1 Diabetes Mellitus

Definition

Diabetes mellitus is a heterogeneous disorder characterized by abnormal metabolism of carbohydrate, fat and protein with persistent fasting or postprandial hyperglycaemia resulting from defects in insulin secretion or insulin action (Skyler et al. 2017). It is diagnosed in one of four ways (see Table 1.1) (American Diabetes 2018). A fasting plasma glucose (PG) of 5.6–6.9 mmol/L (100–125 mg/dL) is considered prediabetes, whereas <5.6 mmol/L (<100 mg/dL) is normal. The oral glucose tolerance test (OGTT) is not recommended for routine clinical use. When classic symptoms are present, the diagnosis is usually straightforward and an OGTT is seldom needed; however, an OGTT may be indicated when mild hyperglycaemia is discovered without symptoms (e.g. in the sibling of a child with diabetes or in children with disorders such as cystic fibrosis (CF) that predispose to diabetes and may be asymptomatic in the early stages).

The incidental discovery of hyperglycaemia without classic symptoms does not necessarily indicate new onset diabetes, especially in young children with an acute illness, who may experience 'stress hyperglycaemia'. The risk of eventually developing diabetes may be increased in some children with incidental or stress hyperglycaemia, especially those with immunologic, metabolic, or genetic markers for type 1 diabetes, and consultation with a paediatric endocrinologist is indicated.

Diabetes mellitus is classified on the basis of its pathogenesis (Table 1.2); it may be the result of severe insulin deficiency or insulin resistance or, more commonly, a combination of milder defects in insulin secretion and action (American Diabetes Association 2018). This chapter primarily focuses on type 1 diabetes, which is the commonest form of diabetes in children. Other causes of diabetes are discussed in Sections 1.21 and 1.24.

Incidence

The incidence of type 1 diabetes in children varies considerably across the world with the Scandinavian countries having the highest incidence; in Finland, 60

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Table 1.1 Criteria for the diagnosis of diabetes mellitus.

1	Fasting plasma glucose ≥126 mg/dL (7 mmol/L)
	or
2	Two-hour plasma glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT)[b]
	or
3	Haemoglobin A_{1c} ≥ 6.5% (48 mmol/mol)
	or
4	In a patient with classic hyperglycaemia symptoms or hyperglycaemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

Definitions are based on venous plasma glucose levels. Glucose meters are useful for screening in clinics and physicians' offices, but the diagnosis of diabetes mellitus must be confirmed by measurement of venous plasma glucose on an analytic instrument in a clinical chemistry laboratory. In the absence of unequivocal hyperglycaemia, criteria 1 – 3 should be confirmed by repeat testing on a different day.

[a] Fasting is defined as no caloric intake for at least eight hours.

[b] OGTT should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

[c] Haemoglobin A1c test should be performed in a laboratory using a method certified by the National Glycohemoglobin Standardization Program (www.ngsp.org).

Table 1.2 Protocol for and interpretation of the oral glucose tolerance test.

Indications

Confirmation of the diagnosis of diabetes mellitus in uncertain cases and diagnosis of impaired glucose tolerance

Preparation

Perform in the morning after fasting overnight for at least eight hours

Procedure

1 Pretest – plasma glucose sample

2 0 minute – administer oral glucose 1.75 g/kg (up to a maximum of 75 g) diluted with water (consume over 5–10 min.)

3 +2 hours – plasma glucose sample

Interpretation

1 Fasting plasma glucose >7.0 mmol/L (126 mg/dL) or 2 h concentration >11.1 mmol/L (200 mg/dL) are diagnostic of diabetes

2 2 h plasma glucose concentration >7.8 mmol/L (140 mg/dL) and <11.1 mmol/L (200 mg/dL) is impaired glucose tolerance

3 Fasting plasma glucose 6.1–6.9 mmol/L (100–125 mg/dL) is impaired fasting glucose

An OGTT should be performed after at least three days of adequate carbohydrate consumption (≥150 g per 1.73 m^2) and is performed using 1.75 g/kg anhydrous glucose dissolved in water for individuals ≤43 kg and 75 g for weight > 43 kg.

new cases per 100 000 children under 15 years of age. The United Kingdom, Canada, the US, and Australia also have high incidences with more than 20 cases per 100 000 children, whereas Asia and Sub-Saharan Africa have much lower rates (China and India 0.1 cases per 100 000 people each year) (Patterson et al. 2014). The reasons for these large variations are unclear but may include genetic factors given the evidence of variations in the incidence of diabetes in different ethnic groups (e.g. in the US, the incidence is higher in non-Hispanic white than African-American or Hispanic youth). However, this difference cannot solely be attributed to genetic factors. In Europe, the risk of type 1 diabetes differs substantially in people who are genetically close but separated by socioeconomic borders. Furthermore, over the past 30 years, the worldwide incidence has steadily increased across all age groups in parallel with an increased standard of living. A European population-based registry showed a 3.9% annual increase in the incidence of type 1 diabetes in children <15 years between 1989 and 2003 (5.4% in the 0–4 year age group) and the US population-based SEARCH for Diabetes in Youth study has shown that the prevalence in people <20 years increased by 21% between 2001 and 2009.

With some exceptions, type 1 diabetes incidence is related to geographic distance north of the equator, and the onset of disease appears to be higher in autumn and winter than in spring and summer. Table 1.3 presents the American Diabetes Association Classification of Diabetes.

Type 1 diabetes is a chronic autoimmune disease caused by an incompletely understood complex interaction between risk-conferring genes and environmental factors resulting over time (years) in immune-mediated, selective destruction and loss of function of pancreatic β-cell mass. This leads to insulin deficiency, symptoms from hyperglycaemia, and lifelong insulin dependence (Insel et al. 2015). Symptoms occur when approximately two-thirds of the pancreatic islets are devoid of ß-cells.

Table 1.3 The American Diabetes Association classification of diabetes.

Type 1 diabetes caused by autoimmune-mediated ß-cell destruction (and idiopathic forms of β-cell dysfunction) usually leading to severe or absolute insulin deficiency
Type 2 diabetes caused by progressive loss of insulin secretion on a background of insulin resistance.
Other specific causes of diabetes Monogenic diabetes syndromes such as neonatal diabetes and maturity-onset diabetes of the young (MODY) Diseases of the exocrine pancreas (such as cystic fibrosis) Drug- or chemical-induced diabetes such as with glucocorticoid use, drugs used for treatment of HIV/AIDS, or after organ transplantation
Gestational diabetes mellitus diabetes diagnosed in the second or third trimester of pregnancy that was not clearly overt diabetes prior to gestation

Although 90% of patients with type 1 diabetes do *not* have a family history of the disease, development of type 1 diabetes is strongly influenced by genetic factors. Children born into families with type 1 diabetes have different lifetime risks depending on whether the mother (6%), father (12%), or a sibling (5–10% by age 20 years) has the disease (Pociot and Lernmark 2016). If a twin develops type 1 diabetes, the lifetime risk for the non-affected dizygotic twin is 6–10%, whereas that for a monozygotic twin is approximately 60%.

Type 1 diabetes is a polygenic disorder; more than 50 susceptibility loci that contribute to the likelihood of developing type 1 diabetes have been identified. The major histocompatibility complex (MHC) region encoding the human leukocyte antigen (HLA) on chromosome 6p21 (the *IDDM1* locus) contributes about 50% of the genetic risk. The insulin gene locus (*INS*) is the second most important susceptibility locus, contributing about 10% of genetic susceptibility. Each of the loci identified through genome-wide association studies has a slight individual effect on the total genetic risk for progression to type 1 diabetes, and gene variants collectively explain ~80% of type 1 diabetes heritability (Pociot and Lernmark 2016).

Most of the loci associated with risk of type 1 diabetes are thought to involve immune responses (Concannon et al. 2009), supporting the notion that genetic influences involve mechanisms that collectively contribute to aberrant immune responsiveness. Genetic susceptibility might also influence responses to environmental stimuli, modify viral responses or physiological pathways. For most of the genetic loci, however, the molecular mechanism of action remains unknown.

Newborn screening has been used to identify children at increased genetic risk who have been followed for the appearance of autoantibodies against ß-cell autoantigens: insulin, glutamic acid decarboxylase (GAD), insulinoma-associated antigen-2 (IA2), and zinc transporter 8 (ZnT8A) that are known to be strongly associated with an increased risk for type 1 diabetes. These autoantibodies can appear as early as age six months, with a peak incidence in the second year of life in genetically susceptible individuals, i.e. they are present months to years before the onset of symptoms. Children who develop two or more islet autoantibodies have a markedly increased likelihood of eventually developing type 1 diabetes, and 100% of those who develop a third and, often, a fourth autoantibody develop clinical type 1 diabetes when followed for 20 years (Ziegler et al. 2013). At the time of diagnosis, more than 90% of individuals with type 1 diabetes have at least one autoantibody, and the presence of autoantibodies against ß-cell autoantigens is a key feature distinguishing type 1 from type 2 diabetes.

Type 1 diabetes is also associated with other autoimmune disorders, most commonly autoimmune thyroiditis. At the time of diagnosis, about 25% of children have thyroid autoantibodies, which predict thyroid dysfunction (most commonly hypothyroidism); Graves' disease occurs in ~0.5% of patients with type 1 diabetes. Addison's disease, likewise, occurs in approximately 0.5% of patients with type 1 diabetes. Coeliac disease is another immune-mediated disorder that occurs with increased frequency in patients with type 1 diabetes, and biopsy-confirmed coeliac disease occurs in 3.5% of individuals with type 1 diabetes compared with 0.3–1% in the general population.

Environment

The increase in incidence described above can only be explained by changes in environment or lifestyle and it is notable that migrants tend to acquire the same risk of type 1 diabetes as the native population in their new area of residence (Rewers and Ludvigsson 2016). Studies of prospective birth cohorts are attempting to identify potential triggers of islet autoimmunity and the natural history of progression to diabetes. Putative triggers include infections, diet, and toxins that affect children in utero, perinatally, or during early

childhood. See Rewers and Ludvigsson (2016) for a review of this topic.

Vaccines

There has been speculation that vaccines might trigger autoimmunity; however, no association has been detected with islet autoimmunity or type 1 diabetes, and a recent meta-analysis concluded that childhood vaccines do not increase the risk of type 1 diabetes (Morgan et al. 2016).

Idiopathic type 1 diabetes

Some forms of type 1 diabetes have no known aetiology. Most patients with idiopathic type 1 diabetes are of African or Asian ancestry. They have permanent insulinopenia and are prone to episodic ketoacidosis, but have no evidence of beta-cell autoimmunity (negative islet autoantibodies). This form of diabetes is strongly inherited but not HLA-associated. Between episodes, patients exhibit varying degrees of insulin deficiency and may intermittently need insulin replacement.

Biochemistry

Insulin is an anabolic hormone that acts on liver, fat, and skeletal muscle to increase glucose uptake, oxidation, and storage, and to decrease glucose production. Insulin also inhibits lipolysis and thereby limits the availability of fatty acids for oxidation and inhibits ketogenesis. Insulin is secreted in two major patterns – basal and in response to food (prandial). Basal secretion produces relatively constant, low plasma insulin levels that restrain lipolysis and hepatic glucose production (from glycogenolysis and gluconeogenesis). The blood glucose concentration is the dominant stimulus for insulin secretion. After a meal, in parallel with the rise in plasma glucose, circulating insulin concentrations rise rapidly, facilitating the entry of glucose into cells via glucose-specific transporters, particularly in skeletal muscle and adipose tissue. Insulin stimulates glycogen synthesis in the liver and skeletal muscle, inhibits hepatic gluconeogenesis, and stimulates fat storage and protein synthesis. Conversely, during fasting, plasma glucose concentrations and insulin secretion decrease, leading to reduced glucose uptake in muscle and adipose tissue, increased lipolysis, and stimulation of hepatic glucose production (from glycogenolysis and gluconeogenesis (Figure 1.1).

In type 1 diabetes, insulin deficiency results in hyperglycaemia and when the plasma glucose concentration exceeds the renal threshold for glucose reabsorption (~180 mg/dL or 10 mmol/L) osmotic diuresis occurs, causing polyuria and polydipsia. Insulin deficiency also causes increased lipolysis with the production of excess free fatty acids and ketoacids (beta-hydroxybutyrate (BOHB) and acetoacetate) leading to hyperketonaemia and ketonuria. When fluid losses exceed intake, particularly when nausea and vomiting occur (typical symptoms of ketosis), dehydration develops. The accumulation of ketoacids in the blood causes metabolic acidosis, which results in compensatory rapid, deep breathing (Kussmaul respiration). Acetone, formed from acetoacetate, accounts for the characteristic smell of the breath (described as the odour of nail polish remover or rotten fruit). Accompanying the lack of insulin is an increase in the levels of stress or counter-regulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) whose metabolic actions are opposite to those of insulin. Thus, a lack of insulin together with increased concentrations of counter-regulatory hormones leads to progressive hyperglycaemia, hyperfattyacidemia, and ketosis and eventually ketoacidosis. Progressive dehydration, acidosis, and hyperosmolality cause decreased consciousness and lead to coma and death if untreated.

Clinical presentation

History

At diagnosis, typical symptoms have usually been present for only a few days to about two weeks or longer especially in type 2 diabetes:

- Polyuria (may cause secondary nocturnal enuresis)
- Polydipsia
- Weight loss
- Anorexia or hyperphagia
- Lethargy
- Constipation
- Infection (especially perineal candidiasis)
- Blurred vision
- Muscle cramps

Although most school-aged children report polyuria and polydipsia, these symptoms may be less obvious in the very young child (e.g. an infant in diapers) in whom the other less characteristic symptoms, especially perineal candidiasis, may predominate.

Clinical manifestations of diabetic ketoacidosis (DKA) include:

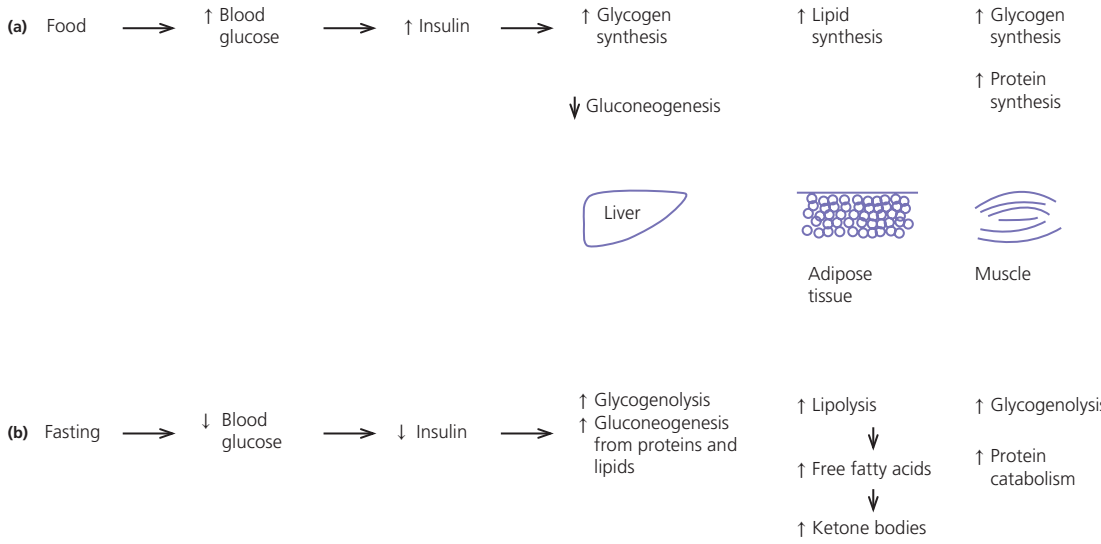

Figure 1.1 Glucose homeostasis: a comparison of (a) the fed state and (b) the fasting state.

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Drowsiness, confusion, progressive obtundation, and loss of consciousness.

Note that symptoms of systemic infection are infrequent; however, one must carefully look for an infection, especially if there is fever.

Examination

Patients with DKA typically are dehydrated. Clinical estimation of the degree of dehydration is imprecise and generally shows only fair to moderate agreement among examiners. The most useful signs for predicting 5% dehydration in young children are:

- prolonged capillary refill time (normal capillary refill is ≤1.5–2 seconds);
- abnormal skin turgor ('tenting' or inelastic skin).

Other useful signs to assess degree of dehydration include: dry mucous membranes, sunken eyes, absent tears, weak pulses, and cool extremities. More signs of dehydration tend to be associated with more severe dehydration; ≥10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, cool extremities, and oliguria.

Children diagnosed with diabetes should be immediately referred to a hospital for evaluation and management.

Differential diagnosis

The diagnosis of type 1 diabetes usually is obvious because the patient has classical symptoms (polyuria, polydipsia, and weight loss), random blood glucose is >11 mmol/L (200 mg/dL) and there is glucosuria with or without ketonuria. Diabetes should also be considered in the differential diagnosis of any child presenting with impaired consciousness and/or acidosis.

Tachypnea and hyperventilation in DKA may lead to the erroneous diagnosis of pneumonia or bronchiolitis. The lack of a cough or wheeze and the absence of abnormal findings on auscultation of the chest and a normal chest radiograph should raise the possibility of a metabolic acidosis such as DKA as the cause of tachypnea. Abdominal pain and tenderness in DKA may suggest a surgical emergency such as appendicitis or acute pancreatitis. Fluid, electrolytes, and insulin therapy will ameliorate the abdominal symptoms within hours. Diabetes should always be considered in children with secondary nocturnal enuresis and those with recurrent or persistent perineal candidiasis.

Acute illnesses such as severe sepsis or a prolonged convulsion may, occasionally, cause hyperglycaemia, glycosuria, and ketonuria. However, these biochemical abnormalities are almost always transient and are rarely associated with a history of previous polydipsia and polyuria. If in doubt, a fasting blood glucose measurement or OGTT (see Table 1.1) should be performed.

A doctor who either suspects or has made a definitive diagnosis of diabetes should immediately refer the child to a specialist for comprehensive assessment and initiation of treatment.

Investigations

At diagnosis, perform the following investigations:
- Plasma glucose concentration;
- Plasma BOHB concentration;
- Serum electrolytes, urea and creatinine concentrations (basic metabolic profile);
- Venous blood gas measurement;
- Complete blood count; note that leukocytosis and a raised C-reactive protein are common in DKA and do not necessarily indicate that an infection is present; an increased haematocrit reflects the degree of extracellular fluid (ECF) loss.
- A minority of children will have evidence of sepsis and need appropriate investigations (e.g. blood culture, chest radiograph, urine microscopy, and culture).
- HbA1c (glycated haemoglobin) is not necessary for initial management, but provides useful information about the duration and severity of antecedent hyperglycaemia.

The criteria for diagnosis of DKA are: plasma glucose ≥200 mg dL (11.1 mmol/L), venous pH < 7.30 or serum bicarbonate <15 mmol/L and 'moderate' or 'large' ketonuria, or serum BOHB ≥3 mmol/L (Wolfsdorf et al. 2018).

Initial management of newly diagnosed type 1 diabetes

Management of the child presenting without ketoacidosis

Hospitalization vs. Outpatient (home) treatment

The goals of initial management of the child with newly diagnosed diabetes mellitus are to restore the fluid and electrolyte balance, to stabilize the metabolic state with insulin, and to provide basic diabetes education and self-management training for the child (when age and developmentally appropriate) and caregivers (parents, grandparents, guardians, older siblings, day-care providers, and babysitters).

The diagnosis of diabetes in a child is a crisis for the family, who require considerable emotional support and time for adjustment and healing. Shocked, grieving, and overwhelmed parents require time to acquire basic ('survival') skills while they are coping with the emotional upheaval that typically follows the diagnosis of diabetes in a child. Even if they are not acutely ill, and depending on local resources and practices, children with newly diagnosed type 1 diabetes may be admitted to hospital to initiate insulin treatment and for diabetes education and self-management training. Outpatient or home-based management is preferred by some centres that have the requisite resources, in particular, the availability of travelling diabetes nurses who will need to visit at least daily in the first few days and maintain regular telephone contact, often outside normal working hours (Lowes and Gregory 2004). The size of the geographical area that needs to be covered is an important consideration. Outpatient or home-based management may have several advantages: the stress of a hospital stay is avoided, the outpatient setting or patient's home is a more natural learning environment for the child and family, and ambulatory treatment reduces the cost of care. Where adequate outpatient and/or home initial management of type 1 diabetes at diagnosis can be provided, studies have shown there is no disadvantage in terms of metabolic control nor increase in acute complications, hospitalizations, psychosocial or behavioural problems or total costs. The decision concerning whether a child with newly diagnosed diabetes should be admitted to hospital depends on several factors: most important are the severity of the child's metabolic derangements, the family's psychosocial circumstances, and the resources available at the treatment centre. Many paediatric diabetes centres offer ambulatory care and provide diabetes education and training in a day care unit for several days following diagnosis.

Hospital admission is necessary if intravenous (IV) therapy is required to correct dehydration, electrolyte imbalance, and ketoacidosis or if there are psychosocial challenges. Children who are ≤5% dehydrated, not nauseous or vomiting, who are not particularly unwell, and have a pH ≥7.30 usually respond well to subcutaneous insulin and oral rehydration.

Outpatient diabetes care

The diabetes team

Optimal care of children with type 1 diabetes is complex and time-consuming. Children with diabetes should be managed by a multidisciplinary diabetes team, which provides diabetes education and care in collaboration with the child's primary care physician. The team should consist of a paediatric endocrinologist or paediatrician with training in diabetes

management, a paediatric diabetes nurse educator (DNE) or diabetes nurse specialist (advanced practice nurse), a dietitian trained in paediatric diabetes nutrition, and a mental health professional (a clinical psychologist or medical social worker). The diabetes team should always be available by telephone to provide guidance and support to parents and patients and to respond to metabolic crises that require immediate intervention.

Initial diabetes education

Education is the foundation of diabetes care and is vital to ensure successful outcomes. Diabetes education provides the knowledge and skills needed to perform diabetes self-care and make the lifestyle changes required to successfully manage the disease. The diabetes education curriculum should be adapted to the individual child and family. Parents and children with newly diagnosed diabetes are usually anxious and overwhelmed and frequently cannot assimilate a large amount of abstract information. Therefore, the education programme should be staged. Initial educational goals should be limited to basic skills so that the child can be safely cared for at home and return to his or her daily routine as soon as possible. Initial diabetes education and self-management training should include: understanding what causes diabetes, how it is treated, how to measure and administer insulin, basic concepts of meal planning, self-monitoring of blood glucose (SMBG) and ketones, recognition, and treatment of hypoglycaemia, and how and when to contact a member of the diabetes team for advice.

Main topics for discussion following diagnosis

If several members of the diabetes team are involved in educating the newly diagnosed child and his or her family, good communication between team members to ensure consistency in the messaging and the specific information given is important. The following topics should be included in the curriculum and discussed with the child and family over a period of several weeks or months following diagnosis:

- Assessment of the family's pre-existing knowledge of diabetes.
- Current knowledge of the cause of diabetes.
- The consequences of having diabetes and its lifelong implications.
- The concept of the 'diabetes team' of professionals who will be involved in the child's care.
- The role of insulin in type 1 diabetes management.
- Practical details of insulin injections.
- When and how to monitor and interpret blood glucose concentrations.
- When and how to measure blood or urinary ketone concentrations.
- Advice about the crucial role of nutrition.
- The effect of exercise on carbohydrate and insulin requirements.
- The causes and consequences of hypoglycaemia and how to treat it.
- Management of diabetes during intercurrent illness ('sick days').
- The 'honeymoon period' of stable glycaemia and reduced insulin requirements following diagnosis.
- Long-term microvascular complications.
- Who to contact in an emergency (including phone numbers).
- Details of outpatient follow-up.
- The importance of always having identification (e.g. medical bracelet) indicating that the person has diabetes.
- Additional sources of information about diabetes.
- Availability of support groups.
- Health insurance issues, sources of and entitlement to financial assistance.
- Future developments.

Requirements on discharge from hospital

The child's primary care physician should be informed of the child's diagnosis, management plan, and discharge from hospital, and the diabetes nurse should communicate with the school nurse or daycare facility to ensure that details of the care plan are in place and understood. The equipment that a child will need on discharge is shown in Table 1.4.

Continuing diabetes education and long-term supervision of diabetes care

When the child is medically stable and parents (and other care providers) have mastered basic diabetes management skills, the child is discharged from the hospital or ambulatory treatment centre. In the first few weeks after diagnosis, frequent telephone contact provides emotional support and helps parents to interpret the results of blood glucose monitoring and, when necessary, insulin doses are adjusted to achieve blood glucose levels in a defined target range. Within a few weeks of diagnosis, many children enter a partial remission (the 'honeymoon' phase), evidenced by normal or near-normal blood glucose levels on a low

Table 1.4 Supplies required at time of discharge.

Lancing device and lancets
Blood glucose meter and test strips
Blood ketone meter and ketone strips or urine ketone test strips
Oral glucose tablets and gel
Glucagon emergency kit
Sharps container
Literature on diabetes management and how to obtain a Medic Alert bracelet/necklace
Pen insulin delivery system, disposable pre-filled pens, or syringes with needles for insulin injections
Insulin cartridges for non-disposable pen-delivery system or insulin vials
Rapid-acting and long- or intermediate-acting insulin (depending on insulin regimen)
Alcohol swabs
Needle clipper

dose (<0.25 U/kg/day) of insulin. By this time, most patients and parents are less anxious, have mastered basic diabetes management skills through repetition and experience, and are now more prepared to begin to learn the intricate details of intensive diabetes management. At this stage, the diabetes team should begin to provide patients and parents with the knowledge they will need to maintain optimal glycaemic control while coping with the effects of exercise, varying food intake, intercurrent illnesses, and the other challenges that normally occur in a child's daily life.

In addition to teaching facts and practical skills, education should promote desirable health beliefs and attitudes in the young person with a chronic incurable disease. For some children, this may be best accomplished in a non-traditional educational setting, such as a summer camp for children with diabetes. The educational curriculum must be concordant with the child's level of cognitive development and has to be adapted to the learning style and literacy and numeracy skills of the individual child and family. Parents, grandparents, older siblings, the school nurse, and other important people in the child's life are encouraged to participate in the diabetes education programme so they can actively share in the diabetes care and ensure that the child with diabetes is not excluded from normal childhood activities (sports, field trips, sleepovers, etc.).

In the first month after diagnosis, the patient and care providers are seen frequently by the diabetes team to review and consolidate the diabetes education and practical skills learned in the first few days and to extend the scope of diabetes self-management training. Thereafter, follow-up visits with members of the diabetes team should occur at least every three months. Regular clinic visits are necessary to ensure that the child's diabetes is being appropriately managed and the goals of therapy are being met. A focused history should obtain information about self-care behaviours, the child's daily routines, the frequency, severity, and circumstances surrounding hypoglycaemic events, details about insulin doses, and blood glucose monitoring data should be reviewed to identify patterns and trends. At each visit, height and weight are measured and plotted on a growth chart. The weight curve is especially helpful in assessing the adequacy of therapy. Significant weight loss usually indicates that the prescribed insulin dose is insufficient or the patient is not receiving all the prescribed doses of insulin. A complete physical examination should be performed at least once or twice each year focusing on blood pressure, stage of puberty, evidence of thyroid disease, examination of the injection sites for evidence of lipohypertrophy (from over-use of the site) or lipoatrophy, and mobility of the joints of the hands.

Each clinic visit provides an opportunity to reinforce the individual patient's blood glucose targets and HbA1c goal, and to increase the patient's and the family's understanding of diabetes management, the interplay of insulin, food, and exercise, and their impact on blood glucose levels. As the child's cognitive development progresses, the child should become more involved in diabetes management and increasingly assume *supervised* age-appropriate responsibility for daily self-care. Parents are encouraged to contact the diabetes team for advice if the pattern of blood glucose levels changes between routine visits, suggesting the need to adjust insulin doses or change the regimen. Eventually, when parents and patients have sufficient knowledge and experience to interpret blood glucose patterns and trends, they are encouraged to independently adjust insulin doses.

Psychosocial aspects of diabetes management

The diagnosis of diabetes in a child or adolescent hurls parents into a frightening and foreign world. They grieve the loss of their healthy child and have to cope with normal distress reactions, including shock,

disbelief and denial, fear, anxiety, anger, and blame or guilt. During this emotionally intense time, parents are expected to rapidly acquire an understanding of the disease and manage the illness at home. Parents should receive the necessary support to begin coping with their emotional distress and not be overwhelmed by unrealistic expectations from a well-meaning diabetes treatment team.

Diabetes also presents family members with the task of being sensitive to the balance between the child's need for a sense of autonomy and mastery of self-care activities and the need for ongoing family support and involvement. The struggle to balance independence and dependence in relationships between the child and family members presents a long-term challenge and raises different issues for families at different stages of child and adolescent development. Focusing on normal developmental tasks at each stage of the child's growth and development provides the most effective structure to address this concern (Anderson et al. 2009).

A medical social worker or clinical psychologist should perform an initial psychosocial assessment of all newly diagnosed patients to identify families at high risk who need additional services. Thereafter, patients are referred to a mental health specialist when emotional, social, environmental, or financial concerns are suspected or identified that interfere with the ability to maintain acceptable diabetes control. Some of the more common problems in families who have a child with diabetes include parental guilt, resulting in poor adherence to the treatment regimen, difficulty coping with the child's frustration and rebellion against treatment, fear of hypoglycaemia, anxiety, depression, missed appointments, financial hardship, or loss of health insurance affecting the ability to attend scheduled clinic appointments and/or purchase supplies. Patients with poor glycaemic control and a history of frequent emergency department visits should be screened for depressed mood (Lawrence et al. 2006). Recurrent ketoacidosis is the most extreme indicator of psychosocial stress, and management of such patients must include a comprehensive psychosocial assessment.

Because childhood is characterized by cognitive and emotional immaturity, successful treatment of paediatric diabetes requires the continuous, active involvement of responsible adults. Moreover, diabetes treatment occurs within a family dynamic, and treatment-related conflicts are common, arising in part from a natural discord in goals between caretakers and the child. Each phase of childhood has unique characteristics that complicate treatment; for example, the normally erratic eating behaviour of toddlers and the unscheduled intense physical play of school-aged children that can hinge on unpredictable factors, such as the weather. Adolescence is characterized by multiple physiologic and psychosocial factors that make glycaemic control even more challenging. Diabetes treatment should be individually tailored to each child, based on age, family resources, cognitive ability, the schedule and activities of the child and family, and their goals and desires.

Rates of psychological ill health in youth with diabetes are high, and longitudinal data indicate that mental health issues in childhood are likely to persist into early adulthood and are prognostic of maladaptive lifestyle practices, long-term problems with diabetes control and earlier-than-expected onset of complications. For these reasons, mental health screening should be routinely performed in diabetes clinics. Screening for behavioural disturbance should begin in children at the time of diagnosis, with further assessment of parental mental health and family functioning for those children identified to be 'at risk'. Interventions can then be targeted based on the specific needs of individual children and families. Additional psychological support is often provided by diabetes nurses and other parents at local and national support groups.

Diabetes Control and Complications Trial (DCCT)

This clinical trial, completed in 1993, proved that near-normal glycaemia delays the onset and slows the progression of microvascular complications, and it set the current standards for treatment of type 1 diabetes. A total of 1441 subjects with diabetes aged 13–39 years were randomized either: (i) to continue with their conventional treatment; or (ii) to receive intensive therapy with increased support from the 'diabetes team' and insulin administered either by three or more injections daily or by a pump (The Diabetes Control and Complications Trial Research Group 1993). After a mean duration of 6.5 years, as compared with conventional therapy, intensive treatment resulted in a reduction in:

- mean HbA1c concentration of nearly 2% (22 mmol/mol);
- the risk of retinopathy by 76%;
- the occurrence of microalbuminuria by 39%;
- the occurrence of neuropathy by 60%.

For every 10% reduction in HbA1c (e.g. 8% vs. 7.2%), there was a 44% reduction in the risk of microvascular complications.

Intensive treatment using the insulin preparations available at the time (i.e. before the development of insulin analogues) was associated with a two-to-three-fold increase in severe hypoglycaemia and a mean weight gain of 4.6 kg when compared with conventional treatment. This study clearly demonstrated that near-normal glycaemia (as measured by HbA1c) significantly reduced the risk of microvascular complications. In the 25 years since the results of this landmark study were announced, the challenge for clinicians has been to implement the principles of intensive diabetes therapy in children and adolescents in routine clinical practice.

Goals of therapy

The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends a target HbA1c of <7.5% (58 mmol/mol) for all age groups (DiMeglio et al. 2018). However, biochemical goals should be individualized, taking into account both medical and psychosocial considerations; i.e. each child should have individually determined targets with the goal of achieving an HbA1c value as close to normal as possible while avoiding frequent episodes of mild to moderate hypoglycaemia and severe hypoglycaemia. Less stringent treatment goals may be appropriate or more realistic for preschool-aged children, children with developmental handicaps, psychosocial challenges, lack of appropriate family support, children who have experienced severe hypoglycaemia, or those with hypoglycaemia unawareness.

Insulin therapy in type 1 diabetes

Initial insulin therapy

At the time of diagnosis, many children with type 1 diabetes are severely insulin-deficient and require insulin replacement to survive. The aim of insulin replacement therapy is to simulate normal plasma insulin patterns as closely as possible. Truly physiologic insulin replacement continues to be an elusive goal owing to: (i) delivery of insulin into the systemic circulation instead of the portal venous system, and (ii) the inability to mimic the first and second phases of normal insulin release in response to eating. Insulin pump therapy or multiple daily insulin (MDI) injections currently are the two methods that most closely mimic normal insulin secretion.

The *ideal* regimen for the newly diagnosed patient is a multiple dose, flexible basal-bolus regimen that provides basal insulin throughout the day and night and insulin boluses before meals and snacks. Rapid-acting insulin is injected approximately 15 minutes before eating; individual doses are adjusted meal-to-meal based on preprandial blood glucose values, anticipated meal macronutrient content, and physical activity. Practical considerations are vitally important when selecting an insulin regimen for a child with type 1 diabetes. Socio-economic circumstances, parental health literacy and numeracy, patient's age, supervision of care, ability and willingness to self-administer insulin several times each day, and difficulty maintaining long-term adherence, all conspire to make physiologic insulin replacement challenging. For these reasons, there is no universal insulin regimen that can be successfully used for *all* children with type 1 diabetes. The diabetes team must design an insulin regimen that meets the needs of the individual patient and is acceptable to the patient and family members(s) responsible for administering insulin to the child or supervising its administration.

The route of insulin administration initially is determined by the severity of the child's condition at presentation. Insulin is usually given intravenously for treatment of DKA; whereas insulin may be administered subcutaneously when children are metabolically stable without vomiting or significant dehydration and ketosis. Whenever appropriate, the newly diagnosed child should commence insulin replacement therapy with a flexible basal-bolus regimen. In some healthcare systems, it is now possible to start insulin pump therapy at the time of diagnosis regardless of the severity of presentation or age of the child.

Three major categories of insulin preparations, classified according to their time course of action, are available (Table 1.5) and various insulin replacement regimens consisting of a mixture of short- or rapid-acting insulin and intermediate- or long-acting insulin are used in children and adolescents, typically given at least two to four (or more) times daily.

Insulin analogues

Rapid-acting insulin analogues incorporate amino acid substitutions, which make them quickly dissociate into monomers following injection and are then rapidly absorbed. Compared with short-acting regular insulin, they produce lower postprandial glucose excursions.

Table 1.5 Types of insulin preparations and approximate insulin action profiles.

Insulin type	Onset of action (h)	Peak of action (h)	Effective duration of action (h)
Rapid-acting analogues			
Aspart, lispro, glulisine	0.25–0.5	1–3	3–5
Regular insulin	0.5–1	2–4	5–8
Intermediate-acting insulin			
Neutral Protamine Hagedorn (NPH), isophane	2–4	4–10	10–16
Long-acting analogues			
Detemir	2–4	None	12–20[a]
Glargine	2–4	None	20–24
Degludec	2–4	None	24–42
Premixed combinations			
50% NPH, 50% regular	0.5–1	dual	10–16
50% NPL, 50% lispro	0.25	dual	10–16
70% NPH, 30% regular	0.5–1	dual	10–16
70% PA, 30% aspart	0.25	dual	15–18
75% NPL, 25% lispro	0.25	dual	10–16

PA, protamine-crystallized insulin aspart suspension; NPL, neutral protamine lispro suspension. PA + soluble aspart and NPL + lispro are both stable pre-mixed combinations of intermediate- and rapid-acting insulins.
The human insulins and insulin analogues are available in vials, pre-filled disposable pen injectors, and cartridges for non-disposable pen injectors.
These data are approximations from studies in adult test subjects. The times of onset, peak, and effective duration of action vary within and between patients and are affected by numerous factors, including size of dose, site and depth of injection, dilution, exercise, temperature, regional blood flow, local tissue reactions.
[a] Dose-dependent; 12 hours for 0.2 U/kg; 20–24 hours for ≥0.4 U/kg.

The three long-acting insulin analogues are characterized by a relatively consistent and prolonged release of insulin without distinct peaks. Insulin glargine has a prolonged duration of action (22–24 hours) and can be injected at any time of day, but is usually given with dinner or at bedtime. The duration of action of insulin detemir is partly dependent on the dose – small doses may last only 12 hours; therefore, it usually has to be injected twice daily. Insulin degludec is an ultra-long-acting insulin with a flat, stable profile at steady state and a duration of action exceeding 24 hours and up to 42 hours. There is some evidence that both glargine and detemir lead to a decrease in the incidence of hypoglycaemia including nocturnal hypoglycaemia. Table 1.6 shows suggested starting total daily insulin dose (units per kg per day).

Table 1.6 Suggested starting total daily insulin dose (units per kg per day).

	No DKA at presentation	DKA at presentation
<6 years or HbA1c <7%	0.15–0.25	0.5–0.75
Prepuberty	0.25–0.5	0.75–1
Puberty	0.5–0.75	1–1.2
Postpuberty	0.25–0.5	0.75–1

While clinical trials comparable to the Diabetes Control and Complications Trial (DCCT) have not been conducted in prepubertal children, it is logical to extrapolate that prepubertal children will also benefit from near-normal glycaemic control. Intensive treatment regimens (MDI injections or insulin pump) are the preferred form of therapy for all patients with type 1 diabetes. Insulin regimens based on one or two daily injections cannot achieve optimal glycaemic control in type 1 diabetes except during the remission ('honeymoon') period, and may incur a greater risk of hypoglycaemia. These regimens, including the use of pre-mixed combination insulins, should only be used when insurmountable barriers preclude the use of a multiple dose insulin regimen.

Split-mixed insulin regimens

When a *two-dose regimen* is used, the total daily dose (TDD) is typically divided as follows: two-thirds before breakfast and one-third is given in the evening. The relative proportion of rapid- or short-acting insulin to intermediate-acting insulin depends on the pre-meal blood glucose value and the carbohydrate content of meals. It is common to start by giving one-third of the pre-breakfast dose as rapid- or short-acting insulin and two-thirds as neutral protamine Hagedorn (NPH), and a similar ratio before dinner. For example, if the TDD for a 30-kg child is 0.75 unit kg (22.5 units): a mixed dose injected before breakfast would consist of 5 units of rapid-acting and 10 units NPH; the pre-dinner dose would be 2.5 units rapid-acting and 5 units NPH. Regular insulin should be injected at least 30 minutes before eating; rapid-acting insulin (lispro, aspart, glulisine) is given 15 minutes before eating.

The optimal ratio of rapid- or short-acting to intermediate- or long-acting insulin for each patient is determined empirically, guided by the results of frequent blood glucose monitoring. At least five daily blood glucose measurements are required to determine the effects of each component of the insulin regimen: before each meal, before the bedtime snack, and once overnight between midnight and 4 a.m. Parents are taught to look for patterns of hyperglycaemia or hypoglycaemia that indicate the need for a dose adjustment. Adjustments are made to individual components of the insulin regimen, usually in 5–10% increments or decrements, in response to patterns of consistently elevated (above the defined target range for several consecutive days) or unexplained low blood glucose levels, respectively. The insulin dose is adjusted until satisfactory blood glucose control is achieved, i.e. at least 50% of blood glucose values are in or close to the child's target range.

At the time of diagnosis, most children have some residual beta-cell function and within several days to a few weeks often enter a period of partial remission ('the honeymoon period'), during which normal or nearly normal glycaemia is achieved with a low dose of insulin. At this stage, the dose of insulin must be reduced to prevent hypoglycaemia, but should not be discontinued. As destruction of the remaining beta-cells occurs over time, the insulin requirement increases ('the intensification phase'), eventually reaching a full replacement dose. The average daily insulin dose in prepubertal children with long-standing diabetes is approximately 0.6–0.8 units/kg/day, and in adolescents 1–1.2 units/kg/day. Obese patients usually are insulin-resistant and require relatively higher TDDs, e.g. overweight or obese adolescents may require up to 1.5 units/kg/day.

Beyond the remission period it is seldom possible without a regimented lifestyle and rigid adherence to a meal plan to achieve near-normal glycaemia with two injections per day and without incurring a greater risk of hypoglycaemia, especially overnight. An important limitation of a two dose 'split-mixed' regimen is that the peak effect of the pre-dinner intermediate-acting insulin (isophane, NPH) tends to occur at the time of lowest insulin requirement (i.e. from midnight to 4 a.m.), increasing the risk of nocturnal hypoglycaemia (Figure 1.2). Thereafter, insulin action decreases from 4 a.m. to 8 a.m., when basal insulin requirements normally increase. Consequently, the tendency for blood glucose levels to rise before breakfast ('the dawn phenomenon') is compounded by the waning insulin effect before breakfast and/or by counter-regulatory hormones secreted in response to a fall in blood glucose levels during sleep, resulting in post-hypoglycaemic hyperglycaemia (the Somogyi phenomenon, see Section 1.7.7.2).

A *three-dose insulin regimen* with mixed short- or rapid- and intermediate-acting insulin before breakfast, only short- or rapid-acting insulin before dinner, and intermediate- or long-acting acting insulin at bedtime, may ameliorate these problems (Figure 1.2). The peak action of the morning dose of NPH occurring at midday may eliminate the need for a dose of rapid-acting insulin at lunchtime (provided lunch does not contain excessive carbohydrate), and this may be necessary in circumstances where nobody is available to administer a pre-lunch dose of rapid-acting insulin to a young child. Insulin regimens that employ intermediate-acting insulin demand consistency in the daily dietary regimen, both with respect to the amounts and timing of food consumed at each meal and snack, and the timing of insulin injections. Furthermore, owing to the time and duration of its peak action, NPH insulin given at bedtime is associated with increased frequency of nocturnal hypoglycaemia as compared to long-acting, 'peakless' basal insulin analogues.

Basal-bolus regimens and continuous subcutaneous insulin infusion (CSII)

Flexible basal-bolus insulin regimens utilize MDI (Figure 1.3) or continuous subcutaneous insulin infusion (CSII) with an insulin pump (Figure 1.3). Flexible regimens more closely simulate normal diurnal insulin profiles, overcome many of the

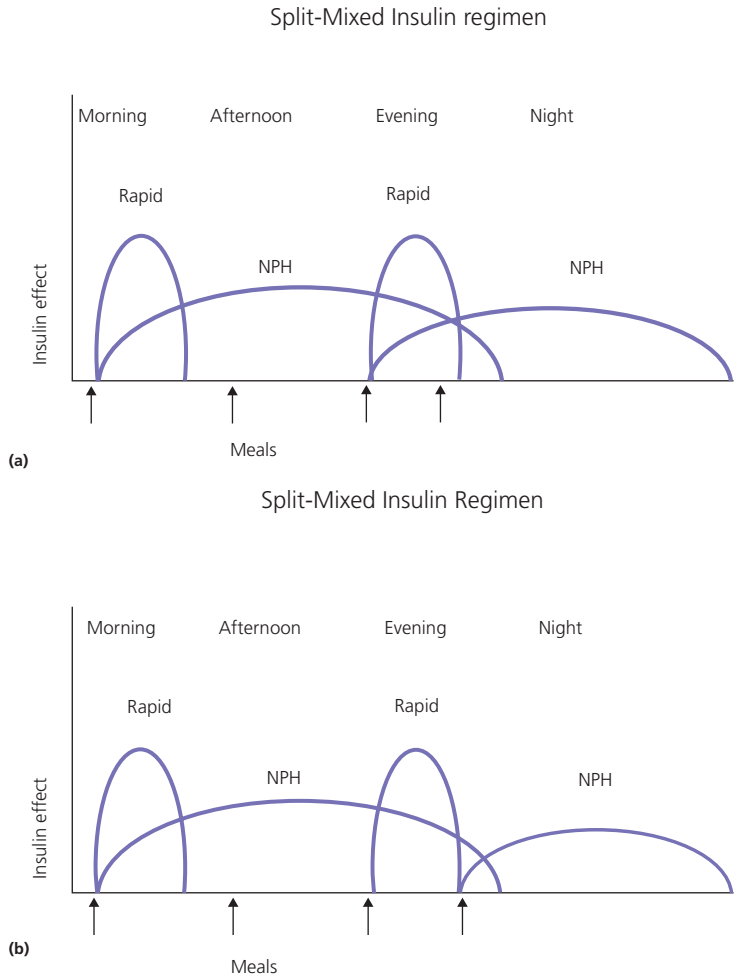

Figure 1.2 Schematic representations of commonly used insulin regimens. (a) Idealized insulin action profiles provided by a regimen consisting of twice-daily mixtures of rapid-acting insulin and intermediate-acting insulin (NPH) injected before breakfast and before dinner. A snack must be eaten at bedtime to reduce risk of nocturnal hypoglycaemia. (b) Idealized insulin action profiles provided by a regimen consisting of a mixture of rapid-acting insulin and intermediate-acting insulin (NPH) before breakfast, rapid-acting insulin before supper/dinner, and a second dose of NPH at bedtime, together with a snack to reduce risk of nocturnal hypoglycaemia.

limitations inherent in split-mixed regimens, and permit greater flexibility with respect to timing and content of meals, and adjustments for exercise. Doses of rapid-acting insulin are selected before each meal or snack, based on pre-meal glucose values, anticipated meal macronutrient content, and physical activity. In the 'basal-bolus' MDI regimen (shown in Figure 1.3), a peakless, long-acting insulin (insulin glargine, detemir, or degludec) is used to provide basal insulin (starting dose typically about 40–50% of the estimated TDD) together with short- or rapid-acting insulin injected 30 or 15 minutes, respectively, before each meal.

Insulin glargine is usually administered once daily in the evening with dinner or at bedtime or before breakfast. It should be injected at about the same time each day; short- or rapid-acting insulin is injected separately before each meal (and large snack), whenever it is eaten. Because it does not have the peak of activity characteristic of NPH, insulin glargine reduces the risk of nocturnal hypoglycaemia. Insulin detemir is an alternative long-acting, 'peakless' basal insulin with pharmacodynamics characteristics similar to those of glargine especially during the first 12 hours after administration. It has a shorter duration of action than glargine and usually has to be administered twice

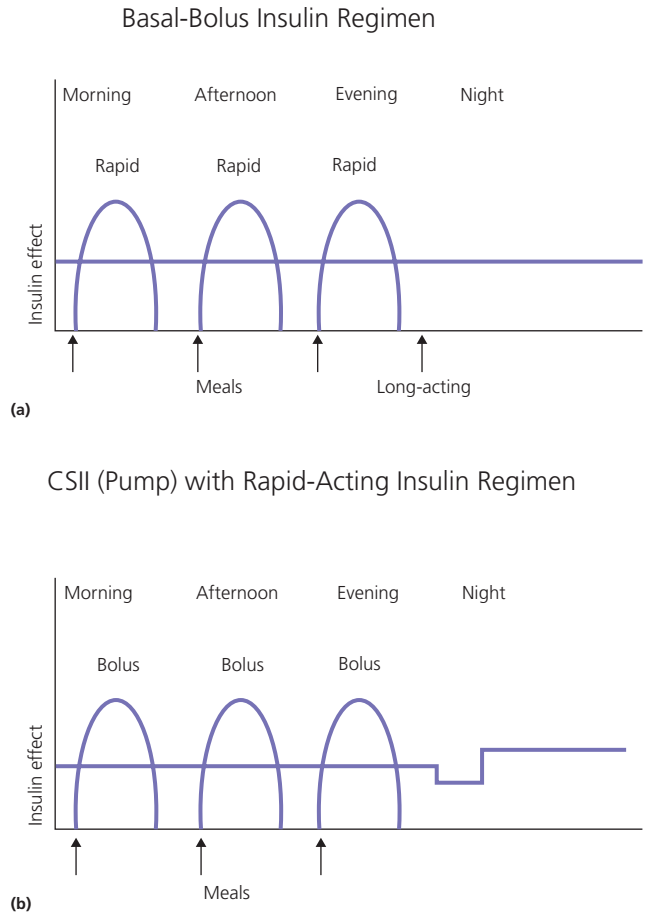

Figure 1.3 (a) Idealized insulin action provided by an insulin regimen consisting of four daily injections; rapid-acting insulin before each meal (denoted by arrows) and a separate single daily injection of a long-acting insulin analogue (glargine, detemir, or degludec), either at bedtime (as shown here) or at dinner or breakfast. (b) Idealized insulin effect provided by continuous subcutaneous insulin infusion via an insulin pump with rapid-acting insulin. In this figure, alternative basal rates are illustrated; insulin delivery is programmed to decrease from midnight to 3 a.m. to decrease risk of nocturnal hypoglycaemia and to increase from 3 a.m. until 8 a.m. to combat the dawn phenomenon. Arrows indicate times of insulin injection or boluses before breakfast, lunch, and the evening meal (supper or dinner).

daily in patients with severe insulin deficiency. Compared to NPH, studies in children and adolescents show a lower risk of hypoglycaemia and lower weight Z-score while its effect on HbA1c is equivalent. The most recently developed long-acting insulin formulation is ultralong-acting insulin degludec, which forms multihexamers resulting in a depot after injection into the subcutaneous tissue. The hexamers slowly dissociate to form monomers that are rapidly absorbed into the circulation. Degludec has a flat and stable pharmacokinetic profile; its major advantage is that it does not have to be injected at precisely the same time each day, which is an attractive feature especially for adolescents whose lifestyles make it difficult to adhere to an inflexible schedule.

Assuming the starting dose in a 60-kg adolescent is 0.75 unit per kg or 45 units per day, the initial dose of long-acting basal insulin might be 20 units (~45% of the TDD) and the insulin-to-carbohydrate ratio 1 unit of rapid-acting insulin per 10 g carbohydrate (calculated using the formula 450/TDD). The initial correction or insulin sensitivity factor is calculated using the formula 1800/TDD. In this example, it would be 1 unit of rapid-acting insulin to lower BG by 40 mg/dL (2.2 mmol/L) to a predetermined target; e.g. 120 mg/dL (11.1 mmol/L) during the day and 150 mg/dL (8.3 mmol/L) at bedtime and overnight. The actual prandial dose, administered ~15 minutes before the meal, is the sum of the individual doses required for carbohydrate coverage and the amount calculated to correct

hyperglycaemia. The above simple formulae are useful to start insulin therapy; however, the optimal doses of rapid-acting insulin must be determined empirically guided by the results of frequent BG measurements, before and ~2 hours after a meal. At least five daily measurements are required to determine the effects of each component of the insulin regimen. The BG concentration should be measured before each meal, at bedtime, and once between midnight and 4 a.m. Patients and parents are taught to look for patterns of hyperglycaemia (>180 mg/dL or 10 mmol/L) or hypoglycaemia (<70 mg/dL or 3.9 mmol/L) that indicate the need for a dose adjustment. Adjustments are made to individual components of the insulin regimen, usually in 5–10% increments or decrements, in response to patterns of consistently elevated (above the target range for several consecutive days) or unexplained low BG levels. The insulin dose is adjusted every 3–5 days until satisfactory BG control is achieved with at least 50% of BG values in the target range.

Practical aspects of insulin treatment

Insulin delivery systems

Insulin has an effective shelf life of at least two years if refrigerated at 4 °C and can be kept at room temperature for up to one month. However, in tropical climates or if kept in a car interior on a hot day, insulin degrades more rapidly. Insulin is administered by a pen delivery system or with a syringe and needle, or via an insulin pump. In general, vials of insulin are cheaper than insulin in disposable pens or pen cartridges. For children with needle phobia, spring-loaded automatic injection devices in which the needle is not visible may be helpful.

Insulin pens

Insulin may be administered using either a preloaded disposable pen or cartridges (different pens for rapid- and long-acting insulins) for a reusable pen device. Pen delivery systems are generally preferred by children as they are quicker and easier to use than syringes and needles, and lead to greater independence.

Syringes and needles

Insulin for injection may be drawn up from a vial and injected using an insulin syringe and needle. When mixing insulins, the rapid-acting clear insulin should be drawn up into the syringe before the intermediate-acting (NPH, isophane), which is a cloudy suspension, i.e. 'clear before cloudy insulin'. Before drawing up the dose into a syringe or injecting via a pen device, any preparation containing intermediate-acting insulin should be gently inverted several times to ensure that the insulin is uniformly suspended. Note that all insulin analogues are clear solutions; patients must be counselled to take special care not to confuse the rapid-acting with the long-acting analogue and accidentally (thinking it is the long-acting insulin) inject a large dose of rapid-acting insulin at bedtime.

Injections

The age at which children start to give their own injections is variable. Peer pressure, which may be experienced by a child attending a diabetes camp where children may see their contemporaries or even younger children administering injections, may motivate a child to learn to self-inject. Parents are strongly advised to supervise insulin injections when children wish to become more independent.

Appropriate injection sites are shown in Figure 1.4. The use of different injection sites and rotation of these sites should be encouraged to avoid the development of lipohypertrophy (Figure 1.5) which may be unsightly and lead to erratic absorption of insulin. If patients avoid injecting into these areas, lipohypertrophy will gradually resolve over a period of several months.

Injection technique

When using short (e.g. 4 or 5 mm) needles, the injection is given at a 90° angle without pinching the skin unless the patient is very thin. In those who find injections painful, distraction techniques can be used or the skin can be numbed with an ice pack before the injection.

Injecting small doses

In infants, the injection of doses as small as 0.5 to 1 unit can result in significant inaccuracies, with the dose actually delivered ranging from 0.89 to 1.23 units. In these circumstances, use of a pen-delivery system, which allows injections of insulin in increments of 0.5 units is recommended. If possible, infants should be managed using an insulin pump which permits accurate delivery of tiny amounts of insulin. Alternatively, insulin may have to be diluted to U10 concentration: 1 line on an insulin syringe corresponds to 0.1 unit of insulin.

Insulin preparations

In solution, human insulin forms hexamers (six-molecule units). The rate of absorption after subcutaneous injection is principally determined by how

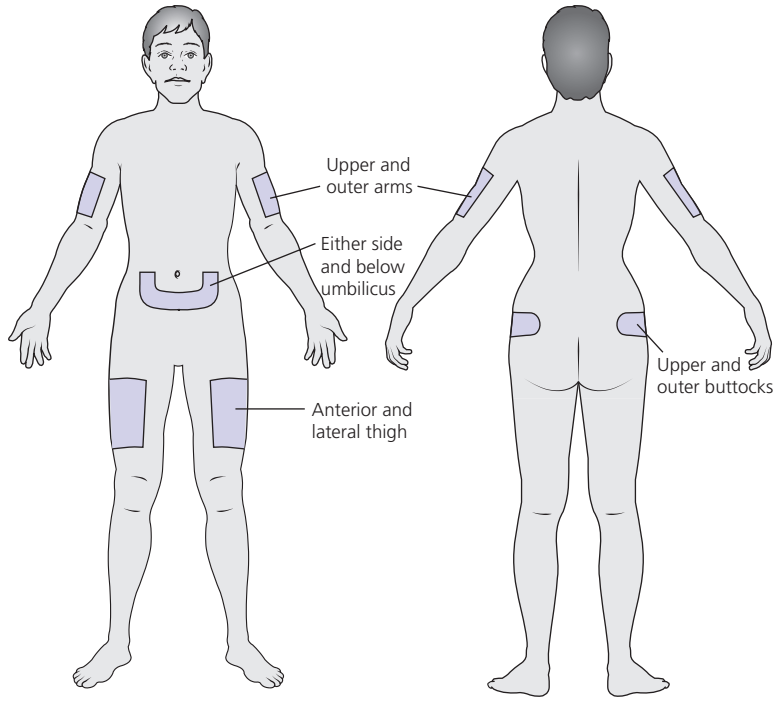

Figure 1.4 Insulin injection sites.

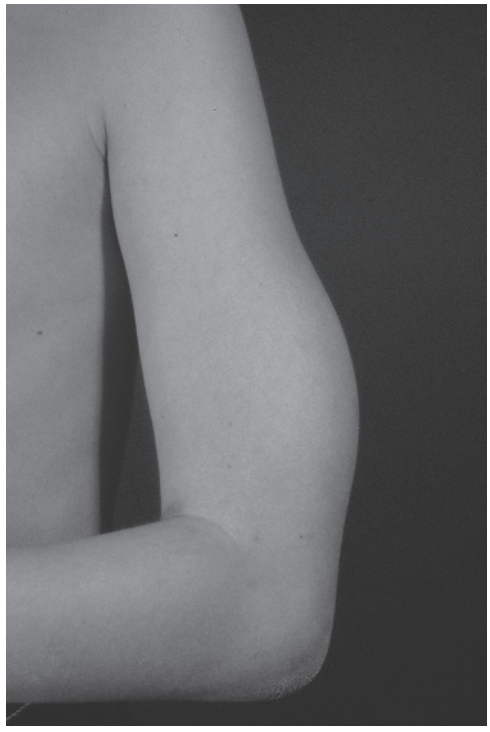

Figure 1.5 Lipohypertrophy on the arm.

quickly the hexamers dissociate into monomers (single molecules), which are absorbed across endothelial barriers. Children should be treated with human insulin analogues in a concentration of 100 units /ml (U100). Table 1.5 shows the most common insulin preparations and their durations of action.

Continuous subcutaneous insulin infusion (insulin pumps)

Despite the introduction of CSII (pump) therapy nearly 40 years ago, widespread adoption of this technology in paediatric diabetes practice has only occurred in the last 15 years. In 1996, less than 5% of patients who started pump therapy were < 20 years of age; over the intervening years there has been a worldwide steady increase in the number of children and adolescents using pump therapy. This may be attributable to recognition of the crucial importance of lowering HbA1c levels to prevent or delay vascular complications together with advances in pump technology. There is considerable worldwide variation in the frequency of pump use, e.g. use of insulin pumps is threefold greater in Germany, Austria, and the United States compared with England and Wales.

An insulin pump has several advantages over insulin injections, e.g. the ability to programme changes in basal insulin delivery to meet an anticipated increase or decrease in need. This feature can be advantageous in combating the dawn phenomenon (especially pronounced in adolescents) or preventing hypoglycaemia during or after strenuous exercise. In addition to programming various basal infusion rates over the course of the day and night, the use of dual wave and square wave bolus delivery significantly lowers postprandial blood glucose levels after meals with a high fat and protein content. Also, because the infusion set typically only has to be replaced every two or three days, the child is spared the discomfort of numerous daily injections. Registries that track outcomes of type 1 diabetes treatment and several single centre observational studies show that children who use a pump have significantly lower HbA1c levels and decreased glycaemic variability, decreased rates of severe hypoglycaemia, and improvements in diabetes-related quality of life, treatment satisfaction, and less fear of hypoglycaemia. A meta-analysis of randomized controlled clinical trials showed that CSII results in a small (~0.5%) improvement in HbA1c (Garvey and Wolfsdorf 2015). Even larger improvements in glycaemic control and hypoglycaemia reduction are possible with insulin pumps that incorporate continuous glucose monitoring (CGM), referred to as sensor augmented pump therapy (Slover et al. 2012).

Although an insulin pump is a complex and sophisticated medical device that requires extensive training in its proper use, with appropriate education and training and with support from parents and a school nurse, most children and adolescents can manage to successfully and safely use an insulin pump and benefit from its advantages. Because only short- or rapid-acting insulin is used with CSII, any interruption in insulin delivery rapidly leads to metabolic decompensation. To reduce this risk, patients must pay meticulous attention to insuring the integrity of the infusion system and must measure their blood glucose levels at least four times daily. A recent study showed a lower rate of DKA with pumps as compared to MDI therapy. Success requires motivation to achieve normal blood glucose levels, frequent blood glucose monitoring, accurate carbohydrate counting, good record-keeping, and frequent contact with the diabetes team. Patients must understand that to be successful CSII therapy requires more time, effort, and active involvement in diabetes care by patients and parents, and considerable education and support from the diabetes team. The individual who is unable to master an MDI regimen is not likely to be successful with CSII. Despite concerns that it might have adverse psychosocial consequences owing to the added burden of treatment, especially in adolescents, the opposite effect has been observed.

The insulin delivery system consists of a programmable pump (about the size of a cell phone) containing a reservoir filled with rapid-acting insulin, which is connected by a plastic infusion tube to a small plastic (or metal) cannula inserted subcutaneously - usually in the abdomen or posterior aspect of the upper arm, anterior thigh or buttocks (in toddlers and infants it is most often inserted in the buttocks) and fixed in place by adhesive tape. Depending on the specific device, changes in the insulin infusion rate as small as 0.025 units /hour can be made. The cannula is usually left in place for two to three days. If the cannula is not changed regularly or if the same site is used recurrently, there is a risk of developing lipohypertrophy or developing an infection at the site.

A 24-hour profile including measurements before each meal, two hours after the meal, at midnight, at 2.00–4.00 a.m. should be carried out at least every other week to enable any necessary dose changes to be made. The absence of a long-acting insulin depot means that if there is an interruption in insulin delivery, blood glucose levels will rise quickly and ketosis can develop in four to six hours. CSII therapy is considerably more expensive than MDI therapy.

Some patients prefer a tubeless disposable 'patch pump' (Figure 1.6), consisting of a micro pump, an insulin reservoir, and a cannula; the integrated device attaches directly to the skin. Insulin is delivered through a small subcutaneous catheter. Patch pumps are free of tubing and are waterproof, which makes them more discreet and allows greater freedom with

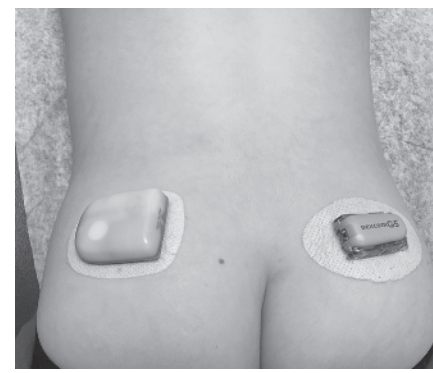

Figure 1.6 An Omnipod® patch pump is on the left buttock and a Dexcom G5® glucose sensor on the right buttock.

activities such as swimming. They are disposable and are lighter and smaller than conventional pumps. They usually need to be reapplied every two or three days. The pump is controlled by a remote device that has an integrated glucose meter and which communicates wirelessly with the patch pump.

CSII can also be used together with CGM sensors that measure glucose levels in the interstitial fluid every few minutes, referred to as sensor augmented pump therapy. The data can be transferred to the pump using Bluetooth technology so that if the blood glucose is below a certain value, for example, 4 mmol/L (72 mg/dL), the insulin pump sets off an alarm and suspends insulin delivery. Some insulin pumps can also be set to raise an alarm if the glucose level is falling rapidly and they will suspend insulin delivery if hypoglycaemia is anticipated to occur within the next 30 minutes ('predictive low glucose suspend'). Recently, interstitial glucose sensing and insulin delivery have been combined to produce a 'hybrid closed loop system', i.e. a version of an artificial pancreas that has been approved for use from 7 years. Such systems increase the number of BG values in the target range and decrease hypoglycaemia. Algorithms to cope with situations such as exercise are currently being devised and new technological innovations and device improvements have had a beneficial impact on the management of diabetes in children and adolescents. Use of an insulin pump permits a flexible lifestyle and eating patterns and is associated with a high degree of satisfaction in appropriately motivated patients.

Insulin regimens and glycaemic control

The technological innovations described above have provided patients with insulin preparations whose pharmacokinetic properties make it possible to crudely simulate physiologic insulin kinetics. It is now possible for children to safely achieve unprecedented levels of glycaemic control without excessive severe hypoglycaemia, and yet in most patients the goal of near-normalization of glycaemic control is not realized. Several recent studies have shown a persistent gap between target HbA1c ranges and the actual values patients attain. The successful implementation of intensive diabetes therapy remains a major challenge, and diabetes care providers should frankly discuss treatment options with the child and parents and explain the advantages and disadvantages of each in attempting to meet the overall goals of treatment. The most suitable regimen for a given child and family should be determined by mutual consent and should be the regimen they will most likely be able to afford and adhere to. These considerations are particularly important in managing children living in economically and socially disadvantaged circumstances and when there is a shortage of food.

Potential problems with insulin therapy

The dawn phenomenon

The dawn phenomenon describes the rise in insulin requirements and blood glucose concentrations in the early morning, approximately 5.00–8.00 a.m. It is most pronounced during puberty and is thought to be caused primarily by the insulin resistance produced by nocturnal growth hormone secretion. This is a difficult problem to resolve in those using twice daily insulin regimens. Possible benefit may be obtained in such patients by dividing the evening injection so that rapid-acting insulin is given prior to the evening meal and intermediate-acting insulin before bedtime (see Figure 1.2a). Alternatively, in patients on a basal-bolus regimen, the pre-bedtime dose of intermediate-acting insulin or long-acting insulin analogue can be increased. When using an insulin pump, the overnight basal rate can be programmed to increase at 3 a.m. until 8 a.m.

The Somogyi phenomenon

This term refers to morning hyperglycaemia caused by the release of counter-regulatory hormones following the occurrence of nocturnal hypoglycaemia. However, when pronounced hyperglycaemia occurs after an episode of nocturnal hypoglycaemia, it usually is attributable to ingestion of an excessive amount of carbohydrate to treat the hypoglycaemia episode. Alternatively, when pre-breakfast hyperglycaemia occurs without preceding nocturnal hypoglycaemia, this usually is caused by inadequate or waning overnight insulinemia.

Insulin therapy in young children: special considerations

Caring for young children with diabetes is challenging for many reasons; one is the need to accurately and reproducibly measure and inject tiny doses of insulin supplied in a concentration of 100 units/ml (U100 insulin). To administer a dose of 1 unit requires the ability to accurately measure 10 µl (1/100 ml) of insulin. A dose change of 0.25 U translates into a volume difference of 2.5 µl in a 300 µl (3/10 cc or 30 unit) syringe. When parents attempt to measure insulin doses in increments of 0.25 U (e.g. 3.0, 3.25, 3.5 U) using a standard commercial 30 unit (300 µl) syringe, they consistently measure more than the prescribed

amount. For these reasons, CSII can be a useful tool to provide U100 insulin in small doses to young children when there is appropriate caregiver education and diabetes team support. However, when injection regimens are used, to enhance accuracy and reproducibility of small doses, insulin should be diluted to U10 (10 units/ml) with the specific diluent available from the insulin manufacturers. Using U10 insulin, each line ('unit') on a syringe is actually 0.1 U of insulin.

Dietary management

Nutrition is a cornerstone of diabetes management and nutrition education and counselling are essential components of a comprehensive programme of diabetes self-management education for patients and their families. There is no 'diabetic diet' per se; rather, nutrition therapy should be individualized according to the family's and patient's usual eating habits and food preferences, religious or cultural considerations, and access to food. Combining blood glucose monitoring with intensive insulin therapy and mastery of carbohydrate counting enables children and adolescents to enjoy dietary flexibility while maintaining glycaemic control in the target range. The focus of dietary management differs between the two major types of diabetes. In type 1 diabetes, the primary goal is to match insulin delivery and carbohydrate consumption to achieve blood glucose levels in the target range. In contrast, children with type 2 diabetes are typically overweight or obese at presentation so that the emphasis is on weight loss, limiting calorie intake, and distributing meals evenly throughout the day.

Growth is an excellent indicator of the adequacy of energy intake, and should be regularly evaluated by plotting height and weight on a growth chart. If growth is not optimal, the diet should be reviewed and, in patients with type 1 diabetes, one should consider inadequate insulin delivery, hypo- or hyperthyroidism, coeliac disease, and adrenal insufficiency as possible causes. For overweight (BMI ≥85th percentile) and obese (BMI ≥95th percentile) youth with either type 1 diabetes or type 2 diabetes, energy consumption must be reduced to arrest weight gain. Table 1.7 shows a general approach to meal management for both type 1 diabetes and type 2 diabetes.

The numerous commercially available 'diabetic foods' are not recommended for children with diabetes, as such foods tend to be expensive and have no particular advantages over a healthy diet based on normal foods. Some 'diabetic foods' also contain the sweetener sorbitol that may lead to diarrhoea when consumed in large amounts. 'Diabetic foods' may also have a high calorie and fat content. Drinks containing sugar should be replaced with those containing artificial sweeteners.

Carbohydrate counting

Carbohydrate is the main nutrient in starches, fruits, milk, and sugar-containing foods and is the major determinant of postprandial blood glucose excursions. The most widely used method for youth with

Table 1.7 General approaches to meal management.

Type 1 diabetes	Split-mixed insulin regimen	• Three meals and two or three snacks daily • Meal times consistent from day-to-day • Meals and snacks spaced 2–3 hours apart • Consistent carbohydrate intake • Snack before bed to decrease risk of overnight hypoglycaemia • Continued education and assessment of readiness to change lifestyle to achieve a Heart Healthy diet
	Flexible basal-bolus or insulin pump therapy	• Carbohydrate content can vary • Must accurately count carbohydrate and match insulin dose using an insulin:carbohydrate ratio • Recommend eating three meals daily • Continued education and assessment of readiness to change lifestyle to achieve a Heart Healthy diet
Type 2 diabetes		• Meal plan to assist with evenly spaced carbohydrate intake and increased emphasis on reducing calories to promote weight loss

type 1 diabetes who use rapid-acting prandial insulin is an individualized insulin-to-carbohydrate ratio (e.g. 1 unit per x grams of carbohydrate). Carbohydrate counting allows flexibility in food choices and enables patients to include a wide variety of foods in their meal plan. An important limitation of carbohydrate counting is that it does not address carbohydrate quality, diet composition, or total caloric intake. Patients should be encouraged to learn about the glycaemic index (GI) of their favourite carbohydrate-containing foods ('fast' vs. 'slow' carbohydrates). Carbohydrates are absorbed slowly from low-GI foods, whereas high-GI foods lead to rapid carbohydrate absorption and a brisk increase in blood glucose levels. The amount of fat, protein, and fibre in food also influences the rate of carbohydrate absorption. For example, meals with a high fat content slow the rate of carbohydrate absorption.

An alternative method, employed by patients who use a fixed dose insulin regimen or for whom carbohydrate counting may be too difficult, is a prescribed carbohydrate meal plan that maintains day-to-day consistency in the carbohydrate content of meals and snacks.

Children and their parents are taught how to read the nutrition facts on food labels for total carbohydrate (grams) per serving. Periodically measuring and weighing foods is recommended to reinforce accurate portion sizes and carbohydrate amounts, which is essential for optimal insulin dosing and to minimize postprandial hyperglycaemia. Numerous nutrition 'apps' are available for smart phones and other digital devices.

Renewed attention has been given to the impact of fat and protein on postprandial glycaemic responses in youth with type 1 diabetes, and evidence suggests that additional insulin to account for protein and fat in a meal is superior to dosing insulin solely based on carbohydrate intake.

Fat

Diabetes is associated with a high risk of early subclinical and clinical cardiovascular disease (CVD), and children with type 1 diabetes are in the highest tier for cardiovascular risk. Saturated and *trans* fatty acids are the principal dietary determinants of plasma low-density lipoprotein (LDL)-cholesterol concentrations. To reduce the risk of CVD, consumption of saturated fat, *trans* fatty acids, and cholesterol must be limited while increasing intake of unsaturated fats and omega-3 fatty acids. Because both glycaemic control and cardioprotective nutrition improve the lipid profile and reduce cardiac risk, patients should be advised to consume less red meat and high-fat dairy foods and eat more poultry, fish, and vegetable proteins, and drink low-fat milk. Children and adolescents with normal plasma lipid concentrations should derive less than 10% of their energy from saturated fats; the daily intake of cholesterol should be <300 mg per day, and consumption of *trans* fatty acids (principally formed by the hydrogenation of unsaturated fats and present in margarine, deep-frying fat, and some processed foods such as biscuits and cakes) should be minimal. In the overweight or obese child, total fat consumption should be reduced.

Nutrition education and formulation of the meal plan

Newly diagnosed children with type 1 diabetes usually present with weight loss; therefore, the initial meal plan includes an estimation of energy requirements to restore and then maintain an appropriate body weight and allow for normal growth and development. Energy requirements vary with age, height, weight, stage of puberty, and level of physical activity. Because the energy needs of growing children continuously change, the meal plan should be re-evaluated at least every six months in young children and annually in adolescents.

Dietary management begins at the time of diagnosis with an assessment by a registered dietitian (clinical nutritionist). The meal plan must take account of the child's school schedule, early or late lunches, physical education classes, after-school physical activity, and differences in a child's activities on weekdays compared with weekends and holidays. Young children typically have three meals and two or three snacks daily, depending on the interval of time between meals, age of the child, and level of physical activity. Although their daily energy intake is relatively constant over time, young children adjust their energy intake at successive meals. The highly variable food consumption from meal-to-meal typical of normal young children is especially challenging when the child has type 1 diabetes. The purpose of snacks is to prevent hypoglycaemia and hunger between meals. If the basal insulin component is adjusted appropriately, patients who use a basal-bolus insulin regimen or pump therapy may not require snacks.

The dietitian's role is to evaluate the patient's and family's knowledge and understanding of nutrition and to formulate an individualized meal plan. Nutrition education and counselling, like all aspects of

diabetes education, should be an ongoing process with periodic review and revision of the meal plan and assessment of the child's and parents' levels of comprehension, ability to analyse and solve problems, and adherence to the nutrition goals. The patient should return to see the dietitian if glycaemic control is poor, growth is failing, weight gain is excessive, or if other problems arise related to dietary management.

The epidemic of obesity has not spared children with type 1 diabetes, and a recent report from the SEARCH study in the US showed a higher prevalence of overweight in youth with type 1 diabetes compared with similarly aged youth without diabetes (22% vs. 16%) (Liu et al. 2010).

Management of the child presenting with ketoacidosis

There is wide geographic variation in the frequency of DKA at presentation of diabetes; worldwide incidence rates range from approximately 15–80%. DKA is a presenting feature in 6–11% of patients with type 2 diabetes. In children with established diabetes, the risk of DKA is increased in those with chronic poor metabolic control and previous episodes of DKA, adolescent girls, children with psychiatric disorders, and those with psychosocial challenges. In patients who use a pump, interruption of insulin delivery for any reason can lead to DKA. Most DKA episodes are caused by insulin omission or treatment error, and the majority of the remainder are due to inadequate insulin treatment during an intercurrent illness.

The diagnostic criteria for the diagnosis of DKA include: hyperglycaemia (glucose>11 mmol/L [200 mg/dL]) with a venous pH < 7.30 or serum bicarbonate <15 mmol/L. Blood BOHB is typically ≥3.0 mmol/L and ketonuria is 'moderate or large'. DKA is classified by its severity: mild (venous pH < 7.30 or bicarbonate<15 mmol/)L, moderate (pH < 7.2 or bicarbonate<10 mmol/L) and severe (pH < 7.1 or bicarbonate <5 mmol/L). Partially treated children and children who have consumed little or no carbohydrate may have only modestly elevated blood glucose concentrations, referred to as 'euglycaemic ketoacidosis'.

The mortality rate from DKA is approximately 0.2%. Death is usually caused by cerebral oedema, but may also be caused by hypokalaemia-induced cardiac arrhythmia, sepsis, aspiration pneumonia, and numerous other rare complications.

Resuscitation

Acute management should follow the general guidelines for paediatric advanced life support (PALS). The protocol described below for the treatment of DKA is largely based on the guidelines published by the International Society of Pediatric and Adolescent Diabetes (Wolfsdorf et al. 2018).

- *Airway:* If the child is comatose, an airway should be inserted and if the level of consciousness is depressed or the child is vomiting, a nasogastric tube should be inserted, aspirated, and left to drain freely.
- *Breathing:* If there is evidence of hypoxia, give 100% oxygen and consider the need for intubation and ventilation. Airway and breathing problems are rare.
- *Circulation:* An IV cannula should be placed and blood samples (including a venous blood gas) obtained for investigations (see Section 1.5). In cases of circulatory impairment (suggested by the presence of prolonged capillary refill and tachycardia), give 10 ml/kg body weight of 0.9% saline intravenously as quickly as possible. The fluid bolus can be repeated (subsequent boluses can usually be given more slowly) until the circulation is restored.

If the child is too ill to weigh, for the purposes of calculating fluid requirements, weight can be estimated from a recent clinic weight or from a centile chart.

Antibiotics should be given if sepsis is thought likely after appropriate samples for culture have been taken.

Initial monitoring

Whenever possible, the child with DKA should be cared for in a high dependency or intensive care unit with experienced nursing staff, and with access to a clinical chemistry laboratory that can provide timely measurements of serum chemistries. In hospitals without a high dependency unit, high dependency care can still be given by providing a high level of nursing care, often on a one-to-one basis. Children with severe DKA – pH <7.1 or bicarbonate <5 mmol/L, compromised circulation, depressed level of consciousness, and those at increased risk for cerebral oedema (<5 years of age) should be treated in a paediatric intensive care unit or in a children's ward that specializes in diabetes and can provide comparable resources and supervision of care.

The following should be documented:

- Hourly vital signs.
- Weight should be measured twice a day.
- A strict fluid balance chart should be kept which includes measurement of urine volume and fluid losses from vomiting and diarrhoea.

• Hourly blood glucose measurements should be performed. Ideally, an additional cannula should be inserted for blood sampling to prevent recurrent, painful venipunctures or finger pricks, which may yield inaccurate blood glucose concentrations when peripheral circulation is poor.
• Venous or capillary blood ketone measurements 1–2 hourly, which measures the main ketone, BOHB, should be performed to quantify the suppression of ketogenesis.
• Venous blood gases, electrolyte and urea concentrations.
• A cardiac monitor should be used to monitor abnormal serum potassium concentrations.
• All patients with DKA should have at least hourly neurological observations and the Glasgow Coma Score should be recorded. The development of a severe headache or change in behaviour should be reported immediately to medical staff as this may be the first sign of cerebral oedema.
• If the patient is comatose or unable to void on demand (e.g. infants and very ill young children), the bladder should be catheterized.

Fluid therapy

The objectives of fluid and electrolyte replacement therapy are: (i) to restore circulating volume; (ii) to replace sodium, potassium, and the extracellular and intracellular water deficits; and (iii) to improve glomerular filtration and thereby enhance the clearance of glucose and ketones from the blood

Fluid requirements

Patients with DKA have a deficit in extracellular fluid (ECF) volume usually in the range 3–10%. Clinical estimates of the volume deficit are subjective and inaccurate. For fluid calculations, use 3–5% in mild DKA, 5–7% in moderate DKA, and 7–10% in cases of severe DKA. For patients with severe volume depletion but not in shock, volume expansion (resuscitation) should begin immediately with 0.9% saline to restore the peripheral circulation. The volume administered typically is 10–20 ml/kg over 1–2 hours, and may need to be repeated until perfusion is adequate. In the rare patient with DKA in shock, rapidly restore circulatory volume with isotonic saline in 20 ml/kg boluses infused as quickly as possible through a large bore cannula with reassessment after each bolus.

Subsequent fluid management (deficit replacement) can be accomplished with 0.45–0.9% saline or a balanced salt solution such as Ringer's lactate, Hartmann's solution, or Plasmalyte. Fluid therapy should begin with deficit replacement plus maintenance fluid requirements. All children will experience a decrease in vascular volume when plasma glucose concentrations fall during treatment. Therefore, it is essential to ensure that they receive sufficient fluid and salt to maintain adequate tissue perfusion.

Deficit replacement should be with a solution that has a tonicity equal to or greater than 0.45% saline (with added potassium chloride, phosphate or potassium acetate; see Section 1.9.5). The decision whether to use an isotonic or a hypotonic solution for deficit replacement should depend on clinical judgement based on the patient's hydration status, the serum sodium concentration, and the effective osmolality. In addition to providing the usual daily maintenance fluid requirement (see example in Table 1.9), replace the estimated fluid deficit at an even rate over 36–48 hours. Except for severely ill patients, oral intake typically begins within 24 hours. At this point, any remaining deficits are replenished by oral intake once DKA has resolved and patients are transitioned to subcutaneous insulin.

Clinical assessment of hydration status and calculated effective osmolality are valuable guides to fluid and electrolyte therapy. The aim is gradually to reduce serum effective osmolality to normal. There should be a concomitant increase in serum sodium concentration as the glucose concentration decreases (sodium should rise by 0.5 mmol/L for each 1 mmol/L decrease in glucose concentration).

Urinary losses should not routinely be added to the calculation of replacement fluid but this may be necessary in rare circumstances such as a patient with severe dehydration and extreme hyperglycaemia (i.e. mixed DKA and hyperglycaemic hyperosmolar state [HHS]).

The sodium content of the fluid should be increased if measured serum sodium concentration is low and does not rise appropriately as the plasma glucose concentration falls.

The fluid infused during initial resuscitation to restore the circulation should be taken into account when calculating fluid requirements and deducted from the total. Maintenance fluid requirements can be estimated using the Holliday-Segar method in Table 1.8 or the body surface area method, 1500 ml/m^2/24 hour (not suitable for use in children <10 kg). Using the Holliday-Segar method to determine the maintenance fluid requirement for an 8-year-old child weighing 25 kg yields 65 ml per hour or 1600 ml per day. This method is not suitable for neonates <14 days old and generally overestimates fluid needs in neonates.

The hourly infusion rate is calculated using the following formula:

Table 1.8 Maintenance fluid requirements in DKA.

Weight	Maintenance fluid requirements (ml per kg per hour)	Maintenance fluid requirements (ml per kg per day)
First 10 kg	4 ml/kg × 10 kg = 40 ml/hr	100 ml/kg × 10 kg = 1,000 ml/d
Second 10 kg	2 ml/kg × 10 kg = 20 ml/hr	50 ml/kg × 10 kg = 500 ml/d
Each additional 1 kg	1 ml/kg × 5 kg = 5 ml/hr	20 ml/kg × 5 kg = 100 ml/d

$$\text{hourly rate} = \frac{48\,\text{hour maintenance} + \text{deficit} - \text{resuscitation fluid already given}}{48}$$

Table 1.9 Example of fluid volume calculation.

An eight-year-old boy weighing 25 kg who is estimated to be 8% dehydrated and who received 10 ml/kg 0.9% saline in the emergency department will need:

Daily maintenance = 1600 ml

Deficit = 25 kg × 8% = 2000 ml

Resuscitation fluid = 250 ml

Total requirements over 48 h = (2 × 1600) + (2000–250) = 4950 ml

Hourly rate = 4950/48 = 103 ml/h

An example of calculations to estimate fluid requirements for a child with DKA is shown in Table 1.9. It is important to double-check these calculations.

The serum sodium concentration is an unreliable measure of the degree of ECF contraction because glucose, largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space, thereby causing dilutional hyponatremia. At presentation in DKA, the serum sodium concentration is usually low. A failure of measured serum sodium levels to rise or a further decline in serum sodium levels with therapy is an ominous sign of impending cerebral oedema.

Clinical assessment of hydration status and calculated effective osmolality (2× [plasma Na] + plasma glucose mmol/L) are valuable guides to fluid and electrolyte therapy. The aim is gradually to reduce serum effective osmolality to normal.

In the early stages of DKA, patients typically are extremely thirsty and request oral fluids. In severe dehydration with impaired consciousness, no fluids should be allowed by mouth. A nasogastric tube may be necessary in the case of gastric paresis, vomiting, or impaired consciousness to decrease the risk of aspiration pneumonia. Oral fluids should only be allowed after resolution of DKA. If substantial clinical improvement has occurred before the completion of the planned 48 hours of rehydration, oral intake can be permitted (provided the child is not vomiting) and the IV infusion rate reduced to take account of the oral intake.

Insulin therapy

Although rehydration alone frequently causes a marked decrease in blood glucose concentration, insulin therapy is essential to restore normal cellular metabolism, normalize blood glucose concentration, and suppress lipolysis and ketogenesis. Start the insulin infusion 1–2 hours after starting fluid replacement therapy, i.e. after the patient has received initial volume expansion. The recommended dose is 0.05–0.1 unit/kg/hour via intravenous infusion (dilute 50 units regular [soluble] insulin in 50 ml normal saline, 1 unit = 1 ml). An intravenous insulin bolus should *not* be used at the start of therapy; it is unnecessary and may increase the risk of cerebral oedema and exacerbate hypokalaemia.

The dose of insulin should usually remain at 0.05–0.1 unit/kg/hour until resolution of DKA (pH >7.30, bicarbonate >15 mmol/L, BOHB <1 mmol/L, and normal anion gap), which typically takes longer than normalization of blood glucose concentrations. If the patient is sensitive to insulin (e.g. some young children with DKA), the dose may be decreased provided that metabolic acidosis continues to resolve. For example, if a young child is receiving 0.05 unit/kg/hour, it may be necessary to reduce the insulin dose to 0.03 unit/kg/hour to prevent hypoglycaemia. During initial volume expansion, the plasma glucose

concentration falls steeply. Thereafter, and after commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L/hour (36–90 mg/dL/hour), depending on the timing and amount of intravenous glucose administration. To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycaemia, 5% glucose should be added to the IV fluid 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 the amount of insulin necessary 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).

In circumstances where continuous IV administration is not possible and in patients with uncomplicated DKA, hourly or two-hourly SC or IM administration of a short- or rapid-acting insulin analogue is safe and may be as effective as IV regular insulin infusion, but, if possible, should not be used in patients whose peripheral circulation is impaired. The initial dose SC is 0.3 unit/kg, followed one hour later by SC insulin lispro or aspart at 0.1 unit/kg every hour, or 0.15–0.20 units/kg every two hours. If blood glucose falls to <14 mmol/L (250 mg/dL) before DKA has resolved, reduce SC insulin lispro or aspart to 0.05 unit/kg per hour to keep blood glucose ≈11 mmol/L (200 mg/dL) until resolution of DKA.

Potassium

Potassium is mainly an intracellular ion and at presentation in DKA there is invariably a large depletion of total body potassium even though initial serum potassium concentrations may be normal or even high. Administration of insulin and the correction of acidosis drives potassium back into the cells, decreasing serum levels. The serum potassium concentration may decrease abruptly, predisposing the patient to a cardiac arrhythmia. Renal dysfunction reduces potassium excretion, contributing to hyperkalaemia. Early potassium therapy should be avoided if anuria is present as a result of acute tubular necrosis.

Replacement therapy is required regardless of the serum potassium concentration, except if renal failure is present. If the patient is hypokalaemic at presentation, start potassium replacement *at the time of* initial volume expansion and *before* starting insulin therapy. Otherwise, start replacing potassium *after* initial volume expansion and concurrent with starting insulin therapy. If the patient is hyperkalaemic, *defer* potassium replacement therapy until urine output is documented (may have to catheterize the bladder). If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalaemia. Prolongation of the PR interval, T wave flattening and inversion, ST depression, prominent U waves, apparent long QT interval (due to fusion of the T and U waves) indicate hypokalaemia. Tall, peaked, symmetrical, T waves and shortening of the QT interval are signs of hyperkalaemia.

The starting potassium concentration should be 40 mmol/L. Subsequent potassium replacement therapy should be based on serum potassium measurements with the goal of maintaining levels within the normal range. Potassium phosphate may be used together with potassium chloride or acetate, e.g. 20 mmol/L potassium chloride and 20 mmol/L potassium phosphate or 20 mmol/L potassium phosphate and 20 mmol/L potassium acetate. The maximum recommended rate of intravenous potassium replacement is 0.5 mmol/kg/hour. If hypokalaemia persists despite a maximum rate of potassium replacement, the rate of insulin infusion should be reduced.

Phosphate

Depletion of intracellular phosphate occurs as a result of osmotic diuresis. The fall in plasma phosphate levels is exacerbated by insulin therapy as phosphate re-enters cells. Clinically significant hypophosphataemia may occur if intravenous therapy without food intake is prolonged beyond 24 hours. Prospective studies have not shown a significant benefit from phosphate replacement and aggressive phosphate administration causes hypocalcaemia.

Acidosis and bicarbonate therapy

Acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, generating bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids. Clinical trials have shown no benefit from bicarbonate administration, which may cause paradoxical CNS acidosis and hypokalaemia. Nonetheless, bicarbonate administration may be beneficial in the rare patient with life-threatening hyperkalaemia and to improve cardiac contractility in patients who are severely acidotic (pH < 6.9) with circulatory failure despite adequate fluid replacement.

If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 minutes.

Anticoagulant prophylaxis

There is a considerable risk of venous thrombosis in young and very sick children with DKA who have central venous catheters inserted and in patients with extreme hyperosmolarity. Prophylactic anticoagulation should be considered in such patients.

Introduction of oral fluids and transition to SC insulin injections

Oral fluids should be introduced only when substantial clinical improvement has occurred. Persistent ketonuria (urine ketone strips measure acetoacetate and acetone) characteristically occurs for several hours after serum BOHB levels have returned to normal; therefore, absence of ketonuria should *not* be used as an endpoint for determining resolution of DKA. When oral fluid is tolerated, IV fluid should be reduced accordingly so that the sum of IV and oral fluids does not exceed the calculated IV rate. When ketoacidosis has resolved and the change to SC insulin is planned, the most convenient time to change to SC insulin is just before a meal. To prevent rebound hyperglycaemia, the first SC injection should be given 15–30 minutes (with rapid-acting insulin) or 60 minutes (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed. After transitioning to SC insulin, frequent blood glucose monitoring is required to avoid marked hyperglycaemia and hypoglycaemia.

Cerebral oedema

The mortality rate from DKA in children is approximately 0.15–0.30%. Cerebral injury is the major cause of mortality and morbidity accounting for 60–90% of all DKA deaths, and from 10% to 25% of survivors of cerebral oedema have significant residual morbidity.

The cause of cerebral oedema is controversial. Some have explained the pathogenesis as the result of rapid fluid administration with abrupt changes in serum osmolality. More recent investigations, however, have found that dehydration and cerebral hypoperfusion may be associated with DKA-related cerebral injury. This has led to the formulation of an alternative hypothesis; namely, that factors intrinsic to DKA and which could be worsened during treatment may be the cause of brain injury. It is noteworthy that the degree of oedema that develops during DKA correlates with the degree of dehydration and hyperventilation at presentation, but not with factors related to initial osmolality or osmotic changes during treatment. Disruption of the blood–brain-barrier has been found in cases of fatal cerebral oedema associated with DKA, which further supports the view that cerebral oedema is not simply caused by a reduction in serum osmolality.

Demographic factors associated with an increased risk of cerebral oedema include: younger age (especially <5 years), new onset diabetes, longer duration of symptoms. These risk associations reflect the greater likelihood of severe DKA. Epidemiological studies have identified several risk factors at presentation or during treatment, including: greater hypocapnia (lower pCO_2) adjusted for degree of acidosis, increased serum urea nitrogen, more severe acidosis at presentation, administration of bicarbonate for correction of acidosis, a marked early decrease in serum effective osmolality, an attenuated rise in serum sodium concentration or an early fall in glucose-corrected sodium during therapy, greater volumes of fluid given in the first four hours, and administration of insulin within the first hour of fluid treatment.

Clinically significant cerebral oedema usually develops within the first 12 hours after treatment has started, but can occur before treatment has begun or, rarely, as late as 24–48 hours after the start of treatment. Symptoms and signs are variable. Onset of clinically overt cerebral oedema often follows an initial period of clinical and biochemical improvement; however, in some cases the patient's state of consciousness may decline from the time of admission.

Signs and symptoms of cerebral oedema include: onset of severe headache or worsening of a headache already present upon arrival, slowing of heart rate, change in neurological status (restlessness, irritability, confusion, increasing drowsiness, incontinence), specific neurological signs (e.g. pupillary abnormalities, cranial nerve palsies, papilloedema), rising blood pressure, decreased oxygen saturation, and respiratory impairment. Dramatic signs such as convulsions, papilloedema, and respiratory arrest are late signs associated with a grave prognosis.

A method of clinical diagnosis based on bedside evaluation of neurological state is shown in Table 1.10. One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4%. Signs that occur before treatment should not be considered in the diagnosis of cerebral oedema.

A chart with the reference ranges for blood pressure and heart rate, which vary depending on height,

Table 1.10 Symptoms and signs of cerebral oedema.

Diagnostic criteria	Major criteria	Minor criteria
• Abnormal motor or verbal response to pain • Decorticate or decerebrate posture • Cranial nerve palsy (especially III, IV, and VI) • Abnormal neurogenic respiratory pattern (e.g. grunting, tachypnea, Cheyne-Stokes respiration, apneusis)	• Altered mentation/fluctuating level of consciousness • Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state • Age-inappropriate incontinence	• Vomiting • Headache • Lethargy or not easily arousable • Diastolic BP >90 mm Hg • Age < 5 years

weight, and gender, should be readily available at the bedside.

The appearance of diabetes insipidus, manifested by increased urine output with a concomitant marked increase in the serum sodium concentration, reflecting loss of free water in the urine, is a sign of cerebral herniation causing interruption of blood flow to the pituitary gland.

Treatment of cerebral oedema

Initiate treatment as soon as the condition is suspected.

- Give mannitol, 0.5–1 g/kg IV over 10–15 minutes.
- Hypertonic saline (3%), 5–10 ml/kg over 30 minutes, may be used as an alternative to mannitol.
- If mannitol has been used as first-line therapy and there is no initial response within 30 minutes, consider using hypertonic saline.
- Mannitol can be repeated after two hours.
- Hyperosmolar agents should be readily available at the bedside.
- Elevate the head of the bed to 30°.
- Transfer to pediatric intensive care unit.
- Reduce the rate of fluid administration by one-third.
- Intubation may be necessary for the patient with impending respiratory failure.
- *After* treatment for cerebral oedema has been started, cranial imaging may be considered, as with any critically ill patient with encephalopathy or acute focal neurologic deficit. The primary concern is whether the patient has a lesion requiring emergency neurosurgery (e.g. intracranial haemorrhage) or a lesion that may necessitate anticoagulation (e.g. cerebrovascular thrombosis).

Other uncommon or rare causes of morbidity and mortality in DKA include:

- Hypokalaemia
- Hypocalcaemia, hypomagnesemia
- Severe hypophosphatemia
- Hypoglycaemia
- Other central nervous system complications: dural sinus thrombosis, basilar artery thrombosis, intracranial haemorrhage, cerebral infarction
- Venous thrombosis
- Pulmonary embolism
- Sepsis
- Rhinocerebral or pulmonary mucormycosis
- Aspiration pneumonia
- Pulmonary oedema
- Adult respiratory distress syndrome (ARDS)
- Pneumothorax, pneumomediastinum, and subcutaneous emphysema
- Rhabdomyolysis
- Ischemic bowel necrosis
- Acute renal failure
- Acute pancreatitis
- Thrombocytopenia-associated multiple organ failure

The diabetes clinic

General principles

Children with diabetes should be seen in a designated diabetic clinic supervised by a paediatrician trained in the care of diabetes, paediatric endocrinologist or paediatric diabetologist. It has been recommended that there be a specialist diabetes nurse for every 100 children with diabetes. Age banding of the clinic may help bring families with similarly aged children together and facilitates group teaching of age-appropriate topics. The clinic should have the resources required to download data from blood glucose meters, insulin pumps, and CGM systems. It is highly advantageous to be able to perform point-of-care HbA1c measurements in the clinic so the results are available to the clinician during the consultation. The clinic should be equipped with a stadiometer for accurate auxology

and should have suitable space for patient education and counselling. Educational literature (e.g. sick day guidelines), DVDs, information about diabetes camp and community resources, and other relevant information for children with diabetes should be available in the clinic.

The clinic visit

At each encounter in the diabetes clinic, the following issues should be addressed:

1 Documentation of general health and life events (e.g. changing school, participation in sports), recent hospital admissions or emergency department visits, insulin regimen, details of hypoglycaemic episodes and school absences.

2 Review of insulin regimen and blood glucose or CGM data.

3 Measurement of blood pressure, height and weight, and review of the growth chart.

4 Examination of injection or infusion sites and fingertips.

5 Measurement of HbA1c every three months.

6 If necessary, provision of advice on adjustments to the insulin regimen based on the results of glucose monitoring and physical activity.

An annual review of patients aged 10 years or older, who have had diabetes for ≥5 years should include:

7 a physical examination for microvascular and other complications of diabetes (Table 1.11);

8 assessment of puberty stage;

9 measurement of thyroid function tests and screening for coeliac disease (at suitable intervals);

10 measurement of cholesterol;

11 screening for microalbuminuria by measurement of the albumin:creatinine (ACR) ratio (ideally in a first morning urine sample);

12 referral to an ophthalmologist to screen for diabetic retinopathy or, if available, retinal photography in the clinic.

Given the multidisciplinary nature of a diabetes clinic, it is helpful to have a team meeting at the end of the clinic to share information about patients (especially those who are not achieving treatment goals) who have attended the clinic.

Monitoring and assessment of diabetes control

Self-monitoring of blood glucose (SMBG)

SMBG is the cornerstone of diabetes self-management and numerous studies show that frequency of SMBG correlates with glycaemic control. Routine SMBG is necessary to determine immediate insulin needs at meal times and to assess response to correcting hyperglycaemia with supplemental insulin or treatment of hypoglycaemia with glucose ingestion. Patients/parents should be encouraged to learn how to interpret patterns and trends of blood glucose data to assess the efficacy of therapy and to adjust individual components of their treatment regimen to achieve defined blood glucose goals. Most glucose meters have an electronic memory and data can be viewed on the device's screen or downloaded to a computer. In

Table 1.11 Points to note on clinical examination of patients with diabetes at annual review.

System	Points to note
Height	Growth failure
Weight	Poor or excessive weight gain
Puberty	Delayed puberty/menarche
Skin	Lipohypertrophy or lipoatrophy at injection sites, necrobiosis lipoidica
Mouth	Presence of caries or other signs of poor dental hygiene
Eyes	Presence of retinopathy/cataracts (through dilated pupils)
Feet	Signs of poor foot care (e.g. calluses from poorly-fitting shoes)
Hands	Finger-prick sites, limited joint mobility ('prayer sign')
Cardiovascular	Hypertension (if present, recheck at the end of the clinic visit)
Endocrine	Goitre, signs of hypothyroidism or hyperthyroidism; diffuse increased skin pigmentation suggestive of Addison's disease
Neurological	Impaired vibration or light touch (monofilament) sense; loss of ankle reflexes

recently diagnosed patients when insulin requirements are changing rapidly, it is valuable for patients/parents to manually record the results in a logbook and to examine the data for patterns and trends so that adjustments can be made when necessary.

For patients using intensive insulin regimens, SMBG should be performed before meals and snacks, occasionally two hours after meals, at bedtime, before, during, and after exercise, and after treatment of hypoglycaemia to ensure restoration of normoglycaemia. Blood glucose should be checked before driving and intermittently when driving for a prolonged period. To minimize the risk of nocturnal hypoglycaemia, blood glucose should be routinely measured at bedtime and between midnight and 4 a.m. once each week or every other week, and whenever the evening dose of insulin is adjusted. If HbA1c targets are not being met, patients should be encouraged to measure BG levels more frequently, including 90–120 minutes after meals. Children who are able independently to perform SMBG must be properly supervised because it is not unusual for children to fabricate data with potentially disastrous consequences.

Practical aspects of BG monitoring

- Children should be encouraged (but not coerced) to perform their own finger-prick BG measurements when they feel able to do so.
- Finger-pricks should be performed on the sides of the fingertips.
- Finger-pricking devices with variable depth settings can make lancing less painful.
- Forearm or thenar eminence blood glucose testing are accurate and acceptable alternatives to finger-prick testing.
- Blood glucose meters with electronic memory allow data to be downloaded to a computer or uploaded to 'the cloud' for review and discussion in clinic.
- Date-expired blood glucose testing strips should not be used as these may lead to inaccurate BG measurements.

Ketone testing

Urine or blood ketones should be measured during acute illness, whenever there is persistent hyperglycaemia (>250–300 mg/dL, 13.9–16.7 mmol/L), and when the patient experiences nausea, vomiting, or abdominal pain. When hyperglycaemia is prolonged in patients who use an insulin pump, ketone measurement provides an additional clue to the possibility of insulin infusion failure. Ketone measurement is a valuable guide to supplemental insulin therapy to prevent or reverse metabolic decompensation, and to determine when referral for urgent care is required (see Section 1.17 on 'sick day' management).

Urine ketone test strips detect acetoacetate (and acetone), and qualitative results are interpreted based on colour changes: 'trace', 'small', 'moderate', or 'large' ketones corresponding to 5, 15, 40, 80–160 mg/dL, respectively. The correlations between interquartile ranges of capillary blood BOHB and urine ketone values are:

0.1–0.9 mmol/L corresponds to + or 'small' urine ketones;
0.2–1.8 mmol/L corresponds to ++ or 'moderate' urine ketones;
1.4–5.2 mmol/L corresponds to +++ or 'large' urine ketones.

False negative readings may occur when the strips have been exposed to air or when the urine is highly acidic (e.g. after consumption of large doses of ascorbic acid). Urine ketone tests using nitroprusside-containing reagents can give false positive results in patients who take valproic acid or any sulfhydryl-containing drugs, including captopril.

Ketone meters for home use measure blood BOHB concentration, which, compared to urine ketone testing, offers the advantage of accurately assessing the biochemical response to treatment and is more efficacious in avoiding emergency room visits. Normally BOHB is <0.6 mmol/L; values >3 mmol/L may indicate impending or actual DKA. Blood ketone strips are, however, considerably more expensive than urine ketone strips; therefore, when expense is a consideration, a cost-effective approach is to reserve blood ketone measurements for young children who cannot reliably provide a urine sample on demand and when urine testing shows 'large' ketonuria.

Glycated haemoglobin or haemoglobin A1c

HbA1c is formed slowly and non-enzymatically when glucose attaches to haemoglobin. Because erythrocytes are freely permeable to glucose, HbA1c is formed throughout the lifespan of the erythrocyte, and its rate of formation is directly proportional to the ambient glucose concentration. HbA1c is a weighted average of blood glucose levels during the life of the erythrocytes (120 days). Therefore, glucose levels on days nearer to the test contribute

substantially more to the HbA1c level than the levels in days further from the test.

Whereas blood glucose and ketone measurements provide valuable information for immediate day-to-day management of diabetes, HbA1c is a measure of average glycaemia over the preceding three months and is a biomarker of the risk for the development of diabetes complications. Laboratories should report their results adjusted to give comparable values to the assay used in the DCCT. The DCCT-aligned normal, non-diabetic range is 4–6% (20–42 mmol/mol).

HbA1c should be measured approximately every three months to determine whether a patient's metabolic control has reached or has been maintained within a target range. The HbA1c is primarily used to monitor the effectiveness of glycaemic therapy and as an indicator for when therapy needs to be modified (Table 1.12). HbA1c underestimates average glucose levels in conditions that shorten the average circulating erythrocyte lifespan, such as haemolysis, sickle cell disease, after blood transfusion, CF, and iron deficiency anaemia. When accurate HbA1c measurement is not possible, as in the above conditions, an alternative measure of chronic glycaemia such as fructosamine should be used. Fructosamine testing determines the fraction of total serum proteins that have undergone glycation. Since albumin is the most abundant protein in blood, fructosamine levels typically reflect albumin glycation. Albumin has a half-life of approximately 20 days; therefore, plasma fructosamine concentration reflects relatively recent (~2 weeks) glycaemia. Some tests specifically quantify glycation of albumin instead of all proteins.

Continuous glucose monitoring

Real-time CGM devices are minimally invasive and accurately measure glucose in the interstitial fluid with a subcutaneous glucose sensor and report a value every five minutes. Depending on the specific CGM system, finger-stick blood glucose values may be needed to calibrate the device. There is a lag of several minutes between plasma glucose and interstitial glucose concentrations; nonetheless, sensor glucose values provide detailed information about patterns and trends in the intervals between SMBG measurements, and especially after meals and during the night. The number of children with type 1 diabetes using CGM for routine diabetes care is rapidly increasing. The benefit of CGM on glycaemic control in type 1 diabetes is directly related to the duration and frequency of its use; near-daily use is associated with a significant reduction in HbA1c levels and less time spent in the hypoglycaemia range. Also, the number of daily finger-pricks can be reduced and parents and children experience less anxiety about nocturnal hypoglycaemia. In addition to cost, barriers to the use of CGM include insertion pain, annoying system alarms, contact dermatitis from the adhesive, and body image issues. For some patients, the hassles outweigh the benefits, which include glucose trend data (including the capability of remote monitoring), opportunities to promptly correct out-of-range glucose levels, and to detect actual or impending hypoglycaemia. As CGM technology improves and increasingly becomes integrated with insulin pumps, the acceptability of CGM devices for long-term use in youth with type 1 diabetes will undoubtedly continue to increase.

Table 1.12 Interpretation of glycated haemoglobin values.

HbA1c (%)[a]	IFCC-HbA1c mmol/mol	Comment
4–5.9	20–41	Within non-diabetic range
6–6.9	42–52	Optimal, ideal glycaemic control in absence of frequent or severe hypoglycaemia
7–7.5	53–59	Optimal, very good glycaemic control in absence of frequent or severe hypoglycaemia
7.6–8.9	60–74	Suboptimal, associated with increased risk of microvascular complications; action to improve control suggested
9–10.9	75–96	High risk, poor compliance; associated with high risk of microvascular complications; action required
≥11	≥97	High risk, poor compliance; insulin omission; associated with high risk of microvascular complications and DKA; action required

[a] DCCT standardized.

Exercise

Several cross-sectional studies of youth with type 1 diabetes show that physical fitness (measured by peak oxygen consumption [VO_2]) is inversely associated with HbA1c; lower peak VO_2 predicts higher HbA1c levels. Also, lack of physical activity (e.g. more time spent viewing television and computer screen time) is associated with poor glycaemic control. Although intervention/training studies in paediatric patients have not consistently shown a beneficial effect of regular physical activity on HbA1c levels, children with diabetes should, nonetheless, be encouraged to participate in sports and include regular exercise in their lives. Physical exercise has numerous benefits: it normalizes the child's life, enhances self-esteem, improves physical fitness, helps to control weight, and *may* improve glycaemic control. Regular exercise increases insulin sensitivity during and immediately after exercise, and again 7–11 hours later. Regular exercise also increases cardiovascular fitness and lean body mass, improves blood lipid profiles, and lowers blood pressure.

Physical exercise is complicated for the child with type 1 diabetes, especially by the need to prevent hypoglycaemia during and after exercise (Riddell et al. 2017). Children with type 1 diabetes are twice as likely to have nocturnal hypoglycaemia during the night after an exercise day as compared with a night after a sedentary day. Inability to spontaneously reduce insulin levels during exercise is the key factor that contributes to the increased risk of hypoglycaemia; however, with proper guidance and planning, exercise can be a safe and enjoyable experience.

In the child with poorly controlled diabetes, vigorous exercise can aggravate hyperglycaemia and ketoacid production; accordingly, a child with ketonuria should not exercise until satisfactory biochemical control has been restored. In type 1 diabetes increased levels of epinephrine and glucagon in response to acute strenuous anaerobic exercise may cause transient hyperglycaemia despite well-controlled diabetes. In contrast, sustained aerobic exercise acutely lowers the blood glucose concentration by variably increasing utilization of glucose depending on the intensity and duration of physical activity and the concurrent plasma insulin level. Hypoglycaemia can usually be prevented by a combination of anticipatory reduction in pre-exercise insulin dose or, with CSII, a temporary interruption or reduction of basal insulin infusion and/or supplemental carbohydrate containing snacks or drinks before, during, and after activity, depending on the intensity and duration of the physical activity and its timing. Nearly all forms of activity lasting more than 30 minutes require some adjustment to food and/or insulin. The optimal strategy depends on the child's insulin regimen and on the timing of exercise in relation to the child's meal plan. Several factors must be considered when selecting the content and size of the snack, including the current blood glucose level, the action profile of insulin most active during and after the period of anticipated exercise, the interval since the last meal, and the duration and intensity of physical activity. The appropriate adjustments for exercise are learned by trial and error; however, a useful initial guide is to provide 0.5–1 gram of carbohydrate per kg of body mass per hour of moderate to strenuous exercise. Prolonged strenuous exercise in the afternoon or evening should be followed by a 10–30% reduction in the pre-supper or bedtime dose of intermediate- or long-acting insulin, or an equivalent reduction in overnight basal insulin delivery in patients using CSII. In addition, to reduce the risk of nocturnal or early-morning hypoglycaemia caused by the lag effect of exercise and reduced counter-regulatory hormone responses during sleep, the bedtime snack should be larger than usual and contain a 'slow' carbohydrate, protein, and fat. Frequent blood glucose monitoring or CGM is essential for the active child with diabetes because it allows identification of trends in glycaemic responses. Records should include blood glucose levels, timing, duration, and intensity of exercise as well as the strategies used to maintain glucose concentrations in the target range.

Exercising the limb into which insulin has been injected accelerates the rate of insulin absorption. Therefore, if possible, the insulin injection preceding exercise should be given in a site (e.g. abdomen if running or cycling) least likely to be affected by exercise. Because physical training increases tissue sensitivity to insulin, when poorly conditioned youth commence participation in organized sports or dramatically increase their level of physical activity (e.g. at the start of summer camp), they should reduce the TDD of insulin by at least 20%, and further adjust the dose of insulin predominantly active during the period of sustained physical activity. The precise dose reduction is empirically determined by measuring blood glucose levels before and after exercise.

Diabetes in preschool-aged children

There are numerous unique features pertinent to the management of very young children with diabetes as shown in Table 1.13.

Table 1.13 Principles of managing diabetes in preschool-aged children.

- The target HbA1c is <7.5% (58 mmol/mol)
- Use an intensive insulin therapy regimen consisting of basal and preprandial meal-adjusted insulin together with frequent blood glucose monitoring.
- Insulin pump therapy is the preferred method of insulin administration; if unavailable, multiple daily injections should be used from the onset of diabetes.
- Preprandial administration of bolus insulin for correction of hyperglycaemia and for coverage of at least part of the meal is preferable to giving the entire dose during or after the meal.
- Introduce carbohydrate counting at onset of diabetes.
- It may be necessary to dilute insulin to be able to accurately administer the small doses required by young children.
- Use insulin syringes with ½ unit markings or insulin pens with ½ unit dosing increments.
- Continuous glucose monitoring is valuable to monitor glycaemia. If unavailable, frequent (up to 7–10) daily blood glucose measurements may be required to maintain optimal control.
- Injection, infusion and sensor insertion sites should be regularly rotated to reduce likelihood of lipohypertrophy, scarring, infection.
- Engage both fathers and mothers in diabetes care from the onset of diagnosis.
- Establish family-centred meal routines and restrict continuous snacking ('grazing') to ensure dietary quality and optimize glycaemic control.
- Provide diabetes education to staff at preschool and school to ensure safe and unrestricted participation in all school activities.
- Optimal glycaemic control with avoidance of extreme hyperglycaemia and hypoglycaemia enables the child to participate, concentrate, and learn.
- Monitoring growth, weight, and body mass index at each visit provides an indication of the adequacy of the child's nutrition and diabetes control.

Source: Modified from (Sundberg et al. 2017).

Diabetes in adolescence

Adolescence is the transitional phase of development between childhood and adulthood. It is a period of great physical and psychological change, including rapid physical growth and sexual maturation, ongoing identity formation, and increasingly powerful influences of social context and peer relationships. For patients with type 1 diabetes, adolescence presents special challenges related to diabetes self-care and glycaemic control, which often deteriorates during this period of life. This is attributable to physiologic increased insulin resistance during puberty as well as developmental and psychosocial factors that may decrease adherence to diabetes care tasks, including the shift in responsibility for care from parent to child, the impact of peer and romantic relationships, and increased risk-taking behaviours. For these reasons, the health care and emotional needs of adolescents differ substantially from those of younger children and adults. The overarching goal is to patiently and persistently educate, guide, support, and encourage the adolescent to maintain blood glucose levels as near to normal as possible, which reduces the risk of long-term complications, while avoiding hypoglycaemia and DKA. Developing a trusting and motivating relationship between health care professionals and the adolescent patient and maintaining continuity of care provides the best opportunity to positively influence adolescent self-care.

The role of the family in adolescent diabetes

The family has a central role in the successful management of diabetes during adolescence and care should be family-centred from the time of diagnosis. Because the adolescent with diabetes is cognitively and emotionally immature, successful treatment requires the active involvement of responsible adults. At the same time, diabetes also requires family members to be sensitive to the balance between the youth's need for a sense of autonomy and mastery of self-care activities and the need for ongoing family involvement and support. The struggle to balance independence and dependence in relationships between the adolescent patient and family members presents a long-term challenge and raises different issues for families at different stages of child and adolescent development. Focusing on normal developmental tasks at each stage of the adolescent's growth and development provides

the most effective framework for addressing these issues (Anderson and Schwartz 2014).

Family conflict around diabetes management is a strong predictor of poor adherence and poor glycaemic control; conversely, children living in supportive family environments with a high level of parent involvement generally have better adherence and glycaemic control. Counselling-based interventions to improve family communication and teamwork in diabetes care have been shown to improve treatment adherence and glycaemic control. Accordingly, the diabetes care team should encourage parents to foster family teamwork around diabetes management (e.g. schedule weekly brief family meetings to discuss 'the week in diabetes') and to view teamwork as a way to teach and empower their child to become a more active participant in his or her care. When communication between parents and the adolescent about diabetes is negative ('shaming and blaming'), involves sarcasm or yelling, or is dishonest (e.g. lying about blood glucose values), family teamwork is impossible to maintain.

Areas for intervention to improve adherence in adolescents with type 1 diabetes

Treatment adherence is closely associated with improved glycaemic control in adolescents with type 1 diabetes and efforts to support and enhance adherence to diabetes self-care tasks in adolescents are critically important. For example, use of a non-medically trained 'care ambassador' to deliver psychoeducational modules and facilitate clinic follow-up has been found to decrease HbA1c levels as well as diabetes-related emergency department visits and hospitalizations in adolescents with type 1 diabetes. Motivational interviewing techniques during routine clinic visits improve HbA1c as well as patient satisfaction. Mobile and internet health technologies are other promising avenues for engaging adolescents. For example, receiving a text-messaging support system ('Sweet Talk') to reinforce diabetes care goals improves diabetes self-efficacy and self-care adherence, and adolescents receiving internet-based education about both diabetes management and behavioural coping had lower HbA1c levels and higher quality of life and diabetes self-efficacy scores after 18 months.

Transition from pediatric to adult diabetes care

Adolescents will eventually need to transfer their care from paediatric to adult diabetes care providers. The developmental stage from the late teens through the twenties has been defined as 'emerging adulthood', a period of competing educational, social, work, and financial demands. As young adults with type 1 diabetes encounter these competing life priorities while simultaneously experiencing decreased parental support, adherence to self-care often declines and glycaemic control may deteriorate. Lack of effective transition from paediatric to adult diabetes care may contribute to fragmentation of health care and increase the risk for adverse outcomes.

The transition process entails numerous challenges, including suboptimal paediatric transition preparation, gaps in care, and increased post-transition hospitalizations. There is no evidence supporting an ideal transition age, and an individualized approach is recommended. A position statement of the American Diabetes Association, in collaboration with a number of professional societies, recommends that paediatric diabetes providers begin to prepare patients for transition to adult care during the early adolescent years and at least one year before actual transfer (Peters and Laffel 2011). Preparation should include a focus on diabetes self-management skills as well as coordination of transfer referrals, direct communication with the receiving adult providers, and a written care summary. Several organizations, including the National Diabetes Education Program and The Endocrine Society, have produced materials to support the transition process (http://www.YourDiabetesInfo.org/transitions; https://www.endocrine.org/education-and-practice-management/quality-improvement-resources/clinical-practice-resources/transition-of-care). In some health care systems, joint transition clinics staffed by both paediatric and adult physicians have been a successful care model for older adolescents and young adults.

Psychological and psychiatric problems

Depression

Major depressive disorders as well as subclinical depressive symptomatology are more common in adolescents with diabetes. A recent study in the US identified symptoms of depression in 13% of youth with type 1 and in 22% with type 2 diabetes, and subclinical depressive symptomatology is associated with poor clinical outcomes. Therefore, in addition to addressing family conflict related to type 1 diabetes and supporting adolescent adherence to diabetes self-management, adolescents with type 1 diabetes should be routinely screened for depression from the time of diagnosis. Interventions can then be

targeted based on the specific needs of individual adolescents and families.

Eating disorders

Adolescent females with type 1 diabetes have a two-fold increased risk of developing an eating disorder compared to their peers without diabetes. Some adolescents manipulate insulin doses or dietary behaviours in order to lose weight. These behaviours should be suspected in adolescents, especially females, unable to achieve and maintain blood glucose targets or who have unexplained weight loss or deterioration of metabolic control. Efficient screening can be performed using a five-question SCOFF Questionnaire designed to clarify suspicion that an eating disorder might exist. Patients with identified eating disorders or deliberate misuse of insulin are at high risk for earlier onset and progression of microvascular complications and mortality, and should receive intensive multidisciplinary care that includes a mental health professional with expertise in eating disorders.

Miscellaneous problems

There is an increased incidence of polycystic ovary syndrome and menstrual irregularities in girls with both type 1 and type 2 diabetes. The menstrual cycle may also affect blood glucose control with rising values in the two to three days before the start of a period. In those in whom this occurs regularly, insulin dosage should be increased during this time.

Hypoglycaemia in youth with diabetes

Hypoglycaemia is the most common acute complication of treatment, and concern about hypoglycaemia is a central issue in treating people with type 1 diabetes. It is the most important barrier to the pursuit and maintenance of near-normal glycaemic control and patients, parents, and the diabetes team must continuously balance the risks of hypoglycaemia against those of long-term hyperglycaemia. Fear of hypoglycaemia is common in children with type 1 diabetes and their parents. An episode of severe hypoglycaemia undermines the confidence of the patient and parents, and fear of a recurrence may induce the patient or parents to change their diabetes management goals. Altered behaviours may include overeating and/or deliberate selection of lower doses of insulin to maintain higher blood glucose levels perceived as being safe, resulting in overall deterioration of glycaemic control over time. For some parents, concern about nocturnal hypoglycaemia may cause more anxiety than any other aspect of diabetes, including the fear of long-term complications.

The normal glucagon response to hypoglycaemia is lost early in the disease in parallel with loss of beta cells, and patients with type 1 diabetes must then depend on sympatho-adrenal responses to prevent or correct hypoglycaemia. Recurrent mild hypoglycaemia itself reduces epinephrine responses and symptomatic awareness of subsequent episodes of hypoglycaemia.

Symptoms and signs of hypoglycaemia

Patients with type 1 diabetes depend on the activation of the sympathetic nervous system and an increase in epinephrine secretion to detect a fall in blood glucose concentration. Symptoms and signs of hypoglycaemia are caused by the counter-regulatory response, which produces neurogenic (autonomic) symptoms, including sweating, trembling (shakiness), tingling, pallor, palpitations, nervousness, and anxiety, or are the result of neuroglycopenia (inadequate fuel for normal brain function), characterized by difficulty concentrating, blurred vision, confusion, odd behaviour, slurred speech, numbness, loss of coordination, drowsiness, seizures, coma, and death. Patients frequently report a combination of both neurogenic and neuroglycopenic symptoms. The most common signs and symptoms of hypoglycaemia in children are weakness, tremor, hunger, fatigue, drowsiness, sweating, headache, and pallor. In contrast to adolescents, autonomic symptoms are less common in children younger than 6 years old whose symptoms of hypoglycaemia are more often neuroglycopenic or nonspecific in nature. Behavioural changes (irritability, tantrums, erratic behaviour, inconsolable crying) are often the primary manifestation of hypoglycaemia in young children. In contrast to adults, who are usually able to distinguish between autonomic and neuroglycopenic symptoms, children and their parents report that symptoms tend to cluster.

The American Diabetes Association defines biochemical hypoglycaemia as blood glucose <70 mg/dL (3.9 mmol/L) (Seaquist et al. 2013). However, healthy 8- to-16-year-old children and adolescents and those with type 1 diabetes may begin to counter-regulate at a higher blood glucose level than adults. As a result, their hypoglycaemia symptoms may occur with blood glucose concentrations in the normal range. Hypoglycaemia in children is often

classified in terms of its severity as mild, moderate, or severe, most episodes being mild. Cognitive impairment does not accompany mild hypoglycaemia and older children are able to recognize the symptoms and treat themselves. Mild symptoms abate within about 15 minutes after treatment with a rapidly absorbed carbohydrate. Moderate hypoglycaemia has both neuroglycopenic and autonomic symptoms, e.g. mood changes, irritability, decreased attentiveness, drowsiness, and behaviour change. Preschool age children, however, invariably require assistance with treatment because they are often confused and their judgement is impaired; also, weakness and lack of coordination may make self-treatment difficult or impossible. Moderate hypoglycaemia causes more protracted symptoms and may require a second treatment with oral carbohydrate. Severe hypoglycaemia is characterized by sufficient cognitive impairment that the assistance of another person is needed for treatment. Such events include episodes of unresponsiveness, unconsciousness, or seizures requiring emergency treatment with glucagon or intravenous glucose. This definition is not applicable to very young children, who, by definition, *always* require assistance for treatment of hypoglycaemia.

Children who have had diabetes for several years may describe a change in their symptoms over time. Autonomic symptoms tend to be less frequent and are more muted, and neuroglycopenic symptoms (e.g. drowsiness, difficulty concentrating, lack of coordination) are more common. Patients must learn to recognize the change in symptoms to prevent severe episodes. The blood glucose concentration at which symptoms occur varies among patients and the threshold may vary in the same individual in parallel with antecedent glycaemic control. Children with poorly controlled diabetes experience symptoms of hypoglycaemia at higher blood glucose concentrations than those with good glycaemic control.

Impact of hypoglycaemia on the child's brain

Owing to maturation of the central nervous system, the youngest children are at greater risk for cognitive deficits from hypoglycaemia. It is difficult, however, to dissect out the contributions of metabolic disturbances (hyperglycaemia and hypoglycaemia) and the psychosocial effects of chronic disease in a young child. Nonetheless, there is evidence linking hypoglycaemia (asymptomatic as well as severe hypoglycaemic events) to neuropsychological deficits. Preliminary findings suggest poorer memory skills, presumed but not proven to be the consequence of recurrent and severe hypoglycaemia. Exposure to severe hypoglycaemia has been associated with increased hippocampal volumes in children with type 1 diabetes, which may represent a pathological reaction to hypoglycaemia during brain development.

Even in the absence of typical symptoms, cognitive function deteriorates at low blood glucose levels. Moderate and severe hypoglycaemia is disabling, affects school performance, and makes driving a car or operating dangerous machinery hazardous. The utmost effort should be made to avoid such events. Repeated or prolonged severe hypoglycaemia can cause permanent central nervous system damage, especially in very young children. Fortunately, hypoglycaemia is a rare cause of death in children with type 1 diabetes.

Frequency of hypoglycaemia

The true frequency of mild (self-treated) symptomatic hypoglycaemia is almost impossible to ascertain accurately because mild episodes are quickly forgotten and are often not recorded. Increased use of CSII and the use of insulin analogues with multiple daily dose insulin regimens that more closely mimic physiologic insulin replacement, increased frequency of blood glucose monitoring, use of CGM, more widespread use of multidisciplinary diabetes care teams, and improvements in patient education have contributed to an overall reduction in risk of severe hypoglycaemia and lower HbA1c levels in recent years. In recent reports, rates of loss of consciousness or seizure are from 4 to 10 events per 100 patient-years.

Causes of hypoglycaemia in diabetes

Hypoglycaemia is the result of a mismatch between insulin, food, and physical activity and can be the result of therapeutic, biologic, and behavioural factors (see Table 1.14).

Nocturnal hypoglycaemia

An increase in plasma epinephrine concentrations is normally the main hormonal defence against hypoglycaemia in type 1 diabetes; however, sleep impairs counter-regulatory hormone responses to hypoglycaemia, both in normal subjects and in patients with

Table 1.14 Causes of hypoglycaemia in children and adolescents with diabetes mellitus.

Insulin errors (inadvertent or deliberate)
Reversal of morning and evening dose
Reversal of short- or rapid-acting insulin and intermediate- or long-acting insulin
Improper timing of insulin administration in relation to food consumption
Excessive insulin dosage
Surreptitious insulin administration; suicide gesture or attempt
Erratic or altered insulin absorption
Inadvertent intramuscular injection
More rapid absorption from exercising limbs
Unpredictable absorption from lipohypertrophy at injection sites
More rapid absorption after sauna, hot bath, sunbathing
Diet
Omission or reduced size of meals or snacks
Delayed snacks or meals
Variable meal composition: carbohydrate with/without protein and fat
Eating disorders and disordered eating
Gastroparesis
Malabsorption, e.g. gluten enteropathy
Exercise
Unplanned physical activity
Prolonged duration and/or increased intensity of physical activity
Strenuous exercise in the afternoon or evening
Failure to reduce the dose of basal insulin to combat the 'lag effect' of exercise
Alcohol and/or drugs
Impaired gluconeogenesis from excessive consumption of ethanol
Impaired cognition from use of ethanol (may cause hypoglycaemia unawareness), marijuana, cocaine, other recreational drugs
Hypoglycaemia-associated autonomic failure
Recurrent hypoglycaemia
Hypoglycaemia unawareness
Defective glucose counter-regulation
Miscellaneous uncommon causes of hypoglycaemia
Adrenocortical insufficiency
Hypothyroidism
Growth hormone deficiency
Renal failure
Decreased insulin requirement in first trimester of pregnancy
Insulin autoantibodies

diabetes, which explains the increased susceptibility to hypoglycaemia during sleep. Furthermore, asymptomatic nocturnal hypoglycaemia may impair counter-regulatory hormone responses. Thus, impaired defences against hypoglycaemia during sleep may contribute to the vicious cycle of hypoglycaemia, impaired counter-regulatory responses, and unawareness of hypoglycaemia (failure to experience autonomic warning symptoms before the onset of neuroglycopenia) either awake or asleep. Recurrent asymptomatic nocturnal hypoglycaemia is an important (but frequently undetected or overlooked) cause of hypoglycaemia unawareness, which, in turn, leads to more frequent and severe hypoglycaemia. Both children and adults studied either in hospital or at home with frequent intermittent or continuous blood glucose measurements during the night, show a high incidence of asymptomatic hypoglycaemia. For example, in the Juvenile Diabetes Research Foundation CGM randomized clinical trial, hypoglycaemic events (two consecutive CGM readings ≤60 mg/dL [3.3 mmol/L] in 20 minutes) occurred during 8.5% of nights (approximately twice per month) and lasted ≥2 hours on 23% of nights with hypoglycaemia. Hypoglycaemia during sleep may exceed four hours in duration, and up to half these episodes may be undetected because the subject does not wake from sleep. The incidence of hypoglycaemia on any given night is affected by numerous factors, including the insulin regimen, the timing and content of meals and snacks, and antecedent physical activity. Long after strenuous physical exercise has ended there is a sustained increase in insulin action on muscle and liver and blunting of the counter-regulatory response to hypoglycaemia. Low blood glucose concentrations in the early morning (before breakfast) are associated with a higher frequency of preceding nocturnal hypoglycaemia, and this knowledge is useful in counselling patients to modify the evening insulin regimen and bedtime snack to prevent more severe nocturnal hypoglycaemia.

Treatment of hypoglycaemia

The aim is to restore blood glucose to ≥100 mg/dL (5.6 mmol/L) as quickly as possible after the first symptom or sign is detected. Except in pre-school-aged children, most episodes of symptomatic hypoglycaemia are self-treated with a rapidly absorbed source of carbohydrate such as glucose tablets or gel, fruit juice, soft drinks, sweets, or crackers. Foods that contain fat together with carbohydrate should be

discouraged because fat slows the absorption of carbohydrate from the gastrointestinal tract. Because glucose tablets raise blood glucose levels more rapidly than orange juice, and the dosage is easily calibrated, they should be the treatment of choice for children old enough to chew and safely swallow large tablets. The recommended dose of glucose is 0.3 grams per kg body weight (5–20 g depending on the child's body weight). The blood glucose concentration should be re-measured 15 minutes after treatment, and if the value does not exceed 70–80 mg/dL (3.9–4.4 mmol/L), treatment should be repeated. The glycaemic response to oral glucose usually lasts less than two hours; therefore, unless a scheduled meal or snack is due within an hour, the patient should be given either a snack or a meal containing carbohydrate and protein.

Hypoglycaemia is common when the child with diabetes is unable to consume or absorb oral carbohydrate because an intercurrent illness (e.g. gastroenteritis) causes nausea and vomiting or due to oppositional behaviour and food refusal in very young children. To maintain blood glucose concentrations in a safe range, parents may either seek emergency medical attention or attempt to force feed oral carbohydrate in an ill child, which often leads to more vomiting. 'Mini-dose' glucagon raises blood glucose by 60 – 90 mg/dL (3.3 – 5 mmol/L) within 30 minutes and its effect lasts approximately one hour. This is an effective method for managing most situations of impending hypoglycaemia at home. First dissolve 1 mg glucagon in 1 ml of diluent; then, using a U-100 insulin syringe children ≤2 years of age receive 2 'units' (20 µg) of glucagon SC, and children >2 years, receive 1 unit (10 µg) per year of age up to a maximum dose of 15 units (150 µg). Blood glucose should be measured every 30 minutes for one hour, and hourly thereafter until the crisis has resolved. If the blood glucose concentration does not increase within 30 minutes, repeat the treatment using double the initial dosage of glucagon.

Severe hypoglycaemia (unresponsiveness, unconsciousness, or seizures) requires emergency treatment with parenteral glucagon (IM or SC). The usual recommended dose is 0.5 mg if the child is <12 years and 1 mg if >12 years. The increase in blood glucose concentration is sustained for at least 30 minutes after glucagon administration. Therefore, it is unnecessary to repeat the dose or force the child to eat or drink for at least 30 minutes. In an emergency department or hospital, the preferred treatment is intravenous glucose (0.3 gram per kg). After bolus administration of glucose, the glycaemic response is transient; therefore, an intravenous glucose infusion should continue until the patient is able to swallow safely.

If severe hypoglycaemia was prolonged and the patient had a seizure, complete recovery of cognitive and neurologic function may take many hours despite restoration of normal blood glucose levels. Transient (Todd's) paralysis may occur; however, permanent hemiparesis and other neurologic sequelae are rare; however, the post-ictal period may be complicated by headache, lethargy, nausea, vomiting, and muscle ache.

Recurrent DKA and its prevention

Recurrent DKA is invariably the result of psychosocial problems and failure to inject insulin. Management of an episode of DKA is not complete until its cause has been identified and an attempt made to prevent recurrence.

- Infection is rarely the cause of DKA when the patient/family is properly educated in diabetes management and is receiving appropriate follow-up care by a diabetes team with a 24-hour telephone helpline.
- In most cases, the cause is either inadvertent or deliberate insulin omission.
- In insulin pump users, the most common cause of DKA is failure to take extra insulin with a pen or syringe when 'pump failure' (interrupted insulin delivery for any reason) occurs.
- Home measurement of blood BOHB concentrations, when compared to urine ketone testing, decreases diabetes-related hospital visits by permitting earlier identification, more accurate quantitation, and treatment of ketosis. Blood BOHB measurements may be especially valuable to prevent DKA in pump users because interrupted insulin delivery rapidly leads to ketosis.
- There usually is an important psychosocial reason for insulin omission such as:
  - an attempt to lose weight in an adolescent girl with an eating disorder;
  - teenage rebellion/rejection of diabetes;
  - a means of escaping an abusive home situation;
  - depression or other reason for inability of the patient to manage diabetes unassisted.
- A psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to development of DKA.
- Insulin omission can be prevented by comprehensive programmes that provide education, psychosocial evaluation, and treatment combined with adult supervision of insulin administration.
- Parents and patients should learn how to recognize and treat ketosis and impending DKA with additional rapid- or short-acting insulin and oral fluids.

• Families should have access to a 24-hour telephone helpline for emergency advice and treatment.
• When a responsible adult administers insulin, the frequency of recurrent DKA decreases dramatically.

The treatment of DKA is described earlier in this chapter (Section 1.9).

Management of diabetes during intercurrent illness ('Sick Day Rules')

An acute febrile illness often leads to a rise in blood glucose and ketone concentrations due to the effects of raised levels of stress hormones and increased insulin resistance. If not properly managed, progression to DKA may ensue. Conversely, diseases associated with diarrhoea and/or vomiting such as gastroenteritis may lead to hypoglycaemia. Families should have clear and concrete guidelines on the management of diabetes during intercurrent illness ('sick day rules'), see Table 1.15. Ketones should be measured whenever:

• the child has abdominal pain;
• there is nausea or vomiting;
• blood glucose is ≥300 mg/dL (16.7 mmol/L) on two consecutive measurements;
• blood glucose is ≥250 mg dL (13.9 mmol/L) upon waking up in the morning;
• the child is febrile.

The important principles for managing diabetes during intercurrent illness include:

• Do not omit or decrease the dose of long- or intermediate-acting insulin (see Table 1.15 for recommendations concerning doses of supplemental rapid-acting insulin).
• Regularly measure blood or urine ketone concentrations.
• Monitor blood glucose concentrations at least before each meal and before bedtime. More frequent monitoring, for example, hourly or every two hours, may be required.
• Consume carbohydrate regularly. If the child has a poor appetite, this may take the form of regular small snacks and/or sugar-containing drinks, rather than large meals.
• Drink plenty of water and/or reduced sugar fluids to counteract the potential dehydration that may be associated with glucosuria and a febrile illness.
• If hypoglycaemia occurs, particularly in association with gastroenteritis and mild ketosis, ensure that the child takes regular, frequent carbohydrate-containing snacks and/or sugary drinks. Oral rehydration solutions are sometimes necessary. Occasionally, glucose gel or mini dose glucagon (see Section 1.15 on hypoglycaemia) are required to treat hypoglycaemia and to help re-establish oral feeds. Vomiting may be treated with a single dose of an anti-emetic to try to improve carbohydrate intake.
• To treat the underlying illness, antibiotics may be required for some infections and antipyretics are also often required. Sugar-free medicines are preferable if available.
• If, despite these measures, the child has persistent vomiting and/or diarrhoea, significant hypoglycaemia, abdominal pain, drowsiness, tachypnoea, the blood glucose and/or ketone concentrations fail to

Table 1.15 Guidelines for managing sick days and correcting ketones.

Blood glucose (mg/dL mmol/L)		Urine ketones	Blood ketones (mmol/L)	Dose of rapid-acting insulin	Monitoring
≤180	≤10	≥Trace	≥0.6	Usual dose	Re-check glucose and ketones in two hours
181–300	10.1–16.7	≥Trace	≥0.6	Usual 'correction factor'[a]	Re-check glucose and ketones in two hours
>300	10.1–16.7	Small	0.6–0.9	Usual 'correction factor'[a]	Re-check glucose and ketones in two hours
>300	10.1–16.7	Moderate	1–1.5	15% of total daily dose or 0.15 units per kg	Re-check glucose and ketones in two hours
>300	10.1–16.7	Large	>1.5	20% of total daily dose or 0.2 unit per kg	Re-check glucose and ketones in two hours

Typical dosing guidelines are individualized based on age, weight, pubertal status, and duration of diabetes.
[a] 5–10% of total daily insulin dose or 0.05–0.1 unit per kg.

respond to changes in insulin treatment, or the parents remain concerned, then they should contact the diabetes nurse, doctor or hospital for further advice.

- In cases of severe gastroenteritis and in those with severe or persistent vomiting, IV fluids may be necessary (e.g. 5% dextrose/0.45% or 0.9% saline with 10 mmol of potassium per 500 ml). In such cases, it is often best to also administer IV insulin. Insulin infusion at a rate approximately equivalent to the child's basal insulin requirement may be used. For example, if the child's TDD of insulin is 0.8 units kg^{-1}, assume 50% (0.4 units kg^{-1}) is basal insulin. Divide this number by 24 to obtain an hourly dose of basal insulin for infusion. In this example, 0.4 divided by 24 = 0.017 unit per kg per hour (round down to 0.015 or up to 0.02 unit per kg per hour). Adjust the rate of insulin (and dextrose) infusion guided by hourly blood glucose measurements.

Management of diabetes when travelling

When travelling, the following principles are recommended for management of the diabetes (Pinsker et al. 2013):

- Patients who are planning to travel overseas should schedule a visit with their diabetes care provider at least 4–6 weeks before departure. Advanced planning will help prevent emergencies that may occur away from home.
- Travel with identification (diabetes identification card, Medic Alert necklace or bracelet), surplus insulin, glucose and ketone monitoring supplies (strips and lancets), spare batteries, syringes, pens, needles or infusion sets. Supplies should include glucose gel and glucagon. All diabetes-related medications and supplies should be taken as carry-on luggage and must NEVER be in checked baggage.
- A letter for the airlines, security and Customs should state the diagnosis and list all the diabetes supplies required.
- Appropriate health insurance must be arranged.
- Open insulin vials retain their potency at room temperature for at least one month. In hot climates, insulin should be stored either in a refrigerator or in thermal insulated bags or containers. Patients who use an insulin pump should change the insulin reservoir every one to two days.
- Suitable snacks (such as breakfast bars, granola bars, trail mix, cheese crackers, etc.) should be kept with the hand luggage in case the child does not like the food on the plane or the meals contain inadequate carbohydrate or there are unexpected travel delays.
- Flying across time zones can cause confusion about how and when to adjust times of insulin administration and insulin dosage.
- Patients should obtain a travel itinerary showing departure and arrival times, duration of flights, and time differences between departure and arrival locations.
- Patients should obtain an individualized insulin dosage plan from their health care provider before departure. During the flight patients should leave their watches unadjusted so that they continue to correspond to the time at the point of departure. This makes it easier to determine the timing of their insulin injections and meals.
- With short flights or where the time zone between departure and arrival changes by less than four hours, no major changes to the insulin regimen are required.
- Travelling east shortens the day ('eastward = less insulin') and may necessitate a reduction in dose of long-acting insulin because insulin doses would, otherwise, be administered closer than normal and could cause hypoglycaemia.
- In contrast, travelling west means a longer day; insulin doses may need to be increased or an additional dose given to 'bridge the gap' ('westward = more insulin').
- Patients who use an insulin pump should continue to use their usual basal rates.
- A basal-bolus insulin regimen is the ideal injection regimen to cope with major time zone travel situations. Patients who are not using an insulin pump should be transferred to a basal-bolus regimen before travelling.
- With long-haul flights crossing time zones, on arrival at the destination, pump users must change the time in the pump to local time. Give usual pre-meal doses of rapid-acting insulin (using usual insulin:carbohydrate ratio and correction factor) before main meals on the airplane and revert to the usual regimen on arrival at the destination.
- Patients who have very tightly controlled blood glucose levels should be aware that changes in altitude can cause unintended insulin delivery from their pumps. During take-off, air pressure decreases and the pump can deliver additional insulin; the converse can occur during descent.
- Frequent blood glucose monitoring (at least every 4–6 hours) is essential for safety during flight and patients should maintain good hydration while in flight.

When on holiday, especially those involving more than usual physical activity, children with diabetes often require substantially less insulin (e.g. 20–30% reductions) than usual to avoid hypoglycaemia. At the start of the holiday, the child should be advised to monitor blood glucose concentrations regularly to guide changes in insulin doses.

Management of diabetes during surgery

The main goals of diabetes management during surgery are to avoid hypoglycaemia, marked hyperglycaemia, and DKA. When feasible, children with diabetes should not undergo elective surgery until they are metabolically stable and blood glucose control has been optimized (HbA1c approximately at or below 7.5%) in the weeks preceding elective surgery. If metabolic control is poor, surgery should be delayed if possible. Both the endocrinology and anaesthesiology services should participate in this assessment. Surgery should be performed in the morning with the patient first on the list whenever possible. In the case of an afternoon list, the patient should be first on the list. Children who present for emergency surgery (e.g. trauma or acute surgical conditions) require a multidisciplinary preoperative assessment with collaborative involvement of both the endocrinology and anaesthesiology services. Surgery often cannot be delayed even if metabolic control is poor, e.g. a child requiring emergency surgery who presents in DKA. The regimen for managing diabetes before, during, and after a surgical or diagnostic procedure should aim to maintain near-normoglycaemia, i.e. a blood glucose concentration in the range 100–200 mg/dL (5.6–11.1 mmol/L).

Evening prior to elective surgery

On the day before elective surgery, blood glucose should be measured before each meal and before bedtime. Blood or urine ketones should also be measured. In patients treated with glargine or detemir pre-bedtime, the usual dose should be administered.

Morning Operations

- No food from midnight.
- Clear fluids may be taken up to four hours pre-operatively.
- On the morning of surgery, no rapid- or short-acting acting insulin should be administered *unless* the blood glucose exceeds 250 mg/dL (13.9 mmol/L).
- Children using multiple daily injection regimens who are undergoing minor or brief procedures should receive their usual morning dose of long-acting insulin on the day of the procedure. Children who use NPH insulin should receive 50% of the usual morning dose.
- Children who require major surgery, especially procedures anticipated to last more than two hours, should have an IV insulin infusion as the preferred perioperative diabetes management plan.
- Patients who use an insulin pump should receive their usual basal rate of insulin until intravenous insulin and IV fluids are commenced.
- Measure blood glucose, serum urea, creatinine and electrolytes, and blood or urinary ketones before commencing surgery to ensure patient is metabolically stable and adequately hydrated.
- Start IV fluids, 5% dextrose/0.45% saline with 20 mmol of KCl/L, at a maintenance rate (for the first 10 kg body weight – 100 ml per kg per day, for each kg between 10 and 20 kg–50 ml per kg per day, and for each kg above 20 kg–20 ml per kg per day).
- Simultaneously start an insulin infusion using a syringe pump (1 unit of Regular insulin/ml) at a rate approximately equivalent to the child's basal insulin requirement. For example, if the child's TDD of insulin is 0.8 units per kg; assume 50% (0.4 units per kg) is basal insulin. Divide this number by 24 to obtain an initial hourly dose of basal insulin for infusion. In this example, 0.4 divided by 24 = 0.017 unit per kg per hour (round down to 0.015 or up to 0.02 unit per kg per hour). Adjust the insulin infusion rate hourly aiming for a blood glucose concentration of 100–200 mg/dL (5.6–11.1 mmol/L).
- Measure blood glucose hourly, or more frequently if necessary pre-, intra- and postoperatively.
- When blood glucose levels are stable in a satisfactory range, frequency of monitoring can be decreased to every two to four hours.
- Continue IV fluids and insulin until the patient tolerates oral fluids and snacks (this may not be until 24–48 hours after major surgery).
- Change to the usual subcutaneous insulin regimen before the first meal is eaten. The intravenous insulin infusion can be stopped 15 minutes after subcutaneous administration of a rapid-acting insulin analogue. Food should be given ~15 minutes after the insulin injection. In the case of children who use a pump, insulin delivery should be resumed 15 minutes before stopping the IV insulin, and a meal bolus dose using the pump can, likewise, be given ~15 minutes before commencing the meal.

• Following minor operations and procedures it usually is possible to discharge the patient after complete recovery from anaesthesia and consumption of oral fluids and a meal.

Afternoon Operations

• Patient can have breakfast with the usual dose of rapid-acting insulin. In patients who use an insulin pump, a bolus is given before breakfast and the usual basal rate can be continued until the IV fluids and insulin are commenced.
• Can have clear fluids up to four hours pre-operatively.
• Measure blood glucose, urea, creatinine and electrolytes, and blood or urine ketones pre-operatively.
• Start an infusion of regular insulin at midday and IV fluids and (see 'Morning operations').
• Then follow protocol for morning operations.

Emergency Surgery

• DKA may present with severe abdominal pain, which may be mistaken for a 'surgical abdomen'. Acute illness may also precipitate DKA.
• Keep patient nil by mouth.
• Obtain IV access.
• Check weight, blood glucose, complete blood count, serum urea, creatinine, electrolytes, venous blood gas, and blood or urine ketones pre-operatively.
• If ketoacidosis is present, follow the DKA protocol and, if possible, delay surgery until the circulating volume has been restored and any major electrolyte imbalances have been corrected.
• In the absence of ketoacidosis, start maintenance IV fluids and an insulin infusion as for elective surgery.

Minor procedures requiring fasting (e.g. endoscopy, grommets, sedated imaging)

For short procedures (with or without sedation or anaesthesia) where a rapid recovery is anticipated, a simplified protocol can be followed by the diabetes/anaesthesiology team. For example, for an early morning procedure between 8.00 and 9.00 a.m., basal insulin can be administered as usual, and breakfast and the pre-meal insulin bolus can be delayed until after completion of the procedure.

Long-term complications of diabetes

Monitoring for development of complications is an important component of comprehensive paediatric diabetes care. Complications are both microvascular (retinopathy, nephropathy, neuropathy) and macrovascular, causing coronary artery, cerebrovascular, and peripheral vascular disease and lead to ischemic heart disease, stroke, lower extremity gangrene, and amputation, respectively. Retinopathy causes visual impairment and blindness; nephropathy causes hypertension and renal failure; neuropathy causes pain, paresthesiae, muscle weakness, and autonomic dysfunction. Among teenagers and young adults who had been diagnosed with diabetes during childhood and adolescence, after a mean diabetes duration of 7.9 years approximately one in three with type 1 diabetes and almost three of four with type 2 diabetes have at least one complication (nephropathy, retinopathy, peripheral neuropathy, autonomic neuropathy) or co-morbidity (hypertension, arterial stiffness) (Dabelea et al. 2017). Clinically significant macrovascular complications affect older adults. Longer duration, older age, and puberty are risk factors for complications. The risk of complications is increased by genetic factors (i.e. a family history of complications), poor glycaemic control, and smoking in both type 1 and type 2 diabetes. Low socioeconomic status is the single strongest predictor of poor diabetes outcomes.

Diabetic retinopathy

Non-proliferative ('background') retinopathy is characterized by microaneurysms, retinal haemorrhages (blot, dot, and flame-shaped) (Figure 1.7), hard exudates (protein and lipid leakage), cotton wool spots (microinfarctions), intraretinal microvascular abnormalities and beading, dilatation, constriction and tortuosity of vessels. This stage is asymptomatic and does not impair vision. Risk factors for retinopathy include poor glycaemic control, longer duration of diabetes, hypertension, hyperlipidaemia, and smoking. Background diabetic retinopathy (BDR) may stabilize, regress with improved glycaemic control, or progress if poor control persists. BDR in childhood rarely progresses to proliferative retinopathy; nonetheless, all patients with retinopathy should be referred to an ophthalmologist.

Proliferative diabetic retinopathy (PDR) is characterized by neovascularization in the retina and/or vitreous posterior surface. The vessels may rupture or bleed into the vitreoretinal space and is vision-threatening. Advanced PDR can result in fibrosis and adhesions that can cause haemorrhage and retinal detachment. Diabetic macular oedema (DME) is characterized by decreased vascular competence and microaneurysm formation, which produces increased

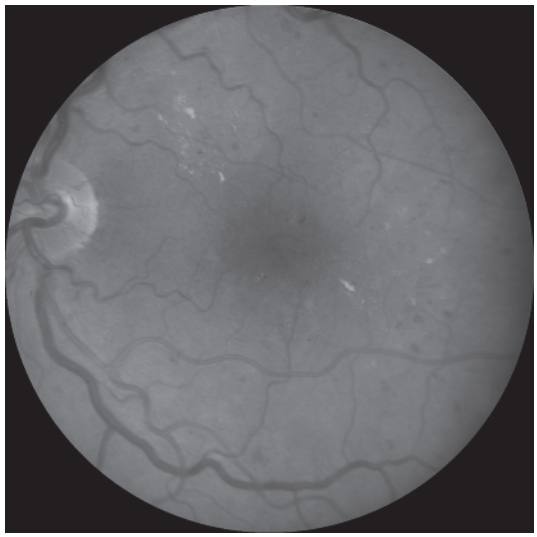

Figure 1.7 Background retinopathy showing scattered 'dots and blots' (microaneurysms and haemorrhages) and exudates. Source: Courtesy of Robert Cavicchi, CRA, FOPS, and Richard Calderon OD, FAOO, Beetham Eye Institute, Joslin Diabetes Center.

exudation and swelling in the central retina. DME is vision-threatening, but is very uncommon in children and adolescents with type 1 diabetes.

Cataracts may develop in patients with diabetes but are rare under the age of 20 years.

The most sensitive detection methods for retinopathy screening are bimicroscopic fundus slit lamp examination through dilated pupils by an ophthalmologist or optometrist and mydriatic seven-field stereoscopic retinal photography. Other commonly used screening methods include mydriatic and non-mydriatic two-field fundal photography, direct ophthalmoscopy, and indirect ophthalmoscopy.

Improvement in diabetes care has been associated with a marked reduction in diabetic retinopathy. For example, in one study, adolescents with a median diabetes duration of 8.6 years showed a decrease in retinopathy from 53% in 1990–1994 to 23% in 2000–2004, and then to 12% in 2005–2009. In a younger age group (11–17 years) with a shorter diabetes duration of only two to five years, the prevalence of mild BDR decreased from 16% in 1990–1994 to 7% in 2003–2006.

Once vision-threatening retinopathy (severe non-proliferative retinopathy and PDR) has been detected, treatment consists of panretinal photocoagulation (laser therapy consisting of multiple discrete outer retinal laser burns, sparing the central macula), which reduces progression of visual loss by more than 50% in patients with PDR. Side-effects include decreased night and peripheral vision and changes in colour perception.

Because retinopathy can worsen rapidly when control is improved in patients with long-standing poor glycaemic control, frequent ophthalmologic monitoring is recommended both before and after initiating intensive diabetes treatment.

ISPAD recommends annual screening from age 10 years (or at onset of puberty if this is earlier), after a diabetes duration of two to five years. For patients with duration <10 years, minimal or no BDR, and well-controlled diabetes, screening by fundus photography may be performed biennially (Donaghue et al. 2018).

Diabetic nephropathy

Diabetic nephropathy is defined as persistent proteinuria >500 mg/24 h, albuminuria >300 mg/24 h, and is usually associated with hypertension and decreased glomerular filtration rate (Donaghue et al. 2018). End-stage renal failure requiring dialysis or kidney transplantation may occur many years later. The prevalence of microalbuminuria increases with duration of diabetes. Risk factors include poor glycaemic control, long-standing diabetes, cigarette smoking, hypertension, and a family history of diabetic nephropathy.

The first clinical sign of incipient nephropathy is a persistently elevated albumin excretion rate (AER), which can be determined by different methods:

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

Because timed urine collections can be difficult to obtain in children, the ACR is widely used to screen for nephropathy. First voided morning urine samples provide the most reliable measurements; however, in practice, it is usually most convenient to measure the ACR whenever the child is in clinic. If the value is abnormal, the measurement must be repeated on a first voided morning urine sample. Proteinuria may be caused by strenuous physical exercise, menstruation (do not obtain urine sample during menses), urinary tract infection, orthostatic proteinuria, and other types of nephritis. The latter should be excluded, especially in children with abnormal albumin excretion and a short duration of diabetes. Microalbuminuria is confirmed by finding

two or all of three consecutive samples abnormal over a 3- to 6-month period. Microalbuminuria can regress, especially in adolescents; however, persistent microalbuminuria predicts progression to end-stage renal failure. In patients with microalbuminuria, attempts should be made to improve glycaemic control, ideally lowering the HbA1c to <7%, and this may lead to normoalbuminuria. Stopping smoking, strict blood pressure control, and exercise should also be advocated.

Angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs) should be used in patients with persistent microalbuminuria, even in the absence of hypertension, to prevent progression to proteinuria. ACEIs can have side effects such as cough and hyperkalaemia (serum electrolytes, urea, and creatinine concentrations should be measured five to seven days after starting treatment). ACEIs and ARBs are also associated with the potential risk of congenital malformations when used during pregnancy. Therefore, adolescent girls must be counselled about the risk and effective contraception recommended.

There is good evidence in adults with type 1 diabetes and microalbuminuria that ACEIs decrease ACR and, in some cases, lead to reversion to normoalbuminuria; as yet, there is no comparable evidence of long-term efficacy and safety in the paediatric population.

Early detection of diabetic nephropathy and timely treatment of hypertension have a pivotal role in the prevention of end-stage renal failure in young people and adults with diabetes. ISPAD recommends annual screening from age 10 years (or at onset of puberty if this is earlier) and after two to five years' diabetes duration (Donaghue et al. 2018).

Blood pressure (BP) should be measured at least annually. Hypertension is defined as average systolic BP and/or diastolic BP >95th percentile for gender, age, and height on more than three occasions. The BP target for adolescents is <130/80 mm Hg. Effective antihypertensive therapy in patients with nephropathy prolongs the time to end-stage renal disease. BP values between the 90th and 95th percentiles are defined as prehypertension. ACEIs are recommended for use in children and adolescents with hypertension.

Diabetic neuropathy

Diabetes insidiously and progressively damages diffusely all peripheral nerve fibres – motor, sensory, and autonomic. The earliest symptoms include numbness and paresthesiae of the feet or hands, decreased vibration sense and sensation to light touch (monofilament examination) and pinprick, and loss of ankle reflexes. Sensory loss in a stocking and glove distribution

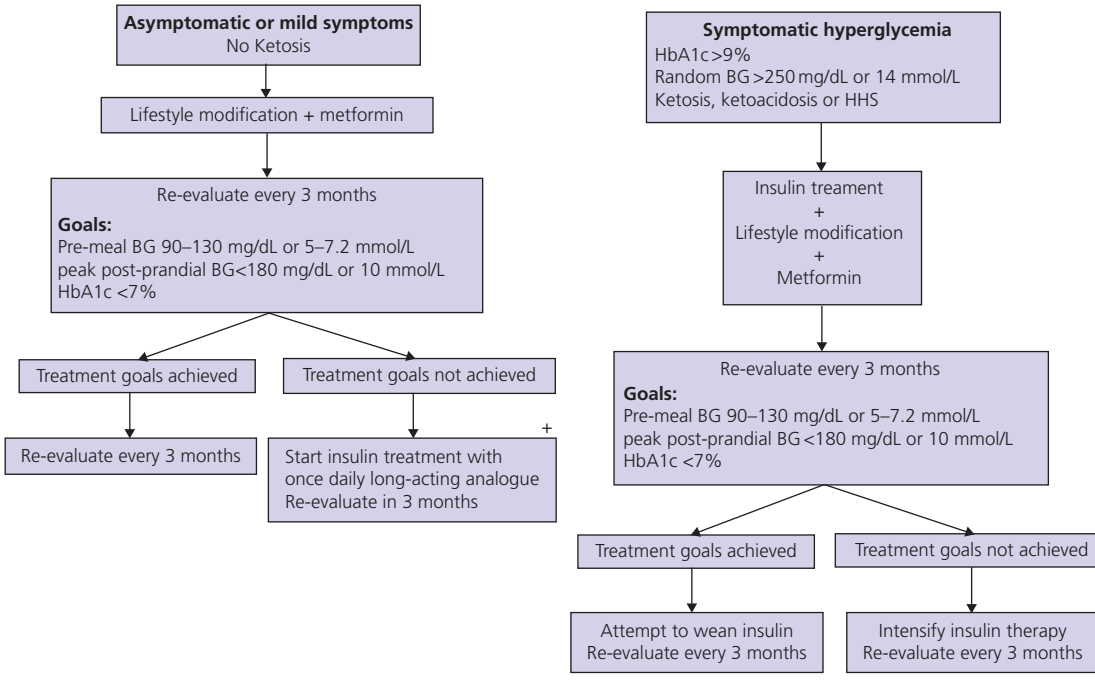

Figure 1.8 Recommended management for type 2 diabetes mellitus in youth.

typically precedes loss of motor function. Autonomic neuropathy can cause postural hypotension, gastroparesis, diarrhoea, bladder paresis, abnormal sweating, and impotence. Clinically significant neuropathy in adolescence is uncommon; however, prevalence rates of peripheral neuropathy varying from <10–27% have been reported.

Dyslipidaemia

The atherosclerotic process begins in childhood. Although CVD events are not expected to occur during childhood, youth with type 1 diabetes may have subclinical CVD within the first decade of diagnosis and are categorized as being in the highest tier for cardiovascular risk. Screening for dyslipidaemia should be performed soon after diagnosis (after glucose control has been established) in all children with type 1 diabetes ≥10 years of age. If LDL cholesterol is within the accepted risk level (<100 mg/dL or 2.6 mmol/L), lipid screening should be repeated every 3–5 years. If lipids are abnormal, annual monitoring is recommended. If the LDL cholesterol value is high (≥2.6 mmol/L, 100 mg/dL), interventions to improve metabolic control, dietary changes (reduced consumption of saturated fat), and increased physical exercise should be instituted. After the age of 10 years, if medical nutrition therapy and lifestyle changes fail to lower LDL cholesterol <160 mg/dL (4.1 mmol/L) or <130 mg/dL (3.4 mmol/L) in patients with one or more CVD risk factors, treatment with a statin should be considered. The goal of therapy is to lower LDL cholesterol to <100 mg/dL (2.6 mmol/L). Statins are potentially teratogenic; therefore, prevention of unplanned pregnancy is of paramount importance.

Premature mortality

Type 1 diabetes is associated with a substantially increased risk of premature death as compared with the general population. Among persons with diabetes younger than 30 years of age, excess mortality is largely attributable to DKA and hypoglycaemia. CVD is the main cause of death later in life. For patients who have very poor glycaemic control, the risk of death from any cause and from CVD is 8 to 10 times as high, respectively, as the general population risk. Several studies have shown an association between the level of glycaemic control (as measured by HbA1c) and all-cause mortality. Improving glycaemic control significantly reduces risk of microvascular complications and CVD.

Type 2 diabetes in children and adolescents

As early as 1916, a phenotypically distinct form of diabetes, now classified as type 2 diabetes mellitus, was recognized in childhood. Since the early 1990s, temporally coinciding with the worldwide increase in childhood obesity, an increase in the prevalence of type 2 diabetes has been reported from paediatric diabetes centres in North America and elsewhere in the world. In the US, type 2 diabetes now accounts for 22% of new cases of diabetes among youth. It is far more common in racial and ethnic minorities: 25% of diabetes cases in Hispanic, African-American and Asian/Pacific Islander patients have type 2 diabetes. Typical risk factors are shown in Table 1.16. In a recent report describing presentation of 503 youths with type 2 diabetes, 67% presented with symptoms of diabetes and confirming laboratory data, whereas 33% were identified by testing asymptomatic at-risk children.

The classic criteria (age at onset and weight) for distinguishing between the two major types of diabetes have become increasingly blurred. Owing to the current high prevalence of overweight and obesity in children and adolescents, many youths with type 1 diabetes are overweight or obese at diagnosis or become overweight within a few years after diagnosis. Both type 1 and type 2 diabetes often present during puberty, a period of life characterized by physiologic insulin resistance; however, type 2 diabetes can occur in severely obese prepubertal children. The increasing incidence of type 2 diabetes in youth now presents

Table 1.16 Risk factors for type 2 diabetes in youth.

- Overweight or obesity associated with insulin resistance
- Family history of type 2 diabetes in first- or second-degree relative
- Ethnicity: in North America, African-American, Hispanic, Pacific Islander, Native American, Canadian First Nation; children and adolescents from the Indian sub-continent living in Europe
- Maternal gestational diabetes
- Small size for gestational age (intrauterine growth restriction)
- Insulin resistance of puberty
- Acanthosis nigricans
- Polycystic ovary syndrome
- Lack of physical activity
- High calorie diet

clinicians with a diagnostic challenge when evaluating a paediatric patient with new-onset diabetes. Distinguishing between type 1 and type 2 diabetes cannot be based on ketone status, body weight, or insulin requirement. In contrast to type 2 diabetes in adults in whom ketonuria is unusual, a substantial fraction of adolescents with type 2 diabetes have ketonuria and between 5.6% and 11% have DKA at presentation, and 2% present with HHS. Furthermore, insulin requirements typically decrease after several weeks of treatment, which may resemble the remission or 'honeymoon' period of type 1 diabetes. Measuring pancreatic islet autoantibodies and a surrogate for insulin secretion (fasting C-peptide levels) in obese patients helps to distinguish between type 1 and type 2 diabetes. A fasting plasma C-peptide level > 0.85 ng/ml (0.28 nmol/L) suggests type 2 diabetes; however, plasma C-peptide levels obtained soon after diagnosis may be transiently low in type 2 diabetes owing to gluco- and lipotoxicity. Repeating the measurement after several weeks or months of therapy will sometimes demonstrate hyperinsulinaemia and insulin resistance, helping to establish a diagnosis of type 2 diabetes.

In summary, a binary classification is not always possible at the time of diagnosis. Patients may have clinical and biochemical features of both insulin deficiency and insulin resistance, i.e. characteristics of both major types of diabetes. Irrespective of the type of diabetes, the choice of initial therapy should be based on the metabolic state, as determined by clinical assessment. Subsequent therapy is then modified, if necessary, guided by the individual patient's response to treatment.

Treatment of type 2 diabetes

As for type 1 diabetes, a multidisciplinary diabetes team, including a physician, DNE, registered dietitian, and behavioural specialist (psychologist or social worker), is essential. In addition to blood glucose control, from the outset, treatment often must include management of comorbidities such as obesity, dyslipidaemia, hypertension, and microalbuminuria. Youth onset type 2 diabetes is an aggressive disease with a higher rate of complications than type 1 diabetes of comparable duration. Intensive intervention is required both for glycaemic control and to mitigate cardiovascular risk factors. An algorithm for managing type 2 diabetes in youth including HbA1c and glycaemic targets is shown in Figure 1.9. Treatment with metformin must not be started until ketosis/ketoacidosis has resolved and the patient is well hydrated.

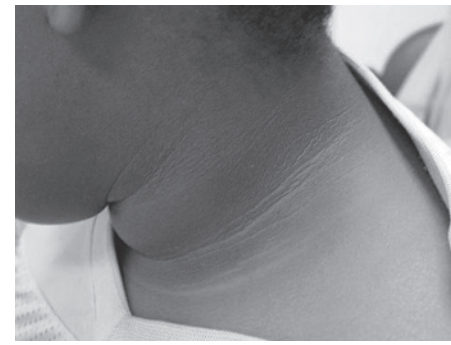

Figure 1.9 Acanthosis nigricans on the neck.

Nonpharmacologic therapy

Weight control and physical activity

Youths with type 2 diabetes are overweight or obese at presentation; the emphasis is on weight loss, limiting caloric intake, and distributing meals evenly throughout the day. Even modest weight reduction alone increases sensitivity to insulin and improves fasting and postprandial blood glucose levels. The aims of treatment are to lose weight, normalize fasting and postprandial blood glucose and haemoglobin A1c levels, identify and treat associated co-morbidities such as hypertension and dyslipidaemia, and to minimize the risk of acute and chronic complications associated with diabetes. Dietary management for patients with type 2 diabetes emphasizes healthy eating to optimize metabolic control while achieving sustained weight loss. Nutrition and lifestyle approaches to treatment should be given at least as much importance as drug therapy. A family-centred approach is essential in paediatric type 2 diabetes and patients and their families must prioritize lifestyle modifications such as eating a balanced diet, maintaining a healthy weight, and exercising regularly. Nutrition recommendations should be culturally appropriate and sensitive to family resources.

Patients and their family members should receive guidance on behaviour modification strategies to change their lifestyle, decrease their consumption of high-energy/high-fat foods, and incorporate daily aerobic physical activity into their lives. Regular physical activity facilitates weight loss, increases HDL cholesterol levels, lowers blood pressure, and improves metabolic control. Fasting serum insulin concentrations decrease and insulin sensitivity improves in obese children who lose weight and exercise regularly. To increase physical activity, the amount of time devoted to sedentary activities and 'screen time' (viewing television, playing video games, surfing the

internet, etc.) must be strictly limited to less than two hours daily. Youths with type 2 diabetes should be encouraged to participate in aerobic exercise with a gradual increase in the frequency, intensity, and duration, aiming for at least 60 minutes daily of moderate/intense physical activity. Exercise tolerance is reduced in obese children; therefore, advice to increase physical activity should be realistic and individualized.

Pharmacologic therapy

Oral agents

Presentation with ketosis or ketoacidosis requires a period of insulin therapy until fasting and postprandial glycaemia have been restored to normal or near normal levels. Similarly, when the distinction between type 1 and type 2 diabetes is unclear, initial treatment should be with insulin. Recent clinical practice guidelines (Springer et al. 2013) recommend initiation of insulin therapy in patients with random blood glucose concentrations ≥250 mg/dL (13.9 mmol/L) or A1c >9% (75 mmol/mol).

Metformin

When insulin treatment is not required, current guidelines recommend a family-centred lifestyle modification programme plus initiation of metformin as first-line therapy for children and adolescents. Metformin is currently the only oral hypoglycaemic agent specifically approved for use in children with type 2 diabetes. Metformin is safe and often efficacious in paediatric patients with type 2 diabetes. Metformin suppresses basal hepatic glucose production and increases insulin-mediated glucose uptake in skeletal muscle, but does not affect insulin secretion or cause hypoglycaemia. It causes a mild reduction in triglyceride and LDL concentrations and its anorectic effect may contribute to modest weight loss. Its most common side-effects are nausea, vomiting, abdominal pain, and diarrhoea. Lactic acidosis is a rare, potentially fatal side-effect. Provided that it is not administered to patients with renal insufficiency (metformin is excreted unchanged in the urine) or poor tissue perfusion, the risk of lactic acidosis is extremely low. Metformin must be discontinued before radiographic studies with iodinated contrast agents, surgery under general anaesthesia, in patients with renal, liver, or heart disease, in patients with dehydration, and whenever tissue perfusion is poor. Because the absorption of vitamin B12 and/or folic acid may be compromised, patients are advised to take a daily multivitamin.

For children 10–16 years of age, the recommended starting dose of metformin is 500 mg once daily. The dose may be increased to 500 mg twice daily, and further increases may be made at weekly intervals in 500 mg increments to a maximum daily dose of 2000 mg. The acute, reversible gastrointestinal adverse effects of metformin may be minimized by administration with or after food, and by using lower dosages, increased slowly, as necessary. The extended release preparation should be initiated at a dose of 500 mg once daily, given with the evening meal. The maximum recommended dose of the extended-release product is 2000 mg per day. In overweight females with polycystic ovary syndrome, a condition that is often associated with type 2 diabetes, menstrual cycles and fertility may be restored to normal. Therefore, sexually active females should be counselled regarding the need for birth control.

Insulin secretagogues (Sulfonylureas and Meglitinides)

Although sulfonylureas have been used in adults for more than half a century, there is only limited evidence of their efficacy in children. A 24-week, randomized, single blind comparative study in type 2 diabetes paediatric patients showed that glimepiride was as safe and effective as metformin in terms of reduction of A1c and incidence of hypoglycaemia. The glimepiride-treated group, however, showed greater weight gain compared to patients treated with metformin.

Thiazolidinediones (TZDs)

Thiazolidinediones (TZDs) are insulin sensitizers that act on the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) and increase insulin sensitivity in muscle and adipose tissue. TZDs have favourable effects on lipid metabolism. Side effects include weight gain and fluid retention, which contraindicates their use in patients with heart failure. TZDs are not approved for use in children, and their use in adults is restricted due to concerns about risk of myocardial infarction with rosiglitazone, risk of bladder cancer with pioglitazone, and decreased bone density risk with both.

Insulin

Although many insulin regimens have been studied and successfully used in adults with type 2 diabetes, comparable data do not exist in paediatric type 2 diabetes. Metformin may be added after normalization of

blood glucose, resolution of ketosis, and correction of dehydration.

Insulin therapy may be necessary in asymptomatic or mildly symptomatic patients who fail to achieve adequate glycaemic control (A1c <7%, 53 mmol/mol) after three months of lifestyle intervention and treatment with maximum doses of metformin. Long-acting insulin analogues (glargine, detemir, or insulin degludec) may be added to metformin at a starting dose of 0.2 units per kg per day at dinnertime or bedtime. Twice daily pre-mixed insulin regimens have been efficacious in adults with type 2 diabetes and a short trial with premixed insulin analogues was also beneficial in children. Basal-bolus therapy (once daily long-acting-insulin combined with short-acting insulin before meals) may be a suitable option in the motivated patient who is willing to perform carbohydrate counting.

Complications and comorbidities of type 2 diabetes

In youth with type 2 diabetes, complications may be present at the time of diagnosis or appear soon thereafter. A recent study showed that among youth with type 2 diabetes diagnosed before age 20 years, high rates of diabetic kidney disease, retinopathy, and neuropathy (20%, 9%, and 18%, respectively), occur after a mean duration of approximately eight years. Moreover, the risk of these complications is more than twofold higher than in those diagnosed with type 1 diabetes, after adjustment for age, disease duration, glycaemia, and obesity, emphasizing the need to begin monitoring youth with type 2 diabetes for development of complications from the time of diagnosis (Dabelea et al. 2017). Comorbidities associated with type 2 diabetes include: obesity, metabolic syndrome, hypertension, microalbuminuria, dyslipidaemia, non-alcoholic fatty liver disease (NAFLD), and acanthosis nigricans (Figure 1.9).

Hypertension

Strict control of blood pressure significantly reduces cardiovascular morbidity and mortality in adults, and similar effects would be expected in children. The aim is to reduce blood pressure to <90th percentile for age, height, and gender. If lifestyle intervention (weight control, regular exercise) is unsuccessful, pharmacological treatment should be initiated with an ACE inhibitor. If the highest recommended dose is ineffective or if the child experiences side effects, a second drug from a different class, such as an ARB, calcium channel blocker, cardioselective beta-blocker, and/or diuretic may be used.

Dyslipidaemia

Dyslipidaemia in childhood tracks into adulthood; therefore, it is reasonable to assume that untreated lipid disorders in children with diabetes increase the risk of CVD later in life. Initial therapy consists of weight control, exercise, optimization of glycaemic control, and discontinuation of tobacco use (if applicable), and a reduced fat diet. Specifically, total and saturated fat intake should be <30% and < 10%, respectively of the total calories consumed. Some children with hyperlipidaemia will require lipid-lowering drug therapy; 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) are recommended as first-line pharmacologic treatment in children with hyperlipidaemia and are approved for use in children as young as 10 years old. Clinical trials in the paediatric age group have shown safety and efficacy similar to that observed in adult studies. The addition of lipid-lowering drugs is recommended when LDL cholesterol (LDL-C) levels are >190 mg/dL (4.9 mmol/L) and in patients with LDL-C > 160 mg/dL (4.1 mmol/L) and a family history of early CVD or other risk factors. Similarly, if after 6 to 12 months of medical nutrition therapy and lifestyle changes LDL-C levels remain >130 mg/dL (3.4 mmol/L), drug therapy is indicated. Lipid-lowering medications are not recommended in pre-menarcheal girls and boys younger than 8–10 years, unless there is a particularly high risk for atherosclerosis.

Miscellaneous practical matters

Driving

Patients with diabetes have a 1.23-fold increased relative risk of accidents compared with those without diabetes, which is the same order of risk as for those with epilepsy. If a teenager with diabetes wishes to drive, the following measures are required:

- The patient needs to inform the driving authorities who may request a medical form to be completed by the patient's physician. In the United Kingdom, assuming the patient has satisfactory health, is not affected by recurrent hypoglycaemia or hypoglycaemia unawareness and has visual acuity greater than 6/9, a licence for three years may be granted.
- Before driving, blood glucose concentrations should be checked, and a long journey should be broken by frequent rests and meals with blood glucose concentrations re-measured.

• If the patient feels hypoglycaemic, the car should be stopped, the engine turned off, the keys removed from the ignition and carbohydrate consumed.
• A supply of carbohydrate-containing snacks should always be kept in the car in case of unexpected delays.

School examinations

The stress of examinations can lead to impaired blood glucose control with adverse effects on academic performance. Glycaemic control should be optimized prior to sitting an examination.

Alcohol, smoking, and recreational drug use

Adolescents with diabetes risk their health by smoking cigarettes and using recreational drugs, and should be strongly discouraged from engaging in their use. Alcohol consumption has been associated with worse glycaemic control, increases the risk for severe hypoglycaemia as a result of impaired hypoglycaemia awareness and hormonal counter-regulatory responses, and hypoglycaemia may be confused with intoxication. Adolescents with type 1 diabetes must receive counselling about the effects of alcohol and be encouraged to abstain or at least consume alcohol in moderation. They should also receive education about blood glucose monitoring and how to prevent and treat hypoglycaemia, and must understand the considerable safety risks associated with driving.

Recreational drugs can lead to sympathetic over-activity (cocaine, amphetamines), hyponatraemia (ecstasy), and hunger (marijuana), leading to increased carbohydrate intake, and may precipitate ketoacidosis. As with alcohol, it may be difficult for the patient with diabetes and others to distinguish between the effect of drugs and hypoglycaemia. Drug addiction may lead to neglect of diabetes self-care with devastating adverse effects on glycaemic control.

The following guidelines are advised:
• The importance of avoiding drinking alcohol and driving must be stressed.
• Do not drink alcohol on an empty stomach or when blood glucose is low.
• Eat while drinking or shortly afterwards.
• If drinking in the evening, before bedtime check blood glucose to ensure it is between 100 and 140 mg/dL (5.6 and 7.8 mmol/L), and eat a snack if it is below this range.
• Do not omit food from your meal plan and replace it with alcohol.
• Avoid beers with low sugar content as these tend to contain higher alcohol concentrations and may lead to hypoglycaemia.
• Limit consumption of low-alcohol beers with increased sugar content.
• Consume dry or medium wines in preference to sweet wines.
• For mixed drinks, choose sugar-free mixers (diet soda, club soda, diet tonic water, water).
• Wear an I.D. that says 'I have diabetes.'

The adverse health effects of smoking are well recognized with respect to future cancer and CVD risk. Use of tobacco considerably increases the risk of onset and progression of nephropathy and macrovascular disease. Avoiding smoking is important to prevent both microvascular and macrovascular complications. A smoking history should be elicited at the initial and follow-up visits. Youth who do not smoke should be discouraged from ever starting and those who do smoke should receive help to quit.

Sexuality and Pre-conception counselling

Hyperglycaemia at conception and in the first weeks of pregnancy increases the risk of adverse maternal and foetal outcomes, including an increased risk of congenital malformations. Counselling about contraception and avoidance of unplanned pregnancy, therefore, is of utmost importance for adolescent females with diabetes.

Most sexually active teenagers with diabetes should be advised to use condoms to protect against sexually transmitted diseases together with a combined oral contraceptive pill. Adolescents with good glycaemic control and without microvascular complications can safely use a combined oral contraceptive pill containing ≤35 μg ethinylestradiol. Before prescribing the pill, hypertension and a family history of deep vein thrombosis should be excluded. Caution should also be exercised in patients with epilepsy and liver dysfunction.

Patients with microvascular disease or risk factors for coronary artery disease can safely use progesterone-only contraception. Further advice should be sought from a gynaecologist or family planning clinic.

Should a teenager with diabetes become pregnant, her medical care should be transferred to an adult physician and an obstetrician experienced in managing pregnant women with diabetes.

Endocrine and other disorders associated with diabetes

Thyroid disease

Autoimmune thyroid disease is the most common endocrinopathy associated with type 1 diabetes, occurring in 17–30% of patients. At the time of diagnosis of type 1 diabetes, approximately 25% of patients have thyroid autoantibodies; however, thyroid autoantibodies per se are poorly predictive of thyroid dysfunction (Triolo et al. 2011). Patients may develop hypothyroidism or, less commonly, hyperthyroidism (0.5%). Subclinical hypothyroidism may be associated with an increased risk of symptomatic hypoglycaemia and with reduced linear growth. Hyperthyroidism causes deterioration of metabolic control and increased insulin requirements. Asymptomatic individuals should be screened for thyroid dysfunction *after* metabolic control has been established (owing to frequent transient abnormalities of thyroid function at the time of diabetes diagnosis) by measuring thyroid stimulating hormone, and every one or two years thereafter. Further details of the investigation and treatment of thyroid disease can be found in Chapter 6.

Addison's disease

Adrenal autoantibodies occur in 1.6–2.3% of individuals with type 1 diabetes; only 1 in 200–300, however, progresses to develop clinical adrenocortical insufficiency. The risk increases to 1 in 30 in patients with two autoimmune processes (i.e. diabetes and thyroiditis). The development of adrenocortical insufficiency in type 1 diabetes is characterized by recurrent unexplained hypoglycaemia and decreasing insulin requirements. Other classical symptoms include fatigue, hyperpigmentation of the skin and mucous membranes, weight loss, abdominal pain or presentation with an adrenal crisis during an intercurrent illness.

The diagnosis of Addison's disease is confirmed by the presence of inappropriately low circulating serum cortisol and markedly increased plasma ACTH concentration in a person with adrenal autoantibodies (anti-21-hydroxylase). Further details of other relevant investigations and of treatment with glucocorticoids and mineralocorticoids can be found in Chapter 8. Adrenal insufficiency, hypothyroidism, and type 1 diabetes (Schmidt syndrome) are manifestations of polyendocrine syndrome type II, a rare autoimmune disorder.

Coeliac disease

Biopsy-confirmed coeliac disease affects from 1.9% to 7.7% of youth with type 1 diabetes <18 years, may be present before the onset of diabetes, and is often asymptomatic. Symptoms of coeliac disease may include diarrhoea, weight loss or poor weight gain, growth failure, abdominal pain or distension, chronic fatigue, anaemia, vitamin D deficiency, malnutrition due to malabsorption, a decrease in insulin requirements and intermittent unexplained hypoglycaemia, or erratic blood glucose concentrations. Approximately 75% of cases of coeliac disease are detected within the first five years after the diagnosis of type 1 diabetes; therefore, screening should be considered soon after the diagnosis of diabetes and repeated every two to five years thereafter. Screening entails measuring serum tissue transglutaminase or anti-endomysial antibodies (document normal total serum IgA levels), followed by small bowel biopsy in antibody positive children. Recent European guidelines suggest that biopsy may not be necessary in symptomatic children with extremely high antibody titres, provided that genetic or HLA testing is supportive, but asymptomatic children at increased risk should have a biopsy.

Treatment of coeliac disease is with a gluten-free diet. The combination of a gluten-free diet and the appropriate diet for a child with diabetes places a significant burden on individuals and families. The advice of a specialist dietitian is needed as compliance may be poor.

Necrobiosis lipoidica diabeticorum

This skin disorder is characterized by collagen degeneration with a granulomatous response, thickening of blood vessel walls, and fat deposition and affects 0.3–1.2% of people with diabetes. It is uncommon in children and more likely to be seen in adolescent females. The condition usually begins as red-brown or violaceous papules or nodules and slowly progresses to yellow-brown, atrophic telangiectatic plaques (Figure 1.10). Ulceration is common (usually occurring after trauma) and lesions may become infected. The lower legs, especially the shins and area above the medial malleoli, are most commonly affected; however, the scalp, face, trunk, genitals, or upper extremities can be affected. The aetiology is unknown. The development of necrobiosis lipoidica is not influenced by glycaemic control and there is no evidence that improving control of diabetes mellitus affects its course. The classic histologic finding is a

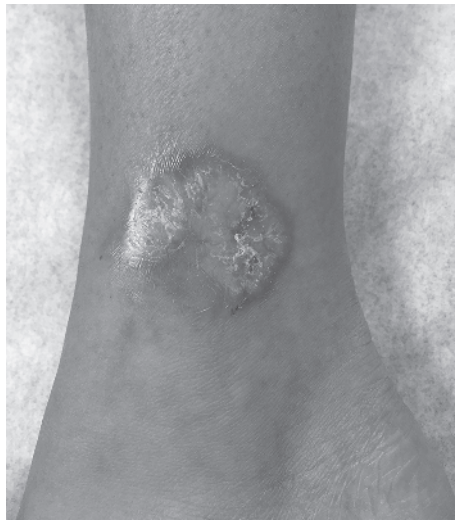

Figure 1.10 Necrobiosis lipoidica diabeticorum above the ankle.

palisaded and interstitial granulomatous dermatitis involving the dermis with extension into the subcutaneous tissue.

Numerous therapies have been used for necrobiosis lipoidica – with unsatisfactory results. Treatment should be directed by a dermatologist and focuses on managing signs and symptoms by inhibiting the inflammatory process and healing ulcerations. Non-ulcerated necrobiosis is often asymptomatic, may stabilize over time, and may not require treatment. The initial choice for non-ulcerated lesions is with a high potency topical corticosteroid applied under occlusion. If the response is unsatisfactory, the next treatment option is intra-lesional corticosteroid injections. Limited data suggest that other treatments may be useful for necrobiosis lipoidica; these include topical tacrolimus, psoralen plus ultraviolet A (PUVA) photochemotherapy, systemic medications, and procedural therapies.

Unusual causes of diabetes in childhood

Monogenic diabetes or maturity onset diabetes of the young (MODY)

Maturity onset diabetes of the young (MODY) is a form of autosomal dominant diabetes mellitus that affects approximately 1–4% of people with diabetes in different populations and typically develops before the age of 25 years. Most patients have a family history of diabetes in two or more consecutive generations. It is characterized by β-cell dysfunction of variable severity depending on the specific gene mutation. Numerous different gene mutations have been shown to cause MODY; however, three genes (*GCK, HNF1A, HNF4A*) account for ~85% of MODY cases (Hattersley et al. 2018).

Biomarker tests help to identify appropriate candidates for genetic testing. Pancreatic islet autoantibodies are negative and patients with monogenic diabetes have significant residual endogenous insulin secretion (measured as stimulated serum or urinary C-peptide), in contrast to classical type 1 diabetes in which insulin secretion usually is minimal beyond the honeymoon period. An online probability calculator (http://www.diabetesgenes.org/content/mody-probability-calculator) can aid in the identification of these individuals.

Management of the most common subtypes (GCK, HNF1A, HNF4A MODY) differs from that of type 1 diabetes as shown in Table 1.17. Identification of the gene mutation in a child with MODY confirms

Table 1.17 Common subtypes of MODY and associated clinical features.

MODY subtype	Gene	Locus	Clinical features	Treatment
1	*HNF4A*	20q12-q31.1	Macrosomia, neonatal hypoglycaemia; renal Fanconi syndrome	Sulfonylurea
2	*GCK*	7p15-p13	Mild asymptomatic hyperglycaemia	No treatment; diet and exercise
3	*HNF1A*	12q24.2	Renal glucosuria	Sulfonylurea
5	*HNF1B*	17q12	Renal developmental abnormalities, genital tract malformations	Insulin

GCK glucokinase; HNF hepatocyte nuclear factor.

whether treatment is necessary, predicts the risk of future complications, and allows for specific genetic counselling.

Neonatal diabetes mellitus

Autoimmune type 1 diabetes is exceedingly rare before age of six months. Most patients diagnosed less than six months of age have a monogenic form of neonatal diabetes and should have genetic testing. In about half the cases, neonatal diabetes is transient and remits within a few weeks or months, but in at least 50–60% of cases diabetes recurs later in life, usually during puberty.

About two-thirds of cases of transient neonatal diabetes mellitus (TNDM) are caused by over-expression of paternally expressed imprinted genes on chromosome 6q24 (paternal uniparental disomy of 6q24 [UPD6], unbalanced paternal duplication of 6q24, or loss of maternal methylation). Most of the remaining cases are caused by activating mutations (prevent closure of the beta cell ATP-sensitive potassium [K_{ATP}] channel and impair insulin secretion in response to hyperglycaemia) in either of the genes (*KCNJ11* or *ABCC8*) encoding the two subunits Kir6.2 and SUR1, respectively, of the K_{ATP} channel. Patients with 6q24 abnormalities are born with severe intrauterine growth retardation (reflecting prenatal insulin deficiency) and usually develop severe non-ketotic hyperglycaemia during the first week of life. Initial treatment consists of rehydration and a continuous IV insulin infusion; thereafter, subcutaneous insulin is introduced and, when possible, patients are best managed by subcutaneous insulin infusion (pump) therapy. Insulin treatment of TNDM may be needed for a few days to 18 months.

The most common cause of permanent neonatal diabetes mellitus (PNDM) is an activating mutation of either *KCNJ11* or *ABCC8*. Heterozygous coding mutations in the *INS* (preproinsulin) gene are the second most common cause of PNDM after K_{ATP} channel mutations. *INS* mutations cause a misfolded proinsulin molecule that is trapped in the endoplasmic reticulum (ER) leading to ER stress and ß-cell apoptosis. There are no significant differences between TNDM and PNDM regarding the severity of intrauterine growth restriction or the age at diagnosis of diabetes. Patients with K_{ATP} channel activating mutations frequently present with DKA, and 20% of patients with *KCNJ11* mutations have associated neurological features, referred to as DEND (developmental delay, epilepsy, diabetes mellitus) syndrome. Approximately 90% of patients with activating mutations in the K_{ATP} channel genes can be successfully switched from insulin to oral sulfonylureas (typical dose of glyburide/glibenclamide ~0.5 mg/kg day, but higher doses may be required).

Diabetes following pancreatectomy for persistent hyperinsulinemic hypoglycaemia of infancy

Infants with severe persistent hyperinsulinaemic hypoglycaemia caused by diffuse disease that is unresponsive to medical treatment often require near-total (95–98%) pancreatectomy to control hypoglycaemia (see Chapter 2 on Hypoglycaemia). A high proportion of these patients will eventually develop diabetes and require insulin treatment. The rate of progression to insulin dependence, however, varies from several months to 14 years or more after surgery.

Cystic fibrosis-related diabetes (CFRD)

Cystic fibrosis-related diabetes (CFRD) is the most common complication of CF in individuals of school age and older. The prevalence of CFRD increases with age from 2% in children ≤10 years of age to 40% in individuals 18–29 years. CFRD is caused by insulin deficiency resulting from slowly progressive destruction of pancreatic islets, and is a distinct form of diabetes mellitus different from either type 1 or type 2 diabetes. Insulin resistance caused by inflammatory cytokines and catecholamines plays a role in its pathogenesis, especially when there are acute exacerbations of pulmonary disease. Glucagon secretion is reduced and DKA is rare.

Development of CFRD is associated with deterioration of lung function and nutritional status, more frequent lung infections, and decreased survival. Insulin treatment can ameliorate these effects. Early diagnosis and treatment, therefore, are crucial to prevent morbidity. Annual screening with an OGTT at a time of baseline health is recommended beginning by age 10 years. In addition, fasting and postprandial blood glucose screening are suggested with acute pulmonary exacerbations. In patients receiving enteral tube feedings, blood glucose should be measured at the midpoint and immediately after a feed. HbA1c should not be used for screening because it is often normal despite hyperglycaemia and has low sensitivity for detecting CFRD.

Treatment consists of insulin therapy, which has beneficial effects on nutritional state, improves pulmonary function and survival, but adds substantially to the burden of CF treatment. The specific insulin

regimen varies according to individual patient characteristics and preferences, responses, and dietary strategies. It should eliminate the catabolic state of CFRD, minimize postprandial hyperglycaemia while avoiding hypoglycaemia, and maintain HbA1c as low as possible. Although HbA1c is not recommended for screening, it is useful for monitoring glycaemic control. Patients with CF benefit from increased caloric intake, including calorie-rich beverages. Patients on insulin therapy should perform SMBG at least three times a day, and HbA1c should be measured every three months. The insulin regimen is adjusted to achieve targets and to ensure weight gain. Annual screening for microvascular complications should be performed, beginning five years after diagnosis.

Miscellaneous disorders

Diabetes is associated with numerous other disorders including Down syndrome, Turner syndrome, Klinefelter syndrome, Prader–Willi syndrome, Wolfram syndrome (diabetes insipidus, diabetes mellitus, optic atrophy, and deafness [DIDMOAD]), asparaginase and glucocorticoid treatment, thalassaemia, and the autoimmune polyendocrine syndromes.

Audit and benchmarking

Auditing and benchmarking against regional, national, or international standards is a valuable method to improve the quality of a diabetes service. A register of all patients is essential to allow auditing and benchmarking to take place. Several aspects of diabetes care can be audited including:

- the adequacy of management of newly diagnosed patients
- HbA1c concentrations;
- evidence of normal growth, weight gain, and puberty;
- frequency of follow-up in the clinic;
- frequency of DKA and severe hypoglycaemia in established patients;
- screening for co-morbidities;
- the incidence of complications;
- patient education;
- patients' satisfaction with the service.

Future developments

- Early diagnosis through genetic and immunological screening of high-risk children and, possibly, in the general population.
- Therapy to arrest progression of beta cell destruction and development of clinical diabetes.
- Immunomodulation in new onset diabetes to preserve or enhance residual insulin secretion.
- Non-invasive methods of accurate glucose monitoring.
- Closed loop insulin delivery systems ('artificial pancreas').
- More rapidly absorbed rapid-acting insulin analogues.
- Approval of medications (e.g. glucagon-like peptide analogues, DPP IV inhibitors, SGLT2, and combined SGLT1/2 inhibitors, etc.) currently used in adults, for treatment of type 2 diabetes in youth.
- The development of stem cell therapy to generate a potentially limitless source of genetically modified, artificially cultured pancreatic β-cells suitable for transplantation.

Controversial points

- Should a new patient with diabetes, but without DKA, be treated in hospital or in an ambulatory setting?
- What are the indications for starting insulin pump therapy?
- What effects do hyperglycaemia and hypoglycaemia have on brain development in preschool-aged children?
- How can the biochemical goals established after the DCCT be achieved in routine clinical practice?
- In adolescents, what is the role of ACE inhibitors in diabetic nephropathy and statins in those with dyslipidaemia?
- What is the role of psychological support and motivational interviewing in helping children and adolescents to improve their glycaemic control and well-being?
- What are the optimal fluid composition and rate of fluid administration to treat DKA?
- What causes cerebral oedema in DKA and how to prevent it?
- Should mannitol or hypertonic saline be used as first-line treatment for cerebral oedema?
- When should adolescents transition to adult care and how to design an effective paediatric to adult diabetes care transition programme?

Potential pitfalls

- Failure to realize that the blood glucose values in a patient's logbook are fictitious (may all be written in the same pen, may not be consistent with the HbA1c result).

- Recommending insulin doses in excess of 1.5 units/kg per day in a patient with a persistently high HbA1c when the most likely explanation is poor compliance and omission of injections or failure to bolus when using a pump.
- Failure to diagnose psychological/psychiatric problems, especially in adolescents, which may account for suboptimal or poor glycaemic control.
- Errors in fluid calculations during therapy of DKA.
- Stopping the insulin infusion during therapy for DKA when hypoglycaemia occurs.
- Inappropriately advising the omission of insulin because the child is ill and not eating, thus increasing the risk of DKA.
- Failure to identify early signs of retinopathy when using direct ophthalmoscopy.
- Losing track of patients, frequently adolescents, who repeatedly fail to attend clinic (more likely to occur if the clinic does not maintain a patient register).
- Failure to consider Addison's disease or coeliac disease as a possible cause for decreasing insulin requirements when the patient is beyond the 'honeymoon period'.
- Failure to distinguish between type 1 and type 2 diabetes, resulting in inappropriate therapy.
- Failure to diagnose MODY in a patient with a suggestive family history or in patients with de novo mutations.

Case histories

Case 1.1

A 14-year-old girl weighs 50 kg, has had recurrent severe hypoglycaemia with two episodes leading to a convulsion and hospital admission. She was diagnosed with type 1 diabetes at nine years of age and is using a basal-bolus insulin regimen with 18 units insulin glargine at 9 p.m. (~40% of the average TDD of 45 units or 0.9 units/kg per day) and pre-meal rapid-acting insulin aspart (1 unit per 10 g carbohydrate) three times daily. There have not been any recent changes in her diet or level of physical activity.

Questions and Answers

1 What investigations would you consider doing?

Measurement of HbA1c concentration to assess overall glycaemic control, thyroid function tests to exclude hypothyroidism, screening serologic tests (tissue transglutaminase and/or anti-endomysial antibody or deamidated gliadin titres) to exclude coeliac disease. Measurement of 21-hydroxylase (anti-adrenal autoantibody) titres, measurement of 8A.M. serum cortisol and plasma ACTH concentrations and consideration of a cosyntropin (Cortrosyn or Synacthen) stimulation test, if the latter are suspicious for adrenal insufficiency, to rule out Addison's disease.

2 If the results of these investigations are normal, what further explanations could account for her recurrent hypoglycaemia?

Self-administration of high doses of insulin. This adolescent girl was not coping with her diabetes and the recurrent hypoglycaemic episodes were 'a cry for help'. The episodes stopped following a referral and advice from the child psychiatry service.

Case 1.2

A 15-year-old boy has had type 1 diabetes for five years, frequently failed to attend diabetes clinic appointments and now presents with short stature and delayed puberty. He was receiving two insulin injections daily: 24 units in the morning before breakfast (mixed insulin with a ratio of short-to intermediate-acting insulin of 30:70) and 12 units in the evening; TDD 0.7 units/kg per day. His height had decreased from the 25th to the 2nd centile since diagnosis and his weight was on the 2nd centile. He had Tanner stage 2 pubic hair and the volume of his testes was 4 ml. His HbA1c concentration was 12.4%.

Questions and Answers

1 How would you investigate this patient?

Detailed dietary assessment and measurement of thyroid function tests and screening for coeliac disease.

2 How would you manage this patient?

The patient has delayed onset of puberty, which is likely to have contributed to his slow growth velocity. The dietary assessment revealed a low calorie intake and the results of his tests for

hypothyroidism and coeliac disease were normal. There had been little change in his diet or insulin dosage since diagnosis. Poor glycaemic control because of an inadequate dosage of insulin and an inadequate dietary intake is the most likely cause for his delayed puberty and short stature. Therefore, he should be advised to increase his dietary intake and significantly increase his daily dosage of insulin (and consider switching to a multiple daily dose insulin regimen) in an effort to improve glycaemic control. If this proves successful, this is likely to stimulate further progression of puberty and the pubertal growth spurt.

Case 1.3

A 15-year-old white youth presented with a 6-week history of polyuria and polydipsia. His father was found to have non-insulin-dependent (type 2) diabetes at the age of 24 years, which was controlled by diet. His paternal grandfather had developed type 2 diabetes at 48 years of age, controlled by diet and an oral sulfonylurea. On examination, his body mass index was 22.4 kg/m^2, he was not dehydrated and appeared well. His blood glucose was 14 mmol/L (252 mg/dL). He had glycosuria but no ketonuria.

Questions and Answers

1 What is the likely diagnosis?

The most likely diagnosis is MODY. Because hyperglycaemia in MODY may be mild and asymptomatic, the age of diagnosis can be considerably later than the age of onset, which is the likely explanation for the late age of diagnosis in the father and grandfather.

2 How would you investigate this boy?

By screening of genes, mutations of which are known to cause MODY. This patient was found to have a mutation of the glucokinase gene (MODY2).

3 Why is it important to establish a precise diagnosis?

The patient can be reassured that he is extremely unlikely to experience complications from his MODY, and he and his family can be counselled about the autosomal dominant inheritance of MODY.

Case 1.4

A three-year-old girl presents for the first time with type 1 diabetes in DKA. She is severely dehydrated and acidotic with a venous pH of 7.08. She is resuscitated in accordance with the local DKA protocol and improves. However, 11 hours after admission she becomes irritable and more difficult to communicate with. She vomits once. The nurse looking after her notes that her heart rate has dropped from 120/min. to 88 min.

Questions and Answers

1 What is the most likely reason for this change in her condition?

The likeliest explanation is that she has developed the complication of cerebral oedema. This can be present at diagnosis but usually presents 4–12 hours after treatment has commenced. A headache (which in this girl may have been the cause of her irritability) and a decrease in the pulse rate of > 20/min (which cannot be explained by sleep or an improvement in the intravascular volume) are important features of cerebral oedema.

2 What immediate investigation should be done?

Measure blood glucose concentration to rule out hypoglycaemia as the cause of her altered behaviour. At a later stage, a CT scan *may* be required to rule out other intracerebral complications such as a thrombosis or a haemorrhage.

3 What should be the management?

A senior paediatrician and anaesthetist should be called urgently. Mannitol (0.5–1 gram per kg IV over 10–15 minutes) or hypertonic (3%) saline (2.5–5 ml per kg over 10–15 minutes) should be given immediately. The patient should be nursed in a 30° head-up position to help venous drainage. If not already in a paediatric intensive care unit, the child should be transferred there as soon as is safely possible. She is likely to require intubation and ventilation.

Case 1.5

A 14-year-old Asian girl presents with a six-week history of polyuria, polydipsia, and a 5-kg weight loss. Her grandfather had developed diabetes when he was in his fifties and takes tablets. On examination, she appears overweight and her BMI is 29 kg/m^{2,} which is between the 98th and 99.6 percentiles. She has pink stretch marks on her abdomen and acanthosis nigricans on the nape of her neck. Her blood glucose is 26 mmol/L (468 mg/dL). She is not acidotic but her urinalysis shows 3+ glucosuria and moderate ketonuria.

Questions and Answers

1 What is the likely diagnosis?

The most likely diagnosis is type 2 diabetes mellitus. She belongs to a high-risk ethnic group, has a family history, acanthosis nigricans, and her BMI centile places her in the obese category. Pink stretch marks can occur in anyone who is obese. The ketonuria is not unusual; occurs in many patients with paediatric type 2 diabetes. In some cases, especially in a patient such as this where there has been weight loss and ketonuria, it can be difficult to distinguish between type 1 and type 2 diabetes.

2 What investigations would help clarify the precise diagnosis?

Measuring pancreatic autoantibodies (islet cell, GAD, IA-2, insulin, ZnT8 antibodies) would help to clarify whether she is an obese girl with type 1 diabetes or has type 2 diabetes. Pancreatic autoantibodies would be negative in type 2 diabetes. Measuring C-peptide, which reflects the amount of insulin that the patient is producing, may also be useful. C-peptide measurement will be most informative after the patient has been treated for a few weeks and metabolic control has been established to minimize the impact of glucose toxicity on beta cell function. C-peptide levels would be normal or increased in type 2 diabetes but low in type 1 diabetes.

3 What treatment should be commenced?

Although this patient is likely to have type 2 diabetes, there is a possibility that she may have type 1. Some patients fall into a grey area between type 1 and type 2 diabetes, i.e. they have features of both types of diabetes. The results of the investigations listed in Answer 2 are likely to take several weeks. In view of this, the high blood glucose level and ketosis, it would be advisable to start this patient on a basal-bolus insulin regimen. Dietary treatment and an exercise regimen are also very important. When the ketosis has resolved, the patient is well hydrated, and the blood glucose has decreased to near normal levels, metformin should be gradually introduced with the aim of increasing the dose of metformin, decreasing the insulin dosages, and eventually, hopefully, treating the patient with metformin alone.

Significant Guidelines/Consensus Statements

American Diabetes Association (2018a). 2. Classification and diagnosis of diabetes: standards of medical care in diabetes – 2018. *Diabetes Care* 41 (Suppl. 1): S13–S27.

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