% (58 mmol/mol) in all age groups (6).

The fact that the insulin analogues are expensive should be taken into consideration when the availability is limited. NPH and Regular insulin are useful alternatives in this situation.

During periods of regular change in consumption of food (e.g. Ramadan) the total amount of insulin should not be reduced but redistributed according to the amount and timing of carbohydrate intake. However, if the total calorie intake is reduced during Ramadan, the daily amount of bolus insulin for meals usually needs to be reduced, for example to two-thirds or three-quarters of the usual dose.

## Implementation

The implementation of optimal use of insulin requires continuous availability of insulin, and includes the ability and resources of self-monitoring of blood glucose, to be able to have a high intensity in titrating insulin doses in relation to carbohydrate intake. Universal guidelines and local protocols, supporting materials, structured patient education programs and well educated health care professionals are also required.

### Guideline on insulin dosage

At diabetes onset (for DKA, see separate protocol)

- ▶ Day 1 (throughout the night): Give Regular insulin every second hour until blood glucose is < 11 mmol/l, then every 4 hours. Dose: < 5 years - 0.1 U/kg, 5 years or older 0.2U/kg. If hourly monitoring of blood glucose cannot be provided, begin with half the above doses.
- ▶ Day 2 (from morning/breakfast): 0.5–0.75U/kg/day, distribution of insulin as below. Adjust doses daily according to blood glucose levels. The morning (and 3am) blood glucose is used for adjusting the bedtime basal dose, premeal levels to adjust the daytime basal insulin. Two hour postprandial blood glucose is used to tailor the meal bolus doses. The breakfast premeal dose is usually the largest bolus dose, due to an insulin resistance in the morning. For mixed insulin, always think of the components separately (i.e. 10 units of mix 70/30 equals 3 units of Regular and 7 units of NPH), and adjust doses as above.

### Insulin requirements

- ▶ 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 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 glycaemic control for an individual child or adolescent without causing obvious hypoglycaemia problems, and resulting in a harmonious growth according to children’s weight and height charts.

### Distribution of insulin dose

- ▶ Children on twice daily regimens often require more (around two-thirds) of their total daily insulin in the morning and less (around one-third) in the evening.
- ▶ On this regimen approximately one-third of the insulin dose may be short-acting insulin and approximately two thirds may be intermediate-acting insulin, although these ratios change with greater age and maturity of the young person.
- ▶ On basal-bolus regimens the night-time intermediate-acting insulin may represent between 30 (typical for Regular insulin) and 50% (typical for rapid-acting insulin) of the total daily insulin dose. Approximately 50% as rapid-acting or 70% as Regular insulin is divided up between three to four premeal boluses. When using rapid-acting insulin for premeal boluses, the proportion of basal insulin is usually higher, as 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 [43,44].

- ▶ Glargine can be given before breakfast, before dinner or at bedtime with equal effect, but nocturnal hypoglycaemia occurs significantly less often after breakfast injection [45].
- ▶ When transferring to glargine as basal insulin, the total dose of basal insulin needs to be reduced by approximately 20% to avoid hypoglycaemia [44]. After that, the dose should be individually tailored.
- ▶ Detemir is most commonly given twice daily in children [46].
  - ▶ When transferring to detemir from NPH, the same doses can be used to start with.

## Evaluation

The individual patient should be followed with regular measurements of HbA<sub>1c</sub> and assessment of clinical status. The treatment facility should take part in benchmarking with comparable centres. National and international benchmarking and longitudinal follow-up between centres as a basis to exchange best practices should be established.

Further randomised controlled trials with sufficient power are necessary to establish the safety and efficacy of new treatment modalities in the paediatric population.

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NUTRITIONAL  
MANAGEMENT

## Recommendations

### Recommended care

1. A specialist paediatric dietitian with experience in childhood diabetes should be part of the interdisciplinary paediatric diabetes team, be available at diagnosis, and in the first year thereafter to provide a minimum of two to four follow-up sessions.
2. Dietary recommendations for children with diabetes are based on healthy eating principles suitable for all children and families with the aim of improving general health, diabetes outcomes and reducing vascular risks.
3. Nutritional advice should be adapted to cultural, ethnic and family traditions as well as the cognitive and psychosocial needs of the individual child (see chapters 5 and 15: Diabetes education and Psychological care).
4. Ongoing annual nutrition counselling and reassessment should be provided as a routine, or more often as required and requested, to monitor the child's growth, lifestyle changes, psychosocial adaptation, and the identification of specific dietary problems such as inadequate or excessive weight gain or dysfunctional eating habits.
5. Children and their families should be given tailored advice about the amount, type and distribution of carbohydrate to include in regular balanced meals and snacks (if appropriate) over the day to promote optimal growth, development and blood glucose control. This advice should be regularly reviewed to accommodate changes in energy requirements, physical activity and insulin therapy.
6. The dynamic relationship between carbohydrate intake, physical activity and insulin should be explained and education provided on the assessment of the carbohydrate content of different foods for both children using fixed insulin regimens and those on intensive insulin therapy.
7. Fluids with a high concentration of sucrose or foods with high levels of saturated fat should be limited or, if possible, avoided.
8. Advice should be given on the use of fluids and foods in the prevention and management of hypoglycaemia, particularly during and following physical activity and sport.
9. Prevention of overweight/obesity is a key strategy of care. Parental support and guidance on self-discipline, energy content of foods, appropriate portion sizes, regular meals, fat and sugar intake and physical activity is essential.
10. Consider advice on the effect of alcohol before the adolescent is exposed to it. Attitudes towards alcohol will vary between countries and cultures. If alcohol is included in the lifestyle of the adolescent, education on the prevention of hypoglycaemia and ways to reduce alcohol intake should be provided.

### Limited care

1. All young people and their families should receive nutritional and dietetic education related specifically to their diabetes.
2. The basic principles of nutritional management are as for Recommended care.
3. Growth monitoring is an essential part of diabetes nutritional management. Energy, carbohydrate and protein intake should be sufficient to achieve optimal growth and maintain an ideal body weight. Excessive restriction of carbohydrate intake to lower blood glucose levels should be avoided.
4. Insulin dosage should match the carbohydrate intake.
5. Recommended daily intakes of vitamins and minerals should be achieved for general health (and vascular protection). Monitoring of at risk nutrients, for example iron and calcium, should occur regularly in susceptible populations.
6. Dietary advice/meal planning should be revised regularly to meet changes in supply of food, changes in appetite related to age and to ensure optimal growth.

7. Conventional insulin regimens demand some consistency in carbohydrate amount and distribution to be successful. An individualised meal plan based on a diet history can assist blood glucose control. However, this requires regular review in a growing child.

### Comprehensive care

1. Intensive insulin regimens allow for more flexible lifestyles, if matching the insulin doses to carbohydrate intake is understood and applied. Insulin to carbohydrate ratios can be calculated as a practical method of applying this principle. This will require an understanding of quantitative carbohydrate estimation or counting. Regularity in meal times and eating routines are still important for optimal glycaemic outcomes.
2. These regimens require a higher level of structured education, monitoring and support to be successful.
3. For children on insulin pump therapy, advice should be provided on appropriate bolus types to use for different meals to attain optimal postprandial glycaemic control.
4. Detailed information may be obtained with the use of Continuous Glucose Monitoring about the effect of different foods on blood glucose levels. This can permit adjustment of insulin dose and delivery at meal-times to optimise postprandial control (see chapter 8: Insulin treatment)
5. The diabetes team should consider whether a screening questionnaire might be helpful in identifying dysfunctional eating habits, including specific eating disorders (See Guideline on Psychological Care)
6. Children and young people engaged in competitive sport will require additional nutritional advice and individualised meal plans for training and competitive situations.

## Rationale

Nutritional management is one of the cornerstones of diabetes care and education (1). Different countries and regions have widely varying cultures and socio-economic status that influence and dominate dietary habits. Although there is strong evidence for nutritional requirements in young people the scientific evidence base for many aspects of diabetes dietary management is weak and often anecdotal. Thus, sensitivity to individual needs, and pragmatism rather than dogmatism is most helpful for effective dietary counselling.

The impact of diabetes on eating behaviour must not be underestimated and may cause psychological disturbance (2). Therefore, dietary and lifestyle changes are assisted optimally by experienced professionals. Education should be patient-centred and include behaviour change approaches, counselling and/or motivational interviewing and should be regularly reviewed to meet the constantly changing needs and the individual requirements of the developing child. In order to be most effective, the dietitian needs to develop a consistent, trusting and supportive relationship with the families concerned and also have clear agreed goals with the interdisciplinary team.

These recommendations target healthy eating principles, optimum glycaemic control, the reduction of CV risk

factors, the maintenance of psychosocial well-being and family dynamics.

## Evidence-base

Nutrition therapy, when used in combination with other components of diabetes care, can further improve clinical and metabolic outcomes (1).

Successful implementation of meal planning with appropriate insulin adjustments has been shown to improve glycaemic control (3,4). Moreover, regularity in meal times and routines where the child and family sit down and eat together, helping to establish better eating practices and monitoring of food intake has been shown to be associated with better glycaemic outcomes (5).

It is advised that total daily energy intake (TDEI) should be distributed so that carbohydrate forms > 50%, fat < 35% (saturated fat < 10%), and protein 10-15%. Sucrose can provide up 10% of TDEI (6).

There is no strong research evidence to demonstrate that one particular educational tool or method of quantifying carbohydrate intake (grams/portions/exchanges/glycaemic index or load) is superior to another (1,7). Most nutrition education tools are based upon the premise that carbohydrate amount and type is recognised as the

primary determinant of the postprandial response (8) and along with distribution of carbohydrate form the basis of most education programmes (9).

The incidence of eating disorders and the detrimental effects on glycaemic control, especially in adolescent females, has a strong evidence base (10).

There is an urgent need for more research and rigorous evaluation of dietetic management in childhood diabetes (11).

## Consideration

- ▶ In all clinical settings it is essential that one of the interdisciplinary paediatric diabetes team (ideally an experienced paediatric dietitian) understands dietary management and is able to offer appropriate specialist advice.
- ▶ Any consideration of the management of diabetes should involve an appraisal of food availability and a patient's dietary intake including food intake and physical activity patterns.
- ▶ Unexpected weight loss may be a sign not only of illness (infections, coeliac disease, etc.) but also of insulin omission or a disorder of eating.
- ▶ Co-morbidities such as coeliac disease require additional specialist dietetic intervention.

## Implementation

It is important that government departments and public health authorities recognise that children and adolescents with diabetes not only require adequate nutrition but specialist dietetic advice to maintain good glycaemic control, optimal growth and weight. Implementation of comprehensive nutritional advice on intensive insulin regimens requires extra resources.

## Evaluation

Regular dietetic evaluation and growth monitoring should be part of routine care of children and adolescents with type 1 diabetes and be recorded as part of clinic consultations.

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DIABETIC  
KETOACIDOSIS

## Recommendations

### Recommended care

Children and adolescents with DKA should be managed in centres experienced in its treatment and where vital signs, neurological status and laboratory results can be monitored frequently.

#### 1. Emergency assessment

- › Perform a clinical evaluation to confirm the diagnosis and determine its cause. Look for evidence of infection.
- › Weigh the patient and use this weight for calculations.
- › Assess clinical severity of dehydration.
- › Assess level of consciousness (Glasgow coma scale).
- › Obtain a blood sample for laboratory measurement of serum or plasma glucose, electrolytes (including bicarbonate or total carbon dioxide [TCO<sub>2</sub>]), blood urea nitrogen, creatinine, osmolality, venous (or arterial in critically ill patient) pH, pCO<sub>2</sub>, haemoglobin and haematocrit or blood count, calcium, phosphorus, and magnesium concentrations. The cause of a high white blood cell count is more often stress than infection.
- › Perform a urinalysis or blood test for ketones (or point-of-care measurement on a fingerprick blood sample using a bedside meter if available).
- › Obtain appropriate specimens for culture (blood, urine, throat), if there is clinical evidence of infection.

If laboratory measurement of serum potassium is delayed, perform an electrocardiogram for baseline assessment of potassium status (see details of EKG features below under section 5: Potassium replacement).

#### 2. 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 catheter should be placed for convenient and painless repetitive blood sampling.
- › A cardiac monitor should be used for continuous electrocardiographic monitoring to assess T-waves for evidence of hyperkalemia or hypokalemia.
- › Give oxygen to patients with severe circulatory impairment or shock.
- › Give antibiotics to febrile patients after obtaining appropriate cultures of body fluids.
- › Catheterize the bladder if the child is unconscious or unable to void on demand (e.g. infants and very ill young children).

#### 3. Fluids and salt replacement

- › For patients who are severely volume depleted but not in shock, volume expansion (resuscitation) should begin immediately with 0.9% saline to restore the peripheral circulation.
  - › The volume and rate of administration depends on circulatory status and, where it is clinically indicated, the volume administered typically is 10 ml/kg/h over 1-2 hours, and may be repeated if necessary, to assure a stable circulatory status.
- › In the rare patient with DKA who presents in shock or severe circulatory collapse, rapidly restore circulatory volume with isotonic saline in 20 ml/kg bolus infused as quickly as possible through a large bore cannula. Repeat if necessary, with careful reassessment after each bolus.
  - › Intraosseous access should be considered after multiple attempts to gain IV access have failed.
- › Fluid management (deficit replacement) should be with 0.9% saline for at least 4-6 hours.

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 section 5: Potassium replacement).

- 】 The rate of fluid (IV and oral) should be calculated to rehydrate evenly over 48 hours.
- 】 Example of volumes of maintenance + 10% deficit, to be given evenly over 48 hours.

Weight (kg)	Infusion rate (ml/kg/h)
4 - 9	6
10 - 19	5
20 - 39	4
40 - 59	3.5
60 - 80	3

*Example: A 6 year old boy weighing 20 kg will be given 80 ml per hour or a total volume of 1920 ml per 24 hours for two days.*

- 】 As the severity of dehydration may be difficult to determine and frequently is under- or overestimated, 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.
- 】 Urinary losses should not routinely be added to the calculation of replacement fluid, but may be advisable in rare circumstances.
- 】 When oral fluid is tolerated, IV fluid should be reduced accordingly, so that the total amount of fluid given to the patient per hour does not exceed the calculated hourly rehydration volume
- 】 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.

#### 4. Insulin therapy

- 】 Start insulin infusion 1-2 hours after starting fluid replacement therapy; i.e. after the patient has received initial volume expansion.
- 】 Correction of insulin deficiency
- 】 Dose: 0.1 unit/kg/hour (e.g. dilute 50 units Regular [soluble] insulin in 50 ml normal saline, 1 unit = 1 ml).
- 】 Route of administration IV.
- 】 An IV bolus is unnecessary and should not be used at the start of therapy.
- 】 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 normalisation of blood glucose concentrations.
- 】 If the patient demonstrates marked sensitivity to insulin (e.g. some young children with DKA and patients with HHS (hyperglycaemic hyperosmolar state), 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. Thereafter, the plasma glucose concentration typically decreases at a rate of 2-5 mmol/l/h, depending on the timing and amount of glucose administration.
- 】 To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycaemia, 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.
- 】 It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycaemia, while continuing to infuse insulin to correct the metabolic acidosis.
- 】 If blood glucose falls very rapidly (> 5 mmol/l/h, 90 mg/dl/h) after initial fluid expansion, consider adding glucose even before plasma glucose has decreased to 17 mmol/l (300 mg/dl).



## 9. Cerebral oedema

Warning signs and symptoms of cerebral oedema include:

- › Headache and slowing of heart rate.
- › Change in neurological status (restlessness, irritability, increased drowsiness, incontinence).
- › Specific neurological signs (e.g. unreactive pupils, cranial nerve palsies).
- › Rising blood pressure.
- › Decreased oxygen saturation.

Treatment of cerebral oedema

- › Initiate treatment as soon as the condition is suspected.
- › Reduce the rate of fluid administration by one-third.
- › Give mannitol 0.5-1 g/kg IV over 20 minutes and repeat if there is no initial response in 30 minutes to 2 hours.
- › Hypertonic saline (3%), 5 ml/kg over 30 minutes, may be an alternative to mannitol, especially if there is no initial response to mannitol.
  - › 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  $p\text{CO}_2 < 2.9 \text{ kPa}$  [22 mm Hg]) has been associated with poor outcome and is not recommended.
- › After treatment for cerebral oedema 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 or haemorrhage, which may benefit from specific therapy.

10. Clinical and biochemical monitoring should include:

- › 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 oedema.
- › Amount of administered insulin.
- › Hourly (or more frequently as indicated) accurate fluid input (including all oral fluid) and output.
- › Capillary blood glucose concentration should be measured hourly.
- › Laboratory tests: serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphorus, haematocrit, and blood gases should be repeated two to four hourly, or more frequently, as clinically indicated, in more severe cases.
- › Urine ketones until cleared or blood  $\beta$ -hydroxybutyrate concentrations (either capillary or serum), if available, every 2 hours.

## Limited care

1. Written guidelines should be available for DKA management in children.
2. Weigh the child.
3. The principles as for Recommended care whenever possible.
4. Potassium:

If IV fluids and insulin are available, but not potassium: after 1 hour of fluid therapy, give a bolus dose of insulin of 0.1 U/kg (0.05 U/kg if younger than 5 years), and then arrange urgent transport to a facility that can provide potassium. If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyperkalemia or hypokalemia.

5. Insulin:

In circumstances where continuous IV administration of insulin is not possible, hourly or 2 hourly SC or IM administration of a short- (Regular insulin) or rapid-acting insulin analogue (insulin lispro, aspart or glulisine) may be as effective as IV regular insulin infusion in patients with uncomplicated DKA. and calcium, should occur regularly in susceptible populations.

6. SC insulin dose: 0.1 unit/kg every 1-2 hours.

7. When blood glucose is < 14 mmol/l (250 mg/dl), give glucose-containing fluids orally, and if needed, reduce SC insulin to 0.05 unit/kg at 1-2 hour intervals to keep blood glucose ~ 11 mmol/l (200 mg/dl) until resolution of DKA.

8. Intravenous fluids:

When IV fluids are unavailable, arrange urgent transport to a facility that can provide IV fluid therapy. Giving insulin before intravenous fluid treatment has been started may precipitate shock, and increases the risk of hypokalemia and cerebral oedema..

9. Give little sips (or small volumes through a syringe) of Oral Rehydrating Solution (ORS) as frequently as possible (without the child vomiting). If vomiting does not occur after 1-2 hours give ORS at a rate of 5 ml per kg body weight per hour.

10. In some cases it may be possible to insert a nasogastric tube and slowly rehydrate with ORS at 5 ml per kg body weight per hour.

11. If ORS is not available, fruit juice and coconut water provide some potassium.

12. Transportation:

If the child cannot be transported (e.g. roads blocked), give oral rehydration as above and SC insulin 0.05 units/kg every 1-2 hours. Decreasing urine ketone concentrations indicate resolving acidosis.

13. Laboratory resources:

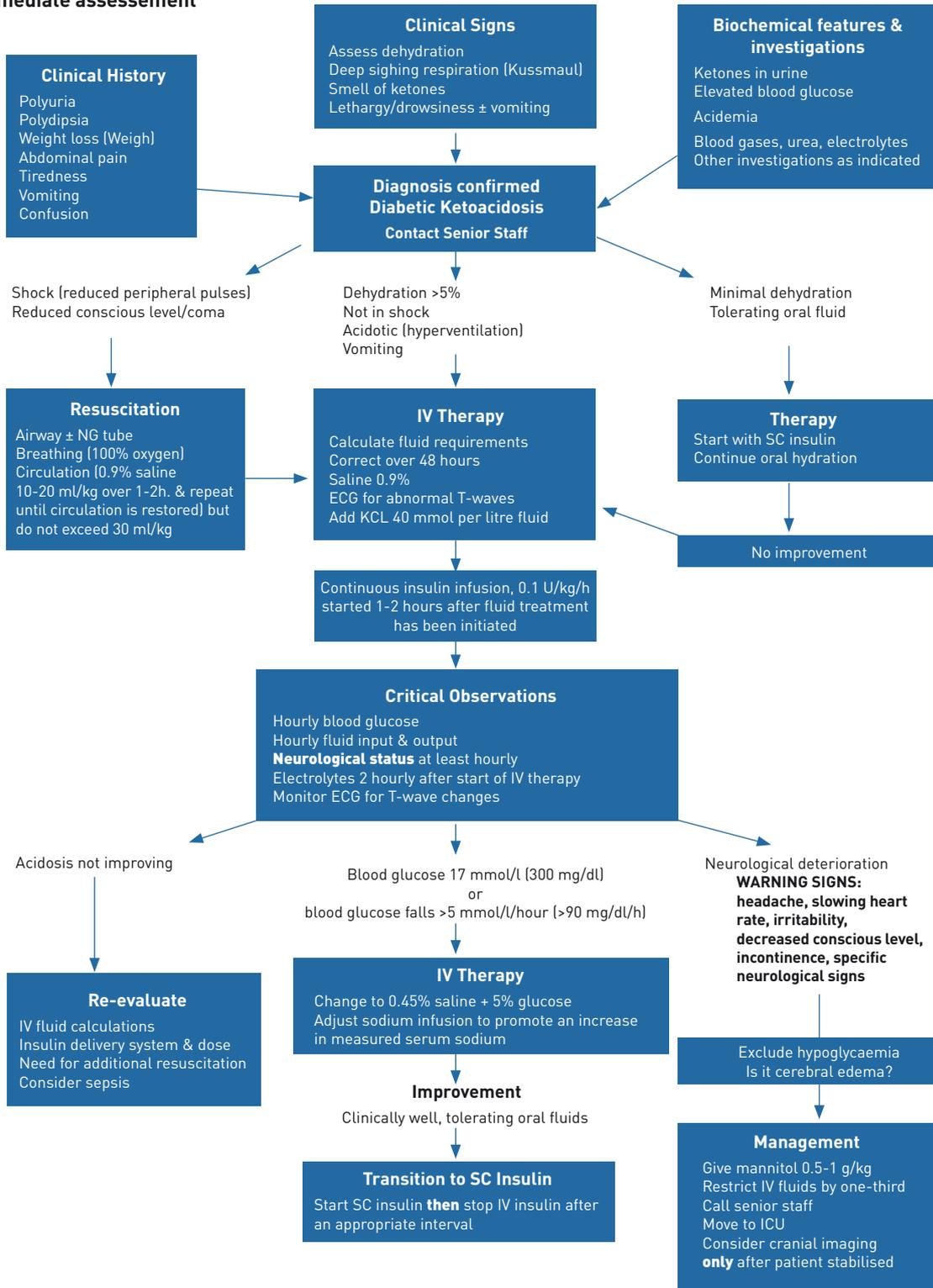
If an acid-base analysis is not available, the diagnosis of ketoacidosis can be made by a bedside  $\beta$ -hydroxybutyrate (blood ketones) test showing a value of 3 mmol/l or greater.

## Comprehensive care

1. A paediatric endocrinologist or paediatric critical care specialist with training and expertise in the management of DKA in children should direct management.
2. The child with severe DKA should receive care in an intensive care unit or comparable high intensity unit.
3. Measurement of blood  $\beta$ -hydroxybutyrate concentration (blood ketones) is useful to confirm ketoacidosis and to monitor the response to treatment. A bedside methods for this analysis should be available. When there is acidosis without increased levels of  $\beta$ -hydroxybutyrate, suspect lactic or hyperchloremic acidosis (measure serum lactate and chloride concentrations).

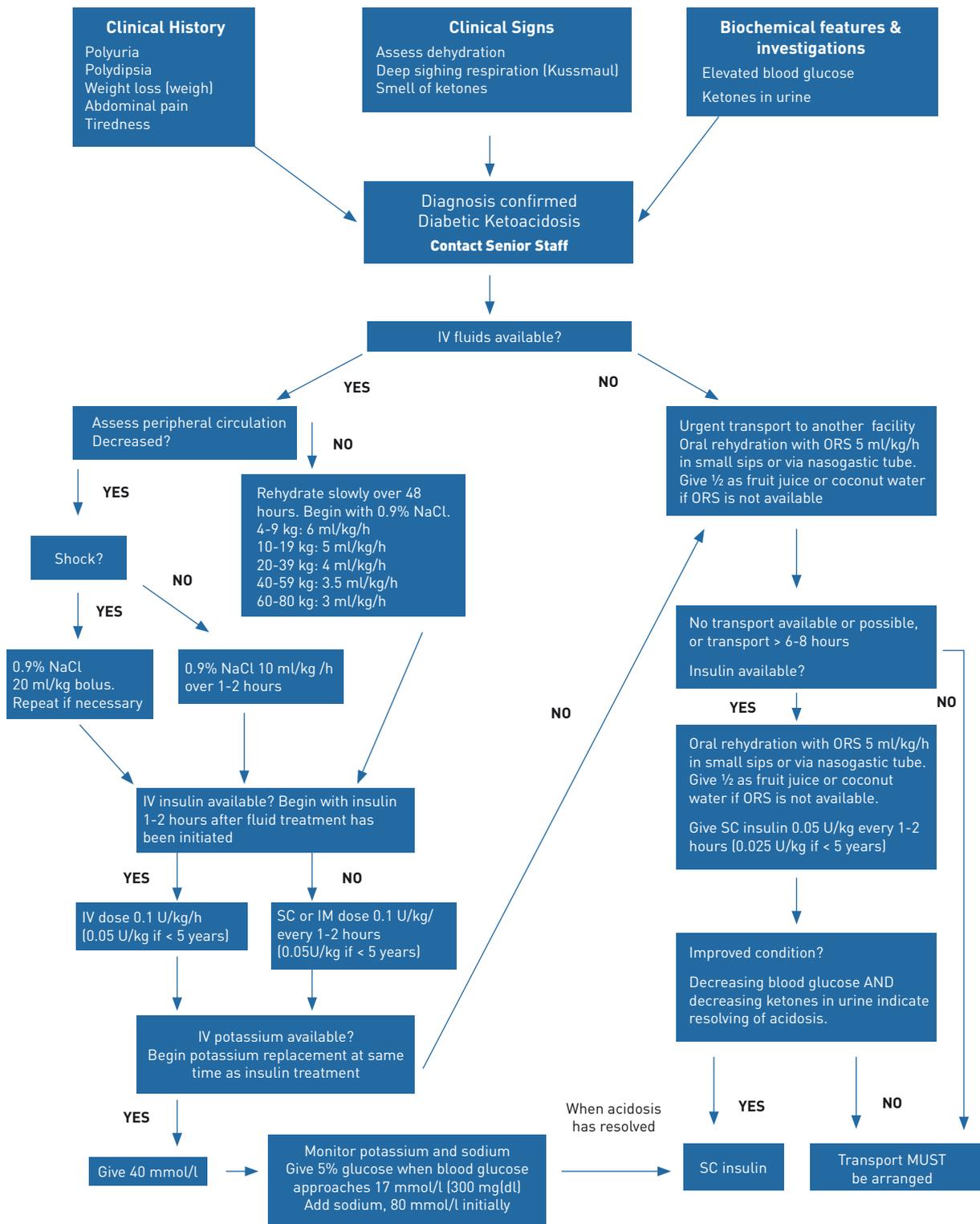
Figure 1. Immediate assessment of recommended care

Immediate assessment



Algorithm for the management of diabetic ketoacidosis  
Source: adapted from Dunger et al. Karger Publ. 1999

Figure 2. Immediate assessment of limited care



## Rationale

DKA results from absolute or relative deficiency of circulating insulin and the effects of increased levels of the counter regulatory hormones (catecholamines, glucagon, cortisol and growth hormone) [1,2]. The combination of low serum insulin and high counter regulatory hormone concentrations causes an accelerated catabolic state with increased glucose production by the liver and kidney and impaired peripheral glucose utilisation resulting in hyperglycaemia, hyperosmolality, increased lipolysis and ketogenesis, causing hyperketonaemia and metabolic acidosis. Hyperglycaemia and hyperketonaemia cause osmotic diuresis, dehydration, and loss of electrolytes, which often is aggravated by vomiting. If these metabolic derangements are not arrested and corrected with exogenous insulin and fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue.

DKA is characterised by severe depletion of water and electrolytes from both the intra- and extracellular fluid compartments. 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.

Successful management of DKA requires 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. There should be documentation on a flow chart of hour-by-hour clinical observations, intravenous and oral medications, fluids, and laboratory results.

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 paediatrician with training and expertise in the management of DKA should direct inpatient management. Patients with DKA have a deficit in extracellular fluid (ECF) volume that usually is in the range 5-10% [3,4]. Clinical estimates of the volume deficit are subjective and inaccurate [5,6]; therefore, in moderate DKA use 5-7% and in severe DKA 7-10% dehydration. The objectives of fluid and electrolyte replacement therapy are: restoration of circulating volume; replacement of sodium and the ECF and ICF deficit of water; improved glomerular filtration with enhanced clearance of glucose and ketones from the blood; reduction of risk of cerebral oedema.

Although rehydration alone causes a rapid decrease in blood glucose concentration [7,8], insulin therapy is essential to normalise blood glucose levels and suppress

lipolysis and ketogenesis [9]. Extensive evidence indicates that «low dose» IV insulin administration should be the standard of care [10]. Start insulin infusion 1-2 hours after starting fluid replacement therapy; i.e. after the patient has received initial volume expansion [11].

Children with DKA suffer total body potassium deficits of the order of 3-6 mmol/kg [3,4,12-14]. The major loss of potassium is from the intracellular pool because of transcellular shifts 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 also 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 [15]. Renal dysfunction, by enhancing hyperglycaemia and reducing potassium excretion, contributes to hyperkalemia [15]. Administration of insulin and the correction of acidosis will drive potassium back into the cells, decreasing serum levels [16]. The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias.

Depletion of intracellular phosphate occurs in DKA and phosphate is lost as a result of osmotic diuresis [3,4,13]. Plasma phosphate levels fall after starting treatment and this is exacerbated by insulin, which promotes entry of phosphate into cells [17-19]. Total body phosphate depletion has been associated with a variety of metabolic disturbances [20-22]. Clinically significant hypophosphatemia may occur if intravenous therapy without food intake is prolonged beyond 24 hours [3,4,13].

Severe acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolised, which generates bicarbonate. 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 [23-26]. Bicarbonate therapy may cause paradoxical CNS acidosis [27,28]; rapid correction of acidosis with bicarbonate causes hypokalemia [27,29,30]. There may be selected patients who may benefit from cautious alkali therapy. These include: patients with severe acidaemia (arterial pH < 6.9) in whom decreased cardiac contractility and peripheral vasodilatation can further impair tissue perfusion, and patients with life-threatening hyperkalemia [31].

When  $\beta$ -hydroxybutyrate (blood ketone) monitoring is performed during the course of treatment [32], the level should decrease by about 0.5-1 mmol/l per hour [33]. Because bedside meters are not accurate above 3 mmol/l

(i.e. levels that occur in DKA), decisions about insulin therapy should not only be based on measurements of blood  $\beta$ -hydroxybutyrate concentrations (34). If blood ketone levels appear not to decrease as expected during the course of treatment and the pH fails to increase or the anion gap does not decrease, then the dose of insulin should be increased.

## Evidence-base

The principles described above 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) (35,36).

Despite much effort to find the cause of cerebral oedema it remains incompletely understood. 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 oedema (35). No treatment strategy can be definitively recommended as being superior to another based on evidence.

## Consideration

The personnel and material resources to optimally manage DKA (as described above) are not uniformly available throughout the world. Health care providers, therefore, must adapt the key principles of DKA management to local circumstances while striving to obtain additional resources necessary to enhance the quality of care for patients with DKA.

## Implementation

The child should receive care in a unit that has:

- ▶ Experienced nursing staff trained in monitoring and management.
- ▶ Written guidelines for management of diabetic ketoacidosis (DKA) in children
- ▶ Access to bedside monitoring of  $\beta$ -hydroxybutyrate (blood ketones) and to a laboratory that can provide frequent and timely measurements of biochemical variables.

A specialist/consultant paediatrician with training and expertise in the management of DKA should direct in-patient management.

## Evaluation

- ▶ The management of an episode of DKA in a patient with known diabetes is not complete until its cause has been identified and an attempt made to treat it. Delayed diagnosis is the cause in new onset diabetes, whereas insulin omission, either inadvertently or deliberately, is the cause in most cases of established diabetes. There is often 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 the inability of the patient to manage his or her own diabetes unassisted. An intercurrent infection is usually not the cause when the patient/family is properly educated in diabetes management, is receiving regular follow-up care, and has telephone access to a diabetes team. In patients who use an insulin pump, the most common cause of DKA is failure to take extra insulin with a pen or syringe when unrecognised failure of insulin delivery occurs (hyperglycaemia with hyperketonaemia or ketonuria). Children seldom have DKA when insulin administration is closely supervised or performed by a responsible adult. A psychiatric social worker or clinical psychologist should be consulted to help to identify the psychosocial reason(s) underlying the development of DKA.
- ▶ The overall mortality rate in paediatric patients with DKA range between 0.15% and 0.3% (35); however, the rate is almost certainly higher in underserved populations with inadequate medical services. Cerebral oedema accounts for between 57% and 87% of all DKA-related deaths.
- ▶ Symptomatic cerebral oedema occurs in 0.5-1% of paediatric DKA episodes and has a high mortality rate (21-24%) (36). Approximately one-fourth of survivors sustain permanent neurological injury. Despite several theories, there is no general agreement concerning the pathophysiologic mechanisms underlying cerebral oedema in DKA (38).
- ▶ The frequency of DKA at clinical onset of diabetes varies widely by geographic region from approximately 15% to 75%, inversely corresponding to the regional incidence (i.e. level of awareness in the community) of type 1 diabetes. DKA at diagnosis is more common in children < 5 years of age and in those social or economic situations that do not permit ready access to medical care.
- ▶ Sustained reductions in the frequency of DKA at onset of diabetes have been reported where zealous efforts have been made to educate the medical community and school personnel concerning the classic symptoms of diabetes and, especially, the significance of secondary nocturnal enuresis (39,40).

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## ASSESSMENT AND MONITORING OF HYPOGLYCAEMIA

## Recommendations

### Recommended care

Children and adolescents with DKA should be managed in centres experienced in its treatment and where vital signs, neurological status and laboratory results can be monitored frequently.

1. The aim of diabetes treatment should be to achieve the best possible glycaemic control without the occurrence of severe hypoglycaemia.
2. Hypoglycaemia should be prevented because:
  - › Its occurrence is frequently predictable;
  - › It is often associated with significant psychosocial dysfunction;
  - › It can lead to permanent long-term sequelae and is potentially life threatening.
3. Hypoglycaemia unawareness should be avoided or reversed promptly in order to achieve optimal glycaemic control without an unacceptable risk for hypoglycaemia.
  - › Patients and parents should be trained to contact their diabetes team if hypoglycaemia unawareness is identified (i.e. hypoglycaemia occurs without symptoms or if symptoms are those of neuroglucopenia, not autonomic symptoms).
  - › Blood glucose goals need to be adjusted upward if recurrent hypoglycaemia and/or hypoglycaemia unawareness is identified.
  - › Hypoglycaemia unawareness can be reversed by scrupulously avoiding blood glucose levels < 3.5–4.0 mmol/ for approximately 2 weeks.
4. Children, parents, schoolteachers, and other caregivers should be given training to recognise the early warning signs of hypoglycaemia and treat low blood glucose immediately and appropriately.
5. Hypoglycaemia treatment requires:
  - › An immediate source of glucose or sucrose.
  - › Equipment for blood glucose measurement for confirmation and safe management of hypoglycaemia.
  - › Glucagon, accessible to all parents and caregivers, especially when the risk of severe hypoglycaemia is high. Education on administration of glucagon is essential.
  - › Urgent access to a facility/mobile service able to administer IV dextrose to reverse severe hypoglycaemia, if glucagon is not available or if the hypoglycaemia is unresponsive to glucagon.
6. Hypoglycaemia can be treated with glucose tablets/sugar lumps or a sweet drink (glucose/sucrose drinks, cola, etc.); approximately 9 grams of glucose is needed for a 30 kg child and 15 grams for a 50 kg child (0.3 g/kg).
  - › Retest blood glucose 10–15 minutes after treatment, to confirm resolution of hypoglycaemia.
  - › Repeat blood glucose 30 minutes later to confirm adequate treatment without overtreatment.

Severe hypoglycaemia with loss of consciousness ± convulsions (particularly if there is vomiting) is most safely and rapidly reversed by an intramuscular or subcutaneous injection of glucagon 0.5 mg for age < 12 years, 1.0 mg for ages > 12 years, or 10–30 mcg/kg body weight (23).
7. Patients should receive education about the times and situations which are risk factors for hypoglycaemia, so increased glucose monitoring can be performed and treatment regimens can be changed.
  - › For example, blood glucose monitoring should be performed prior to exercise, and extra carbohydrates should be eaten based on the blood glucose level and the expected intensity and duration of the exercise.

8. Hypoglycaemic episodes should be assessed to determine the cause evaluating:
  - › Insulin action profile (time of insulin administration, peak insulin action, and intensity of insulin action);
  - › Recent food intake (timing and amount of carbohydrates eaten and peak blood glucose effect of recent food);
  - › Recent physical activity (timing, duration, and intensity).
9. If unexplained hypoglycaemia is frequent, evaluation for unrecognised celiac and Addison's disease should be considered.
10. Children and adolescents with diabetes should wear some form of identification or warning of their diabetes (e.g. Medic Alert).

### Limited care

1. Health care systems should work toward making blood testing available for confirmation and treatment of hypoglycaemia.
2. All possible Recommended care recommendations should be implemented with emphasis on:
  - › Training of the child and all caregivers to recognise early warning signs of hypoglycaemia and treat low blood glucose immediately;
  - › Educating patients and families as to times and situations associated with increased risk of hypoglycaemia and when treatment regimens may need to be changed to adapt to these situations and prevent hypoglycaemia.
3. When possible, severe hypoglycaemia should be treated with glucagon or IV dextrose.
  - › If glucagon or IV dextrose is not available, a common practice is to administer a rapid-acting source of glucose (e.g. glucose gel or honey) into the buccal pouch. However, the efficacy of this practice is anecdotal and there is no scientific evidence for absorption of glucose from the buccal mucosa. On the contrary, there is one study in adults showing no buccal absorption of glucose [53].
  - › Rectal absorption of glucose is very poor and this route should not be recommended.

### Comprehensive care

1. Comprehensive care recommendations include all of the recommendations above for Recommended care.
2. The choice of insulin therapy, i.e. analogue insulins, may decrease the risk of hypoglycaemia while improving HbA<sub>1c</sub>.
3. The use of continuous glucose monitors may decrease the risk of hypoglycaemia and may improve HbA<sub>1c</sub>.
4. A patient with repeated severe hypoglycaemia may benefit from a trial with insulin pump therapy.
5. Continuous Glucose Monitoring (CGM) should be available for monitoring of suspected nighttime hypoglycaemia.

## Rationale

Hypoglycaemia is the result of a mismatch between insulin dose, food consumed, and recent exercise and is rarely, if ever, a spontaneous event. A careful review of blood glucose records will yield a retrospective prediction of the hypoglycaemic event for at least 50% of events (1). Hypoglycaemia is a major limiting factor in attempts to achieve near normal blood glucose levels because hypoglycaemia can be accompanied by unpleasant, embarrassing, and potentially dangerous symptoms and causes significant anxiety and fear in the patient and their caregivers (2,3). Additionally, in its extreme manifestations, hypoglycaemia can lead to permanent sequelae and even death (4-6). For these reasons, every effort should be made to limit severe hypoglycaemia. Understanding how insulin, food, and exercise must be balanced in order to achieve near normoglycaemia and reduce the risk of hypoglycaemia is essential for all patients and families living with diabetes.

## Evidence-base

These recommendations are primarily based on the ISPAD Clinical Practice Consensus Guideline on Assessment and Management of Hypoglycaemia in Children and Adolescents with Diabetes (7). Many factors influence the occurrence and symptoms of hypoglycaemia and an understanding of these is necessary in order to be able to provide good advice to families and other care providers on hypoglycaemia treatment and prevention.

Intensive diabetes management initially resulted in a dramatic increase in the rate of hypoglycaemia in adolescents (8). Greater experience with intensive therapy and use of analogue insulins decreased the rates of severe hypoglycaemia to 8-30 episodes per 100 patient-years of diabetes exposure (9). Predictors of severe hypoglycaemia are: age (infancy and adolescence) (10); increased duration of diabetes; lower HbA<sub>1c</sub> and higher insulin dose (11). Additional factors are exercise and the balance of insulin with food. Further studies are needed provide current data on the direct and indirect cost (e.g. lost productivity and diminished quality of life) of hypoglycaemia.

The signs and symptoms are often the signs and symptoms of autonomic (adrenergic) activation but severe hypoglycaemia is also accompanied by neurological dysfunction (neuroglycopenia). Children may exhibit behavioural or mood changes when their blood glucose falls but remains within or above the normal range. Autonomic signs and symptoms include trembling, pounding heart, cold sweatiness, pallor, headache and nausea. Neuroglycopenic signs and symptoms include difficulty concentrating, blurred or altered vision, difficulty hearing, slurred speech, altered judgment and confusion, unsteady gait, loss of consciousness, seizure and death. Behavioural

and mood changes include irritability, erratic behaviour, nightmares, and inconsolable crying.

Blood glucose values below 3.3-3.9 mmol/l (60-70 mg/dl) are generally agreed to place the individual at risk for severe hypoglycaemia and a value of 3.9 mmol/l (70 mg/dl) is recommended for evaluating therapies designed to alter frequency of hypoglycaemia (12,13). This level is also recommended as the lower blood glucose target children and adults with insulin-treated diabetes in order to avoid hypoglycaemia and maintain consistency in reporting hypoglycaemia.

The blood glucose threshold for activation of autonomic signs and symptoms is related to activation of counter-regulatory hormones and has been shown to be higher in children than in adults and to vary directly with the level of blood glucose control (higher HbA<sub>1c</sub>, higher blood glucose threshold) (14,15). The blood glucose threshold for symptoms may be affected by antecedent hypoglycaemia or hyperglycaemia (16,17).

The blood glucose threshold for neuroglycopenia neither varies as much with the level of glucose control nor with antecedent hypoglycaemia (18). Neuroglycopenia occurs before autonomic activation when hypoglycaemia unawareness is present (2). This phenomenon is an important cause of severe hypoglycaemia, accounting for 36% of the hypoglycaemia in awake individuals with type 1 diabetes (19). Hypoglycaemia awareness can be reversed by avoiding hypoglycaemia for 2-3 weeks (20).

**Hypoglycaemia** is defined as an event when a blood glucose level of  $\leq 3.9$  mmol/l (70 mg/dl) is documented and the child or parent is aware of, responds to, and treats the hypoglycaemia orally. This may be symptomatic or asymptomatic. In addition, an event may occur when symptoms typical of hypoglycaemia occur and are relieved by treatment but the blood glucose value is  $> 3.9$  mmol/l. This may occur if the blood glucose level falls rapidly or may occur in patients with chronically poor glycaemic control. This is termed relative hypoglycaemia. There is no evidence of any neurocognitive harm from relative hypoglycaemia but, without appropriate patient education, it may become a barrier to achievement of more optimal glycaemia. With severe hypoglycaemia the child has altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma  $\pm$  convulsions and may require parenteral therapy (glucagon or IV dextrose).

**Treatment of moderate hypoglycaemia** should be provided promptly and should provide immediate oral, rapidly absorbed, simple carbohydrate calculated to raise blood glucose level to approximately 5.6 mmol/l (100 mg/dl). For moderate hypoglycaemia in adults, 20 g of oral, rapidly absorbed, simple carbohydrate, e.g. glucose tablets,

glucose/sucrose drinks, cola, etc., will raise the blood glucose by approximately 2.5-3.6 mmol/l (45-65 mg/dl) (21). For a child, this translates to approximately 0.3g/kg, i.e. approximately 9 grams of glucose is needed for a 30 kg child and 15 grams for a 50 kg child. The amount of carbohydrate required will depend also on the type of insulin therapy, proximity to recent insulin dosage, the intensity of antecedent exercise as well as other factors (22). If sucrose or fructose is used, slightly higher amounts are required compared to pure glucose (21).

- 】 Chocolate, whole milk and other foods containing fat will cause the sugar to be absorbed more slowly and should be avoided as the initial treatment of hypoglycaemia.
- 】 After treatment, wait 10-15 minutes, retest blood glucose, if no response or an inadequate response, then repeat oral intake as above. Retest the blood glucose in another 20-30 minutes to confirm that target glucose has been maintained and not exceeded.
- 】 For initially lower glucose values, as symptoms improve or euglycaemia is restored, the next meal or snack may be ingested (e.g. fruit, bread, cereal, and milk) to prevent recurrence of hypoglycaemia.

**Treatment of severe hypoglycaemia.** Urgent treatment is required. Severe hypoglycaemia with loss of consciousness  $\pm$  convulsions (particularly if there is vomiting) is most safely and rapidly reversed by an intramuscular or subcutaneous injection of glucagon 0.5 mg for age < 12 years, 1.0 mg for ages > 12 years, or 10-30 mcg/kg body weight (23). In a hospital setting, IV glucagon may be given. If glucagon is unavailable or recovery is inadequate, intravenous dextrose should be administered slowly by trained personnel over several minutes, e.g. dextrose 10-30% at a dose of 200-500 mg/kg (dextrose 10% is 100 mg/ml) to reverse the hypoglycaemia. Rapid administration, or excessive concentration, i.e. dextrose 50%, may result in an excessive rate of osmotic change. In the recovery phase after treatment of severe hypoglycaemia, close observation and blood glucose monitoring is essential because recurrent hypoglycaemia may occur and vomiting is common. Should recurrent hypoglycaemia occur, the child will require additional oral carbohydrate and/or IV infusion of dextrose e.g. dextrose 10%, 2-5 mg/kg/min (1.2-3.0 ml/kg/h).

**Family education to reduce risk of hypoglycaemia.** Families should receive education about risk factors for hypoglycaemia including the times when hypoglycaemia is more likely to occur so that more frequent glucose monitoring may be initiated. Hypoglycaemia occurs more frequently when the treatment regimen is altered (more insulin, less food, and more exercise); in younger children; with lower HbA<sub>1c</sub> levels (22,24,25); when there are frequent low blood glucose levels; when awareness of

autonomic symptoms is reduced (18); during sleep; after the ingestion of alcohol (26). Alcohol suppresses gluconeogenesis and may induce hypoglycaemia unawareness. In combination with exercise, drinking can lead to severe hypoglycaemia, which may occur 10-12 hours after the exercise or alcohol ingestion.

#### **Choice of the diabetes treatment regimens can reduce hypoglycaemia risks**

**Insulin.** A review of insulin action profiles, with consideration of the patient/family schedule for meals and selection of the best action profiles for their schedule will reduce hypoglycaemia. The use of continuous subcutaneous insulin infusion systems (CSII or pumps) and insulin analogues have been shown to decrease mild to moderate hypoglycaemia (27,28,29). Studies have not been powered to show a difference in severe events.

**Food.** Food intake (timing and content) should be adjusted so that glycaemic peaks are most closely matched to insulin action peaks. Daytime and bedtime snacks may need to be added to the meal plan, especially in younger children or if intermediate-acting insulin is used. Adjusting the meal insulin dose for the blood glucose value and the carbohydrate content of the meal may be helpful in decreasing the risk for postprandial and nocturnal hypoglycaemia (30).

**Exercise.** Review the timing, duration, and intensity of routine exercise so that food intake and insulin dose adjustments can be adjusted to effectively prevent marked reductions in blood glucose levels. Exercise increases the risk for hypoglycaemia during, immediately after, as well as 2-12 hours after exercise; the risk depends on many factors including duration and intensity of exercise, type of insulin, and site of injection (22,31,32). Blood glucose levels below 6.7-8.3 mmol/l (120-150 mg/dl), prior to sustained aerobic exercise (75 minutes) is associated with an increased risk of hypoglycaemia (33). Discontinuing CSII therapy during exercise may help to prevent exercise-related hypoglycaemia (31,33). For children using injected insulin, 30-45 g of oral carbohydrate may be required to prevent hypoglycaemia for a 30 kg child and 50-75 grams for 50 kg child, additional carbohydrate will usually be required if exercise occurs at the peak of insulin action or is more prolonged (55-57). A decrease in the usual insulin dose after intense exercise (a reduction in overnight long-acting/basal insulin or basal rate in pump or reductions in subsequent mealtime boluses) may be required to prevent nocturnal hypoglycaemia. Additional recommendations for carbohydrate intake during exercise may be helpful (32,34).

**Blood glucose monitoring.** Frequent blood glucose monitoring, with special attention to overnight (01:00-05:00 am) levels, is one of the most important ways to detect mild-moderate hypoglycaemia and prevent severe epi-

sodes. Continuous glucose monitoring has revealed that prolonged hypoglycaemia may occur during the night; this technology appears to offer a significant advance in detection and avoidance of hypoglycaemia (35). This technology may allow lower blood glucose levels without an increased risk of hypoglycaemia. The ultimate goal remains the development of automatic, glucose driven 'closed-loop' insulin delivery system (36).

**Nocturnal hypoglycaemia** is often asymptomatic, may not awaken the individual, and may be prolonged (37,38); counter-regulatory responses to low blood glucose may be impaired during sleep. Using intermittent glucose monitoring, nocturnal hypoglycaemia has been shown in 30-45% of children treated with the combination of evening Regular (soluble) and intermediate-acting insulin (25,38). During outpatient evaluation of continuous glucose monitoring (CGM), every participant had at least one nocturnal episode of subcutaneous hypoglycaemia (39) within six months. Nocturnal hypoglycaemia is not regularly predictable on the basis of a bedtime blood glucose level and can only be confirmed by blood glucose tests at regular intervals during the night or continuous glucose monitoring. A bedtime snack containing carbohydrate as well as fat and protein may be useful in preventing nocturnal hypoglycaemia, but this should not be at the expense of high overnight blood glucose levels. Slowly absorbed complex carbohydrate (uncooked corn starch) at bedtime may be helpful especially following strenuous exercise in the afternoon or evening (30). While nocturnal hypoglycaemia may be asymptomatic, it should be suspected if prebreakfast blood glucose is low, or if impaired thinking, lethargy, altered mood, or headaches are experienced on waking and/or confusional states, nightmares, or seizures occur during the night. Use of long-acting insulin analogues or CSII decreases the risk of nocturnal hypoglycaemia (27,28).

**Review of hypoglycaemic episodes.** Every hypoglycaemic episode should be assessed carefully to determine its cause and if changes in the treatment regimen are indicated. Evaluation should include: insulin action profile, prior food intake and meal insulin dose as well as recent physical activity and management adjustments for the exercise. Additional evaluation should include possible missed signs and symptoms of early hypoglycaemia and if a blood glucose measurement was performed at the time of the hypoglycaemic symptoms and repeated after treatment. These steps are especially helpful for adolescents who may not be meticulous in determining or administering their insulin doses or attending to signs of hypoglycaemia.

#### **Celiac disease and Addison's disease may increase hypoglycaemic risk**

Celiac disease, present in 4-10% of children with type 1 diabetes, and Addison's disease, present much less

commonly, may also increase the risk for hypoglycaemia. When frequent unexplained hypoglycaemia occurs, evaluation for celiac disease and/or Addison's Disease is warranted.

**Brain dysfunction and neurological sequelae of hypoglycaemia.** On a practical basis, episodes of mild-moderate hypoglycaemia, even if asymptomatic, as well as severe hypoglycaemia, have important implications for school and social well-being. These include cognitive dysfunction (40), reduced awareness of low blood glucose, possible injury or accident, and significant fear of hypoglycaemia, resulting in intentional decreases in insulin dosing resulting in elevated glucose levels and increased HbA<sub>1c</sub> (41). Most studies, but not all (42), have shown an association between hypoglycaemia and decrease in cognitive functioning in children with type 1 diabetes, particularly those diagnosed before the age of 5-6 years. Hypoglycaemic seizures lead to significant declines in verbal abilities (5), memory skills (40, 43), and ability to organise and recall information. The latter may be impaired even after mild hypoglycaemia. Patients with severe hypoglycaemia also reported lower global quality of life.

Early-onset diabetes and chronic hyperglycaemia may also decrease cognitive functioning in very young children (44-46), and brain imaging studies show that both hypoglycaemia and hyperglycaemia cause changes in mental efficiency and in the white and gray matter of developing brains (46, 47). Intensive insulin treatment in the DCCT cohort (aged 13-39 years at baseline), while increasing the incidence of hypoglycaemia, has not led to a significant worsening of neuropsychological or cognitive functioning during the trial as well as 18 years after entry into the trial (48).

**Death.** Hypoglycaemia is a significant factor in excess mortality in patients with diabetes (49). Despite recent improvements in therapy, diabetes-related mortality among children has not declined for 14 years, and a recent US report suggests a slight increase in diabetes-associated mortality beginning in 1993-1994 (50). Sudden nocturnal death in young persons with type 1 diabetes has been described and is known as the 'dead in bed' syndrome. It appears to be responsible for about 6% of deaths in diabetic patients aged below 40 years (51, 52). Nocturnal hypoglycaemia has been implicated as the cause for these deaths, consistent with the high frequency of nocturnal hypoglycaemia reported by the DCCT and more recent studies using continuous glucose monitoring (37).

## **Consideration**

Hypoglycaemia should be prevented because its occurrence is frequently predictable, and it is often associated with significant psychosocial dysfunction; more importantly,

it can lead to permanent long-term sequelae and is potentially life threatening.

## Implementation

Health care systems should work toward making blood testing available for confirmation and treatment of hypoglycaemia. Rapid means to reverse hypoglycaemia should be available to all children with diabetes.

Children, their parents, and other caregivers should be educated with regard to how insulin, food, and exercise must be balanced in order to achieve near normoglycaemia and reduce the risk of hypoglycaemia. Particular attention should be given to training children and their caregivers to recognise the early warning signs of hypoglycaemia and treat low blood glucose immediately and appropriately. To quickly reverse hypoglycaemia unawareness, patients and their parents should be trained to contact their diabetes care provider if hypoglycaemia is documented without symptoms or if the symptoms are those of neuro-glucopenia and not autonomic symptoms (i.e. hypoglycaemia unawareness). A careful assessment of the patient's signs and symptoms of hypoglycaemia should be part of the routine care of children and adolescents with type 1 diabetes at every visit and the treatment regimen should be evaluated to determine if changes are needed to decrease the risk for hypoglycaemia while maintaining blood glucose targets. This assessment should be recorded as part of the consultation record.

## Evaluation

Frequency and severity of hypoglycaemia should be evaluated at all visits with healthcare providers and as part of ongoing care by parents and care-givers by reviewing glucometer downloads or glucose log books. Children, parents and other care-givers' understanding of how to monitor for, treat, and reduce the occurrence of hypoglycaemia should be evaluated routinely at healthcare visits as well as how insulin, food, and exercise interact with the goal of reducing the risk of hypoglycaemia.

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SICK DAY  
MANAGEMENT

## Recommendations

### Recommended care

1. The diabetes care team should provide clear guidance to patients and families on how to manage diabetes during intercurrent illnesses to avoid the complications of ketoacidosis, dehydration, uncontrolled or symptomatic hyperglycaemia and hypoglycaemia. Periodic review and re-education should include instruction on recognition and treatment during sick days.
2. During sick days, do not stop insulin.
3. During sick days, the insulin dose may need to be increased or decreased temporarily.
4. When vomiting occurs in a child with diabetes, it should always be considered a sign of insulin deficiency until proven otherwise.
5. More frequent monitoring of blood or urine glucose as well as blood or urine ketones is required during sick days.
6. If home glucose and/or ketone monitoring is unavailable, then urgent or emergent consultation with the health care team should be arranged while attempts at maintaining hydration are utilised.
7. Sources of simple sugar and electrolyte (sodium chloride) containing fluids (like the WHO ORS solution) must be available for emergency use during sick days when loss of appetite is common. This should include clean/boiled/purified cool water to provide hydration. Sugar-containing liquids are helpful to prevent hypoglycaemia and starvation ketosis.
8. Any underlying illness causing metabolic derangement should be diagnosed and treated.
9. Appropriate treatment of fever should be instituted to decrease risk of dehydration.
10. Appropriate treatment of nausea and vomiting would include correction of the primary illness, identification and treatment of hypoglycaemia and identification and treatment of insulin deficiency or insulin resistance associated with the primary illness. Pump failure can be a cause of ketosis and nausea/vomiting.
11. Recognition of ongoing or more severe dehydration and potential for decompensated diabetic ketoacidosis and coma must be taught, recognised by the patient and family caregivers and means of contacting health care professionals for institution of intravenous or other parental rehydration established. Actual weight with a scale several times each day will help to identify more serious dehydration and fluid losses requiring non-home care and parenteral rehydration.
12. Additional insulin is usually provided based upon one of several formulas:
  - a. 5-10% of total daily dose of insulin (or 0.05-0.1 U/kg) as short or rapid-acting insulin repeated every 2-4 hours based upon elevated blood glucose results if there are negative or small amounts of ketones.
  - b. 10-20% of total daily dose of insulin (or 0.1 U/kg) as short or rapid-acting insulin repeated every 2-4 hours based upon elevated blood glucose results if there are moderate or large amounts of ketones.
  - c. The basal insulin, especially if insulin pump treatment is being used, may also need to be increased depending upon individual illness requirements, blood glucose and ketone monitoring results.
13. Written guidelines for sick day management should be available and individualised for each child and adolescent with appropriate identification of who in the family will provide support and assistance under such circumstances. Education and periodic re-education of sick day management should occur at least annually.
14. Sometimes illness is associated with hypoglycaemia rather than hyperglycaemia, especially if there is a gastrointestinal illness rather than a respiratory illness. Blood glucose monitoring is important for recognition of when this occurs. With gastroenteritis, insulin doses usually need to be decreased, but there is a risk of subsequent

ketoacidosis if they are decreased too much. Sugar-containing drinks should be given in small sips, along with small doses of insulin. If ketones develop, this is an indication that the child needs more carbohydrates (and more insulin). Treatment of hypoglycaemia includes rapid-acting glucose, sucrose and/or fructose tablets, liquids or intravenous glucose.

15. Mini-glucagon dose regimens (Table 1) can also be used (16), if available, to boost glucose levels for several hours during such hypoglycaemia-associated illnesses.

**Table 1: Recommended Dose for Mini-dose Glucagon**

Age (yrs)	Quantity			
	mcg ( $\mu$ g)	Mg	Mls (1 mg/ml)	Units on insulin syringe
≤ 2	20	0.02	0.02	2
2 – 15	10 per year of age	0.01 per year of age	0.01 per year of age	1 per year of age
>15	150	0.15	0.15	15

\* Note that the doses recommended above are quite different from emergency doses given in case of severe hypoglycaemia.

### Limited care

1. Education about what may occur with any intercurrent illness must be provided to all patients and family members with periodic re-education of these same general principles at least annually.
2. Monitoring of home blood glucose at least 4-6 hourly and urine ketones should be available during sick days.
3. If home glucose or ketone monitoring is unavailable, systems should be established for contacting health care professionals and/or emergency personnel for evaluation and treatment of potential hyperglycaemic crises, ketoacidosis as well as hypoglycaemic crises.
4. Fluid intake should be increased, especially in hot climates.
5. Unknown or uncertain alternative medicine co-prescription should be avoided.
6. While awaiting emergency treatment or evacuation by health care professionals during sick days, appropriate initial sugar and electrolyte solutions (like the WHO ORS solution) and advice on their administration should be provided.

### Comprehensive care

1. Children and adolescents as well as members of their family should understand the concepts of sick day management, including treatment and prevention of ketoacidosis, hyperglycaemia associated with most intercurrent illnesses and occasional hypoglycaemia associated with some intercurrent illnesses.
2. Optimum management of sick days includes availability not only of education, but also blood glucose monitoring equipment and supplies, blood and urine ketone supplies and contact with health care professionals for ongoing guidance and support.
3. Optimum health care professional management of sick days includes up-to-date knowledge of such sick day management, available telephone consultation with patients and family members, available emergency transportation to appropriate facilities when needed, available laboratory and bedside monitoring equipment and supplies, appropriate supplies for intravenous or other parental fluid and electrolyte replacement and specific neurosurgical or other surgical and intensive care support for the most severe episodes of ketoacidosis or hypoglycaemic comas.

4. Blood ketone testing may provide earlier evidence of ketosis and ketoacidosis, and may ultimately supplant urinary ketone testing as it becomes more readily available. See Table 2 for interpretation.
5. Special circumstances during sick days may arise with preschool age children, in those with other concomitant illnesses in addition to diabetes and where there are serious financial, psychosocial or educational barriers to optimum care.
6. Children and adolescents being treated with insulin pumps may have their “sick days” precipitated by interruption of insulin delivery through infusion site failure, catheter occlusion or obstruction as well as actual mechanical failure of the insulin pump mechanisms. The measurement of blood ketones will make it easier to detect and follow the treatment of pump failure. With insulin pump treatment, education should address such possibilities, and alternative insulin delivery systems (i.e. pens or syringes) should be available for use.

**Table 2: How to Calculate the Amount of Extra Insulin on Sick Days**

Ketones		Blood glucose				
Blood ketones mmol/l	Urine ketones	< 5.5 mmol/l < 100 mg/dl	5.5- 10 mmol/l 100-180 mg/dl	10-14 mmol/l 180-250 mg/dl	14-22 mmol/l 250-400 mg/dl	> 22 mmol/l > 400 mg/dl
< 0.6	Negative or trace	Do not give extra insulin. May need to consider mini-doses of glucagon (see Table 1 if <4mmol (70 mg/dl)	No need to worry.	Increase dose of insulin for next meal if BG is still elevated	Give extra 5% of TDD or 0.05 U/kg	Give extra 10% of TDD or 0.1 U/kg. Repeat if needed.
		Check BG and ketones again in two hours.				
0.6-0.9	Trace or small	Starvation ketones. Extra carbohydrates and fluid are needed.	Starvation ketones. Extra carbohydrates and fluid are needed.	Give extra 5% of TDD or 0.05 U/kg	Give extra 5-10% of TDD or 0.05-0.1 U/kg.	Give extra 10% of TDD or 0.1 U/kg Repeat if needed.
1.0-1.4	Small or Moderate	Starvation ketones. Extra carbohydrates and fluid are needed.	Starvation ketones. Extra carbohydrates and fluid are needed. Give ordinary bolus dose.	Extra carbohydrates and fluid are needed. Give 5-10% of TDD or 0.05-0.1 U/kg.	Give extra 10% of TDD or 0.1 U/kg	Give extra 10% of TDD or 0.1 U/kg.
1.5-2.9	Moderate or large	High levels of starvation ketones. Check BG meter. Recheck BG and ketones Extra carbohydrates and fluid are needed.	High levels of starvation ketones. Extra carbohydrates and fluid are needed. Give 5% of TDD or 0.05 U/kg. Repeat when blood glucose has risen.	Extra carbohydrates and fluid are needed. Give 10% of TDD or 0.1 U/kg.	Give extra 10-20% of TDD or 0.1 U/kg. Repeat dose after 2 hours if ketones do not decrease.	
		May need IV glucose if child cannot eat or drink. <b>Risk of developing ketoacidosis!</b> Check BG and ketones every hour.				
≥ 3.0	Large	Very high levels of starvation ketones. Check BG meter. Recheck BG and ketones Extra carbohydrates and fluid are needed. “	Very high levels of starvation ketones. Extra carbohydrates and fluid are needed. Give 5% of TDD or 0.05 U/kg. Repeat when blood glucose has risen. “	Extra carbohydrates and fluid are needed. Give 10% of TDD or 0.1 U/kg.	Give extra 10-20% of TDD or 0.1 U/kg. Repeat dose after 2 hours if ketones do not decrease.	
		<b>There is an immediate risk of ketoacidosis if the blood ketone level is ≥ 3.0 mmol/l. Insulin treatment is needed urgently! Consider evaluation of patient at emergency department.</b>				

- 】 To calculate the Total Daily Dose (TDD), add up all the insulin given on a usual day (ie. rapid-/short-acting + intermediate/long-acting) or sum of basal rate and boluses in a pump. Do not include additional boluses given for unexpected hyperglycemia.
- 】 High blood glucose and elevated ketones indicate a lack of insulin. "Starvation blood ketones" are usually below 3.0 mmol/L.
- 】 When the child is feeling sick or vomits, and the BG is below 10-14 mmol/L (180-250 mg/dl, see table), he/she must try to drink sugar-containing fluids in small portions to keep the BG up. When ketone levels are raised, priority is to give extra insulin, and this will be difficult if BG is low.
- 】 Extra insulin may be given as rapid-acting insulin analogues or short-acting regular insulin, but rapid-acting if available is preferred.
- 】 Short-acting insulin can be given intramuscularly to speed up absorption.
- 】 The ketone level may increase slightly (10-20%) within the first hour after giving extra insulin, but after that it should decrease [E].

## Rationale

Children whose diabetes is under good metabolic control should not experience more illness or infections than children without diabetes (1-4). However, when any illness occurs in someone with diabetes, the potential for either hyperglycaemia, hyperglycaemia with ketosis, hyperglycaemia with ketoacidosis or hypoglycaemia exists, and requires education and treatment to prevent exacerbation or even possible death (2-5). In some parts of the world where access to medical care, insulin or parenteral fluids is problematic, the added metabolic stress of an illness in someone with diabetes can be life threatening. Many illnesses are associated with higher levels of stress hormones which promote gluconeogenesis and insulin resistance (2-5). Severe illness increases ketone body production because of inadequate provision of insulin under such circumstances, and thus can contribute to acidosis, nausea and vomiting, furthering dehydration and ultimately compromise acid-base balance producing metabolic decompensation, ketoacidosis, coma and death (6). Illnesses associated with vomiting and diarrhoea, such as gastroenteritis, often lower blood glucose levels rather than causing hyperglycaemia while at the same time producing a type of starvation ketosis which exacerbates the situation (2-6). Hypoglycaemia with ketosis rather than hyperglycaemia and ketoacidosis may ensue. Education about the effects of intercurrent illness ("sick days") is a critical component of diabetes management at home and must be adapted to the educational abilities and the treatment possibilities of the particular situation in different parts of the world (2,4). Re-education is also necessary since forgetting the "rules" (i.e. when to check urine or blood ketone levels, for instance), or forgetting to maintain such emergency supplies are also common (2).

## Evidence-base

Numerous chapters and review articles about sick day management and ketoacidosis have been published over the years, with the more recent teaching manuals (5,7-13) also providing specific guidelines for home treatment, identification of problems and advice as to when professional assistance is available. These are available in many different languages and most diabetes centres have protocols for what is taught to patients and family members for sick day management. Specific management issues for sick days when patients are using insulin pumps (7,14,15), and specific management of hypoglycaemia during intercurrent illness and specific use of mini-glucagon treatment to immediately boost hypoglycaemia to euglycaemic levels (16).

## Consideration

There are few published scientific studies of home management of sick days so recommendations are mostly based upon expert opinion and consensus as written in textbooks and review articles (17). More recent introduction of blood ketone testing strips and meters suggests that earlier identification of ketosis and ketoacidosis may be possible utilising blood rather than urine ketone testing, and reductions in emergency room visits and hospitalisations may be possible if such systems can be made more available, costs reduced and training maintained for continued usage by those with diabetes (18-23). Table 2 shows interpretation of blood and urine ketones at different blood glucose levels. It is adapted from (4, 19, 23, 24). No data are available from clinical trials. In a child or adolescent with an intercurrent illness, urgent medical attention, ideally with a diabetes specialist, must be obtained or emergency hospital evaluation sought in the following situations (2,5,7-11,15):

- › The underlying condition is unclear
- › Weight loss continues suggesting worsening dehydration
- › Vomiting persists
- › Blood glucose levels continue to rise despite provision of extra insulin
- › Hypoglycaemia persists or nausea and vomiting prevent appropriate hypoglycaemia treatment
- › Ketonuria or ketonemia persists/worsens and does not respond to extra insulin and fluid administration at home
- › The child or adolescent is exhausted, hyperventilating, continues to have excessive urination, continues to lose weight and gets more dehydrated or has severe abdominal pain
- › The child or adolescent has new neurologic symptoms such as confusion or severe headache or becomes unresponsive or comatose
- › Parents or other family caretakers become exhausted
- › Communication with family is or becomes difficult/impossible to sustain.

## Implementation

Specific protocols for education of patients and families, re-education and reminders depend upon the economic circumstances as well as reading ability, level of health care provided by the government or insurance companies and interest of the general paediatric health care community and specifically the paediatric diabetes community. In many places, such care is provided by internists or family physicians because of the lack of paediatric diabetes specialty services or training. In other places, the disorganisation of care is a critical component of the lack of services, including education and supplies needed for even minimal sick day management of those with diabetes. In other instances, the psychosocial barriers (2,4,9) are extremely important in hampering appropriate delivery of care or even information. The expense of home blood glucose monitoring or even insulin and pens or syringes as well as the expense of urine or blood ketone testing equipment all may contribute to poor outcomes even in rich societies.

## Evaluation

While expert opinion around the world can produce such consensus guidelines (17), more sophisticated prospective and crossover clinical paediatric and adolescent studies would be beneficial to address the research and clinical questions still unanswered regarding optimal sick day management questions, including but not limited to the best way of education and empowering such patient and family self-care (2).

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# 13

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EXERCISE

## Recommendations

### Recommended care

1. Exercise is very beneficial and diabetes is no bar to participation. Regular exercise and participation in sport should be encouraged.
2. Information should be provided for schools and nurseries about diabetes and exercise.
3. Patients/families should be given tailored advice about what and how much carbohydrate to take before during and after exercise, as well as advice about insulin adjustment.
4. There should be access to a paediatric dietitian with diabetes experience.
5. Blood glucose needs to be measured before exercise, and when need arises during exercise.
6. The insulin dose prior to exercise may often need to be decreased.
7. Hypoglycaemia may be anticipated during or shortly after exercise but is also possible up to 24 hours afterwards, due to increased insulin sensitivity.
8. Risk of post-exercise nocturnal hypoglycaemia is high, and particular care should be taken if bedtime blood glucose < 7.0 mmol/L (125 mg/dl).
9. Approximately 1-1.5 g carbohydrate/kg body weight/hour should be consumed during strenuous exercise if a reduction in insulin is not instituted.
10. Sugar-free fluids should be consumed to avoid dehydration.
11. Performance in sports like hockey, soccer and sailing where a certain amount of cognitive function and precision is necessary, may be better performed during normoglycaemia.
12. Where unaccustomed exercise is being taken, e.g. at a diabetes camp, a significant reduction in total daily dose of insulin (20-50%) may be necessary to avoid hypoglycaemia.
13. Any exercise is dangerous and should be avoided if pre-exercise blood glucose levels are high (> 14 mmol/L, 250 mg/dl) with ketonuria/ketonaemia. Give approximately 0.05 U/kg or 5% of TDD (total daily dose, including all meal bolus doses and basal insulin or basal rate in pump), and postpone exercise until ketones have cleared. If ketones cannot be measured, a child who is feeling nauseous should not participate in exercise.
14. Special care should be taken at high altitude where the symptoms of hypoglycaemia may be confused with those of hypoxia/altitude sickness.
15. Patients who have proliferative retinopathy or nephropathy should avoid exercise likely to result in high arterial blood pressure.
16. Patients with advanced neuropathy should avoid exercise like soccer.

### Limited care

1. Exercise is very beneficial and diabetes is no bar to participation.
2. Blood glucose control may be helped by exercise.
3. Adjustments to food and insulin may be required depending upon the type and duration of exercise.
4. If unable to monitor glucose, take a snack before exercise and decrease insulin dose before exercise. Also decrease basal insulin during the night if not exercising daily.

### Comprehensive care

1. Children and young people engaged in competitive or more serious sport will require additional support which should include detailed discussion about the activity and tailoring of advice on insulin and food adjustments according to diary entries with blood glucose results.
2. For most children and adolescents, choice of insulin regimen will not be influenced heavily by the amount of activity undertaken but in serious/competitive sport, multi-injection regimen or CSII is likely to be necessary to afford sufficient flexibility.
3. Detailed information gathering may include the use of Continuous Glucose Monitoring (CGM) equipment.

## Rationale

Children and adolescents can all benefit from exercise and participation in sport. This is also true in diabetes such that, in the 1950s Joslin proposed that exercise is the third essential component in blood glucose regulation after insulin and dietary management. The other benefits are also considerable and include general fitness, a sense of well-being and the psycho-social aspects of group participation.

## Evidence-base

The ISPAD Clinical Practice Consensus Guideline on Exercise in Children and Adolescents with Diabetes (1) was based upon a thorough review of the literature and an updated review was conducted for these recommendations. This Guideline provides detailed discussion and information about the effects of exercise and the recommendations for insulin and carbohydrate adjustment together with a comprehensive reference list. Many factors influence the response to exercise in diabetes and an understanding of these is necessary in order to be able to provide good advice. Although the evidence for a positive effect of exercise upon glycaemic control (i.e. HbA<sub>1c</sub>) is weak, there is growing evidence of the benefits of regular physical activity upon cardiovascular risk factors (2). Aerobic capacity is lower and the fatigue rate is higher in youth with type 1 diabetes when glycaemic control is less than optimal (i.e. HbA<sub>1c</sub> > 7.5 %) (3). Cognitive performance has been shown to be slower in youth with diabetes when they are either hypoglycaemic or hyperglycaemic (4), which could affect performance in sports like hockey, soccer and sailing where a certain amount of cognitive function and precision is necessary.

While it is recognised that moderate intensity exercise increases the risk of hypoglycaemia and vigorous exercise is associated with the release of adrenaline and glucagon which may provoke ketosis, it is now recognised that much of children's play and team sports may more properly be categorised as intermittent high intensity exercise. The hormonal response to this may be different and require more carefully tailored advice about food and insulin adjustment (1,5). Detailed advice for children and adolescents participating in exercise has been published (6).

## Consideration

Any consideration of the management of diabetes must involve an appraisal of a patient's activity/sport and support for their continuation. It is important for health professionals to understand the relevant factors so that they can offer appropriate advice.

## Implementation

Public health campaigns in most countries now include plans to tackle obesity and include encouragement to participate in exercise and sport. Patients with type 1 diabetes must be included in initiatives, although it should be made clear to those responsible for such work that these individuals do not have diabetes as a consequence of obesity.

## Evaluation

It should be part of the routine care of children and adolescents with type 1 diabetes to enquire about their regular physical activity and to encourage their participation in sports, school trips, camps, etc. This should be recorded as part of the consultation record.

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MANAGEMENT  
OF CHILDREN  
REQUIRING  
SURGERY

## Recommendations

### Recommended care

1. Centres performing surgical procedures on children with diabetes should have available written protocols for pre- and post-operative management of diabetes on the wards where children are admitted.
2. To ensure patient safety, careful liaison is required among surgical, anaesthesia and children's diabetes care teams before admission to hospital for elective surgery and as soon as possible after admission for emergency surgery.
3. Whenever possible, surgery on children and adolescents with diabetes should be performed in centres with appropriate personnel and facilities to care for children with diabetes.
4. Children requiring major surgery must be admitted to hospital for general anaesthesia.
5. IV access, infusion of glucose and frequent blood glucose monitoring is essential whenever general anaesthesia is given. Glucose 5% is usually sufficient; glucose 10% may be necessary when there is an increased risk of hypoglycaemia. Aim for blood glucose levels between 5-10 mmol/l (90-180 mg/dl) during surgical procedures in children.
6. To minimise the risk of hypoglycaemia, children should receive a glucose infusion when fasting for more than 2 hours before a general anaesthesia.
7. Children should be carefully monitored by means of capillary blood glucose measurement, because stress caused by surgery may cause hyperglycaemia and increase insulin requirements.
8. Consider admission to hospital prior to elective surgery for assessment and stabilisation if glycaemic control is poor. If control remains problematic, surgery should be cancelled and re-scheduled.
9. Procedure on day of general surgery:
  - ▶ Procedures preferably should be first on the list, ideally in the morning.
  - ▶ No solid food for at least 6 hours prior to surgery.
  - ▶ Omit the usual morning insulin dose.
  - ▶ At least 2 hours before surgery start an IV insulin infusion (dilute 50 units Regular [soluble] insulin in 50 ml normal saline; 1 unit = 1 ml) and glucose 5% (10 % if there is concern about increased risk of hypoglycaemia). If blood glucose is high (> 14 mmol/l, 250 mg/dl), use 0.45 or 0.9% NaCl without glucose and increase insulin supply, but add 5% dextrose when blood glucose falls below 14 mmol/l (250 mg/dl).
  - ▶ Start infusion at 0.025 ml/kg/h (i.e., 0.025 U/kg/hour) if blood glucose is <6-7 mmol/l, 0.05 ml/kg/h if 8-12 mmol/l, 0.075 ml/kg/h between 12-15 mmol/l and 0.1 U/kg/h if > 15 mmol/l.
  - ▶ Monitor blood glucose hourly before surgery and every 30-60 minutes during the operation and until the child recovers from anaesthesia. Adjust IV insulin accordingly.
  - ▶ Do not stop the insulin infusion if BG <5-6 mmol/l (90 mg/dl) as this will cause rebound hyperglycemia. Reduce the rate of infusion.
  - ▶ The IV insulin infusion may be stopped temporarily if BG <4 mmol/l (55 mg/dl) but only for 10-15 min.
10. Maintenance fluid guide:
  - ▶ Glucose: 5 % glucose; 10 % if there is concern about hypoglycaemia. If BG is high (>14 mmol/l, 250 mg/dl), normal saline without glucose and increase insulin supply but change to 0.45% saline with 5% dextrose when BG falls below 14 mmol/l (250 mg/dl).
  - ▶ Sodium: Give 0.45% saline with 5% glucose, carefully monitor electrolytes, and change to 0.9% saline if plasma Na concentration is falling.

- › Potassium:  
Monitor electrolytes. After surgery, add potassium chloride 20 mmol to each litre of intravenous fluid.
- › Example of calculation of maintenance requirements (tables for this vary between centres, use one that is locally agreed and established):

	Body Weight	Fluid Requirement/24h
<b>for each kg between</b>	3–9 kg	100 ml/kg
<b>for each kg between</b>	10–20 kg	add an additional 50 ml/kg
<b>for each kg over</b>	20 kg	add an additional 20 ml/kg

(max 2000 ml/24h female, 2500 ml/24h male)

#### 11. Patients on insulin pumps:

- › If the general anaesthesia is short (< ~ 1 hour), the pump can be continued at the basal rate, keeping IV glucose 5% infusion at the maintenance rate (see above). Do not give a morning/meal bolus dose unless necessary to correct hyperglycaemia.
- › When necessary, correction doses can be given with the pump preoperatively and postoperatively. Alternatively, give extra IV insulin to keep perioperative blood glucose within target.

#### 12. Minor procedures requiring fasting:

- › For short procedures (with or without sedation or anaesthesia) and when rapid recovery is anticipated, a simplified protocol may be formulated by personnel experienced in the anaesthesia for children with diabetes.
- › Early morning procedure (e.g. 8:00-9:00am).
- › Twice daily insulin regimen: 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 on insulin pump): 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.
- › Delay insulin and food until immediately after completion of the surgical procedure.

#### 13. Surgery in children and adolescents with 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 at least 24 hours before the procedure for elective surgery. In the event of emergency surgery and metformin is stopped < 24 hours before surgery, insure optimal hydration with IV fluids before, during and after surgery.
  - › Sulphonylureas or thiazolidinediones: stop for the day of surgery.
- › Monitor blood glucose hourly and if greater than 10 mmol/l (180 mg/dl) treat with IV insulin, as for elective surgery, to normalise levels, or SC insulin if it is a minor procedure.

### Limited care

1. DKA, ketosis or severe hyperglycaemia will necessitate correction, and might delay surgery.
2. Children requiring surgery need insulin, even if fasting, to avoid ketoacidosis.
3. Children requiring major surgery should be referred to a centre with appropriate resources.

4. Elective surgery should if possible be scheduled as the first case on a surgical list, preferably in the morning.
5. No solid food for at least 6 hours prior to general anaesthesia.
6. Clear fluids (including breastmilk) are allowed up to 4 hours before anaesthesia (check with anaesthetist).
7. Emergency surgery:
  - ▶ If DKA is present, follow protocol for DKA and delay surgery until circulating volume and electrolyte deficits are corrected.
  - ▶ If there is no DKA, follow protocol as for elective surgery.

### Comprehensive care

1. Major Surgery that requires more prolonged general anaesthesia is associated with greater risks of metabolic decompensation, and should be performed in a hospital with access to a Pediatric Intensive Care unit.
2. A bedside meter for blood ketone ( $\beta$ -hydroxybutyrate) levels is valuable in a hospital setting, and may suffice for monitoring of situations requiring extra insulin and, possibly, adding glucose to intravenous fluids for correction.

## Rationale

When children with diabetes require surgery or other procedures requiring sedation or anaesthesia, optimal management should maintain adequate hydration and near to normal glycaemia, while minimising the risk of hypoglycaemia. The stress of surgery may cause acute hyperglycaemia, which increases the risk of postoperative infection (1,2).

Evidence-based controlled studies of perioperative care in children have not been conducted, but a review of paediatric management has recently been published in the anesthesiology literature (3). The current ISPAD Clinical Practice Recommendations (4) are consistent with the recommendations in this reference.

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

- a) Minor surgery or procedures that require a brief general anesthetic (or heavy sedation), usually of less than one hour duration, and which should not have a major impact on glycaemic 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.
- b) Major surgery that requires more prolonged general anaesthesia 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. It is important to recognise that DKA may present as an «acute abdomen» and that acute illness may precipitate DKA (with severe abdominal pain).

See reference (3) and (4) for specific details on algorithms for different types of paediatric insulin regimens during surgery.

## Evidence-base

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) (5). However, when blood glucose is maintained between 6.8 and 9.3 mmol/l (122-168 mg/dl), there was no difference in the risk of postoperative wound infections after major vascular surgery (6). Maintaining blood glucose 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% (7). Improved postoperative glycaemic control (plasma glucose levels of 4.5-6.0 mmol/l (~80-110 mg/dl) using continuous IV insulin infusion significantly decreased mortality and morbidity in patients who required postoperative intensive care and mechanical ventilation after major surgery (8). With this degree of tight glycaemic control, 5.2% of subjects experienced hypoglycaemic episodes compared to 0.8% in the control group; however, none of the episodes was severe (9).

To achieve optimal glycaemic control, insulin dosage may need to be increased on the day of major surgery

and for approximately 2 days after surgery. This is best achieved by continuous IV insulin infusion even after the resumption of oral feeding (10).

A few studies in adults that compared different methods of achieving glycaemic control during minor and moderate surgery did not demonstrate any adverse effects of maintaining perioperative glycaemic levels between 5-11 mmol/l (~ 90-200 mg/dl) (11-13) .

## Consideration

As there are few relevant scientific papers on management during surgery, the recommendations are mostly based on expert consensus.

## Implementation

The safe implementation of intensive glycaemic control with a continuous IV insulin infusion requires a written protocol and staff training to ensure effectiveness and to minimise the risk of hypoglycaemia. The benefits of tight glycaemic control must be weighed against the risk of perioperative hypoglycaemia, which may not be recognised during anaesthesia; however, this risk can be mitigated by frequent capillary blood glucose monitoring.

## Evaluation

Appropriate perioperative glycaemic targets for brief and minor surgical procedures are less clear. To date, no intervention studies have assessed the impact of different blood glucose levels on morbidity or mortality in these circumstances. Paediatric studies need to be done in this area.

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PSYCHOLOGICAL  
CARE

## Recommendations

### Recommended care

1. Resources should be made available to the interdisciplinary paediatric diabetes team, to provide easy access to professionals with expertise in the mental and behavioural health of children and adolescents.
2. Mental and behavioural health specialists should be available to interact not only with patients and families at clinic visits to conduct screening and more complete assessments of psychosocial functioning, but also to support the diabetes team in the recognition and management of mental health and behaviour problems.
3. The diabetes team should have training in the recognition of more severe psychopathology requiring the help of consulting psychiatrists to whom there should be easy access. Screening for depression should be done when necessary.
4. All mental and behavioural health specialists consulting in the clinic should have training in paediatric diabetes and its management .
5. The diabetes team should strive to maintain regular, consistent and uninterrupted contact with patients and their families. When clinic visits are missed or infrequent, other modes of contact should be made available such as by phone, text or email.
6. Assessment of developmental progress in all domains of quality of life (i.e. physical, intellectual, academic, emotional and social development) should be conducted on a routine basis.
7. It is important to monitor the school performance of children who developed diabetes before age 5 years and with a history of significant hypoglycaemic episodes at early ages. These children, as well as all children experiencing learning difficulties at school, should be referred for a psycho-educational or neuropsychological evaluation.
8. Specific diabetes care plans should be formulated for the school setting and training conducted with school staff concerning diabetes management.
9. The diabetes team should provide routine assessment of developmental adjustment to and understanding of diabetes management, including diabetes-related knowledge, insulin adjustment skills, goal setting, problem-solving abilities, regimen adherence, self-care autonomy and competence (especially just before adolescence). These assessments are particularly important in young people not achieving treatment goals or who exhibit chronically poor metabolic control (high HbA<sub>1c</sub>, recurrent DKA).
10. The diabetes team should aim to provide an assessment of general family functioning (conflict, cohesion, adaptability, parental psychopathology), emotional behaviour at the personal level (including the early identification of depression) and diabetes-related functioning (communication, parental involvement and support, roles and responsibilities for self-care behaviours) especially when there is evidence of cultural, language or family problems or difficulties in adjustment to diabetes.
11. The diabetes team should be trained in counselling techniques to enable young people and parents to understand how they may benefit from improvements in glycaemic control, and advances in diabetes management, including the intensification of insulin regimens.
12. Adolescents should be encouraged to assume increasing self-care and responsibility for diabetes management tasks but with continuing, mutually agreed parental involvement and support. The transition to adult diabetes care should be discussed, negotiated and carefully planned between adolescents, their parents and the adult diabetes team well in advance of the actual transfer to adult care (see chapter 16: Diabetes in adolescence).

### Limited care

1. Diabetes care for young people should include the recognition of the potentially serious impact of diabetes on both psychosocial functioning in the child, adolescent and the family and also the adverse effects on metabolic control.

2. Professionals caring for young people with diabetes should be prepared to discuss the psychological difficulties associated with diabetes (including depression, acting out, rebellion) and have access to other professionals with more specialist expertise in this field.

### Comprehensive care

1. Mental and behavioural health specialists should be available in clinic and include psychologists and social workers trained in paediatric diabetes.
2. Identification of psychosocial adjustment problems, depression, eating disorders, and other psychiatric disorders should be conducted at planned intervals by mental health specialists.
3. The diabetes team should be trained to provide interventions for patients and families (including the training parents in effective behaviour management skills) at key developmental times, particularly soon after diagnosis and prior to adolescence. These interventions should emphasise appropriate family involvement and support (i.e. teamwork) in diabetes management, effective problem-solving and self-management skills, and realistic expectations about glycaemic control.
4. Evidence-based psychosocial, behavioural, or psychiatric interventions should be made available for patients or families exhibiting conflict, disordered communication, behavioural or psychiatric difficulties or adherence problems affecting glycaemic control. In these contexts, training in empowerment techniques and motivational interviewing may be useful.

## Rationale

The ISPAD Consensus Guidelines 2000 stated that “Psychosocial factors are the most important influences affecting the care and management of diabetes” and made the following three general recommendations (1):

1. Social workers and psychologists should be part of the interdisciplinary health care team.
2. Overt psychological problems in young persons or family members should receive support from the diabetes care team and expert attention from mental health professionals.
3. The diabetes care team should receive training in the recognition, identification, and provision of information and counselling on psychosocial problems related to diabetes.

These broad statements form the basis of the recommendations above.

## Evidence-base

Substantial research over the past four decades provides evidence for the significant role of psychosocial factors in the management of type 1 diabetes in children and adolescents (2,3). The recommendations reflect the main findings from studies of psychological adjustment, psychiatric disorders, neurocognitive and educational functioning, family dynamics, social support, stress and

coping, quality of life, and behavioural interventions in children and adolescents with type 1 diabetes.

Research findings indicate children with type 1 diabetes are at risk for adjustment problems during the initial period of adaptation after diagnosis. When adjustment problems exist, children are at higher risk for continuing difficulties (4). There is growing evidence that young people with diabetes appear to have a greater incidence of psychiatric disorders (5), including a higher incidence of eating disorders (especially females), and that these are associated with poor glycaemic control (6).

Poor metabolic control has been associated with a number of other psychosocial problems including depression, anxiety and poor self-esteem. When psychological adjustment problems persist into late adolescence, there is evidence indicating greater risk for poor diabetes management during early adulthood (2).

Studies of neurocognitive functioning indicate that young people with diabetes are at increased risk for information processing weaknesses and learning problems, especially with early diabetes onset and history of severe hypoglycaemia or chronic hyperglycemia. Research also indicates that diabetic youths are more likely to have learning problems, with such problems being more frequent among boys than girls. Academic achievement and school performance are lower in children with poor metabolic control (7).

Research demonstrates that family factors are integral to the management of diabetes in children (8). The findings from a number of cross-sectional and prospective studies have shown that high levels of family cohesion, agreement about diabetes management responsibilities, and supportive behaviours are associated with better regimen adherence and glycaemic control. Significant family dysfunction has been observed in clinical studies of adolescents with recurrent DKA. Socio-demographic factors such as single-parenthood, lower income and ethnic minority status are associated with greater risk for poor control of diabetes (2).

Social support from parents and other family members is especially important for children and adolescents with type 1 diabetes. Research has shown that family members who provide high levels of support for diabetes care have youngsters who adhere better to diabetes regimens (9). Young people may also receive considerable emotional support from their friends. When youth attribute negative peer reactions to their self care, they are more likely to have adherence difficulties, increased diabetes stress and have worse glycaemic control (10).

Better quality of life is associated with better glycaemic control, but the relationship between glycaemic control and quality of life appears modest (2).

The results of controlled intervention research has shown that family-based interventions utilising positive reinforcement and behavioural contracts, communication skills training, negotiation of diabetes management goals, problem-solving and development of self-management skills, have led not only to improved regimen behaviours and glycaemic control, but also to improved family relationships (3,11-13). Group interventions for young people with diabetes targeting coping skills have also shown positive effects on regimen adherence, glycaemic control, and quality of life (14). Individual interventions with adolescents have shown motivational interviewing to improve long-term glycaemic control and psychosocial outcomes (2,15).

## Consideration

- ▶ Psychosocial problems may already exist at the time of diagnosis and be exacerbated by difficulties of management in the early days of diabetes.
- ▶ It is crucial to maintain consistent contact with families, as research findings indicate that children who have infrequent and irregular visits with the health care team or do not have continuing support from parents are more likely to have problems with metabolic control. This is particularly so when the young person has not developed adequate self-care behaviours.
- ▶ Adolescence represents a high risk time for diabetes management, with physiological and psychosocial changes resulting in deterioration in adherence.

## Implementation

A number of controlled studies have shown the efficacy of psychosocial and behavioural interventions for children and adolescents with diabetes, although the literature is not without limitations. Most of these interventions have included the family as an integral part of management.

The results of these studies indicate that family-based, behavioural procedures such as goal-setting, self-monitoring, positive reinforcement, behavioural contracts, supportive parental communications, and appropriately shared responsibility for diabetes management have improved regimen adherence and glycaemic control.

Psychoeducational or psychosocial interventions with children and their families that promote problem-solving skills and increase parental support early in the disease course may improve family functioning and glycaemic control.

Research has shown that when parents allow older children and adolescents to have self-care autonomy without sufficient cognitive and social maturity, youths are more likely to have problems with diabetes management. Thus, a critical aspect of behavioural family management of diabetes is finding ways for parents and family members to remain involved and supportive, but not intrusive, in their youngsters' daily care.

## Evaluation

Routine assessment of the psychosocial functioning of children and their families is important in the overall evaluation of the care of young people with diabetes.

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DIABETES IN  
ADOLESCENCE

## Recommendations

### Recommended care

Adolescents require care and education which is distinctly different from younger children and adults. The interdisciplinary paediatric diabetes team providing care for adolescents with diabetes should:

1. Identify the components of care unique to adolescents.
2. Understand the psychosocial and physiological development of adolescence, and that diabetes inhibits some adolescents from exploring life, while causing others indulge in significant risk taking behaviour.
3. Develop communication skills appropriate for this age group (patient-centred, non-judgemental, supportive and observing confidentiality).
4. Recognise that adolescents experience a strong need to fit in and be accepted outside the family, most importantly by peers, and this may cause conflicts within the family.
5. Understand the physiological and psychological reasons for unstable control in adolescence.
6. Discuss the importance of not missing injections of insulin, and the benefits of blood glucose monitoring.
7. Discuss the likelihood and risks of both recurrent hypoglycaemia and chronic hyperglycaemia.
8. Provide information on and understanding the effects on diabetes of travelling, sport, different levels of activity from high activity pursuits to significant inactivity, teenage diabetes camps, support groups, discussion meetings and other recreational activities.
9. Advise that adolescents should inform friends about the risks, symptoms and treatment of hypoglycaemia during the altered routine of social engagements, especially as they leave the home environment.
10. Identify the need to discuss risk taking behaviours, exposure to smoking, alcohol and illicit drugs.
11. Learn the signs of serious mental health problems (e.g. depression, eating disorders, "diabetes burnout", illicit drug use, mental slowness, ADHD and neglectful or abusive family situations), identify the need for specialised psychological counselling and have easy access to mental health experts.
12. Offer advice on sexual health, contraception, employment and driving (see chapter 15: Psychological care).
13. Discuss and provide planned transition to adult care at the most appropriate time.

### Limited care

1. To provide care and education for the adolescent which recognises the special and different needs of this age group.
2. To encourage young people to recognise the immediate benefits of better control and to negotiate small achievable targets.
3. To advise and negotiate on the need to take enough insulin to maintain optimal growth, not just to avoid ketoacidosis.
4. To recognise conflict between the demands of diabetes management and the adolescent's social development and peer activities.
5. To organise regular screening for early signs of complications, to encourage a practical understanding of the benefits of improved metabolic control.
6. To help the adolescent and parents to understand that continuing cooperative parental involvement may help to maintain better levels of diabetes care.

## Comprehensive care

1. A separate clinic space for adolescents and emerging adults should be made available with mental and behavioural health specialists being present whenever possible (see chapter 15: Psychological care).
2. The diabetes team should help parents in their changing role from full responsibility towards a gradual transition to cooperative care with the adolescent.
3. A variety of educational opportunities should be offered including open-ended adolescent-orientated discussion and negotiation, discussing health-related quality of life issues, risk-taking behaviours, problem solving, target setting, age-appropriate written materials, utilising newer technologies such as CDs/DVDs, text messaging, email, the internet, peer involvement and group learning.
4. Specific issues should be discussed, such as the potential benefits of intensified insulin management, hypoglycaemic unawareness, fears about hypoglycaemia and its association with poorer metabolic control, hypoglycaemia and work performance, sports and driving.

## Rationale

Adolescence is the transitional phase of development between childhood and emerging adulthood which incorporates the biological and psychosocial changes of puberty. It imposes unique challenges on the individual with diabetes, their family and the diabetes care team.

Although the majority of adolescents adapt well to the difficult challenges of puberty, their health care and emotional needs are distinctly different from those of younger children or older adults.

Adolescence involves training to become an independent adult and may result in failures and mistakes as well as success.

Adolescence may be the time when vascular complications first become apparent.

## Evidence-base

The transitional phase of adolescence is frequently associated with a deterioration in metabolic control (1-3), often attributable to erratic meal and exercise patterns, poor adherence to treatment regimens, hazardous and risk taking behaviours, eating disorders and endocrine changes associated with puberty, leading to greater insulin resistance.

Changes in body habitus, particularly weight gain in females (3) can be unwanted diabetes-related side effects, sometimes associated with changes in the tempo of pubertal maturation provoking insulin omission to effect weight loss.

The weighted evidence base supporting these recommendations has been recently reviewed (4-6).

Optimal care of adolescents with diabetes has not been subjected to rigorous scientific studies, and research results are conflicting. However, psycho-educational interventions have been extensively reviewed and conclude that they may have beneficial outcomes, but the effects are only modest and the effects are more on psychological outcomes than glycaemic control (7).

There is evidence that parental support and involvement throughout adolescence is associated with better outcomes (1,8).

There is evidence that a significant number of young people fail to transfer successfully from paediatric to adult care. This is often associated with poor metabolic control (1,2) and the emergence of vascular complications (9).

## Consideration

- ▶ Adolescence, a transitional phase of development, imposes unique challenges for the individual with diabetes, families and health care teams.
- ▶ The health care needs of adolescents are distinctly different from those of children and adults.
- ▶ Adolescence is often associated with a deterioration in metabolic control due to a variety of physiological and psychosocial factors.

## Implementation

It is important that governmental, educational and public health authorities recognise that adolescents and

emerging adults with diabetes are special groups who require specialised education and facilities to help to prevent serious long-term complications of diabetes including the drop-out of members of these groups from clinic attendance and surveillance.

## Evaluation

Diabetes teams should be able to register the numbers of adolescents in their district or region, and be able to monitor attendance and metabolic control. Mechanisms should be available for recalling patients who repeatedly fail to attend clinics.

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## Further reading

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MICROVASCULAR AND  
MACROVASCULAR  
COMPLICATIONS

## Recommendations

### Recommended care

1. Improvement in glycaemic control reduces the risk for onset and progression of diabetes vascular complications.
2. Blood pressure should be measured at least annually.
  - 】 Blood pressure values should be maintained at less than the 95<sup>th</sup> centile for age or 130/80 for young adults. ACE-inhibitors are recommended treatment and have been effective and safe in children in short-term studies, but are not safe during pregnancy.
3. Cessation of smoking/never initiating smoking will reduce progression of complications.
4. Initial eye examination should occur shortly (preferably within 3 months) after diagnosis to detect cataracts or major refractive errors which require treatment for binocular vision.
5. Screening for retinopathy should start from age 11 years and after two years diabetes duration.
  - 】 Minimum assessment for retinopathy should be by ophthalmoscopy through dilated pupils by an experienced observer. The frequency of retinopathy screening in general should occur annually, but should be more frequent if there are high risk features for visual loss.
  - 】 Laser treatment reduces the rate of visual loss for vision-threatening retinopathy.
6. Annual screening for microalbuminuria should start from age 11 years and after two years diabetes duration.
7. Two of three urine collections should be used as evidence of microalbuminuria, defined as:
  - 】 Albumin excretion rate (AER) 20-200 µg/min or AER 30-300 mg/day.
  - 】 Albumin/creatinine ratio (ACR) 2.5-25 mg/mmol (males) and 3.5-25 mg/mmol (females, because of lower creatinine excretion) on first morning urine specimen; random ACR is higher.
  - 】 Albumin concentration (AC) 30-300 mg/l (on early morning urine sample).
  - 】 Microalbuminuria may resolve, be intermittent or persist. Confounders are urinary tract infections, exercise and menstrual bleeding.
  - 】 For persistent microalbuminuria, ACE-inhibitors or ARBs will increase regression and reduce progression to proteinuria (protein > 500mg/day or 300 mg/l on early morning urine sample).
8. Screening for fasting blood lipids should be performed when diabetes is stabilised in children aged over 12 years. If there is a family history of hypercholesterolaemia, early CVD or if the family history is unknown, screening should start at age 2 years.
  - 】 If normal results are obtained, screening should be repeated every 5 years.
  - 】 Target for LDL-C should be lower than 2.6 mmol/l (100 mg/dl). If interventions to improve metabolic control and dietary changes cannot lower to target, statins should be considered although long-term safety is not established.
9. Peripheral and autonomic neuropathy should be assessed by history and physical examination from age 11 years with two years diabetes duration.

### Limited care

1. The principles as for Recommended care.
2. Blood pressure should be measured at least annually and antihypertensive medication used if > 95<sup>th</sup> centile or > 130/80. ACE inhibitors are preferred but other antihypertensive agents, such as calcium channel blockers and diuretics can be used.
3. Examine eyes and visual acuity annually for retinopathy and cataracts after two years diabetes duration, and annually thereafter.

4. Measure urinary protein annually for nephropathy (> 500mg/day) after two years diabetes duration, and annually thereafter.
5. Examine feet annually for neuropathy, infections, ulcers after two years duration, and annually thereafter.

### Comprehensive care

1. The principles as for Recommended care.
2. Confirmation of hypertension may be assisted by 24 hour ambulatory blood pressure measurements.
3. 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 years, minimal background retinopathy on fundal photography and reasonable glycaemic control, biennial assessment by fundal photography can occur.
4. Assessment for retinopathy should be by fundal photography with or without mydriasis.
5. Annual screening for microalbuminuria should be undertaken by:
  - a. Timed overnight or 24 hour urine collections (AER).
  - b. First morning urine: albumin/creatinine ratio (ACR).
6. Peripheral and autonomic neuropathy should be assessed by history, physical examination and quantitative sensory tests for vibration, thermal sensation or light touch.

## Rationale

Diabetes vascular complications can lead to severe morbidity and mortality. Diabetes microvascular complications are retinopathy, neuropathy and nephropathy which is preceded by microalbuminuria. Macrovascular complications are coronary artery disease, cerebrovascular disease and peripheral vascular disease.

Childhood and adolescence is a period during which intensive education and treatment may prevent or delay the onset and progression of complications. Retinopathy causes visual loss and blindness. Diabetic nephropathy causes hypertension and renal failure. Neuropathy causes pain, paresthesiae, muscle weakness and autonomic dysfunction. Macrovascular disease causes cardiac disease, stroke and peripheral vascular disease with limb loss.

The purpose of screening for subclinical diabetes complications is to delay progression to clinical complications. Early assessment and early treatment means better outcomes. The most important principle is to achieve as near normal glycaemic control as possible. Other known risk factors are high blood pressure, smoking and hyperlipidaemia. When retinopathy has progressed to a certain level of severity, laser treatment has a good chance of reducing further vision loss. Persistent microalbuminuria has been shown to predict the progression to end stage renal failure (1-6) and is associated with an increased risk of macrovascular disease (7,8).

Early detection of diabetic nephropathy and timely treatment of blood pressure have a pivotal role in the prevention of end-stage renal failure in young people and adults with diabetes.

## Evidence-base

### *Glycemic control*

The Diabetes Control and Complications Trial (DCCT) was a multicentre, randomised controlled clinical trial involving 1,441 patients with type 1 diabetes conducted in North America from 1983-1993 (9). The patients were randomised to intensive or conventional treatment. After completion of the DCCT (a median of 6.4 years), the Epidemiology of Diabetes Interventions and Complications (EDIC) study continued to follow patients (10). After four years, there was no significant difference in HbA<sub>1c</sub> between the former intensive and conventional treatment groups.

The DCCT provided unequivocal evidence that intensive diabetes treatment compared with conventional treatment conferred a significant risk reduction for all microvascular complications: retinopathy, microalbuminuria and neuropathy (9).

The EDIC study showed that this positive effect continued even after equalization of metabolic control as measured by HbA<sub>1c</sub>, i.e. that there was a memory effect of the improved glycaemic control during the DCCT study. In addition, it showed a positive effect of intensive therapy

for macrovascular disease: CV events were reduced by 50% ten years after the end of DCCT (11).

In the adolescent cohort (195 adolescents aged 13-17 years at recruitment), intensive treatment reduced the risk and progression of background retinopathy by 53%, clinical neuropathy by 60% and microalbuminuria by 54%. The difference in HbA<sub>1c</sub> 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 (10).

#### *Other risk factors*

Longer duration of diabetes, older age and puberty are risk factors for complications (12). The prepubertal years of diabetes duration do have a major impact, but significantly lesser compared to the years from the onset of gonadarche (13). For the same diabetes duration, age and puberty increase the risk for retinopathy and elevated albumin excretion rate (14).

Smoking is associated with an increased risk of developing persistent microalbuminuria or macroalbuminuria (15,16). The evidence for the effect of smoking on retinopathy is less clear. Type 1 diabetes and smoking interact to produce excess CV morbidity and mortality (17).

Hypertension has a greater impact on CVD in diabetic patients than in non-diabetic individuals (18). Blood pressure control (< 130/80 mmHg in adults) is effective in decreasing CV morbidity and mortality in diabetes (19).

Dyslipoproteinemia was associated with microalbuminuria and retinopathy development in the DCCT/EDIC (20,21). This included higher total and LDL-C and higher triglyceride levels for microalbuminuria, as well as larger LDL particle size and apoprotein B in men.

Family history of complications increases the risk for nephropathy (22) and retinopathy (23). A family history of early CVD (before 55 years of age), lipid disturbances, type 2 diabetes, hypertension (24) and smoking place the individual with diabetes at higher risk of CVD.

Higher BMI is a risk factor for retinopathy (25), neuropathy (26), microalbuminuria (27) and CVD (28).

Life style issues: in adults, sedentary men with diabetes have higher mortality than active individuals (29). No paediatric studies are available.

#### *Specific treatments*

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 area 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 (2,30). Side effects of treatment are decreased night and peripheral vision and subtle changes in colour perception. Complications of laser therapy are vitreal and choroidal haemorrhages or visual sequelae of misplaced burns.

Effective antihypertensive therapy in patients with nephropathy prolongs the time to end-stage renal disease (31). A recent prospective study has shown improved prognosis of renal function from 5 to 7 years from onset of nephropathy to end-stage renal disease to a median of 21.7 years (32), predominantly due to aggressive antihypertensive treatment, with smaller contributions from improved glycaemic control and smoking cessation.

Blood pressure values between the 90<sup>th</sup> and 95<sup>th</sup> percentiles (see Table 1) are defined as prehypertension (33,34). Protocols and reference values for 24 hour ambulatory blood pressure monitoring in children have also been published (23,35). ACE-inhibitors are recommended for use in children and adolescents with hypertension (36). The starting dose of captopril is 6.25mg (increasing to 12.5 to 25-75mg per day in two to three doses) and for enalapril is 5mg (increasing to 10-40mg per day in one to two doses). They have been effective and safe in children in short-term studies (37,38). The clinical beneficial effect of ARBs in hypertension is similar to that observed with ACE-inhibitors, but have not been formally evaluated, nor used extensively in children.

ACE-inhibitors and ARBs reduce progression from microalbuminuria to macroalbuminuria and increase the regression rate to normoalbuminuria (39). For those with microalbuminuria, ACE-inhibitors and ARBs reduce the time to doubling of serum creatinine. Whilst ACE-inhibitors reduces all-cause mortality, ARBs use was associated with higher all-cause mortality compared with placebo.

Despite the above evidence mainly in adults, there are still some concerns regarding the use of ACE-inhibitors in protecting long-term renal function in young people without hypertension. In meta-analysis of individual patient data, the beneficial effects were more modest in those with the lowest levels of microalbuminuria (40). Young people with microalbuminuria would potentially be taking ACE-inhibitors for decades. Side effects include cough (for ACE-inhibitors), hyperkalemia, headache and impotence (39). Furthermore an increase in major congenital malformations has recently been reported in nondiabetic women after first trimester exposure to ACE-inhibitors, but not with other antihypertensive agents (41).

Atherosclerosis starts in childhood and adolescence as shown by intima-media thickness of the carotids and aorta (42), and silent coronary atherosclerosis measured

by intravascular ultrasound in young adults with childhood onset diabetes (43). Silent coronary atherosclerosis (9,43) and CV events (11) are strongly associated with poor glycaemic control.

Changes in lipids associated with increased CV risk are also associated with central obesity in type 1 diabetes (as well as type 2 diabetes) (45). Individuals with type 1 diabetes are as much at risk for hypercholesterolaemia as the nondiabetic population. The prevalence approached 50% of young adults in one study (46). The prevalence of elevated non-HDL-C was 25% in a study of individuals less than 21 years of age with type 1 diabetes (47).

In adults, statins are effective in the primary and secondary prevention of major CV events, stroke and limb revascularisation in patients with diabetes (48). The Heart Protection Study was a 5 year interventional study of 5,963 patients with diabetes, 10% of whom had type 1 diabetes. This effect was independent of glycaemic control and cholesterol levels.

Short-term trials have shown that simvastatin, lovastatin and pravastatin are effective and safe in children and adolescents (49-51). 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 needs to be determined in randomised 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 (52).

## Consideration

The child with diabetes who receives limited care is more likely to develop diabetes long-term complications at an earlier age. Screening for subclinical complications is appropriate if treatment for intervention is available. Antihypertensive drugs, including ACE-inhibitors and ARBs, and lipid-lowering drugs, statins, whilst expensive can delay onset of complications.

## Implementation

Screening programs for diabetes complications are costly to set up, but provide early treatment and attention to risk factors which will reduce the long-term morbidity and mortality from diabetes complications.

## Evaluation

The impact of improved glycaemic control and attention to risk factors should reduce the prevalence of diabetes complications. Outcomes from diabetes vascular disease should be monitored.

Documentation of procedures of screening and treatment is recommended in order to evaluate the rate of complications and success of interventional strategies for care in each centre. National and international benchmarking and longitudinal follow-up of complications between centres may serve as a basis to improve quality of screening and treatment procedures.

**Table 1. Blood pressure centiles in relation to length**

Height (cm)	Boys SBP 90 <sup>th</sup> centile	Boys SBP 95 <sup>th</sup> centile	Boys DBP 90 <sup>th</sup> centile	Boys DBP 95 <sup>th</sup> centile	Girls SBP 90 <sup>th</sup> centile	Girls SBP 95 <sup>th</sup> centile	Girls DBP 90 <sup>th</sup> centile	Girls DBP 95 <sup>th</sup> centile
100	109	112	65	70	110	113	66	70
110	113	118	68	72	112	115	68	72
120	115	120	70	73	114	118	70	74
130	117	122	72	74	118	123	72	75
140	120	124	73	75	122	126	73	76
150	125	130	74	77	125	130	74	77
160	133	138	75	79	129	134	75	78
170	140	146	77	81	133	138	76	80
180	144	151	79	83				
190	143	148	81	84				

Blood pressure is measured in mmHg; SBP systolic blood pressure; DBP diastolic blood pressure (53). In persons with diabetes, antihypertensive medication should be used if BP is > 95<sup>th</sup> centile or > 130/80.

On-line instructions and normal BP levels for age, sex, and height are available at: [www.nhlbi.nih.gov/health/heart/hbp/hbp\\_ped.pdf](http://www.nhlbi.nih.gov/health/heart/hbp/hbp_ped.pdf)

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OTHER  
COMPLICATIONS  
AND ASSOCIATED  
CONDITIONS

## Recommendations

**Diabetes is associated with other autoimmune diseases and can affect growth and physical development.**

### Recommended care

1. Monitoring of growth and physical development with the use of growth charts is an essential element in the continuous care of children and adolescents with type 1 diabetes.
2. Screening of thyroid function by analysing circulating TSH at the diagnosis of diabetes and, thereafter, every second year in asymptomatic individuals without goitre. More frequent assessment is indicated if goitre is present.
3. Screening for coeliac disease should be carried out at the time of diagnosis and every year for the first 5 years, less frequently 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.
4. Children with type 1 diabetes detected to have coeliac disease on routine screening should be referred to a paediatric gastroenterologist and on confirmation of the diagnosis by means of small bowel biopsy, should receive support from a paediatric dietitian with experience of diabetes and gluten-free diets.
5. 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 intervention for lipodystrophy, necrobiosis lipoidica or limited joint mobility.

### Limited care

1. Principles for care as for Recommended care.
2. If small bowel biopsy is not possible in a child with positive screening tests, then a trial of a gluten-free diet is recommended if celiac disease is suspected. Response should be determined from improvement in growth, bowel habit and reduction in titre of screening antibodies.

### Comprehensive care

1. Principles for care as for Recommended care.
2. Measurement of thyroid antibodies additionally to TSH measurement as part of thyroid screening is recommended at the diagnosis of diabetes and, thereafter, every second year in asymptomatic individuals without goitre. More frequent assessment is indicated otherwise.

## Rationale

Children with diabetes are at increased risk of developing disease-related complications like impaired growth and pubertal development, lipodystrophy, necrobiosis lipoidica diabetorum, limited joint mobility or oedema as well as other autoimmune diseases, particularly thyroid and celiac disease.

## Evidence-base

Poor gain of height and weight, hepatomegaly, abdominal pain, elevated liver transaminases, and late pubertal development (Mauriac syndrome) might be seen in children with persistently poorly controlled diabetes (1). Insulin insufficiency, coeliac disease and other gastrointestinal disorders should be considered in this setting.

Increased height at diagnosis of type 1 diabetes has been frequently reported but does not always persist (2). Encouragingly, a recent Australian study showed that children treated with modern regimens (diagnosed after 1990) maintained their increased height better than children diagnosed before 1991 (3), however without becoming significantly taller in their final height than the general population.

Lipoatrophy at the insulin injection sites is now seen infrequently with the use of human insulin. It does still occur rarely in pump patients treated with rapid-acting analogues and in patients treated with long-acting analogues.

Lipohypertrophy is a more frequent complication of insulin therapy (up to 48%) (4). The major cause is non-rotation of injection sites and most importantly insulin may be absorbed erratically and unpredictably from these areas. Necrobiosis lipoidica diabetorum describes well circumscribed, raised reddish lesions sometimes progressing to central ulceration, usually seen in the pre-tibial region. The reported prevalence in children varies from 0.06% to 10% (5,6).

Limited joint mobility (LJM) is the earliest clinically apparent long-term complication of type 1 diabetes in childhood. It is a bilateral painless, but obvious, contracture of the finger joints and large joints, associated with tight waxy skin. 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 particularly the wrist and elbow, but also ankles and cervical and thoracolumbar spine. The limitation is only mildly disabling even when severe. LJM is associated with a three to four-fold risk for retinopathy, nephropathy, and neuropathy (7,8,9).

A simple examination method is to have the patient attempt to approximate palmar surfaces of the interphalangeal joints (10). Passive examination is essential to confirm that inability to do so is due to LJM.

Generalised oedema due to 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 (11,12). The oedema spontaneously resolves over a period of days to weeks with continued good glycaemic control. In severe cases, ephedrine has been an effective treatment (13).

Primary hypothyroidism due to autoimmune thyroiditis occurs in approximately 3-8% (14), or 0.9 per 100 patient years (15), of children and adolescents with diabetes. Clinical features may include the presence of a painless goitre, increased weight gain, retarded growth, tiredness, lethargy, cold intolerance and bradycardia. Diabetic control is usually not significantly affected. In case of painless goitre without thyroid antibodies other causes should be evaluated as iodine deficiency or malignancy. Hyperthyroidism is less common than hypothyroidism in association with diabetes (16), but still more common than in the general population.

Coeliac disease occurs in 1-10% of children and adolescents with diabetes or 0.7 per 100 patient years (17). It is often asymptomatic and not necessarily associated with poor growth or poor diabetes control (although it should be excluded in such situations). 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 (18).

The risk of coeliac disease is higher in younger children and females, with a threefold higher risk being seen in children age < 4 years than in those age > 9 years (19). It is common at diagnosis and subsequent annual screening shows seroconversion especially within the first two to five years of diabetes (20).

Vitiligo is an acquired pigmentary disorder characterised by a loss of melanocytes resulting in white spots or leukoderma. It is a common autoimmune condition associated with type 1 diabetes and is present in about 6% of diabetic children.

Up to 2% of patients with type 1 diabetes have detectable antiadrenal autoantibodies (21,22). Addison's disease can be associated with type 1 diabetes in the Autoimmune Polyglandular Syndromes (APS 1 and 11). APS 1 is associated with mucocutaneous candidiasis and hypoparathyroidism.

## Consideration

There is no role for human growth hormone therapy in the poorly growing child with diabetes, unless it is associated with documented growth hormone deficiency.

Once the child or adolescent has reached a satisfactory weight after diagnosis of diabetes and start of insulin treatment, 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 (23). Increased weight gain is a side effect of intensive insulin therapy with improved metabolic control (24,25). As obesity is a modifiable CV risk factor, careful monitoring and management of weight gain should be emphasised in diabetes care. Increased weight is associated with increased risk of hyperandrogenism and PCOS in women with type 1 diabetes (26).

A wide variety of treatments for necrobiosis lipoidica diabetorum 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 UVA treatment (PUVA). None has been proven useful in controlled clinical trials, and many of these treatments have significant side effects.

Hyperthyroidism in a child with diabetes 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.

Addison's disease is suspected by the clinical picture of frequent hypoglycaemia, unexplained decrease in insulin requirements, increased skin pigmentation, lassitude, weight loss, hyponatremia and hyperkalemia.

Treatment of vitiligo is difficult and multiple therapies have been tried with little success.

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 for coeliac disease.

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). Whilst 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. The introduction of gluten-free diet can result in an increase in height-for-weight (27), improved well-being and increased bone mineral density (28,29,30).

## Implementation

The individual patient should be followed with regular measurement of growth and physical development as well as assessment of clinical status.

Screening for the most frequent associated autoimmune disorders i.e. thyroid dysfunction and coeliac disease is strongly recommended even in apparently clinically healthy subjects with type 1 diabetes.

The screening for coeliac disease is based on the detection of IgA endomysial (EmA) antibodies and IgA antibodies against tissue transglutaminase (tTG). IgA deficiency (which is present in 1:500 people) should be excluded when screening for coeliac disease by measuring the total IgA level. If the child is IgA deficient, then IgG anti-gliadin and IgG tTG antibodies should be used for screening (31). In the presence of an elevated antibody level, a small bowel biopsy is needed to confirm the diagnosis of coeliac disease (MARSH Classification) (32). A gluten-free diet normalises the bowel mucosa and frequently leads to disappearance of antibodies, but may not necessary lead to improved diabetic control (16,33).

## Evaluation

Every patient with diabetes should be screened at diagnosis and during follow-up for diabetic complications and associated conditions. In case of positive results therapeutic interventions should be considered with subsequent regular care and monitoring of the complication.

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# ACRONYMS AND ABBREVIATIONS

<b>A2B</b>	angiotensin-II receptor blocker
<b>ACE-inhibitor</b>	angiotensin converting enzyme inhibitor
<b>ACR</b>	albumin:creatinine ratio
<b>AER</b>	albumin excretion rate
<b>BMI</b>	body mass index
<b>BP</b>	blood pressure
<b>CSII</b>	continuous subcutaneous insulin infusion
<b>CT</b>	computed tomography
<b>CV</b>	cardiovascular
<b>CVD</b>	cardiovascular disease
<b>DCCT</b>	Diabetes Control and Complications Trial
<b>DKA</b>	diabetic ketoacidosis
<b>DSME</b>	diabetes self-management education
<b>eGFR</b>	estimated glomerular filtration rate
<b>EU</b>	European Union
<b>HbA<sub>1c</sub></b>	glycated haemoglobin
<b>HDL-C</b>	high-density lipoprotein cholesterol
<b>HNF</b>	hepatocyte nuclear factor
<b>IM</b>	intramuscular
<b>IV</b>	intravenous
<b>LDL-C</b>	low-density lipoprotein cholesterol
<b>LJM</b>	limited joint mobility
<b>MDI</b>	multiple daily injections
<b>MODY</b>	maturity-onset diabetes of the young
<b>NAFLD</b>	non-alcoholic fatty liver disease
<b>NPH</b>	neutral protamine Hagedorn
<b>OGTT</b>	oral glucose tolerance test
<b>PCOS</b>	polycystic ovary syndrome
<b>SC</b>	subcutaneous
<b>SMBG</b>	self-monitoring of blood glucose
<b>TDD</b>	total daily dose
<b>TDEI</b>	total daily energy intake
<b>TSH</b>	thyroid stimulating hormone
<b>US</b>	United States
<b>USA</b>	United States of America
<b>WHO</b>	World Health Organization



## **Disclaimer**

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