1 Diabetes Mellitus

Definition

Diabetes is diagnosed in the presence of either a blood glucose concentration of >11.1 mmol/L (200 mg/dL) or a fasting glucose concentration of >7 mmol/L (126 mg/dL). A fasting blood glucose level of 5.6–6.9 mmol/L (100–125 mg/dL) is considered prediabetes, while a level < 5.6 mmol/L (<100 mg/dL) is normal. The diagnosis of diabetes, when symptoms are present, is usually straightforward and a glucose tolerance test is rarely needed. Glucose tolerance testing may be indicated following the identification of a borderline blood glucose concentration (e.g. in the sibling of a child with diabetes, or in children with disorders such as cystic fibrosis which predispose to diabetes and which, in the early stages, may be asymptomatic). The protocol for and interpretation of results from an oral glucose tolerance test is shown in Table 1.1.

Diabetes is a heterogeneous condition which may be classified on the basis of pathogenesis (Table 1.2). Most of this chapter focuses on type 1 diabetes, which is by far the most common form of diabetes in children. Other causes of diabetes are discussed on p. 30 and 35.

Incidence

The incidence of type 1 diabetes in children (0–18 years) is approximately 20/100,000 in the United Kingdom (prevalence 1 in 500), but varies from 0.6/100,000 in China to 42.9/100,000 in Finland. 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 USA, white people have a higher incidence than non-whites). There is a family history of type 1 diabetes in 10% of cases. The risk of

Practical Endocrinology and Diabetes in Children, Third Edition. Joseph E. Raine, Malcolm D.C. Donaldson, John W. Gregory, Guy Van Vliet.
 Published 2011 by Blackwell Publishing Ltd.

Table 1.1 Protocol for 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 an overnight fast

Procedure
1. Pre test—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 minutes)
3. +2 hours—plasma glucose sample

Interpretation
1. Fasting plasma glucose $\geq$ 7.0 mmol/L (126 mg/dL) or 2 h concentration $\geq$ 11.1 mmol/L (200 mg/dL) are diagnostic of diabetes
2. 2 h plasma glucose concentration $\geq$ 7.8 mmol/L (140 mg/dL) and $<$ 11.1 mmol/L (200 mg/dL) suggests impaired glucose tolerance
3. Fasting plasma glucose 6.1–6.9 mmol/L (110–125 mg/dL) suggests impaired fasting glycaemia

developing type 1 diabetes for an individual with an affected relative is outlined in Table 1.3. If a twin develops type 1 diabetes the lifetime risk to a non-affected monozygotic twin is approximately 60%, whereas that for a dizygotic twin is 8%. Environmental effects are probably important as the incidence rises in the winter months. The incidence of type 1 diabetes in children is set to rise over the next 10 years in Europe, especially in those under 5 years of age. Currently, the peak incidence occurs in those aged 11–14 years.

Table 1.2 The American Diabetes Association Classification of Diabetes.

Type 1 Immune-mediated and idiopathic forms of β-cell dysfunction which lead to absolute insulin deficiency

Type 2 A disease of adult or occasionally adolescent onset ranging from predominantly insulin resistance with relative insulin deficiency to predominantly an insulin secretory defect with insulin resistance

Other specific types of diabetes
Includes a wide range of specific types of diabetes including the various genetic defects of β-cell function, genetic defects in insulin action and diseases of the exocrine pancreas (e.g. cystic fibrosis)

Gestational diabetes mellitus
Impaired glucose tolerance and impaired fasting glucose

Table 1.3 The risk of developing type 1 diabetes for an individual with an affected relative.

Relative with type 1 diabetes	Risk to individual (%)
Sibling	8
Mother	2–3
Father	5–6
Both parents	30

Aetiology and pathogenesis

The precise cause of type 1 diabetes is unknown but there are a number of possible contributory factors.

Autoimmune

Several autoantibodies have been identified in newly diagnosed cases of type 1 diabetes and there is some evidence that this process starts as early as 6–12 months of age. These include islet cell antibodies (60–90% of new patients), glutamic acid decarboxylase antibodies (65–80%) and insulin antibodies (30–40%). Type 1 diabetes is also associated with other autoimmune disorders such as Hashimoto's and Graves' disease (3–5%), coeliac disease (2–5%) and Addison's disease (<1%). Some patients with type 1 diabetes have a negative autoantibody profile.

Genetic

Numerous susceptibility loci—genes that predispose to type 1 diabetes—have been found. The most important loci are located in the major histocompatibility complex (MHC) region on the short arm of chromosome 6, which contains genes that regulate the immune response. For example, the presence of DR3 and DR4 are associated with a high risk of developing diabetes. The homozygous absence of an aspartate residue at position 57 on the DQB chain leads to an approximate 100-fold increase in the risk of developing type 1 diabetes. Conversely, there are also protective alleles such as DRB1*1501 and DQB1*0602. Genetic factors play a greater part in the aetiology of type 1 diabetes in children diagnosed under the age of 5 years. The risk of a sibling developing diabetes is therefore higher in this group, being 12% by the age of 20 years.

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Genetic and autoimmune markers have been used in research studies to try and predict the risk of siblings of patients with type 1 diabetes developing the disease.

Viral

Epidemics of viral infections and the autumn and winter months are associated with an increase in the incidence of diabetes. Several viruses (e.g. coxsackie B, enteroviruses, rubella virus, mumps virus and cytomegalovirus) have been implicated in the aetiology of type 1 diabetes. Possible mechanisms for their effect include molecular mimicry in which the immune response to the infection cross-reacts with islet antigens. Alternatively, viral infections, including those occurring antenatally, may have more direct effects on peri-insular or β-cells.

Nutritional

Breastfeeding seems to provide protection against the risk of developing type 1 diabetes. Whether this is a direct effect of breast milk or is related to the delayed introduction of cow's milk is unclear. Many new patients with type 1 diabetes have IgG antibodies to bovine serum albumin, a protein in cow's milk with similarities to the islet cell antigen. This protein may stimulate autoantibody production leading to islet cell destruction as a result of molecular mimicry.

Chemical toxins

Ingestion of the rodenticide vacor is associated with the development of type 1 diabetes.

Stress

Prior to the onset of type 1 diabetes, adults have been shown to experience more 'severe life events' than a control group. The cause for this effect is unclear but may relate to stress-induced impairment of resistance to infection in genetically susceptible individuals.

Biochemistry (Figure 1.1)

Insulin is an anabolic hormone with a key role in glucose metabolism and important effects on fat and protein metabolism. Following a meal, circulating concentrations of insulin rise, facilitating the entry of glucose into cells via glucose-specific transporters, particularly in the muscles and adipose tissue. Insulin stimulates glycogen synthesis in the liver and muscle, inhibits gluconeogenesis in the liver, and stimulates fat and protein synthesis. Conversely, during fasting, glucose concentrations and insulin secretion fall leading to absence of glucose uptake in muscle and adipose tissue, with stimulation of glycogenolysis in the liver and muscles and hepatic gluconeogenesis (from amino acids and ketones).

In subjects with type 1 diabetes, insulin deficiency results in hyperglycaemia which, when the renal threshold for glucose is exceeded, leads to an osmotic diuresis causing polyuria and secondary polydipsia. When fluid losses exceed intake, particularly when vomiting is also occurring, dehydration develops. Insulin deficiency also causes lipolysis with the production of excess free fatty acids and ketone bodies (3-hydroxybutyrate and acetoacetate) leading to ketonuria. The accumulation of ketoacids in the blood causes a metabolic acidosis which results in compensatory rapid, deep breathing (Kussmaul respiration). Acetone, formed from acetoacetate, is responsible for the sweet smell of the breath. Furthermore, there is an increase in stress hormone (glucagon, adrenaline, cortisol and growth hormone) production which, because of their effects on metabolism, leads to a further rise in blood glucose and other intermediary metabolite concentrations. Progressive dehydration, acidosis and hyperosmolality cause decreased consciousness and, if untreated, can lead to coma and death.

Clinical presentation

History

At diagnosis, the following symptoms may have been present from 1 week to 6 months:

- Polyuria (may cause nocturnal enuresis)
- Polydipsia
- Weight loss
- Anorexia or hyperphagia
- Lethargy
- Constipation
- Infection (especially candidal skin infections)
- Blurred vision
- Hypoglycaemia (rare, probably represents islet cell instability in the early stages of diabetes)

Although most school-aged children will report polyuria and polydipsia, these symptoms may be less obvious in the very young child who may be relatively asymptomatic (e.g. polyuria will be less obvious in an infant in nappies) in whom the other less characteristic symptoms may predominate.

Patients with diabetic ketoacidosis (DKA) may also have:

- vomiting;
- abdominal pain; and
- symptoms of systemic infection.

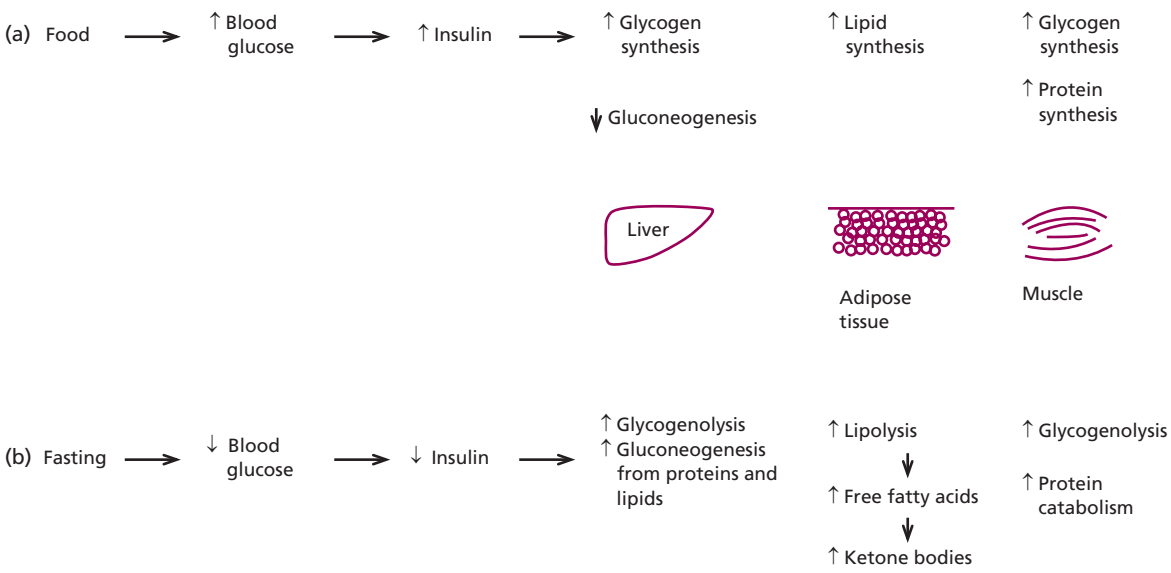

Fig. 1.1 Glucose homeostasis—a comparison of (a) fed state and (b) fasting state.

Examination

At diagnosis, most (approximately 75%) patients will not have DKA. These individuals may only have evidence of weight loss or, possibly, candidal skin infection. Patients with DKA may demonstrate the following:

- *Dehydration:*
  - 5%—dry mucous membranes, decreased skin turgor
  - 10%—sunken eyes, poor capillary return
  - >10%—hypovolaemia, tachycardia with thready pulse, hypotension
- Sweet smelling breath
- Kussmaul breathing (tachypnoea with hyperventilation)
- Depressed consciousness/coma
- Signs of sepsis (fever is not a feature of DKA and suggests sepsis)
- Ileus
- Signs of cerebral oedema (e.g. deteriorating level of consciousness)

Children less than 5 years old are more likely to present with DKA partly as a result of their clinical presentation not having been recognized by health professionals as being compatible with diabetes, leading to a delay in diagnosis and referral to hospital. Other factors that increase the risk of presenting with DKA include low socioeconomic status, medication with high dose steroids and the absence of a first degree relative with type 1 diabetes. Children diagnosed with diabetes should be referred to hospital on the same day.

Differential diagnosis

In the vast majority of cases the diagnosis of type 1 diabetes is obvious because of the presence of the classical symptoms of polyuria, polydipsia and weight loss, associated with a random blood glucose >11 mmol/L (200 mg/dL) and glycosuria with or without ketonuria. Diabetes should be considered in the differential diagnosis of any child presenting with impaired consciousness and/or acidosis.

Tachypnoea and hyperventilation in DKA may lead to the erroneous diagnosis of pneumonia. However, the lack of a cough or wheeze and the absence of abnormal findings on auscultation and/or a normal chest radiograph should raise the possibility of an alternative diagnosis such as diabetes. Abdominal pain and tenderness in DKA may suggest a surgical emergency such as appendicitis. However, appropriate fluid, insulin and electrolyte therapy will usually ameliorate the abdominal symptoms within hours. Diabetes should also be considered as a possible diagnosis in children with secondary nocturnal enuresis.

Acute illnesses, for example severe sepsis or a prolonged convulsion, may occasionally cause hyperglycaemia, glycosuria and ketonuria. However, these features are almost always transient and are rarely associated with previous

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polydipsia and polyuria. If in doubt, a fasting blood glucose or oral glucose tolerance test (Table 1.1) should be performed.

A family doctor who suspects or has made a definitive diagnosis of diabetes should refer the child promptly to a paediatrician. Children should be assessed on the day of referral or, if not unwell and in the absence of signs of DKA, the following day.

Investigations

At diagnosis, it is advisable to perform the following investigations:

- Plasma glucose concentration.
- Venous blood gas measurement (venous blood has a very similar pH and pCO_2 to arterial blood).
- Serum electrolytes, urea and creatinine concentrations (sodium and potassium measurements from the blood gas machine give provisional figures till the laboratory values are back).
- Full blood count (FBC) (leukocytosis, and a raised CRP, are common in DKA and do not necessarily mean that infection is present; an increased haematocrit will reflect the degree of extracellular fluid loss).
- A minority of children will have signs of sepsis and need appropriate investigations (e.g. blood culture, chest radiograph, urine microscopy and culture).
- Thyroid function tests (TFTs) and coeliac antibodies (to monitor these associated conditions).

At diagnosis, most patients have ketonuria but the presence of an abnormally low pH (i.e. venous pH$<$7.30) is suggestive of DKA.

Management of the child presenting without ketoacidosis

Hospitalization vs. outpatient (home) treatment

Hospital admission is necessary if intravenous (IV) therapy is required to correct dehydration, electrolyte imbalance and ketoacidosis, or if there are psychosocial difficulties. Children who are $\leq$ 5% dehydrated, not nauseas or vomiting, who are not particularly unwell and who have a pH $\geq$7.30 usually tolerate subcutaneous insulin and oral rehydration. Whether such a child with newly diagnosed diabetes can be treated at home will depend primarily on the availability of 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. The size of the geographical area that needs to be covered is also a factor. The advantages of home treatment include giving the family more confidence in dealing with diabetes at home, a more comforting environment, and less disruption and financial cost to the family. There is also some evidence that home treatment is cheaper, reduces subsequent readmissions and improves glycaemic control. The disadvantages include the risk of complications such as hypoglycaemia, which may occur before the family are sufficiently experienced to cope with it. To avoid this, home-managed children are often started on a dose of insulin of slightly less than 0.5 units/kg per 24 hours with the dose gradually being increased over the next few weeks according to the blood glucose concentrations. Some families prefer the security of being in hospital.

Many centres also offer the alternative of ambulatory care and provide diabetes education and training in a day care unit for several days following diagnosis.

Main topics for discussion following diagnosis

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

- Their pre-existing knowledge of diabetes.
- Our 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 their care.
- The role of insulin in type 1 diabetes management.
- Practical details of insulin injections.
- Practical details regarding when and how to monitor and interpret blood glucose concentrations.
- Appropriate dietetic advice (see section 'Diet').
- The effect of exercise on carbohydrate and insulin requirements.
- The causes and consequences of hypoglycaemia and how to treat it.
- When and how to measure blood or urinary ketone concentrations.
- Management of diabetes during intercurrent illness.
- The 'honeymoon period' of relatively 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 carrying identification (e.g. medical bracelets, etc.) indicating that the individual has diabetes.
- Additional sources of information about diabetes.
- Availability of support groups.
- Sources and entitlement to financial aid.
- Future developments.

Diet

In view of the important effects of diet on glycaemic control and other longer term adverse effects of diabetes, a newly diagnosed patient and their family should be referred to a dietitian who specializes in childhood diabetes within days of diagnosis. Several education sessions with the dietitian, preferably as part of the family's visit to the diabetes outpatient clinic, are usually required in the first weeks following diagnosis.

Principles of diet

Children should be encouraged to eat regular meals containing complex carbohydrates (e.g. potatoes and cereals), to reduce their intake of refined sugars, fats and salt, and to increase their dietary fibre content. The advice should be tailored to the patient's lifestyle and, where possible, should avoid drastic changes. No particular food should be considered forbidden as this may lead to disturbed attitudes to food. Furthermore, to deprive children of some foods such as sweets, which their friends consume regularly, may be psychologically damaging. Foods with high sugar content can be taken before exercise, incorporated into a main meal or used as a source of energy during illness when children have a poor appetite.

Dietary compliance may be improved if the whole family can make similar dietary modifications and the concept of a 'healthy' diet should be encouraged. Families should also be educated about the dietary treatment of the child experiencing hypoglycaemia or intercurrent illness and dietary management during parties and holidays.

Timing of meals and snacks

Children receiving twice daily injections of combined rapid- and intermediate-acting insulin require three main meals at regular intervals and usually also need a bedtime snack as a precaution against nocturnal hypoglycaemia. Occasionally, extra snacks are required if there are significant delays with meal times or if the child has only eaten a small proportion of a main meal. Preschool-aged children may have unpredictable eating habits and may require frequent, small meals.

Those on a basal bolus regimen with a long-acting insulin analogue such as glargine or detemir should not require a bedtime snack though one may wish to give this snack for the first few weeks following the commencement of that regimen. Children on a basal bolus regimen or continuous subcutaneous insulin infusion (CSII) need to have the ability to adjust the dose of their bolus rapidly-acting insulin in line with their carbohydrate intake.

Dietary composition

Caloric intake does not need to be calculated or altered unless the child is over- or underweight. It is recommended that approximately 35% of dietary energy intake should be derived from fat (mainly mono- and polyunsaturated fats), 15% from protein and 50% from carbohydrate.

There are several approaches to the dietetic management of diabetes:

1 Children can be encouraged to choose a certain number of carbohydrate-containing foods ('portions') from a list of such foods, at each meal and snack.

2 Food intake is based on the principles of a normal healthy diet.

3 In the past, families were taught about the carbohydrate exchange system in which 10 g of carbohydrate was equivalent to one exchange and meals were calculated on the basis of the number of 'exchanges' required. Because of uncertainties about the precise carbohydrate content of food and its physiological effects, dietary education on the basis of the carbohydrate exchange system was to a large extent abandoned in the 1990s. However, recently there has been renewed interest and emphasis in a quantitative rather than a qualitative approach to diet in diabetes management. In fact, so-called carbohydrate counting has now become standard for all patients on basal bolus and CSII regimens. A dietary regimen called Dose Adjustment For Normal Eating (DAFNE) has been introduced in many centres for the management of adults with diabetes. Modified schemes for children are also used in many hospitals. Computerized nutritional weighing scales can facilitate this process. The food is weighed, the nature of the food inputted and the carbohydrate content of the food is calculated by the computer. Various books are also available with information on the carbohydrate content of different foods. Detailed education is given on the carbohydrate content of food and the dose of rapidly-acting insulin required for a set amount of carbohydrate.

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Most prepubertal children are started on 0.5 units of rapidly-acting insulin for every 10 g and most pubertal children on 1 unit of rapidly-acting insulin per 10 g of carbohydrate. However, these ratios can change and pubertal children in particular may need much higher doses of rapidly-acting insulin, sometimes up to 3 units per 10 g of carbohydrate. In children on insulin pump therapy, the '500 rule' is usually used to calculate the amount of carbohydrate (in grams) for every 1 unit of rapidly-acting insulin. This is worked out by dividing 500 by the total daily dose (TDD) of insulin and this provides the number of grams of carbohydrate covered by 1 unit of rapidly-acting insulin. For example, if the TDD of insulin is 25 units, then we get $500/25 = 20$. Therefore, 20 g of carbohydrate will be covered by 1 unit of rapidly-acting insulin. This is equivalent to saying that 0.5 unit of rapidly-acting insulin should be given for every 10 g of carbohydrate.

A more liberal diet is permissible with this approach with multiple insulin boluses being given in line with the carbohydrate intake. It is common for pubertal children, who often have a large appetite, to have a snack on return from school and a bolus of rapidly-acting insulin can be given with this frequently large snack. Good control has been achieved with these regimens, which is partly due to improved dietary management and the additional education involved when commencing these regimens. An improved quality of life has also been associated with these regimens.

There is a risk of unwanted weight gain with basal bolus and CSII regimens and the diet should be closely supervised in these patients. Weight gain can be due to glucose calories no longer being lost in the urine as glycaemic control improves. These regimens can also be associated with an increased frequency of hypoglycaemia which may lead to more food being eaten to counteract it. There may also be excessive eating of desserts and sweets, as confidence in carbohydrate counting grows. Weight gain can also occur if the fat content of food is not considered or if patients eat more high-calorie foods and larger portions.

When carbohydrate counting, one should also be aware of the glycaemic index (GI) of food. Low-GI foods will lead to a slow and gradual absorption of carbohydrates whereas high-GI foods will lead to fast carbohydrate absorption and a rise in blood glucose. The amount of fat, protein and fibre in food will influence the GI and carbohydrate absorption. For example, the greater the amount of fat, the slower the absorption.

The numerous commercially available 'diabetic foods' are not generally 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. Diabetic foods may also have a high calorie and fat content. Non-alcoholic drinks containing sugar should be replaced with those containing artificial sweeteners.

Insulin therapy

A number of different insulin regimens are available. It is important to be flexible when choosing an insulin regimen and to bear in mind the families' needs and wishes. The initial insulin regimen may require changing if glycaemic control is poor or if there are practical difficulties. Following diagnosis, most children will require approximately 0.5 units of insulin per kilogram body weight daily although this may decrease substantially during the first few months of therapy (occasionally to the point where patients may be transiently, completely weaned off insulin) during the so-called 'honeymoon period'. This period, which represents partial recovery of the existing β-cell mass, may last from a few months up to 2 years. Parents should be warned that insulin requirements will increase significantly at the end of the 'honeymoon period'.

For most children, a basal bolus regimen is most appropriate. Basal bolus regimens comprise injections of rapidly-acting insulin prior to each main meal with an injection of a long-acting insulin analogue prior to bedtime. The latter provides a basal 'peakless' level of insulin for up to 24 hours (Table 1.9). There is also some evidence that nocturnal hypoglycaemia is less common with the long-acting insulin analogues as compared to isophane. Normally, approximately 40% of the TDD of insulin is given at bedtime as a long-acting insulin analogue (glargine is usually given at bedtime but as it lasts for 24 hours it can be given at any time of day and in some children is given at breakfast time, detemir is usually given at bedtime but can be given at breakfast time or occasionally is required both at bedtime and breakfast time). The remaining insulin is given as rapidly-acting insulin and is split between the pre-breakfast, lunch and evening meal injections. Carbohydrate counting and correction doses determine the precise amount of insulin given with each meal. The correction dose is calculated by dividing 100 by the TDD. One unit of rapidly acting insulin will decrease the glucose level by approximately 100/TDD. The correction dose is usually used to normalise an abnormally raised glucose level, typically to 6–8 mmol/L.

Basal bolus regimens allow flexibility with regard to the timing and size of meals, and are popular with teenagers as they lead to greater independence. In those children who are on a ratio of 1 unit or less of rapidly-acting insulin to every 10 g of carbohydrate, a carbohydrate snack of up to

15 g can be ingested without a bolus. However, in those on an insulin to carbohydrate ratio of >1 unit: 10 g, an insulin bolus may be required with carbohydrate snacks of <15 g. In children reluctant to administer a pre-lunch injection at school or in whom there are difficulties with a full basal bolus regimen, an intermediate solution is to give mixed insulin before breakfast, rapidly-acting insulin prior to the evening meal and intermediate-acting insulin (isophane) prior to bedtime.

Possible alternative regimens in children under 4 years of age include a CSII, once daily glargine/detemir or isophane before breakfast, once daily glargine/detemir or isophane before breakfast with rapidly-acting insulin prior to the evening meal, twice daily isophane and twice daily mixed insulin with approximately 70% of the TDD being given at breakfast time.

In older children the use of twice daily injections, using a mixture of rapidly-acting and intermediate-acting insulin most commonly in a ratio of 25–30%:70–75% with approximately 70% of the TDD being given at breakfast time is also a possible alternative which can provide good control, especially in the first year of treatment during the 'honeymoon period'. CSIIs are a further alternative.

Although hypoglycaemic episodes are unusual in newly diagnosed patients, care should be taken to avoid these in children treated at home until the family have had the appropriate training. Children initially treated in hospital are less active than at home and most will experience a fall in their blood glucose following discharge.

It has been suggested that aggressive insulin therapy to achieve early onset of normoglycaemia may help maintain residual β-cell function and lead to a prolonged 'honeymoon period'. However, there is insufficient evidence to prove this and the possible benefits of tight glycaemic control may be outweighed by the risks of hypoglycaemia.

Psychological support

The diagnosis of diabetes is invariably a shock to the child and family. Psychological or psychiatric problems may arise, particularly at diagnosis or during adolescence (see p. 28). Psychological support can be provided by a psychologist or psychiatrist as well as by diabetes nurses, other parents, and local and national support groups.

Requirements on discharge from hospital

The family doctor should be informed of the child's diagnosis and discharge from hospital, and the school or nursery should be visited by the diabetes nurse and ideally also by the dietitian to ensure that suitable information and arrangements are in place. The equipment that a child will need on discharge is shown in Table 1.4.

Table 1.4 Equipment required on discharge.

Lancets or other finger-pricking devices
Blood glucose testing strips
Blood glucose meter
Oral glucose gel
Glucagon kit
Blood or urinary ketone testing sticks
Sharps bin
Literature on diabetes and how to obtain medical bracelets/necklaces
Pen-delivery system, disposable pre-filled pens or syringes with needles for insulin injections
Insulin cartridges for pen-delivery system or insulin vials
Rapid-acting insulin
Alcohol swabs
Needle clipper

Management of the child presenting with ketoacidosis

Approximately 25% of new patients with type 1 diabetes will present with DKA (in type 2 diabetes, DKA is a presenting feature in <10% of patients). In children with established diabetes, the risk of DKA is increased in those with poor metabolic control and previous episodes of DKA, adolescent girls, children with psychiatric disorders including eating disorders and those with psychosocial difficulties. Inappropriate interruption of insulin pump therapy may also lead to DKA. 75% of DKA episodes are associated with insulin omission or treatment error. The majority of the remainder are due to inadequate insulin treatment during an intercurrent illness.

The diagnosis can be made on clinical and biochemical grounds. The biochemical criteria for the diagnosis of DKA include hyperglycaemia (glucose>11 mmol/L (200 mg/dL)) with a venous pH<7.30 and/or bicarbonate < 15 mmol/L (15 mEq/L). The blood glucose concentration is usually elevated but in 8% of cases may be <15 mmol/L (270 mg/dL). Blood ketone levels are generally > 3.0 mmol/L but some well children who do not fulfill the DKA criteria may have ketone levels >6.0 mmol/L. There is also ketonuria. DKA can be further classified by its severity – mild (venous pH<7.30 and/or bicarbonate<15 mmol/L (15 mEq/L)), moderate

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(pH<7.2 and/or bicarbonate<10 mmol/L) and severe (pH<7.1 and/or bicarbonate <5 mmol/L).

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

Resuscitation

DKA is a medical emergency and resuscitation should follow the 'ABC' scheme. The protocol which follows for the treatment of DKA is largely based on that published by the European Society of Paediatric Endocrinology and the Lawson Wilkins Paediatric Endocrine Society (Dunger, D.B. *et al*. 2004) and by the British Society of Paediatric Endocrinology and Diabetes (BSPED) (Edge, J.A. 2009).

- *Airway:* If the child is comatose, an airway should be inserted and if the conscious level is depressed or the child is vomiting, a nasogastric tube should be passed, aspirated and left on free drainage.
- *Breathing:* If there is evidence of hypoxia, give 100% oxygen and consider the need for intubation and ventilation. However, airway and breathing problems are rare.
- *Circulation:* An IV cannula should be sited and blood samples (including a venous blood gas) taken for investigations (see p. 5). In cases of circulatory impairment (suggested by the presence of poor capillary refill and tachycardia), give 10 mL/kg body weight of 0.9% saline intravenously as quickly as possible. This can be repeated with further boluses (subsequent boluses can usually be given more slowly) to a maximum total of 30 mL/kg until the circulation is restored.

If at presentation 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

The child should ideally be nursed in either a high dependency or intensive care unit. 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 1:1 basis. If the child is under 2 years of age, has a pH <7.1, is severely dehydrated with shock, has a depressed level of consciousness with a risk of aspiration from vomiting or if staffing levels are poor then the case should be discussed with a paediatric intensive care unit (PICU) consultant as the child may require intensive care.

The following should be documented:

- Hourly BP and basic observations.
- Weight should be measured twice a day.
- A strict fluid balance chart should be kept which should include measurement of urine volumes 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 finger pricks.
- Venous or capillary blood ketone testing 1–2 hourly, which measures the main ketone – β-hydroxybutyrate – should be performed to quantify the suppression of ketogenesis (urine testing for ketones is an inferior test which measures acetone which is not the main ketone produced).
- Blood gases, electrolyte and urea concentrations.
- A cardiac monitor should be used to monitor abnormal serum potassium concentrations (hypokalaemia is suggested by flat T waves and dysrhythmias, whereas hyperkalaemia is indicated by the presence of tall, peaked T waves with dysrhythmias).
- All patients with DKA should have at least hourly neurological observations and if comatose the Glasgow Coma Score should be recorded. The development of a 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 there is difficulty monitoring fluid losses, a urinary catheter should be inserted.

Fluid therapy

Calculation of fluid requirements

Once the circulating fluid volume has been restored, ongoing fluid requirements can be calculated as follows:

$$\text{fluid requirement} = (\text{fluid maintenance} + \text{fluid deficit}) - \text{fluid used for resuscitation}$$

The fluid deficit should be replaced over 48 hours and can be calculated from:

$$\text{fluid deficit (L)} = \%\text{dehydration} \times \text{body weight (kg)}$$

The extent of dehydration is usually 3–8%. Grades are mild 3%, moderate 5%, severe 8%, and shock. Most children are classed as 5 or 8% dehydrated. Dehydration is often overestimated and, for the purposes of calculating fluid requirements, the fluid deficit used should not exceed

Table 1.5 Maintenance fluid requirements in DKA.

Weight (kg)	Maintenance fluid requirements (mL/kg/24h)
0–12.9	80
13–19.9	65
20–34.9	55
35–59.9	45
> 60	35

N.B.: Neonatal DKA requires special consideration and larger volumes of fluid than those quoted may be required, usually 100–150 mL/kg/24 h.

8% of body weight. The fluid used 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 from Table 1.5.

The hourly infusion rate is calculated using the following formula:

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

Significant ongoing fluid losses, such as vomiting or excess diuresis, should also be replaced. An example of calculations to estimate fluid requirements for a child with DKA is shown in Table 1.6. It is always important to double-check these calculations. The BSPED DKA guideline has a link to both a fluid calculator and an observations and results flow chart.

Table 1.6 Example of fluid volume calculation.

An 8-year-old boy weighing 27 kg who is 8% dehydrated and who required 10 mL/kg 0.9% saline during resuscitation will need:
Daily maintenance = 27 kg × 55 mL = 1485 mL
Deficit = 27 kg × 8% = 2160 mL
Resuscitation fluid = 270 mL
Total requirements over 48 hours = (2 × 1485) + 2160 − 270 = 4860 mL
Hourly rate = 4860/48 = 101 mL/h

Ongoing fluid prescription

At presentation in DKA, the serum sodium concentration is usually low. This is mainly caused by a deficit in body sodium. Hypernatraemia may be present if water loss has been severe and has exceeded sodium losses. The following solutions should be available from the pharmacy: 500 mL bag of 0.9% saline/5% dextrose containing 20 mmol KCl and 500 mL bag of 0.45% saline/5% dextrose containing 20 mmol KCl. Following resuscitation, 0.9% saline with 20 mmol KCl in 500 mL should be used. This sodium concentration should be used for at least the first 12 hours of rehydration. After 12 hours, if the plasma sodium level is stable or increasing the bag can be changed to 500 mL of 0.45% saline/5% dextrose/20 mmol KCl. However, if the plasma sodium is falling continue with 0.9% saline/20 mmol KCl in 500 mL. Glucose may also be required in the bags depending on the blood glucose level. Some authorities believe that corrected sodium levels give an indication of the risk of cerebral oedema. The corrected sodium can be calculated from the formula: corrected Na = Na + 0.4 (glucose − 5.5 mmol/L). A rougher, quicker estimate is to add 0.3 mmol/L of sodium for every 1 mmol of glucose above 5.5 mmol/L. Corrected sodium levels should rise with therapy. Once the plasma glucose concentration has fallen to 14 mmol/L (250 mg/dL) glucose should be added to the fluid.

In the early stages of DKA, patients often experience marked thirst 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 following a significant clinical improvement with no vomiting. If a substantial clinical improvement has occurred prior to the 48 hours of rehydration, oral intake can proceed and the IV infusions reduced to take account of the oral intake.

Potassium administration

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. Early addition of potassium to the fluid regimen (40 mmol/L) is essential even if the serum concentration is normal as insulin will drive glucose and potassium into the cells producing

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a rapid fall in serum potassium concentrations and increased potassium requirements.

Following resuscitation potassium should be added to the IV fluids as soon as urine output has been established. In the rare cases where there is doubt about the urine output, the patient should be catheterized. Early potassium therapy should be avoided if anuria is present as a result of acute tubular necrosis. The serum potassium concentration should be maintained between 4 and 5 mmol/L. Very occasionally, more than 40 mmol/L may be required.

Phosphate

Depletion of intracellular phosphate also occurs. The fall in plasma phosphate levels is exacerbated by insulin therapy as phosphate re-enters the cells. Phosphate depletion may last for several days after the DKA has resolved. Prospective studies have failed to show any significant benefit from phosphate replacement, and phosphate administration may lead to hypocalcaemia.

Insulin therapy

Rehydration alone will lead to a fall in plasma glucose and ketone concentrations. There is some evidence that cerebral oedema is more likely if insulin is started early. Insulin therapy should therefore only be started at least 1 hour after the start of fluid therapy. Insulin helps reverse the underlying metabolic abnormalities by further reductions in the glucose concentration and by prevention of ketone body formation.

The insulin infusion should be prepared by adding 50 units (0.5 mL) of soluble insulin (e.g. actrapid) to 49.5 mL of 0.9% saline in a 50 mL syringe pump to produce an insulin concentration of 1 unit/mL. This may be connected to the fluid infusion through a Y-connector and prescribed as follows:

- The insulin solution should run at 0.1 mL/kg/h.
- When the blood glucose has fallen to 14 mmol/L (250 mg/dL), alter the fluid to one containing 5% dextrose.
- The insulin infusion should not be stopped before the acidosis has corrected as insulin is required to switch off ketone production. Nor should it be stopped whilst glucose is being infused. If the blood glucose falls to <4 mmol/L (72 mg/dL), a bolus of 2 mL/kg of 10% dextrose should be given and the dextrose concentration in the fluid increased. Insulin can temporarily be reduced for 1 hour.
- If needed, a solution of 10% glucose with 0.45% saline can be made up by adding 50 mL 50% glucose to a 500 mL bag of 0.45% saline/5% glucose with 20 mmol KCl.
- When the pH is >7.30, the blood glucose concentration $\leq$ 14 mmol/L (250 mg/dL), and a glucose infusion has been started, the insulin infusion rate can be reduced, but not to less than 0.05 units/kg/h.

In children who are already on long-acting insulin (especially glargine (lantus)), this can be continued at the usual dose and time throughout DKA treatment, in addition to the IV insulin infusion, in order to shorten the length of stay after recovery from DKA. In children on CSII pump therapy, the pump should be stopped when starting DKA therapy.

Acidosis and bicarbonate therapy

Adequate hydration and insulin therapy will reverse even a severe acidosis. Appropriate hydration will also reverse any lactic acidosis, which may account for 25% of the acidaemia, due to poor tissue perfusion and renal function. Continuing acidosis usually reflects inadequate fluid resuscitation or insulin therapy. The use of bicarbonate therapy is very rarely required. Bicarbonate should only be considered to improve cardiac contractility in patients who are severely acidotic (arterial pH$<$6.9) with circulatory failure despite adequate fluid replacement. **Bicarbonate should never be given without prior discussion with a senior doctor.**

Anticoagulant prophylaxis

There is a significant risk of femoral vein thrombosis in young and very sick children with DKA who have femoral lines inserted. Therefore, anticoagulation with 100 units/kg per day as a single dose of fragmin should be considered in these children. Children who are significantly hyperosmolar may also require anticoagulant therapy.

Subsequent management

Although plasma glucose concentrations may fall to near normal levels within 4–6 hours of treatment of DKA, the metabolic acidosis may take 24 hours or longer to resolve. Subsequent management should include the following:

- Blood gases and electrolyte and urea concentrations should be re-evaluated 2 hours after the start of treatment and 4 hourly thereafter, or more frequently if there are clinical concerns, until the child has recovered.
- The rate and composition of the IV fluid prescription should be reviewed regularly and adjusted according to the electrolyte results and fluid balance.

• If there is continuing massive polyuria, the rate of infusion of IV fluids may need to be increased. If there are large gastric aspirates, these will need replacing with 0.45% saline with KCl.
• Once the blood gases and electrolyte concentrations normalize, the frequency of blood sampling can be decreased and discontinued once the child is tolerating oral fluids and food.
• The frequency of bedside capillary blood glucose measurements may be reduced to 2 hourly if plasma glucose concentrations are relatively stable while the child is receiving IV dextrose.
• If the acidosis or hyperglycaemia do not improve after 4–6 hours, the patient should be reassessed by a senior doctor. Insufficient insulin and insulin errors, inadequate rehydration, sepsis, a hyperchloraemic acidosis, or salicylate or other prescription or recreational drugs may be the cause. More insulin, further 0.9% saline or antibiotics may be required.
• Use bedside blood (or urine) ketone testing to confirm that ketone levels are falling. If they are not falling check the infusion lines, the calculation and dose of insulin and consider giving more insulin.
• IV fluids should be continued until the child is drinking well and able to tolerate food. Once the blood ketone levels are below 1.0 mmol/L, subcutaneous insulin can be started (urinary ketones may take longer to clear).
• When the patient is started on a conventional subcutaneous insulin regimen (see above for regimen for new patients, established patients can return to their previous regimen), the insulin infusion should be discontinued 60 minutes (if using actrapid) or 10 minutes (if using Novorapid or Humalog) after the first subcutaneous injection to avoid rebound hyperglycaemia. In the case of patients on CSII therapy, this can be restarted when blood ketones are < 0.6 mmol/L.

Cerebral oedema

Cerebral oedema has a mortality rate of approximately 25%. Significant neurological morbidity is present in 10–26% of survivors. It occurs in approximately 0.3–1% of cases of DKA.

Aetiology

The aetiology of cerebral oedema is poorly understood and even with optimum management of DKA, cases still occur. It is more common in children under 5 years of age and in newly diagnosed cases. A fall in sodium concentration following treatment, a severe acidosis, the use of bicarbonate, marked hypocapnia and a high urea at presentation have all been implicated as risk factors. Much of the treatment is aimed at minimizing these possible contributory factors.

Clinical features

Cerebral oedema usually occurs 4–12 hours after the start of treatment and often follows an initial period of clinical and biochemical improvement. However, in some cases the patient's state of consciousness may decline from admission onwards, whereas in others cerebral oedema may occur after 48 hours. Typical symptoms and signs include:
• onset or worsening of headache (this is often present initially in DKA and should improve with treatment);
• confusion;
• irritability;
• reducing conscious level (patients are often drowsy at presentation but this should improve with treatment);
• pupillary abnormalities/cranial nerve palsies;
• hypertension and bradycardia;
• decerebrate or decorticate posturing; and
• oxygen desaturations and respiratory impairment.

More dramatic signs such as convulsions, papilloedema and respiratory arrest are late signs associated with a very poor prognosis.

Treatment

If cerebral oedema is suspected, senior staff should be informed immediately and the following measures should be taken urgently whilst arranging transfer to a PICU:
• Hypoglycaemia should be excluded.
• Give hypertonic (2.7%) saline (5 mL/kg over 5–10 minutes) or mannitol 0.5–1 g/kg (= 2.5–5 mL/kg 20% mannitol over 20 minutes). This should be given **as soon as possible** if warning signs such as a headache and pulse slowing occur.
• Fluids should be restricted to half maintenance with the deficit replaced over 72 rather than 48 hours.
• The child should be discussed with a PICU consultant and transferred to a PICU. Do not intubate and ventilate until an experienced doctor is available.
• Once the child is stable an urgent computed tomography scan should be performed to exclude other problems such as cerebral thrombosis, haemorrhage or infarction.
• A repeat dose of mannitol may be required after 2 hours if there is no initial response.

Other complications

• *Infections:* Antibiotics are not routinely given unless a significant bacterial infection is suspected.

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• *Abdominal pain:* This is common and may be due to liver swelling, gastritis, bladder retention or ileus. However, surgical conditions such as appendicitis rarely occur and a surgical opinion may be required once DKA is stable. A raised amylase is common in DKA.
• Other problems are pneumothorax +/− pneumomediastinum, interstitial pulmonary oedema, unusual infections (e.g. tuberculosis) and hyperosmolar hyperglycaemic non-ketotic coma.

The diabetes clinic

General principles

Children with diabetes should be seen in a designated diabetic clinic supervised by a senior paediatrician trained in the care of diabetes. It has been recommended that, within a clinical service, there be a specialist nurse for every 70 children with diabetes. Where possible, the clinical service should provide care for a minimum of 40 patients with diabetes to allow the necessary accumulation of expertise. 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 be held in a paediatric environment with facilities for auxology. Separate arrangements should be made for clinics for adolescents, which are described later in this chapter. Educational literature, DVDs and information about holidays for children with diabetes should be available.

The clinic visit

The following staff should ideally be available at each clinic:
• Paediatrician with expertise in diabetes.
• Diabetes nurse specialist (DNS) with paediatric training or expertise.
• Dietitian with paediatric experience.
• Psychologist.
• Social worker to provide financial and other advice to the family.

Any child with diabetes attending the diabetes clinic should undergo the following:
1 Documentation of general health and life events (e.g. changing school), recent hospital admissions, insulin regimen, details of hypoglycaemic episodes and school absences.
2 Review of practical aspects of blood glucose monitoring and insulin injections.
3 If necessary, provision of advice on adjustments to the insulin regimen in light of the results of blood glucose monitoring.
4 Measurement of height and weight.
5 Examination of injection sites.
6 Three-monthly measurement of glycosylated haemoglobin.
7 An annual review of all patients aged 11 years or older, who have had diabetes for ≥2 years, which should include:
• a physical examination for microvascular and other complications of diabetes (Table 1.7);
• TFTs;
• random cholesterol measurement;
• screening for microalbuminuria by measurement of the albumin:creatinine ratio in an early morning urine sample; and
• many centres perform retinal photography in addition to a clinical examination of the fundi (if the latter is abnormal then retinal photography is recommended to delineate the degree of retinopathy).

Details of the consultation (and non-attendance) should be documented using either paper records or computer software to enable future audit. Given the multidisciplinary nature of a diabetes clinic, it is often helpful to have a team meeting at the end of the clinic to share information about patients who have attended clinic.

Insulin treatment

Insulin delivery systems

Insulin has an effective shelf life of at least 2 years if kept in a refrigerator at 4°C and can be kept at room temperature for up to 1 month. However, if kept in tropical climates, car interiors or freezer compartments insulin may degrade more rapidly. Insulin is most commonly administered by a pen-delivery system, a pump or using syringes and needles. In general, vials of insulin are cheaper than insulin in pen cartridges, which in turn are cheaper than insulin-filled disposable pens. For children with needle phobia, spring-loaded automatic injection devices in which the needle is not visible, or transjector systems in which a jet of insulin is delivered at sufficiently high pressure that it penetrates the skin without the need for a needle may be helpful.

Insulin pens

Using a pen-delivery system, insulin may be administered using either a preloaded disposable device or cartridges fitted into 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.

Table 1.7 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 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) verrucae
Hands	Finger-prick sites Limited joint mobility ('prayer sign')
Cardiovascular	Hypertension (if present, recheck at the end of the clinic visit)
Endocrine	Goitre or other signs of hypothyroidism or hyperthyroidism Increased pigmentation suggestive of Addison's disease
Neurological	Impaired vibration or pinprick sense Loss of ankle reflexes

Syringes and needles

Insulin for injection may be drawn up from a vial and injected using a syringe and needle system. A choice is available between using premixed insulin preparations or mixing separate supplies of rapid- and intermediate-acting insulins within the syringe by the patient. When mixing insulins the rapidly-acting clear insulin should be drawn up into the syringe prior to the intermediate-acting (isophane), cloudy insulin. Any preparation containing intermediate-acting insulin should be gently inverted several times prior to use. Although mixing of separate insulins allows, in theory, greater flexibility, there is little evidence that in routine clinical practice this leads to better glycaemic control than that which can be achieved using premixed insulins. Furthermore, mixing separate insulins is time-consuming and requires manual dexterity.

Injections

Depending on the maturity and confidence of the individual patient, children as young as 5 years can be taught to administer their own injections of insulin. However, the age at which children start to give their own injections is very variable. Peer pressure, such as that which may be experienced by a child attending a diabetic camp, where children may see their contemporaries, or even younger children, administering injections may help a child learn to self-inject.

Appropriate injection sites are demonstrated in Figure 1.2. The use of different injection sites and rotation of these sites should be encouraged to avoid the development of lipohypertrophy (Figure 1.3) which may be unsightly and lead to erratic absorption of insulin. If patients avoid injecting into these areas, lipohypertrophy will resolve, typically within 3 months.

Clinically significant variations in the amount of insulin absorbed from each injection can occur as a result of the factors listed in Table 1.8.

Injection technique

It is unnecessary to clean the skin prior to a subcutaneous insulin injection. It is recommended that patients be taught to give the injection at a 45° angle to the surface of the skin. When using the very short (e.g. 5 mm) needles the injection can be given vertically 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 rubbed with an ice cube prior to the injection. Pen needles can be used up to three times before

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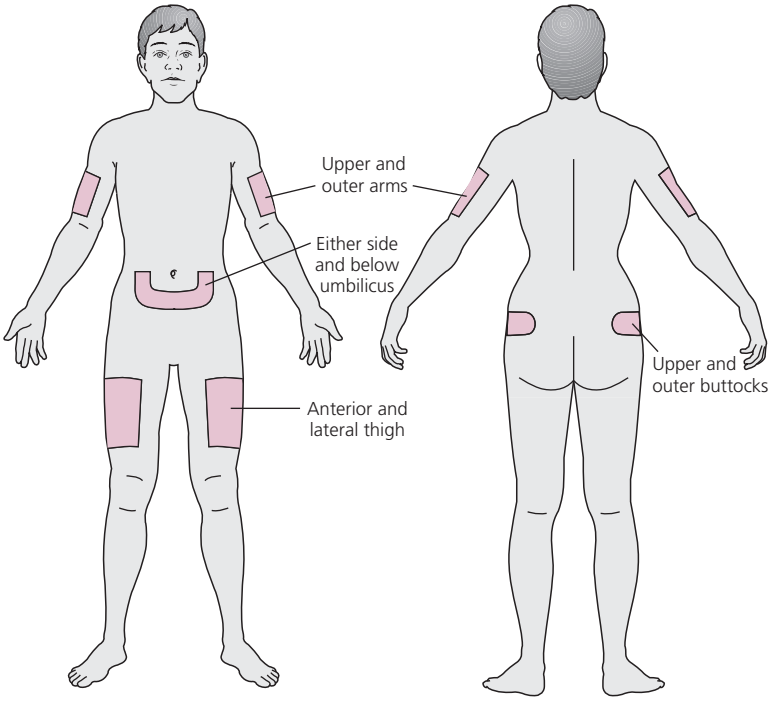

Fig. 1.2 Appropriate insulin injection sites.

being changed. More frequent use will lead to blunting and painful injections.

Insulin requirements

Suggested starting dosages of insulin are shown on p. 7. In established patients, it is unusual for prepubertal children to require more than 0.8 units of insulin/kg per day. In contrast, children in puberty may require up to 2 units/kg per day. Obese patients may be insulin resistant and require relatively higher dosages.

Altering insulin dosage

In children under 10 years insulin dosage can be altered by 1–2 units per day and in children over 10 years by 2–4 units per day, depending on the results of blood glucose

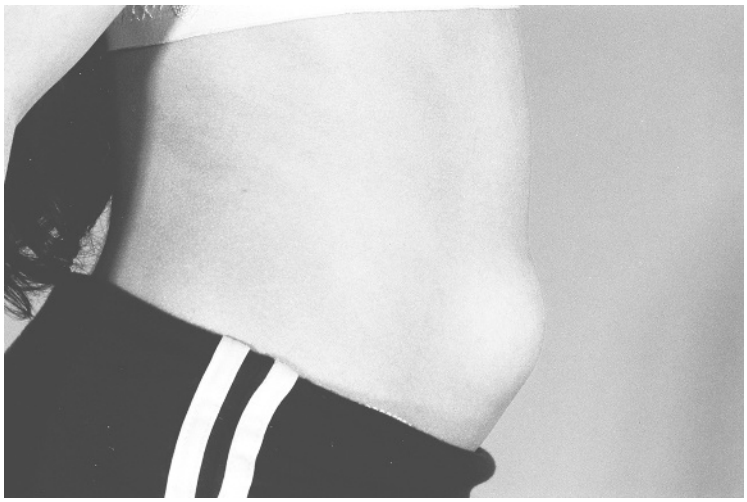

Fig. 1.3 Lipohypertrophy.

Table 1.8 Factors affecting insulin absorption.

Slower insulin absorption	Faster insulin absorption
Leg or arm injection sites	Abdominal injection site
Subcutaneous injection	Intramuscular injection
Lipohypertrophy	Exercise
Cold skin	Peripherally vasodilated
Obese subjects	Thin subjects

testing. Following any change in insulin dosage, blood glucose concentrations should be monitored carefully for 2–4 days to assess the effect.

Injecting small doses

In infants, the injection of doses of insulin as small as 1 unit can result in significant inaccuracies, with the dose actually delivered ranging from 0.89 to 1.23 units. In these circumstances, it is recommended that pen-delivery systems available from the manufacturers of insulin which allows injections of insulin in increments of 0.5 units are used.

Insulin preparations

In solution, human insulin forms hexamers (six-molecule units) which are slowly absorbed across endothelial barriers when insulin is injected subcutaneously. The rate of absorption is mainly determined by how quickly these hexamers dissociate into monomers (single molecules), which are rapidly absorbed at the injection site. Children with diabetes should be treated with human sequence or human insulin analogues. In the United Kingdom, this is usually available in a concentration of 100 units/mL (U100) although more dilute forms may be necessary for the treatment of infants receiving very small doses of insulin. Table 1.9 outlines the most common preparations of insulin available to treat children in the United Kingdom and their duration of action.

Most children are treated using basal bolus regimens or CSII. A minority are treated with twice daily injections of a premixed insulin. Several insulins are very similar in their duration of action. To simplify matters and to avoid confusion, it is therefore recommended that a 'diabetes team' limit the number of insulins they use.

Insulin analogues

Rapidly-acting insulin analogues incorporate amino acid substitutions which make them quickly dissociate into monomers and dimers following injection and therefore lead to rapid absorption. They can be given just prior to a meal or, in young children in whom there is concern about how much food they will actually eat or where there may be food refusal, within 15 minutes of starting a meal. Compared with short-acting insulin, they produce lower postprandial glucose excursions but higher preprandial glucose concentrations. They may, therefore, be helpful in children who become hypoglycaemic prior to lunch. They do not lead to a decrease in the overall incidence of hypoglycaemia but there is some evidence that they lead to a decrease in the incidence of severe hypoglycaemia. Compared with conventional insulin, these analogues are associated with a very small decrease in HbA1c of approximately 0.1%.

Rapidly-acting analogues are also available in a premixed form with intermediate-acting insulin. They decrease postprandial glucose concentrations, but when compared to similar mixtures of conventional insulin have similar effects on the HbA1c and the incidence of hypoglycaemia.

Recently, two long-acting insulin analogues have been developed. They both lead to a consistent and prolonged release of insulin with no peaks. Insulin glargine has glycine instead of asparagine at position 21 on the A-chain and has two arginines added to the carboxyl terminal of the B-chain at positions 31 and 32. These changes result in a low solubility at neutral pH but total solubility at the pH of its injection solution (pH 4). Following injection, the pH of the insulin solution increases, leading to the formation of micro-precipitates, from which small amounts of glargine are gradually absorbed into the circulation. This leads to a prolonged duration of action (22–24 hours). It can be injected at any time but is usually given in the evening. There is some evidence that there is a decreased incidence of nocturnal hypoglycaemia when it is given at breakfast.

Insulin detemir has the terminal amino acid (B30) in the B-chain deleted and a 14-carbon fatty acid attached at position B29. This leads to a prolonged duration of action as a result of two mechanisms: albumin binding via a fatty acid side-chain retains insulin in the subcutaneous depot and strong self-association of insulin detemir hexamers at the injection site. The duration of action is partly dependant on the dose with lower doses lasting 12 hours and higher doses lasting up to 24 hours. It is administered once or occasionally twice daily. Glargine and detemir are licensed in the United Kingdom for patients aged 6 years and above, but have been used in younger children as well.

Insulin glargine and detemir have provided new opportunities to optimize glycaemic control. Both result in

Table 1.9 Insulin preparations commonly used to the treatment of children in the UK.

			Approximate time course of action		
Preparation	Manufacturer	Formulations	Onset	Peak	Duration
1) Rapidly acting insulin					
Humalog (insulin lispro)	Lilly	vial, cart, pen	15 mins	30–70 mins	2–5 h
Nororapid (insulin aspart)	Novo Nordisk	vial, cart, pen	15 mins	1–3 h	3–5 h
2) Short acting insulin (Soluble, neutral)					
Human Actrapid	Novo Nordisk	vial	30 mins	1–2 h	6–8 h
Humilin S	Lilly	vial, cart	30 mins	1–2 h	6–8 h
3) Intermediate acting insulin (isophane)					
Human Insulatard	Novo Nordisk	vial, cart, pen	2 h	4–6 h	8–12 h
Humilin I	Lilly	vial, cart, pen	2 h	4–6 h	8–12 h
4) Biphasic Insulins (mixed insulins)					
Human Mixtard 30 (30% actrapid /70% insulatard)	Novo Nordisk	vial, cart, pen	30 mins	2–6 h	8–12 h
Humilin M3 (30% Humilin S/70% Humilin I)	Lilly	vial, cart, pen	30 mins	2–6 h	8–12 h
Humalog Mix 25	Lilly	cart, pen	15 mins	1 h	8–12 h
Humalog Mix 50	Lilly	pen	Same time course as Mix25 but increased intensity of early action		
Novomix 30	Novo Nordisk	cart, pen	15 mins	1–4 h	8–12 h
5) Long acting Insulins					
Insulin glargine	Aventis Pharma	vial, cart, pen	2 h	Peakless	24 h
Insulin detemir	Novo Nordisk	cart, pen	2 h	Peakless	12–24 h

Vial: Stardard 10 ml bottle to use with Syringe. Cart: 3 ml Cartridges for reusable pen. Pen: disposable 3 ml pens
Aventis Pharma also produce Insuman rapid, Insuman basal and Insuman Comb 15, 25 and 50

glycaemic control that is at least comparable to that using isophane insulin. Some studies comparing basal bolus regimes with isophane or glargine have shown that the use of glargine leads to a small (0.1–0.5%) decrease in HbA1c, but other studies have shown no difference. There is some evidence that both glargine and detemir lead to a decrease in the incidence of hypoglycaemia including nocturnal hypoglycaemia. Weight gain with both these insulins may be less than that with isophane insulin.

Basal bolus regimen

This regimen is discussed on p. 7–8. When converting from twice daily insulin injections to a basal bolus regimen, the total number of units is often decreased by 10% to reduce the risk of hypoglycaemia. Normally, approximately 40% of the TDD of insulin is given at bedtime as a long-acting insulin analogue with the remaining insulin being given prior to breakfast, lunch and the evening meal in the form of rapidly-acting insulin. When converting from a basal bolus regimen containing isophane to one with a long-acting insulin analogue, the same number of units of the analogue is usually given. In the case of glargine, and occasionally with detemir, the dose of rapidly-acting insulin prior to meals (the ratio of rapidly-acting insulin to carbohydrate when carbohydrate counting) may need to be lowered if there is good glycaemic control. If daytime blood glucose levels are generally high then the insulin to carbohydrate ratio can be left unaltered.

As with any significant change in insulin regimen blood glucose levels should be tested frequently to see what effect the change has had. It can take up to 2 weeks for the full effects of a change in regimen to become apparent.

Example of how to convert a patient from twice daily insulin to a basal bolus regimen

- Patient received 44 units of a 30:70 premixed insulin in the morning and 22 units of the same insulin in the evening.
- Decrease total daily dosage of insulin from 66 to 60 units.
- Initially, try 24 units (40%) of a long-acting insulin analogue prior to bedtime.
- Use rapidly-acting insulin and carbohydrate counting to determine the correct dose prior to each meal.
- Adjust doses of insulin in light of blood glucose test results (also use correction doses).

Once on this regimen, the bedtime dose should be slowly adjusted to achieve an average morning fasting glucose concentration of 6 mmol/L (110 mg/dL). Further adjustments can then be made to the preprandial doses. Typical pre-meal doses in adolescents vary from 4 units for a small breakfast to 20 units for a large meal.

Continuous subcutaneous insulin infusions (insulin pumps)

Insulin pumps are used in <5% of children in the United Kingdom and in about 25% of children in the USA. They can be used at all ages. The devices consist of a programmable pump (which may be as small as a match box) containing rapidly-acting insulin which is connected by an infusion line to a small plastic/metal cannula inserted subcutaneously usually in the abdomen (in toddlers and infants it is often inserted in the buttock) and fixed by tape. The cannula is usually left in place for 2–3 days. If the cannula is not changed regularly or if the same site is recurrently used, there is a risk of lipohypertrophy. Changes in the insulin infusion rate as small as 0.025 units/h can be made. Blood glucose should be tested at least four times a day including morning and late evening. A 24-hour profile including measurements before each meal, 2 hours following the meal, at midnight, at 2.00–3.00 a.m. +/− 5.00 a.m. should be carried out at least every other week to help enable any necessary changes to be made. The absence of a long-acting insulin depot means that if there is a problem with insulin delivery, blood glucose levels will rise quickly and ketosis can develop in 4–6 hours. CSII therapy is more expensive than current standard therapy and in the United Kingdom costs £2500–3500 with consumables costing about £1800 per year.

The indications for CSIIs in the United Kingdom have recently been liberalized. Pumps are recommended as a treatment option for children aged 12 years and above with type 1 diabetes when multiple daily injections (MDI) insulin therapy results in disabling hypoglycaemia or fails to reduce the HbA1c level below 8.5%, and for children under 12 years of age whenever MDI therapy is impractical or inappropriate. It should only be continued if it reduces the HbA1c or the frequency of hypoglycaemic episodes. It is important that patients and their families are committed, competent and interested in using CSII treatment.

There is evidence that CSIIs reduce the HbA1c by 0.5–1% as well as decrease the incidence of hypoglycaemia. Most patients maintain the same weight following pump therapy. Some may gain weight if the HbA1c falls as they stop loosing glucose in their urine. The increased ease of administering boluses can also lead to overeating and weight gain. Others adopt a healthier dietary intake when they start pump therapy, eat smaller meals with smaller boluses and loose weight.

Before commencing CSII therapy, a lot of education about the pump is required and for the majority of patients further refining of carbohydrate counting skills. Patients should be allowed to choose the pump they prefer from the selection available. Pumps differ in size, weight, ease of use, features including dosage increments, cost and customer backup. Support and training are provided by the diabetes team with additional support from the company representative as necessary. Ideally, there should be a structured education programme over several days to teach families about CSII therapy. However, patients' and families' learning curves and working schedules vary and others spread the education over several half days over a period of 1–2 weeks. Daily contact is important over the first couple of weeks. Some units provide 24-hour diabetic support by their nursing/medical staff whilst others rely on a mixture of the 24-hour support provided by the pump manufacturer's company and out of hours by the support provided by the on-call medical staff and the resident ward nursing staff.

When commencing a patient on CSII therapy patients have the option of starting with a saline trial to get used to the pump and its controls for a few days or commencing directly on insulin. When changing a patient from their MDI regimen to CSII therapy the dose of glargine or detemir given the previous night is halved, or omitted if glargine or detemir is given in the morning. The

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normal dose of rapidly-acting insulin is given with breakfast and CSII therapy is usually commenced mid-morning. The TDD of insulin chosen is dependent on the patient's HbA1c, average blood glucose, weight and frequency of hypos. The difficulty is that it may be difficult to determine if the HbA1c is high because the patient is on insufficient insulin or whether that is due to their not taking their insulin. Most patients experience a significant decrease in their TDD of insulin when they convert to CSII therapy. For this reason, and to be cautious, the patient's TDD is often decreased by 25% at the start of pump therapy. Approximately 50% of the TDD is given as basal insulin. The remainder is administered as bolus doses. The same insulin to carbohydrate ratio may be maintained but often this ratio is lowered by about 20–25%; for example, the ratio may be changed from 1 unit of rapidly-acting insulin for every 10 g of carbohydrate (1:10) to a 1:12 ratio. The same correction dose (also known as 'insulin sensitivity factor') may be kept but again this is often reduced by about 20–25%; for example, the correction dose may be changed from 1 unit of rapidly-acting insulin to lower the blood glucose by 4 mmol/L (72 mg/dL) to 1 unit to lower the blood glucose by 5 mmol/L (90 mg/dL), the aim being to decrease the blood glucose to 7 mmol/L (125 mg/dL). These reductions are made to try and decrease the risk of hypoglycaemia following the commencement of pump therapy. When starting a newly diagnosed patient on CSII therapy (this is done in some centres, most often in children < 3 years), the TDD is often calculated as 0.5 units/kg per day with about 50% of the TDD being given as basal insulin (on occasion, a higher percentage of the TDD will be required as basal insulin). The '500 rule' (see page 7) is often used to calculate the insulin to carbohydrate ratio and the correction dose is worked out by dividing 100 by the TDD. There can be a lot of variability in glycaemic control following pump initiation and close monitoring is required in the initial stages.

A minority of patients use the pump at night only with multiple rapidly-acting insulin injections during the day and intermediate acting insulin (e.g. isophane) in the morning. This may be done in patients who are reluctant to wear the pump during the day, when there are difficulties with adult supervision during the day, if there are problems with night-time hypos, or if there are difficulties with high blood glucose levels in the early morning. A night-time pump may also be useful during a holiday when the patient may be exercising and swimming a lot during the day. In such cases, the morning intermediate insulin may not be necessary.

On occasion a patient may want to revert from CSII therapy to pen/syringe treatment; for example, if going on holiday. In such cases, the TDD should be increased by 10% with 30% of the TDD being administered as long-acting insulin. It may be best to make this change a few days before going on holiday to get used to this mode of treatment again.

Initially, we use the same basal rate for the whole day. However, different rates may be necessary for different parts of the day and temporary changes in the basal rate may be required when the patient is ill (usually an increase) or during exercise (a decrease). An increase in the basal rate may also be necessary in the days leading up to menses or if the patient is on a drug known to increase blood glucose levels, for example steroids. Young children often have their highest basal rate between 9.00 p.m. and 12.00 a.m. whereas adolescents who secrete a lot of GH overnight may require high basal rates in the early hours of the morning to counter the dawn phenomenon (see page 21). One way of altering the daytime basal rates is to divide the day into three with each time span containing a main meal. The blood glucose should be measured before the meal for several days to help evaluate the basal rate. If the blood glucose is <5 mmol/L (90 mg/dL), then the basal rate prior to the meal should be decreased by 0.05 units/h if the rate is <0.3 units/h, by 0.1 unit/h if the rate is 0.3 to 0.975 units/h and by 0.2 units/h if the rate is > 1 unit/h. Conversely, if the blood glucose is >10 mmol/L (180 mg/dL), then the basal rate prior to the meal should be increased by 0.05 units/h if the rate is <0.3 units/h, by 0.1 units/h if the basal rate is 0.3 to 0.975 units/h and by 0.2 units/h if the rate is >1 unit/h. A further way of adjusting the daytime basal rate is to miss breakfast and the accompanying bolus, and to measure the blood glucose hourly till lunchtime. If the blood glucose level rises then an increase in the basal dose is required and vice versa. This process can be repeated with the other meals. In children this period of fasting may be difficult to achieve but parents can try and give food containing virtually no carbohydrate (e.g. eggs or carrots).

Bolus doses are given at meal times, their size depending on the amount of carbohydrate ingested. Even a 10 g carbohydrate snack should be accompanied by a bolus (compare to basal bolus regime) page 7–8. Additional correction doses may be necessary at the same time if the blood glucose is high, or at other times when the blood glucose is raised; for example, during illness. There are different types of boluses. A standard bolus delivers the whole bolus immediately whereas a square or extended bolus administers it over a variable period of time, for example

2 hours. Dual or combination boluses can also be administered which deliver varied combinations of the above two boluses, for example 50% standard bolus and 50% square bolus. Square or dual boluses may be preferred for a meal rich in fat, for example a pizza; a meal with a low glycaemic index; or when food will be eaten over a protracted period of time, for example a party; or if it is uncertain how much food the child will eat.

CSIIs can help in calculations of the necessary bolus dose. Insulin pumps have a built-in calculator which can be pre-programmed with the relevant insulin to carbohydrate ratio, the insulin sensitivity factor and the blood glucose targets. If the glucose reading and the amount of carbohydrate to be eaten are entered, the pump can work out the bolus dose. This calculation will include any necessary correction dose and will also take into account any 'insulin on board' from the last bolus that was administered that may still be acting. Patients can input into the pump their favourite foods and their carbohydrate content to create a food list, thus further facilitating carbohydrate counting when the same food is eaten again.

There is some evidence that there is a slightly increased risk of DKA, especially in the first few weeks following the initiation of CSII therapy. However, a recent study showed a lower rate of DKA in CSII users. Patients and parents should be aware of the symptoms of insulin deficiency such as polyuria, polydipsia, nausea, vomiting, abdominal pain, tachypnoea and drowsiness. Blood ketone sticks are useful as they detect raised ketone levels several hours earlier than urine ketone sticks. If the blood glucose is >14 mmol/L (250 mg/dL) and blood ketones are ≥ 0.6 mmol/L (or urine ketones are moderate or large), this indicates an interruption in insulin delivery or an increased requirement for insulin, for example due to infection. 0.1 unit/kg of rapidly-acting insulin should be administered with a pen or syringe. The pump and infusion set should not be used as they may not be working properly. The blood glucose should be measured hourly. If it does not fall, the same insulin dose can be repeated every 2 hours. Blood ketones should also be measured 2 hourly to document if they are falling. If the situation is not improving then the insulin cartridge, infusion set and cannula/needle should be changed. The skin should also be examined for signs of erythema which would indicate infection, or moisture which would suggest an insulin leak. Large amounts of sugar-free fluids should be drunk. If the blood glucose is ≤ 11 mmol/L (200 mg/dL) and blood ketone levels are still elevated, then sugar containing fluids should be drunk and additional rapidly-acting insulin should be administered. One should **always** have insulin to be administered with a pen or syringe in case of a problem with the pump.

Hypoglycaemia should be treated by administering 15 g of rapidly-acting carbohydrate; for example, 4–5 glucose tablets or 90 mL of a sugary drink or fruit juice (check the label). The glucose level should be checked after 15 minutes. If it is still <4 mmol/L, then the above procedure should be repeated. In contrast to MDI therapy, the rapidly-acting carbohydrate does not need to be followed up with a longer-acting source of carbohydrate as there is no long-acting insulin present. In the case of a major hypo with unconsciousness, the insulin pump should be stopped and appropriate action taken (see 'Hypoglycaemia' p. 26). The cause of the hypoglycaemia (basal rate too high, increased physical activity with an insufficient reduction in the basal rate, miscalculation of a meal bolus, or alcohol) should be determined and any necessary changes implemented.

During some exercises such as swimming or contact sports, the pump can be disconnected for 1 hour. Alternative approaches to exercise include having a snack prior to the exercise, or if one is exercising shortly after having had a meal with a premeal bolus, to decrease the meal bolus.

In other cases, and especially in the case of prolonged exercise such as a 4-hour tennis match, the best plan is to reduce the basal rate. This may need doing 1–2 hours prior to the exercise as it takes 1–2 hours before a decrease in the basal rate has an effect. This would be necessary especially if the hypos were occurring early in the course of the exercise. For instance, the basal rate may need decreasing by up to 50% 1–2 hours prior to the start of the exercise until 1–2 hours following the end of the exercise. Further decreases in the basal rate may be necessary and regular testing before, during and after exercise should help determine the appropriate basal rate. Exercise can also lead to hypoglycaemia up to 24 hours following the exercise. In the case of strenuous exercise carbohydrate will also need to be taken during the exercise and following the exercise. If the exercise has been in the afternoon or evening, the basal rate may need decreasing by 10–20% until the following morning. In children attending sports camps the basal rate should be decreased by about 20% on the first day of activities and then adjusted according to the blood glucose readings.

The approach to illness in children with a CSII is similar to that of high blood glucose readings with raised blood ketone levels. Fever and the stress of illness nearly always raise blood glucose levels. Meal boluses should be continued even if one is eating less. Correction doses should be given as appropriate. The basal rate should be increased

by 10–20% if the blood glucose level remains high. The blood glucose should be checked every 2–4 hours and blood ketones should also be measured frequently. Further increases in the basal rate may be necessary. 0.1 unit/kg of rapidly-acting insulin should be administered if the blood glucose is >14 mmol/L (250 mg/dL) with blood ketones $\geq$ 0.6 mmol/L. A further similar dose should be given every 2 hours until the blood glucose is <10 mmol/L (180 mg/dL) and the ketone levels are falling. All extra insulin doses should be given with a pen or syringe if the blood glucose has risen suddenly in case the rise is due to a problem with the pump. Large amounts of glucose-free fluid should also be drunk to increase the excretion of ketones and to prevent dehydration. When the blood glucose is <11 mmol/L (200 mg/dL), glucose containing drinks should be drunk. In the case of nausea, small amounts should be drunk frequently. If hypoglycaemia is a problem then sweet drinks should be drunk and the basal rate should be lowered.

Schools and nurseries should be told that a pupil in their class is about to start or has started on insulin pump therapy. Ideally the DNS, but if that is not possible the parent, should teach the patient's carers how to administer a bolus.

Problems with the CSII may be due to the pump itself (failure, flat batteries), the insulin reservoir/cartridge (empty or plunger stuck), the infusion set (blocked), the cannula (blocked or dislodged), or the insertion site (infected, lipohypertrophy). Furthermore, there may be leaks between the connections. The first sign of a malfunction may be a rise in the blood glucose that may precede the pump alarming. The pump safety features can be personalized to alert the user before the insulin cartridge or battery run too low. Various other alarms are also programmed into the pumps. These include occlusion alarms. If an alarm occurs in the middle of a bolus the pump will state how much of the bolus it has delivered. However, how much of the bolus the patient has received will depend on whether the occlusion was partial or total and how far down the infusion line it occurred. The alarm can also go off if no buttons have been pressed for a set length of time. It can also be programmed to limit the maximum basal and bolus rates to avoid overdosage. The pump can also be 'locked' to prevent the accidental pushing of buttons.

Clinic visits involve reviewing the blood glucose levels to identify if there are any patterns that would justify alterations in the basal or bolus rates, measurements of the HbA1c, discussions of any problems with the pump, dietetic issues, etc.

Some CSIIs have remote controls that enable the bolus dose to be given more easily and discretely. Some remote controls can also be used as glucose meters and to input data into the pump.

Recently, a new type of pump called a 'patch pump' has been developed, for example the OmniPod. Patch pumps comprise of a micro pump, an insulin reservoir (patch) and a cannula, and attach directly to the skin. Insulin is delivered through the very small integrated subcutaneous catheter. Patch pumps are free of tubing which makes them more discrete and allows greater freedom with activities. They are disposable or semi-disposable and many are lighter and smaller than conventional pumps. They are controlled by a remote control device that communicates wirelessly with the patch pump and which often doubles up as a glucose meter. They usually need to be reapplied every 3 days.

CSIIs can also be used with continuous glucose monitoring sensors that measure glucose levels in the interstitial fluid every few minutes. These sensors are usually used for a few days in a month rather then continuously. 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 alarms and stops. Some insulin pumps can also be set to alarm if the glucose level is falling rapidly. It is hoped that in the near future, the two will be combined to provide a reliable closed loop system, i.e. an artificial pancreas. There is evidence that such systems increase the number of readings in the target range and decrease hypoglycaemia. Various algorithms for such a device to cope with situations such as exercise (where absolute glucose values and trends are looked at) are currently being devised in this promising research avenue that could greatly improve the management of diabetes.

The use of CSIIs is increasing in the United Kingdom and in many other countries, especially as technology improves. The pump enables a flexible life style and eating patterns and is associated with a high degree of satisfaction in appropriately motivated patients.

Potential problems with insulin therapy

The dawn phenomenon

The dawn phenomenon describes the rise in insulin requirements and blood glucose concentrations in the latter part of the night, approximately 5.00–8.00 a.m. It occurs mainly in puberty and is thought to be caused by the insulin resistance produced by nocturnal GH 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 prior to bedtime. Alternatively, in patients on a basal bolus regimen the pre-bedtime dose of intermediate-acting insulin or long-acting insulin analogue can be increased.

The Somogyi phenomenon

This is said to be the 'rebound' morning hyperglycaemia which may occur following nocturnal hypoglycaemia caused by the release of counter-regulatory hormones such as glucagon, adrenaline and cortisol. Whether this phenomenon exists is open to debate and it may be the consequence of the excessive ingestion of refined carbohydrates used to treat the episode of nocturnal hypoglycaemia.

Monitoring glycaemic control

Blood glucose testing

A number of studies have shown that greater frequency of blood glucose monitoring improves metabolic control. The following principles for home blood glucose monitoring are recommended:

- Children should be encouraged to perform their own finger-prick blood glucose testing at as young an age as they feel able to do so (sometimes as young as 5 years old).
- Finger pricks should be performed on the sides of the fingertips.
- Finger-pricking devices with variable depth settings can make testing less painful.
- Forearm blood glucose testing is an acceptable and accurate alternative to finger-prick testing.
- Electronic blood glucose meters with a memory, which may allow data to be downloaded onto a computer for discussion in clinic, are useful for recording results but need regular calibration.
- Date-expired blood glucose testing strips should be avoided as use of these may lead to inaccurate blood glucose estimations.
- The child should be encouraged to monitor blood glucose concentrations regularly, prior to each main meal and at bedtime. On rare occasions, it may be helpful to monitor values 2 hours after a main meal.
- More frequent blood glucose testing may be indicated if the child is unwell, partaking in unusual amounts of physical activity or feels hypoglycaemic.
- Devices that regularly monitor glucose readings, in some cases at intervals of <5 minutes have recently become available. The devices are inserted subcutaneously and measure interstitial fluid glucose, which with the best devices is within 15% of blood glucose. They can be left in place for 3–6 days and are usually used intermittently; for example, on an ad hoc basis or for a few days a month. These devices, that can be used with injections or CSII therapy, have been shown to detect hypoglycaemia more frequently than conventional monitoring, and may also have hypoglycaemia and hyperglycaemia alarms. Conventional blood glucose testing is still required to calibrate the device. The monitoring can be performed retrospectively, when there is no contemporaneous display of sensor readings or in real time. Real-time monitors will demonstrate trends in glucose levels. However, there is a lag of at least 15 minutes between blood and interstitial glucose levels which increases when the blood glucose is changing rapidly, for example during exercise. Absolute interstitial glucose values are, therefore, not always the same as blood glucose levels and the interstitial glucose value should be checked with a blood glucose value prior to any therapeutic action being taken. Data can be analysed in relation to insulin doses, carbohydrate intake and exercise. These devices are helpful in monitoring suspected nocturnal hypoglycaemia and/or early morning hyperglycaemia, suspected unrecognized hypoglycaemia (for example low HbA1c without reported hypoglycaemia), disabling hypoglycaemia especially in those with hypoglycaemia unawareness and to help with further optimization of MDI or CSII when the HbA1c cannot be lowered in spite of apparent optimal treatment. There is some evidence that such devices can help lower the HbA1c and decrease the incidence of severe hypoglycaemia.
- The child should aim for pre-meal blood glucose concentrations of approximately 4–8 mmol/L (72–145 mg/dL), pre-bedtime values of 7–10 mmol/L (125–180 mg/dL) and <10 mmol/L (180 mg/dL) 1–2 hours after meals.
- In children under 5 years of age acceptance of slightly higher blood glucose concentrations may be necessary to avoid hypoglycaemia which may be a consequence of variable feeding patterns.

Blood and urinary ketone testing

Blood ketone sticks measure β-hydoxybutyrate which is the main ketone produced in insulin deficiency states. Urine sticks measure acetoacetone which is a less important ketone. Blood ketones also provide a more up to date assessment of the body's ketone production and the patient's status in the same way as blood glucose does when compared to a urine glucose measurement. Ketone levels

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Table 1.10 Interpreting glycosylated haemoglobin values.

DCCT-HbA1c (%)	IFCC-HbA1c (mmol/mol)	Comment
4.0–5.9	20–41	Within non-diabetic reference range, possibility of frequent hypoglycaemia
6.0–6.9	42–52	Ideal glycaemic control
7.0–7.5	53–59	Very good glycaemic control in the absence of complications
7.6–8.9	60–74	Associated with increased risk of microvascular complications. Advise to improve glycaemic control
9.0–10.9	75–96	Compliance likely to be a problem. Associated with high risk of microvascular complications
> 11.0	> 97	Poor compliance, probably associated with omission of insulin injections and unrestricted diet

should be measured during illness or when blood glucose concentrations are unusually high, particularly when associated with symptoms of polyuria, polydipsia, nausea or abdominal pain. The presence of hyperglycaemia and significantly raised blood (>1.5 mmol/L) or urine (+++) ketone levels indicates that DKA may be present or that urgent increases in the dosage of insulin are required to avoid this happening.

Glycosylated haemoglobin measurement

HbA1c is formed by the adduction of glucose to adult haemoglobin and reflects average blood glucose values during the previous 2–3 months. It has been recommended that to assist audit, laboratories should report their results adjusted to give comparable values to the assays used in the Diabetes Control and Complications Trial (DCCT). The DCCT-aligned normal, non-diabetic range is 4–6%.

For clinics, bench-top machines for the measurement of blood HbA1c concentrations are now available and have the advantage of providing results for discussion with the patient while they are attending clinic. Such machines, however, require careful maintenance and quality control.

Haemoglobin variants may interfere with the HbA1c assays (DCCT and International Federation of Clinical Chemistry and Laboratory Medicine (IFCC)) and lead to misleading results. In such cases, the HbA1c can be used to look at trends, the patient's glycaemic control needs to be inspected more closely, and the serum fructosamine assay which provides a measure of glycaemia in the previous 2 weeks and which is less accurate than HbA1c values may be used if available.

The American Diabetes Association (ADA) have recommend aiming for a HbA1c of <8.5% in toddlers, <8% in children and <7.5% in teenagers. The clinical interpretation of HbA1c measurements is shown in Table 1.10. Recently, many laboratories have changed to the IFCC standardized values which are more accurate and are reported in mmol/mol of haemoglobin and as whole numbers. Currently, many laboratories supply HbA1c results both as a % (DCCT-aligned) and as mmol/mol (IFCC). It is planned to change in 2011 from DCCT-aligned values to the more specific IFCC standardized values. This will also make global comparisons of HbA1c easier. Depending on glycaemic control, HbA1c concentrations should be measured every 3–6 months.

Diabetes control and complications trial (DCCT)

This trial, published in 1993, is arguably the most important publication on diabetes in the last 17 years. A total of 1441 subjects with diabetes aged 13–39 years were randomized to either: (1) continue with their conventional treatment; or (2) receive intensive therapy with increased support from the 'diabetes team' and insulin administered either by a pump or by three or more injections daily. After a mean time interval of 6.5 years, compared with conventional therapy, intensive treatment resulted in a reduction in:

- mean HbA1c concentration of approximately 2%;
- the risk of retinopathy by 76%;
- the occurrence of microalbuminuria by 39%; and
- the occurrence of neuropathy by 60%.

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

The disadvantages of intensive treatment included 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 the reduction in risk of the microvascular complications of diabetes which can result from improved glycaemic control. Furthermore, for a given mean HbA1c there was a significantly lower incidence of complications in the intensively treated group suggesting that this form of therapy produces less glycaemic excursion, thereby lowering the risk of complications. The challenge for clinicians, however, is to discover how to apply an intensive therapeutic regimen in standard clinical practice in a manner that will be acceptable to most adolescents.

Effect of exercise on blood glucose control

Exercise is beneficial to children with diabetes as it results in:

- reduced blood glucose concentrations;
- increased insulin sensitivity;
- reduced serum lipid concentrations; and
- reduced risks of hypertension and heart disease.

Ideally, blood glucose monitoring should occur before and after exercise. Hypoglycaemia can be avoided by taking complex carbohydrate in the form of a snack before exercise and/or by decreasing the dose of insulin by approximately 10–20%. In school, the teacher should be aware that the child has diabetes and carbohydrate (e.g. glucose tablets or drinks) should be available for the treatment of hypoglycaemia. Exercise can also lead to delayed hypoglycaemia (e.g. during the night) and in such circumstances additional complex carbohydrate should be taken with the bedtime snack. Occasionally, short-duration exercise can cause hyperglycaemia because of the increased secretion of counter-regulatory hormones (e.g. adrenaline) which raise blood glucose.

Diabetes in preschool-aged children

There are a number of factors which are pertinent to the management of very young children with diabetes as shown in Table 1.11.

Table 1.11 Characteristics of preschool-aged children with diabetes.

Atypical symptoms at diagnosis
Increased insulin sensitivity
Practical difficulties administering insulin injections
Prolonged night-time fast
Frequent bottle feeds in infancy
Food refusal
Inability to communicate symptoms of impending hypoglycaemia
Frequent infective illnesses often associated with vomiting
Rapid growth and neurodevelopment
Complete dependency on others to supervise their diabetes

Diabetes in adolescence

Transition clinics

Transition refers to the period between childhood and adulthood. Adolescence is accompanied by many physical and psychosocial changes. There is also a gradual change from total dependence on one's parents for treatment to independent self-management. These changes can be difficult to negotiate for patients and parents, and there is often a deterioration in glycaemic control in adolescents. It has been increasingly recognized in recent years that transition clinics (sometimes also called adolescent, teenage or young person's clinics) are of benefit to adolescents with significant chronic conditions and their families.

Ideally, in these clinics patients should be seen jointly by the paediatric and adult physician with the paediatrician introducing the patient to the adult physician. In some clinics, joint consultations are only done initially whilst in others this pattern is maintained.

The venue of the clinic varies according to local circumstances. Usually, it takes place in the hospital adult clinic but it may also take place in the paediatric clinic or in a community clinic. The environment should be appropriate for teenagers with appropriate literature, computer games and so forth.

Young adults from 14–25 years are seen in these clinics with the age range of individual clinics being very variable. Some clinics focus on the 14–18 year age group whist

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others will see mainly 18 to 25-year-old patients. When to transfer a patient to the transition clinic should depend primarily on the wishes of the young person and their family. The doctor's wishes (e.g. wanting to see a patient with type 2 diabetes with an adult physician) and local protocols will also influence this decision. Surveys have suggested that young people favour the age of approximately 18 for transfer to adult care. Discussion and planning will improve clinic attendance. The transfer may need to be planned well in advance to avoid overly long gaps between appointments.

Attendance rates can be very low and a telephone call and/or a text message 1–2 days prior to the appointment, in addition to the standard letter, can help improve attendance.

The patient may be seen with their parent(s), on their own or with a friend. Group sessions held at the same time as the clinic, for instance organized and facilitated by the DNS, where young people can exchange views about their diabetes and their ways of coping with it can be useful. As well as the doctor, DNS and dietitian, the presence of a psychologist or psychiatrist at these clinics can be very helpful. Attendance at 3–4 monthly intervals is advocated as frequent attendance is associated with better control. Though diabetic control often deteriorates in adolescence, one study demonstrated that the HbA1c improved on transfer to an adult clinic.

Paediatric clinics often permit laxer glycaemic control and focus more on particular areas such as school progress. It is important that paediatric and adult physicians get on well in transition clinics, and have agreed strategies and education programmes. Transition clinics may focus more on subjects such as exercise. Tighter glycaemic control is advocated aiming for preprandial blood glucose levels of 4–7 mmol/L (72–125 mg/dL) and levels of $\leq$ 9 mmol/L (160 mg/dL) postprandially, as control should be easier post puberty and with increasing maturity. A more intensive approach to insulin therapy is advocated and the use of insulin pumps is often discussed. In the United Kingdom, there is often no routine screening in adult clinics for thyroid disease or coeliac disease as these conditions are uncommon in adults. In contrast, there is a greater focus on screening and monitoring for microvascular and macrovascular complications which increase in incidence with age.

The clinics should also provide a forum for the education and discussion of subjects of particular relevance to teenagers such as contraception, alcohol and smoking.

It is also important for the patient to know which doctor, DNS and dietitian they should liase with and whether they would be admitted to a paediatric or adult ward should they require admission.

Insulin requirements

Insulin requirements increase in puberty partly because of the rapid increase in size and appetite, and partly because of increasing growth hormone secretion which leads to a degree of insulin resistance. This results in increased difficulty in maintaining good glycaemic control (including the dawn phenomenon) and, particularly for girls, an increased tendency to be overweight. Insulin requirements may be greater than 1.3 units/kg per day and on occasion may be as large as 2 units/kg per day. Inadequate insulin therapy may cause delayed puberty and impaired growth.

Insulin regimens

The results of the DCCT suggest that the basal bolus regimen or CSII should be used in children over 13 years. For some adolescents, giving an injection before lunch at school may not be practical. In such patients, a three-injection regimen – mixed insulin before breakfast, rapidly-acting insulin prior to the evening meal and intermediate-acting insulin (isophane) or the long-acting insulin analogue detemir before bedtime – may provide a useful compromise. Adolescents may be more concerned with short-term problems such as an increased risk of hypoglycaemia, which may lead to loss of a driving licence, than with decreasing the risk of longer term complications.

Psychological and psychiatric problems

Psychological problems are common during puberty. The presence of a psychologist or psychiatrist in clinic is particularly valuable in this age group. It is important to differentiate between the normal psychological changes of adolescence and a pathological response to a chronic disease. The latter may lead to depression and require skilled psychiatric care.

Many patients will not comply with the diet and some may even binge. A higher than average number of diabetic children, particularly girls, have eating disorders. Abnormal eating patterns may develop as a means of manipulating parents. Most eating disorders are mild and do not require formal intervention. However, occasionally a patient will develop anorexia nervosa or bulimia. These conditions can be very difficult to treat in a patient with diabetes and often necessitate a prolonged admission to an adolescent psychiatric unit. Some adolescents may smoke

and others may start using recreational drugs. They should be strongly dissuaded from both.

Not infrequently, adolescents fail to comply with their insulin treatment, experimenting with omission and/or reduction of their insulin doses, sometimes in an effort to manipulate their weight. Poor compliance may also occur in their failure to monitor blood glucose concentrations. Results in the record book can be fabricated. Recordings which for many days have been documented in the same pen, a significant discrepancy between the results and the HbA1c value, apparently excessively large insulin requirements (>1.75 units/kg per day) and poor clinic attendance are suggestive of poor compliance. Negotiating appropriate solutions to these difficult problems may take considerable patience and skill, and psychological support may be particularly helpful. There is some evidence that motivational interviewing, a counselling approach to behaviour change, may improve well-being and glycaemic control in adolescents with diabetes.

The problems listed above can lead to an increased incidence of DKA and hypoglycaemia. Furthermore, puberty is the time when the early signs of microvascular complications, such as background diabetic retinopathy, may become evident.

Miscellaneous problems

There is an increased incidence of polycystic ovary syndrome and menstrual irregularities in girls with diabetes. The menstrual cycle may also affect blood glucose control with rising values in the 2–3 days prior to the start of the period. In those in whom this occurs regularly, insulin dosage can be increased during this time.

Hypoglycaemia

In children with diabetes, hypoglycaemia may be defined as a blood glucose concentration less than 4 mmol/L (72 mg/dL). However, children whose glycaemic control is poor may experience hypoglycaemic symptoms at concentrations above 4 mmol/L (72 mg/dL) if a rapid fall in blood glucose has occurred.

Causes of hypoglycaemia

Although in up to half of cases there may be no obvious cause, hypoglycaemia may be caused by:

- a missed or delayed snack or meal;
- exercise (may also cause delayed hypoglycaemia);
- alcohol;
- an overdose of insulin;
- impaired food absorption as a result of gastroenteritis or coeliac disease; or
- Addison's disease.

Symptoms and signs of hypoglycaemia

Symptoms of hypoglycaemia are unusual with blood glucose concentrations above 3 mmol/L (55 mg/dL) and a surprising number of children, particularly those with very good glycaemic control or those with recurrent blood glucose values below 4 mmol/L (72 mg/dL), will have no symptoms even with glucose values below 2 mmol/L (36 mg/dL) (so-called 'hypoglycaemia unawareness'). The inability to respond to the usual warning signs of hypoglycaemia can lead to severe hypoglycaemia.

Fortunately, most school-aged children are quickly able to recognize the symptoms of hypoglycaemia (see Table 2.1). In young children symptoms are less obvious and may result in more severe hypoglycaemia. Chronic mild hypoglycaemia may affect concentration, school performance and intellectual function. Early age of onset of diabetes is associated with mesial temporal sclerosis. Hypoglycaemic seizures may lead to deficits in perceptual, motor, memory and attention tasks, and may also have an effect on grey matter volume.

Nocturnal hypoglycaemia

Nocturnal hypoglycaemia is common. Blood glucose concentrations fall to their lowest levels between 3.00 a.m. and 4.00 a.m. Severe hypoglycaemia is more common at night. This may be because the patient is asleep and unaware of symptoms of impending hypoglycaemia or because of an impaired response from the counter-regulatory hormones. Nocturnal hypoglycaemia may be suggested by disturbed sleep, excessive sweating, morning headaches, difficulty waking from sleep or convulsions. Continuous glucose monitoring systems (e.g. GlucoWatch Biographer) may be helpful in monitoring nocturnal blood glucose concentrations in patients with suspected or confirmed nocturnal hypoglycaemia. Parents may be afraid that their child will die in the middle of the night from hypoglycaemia – the so-called 'dead in bed' syndrome. This syndrome, thought to be caused by hypoglycaemia, is extremely rare (no recorded cases under 7 years of age) and parents should be reassured that it is very unlikely because of the effect of the counter-regulatory hormones.

Treatment of hypoglycaemia

Good glycaemic control is likely to be associated with occasional hypoglycaemic episodes which, if mild, may be acceptable. Avoidance of recurrent blood glucose

concentrations below 4 mmol/L (72 mg/dL) may prevent the development of hypoglycaemia unawareness. Hypoglycaemia may be treated by:

- the ingestion of short-acting carbohydrate (e.g. glucose tablets or drinks or a snack-sized chocolate bar) followed by complex carbohydrate (bread, cereal or pasta) to prevent a recurrence;
- application of a glucose gel (e.g. glucogel) to the inside of the mouth and its massage into the buccal mucosa or gums in a child who refuses or is unable to take any food or drink;
- intramuscular glucagon (0.5 mg if body weight <25 kg, 1 mg if weight >25 kg) in unconscious or fitting patients who should be placed in the 'recovery position'. Side effects of glucagon include nausea, vomiting, diarrhoea and hypokalaemia. Glucagon can also be administered subcutaneously. There is some evidence to show that it is equally efficacious when administered this way; and
- in hospital with 2 mL/kg of 10% dextrose given intravenously.

A hypoglycaemic convulsion may be accompanied by a normal blood glucose concentration because of the effect of the counter-regulatory hormones. In patients with neurological signs and in those who remain in a coma following treatment, other disorders (e.g. epilepsy or meningitis) should be considered.

Nocturnal hypoglycaemia may be prevented by:

- decreasing the evening/bedtime insulin dose;
- increasing the evening snack;
- the use of rapid-acting human insulin analogues;
- the use of long-acting human insulin analogues;
- the use of CSII; and
- ensuring that young children on twice daily or basal bolus regimens going to bed at 07.00 p.m. have a blood glucose concentration >10 mmol/L (180 mg/dL) and older children going to bed at 10.00 p.m. a value >7 mmol/L (125 mg/dL). If the blood glucose concentration is below these levels, a snack, a larger than usual snack or, if a snack has already been eaten, a second snack should be consumed.

Recurrent DKA

Recurrent DKA is a particular problem in adolescents and may be fatal. It may be precipitated by:

- poor compliance with insulin therapy or diet (when responsible adults administer insulin a tenfold reduction in episodes of DKA has been reported);
- infection;
- stress;
- alcohol; or
- psychosocial problems.

The treatment of DKA is described earlier in this chapter (page 8).

Management of diabetes during intercurrent illness

Acute febrile illness often leads to a rise in blood glucose due to raised levels of stress hormones and gluconeogenesis which may progress to DKA. Conversely, diseases associated with diarrhoea and/or vomiting such as gastroenteritis may lead to a fall in blood glucose and hypoglycaemia. Families should have clear guidelines on the management of diabetes during intercurrent illness ('sick day rules').

The following are the important principles for the management of diabetes during intercurrent illnesses:

- Do not to stop insulin therapy.
- Monitor blood glucose concentrations frequently, at least prior to each meal and prior to bedtime. Sometimes much more frequent monitoring, for example hourly, is required.
- Eat carbohydrate regularly. If the child has a poor appetite this may take the form of regular small snacks and/or sugary drinks, rather than large meals.
- Drink plenty of water and/or reduced sugar fluids to counteract the potential dehydration that may be associated with glycosuria and a febrile illness.
- Test blood or urine regularly for ketones.
- Adjust the dosage of insulin, increasing as necessary to treat hyperglycaemia and ketosis. For example, in cases where the blood glucose is > 14–22 mmol/L (250–400 mg/dL) with blood ketones <0.6 mmol/L (or urine ketones negative or trace) give 0.05 units/kg of rapidly-acting insulin. If these glucose readings are accompanied by blood ketones ≥1.0 mmol/L (or urine ketones moderate or large) give 0.1 unit/kg. If the blood glucose is >22 mmol/L (>400 mg/dL) then 0.1 unit/kg of rapidly-acting insulin should be administered irrespective of the presence or absence of blood or urinary ketones. If the blood glucose and/or ketones do not decrease then the dose of rapidly-acting insulin can be repeated after 2 hours. This scheme is easiest to implement in children on a basal bolus regimen. In those on a twice daily mixed insulin regimen it will entail additional injections of rapid-acting insulin following the standard injections and

Table 1.12 Suggested insulin infusion rates during surgery (same sliding scale can be used in cases of diarrhoea and vomiting).

Blood glucose concentration in mmol/L (mg/dL)	Suggested insulin infusion rate (units/kg/h)
< 4 (72)	0.01 with 2 mL/kg bolus of 10% dextrose
4–6.9 (72–124)	0.02
7.0–11.0 (125–199)	0.04
11.1–17.0 (200–306)	0.06
17.1–22.0 (307–396)	0.08
> 22.0 (> 396)	0.10

Do not stop the insulin infusion if the blood glucose is < 4 mmol/L (72 mg/dL) as this will cause hyperglycaemia. Reduce the rate of the insulin infusion further. Continue with the glucose infusion and increase the rate if required.

during the day. Blood glucose should be measured frequently when additional insulin is required. The approach to intercurrent illness in children on CSII therapy is discussed on p. 20.

- If hypoglycaemia occurs, particularly in association with gastroenteritis and mild ketosis, ensure that the child takes regular, frequent amounts of carbohydrate snacks and/or sugary drinks. Oral rehydration solutions are sometimes necessary. Occasionally, glucogel or glucagon are required to treat hypoglycaemia and to help re-establish oral feeds. Vomiting may be treated with a single injection of an anti-emetic to try and improve carbohydrate intake. The insulin dosage may need to be reduced to two-thirds or a half of the regular dose.
- In cases of severe gastroenteritis and in those with severe or persistent vomiting, IV fluids may be necessary (e.g. 5% dextrose/0.45% saline with 10 mmol of potassium per 500 mL). In such cases, it is often best to also administer IV insulin. Insulin infusion rates such as those outlined in Table 1.12 may be used, initially with hourly blood glucose measurements.
- 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 respond to changes in insulin treatment, or the child is under 5 years, or the parents remain concerned, then they should contact the diabetes nurse, doctor or hospital for further advice.

Management of diabetes when travelling

When travelling, the following principles are recommended for the management of the diabetes:

- At least twice as much insulin and equipment as would normally be required should be taken with one set of supplies taken as hand luggage. Supplies should include glucogel and glucagon.
- A letter for Customs stating the diagnosis and outlining the equipment required should be taken.
- Appropriate insurance must be arranged.
- In very hot climates, insulin should be kept refrigerated. In patients on CSII the insulin cartridge should be changed every 1–2 days.
- Snacks 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.
- With short flights or where the time zone between departure and arrival changes by less than 4 hours, no major changes to the insulin regimen are required.
- With long-haul flights crossing time zones, the most straight forward approach is to give 15–20% of the TDD of insulin as rapidly-acting insulin before main meals on the plane and to revert to the usual regime on arrival at the new destination.

When on holiday, especially those involving physical activities, children with diabetes often require less insulin than usual to avoid hypoglycaemia. At the start of the holiday, the child should be advised to monitor blood glucose concentrations regularly to help decide what changes in insulin treatment are required.

Psychological aspects of diabetes management

Ideally, a psychologist should meet with the family in clinic and be involved in the patient's care from the time of diagnosis. Additional support for the family can be gained by introducing them to other families with children with diabetes, local support groups or national diabetes associations. The child may benefit from meeting other children with diabetes by going on clinic 'away-day' trips, adventure weekends or holidays for children and families with diabetes. Whenever possible, positive encouragement should be given to the patient as

constant negative criticism by the clinical staff and/or family is unlikely to encourage compliance.

Needle phobia occasionally occurs in younger children. This problem may be helped by the child watching the parents performing blood tests or giving injections to themselves or to a teddy bear or doll. Spring loaded and jet injectors can also help (see p. 13). Various blood-testing devices exist which allow the depth of penetration of the needle into the skin to be altered. Behaviour therapy under the supervision of a clinical psychologist can also help.

Psychological problems which are common in adolescence are described on p. 25. In addition to these, severe stress, obsessive behaviour in relation to monitoring and occasionally problems from overprotective parenting may be encountered.

Management of diabetes during surgery

There are many protocols for the perioperative management of children with diabetes. These need to be agreed by the diabetes, anaesthetic and surgical teams in the hospital. The main goals of the management of diabetes during surgery are to avoid hypoglycaemia, hyperglycaemia and DKA. Blood glucose control should be optimized in the weeks preceding elective surgery. Ideally, 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 if possible.

Evening prior to elective surgery

The day prior to elective surgery, blood glucose should be measured before each meal and before bedtime. Blood or urinary ketones should also be measured. In patients treated with glargine or detemir pre-bedtime, half the dose should be administered. Severe hyperglycaemia or ketosis will require overnight correction, using maintenance IV fluids and IV insulin. If ketosis persists, surgery may need to be delayed or postponed.

Morning operations

- No solid food from midnight.
- Clear fluids may be taken up to 4 hours pre-operatively.
- Omit morning insulin dose (in patients on CSII the normal basal rate can be continued till the IV fluids and insulin are commenced).
- Measure FBC, urea and electrolytes (U and Es), and blood or urinary ketones pre-operatively.
- Start IV fluids, 5% dextrose/0.45% saline with 20 mmol of KCl/litre, at a maintenance rate (for the first 10 kg body weight – 100 mL/kg per day, for each kg between 10 and 20 kg – 50 mL/kg per day, and for each kg above 20 kg – 25 mL/kg per day) between 6.00 and 8.00 a.m.
- Simultaneously start an insulin infusion. Insulin should be administered as a continuous infusion, using a syringe pump (1 unit of short-acting insulin/mL) and the rate adjusted according to the sliding scale shown in Table 1.12 aiming for a blood glucose concentration of 6–12 mmol/L.
- Hourly blood glucose monitoring pre-operatively and half hourly monitoring perioperatively.
- Hourly blood glucose monitoring 4 hours postoperatively and subsequently 1–2 hourly depending on the blood glucose until the usual regime is restarted.
- Measure U and Es postoperatively and subsequently as indicated.
- 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 taken. The insulin infusion can be stopped 10 minutes after administering subcutaneous insulin containing a rapidly-acting insulin analogue. Food can be given at the same time as the insulin injection. In the case of children on CSII, this should be started 15 minutes prior to stopping the IV insulin. A bolus dose using the CSII can then be given with the meal.
- Following minor operations it may be possible to discharge the patient after the evening meal if the child has fully recovered.

Afternoon operations

- Patient can have breakfast with the usual dose of rapidly-acting insulin. In patients on CSII, the normal bolus can be given with breakfast and the basal rate can be continued until the IV fluids and insulin are commenced.
- Can have clear fluids up to 4 hours pre-operatively.
- Measure FBC, U and Es, and blood or urinary ketones pre-operatively.
- Start IV fluids and an insulin infusion at midday (see 'Morning operations').
- Then follow protocol for morning operations.

Emergency surgery

- Remember that 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.

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• Check weight, FBC, U and Es, blood glucose, a venous gas and blood or urinary ketones pre-operatively.
• If ketoacidosis is present, follow the DKA protocol and delay surgery until the circulating volume has been restored and any 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)

For short procedures (with or without sedation or anaesthesia) where a rapid recovery is anticipated, a simplified protocol can sometimes be followed by the diabetic/anaesthetic team. For instance, for an early morning procedure between 8.00 and 9.00 a.m. insulin and breakfast can be delayed and given immediately after completion.

Type 2 diabetes mellitus

Type 2 diabetes is most common over the age of 40 years but is becoming more frequent in adolescence. In the United Kingdom at present, approximately 1% of children under 16 years of age with diabetes have type 2 diabetes. In contrast, data from the USA shows that up to 33% of newly diagnosed patients with diabetes aged 10–19 years have type 2 diabetes. Prevalence rates in the USA suggest that 0.41% of teenagers have type 2 diabetes. More specifically, in obese children and adolescents in the USA, the prevalence of impaired glucose tolerance was 25% and of silent type 2 diabetes 0.4%, independent of ethnicity. Many of these patients had high risk factors for type 2 diabetes including a positive family history, a sedentary lifestyle predisposing to obesity, and African, Hispanic or Asian ancestry. Type 2 diabetes is also more common in females and in infants born small for gestational age who have remained short.

Type 2 diabetes is characterized by diminished pancreatic insulin secretion and insulin resistance. Islet cell and glutamic acid decarboxylase (GAD) antibodies are absent. Children with type 2 diabetes may be asymptomatic and therefore those at high risk (primarily children who are obese and have a family history of type 2 diabetes) should be screened. Most children with type 2 diabetes are overweight at diagnosis and present with absent or mild polyuria and polydipsia, little or no weight loss, hyperglycaemia and glycosuria without ketonuria. However, up to one-third have ketonuria at diagnosis and 5–25% of patients who are subsequently classified as having type 2 diabetes have ketoacidosis at presentation. It can therefore be difficult, initially, to distinguish between type 1 and type 2 diabetes (especially in overweight adolescents). Acanthosis nigricans (see Figure 1.4), polycystic ovary syndrome, hypertension, fatty liver disease and lipid disorders may also be present.

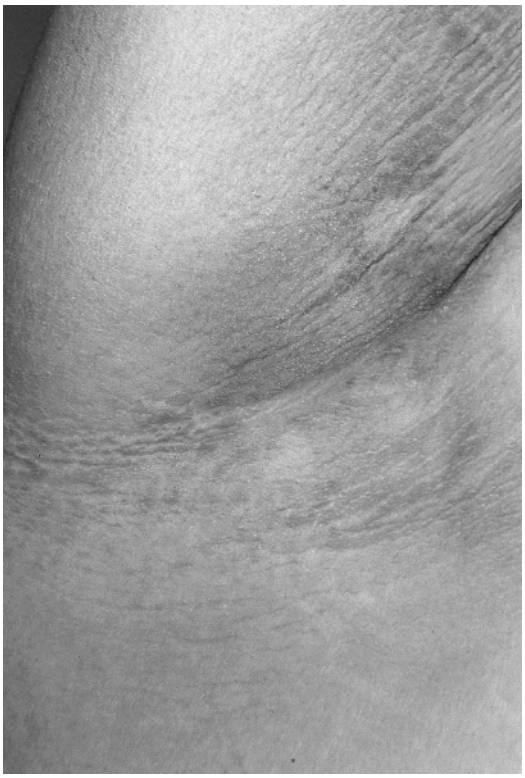

Fig. 1.4 Acanthosis nigricans.

As with type 1 diabetes, the aims of treatment are the normalization of blood glucose measurements and HbA1c, and to decrease the incidence of long-term microvascular complications. The mainstay of treatment of type 2 diabetes involves restriction of dietary carbohydrate, increased physical activity and weight reduction if obese. These measures may lead to good glycaemic control but most patients also require drug therapy at diagnosis or subsequently. The following medications can be considered:
• Biguanides (e.g. metformin), which in the presence of residual endogenous insulin secretion reduces insulin

resistance, thereby reducing β-cell demand and prolonging β-cell life.

- Sulphonylureas (e.g. gliclazide), which augment insulin secretion and therefore requires residual β-cell activity to be effective.
- Insulin therapy.

Metformin is the only biguanide therapy available. With metformin treatment, hypoglycaemia is very rare and less common than with the sulphonylureas. Oral treatment with metformin can be started with a dosage of 250 mg twice daily and increased, depending on the response, to 500 mg three times daily, or 1 g twice daily. The tablets should be taken with meals as they can cause nausea, abdominal discomfort and diarrhoea. If monotherapy with metformin is unsuccessful after 3–6 months, then a sulphonylurea or insulin can be added. Insulin is required at diagnosis in patients who present acutely with hyperglycaemia and significant ketosis or ketoacidosis. At a later stage insulin may be required if blood glucose control is poor with HbA1c >7% in spite of intensive oral medication and appropriate diet and exercise. About 10% of patients with type 2 diabetes eventually require insulin. In extremely obese diabetic adolescents with type 2 diabetes significant weight loss, an improvement in cardiovascular disease risk factors such as hypertension, and remission of type 2 diabetes may occur after bariatric surgery.

There is some evidence that in type 2 diabetes presenting in adolescents microvascular complications may be present at diagnosis and their rate of progression may be faster than in patients with type 1 diabetes. Patients should therefore be screened at diagnosis for microalbuminuria, have their blood pressure measured and have LFTs to screen for fatty liver disease. Retinal photography should be performed shortly after diagnosis and fasting lipids should be measured 1–3 months after diagnosis following metabolic stabilization. Patients may require treatment with anti-hypertensives or statins.

It is often useful to discuss treatment with an adult diabetologist as they have greater experience than paediatricians of this disorder.

Long-term complications of diabetes

Long-term complications may be microvascular (retinopathy, nephropathy, neuropathy) or macrovascular (ischaemic heart disease, peripheral vascular disease). Microvascular complications may develop in puberty or early adulthood whereas macrovascular complications affect older adults. Low socio-economic status is the single strongest predictor of poor diabetic outcome. The longer the duration of diabetes, the greater the risk of complications which increase significantly following puberty. The risk of complications may also be increased by genetic factors, poor glycaemic control and behaviour such as smoking. Diabetes is associated with a decreased lifespan of up to 15 years.

Nephropathy

The prevalence of microalbuminuria is approximately 25% and 50% after 10 and 20 years of diabetes, respectively. Diabetic renal disease may lead to chronic renal failure and necessitate dialysis or renal transplantation. Risk factors include poor glycaemic control, long-standing diabetes, smoking, and a family history of diabetic nephropathy and hypertension.

Nephropathy is preceded by the development of persistent microalbuminuria, which affects approximately 10% of children and adolescents. The urinary albumin:creatinine ratio (ACR) is used as a screening tool for this complication as timed urine collections can be difficult in children. It can be measured at any time but the most accurate measurements are those done on the first voided morning urine sample. In practice, we measure the ACR at whatever time we see the child and if it is raised (which may be due to orthostatic proteinuria) we repeat the measurement on the first voided morning urine. It should also be remembered that proteinuria may be secondary to other causes such as periods and urinary tract infections. In the United Kingdom, annual ACR measurements of the first voided urine and annual blood pressure measurements are recommended from 12 years of age onwards. In the case of raised values (which equates in many laboratories to values above 3.5 mg/mmol in females and above 2.5 mg/mmol in males and in the USA to values $\geq$ 30 μg/mg), the ACR should be repeated at least 3 monthly. The presence of persistent microalbuminuria may be defined as a raised ACR in two out of three early morning urines within a 3–6 month period. About 50% of patients with microalbuminuria revert to normoalbuminuria. The significance of this intermittent type of protein leak is unknown. A proportion will maintain normoalbuminuria whilst others will re-develop microalbuminuria and of those some will develop macroalbuminuria.

In patients with microalbuminuria, attempts should be made to improve glycaemic control, ideally lowering the HbA1c to < 6.5%, and this may lead to normoalbuminuria. Stopping smoking, exercise, a low-protein diet and blood pressure control should also be advocated. Patients with persistent microalbuminuria should have their blood

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pressure and their serum urea, electrolytes and creatinine concentrations measured and a renal ultrasound performed. This is required to help exclude other causes of microalbuminuria and to quantify the extent of any renal damage.

If the microalbuminuria persists treatment with an angiotensin-converting enzyme (ACE) inhibitor, for example lisinopril, should be considered, even in the absence of hypertension. There is good evidence in adults with type 1 diabetes and microalbuminuria that ACE inhibitors can lead to a reduction in the ACR and in some cases to reversion to normoalbuminuria, and these drugs are recommended for these patients. In the United Kingdom, there is no clear guidance on the use of ACE inhibitors in the paediatric population. It may have the same benefits as in adults. However, there is currently no evidence of any long-term benefit and ACE inhibitors can have side effects such as a cough and hyperkalaemia (serum electrolytes, urea and creatinine concentrations should be measured 5–7 days after starting treatment). Further research is necessary to evaluate their role and their current use in children under 16 years of age is controversial. It is advisable to discuss these cases with an adult diabetologist or a nephrologist.

Eye disease

The prevalence of retinopathy in adolescents varies from 18 to 47%. More than 90% of patients with type 1 diabetes will eventually develop some degree of retinopathy. Risk factors include poor glycaemic control, increased duration of diabetes, hypertension, hyperlipidaemia and smoking.

The earliest sign of diabetic eye disease is the development of background retinopathy, which consists of microaneurysms and haemorrhages with exudates which do not involve the macula (Figure 1.5). This stage is asymptomatic and does not damage vision. It may stabilize, regress with improved glycaemic control or progress if poor control continues.

Background diabetic retinopathy may, but rarely in childhood, progress to proliferative retinopathy. This can be successfully treated in its early stages with laser photocoagulation therapy. All patients with retinopathy should be referred to an ophthalmologist.

Cataracts may affect patients with diabetes but is very rare under the age of 20 years. In the United Kingdom, annual screening for diabetic retinopathy using digital retinal photography takes place from 12 years onwards.

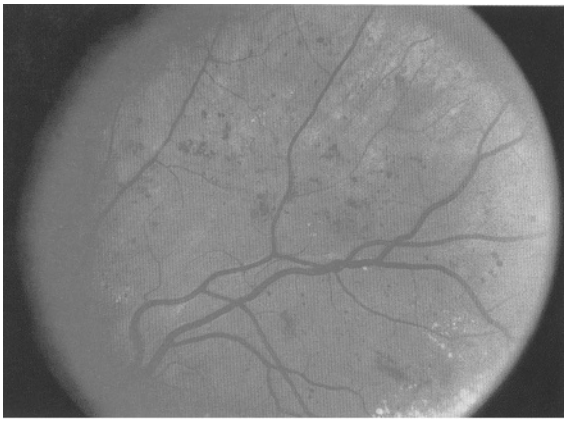

Fig. 1.5 Background retinopathy showing scattered 'dots and blots' (microaneurysms and haemorrhages) and exudates.

Neuropathy

The earliest symptoms include numbness and paraesthesia of the feet or hands with evidence of decreased vibration sense, loss of ankle jerk reflexes and a diminution in sensation to pinprick on clinical examination. However, clinically significant neuropathy in adolescence is very rare, although subclinical neuropathy demonstrated by abnormalities of motor nerve conduction velocity have been reported in 20–57% of children with diabetes.

Lipids

There is evidence that lipid levels are raised in children with type 1, and even more so in those with type 2 diabetes. However, in the United Kingdom routine screening of lipid levels in children and adolescents with type 1 diabetes is not recommended. Nevertheless, it is performed annually in some centres. If raised, the possibility of familial hyperlipidaemias should be considered. Treatment using dietary measures, life style changes or statins may need to be considered. Statin therapy is controversial in adolescents and there is no long-term outcome or safety data.

Mortality

Mortality in young adults with diabetes is increased primarily as a result of poor glycaemic control resulting in DKA or hypoglycaemia. Mortality in older individuals is raised mainly as a result of circulatory disorders, especially myocardial infarction. A reduction in life expectancy of up to 15 years has been reported. However, because of improvements in treatment, the prognosis in diabetes is constantly improving.

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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 (in the United Kingdom, the Driving and Vehicle Licensing Authority) 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 3 years may be granted.
- Prior to driving, blood glucose concentrations should be checked, and a long journey should be broken by frequent rests and meals with blood glucose concentrations remeasured as required.
- If the patient feels hypoglycaemic, the car should be stopped, the engine turned off, the keys removed from the ignition and carbohydrate consumed.
- Stores of carbohydrate 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 examinations to try and ensure optimal performance.

Employment

Patients with diabetes should be aware that they are ineligible for certain careers. In the United Kingdom, these include the armed forces, being an airline pilot and driving heavy goods or public service vehicles.

Alcohol

Ingestion of alcohol may cause a number of problems including an increased risk of hypoglycaemia and DKA with symptoms that may make it difficult for the patient or others to distinguish between drunkenness and hypoglycaemia. The following guidelines are advised:

- The importance of avoiding drinking alcohol and driving should be stressed.
- Not to drink alcohol on an empty stomach.
- To eat while drinking or shortly afterwards.
- If drinking in the evening, to take a snack prior to bedtime.
- Not to substitute the carbohydrate content of alcohol for that contained in meals and snacks when estimating dietary carbohydrate requirements.
- To avoid beers with low sugar content as these tend to contain higher alcohol concentrations and may lead to hypoglycaemia.
- To limit consumption of low-alcohol beers with increased sugar content.
- To consume dry or medium wines in preference to sweet wines.
- To use sugar-free mixers when drinking spirits.

Drug abuse

Cigarettes and recreational drugs are widely available to adolescents and their use should be strongly discouraged. Little is known about the effects of recreational drugs on diabetes. Marijuana may stimulate the appetite and lead to binge eating with a rise in the blood glucose concentration. Drug addiction may lead to neglect of the management of diabetes with adverse effects on glycaemic control. As with alcohol, it may be difficult for a patient with diabetes and others to distinguish between the effect of drugs and hypoglycaemia.

Contraception and pregnancy

To avoid unwanted pregnancies, most teenagers with diabetes should be advised to choose between using a condom or the combined oral contraceptive pill. Using a condom has the advantage of protection against sexually transmitted diseases. Adolescents with good glycaemic control and without microvascular complications can safely use a low-dose combined oral contraceptive pill containing $\leq$35 μg ethinyloestradiol. Prior to 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 the progesterone-only 'mini-pill', which is marginally less effective than the combined oral contraceptive. Further advice should be sought from a gynaecology or family planning clinic.

Poor glycaemic control in pregnancy may increase the risk of congenital abnormalities and stillbirth. There is also an increased risk of macrosomia, preterm birth and neonatal hyperinsulinism with hypoglycaemia. To reduce the risk of adverse effects of maternal diabetes on the foetus, pre-pregnancy clinics have been developed to provide advice to women with diabetes in advance of conception.

Topics discussed at these clinics include the optimization of control, diet, cessation of smoking and alcohol, possible changes in other medications (e.g. angiotensin converting enzyme inhibitors), folate therapy and assessment of retinal, renal and thyroid status. Should a teenager with diabetes become pregnant, their medical supervision should be shared with an adult physician and an obstetrician with experience in managing pregnant women with diabetes.

Endocrine and other disorders associated with diabetes

Thyroid disease

This is the most common autoimmune endocrinopathy associated with diabetes. The possibility of occult thyroid disease should be considered at diagnosis and when a patient is assessed at the annual review. Thyroid microsomal antibody titres are abnormally elevated in 7–24% of children with diabetes, although their predictive value for the development of clinically significant thyroid disease is poor. Hypothyroidism affects approximately 3.9% of children with diabetes. It may be asymptomatic and significant changes in glycaemic control are not usually observed, although hypothyroidism may on occasion lead to a decrease in insulin requirements and to hypoglycaemia.

Hyperthyroidism affects 1% of children with diabetes and may also be relatively asymptomatic. However, hyperthyroidism may also be associated with increased insulin requirements. Further details of the investigation and treatment of thyroid disease can be found in Chapter 6.

Addison's disease

Addison's disease is a potentially life-threatening autoimmune disorder which affects 0.03% of individuals with diabetes. It commonly presents with evidence of recurrent hypoglycaemia and unexpectedly falling 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 should be confirmed by the presence of adrenal autoantibodies and inappropriately low circulating serum cortisol concentrations. Further details of other relevant investigations and of treatment with glucocorticoids and mineralocorticoids can be found in Chapter 8.

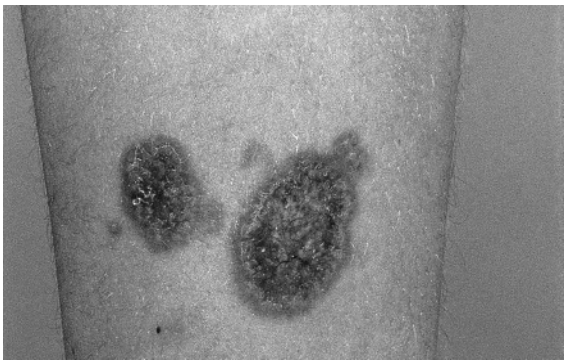

Fig. 1.6 Necrobiosis lipoidica diabeticorum on the shin.

Coeliac disease

Coeliac disease affects 3–5% of the diabetic population and may be present prior to the onset of diabetes. It is usually asymptomatic although it may present with diarrhoea, abdominal distension, anaemia or poor weight gain and linear growth. Malabsorption may lead to a fall in insulin requirements and to a predisposition to hypoglycaemia. The possibility of coeliac disease can be further investigated by the measurement of coeliac antibodies (the antitransglutaminase and antiendomysium antibodies are the most specific) and the diagnosis can be confirmed by the demonstration of the classical histological findings on a jejunal biopsy.

Treatment of coeliac disease requires a gluten-free diet. The combination of the dietary implications of a gluten-free diet and the appropriate diet for a child with diabetes can pose particular difficulties for the family and specialist dietetic advice is needed as compliance may be poor.

Necrobiosis lipoidica diabeticorum

Necrobiosis lipoidica diabeticorum affects 0.3% of people with diabetes. In childhood, it is most likely to occur in teenagers but is more common in adults. The aetiology is unknown. The lesions consist of slowly growing round or irregular non-scaling plaques with atrophic yellow centres, surface telangiectasia and livid, sometimes raised, erythematous borders (Figure 1.6,). They usually occur on the shins but may also affect the feet, arms, hands or face. The development of necrobiosis lipoidica diabeticorum is not influenced by glycaemic control. Complications include infection and ulceration of the lesions.

Approximately 20% of lesions resolve spontaneously. Treatment is difficult and consists mainly of a cosmetic approach using camouflage skin creams. Limited success

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has been achieved from the use of topical and systemic steroids and in extreme cases skin grafts may be necessary.

Unusual causes of diabetes in childhood

Maturity onset diabetes of the young (MODY)

MODY is a rare form of autosomal dominant diabetes mellitus developing before the age of 25 years which affects 1–2% of people with diabetes. Patients have a strong family history of diabetes in two or more consecutive generations. It results from β-cell dysfunction with the severity of the dysfunction depending on the underlying gene mutation. To date, nine mutations have been shown to cause MODY and these account for > 80% of patients.

MODY2 is caused by a mutation of the glucokinase gene on chromosome 7p. This leads to mild hyperglycaemia that develops in childhood and rarely requires specific treatment or results in complications.

MODY1 is caused by a mutation of the hepatic nuclear factor 4 alpha gene on chromosome 20q and MODY3 by a mutation of the hepatic nuclear factor 1 alpha gene on chromosome 12q. These forms of MODY lead to diabetes in adolescence which, unlike MODY2, requires treatment with sulphonylureas or occasionally insulin and may lead to microvascular complications. The identification of the gene mutation in a child with MODY confirms whether or not treatment is necessary, predicts the risk of future complications and allows specific genetic counselling.

Neonatal diabetes mellitus

Transient neonatal diabetes is rare with an incidence of 1 in 400,000 births. Most genetic mutations causing these cases are spontaneous but some of these patients have been shown to have paternal uniparental isodisomy of chromosome 6. Transient neonatal diabetes is thought to be caused by a delay in the maturation of the β-cells leading to hypoinsulinaemia. Intrauterine growth retardation (IUGR) is usually present. Permanent neonatal diabetes is even rarer and may be associated with neurological abnormalities. A proportion of these patients have activating mutations in the *KCNJ11* gene, which encodes the ATP-sensitive potassium channel subunit Kir6.2 in the pancreatic β-cell. Others may have insulin gene mutations.

The condition presents in the first few days or weeks of life with polydipsia, polyuria, marked weight loss, severe dehydration and vomiting. Hyperglycaemia and glycosuria are present but ketonaemia (or ketonuria) is unusual.

Initial treatment consists of rehydration and a continuous IV infusion of insulin. Thereafter, once daily subcutaneous injections of long-acting insulin can be introduced, though some patients are best managed by subcutaneous insulin pump therapy. Treatment in transient neonatal diabetes may be needed for a few days to 18 months (median 3 months). However, some of these patients may develop type 2 diabetes in later life.

Diabetes following pancreatectomy for persistent hyperinsulinaemic hypoglycaemia of infancy

Severe persistent hyperinsulinaemic hypoglycaemia of infancy may require treatment with a 95% pancreatectomy in early life (see Chapter 2). A proportion of these patients will progress to develop diabetes several months or years following surgery. It is usually relatively easy to achieve satisfactory glycaemic control in these patients, possibly because of residual pancreatic insulin secretion and reduced glucagon secretion.

Diabetes secondary to cystic fibrosis

Diabetes can develop in 5–10% of adolescents and young adults with cystic fibrosis and is thought to be caused by islet cell damage from chronic pancreatic inflammation. As with diabetes following pancreatic resection, glucagon secretion is reduced and DKA is rare, although these patients are at greater risk of hypoglycaemia than those with type 1 diabetes.

The diagnosis may be made on clinical grounds, by measuring the fasting glucose or the HbA1c. The most sensitive test is the oral glucose tolerance test.

Treatment consists of insulin therapy although the dosage of insulin required varies widely. These patients require close liaison between the paediatric diabetes and cystic fibrosis teams. The dietary management of these children may be rather different from that of type 1 diabetes because of difficulties with malabsorption and a frequently poor nutritional state. The adequacy of management of the diabetic aspects of these cases includes monitoring of both glycaemic control and weight gain.

Miscellaneous disorders

Diabetes is also associated with a number of other disorders such as Down's syndrome, Turner's syndrome, Klinefelter's syndrome, Prader–Willi syndrome, DIDMOAD syndrome, asparaginase and steroid treatment, thalassaemia and the autoimmune polyendocrine syndromes.

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Audit

Auditing practice against agreed regional, national or international standards is an essential part of running a diabetes service. A register of all patients is essential to allow audit to take place. Increasingly, these registers are computer based. Several aspects of diabetes care can be audited including:

- HbA1c concentrations;
- evidence of normal growth, weight gain and puberty;
- the adequacy of management of newly diagnosed patients, DKA, hypoglycaemia or diabetes during surgery;
- the completeness of the annual review process;
- the incidence of complications;
- patient education; and
- the patients' satisfaction with the service.

Information gained from audit can be used to promote service developments.

Future developments

- Prophylactic therapy or earlier diagnosis through genetic and immunological screening of high-risk children.
- Immunotherapy to help prolong the life of insulin producing islet cells.
- Non-invasive methods of glucose monitoring.
- Improved versions of an artificial pancreas.
- Administration of insulin by alternative routes (e.g. oral, nasal, inhalation and transdermal).
- Glucagon-like peptide analogues which have glucose lowering effects and are used in type 2 diabetes may have a role in type 1 diabetes.
- Improvements in the management and outcome of pancreatic and islet cell transplantation.
- 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 the initial insulin infusion rate for DKA be 0.05 or 0.1 units/kg per hour in young children?
- Why does cerebral oedema occur?
- Should mannitol or hypertonic saline be used in the treatment of cerebral oedema?
- Should a new patient with diabetes, but without DKA, be treated in hospital or at home?
- From what age and at what stage is an annual review necessary?
- What should the annual review comprise of?
- What are the indications for starting or changing a patient to an insulin pump?
- How much of a risk factor for future complications is poor glycaemic control before puberty?
- How can the implications of the results of the DCCT study be applied in routine clinical practice?
- In adolescents what is the role of ACE inhibitors in diabetic nephropathy and statins in those with hyperlipidaemia?
- What is the role of psychological support and motivational interviewing in helping children and adolescents to improve their glycaemic control and well-being?

Potential pitfalls

- Failure to realize that the blood glucose readings in a patient's book are fictitious (may all be written in the same pen, may not be in keeping with the HbA1c result).
- Recommending insulin doses in excess of 1.5 units/kg per day to help lower a high HbA1c when the most likely explanation is poor compliance and omission of injections.
- Failure to diagnose psychological/psychiatric problems, especially in adolescents, which may also be having an impact on 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.
- Omitting to perform annual reviews.
- Failure to identify the early signs of retinopathy when using direct ophthalmoscopy.
- Loosing track of patients, frequently adolescents, who often repeatedly fail to attend clinic (more likely to occur if no patient register is kept).
- Failure to consider Addison's 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 only mild abnormalities of glucose homeostasis and a relevant family history.

Significant guidelines/consensus statements

British Society of Paediatric Endocrinology and Diabetes (BSPED) Recommended DKA guidelines (2009). Website: www.bsped.org.uk/professional/guidelines

As well as the DKA guidelines, there is also a DKA calculator and a DKA flowchart. The guidelines include modifications made in light of the European Society of Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetes mellitus (*Archives of Disease in Childhood* (2004) **89**, 188–194) and the guidelines produced by the International Society for Pediatric and Adolescent Diabetes (*Pediatric Diabetes* (2007) **8**, 28–43).

International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical practice consensus guidelines (2009). Website: www.ispad.org Contains up to date consensus guidelines on many aspects of paediatric diabetes.

Type 1 Diabetes: Diagnosis and Management of Type 1 Diabetes in Children, Young People and Adults (2004 with update in 2009). Guideline issued by the British National Institute of Clinical Excellence. Website: www.nice.org.uk/nicemedia/pdf/CG015NICEguidelineUpdate.pdf

Lawson Wilkins Pediatric Endocrine Society. Continuous subcutaneous insulin infusion in very young children with type 1 diabetes (2006). Website: www.lwpes.org/policystatements/policyStatements.cfm

Useful information for patients and parents

Diabetes UK Website: www.diabetes.org.uk

American Diabetes Association (ADA) Website: www.diabetes.org

Juvenile Diabetes Research Foundation International Website: www.jdrf.org

Children with Diabetes Website: www.childrenwithdiabetes.com

These sites contain educational material, information on research, news and online support. Diabetes UK and the ADA have special sections for children and adolescents.

European Society for Paediatric Endocrinology Website: www.eurospe.org/patient. Information booklet on type 2 diabetes and obesity (available in English, French, Italian, Spanish and Turkish).

Case histories

Case 1.1

A 14-year-old girl had recurrent severe hypoglycaemia with two episodes leading to a convulsion and hospital admission. She was diagnosed with type 1 diabetes at 9 years of age and was treated with twice daily injections of premixed insulin with a ratio of short- to intermediate-acting insulin of 30:70, 30 units before breakfast and 18 units before the evening meal (0.9 units/kg per day). There had not been any recent changes in her diet or levels of physical activity.

Questions

1 What investigations would you consider doing?
2 If the results of these investigations proved normal, what further explanation could account for her recurrent hypoglycaemia?

Answers

1 Measurement of HbA1c concentration to assess overall glycaemic control, TFTs to exclude hypothyroidism and anti-endomysial antibody titres to exclude coeliac disease. Measurement of adrenal autoantibody titres and a Synacthen stimulation test may also be required to rule out Addison's disease.
2 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 who had had type 1 diabetes for 5 years and who was a frequent non-attendee at clinic presented with short stature and delayed puberty. He was receiving premixed insulin with a ratio of short- to intermediate-acting insulin of 30:70, 24 units in the morning and 12 units in the evening (0.7 units/kg per day). His height had fallen from the 25th to the 2nd centile since diagnosis and his weight was on the 2nd centile. His testes were 4 mL in volume with Tanner stage 2 pubic hair. His HbA1c concentration was 11.4%.

Questions

1 How would you investigate this patient?
2 How would you manage this patient?

Answers

1 Detailed dietary assessment and measurement of TFT and anti-endomysial antibodies.
2 The patient appears to have delay in the onset of puberty which is likely to have contributed to his poor growth velocity in recent years. The dietary assessment revealed a poor 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 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 boy presented with a 6-week history of polyuria and polydipsia. His father had developed type 2 diabetes at the age of 35 years, which was controlled by diet. His paternal grandfather had developed type 2 diabetes at 48 years of age, controlled by diet and gliclazide. On examination his body mass index was 22.4 kg/m^2 and he was well and not dehydrated. His blood glucose was 19 mmol/L. He had glycosuria but no ketonuria.

Questions

1 What is the likely diagnosis?
2 How would you investigate this boy?
3 Why is it important to establish a precise diagnosis?

Answers

1 The most likely diagnosis is MODY. As 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 By screening of genes, mutations of which are known to cause MODY. This patient was demonstrated to have a mutation of the glucokinase gene (MODY2).
3 The patient can be reassured that he is most 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 3-year-old girl presents for the first time with type 1 diabetes in DKA. She is dehydrated and acidotic with a pH of 7.08. She is resuscitated in accordance with the local DKA protocol and improves. However, 11 hours after admission she becomes restless and irritable, and more difficult to communicate with. She has one vomit. The nurse looking after her notes that her pulse has dropped from 120/min to 88/min.

Questions

1 What is the likeliest reason for this change in her condition?
2 What immediate investigation should be done?
3 What should be the management?

Answers

1 The likeliest explanation is that she has developed the complication of cerebral oedema. This can be present at diagnosis but more 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 early features.
2 A blood glucose should be done to rule out hypoglycaemia as the cause of her behaviour. At a later stage, a CT scan will be required to rule out other intracerebral complications such as a thrombosis or a haemorrhage.
3 A senior paediatrician and anaesthetist should be called urgently. Hypertonic (2.7%) saline or mannitol should be given as soon as possible. The patient should be nursed in a 20° head-up position to help venous drainage. Fluids should be restricted to half maintenance and the deficit replaced over 72 rather than 48 hours. The child

should be discussed with a paediatric intensive care consultant and transferred there as soon as is safely possible. She is likely to require intubation and ventilation to help maintain her $PaCO_2$ at 4.0–4.5 kPa.

Case 1.5

A 14-year-old Asian girl presents with a 6-week history of polyuria, polydipsia and weight loss. Her grandfather had developed diabetes when he was in his 50s and takes tablets. On examination, she appears overweight and her BMI is calculated as 29 kg/m^2 which is between the 98 and 99.6 percentiles on the BMI chart. She has some pink stretch marks and acanthosis nigricans. Her blood glucose is 26 mmol/L (468 mg/dL). She is not acidotic but has 3+ of glucose and moderate ketones in her urine.

Questions

1 What is the likely diagnosis?
2 What investigations would help clarify the precise diagnosis?
3 What treatment should be commenced?

Answers

1 The likeliest diagnosis is type 2 diabetes mellitus. She belongs to a high-risk ethnic group, has a family history, acanthosis and her BMI centile places her in the obese category. Pink stretch marks can occur in anyone who is obese. The ketonuria is unusual but does occur in a third of cases. In some cases, especially in one such as this where the patient has had weight loss and ketonuria, it can be difficult to distinguish between type 1 and type 2 diabetes.
2 Measuring islet cell and GAD antibodies would help (we don't usually measure insulin antibodies which are the least common). These would be negative in type 2 diabetes. Measuring C-peptide, which reflects the amount of natural insulin that the patient is producing, would also be useful. This would be normal or increased in type 2 diabetes but low in type 1 diabetes.
3 Though this patient is likely to have type 2 diabetes there is a possibility that it may be type 1. Some patients fall into a grey area between type 1 and type 2 diabetes. The results of the investigations listed in Answer 2 are likely to take several weeks. In view of this, the high blood glucose and the ketosis, it would be advisable to start this patient on a basal bolus regimen. Dietary treatment and a good exercise regime are also very important. When the ketosis has resolved and the blood glucose has come down 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.

When to involve a specialist centre

- Neonatal diabetes mellitus.
- Diabetes associated with hyperthyroidism or Addison's disease.
- Diabetes associated with cystic fibrosis or following pancreatic resection.
- If proliferative retinopathy or deteriorating renal function is present.

Further reading

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