BMJ Best Practice

Type 1 diabetes

Straight to the point of care

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Summary

Type 1 diabetes mellitus is a metabolic disorder characterised by hyperglycaemia due to absolute insulin deficiency.

Patients most often present with a few days or weeks of polyuria, polydipsia, weight loss, and weakness.

Some patients may present with diabetic ketoacidosis.

Intensive glycaemic control has been shown to decrease the incidence of microvascular and macrovascular complications.

Microvascular complications include retinopathy, nephropathy, and neuropathy.

Macrovascular complications include coronary artery, cerebrovascular, and peripheral vascular disease.

Definition

Type 1 diabetes mellitus is a metabolic disorder characterised by hyperglycaemia due to absolute insulin deficiency. The condition develops due to destruction of pancreatic beta cells, mostly by immune-mediated mechanisms. In some patients there may be no evidence of autoimmune destruction of pancreatic beta cells; this is called idiopathic type 1 diabetes.

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Epidemiology

Type 1 diabetes accounts for about 5% to 10% of all patients with diabetes. It is the most commonly diagnosed diabetes of youth (under 20 years of age) and causes ≥85% of all diabetes cases in this age group worldwide.[5] It is estimated that 1,110,100 people aged 0-19 years have type 1 diabetes worldwide, with 128,900 newly diagnosed cases each year.[6]

There is significant geographic variation in the incidence of type 1 diabetes.[7] It is more common in Europeans and less common in Asians with age-adjusted incidence rates ranging from 0.1 per 100,000 per year in parts of China to 40.9 per 100,000 per year in Finland.[7] Worldwide, the incidence of type 1 diabetes is increasing by 3% every year, although the reasons for this are unclear.[8] [9] [10] [11] One report showed a more rapid increase in non-white racial and ethnic groups.[12]

Type 1 diabetes can present at any age, with the highest incidence observed in children aged 10-14 years.[13] There is a slight male predominance, particularly after puberty.[13]

Aetiology

Certain human leukocyte antigen (HLA)-DR/DQ gene polymorphisms, particularly HLA-DR and HLA-DQ alleles, increase susceptibility to, or provide protection from, the disease.[14] In susceptible individuals, environmental factors may trigger the immune-mediated destruction of pancreatic beta cells. Although the geographical variation in disease prevalence and increasing worldwide incidence of type 1 diabetes argue for a major environmental contribution to pathogenesis, the specific factors involved remain unknown.[15] Among viruses, the strongest associations have been found with human enteroviruses.[16] [17] [18] Among dietary factors, supplementation with vitamin D may be protective.[19] [20] Further research is required to determine the effect of cow's milk, early introduction of cereals, or maternal vitamin D ingestion on type 1 diabetes risk.[21] [22] [23] Coeliac disease shares the HLA-DQ2 genotype with type 1 diabetes, and is more common among those with type 1 diabetes.[24] [25] The incidence of type 1 diabetes may also be higher among those with coeliac disease, although a causal relationship is not suggested.[26]

Pathophysiology

Type 1 diabetes usually develops as a result of autoimmune pancreatic beta-cell destruction in genetically susceptible individuals.[15] Up to 90% of patients will have autoantibodies to at least one of three antigens: glutamic acid decarboxylase; insulin; and a tyrosine-phosphatase-like molecule, islet auto-antigen-2 (IA-2).[27] Over 25% of individuals without one of these or islet cytoplasmic autoantibodies will have positive antibodies to ZnT8, a pancreatic beta-cell-specific zinc transporter.[28] In addition, 10% of adults who have been classified as having type 2 diabetes may have circulating islet cell antibodies or antibodies to glutamic acid decarboxylase, indicating autoimmune destruction of beta cells.[29]

Beta-cell destruction proceeds sub-clinically for months to years as insulitis (inflammation of the beta cell). When 80% to 90% of beta cells have been destroyed, hyperglycaemia develops. Insulin resistance has no role in the pathophysiology of type 1 diabetes. However, with increasing prevalence of obesity, some patients with type 1 diabetes may be insulin resistant in addition to being insulin deficient.

Patients with insulin deficiency are unable to utilise glucose in peripheral muscle and adipose tissues. This stimulates the secretion of counter-regulatory hormones such as glucagon, adrenaline (epinephrine), cortisol, and growth hormone. These counter-regulatory hormones, especially glucagon, promote gluconeogenesis,

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glycogenolysis, and ketogenesis in the liver. As a result, patients present with hyperglycaemia and anion gap metabolic acidosis.

Long-term hyperglycaemia leads to vascular complications due to a combination of factors that include glycosylation of proteins in tissue and serum, production of sorbitol, and free radical damage. Microvascular complications include retinopathy, neuropathy, and nephropathy. Macrovascular complications include cardiovascular, cerebrovascular, and peripheral vascular disease. Hyperglycaemia is known to induce oxidative stress and inflammation. Oxidative stress can cause endothelial dysfunction by neutralising nitric oxide. Dysfunctional endothelium allows entry of low-density lipoprotein into the vessel wall, which induces a slow inflammatory process and leads to atheroma formation.[30]

Classification

World Health Organization (WHO) 2019

In an update to its previous classification systems, the WHO's 2019 classification of diabetes no longer includes subtypes of type 1 diabetes.[1] A 'hybrid' category has been introduced to describe atypical cases with features of both type 1 and type 2 diabetes.

Case history

Case history #1

A 12-year-old white girl is brought to the emergency department by her parents due to 12 hours of rapidly worsening nausea, vomiting, abdominal pain, and lethargy. Over the last week she has felt excessively thirsty and has been urinating a lot. Physical examination reveals a lean, dehydrated girl with deep rapid respirations, tachycardia, and no response to verbal commands.

Other presentations

The rate of beta-cell destruction varies in type 1 diabetes. In some patients, there may be a slow destruction leading to gradual onset of symptoms that is clinically indistinguishable from type 2 diabetes. There is also a slow-progressing form of autoimmune diabetes known as latent autoimmune diabetes in adults (LADA).[2] The patient with LADA may not require insulin treatment for some years and it can therefore be mistaken for type 2 diabetes in the early stages.[3] Based on results from a retrospective study, features that suggest the presence of LADA rather than type 2 diabetes include two or more of the following: age of onset <50 years, acute symptoms of polydipsia and/or polyuria and/or unintentional weight loss before diagnosis, body mass index less than 25 kg/m², and personal or family history of autoimmune disease.[4]

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Approach

Clinical presentation

Type 1 diabetes can be diagnosed at any age, with a peak around 10 to 14 years.[13]

In children and young people aged under 18 years of age, the signs of type 1 diabetes include:[35]

- Hyperglycaemia (random plasma glucose ≥11.1 mmol/L [≥200 mg/dL])
- Polyuria
- Polydipsia
- Weight loss
- Excessive tiredness.

Other symptoms such as blurred vision may occur.[36]

Adults with type 1 diabetes typically present with hyperglycaemia and usually (but not always) one or more of:[37]

- Ketosis
- Rapid weight loss
- Age <50 years
- BMI <25 kg/m²
- Personal and/or family history of autoimmune disease.

Rarely, an adult patient is diagnosed with type 1 diabetes during routine blood tests. The condition is diagnosed long before its chronic complications have developed.

Many patients present with diabetic ketoacidosis, an acute complication of type 1 diabetes.[38] [39] These patients have symptoms of dehydration and acidosis such as nausea, vomiting, abdominal pain, tachypnoea, tachycardia, and lethargy. See our topic Diabetic Ketoacidosis.

There is also a slow-progressing form of autoimmune diabetes known as latent autoimmune diabetes in adults (LADA).[2] The patient with LADA may not require insulin treatment for some years and it can therefore be mistaken for type 2 diabetes in the early stages.[2] Features that suggest the presence of LADA rather than type 2 diabetes include two or more of the following: age of onset <50 years, acute symptoms, body mass index less than 25 kg/m², and personal or family history of autoimmune disease.[4]

Diagnosis in children

Suspect diabetes in children and young people under 18 years of age using the World Health Organization (WHO) criteria:[35] [1]

- In a symptomatic patient, random plasma glucose of ≥11.1 mmol/L (≥200 mg/dL) or
- Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL) or
- Plasma glucose ≥11.1 mmol/L (≥200 mg/dL) 2 hours after 75 g oral glucose or
- Glycosylated haemoglobin (HbA1c) ≥6.5% (≥48 mmol/mol).

Bear in mind that a repeat confirmatory test is required in most cases.

If you suspect the child has type 1 diabetes refer immediately (on the same day) to a multidisciplinary paediatric diabetes team who can confirm the diagnosis and give immediate care.[35]

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Assume type 1 diabetes in children and young people unless there are strong indications of type 2 diabetes, monogenic or mitochondrial diabetes.[35] See our topic Type 2 diabetes in children.

- Consider type 2 diabetes in a child or young person with suspected diabetes who:[35]
    - Has a strong family history of type 2 diabetes
    - Is obese at presentation
    - Is of black or Asian family origin
    - Has no insulin requirement, or has an insulin requirement of less than 0.5 units/kg body weight/day after the partial remission phase
    - Shows evidence of insulin resistance (for example, acanthosis nigricans).
- Consider other types of diabetes (i.e., not type 1 or 2) in a child or young person with suspected diabetes who has any of the following features:[35]
    - Diabetes in the first year of life
    - Ketonaemia during episodes of hyperglycaemia
    - Associated features, such as optic atrophy, retinitis pigmentosa, deafness, or another systemic illness or syndrome.
- Monogenic diabetes accounts for up to 4% of paediatric diabetes and insulin treatment is inappropriate in these cases.[40] The two main forms of monogenic diabetes are maturity-onset diabetes of the young (MODY) and neonatal diabetes mellitus (NDM). In NDM, diabetes is diagnosed in the first 6 months of life and may be transient (resolution by 12 months of age) or permanent. More than 90% of cases of permanent neonatal diabetes mellitus are caused by a KCNJ11 or ABCC8 genetic change which affects the link between sensing of glucose levels and release of insulin from the pancreatic β-cell.[41] Genetic testing is definitive and can be used to counsel the patient and family members.

Do not routinely measure C-peptide and/or diabetes-specific autoantibody titres at initial presentation to distinguish type 1 diabetes from type 2 diabetes. The National Institute for Health and Care Excellence (NICE) in the UK recommends only considering measuring C-peptide if there is difficulty distinguishing type 1 diabetes from other types.[35]

- If C-peptide testing is indicated, bear in mind that it has better discriminative value the longer the test is done after initial presentation.[35]
- In clinical practice, C-peptide testing should only be done with a paired glucose. In practical terms, this can be achieved by using C-peptide on a single non-fasting random blood or urine sample after the patient has eaten one of their own meals.[42] Otherwise, C-peptide might be suppressed, making a false positive result more likely. This is a particular concern if the patient has been started on therapy that can cause hypoglycaemia (e.g., insulin).

See Monitoring section for information on initial screening tests and ongoing monitoring in children with type 1 diabetes.

Diagnosis in adults

NICE recommends diagnosing type 1 diabetes on clinical grounds if an adult patient presents with hyperglycaemia, bearing in mind the typical features of clinical presentation detailed above.[37]

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- Do not discount a diagnosis of type 1 diabetes if the patient has a BMI >25 kg/m² or is aged over 50 years.[37]

On diagnosis, immediately refer the patient to the local eye screening service.[37] Screening must be performed:[37]

- As soon as possible and no later than 3 months from initial referral
- Every year thereafter.

See Monitoring section for more information on initial screening tests and ongoing monitoring in adults with type 1 diabetes.

Do not routinely measure C-peptide and/or diabetes-specific autoantibody titres to confirm type 1 diabetes in adults. NICE recommends only considering these tests if:[37]

- You suspect type 1 diabetes but the presentation includes atypical features (e.g., age >50 years, BMI >25 kg/m², slow evolution of hyperglycaemia or long prodrome)
- Type 1 diabetes has been diagnosed and treatment started but you have a clinical suspicion that the person may have a monogenic form of diabetes, and C-peptide and/or autoantibody testing may guide the use of genetic testing
- Classification is uncertain, and confirming type 1 diabetes would have implications for availability of therapy (for example, continuous subcutaneous insulin infusion [CSII or 'insulin pump'] therapy).

When C-peptide and/or diabetes-specific autoantibody titres are indicated, bear in mind that:[37]

- Autoantibody tests have their lowest false negative rate at the time of diagnosis; the false negative rate rises thereafter
- C-peptide has better discriminative value the longer the test is done after diagnosis
- With autoantibody testing, carrying out tests for two different diabetes-specific autoantibodies, with at least one being positive, reduces the false negative rate
- In clinical practice, C-peptide testing should only be done with a paired glucose. In practical terms, this can be achieved by using C-peptide on a single non-fasting random blood or urine sample after the patient has eaten one of their own meals.[42] Otherwise, C-peptide might be suppressed, making a false positive result more likely. This is a particular concern if the patient has been started on therapy that can cause hypoglycaemia (e.g., insulin).

Advice to adults with type 1 diabetes should be co-ordinated between a multidisciplinary team with skills in diabetes care.[37]

History and exam

Key diagnostic factors

hyperglycaemia (common)

- Random plasma glucose ≥11.1 mmol/L (≥200 mg/dL). A typical presenting feature.[37] [35]

polyuria (common)

- Getting up at night to urinate is typical.[35]

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polydipsia (common)

- Getting up at night to drink water is typical.[35]

Other diagnostic factors

young age (common)

- Usually presents in childhood or adolescence with the highest incidence observed in children aged 10-14 years, but can occur at any age.[13]

weight loss (common)

- Weight loss occurs at onset; often rapid in adults.[37] [35]

blurred vision (common)

- Occurs with high or fluctuating blood sugar levels.

nausea and vomiting (common)

- Suggest diabetic ketoacidosis. See our topic Diabetic ketoacidosis.

abdominal pain (common)

- Suggests diabetic ketoacidosis. See our topic Diabetic ketoacidosis.

clinical#dehydration (common)

- Suggests diabetic ketoacidosis. See our topic Diabetic ketoacidosis.

abdominal pain (common)

- Suggests diabetic ketoacidosis. See our topic Diabetic ketoacidosis.

tachypnoea (common)

- Suggests diabetic ketoacidosis. See our topic Diabetic ketoacidosis.

lethargy (common)

- Excessive tiredness is a typical presenting feature in children in particular.[35]
- May suggest diabetic ketoacidosis. See our topic Diabetic ketoacidosis.

coma or altered mental status (uncommon)

- Suggests diabetic ketoacidosis. See our topic Diabetic ketoacidosis.

Risk factors

Strong

genetic predisposition

- Over 50 genetic loci associated with type 1 diabetes risk have been identified.[15] [31] Genetic variation in the HLA region (involved in the immune response), accounts for a large proportion, with HLA DR4-DQ8 and HLA DR3-DQ2 conferring the highest risk.[15] [14]

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- The risk of type 1 diabetes in children with an affected family member is 5% (compared to a risk of 0.3% in children without an affected family member).[14] In one study, concordance for type 1 diabetes was 27.3% in monozygotic twins and 3.8% in dizygotic twins.[32]
- In genetically susceptible individuals, environmental factors may trigger the immune-mediated destruction of pancreatic beta cells.[15]

Weak

geographical region

- There is significant geographical variation in the incidence of type 1 diabetes, and it is more common in European people and less common in Asian people.[7] Human leukocyte antigen (HLA) risk profile for type 1 diabetes is widening over time, which may reflect increased environmental influence on susceptible genotypes.[33] Regional variation suggests different contributing risk exposures.[15]

infectious agents

- Strongest evidence to date is for human enteroviruses.[16] [17] [18]

dietary factors

- Among dietary factors, supplementation with vitamin D may be protective.[19] [20] Further research is required to determine the effect of cow's milk, early introduction of cereals, or maternal vitamin D ingestion on type 1 diabetes risk.[21] [22] [23] There is no consensus about the effect of breastfeeding on risk for type 1 diabetes.[34]

Investigations

1st test to order

Test	Result
random plasma glucose (children) • Confirms diagnosis in the presence of symptoms of polyuria, polydipsia, and unexplained weight loss.[1] Bear in mind that a repeat test is required in most cases.	**≥11.1 mmol/L (≥200 mg/dL)**
fasting plasma glucose (children) • Fasting is defined as no caloric intake for at least 8 hours.[1] Bear in mind that a repeat test is required in most cases.	**≥7.0 mmol/L (≥126 mg/dL)**
2-hour plasma glucose (children) • Plasma glucose is measured 2 hours after 75 g oral glucose load.[1] Bear in mind that a repeat test is required in most cases.	**≥11.1 mmol/L (≥200 mg/dL)**
HbA1c (children) • Reflects degree of hyperglycaemia over the preceding 3 months. Bear in mind that a repeat test is required in most cases.	**≥6.5% (≥48 mmol/mol)**
clinical diagnosis (adults) • In adults, diagnose type 1 diabetes on clinical grounds if the patient presents with hyperglycaemia, bearing in mind that people with type 1 diabetes typically (but not always) have one or more of: ketosis, rapid weight loss, age <50 years, BMI <25 kg/m², personal and/or family history of autoimmune disease.[37]	**clinical diagnosis**

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Other tests to consider

Test	Result
plasma or urine ketones • In the presence of hyperglycaemia suggest type 1 diabetes.	**medium or high quantity**
C-peptide • The National Institute for Health and Care Excellence (NICE) in the UK recommends only considering measuring C-peptide in the following circumstances: • 1. In a child or adult: there is difficulty distinguishing type 1 diabetes from other types.[37] [35] • 2. In an adult: you suspect type 1 diabetes but the presentation includes atypical features (e.g., age >50 years, BMI > 25 kg/m², slow evolution of hyperglycaemia or long prodrome).[37] • 3. In an adult: type 1 diabetes has been diagnosed and treatment started but you have a clinical suspicion that the person may have a monogenic form of diabetes, and C-peptide may guide the use of genetic testing.[37] • If C-peptide testing is indicated, bear in mind that it has better discriminative value the longer the test is done after initial presentation.[37] [35] • In clinical practice, C-peptide testing should only be done with a paired glucose. In practical terms, this can be achieved by using C-peptide on a single non-fasting random blood or urine sample after the patient has eaten one of their own meals.[42] Otherwise, C-peptide might be suppressed, making a false positive result more likely. This is a particular concern if the patient has been started on therapy that can cause hypoglycaemia (e.g., insulin). • C-peptide is a by-product formed when proinsulin is processed to insulin. Therefore, its levels reflect insulin production. Half life of C-peptide is 3 to 4 times longer than that of insulin. Low or undetectable C-peptide level indicates absence of insulin secretion from pancreatic beta cells.	**low or undetectable**
autoimmune markers • These include autoantibodies to glutamic acid decarboxylase, insulin, islet cells, islet antigens (IA2 and IA2-beta), and the zinc transporter ZnT8. • The National Institute for Health and Care Excellence (NICE) recommends only considering measuring diabetes-specific autoantibody titres in an adult in the following circumstances:[37] • 1. You suspect type 1 diabetes but the presentation includes atypical features (e.g., age >50 years, BMI > 25 kg/m², slow evolution of hyperglycaemia or long prodrome). • 2. Type 1 diabetes has been diagnosed and treatment started but you have a clinical suspicion that the person may have a monogenic form of diabetes, and C-peptide and/or autoantibody testing may guide the use of genetic testing. • 3. Classification is uncertain, and confirming type 1 diabetes would have implications for availability of therapy (for example, continuous subcutaneous insulin infusion [CSII or 'insulin pump'] therapy). • If diabetes-specific autoantibody titres are indicated, bear in mind that they have their lowest false negative rate at the time of diagnosis; the false negative rate rises thereafter.[37] Carrying out tests for two	**positive**

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Test	Result
different diabetes-specific autoantibodies, with at least one being positive, reduces the false negative rate.[37] • Presence indicates autoimmune beta-cell destruction.	

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Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Monogenic diabetes: maturity onset diabetes of the young	• Maturity-onset diabetes of the young (MODY) is the most common form of monogenic diabetes and affects 1% to 2% of people with diabetes.[43] • MODY is caused by mutation of a single gene (i.e., monogenic). It has autosomal dominant inheritance and should be suspected in cases of diabetes in non-obese, young patients (adolescence or young adult) with family history of diabetes in two or more successive generations.[44] • Presents with non-ketotic, non-insulin-dependent diabetes that responds to oral glucose lowering drugs.[45]	• C-peptide present. • Autoantibodies absent. • Genetic testing in patients with high index of suspicion identifies mutations most commonly in genes encoding glucokinase and transcription factors.[45]
Neonatal diabetes	• Diabetes diagnosed under 6 months of age.[46] • Usually isolated diabetes in an autosomal dominant pattern of inheritance. • Some monogenic causes are characterised by a variety of syndromic features.[47]	• Genetic testing with majority of mutations in the genes encoding the adenosine triphosphate-sensitive potassium channel and the insulin gene.[47]
Latent autoimmune diabetes in adults (LADA)	• Typical age of onset of diabetes is over 30 years old. Patients are usually non-obese and respond initially to lifestyle modifications and oral agents. Production of insulin gradually decreases (between 6 months and 5 years), such that treatment with insulin is required.[2] • LADA is considered a subset of type 1 diabetes; however, patients with LADA are frequently misclassified as having type 2 diabetes.	• Low to normal initial C-peptide level. • Can be positive for at least 1 of the 4 antibodies commonly found in type 1 diabetic patients.[2]
Type 2 diabetes	• Typically, signs of insulin resistance (such as	• C-peptide present. • Autoantibodies absent.

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Condition	Differentiating signs / symptoms	Differentiating tests
	acanthosis nigricans) should be sought and in their absence clinical suspicion of type 1 diabetes is greater. • Signs of more marked insulin deficiency (for example, glycaemic lability as well as susceptibility to ketosis) raise suspicion of type 1 diabetes. • Older age and slow onset, obesity, a strong family history, absence of ketoacidosis, and initial response to oral anti-hyperglycaemic drugs are typical of type 2 diabetes.	• Testing for C-peptide and autoantibodies usually not required.

Criteria

World Health Organization (WHO) criteria[1]

- In a symptomatic patient, random plasma glucose of ≥11.1 mmol/L (≥200 mg/dL) or
- Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL) or
- Plasma glucose ≥11.1 mmol/L (≥200 mg/dL) 2 hours after 75 g oral glucose or
- Glycosylated haemoglobin (HbA1c) ≥6.5% (48 mmol/mol).

Screening

Routine screening is not recommended for type 1 diabetes due to a low population prevalence. Screening for antibodies that confer high risk is also not recommended because animal and human studies have not confirmed the utility of treatment (e.g., with nicotinamide; or oral, parenteral, or nasal insulin) to prevent or delay type 1 diabetes in high-risk individuals. Screening for related antibodies is only recommended in the context of a clinical research study.[48]

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Approach

In the short term, insulin is life-saving in the management of type 1 diabetes because it prevents diabetic ketoacidosis, a potentially life-threatening condition. See our topic Diabetic ketoacidosis.

The long-term goal of insulin treatment is the prevention of chronic complications by maintaining blood glucose levels as close to normal as possible. Generally, glycosylated haemoglobin (HbA1c) goals determine the aggressiveness of therapy, which is in turn individualised.

The National Institute for Health and Care Excellence (NICE) in the UK recommends an HbA1c target level of 48 mmol/mol (6.5%) or lower.[35] [37]

- A less stringent target may be appropriate for some patient groups including very young children, older adults, people with a history of severe hypoglycaemia, and those with limited life expectancies, advanced microvascular or macrovascular complications, or comorbid conditions.[46]
- If the patient is a child or young person, be aware that a stringent target can cause emotional distress and/or conflict with family members or carers and a compromise may need to be agreed.[35]
- If the patient is an adult, agree an individualised HbA1c aim with them, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation, and history of hypoglycaemia.[37]

Measure HbA1c levels at least:

- Every 3 months in children and young people aged under 18 years[35]
- Every 3 to 6 months in adults.[35]

Optimal glucose levels in type 1 diabetes require attention to diet, exercise, and insulin therapy. All three components should be co-ordinated to minimise symptoms and the risk of complications. Self-monitoring of blood glucose (SMBG) is a core component of self care.

Glucose monitoring in children

Advise children (and/or their family members or carers) to routinely perform at least five capillary blood glucose tests every day.[35]

- More frequent testing will be needed to support safe exercise and during intercurrent illness.

Children and young people aged under 18 years should aim for:[35]

- On waking: a fasting plasma glucose level of 4-7 mmol/L (72-126 mg/dL)
- Before meals at other times of day: a plasma glucose level of 4-7 mmol/L (72-126 mg/dL)
- After meals: a plasma glucose level of 5-9 mmol/L (90-162 mg/dL)
- When driving: a plasma glucose level of at least 5 mmol/L (90 mg/dL).[49]

Give ongoing real-time continuous glucose monitoring (CGM) with alarms to children and young people who have any one of:[35]

- Frequent severe hypoglycaemia
- Impaired awareness of hypoglycaemia associated with adverse consequences (e.g., seizures or anxiety)

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- Inability to recognise, or communicate about, symptoms of hypoglycaemia (e.g., because of cognitive or neurological disabilities).

Consider ongoing real-time CGM for:[35]

- Neonates, infants and pre-school children
- Children and young people who participate in high levels of physical activity (e.g., sport at a national level)
- Children and young people with comorbidities (e.g., anorexia nervosa) or who are receiving treatments that can make it difficult to control blood glucose (e.g., corticosteroids).

Glucose monitoring in non-pregnant adults

Teach the patient self-monitoring skills at the time of diagnosis and initiation of insulin therapy. Review these skills with them at least once a year. Include information on:[37]

- How to measure their blood glucose
- How to interpret the results
- What action to take.

Support adults with type 1 diabetes to check their blood glucose at least 4 times a day.[37] Increase to up to 10 times a day if any of the following apply:[37]

- The patient's agreed HbA1c target is not met
- The frequency of hypoglycaemia episodes increases
- There is a legal requirement to do so (e.g., before driving)
- While the patient is ill
- Before, during, and after sport
- While planning pregnancy, during pregnancy, and while breastfeeding
- If there is any other reason to know blood glucose levels more than 4 times a day (e.g., impaired awareness of hypoglycaemia; high-risk activities).

Bear in mind that additional testing (more than 10 times a day) might be indicated:[37]

- If the patient has impaired awareness of hypoglycaemia
- Depending on the patient's lifestyle (e.g., if they drive for long periods or have a high-risk job).

In practice, most adults with type 1 diabetes are likely to be checking their blood glucose between 4 and 10 times a day.

Advise adults with type 1 diabetes to aim for:[37]

- On waking: a fasting plasma glucose level of 5-7 mmol/L (90-126 mg/dL)
- Before meals at other times of day: a plasma glucose level of 4-7 mmol/L (72-126 mg/dL)
- After meals: a plasma glucose level of 5-9 mmol/L (90-162 mg/dL) at least 90 minutes after eating
- Bedtime: a personalised plasma glucose level that takes into account the timing of their last meal and its related insulin dose, and is consistent with the recommended fasting level on waking.

If the patient drives, ensure they are aware of the relevant local advice on plasma glucose level. In the UK, the Driver and Vehicle Licensing Agency (DVLA) advises to aim for a level of at least 5 mmol/L (90 mg/dL) before driving.[49]

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Some adults with type 1 may require glucose measurement with real-time continuous glucose monitoring (CGM). Real-time CGM, worn by a patient on a regular basis, may help improve glycaemic levels.[50] [51] [52] The glucose sensors used in CGM are not reliable at lower ranges of glucose, and thus do not eliminate the need for finger sticks. Development of these systems is ongoing.[53] CGM is also less accurate than traditional capillary blood glucose monitoring methods. However, it provides information on glucose trends, provides alarms to alert patients to impending hypo- or hyperglycaemia, and can reduce episodes of hypoglycaemia.[54] [55]

The National Institute for Health and Care Excellence (NICE) in the UK recommends considering real-time CGM if any of the following apply despite optimised insulin therapy and conventional self-monitoring of blood glucose, provided CGM can be overseen by a centre with expertise in its use and the patient is able to commit to using it at least 70% of the time and calibrating it as needed:[37]

- More than one episode a year of severe hypoglycaemia with no obviously preventable precipitating cause
- Complete loss of awareness of hypoglycaemia
- Frequent (more than two episodes a week) asymptomatic hypoglycaemia that is causing problems with their daily activities
- Extreme fear of hypoglycaemia
- Hyperglycaemia (HbA1c level of 75 mmol/mol [9%] or higher) that persists despite testing at least 10 times a day. Continue real-time CGM only if HbA1c can be sustained at or below 53 mmol/mol (7%) and/or there has been a fall in HbA1c of 27 mmol/mol (2.5%) or more.

NICE is reviewing the guidance with a view to extending the criteria for CGM eligibility to include people with sub-optimal glycaemic control.[37]

Sick-day rules

Give the patient clear and individualised oral and written advice (‘sick-day rules’) about how to adapt management during intercurrent illness.[37] [35] This illness plan should include:

- Monitoring blood glucose
- Monitoring and interpreting blood ketones (see below)
- Adjusting their insulin regimen
- Adapting food and drink intake
- How to seek further advice.

Ketone monitoring

Ketone monitoring is an additional aspect of management. Insufficient insulin can lead to increased ketone levels which, if untreated, can lead to progressive dehydration and diabetic ketoacidosis (DKA). DKA is a severe life-threatening complication. See our topic Diabetic ketoacidosis.

The risk of DKA is increased if the patient has an illness (e.g., flu or a urinary tract infection) or has missed some insulin doses.

Offer children and young people with type 1 diabetes blood ketone testing strips and a meter. Advise the patient (and/or their family members or carers) to test for ketonaemia if they are ill or have hyperglycaemia.[35]

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Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults, to facilitate self-management of an episode of hyperglycaemia.[37]

Diet and exercise

Support the patient (and their family members or carers, as appropriate) to develop a good working knowledge of nutrition and how it affects their diabetes.[35] [37]

- There is no standardised dietary advice that is suitable for all individuals with diabetes.[46]
- Individualised nutrition advice should be based on personal and cultural preferences, health literacy and numeracy, access to healthful food choices, and willingness and ability to make behavioural changes. It should also address barriers to change.
- Nutritional recommendations should be modified to take into account: excess weight and obesity, those who are underweight, disordered eating, hypertension and renal failure.[37]
- All patients with diabetes should receive individualised medical nutrition therapy, preferably provided by a registered dietitian who is experienced in providing this type of therapy to diabetes patients.[56]

Carbohydrate counting (with adjustment of insulin dose according to an insulin:carbohydrate ratio) or consistent carbohydrate intake with respect to time and amount may improve glycaemic control. The UK National Institute for Health and Care Excellence (NICE) recommends a low glycaemic index diet to improve blood glucose control in children and young people but does not recommend this approach in adults.[37] [35] Rapid-acting insulins may make timing of meals less crucial than in the past, but regular meals are still important.

Encourage the patient to undertake physical activity on a regular basis.

- Patients with type 1 diabetes can safely exercise and manage their glucose levels.[40] [57] [58] Be aware that in practice many patients find exercise challenging, particularly as acute exercise increases the risk of dysglycaemia.[58] Therefore the patient will need access to ongoing support, education and input from educators to help them incorporate exercise into daily life.
- Pre-exercise carbohydrate intake and insulin doses can be effectively modified to avoid hypoglycaemia during exercise and sports.[59]
- Hypoglycaemia can occur up to 24 hours after exercise and may require reducing insulin dosage on days of planned exercise. A carbohydrate snack (10-20g) should be given at the start of exercise if the patient's blood sugar is <5.0 mmol/L (<90 mg/dL).[58]

The following should be assessed prior to starting an exercise programme: age; physical condition; blood pressure; and presence or absence of autonomic neuropathy or peripheral neuropathy, pre-proliferative or proliferative retinopathy, or macular oedema. Vigorous exercise may be contraindicated with proliferative or severe pre-proliferative diabetic retinopathy. Non-weight-bearing exercise may be advisable in patients with severe peripheral neuropathy.

Be alert to the possibility of bulimia nervosa, anorexia nervosa and disordered eating in patients with type 1 diabetes with:[37]

- Over-concern with body shape and weight
- Low BMI
- Hypoglycaemia
- Sub-optimal overall blood glucose control.

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Consider an early (or if needed, urgent) referral to local eating disorder services for patients with type 1 diabetes who have an eating disorder.[37]

Initiating insulin

Intensive therapy with insulin should be started as soon as possible after diagnosis.[60] Unlike older regimens that used non-physiological insulin dosing, intensive therapy aims to mimic physiological insulin release by combining basal insulin with bolus dosing at mealtimes. Both continuous infusion with an insulin pump and a regimen of multiple daily injections (MDI) can provide intensive therapy.[61] See Regimens below.

Insulin dosing

An initial total daily dose of insulin in adults can be 0.2 to 0.4 units/kg/day. In children, an initial daily dose will be 0.5 to 1.0 units/kg/day, and during puberty the requirements may increase to as much as 1.5 units/kg/day. Often, when first started on insulin, patients with type 1 diabetes will experience a honeymoon period, during which they may require fewer units each day. In general, one half of the total dose is given as basal insulin and one half as bolus dosing.[46] The bolus dosing is divided and given before meals. Basal dose timing varies according to individual patient requirements and the type of insulin used (e.g., insulin detemir is usually given once or twice daily depending on the patient's needs, insulin glargine and insulin degludec are usually given once daily at any time of the day, but preferably at the same time every day). Administration times may vary; check your local guidelines for more information. Patients need to self-monitor their blood glucose levels. In adults, the insulin doses can be adjusted every 2 to 3 days to maintain target blood glucose. Encourage children and young people who are having multiple daily insulin injections to adjust the insulin dose if appropriate after each blood glucose measurement.[35]

To maintain an HbA1c target of 48 mmol/mol (6.5%) or lower, advise adults with type 1 diabetes to aim for:[37]

- On waking: a fasting plasma glucose level of 5-7 mmol/L (90-126 mg/dL)
- Before meals at other times of day: a plasma glucose level of 4-7 mmol/L (72-126 mg/dL)
- After meals: a plasma glucose level of 5-9 mmol/L (90-162 mg/dL) at least 90 minutes after eating
- Bedtime: a personalised plasma glucose level that takes into account the timing of their last meal and its related insulin dose, and is consistent with the recommended fasting level on waking.

Children and young people aged under 18 years should aim for:[35]

- On waking: a fasting plasma glucose level of 4-7 mmol/L (72-126 mg/dL)
- Before meals at other times of day: a plasma glucose level of 4-7 mmol/L (72-126 mg/dL)
- After meals: a plasma glucose level of 5-9 mmol/L (90-162 mg/dL).

If the patient drives, ensure they are aware of the relevant local advice on plasma glucose level. In the UK, the Driver and Vehicle Licensing Agency (DVLA) advises to aim for a level of at least 5 mmol/L (90 mg/dL) before driving.[49]

The simplest approach to covering mealtime insulin requirements is to suggest a range of doses, such as 4 units for a small meal, 6 units for a medium-sized meal, and 8 units for a larger meal. For greater flexibility of carbohydrate content of meals, pre-meal insulin can be calculated based on the estimated amount of carbohydrate in the meal and the patient's individual insulin-to-carbohydrate ratio. Online

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structured education programmes can help patients with these strategies - see Structured education below.

Check your local protocol for the recommended insulin-to-carbohydrate ratio. Most adults in the UK are advised to start with a ratio of 1 unit of mealtime insulin for every 10 g of carbohydrate in the meal, although a more conservative approach (e.g., 1 unit per 15g carbohydrate) is more usual practice in some other countries.[66] Patients can use the carbohydrate content per serving listed on food packaging to assess the number of grams in their anticipated meal, but carbohydrate counting is best learned with the help of a dietitian or via a structured diabetes education programme.[37] Using a food diary and 2-hour postprandial blood glucose measurements, the insulin-to-carbohydrate ratio can be adjusted. A correction (or adjustment) dose may be added to the bolus insulin based on the pre-meal blood glucose level. Correction dosing can also be calculated using the patient's total daily dose of insulin (TDD) if food intake is stable. The correction dose can be added to the patient's mealtime insulin requirement (whether based on general meal size or carbohydrate counting) and given as the total bolus dose.

Regimens

Offer the patient, whether they are an adult or child, a multiple daily injection basal-bolus insulin regimen from diagnosis.[37] [35] Do not offer adults newly diagnosed with type 1 diabetes twice-daily mixed, basal only, or bolus only insulin regimens.[37]

Using a combination of long-acting insulin (insulin detemir, degludec, or glargine) for basal dosing, and rapid-acting insulin (insulin lispro, aspart, or glulisine) for bolus dosing, MDI regimens can be designed based on physician and patient preference and modified based on glucose monitoring data. In the UK, NICE recommends for adults:[37]

- Basal insulin therapy:
    - Offer twice-daily insulin detemir, or one of the following alternatives:
        - An insulin regimen that the patient is established on and meeting their agreed treatment goals
        - Once-daily insulin glargine if the patient cannot tolerate insulin detemir or has a strong preference for once-daily basal injections
        - Once-daily insulin degludec if there is a particular concern about nocturnal hypoglycaemia
        - Once-daily ultra-long-acting insulin, e.g., insulin degludec, if the patient needs help from a carer or healthcare professional to administer injections.
    - Consider other basal insulin regimens if the patient does not meet their treatment goals with the above options, taking into account the patient’s preferences and comorbidities, risk of hypoglycaemia and diabetic ketoacidosis, and any concerns around adherence.
- Bolus dosing: analogue rapid-acting insulins as the first-line choice.

There is no consensus as to whether insulin analogues are superior to conventional insulins for glycaemic control or reductions in complications.[67] [68]

In the past, many patients were managed with twice-daily injections of a mixture of rapid-acting and intermediate-acting insulin. This regimen may be used if patients are unable to safely self-manage with MDI, but it is no longer a first-line recommendation for management because of its lack of flexibility.

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An insulin pump (continuous subcutaneous insulin infusion [CSII]) may be considered in some patients for whom MDI regimens are inappropriate or unsuccessful. In the UK, NICE recommends an insulin pump as an option for:[35] [69]

- Children younger than 12 years for whom MDI therapy is impractical or inappropriate. These patients would be expected to have a trial of MDI therapy at some point between the ages of 12 and 18 years.
- Adults and children 12 years and older whose attempts to achieve target HbA1c levels with an MDI regimen have resulted in disabling hypoglycaemia with a significant impact on quality of life. The pump should only be continued if it results in a sustained fall in HbA1c levels and/or a reduction in the frequency of hypoglycaemia episodes.

The insulin pump has a subcutaneous insulin infusion port which is changed every 3 days. The pump uses short-acting or rapid-acting insulin, and provides a basal rate of insulin and delivers mealtime bolus dosing. However, the patient (or a parent or carer) must still measure blood glucose frequently (in practice, 4-7 times each day) in order to adjust the pump to deliver the appropriate amount of insulin. Insulin pumps may reduce hypoglycaemia, especially when combined with continuous glucose monitoring (CGM) systems and threshold suspend features, and improve HbA1c, while providing greater flexibility.[54] [70] [71] [72] [73] Because of the monitoring and dose adjustment required, use of a pump requires a motivated patient skilled in diabetes self-management and with access to practitioners trained in pump therapy.[74] [75] If the patient is a child, they will need strong family support in place.[74]

Insulin pumps with glucose sensors integrated into the same unit are called sensor-augmented insulin pumps. Functionality between sensor and pump has been integrated in one available device: a 'closed loop' system. The basal insulin delivery can be determined automatically based on sensor glucose levels. These integrated devices use a computerised control algorithm to create the hybrid closed loop insulin delivery system, which functions as an artificial pancreas.[40] [76] [77] In clinical trials, such systems have been shown to reduce the risk of nocturnal hypoglycaemia and to improve glucose control, including in children.[78] [79] [80] Some models come with smartphone apps that can be used to monitor glucose and insulin dosing. Use of sensors and sensor-augmented pumps is increasing.

Remind the patient to rotate injection sites within the same body region. The Medicines and Healthcare products Regulatory Agency (MHRA) advises this is to prevent or reduce the risk of developing cutaneous amyloidosis (insulin lipodystrophy) at the injection site which may lead to poor diabetes control caused by lack of insulin absorption due to the amyloid mass.[81]

Insulin should not be withdrawn from insulin pen devices or cartridges.[37] NHS England warns that the strength of insulin in pen devices can vary by multiples of 100 units/mL, whereas insulin syringes have graduations only suitable for calculating doses of standard 100 units/mL. If insulin extracted from a pen or cartridge is of a higher strength than intended, and that is not considered in determining the volume required, it can lead to a significant and potentially fatal overdose.[82]

Ensure the risk of medication errors with insulins is minimised by:

- Prescribing insulins by brand name[37]
    - There are a number of 'sound-a-like' insulins and, in some cases, multiple different strengths and formulations of each type of insulin[83]

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- Following local guidance on minimising the risk of medication error with high strength, fixed combination and biosimilar insulin products.[37] [MHRA: High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error] (https://www.gov.uk/drug-safety-update/high-strength-fixed-combination-and-biosimilar-insulin-products-minimising-the-risk-of-medication-error?UNLID=753360727201648136 2#dose-conversion-when-switching-between-standard-and-high-strength-insulin-products)

Technological advances

There have been significant advances in technology for managing type 1 diabetes. Evolving technology offers the potential to support glycaemic management, reduce complications and the burden and risks of hypoglycaemia, while improving the patient's quality of life.[84]

In addition to insulin pump therapy and real-time CGM, the advent of intermittently scanned CGM (flash glucose monitoring) empowers the patient to easily access detailed data on their glucose levels, including the direction and rate of change.[84] Flash glucose monitoring, where the patient checks interstitial glucose levels by intermittently scanning a subcutaneous sensor using a reader or a smartphone app, is currently available in many countries for people with type 1 diabetes who meet specific regional criteria. In England, the NHS England criteria, estimated to represent up to 20% of those with type 1 diabetes, span a number of patient groups, including any patient who needs to monitor their blood glucose >8 times per day or who has disabling hypoglycaemia episodes.[85]

Structured education

Accredited online structured education programmes further empower people with diabetes to manage their own condition, by providing remote support to the patient as a complement to their usual appointments.[86]

- NICE in the UK recommends offering all adult patients with type 1 diabetes access to an evidence-based structured education programme 6 to 12 months after diagnosis.[37]
- Offer children and young people and their families a continuing education programme from the point of diagnosis that is tailored to take account of age and maturity.[35]

Awareness of hypoglycaemia

Hypoglycaemia is the most common and potentially most serious side effect of insulin therapy. It can lead to decreased quality of life; severe hypoglycaemia is a medical emergency which can cause confusion, seizures, and coma. Severe hypoglycaemia is defined as any low blood glucose level leading to cognitive impairment requiring assistance from another person for recovery. Assess the patient's awareness of hypoglycaemia at each annual review.[37] In adults, use the Gold score or Clarke score.[37]

Episodes of hypoglycaemia occur with different frequency among patients. Patients should check a 3 a.m. blood glucose if there is concern about risk of nocturnal hypoglycaemia. To manage nocturnal hypoglycaemia (symptomatic or detected on monitoring), review the patient's knowledge and self-management skills, current insulin regimen, evening eating habits and previous physical activity.[37] Opt for an insulin type and regimen that is less likely to induce low glucose levels at night.[37] A bedtime snack is not always an effective way of decreasing the risk of nocturnal hypoglycaemia.[87] However, a bedtime snack without insulin (or overnight basal insulin reduced by 20%) is recommended if the patient exercises in the afternoon or evening.[57] Bedtime snacks might also be a suitable approach for patients in hospital.

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Alcohol may cause acute hypoglycaemia, but both alcohol and exercise can cause delayed hypoglycaemia (by up to 24 hours).

Work with the patient to determine contributing factors, and the ability of the patient to recognise and treat hypoglycaemia appropriately. Advise patients (or parents/carers) that it is important to always have immediate access to a source of fast-acting glucose and blood glucose monitoring equipment so that they can respond quickly to symptoms or signs of hypoglycaemia.[37] [35] Train and equip the patient's family, friends and/or carers (as appropriate) to give intramuscular glucagon for severe hypoglycaemia in an emergency.[37] [35]

Immediately treat mild to moderate hypoglycaemia in children and young people with oral fast-acting glucose, e.g., 10-20 g (liquid carbohydrate may be easier to swallow than solid). Fast-acting glucose may need to be given in frequent small amounts, because hypoglycaemia can cause vomiting.[35] Recheck the patient's blood glucose levels within 15 minutes (fast-acting glucose should raise blood glucose levels within 5-15 minutes), and give more fast-acting glucose if they still have hypoglycaemia.[35] As the patient's symptoms improve or their blood glucose levels return to normal, give oral complex long-acting carbohydrate to maintain blood glucose levels, unless the child or young person is about to have a snack or meal or having a continuous subcutaneous insulin infusion.[35]

For children and young people with type 1 diabetes who are in hospital, treat severe hypoglycaemia with 10% intravenous glucose if rapid intravenous access is possible. For children and young people with type 1 diabetes who are not in hospital, or if rapid intravenous access is not possible, treat severe hypoglycaemia with intramuscular glucagon or a concentrated oral glucose solution.[35] Do not use oral glucose solution if they have reduced consciousness, because this could be dangerous.[35] Seek senior assistance if the patient's blood glucose levels do not respond or symptoms continue for more than 10 minutes.[35] As symptoms improve or blood glucose levels return to normal, and once the child or young person is sufficiently awake, give oral complex long-acting carbohydrate to maintain normal blood glucose levels. Check blood glucose repeatedly in children and young people who have persistently reduced consciousness after a severe hypoglycaemic episode, to determine whether further glucose is needed.[35]

If the patient is an adult and able to ingest orally, hypoglycaemia can be treated with a fast acting form of glucose.[37] If oral intake is not possible owing to a decreased level of consciousness, glucagon is required.[37] This can be administered intramuscularly (by a family member or friend who has been shown how to do this) or intravenously (by a healthcare professional adept at obtaining intravenous access).[37] The patient should be monitored for response at 10 minutes, and then given intravenous glucose if their level of consciousness is not improving significantly. Once it is safe for the patient to have it, they can be given oral carbohydrate. The patient will need continued observation by someone who has been warned of the risk of relapse.[37]

If hypoglycaemia becomes unusually problematic or frequent, review the possible causes including: inappropriate insulin regimens (incorrect dose distributions and insulin types); meal and activity patterns, including alcohol; injection technique and skills, including insulin resuspension if necessary; injection site problems; possible organic causes including gastroparesis; changes in insulin sensitivity (including drugs affecting the renin–angiotensin system and renal failure); psychological problems; previous physical activity; lack of appropriate knowledge and skills for self-management.[37] Consider referring children and young people with type 1 diabetes for assessment of cognitive function if they have frequent hypoglycaemia or recurrent seizures.[35]

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Goal not met

If glycaemic levels are not appropriate as measured by the HbA1c or by episodes of hypoglycaemia, re-visit the patient's diet, exercise, and insulin regimen. Children and adolescents may have erratic eating patterns or snack frequently. Consider the possibility of non-adherence to therapy, particularly in adolescent patients.[35] Bear in mind that people with diabetes might be struggling to manage their diabetes effectively owing to psychological and social challenges; these patients will require an integrated multi-disciplinary approach, including psychologists, psychiatrists and support workers.[88] Specifically consider whether an eating disorder, and associated concerns about body size and weight, might be influencing how the patient uses their insulin.[37]

Consultation with a dietitian is an invaluable part of the treatment approach, as patients can learn how to count carbohydrates and adjust their pre-meal insulin to allow for flexibility in meal content and activity. Consistent fasting or overnight hyperglycaemia may require an increase in basal insulin. Pre-prandial and postprandial hyperglycaemia may be due to inadequate insulin coverage for the most recent meal, and may be addressed by considering carbohydrate content of meals, the patient's assessment of their carbohydrate intake, and subsequent pre-meal insulin dosing and timing (around 15 minutes before meals is ideal).

Other conditions contributing to unstable diabetes and that co-exist most commonly with diabetes include coeliac disease, thyroid disease, Addison's disease, and psychosocial distress. Coeliac disease, thyroid disease, and psychosocial distress should be screened for at diagnosis and on a regular basis, while increased clinical suspicion should prompt screening for Addison's disease and pernicious anaemia.

Adjuncts to insulin in adult patients

Consider adding metformin to insulin therapy if an adult patient has a body mass index (BMI) of 25 kg/m² or above (23 kg/m² or above for people from South Asian and related minority ethnic groups) and wants to improve their blood glucose control while minimising their effective insulin dose.[37] However, the benefits of this approach have been the subject of debate.[89] [90]

Bear in mind that some patients with type 1 diabetes might be taking dapagliflozin as an adjunct to insulin, an approach that was previously recommended by NICE in the UK for certain patients. However, dapagliflozin is no longer licensed for treating type 1 diabetes in the UK or Europe and should not be used for this patient group, after the manufacturer voluntarily removed this indication for its use in October 2021. The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the European Medicines Agency have advised that if your patient is already taking dapagliflozin:[91] [92]

- This should be reviewed and discontinued by, or in consultation with, a specialist as soon as clinically practical
- After stopping dapagliflozin treatment, frequent blood glucose monitoring is recommended
- An increased insulin dose may be needed, which should be undertaken carefully to minimise the risk of hypoglycaemia or hyperglycaemia.

The MHRA also advised that a small increase in blood pressure may be seen upon discontinuation, since dapagliflozin has a diuretic effect.

The withdrawal of this indication is not due to any new safety concerns, and other indications for dapagliflozin remain unchanged. Additional risk minimisation materials to mitigate the risks of diabetic ketoacidosis in patients with type 1 diabetes are no longer available.[91]

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Planning pregnancy

Infants of women with diabetes are at high risk of major congenital malformations and miscarriage.[93] Pre-conception diabetes care reduces this risk.[94] Pre-conception counselling should, therefore, be incorporated in the routine diabetes clinic visit for all women of childbearing potential.[95] Hyperglycaemia during early pregnancy is associated with an increased risk of congenital anomalies whereas hyperglycaemia in the second and third trimesters is associated with fetal growth acceleration, preterm birth, and neonatal complications.[96]

Women with type 1 diabetes should use an effective method of contraception until they plan pregnancy.[95]

The National Institute for Health and Care Excellence (NICE) in the UK recommends that HbA1c should be <48 mmol/mol (6.5%) before conception if this can be achieved without problematic hypoglycaemia.[95] Any reduction towards this target is likely to reduce the risk of congenital malformations. NICE recommends up to monthly measurement of HbA1c levels for women with diabetes who are planning a pregnancy.[95]

Women should be evaluated before pregnancy for retinopathy, nephropathy, neuropathy, and possible cardiovascular disease, which may worsen during or complicate pregnancy.[95] In addition to the complications noted above, infants of mothers with hyperglycaemic diabetes are at risk of macrosomia and neonatal distress. Pre-eclampsia is also more common in diabetic pregnancies. Euglycaemia or near-euglycaemia reduces the risk of complications.

Statins, ACE inhibitors, and angiotensin-II receptor blockers should be discontinued before pregnancy (or as soon as pregnancy is confirmed).[95]

Advise women with diabetes who are planning to become pregnant to take folic acid (and continue this until 12 weeks of gestation).[95]

During pregnancy

During pregnancy, women should be cared for by a multi-disciplinary team, including a dietitian, a nurse educator, an endocrinologist, and an obstetrician.

Statins, ACE inhibitors, and angiotensin-II receptor antagonists should be discontinued before pregnancy or as soon as pregnancy is confirmed (alternative anti-hypertensive agents suitable for use during pregnancy should be substituted).[95]

Offer pregnant women with pre-existing diabetes retinal assessment by digital imaging with mydriasis using tropicamide following their first antenatal clinic appointment (unless they have had a retinal assessment in the last 3 months), and again at 28 weeks. If any diabetic retinopathy is present at booking, perform an additional retinal assessment at 16 to 20 weeks.[95]

Advise women with diabetes who are pregnant to take folic acid until 12 weeks of gestation.[95]

- Women with diabetes have an increased risk of having infants with neural tube defects, compared with the general population.[97]

Intensive insulin treatment with a multiple daily injection (MDI) regimen or insulin pump is important. Commonly used insulins during pregnancy include isophane (NPH), detemir, neutral, lispro, and aspart.[98] The Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial

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(CONCEPTT) showed that use of real-time (RT)-CGM during pregnancy in women with type 1 diabetes was associated with improved glycaemic control and neonatal outcomes compared with women who used only self-monitoring of blood glucose (SMBG).[99] In the UK, NICE recommends offering CGM to all pregnant women with type 1 diabetes. Flash glucose monitoring can be offered to any woman who expresses a clear preference for it and/or is unable to use CGM.[95] [100] The Association of British Clinical Diabetologists has published guidance on the use of diabetes technology in pregnancy.[96]

NICE recommends isophane insulin as the first-choice for long-acting insulin during pregnancy in diabetes of any aetiology.[95] In practice, in women with type 1 diabetes who are already established on a basal-bolus insulin routine and have achieved good glycaemic control before pregnancy using a long-acting insulin analogue such as detemir or glargine, it may be more appropriate to continue this through pregnancy. There are no large randomised trials supporting the safety of insulin glargine in pregnant patients with diabetes.[101] However, insulin glargine has been safely used in many patients during pregnancy. Limited evidence suggests rapid-acting insulin analogues (aspart or lispro) may be associated with a reduced risk of hypoglycaemia and improved glycaemic control compared with regular human insulin.[95] There are few data comparing outcomes for insulin pump therapy (continuous subcutaneous insulin infusion or CSII) versus multiple daily injections of insulin for pregnant women with diabetes.[102] One randomised controlled trial reports better glycaemic outcomes with use of multiple daily injection therapy versus insulin pump therapy.[103]

Consider adding metformin to insulin therapy during pregnancy (and in the preconception period), when the likely benefits from improved blood glucose control outweigh the potential for harm.[95] This is most likely to be the case in women who have insulin resistance in addition to insulin deficiency and is a recommended consideration if the woman has a body mass index (BMI) of 25 kg/m² or above (23 kg/m² or above for people from South Asian and related minority ethnic groups) and wants to improve their blood glucose control while minimising their effective insulin dose.[37]

NICE guidelines recommend the following blood glucose targets in pregnant women with pre-existing type 1 diabetes (as long as these are achievable without causing problematic hypoglycaemia):[95]

- Fasting: <5.3 mmol/L (<95.4 mg/dL), and
- 1 hour after meals: <7.8 mmol/L (<140.4 mg/dL), or
- 2 hours after meals: <6.4 mmol/L (<115.2 mg/dL).

Advise pregnant women with diabetes who are on insulin to maintain their capillary plasma glucose level above 4 mmol/L (72 mg/dL).[95]

Measure HbA1c levels in all pregnant women with pre-existing diabetes at the booking appointment to determine the level of risk for the pregnancy. Consider measuring HbA1c levels in the second and third trimesters of pregnancy for women with pre-existing diabetes to assess the level of risk for the pregnancy.[95]

- The level of risk for the pregnancy for women with pre-existing diabetes increases with an HbA1c level above 48 mmol/mol (6.5%).[95]

Pregnant women should test their fasting, pre-meal, 1-hour post-meal, and bedtime blood glucose levels every day.[95] The pattern should be examined every few weeks early in pregnancy so that nutrition content and timing, exercise patterns, and the insulin doses can be modified to achieve optimal control. Insulin requirements generally increase early in pregnancy, then decrease from about 8 to 16 weeks before rising throughout the rest of the pregnancy.

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Advise pregnant women with type 1 diabetes to take aspirin from 12 weeks until the birth of the baby.[95] [104]

- These women are at high-risk of pre-eclampsia.[104]

Ongoing monitoring and support for all patients

The therapy of people with type 1 diabetes also involves management of comorbid conditions (e.g., autoimmune diseases), monitoring to include regular eye examinations, treatment of dyslipidaemia, and blood pressure control. Recommend blood pressure management at 135/85 mmHg for adults with type 1 diabetes. If the patient has albuminuria or 2 or more features of metabolic syndrome, recommend blood pressure management at 130/80 mmHg.[37] Foot care is also an essential part of management.[46] [37] [35] See Monitoring section.

Psychosocial screening and support can help to ameliorate distress and improve the individual's and family's capacity for self-care.[105] [106] [107]

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing		(summary)
children and non-pregnant adults		
	1st	**basal-bolus insulin**
	adjunct	**pre-meal insulin correction dose**
	adjunct	**metformin**
	2nd	**fixed-dose insulin (adults only)**
pregnant		
	1st	**basal-bolus insulin**
	adjunct	**metformin**
	plus	**low-dose aspirin**

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Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

children and non-pregnant adults

1st **basal-bolus insulin**

Primary options

» insulin detemir
-or-
» insulin glargine
-or-
» insulin degludec
--AND--
» insulin lispro
-or-
» insulin aspart
-or-
» insulin glulisine

» Offer the patient, whether they are an adult or child, a multiple daily injection basal-bolus insulin regimen from diagnosis.[37] [35] Do not offer adults newly diagnosed with type 1 diabetes twice-daily mixed, basal only, or bolus only insulin regimens.[37]

» Using a combination of long-acting insulin (insulin detemir, degludec, or glargine) for basal dosing, and rapid-acting insulin (insulin lispro, aspart, or glulisine) for bolus dosing, multiple daily injections (MDI) regimens can be designed based on physician and patient preference and modified based on glucose monitoring data.

» In the UK, the National Institute for Health and Care Excellence (NICE) recommends twice-daily insulin detemir as basal insulin therapy for adults.[37] NICE advises considering one of the following alternatives to twice-daily insulin detemir: an insulin regimen that the patient is established on and meeting their agreed treatment goals; once-daily insulin glargine if the patient cannot tolerate insulin detemir or has a strong preference for once-daily basal injections; once-daily insulin degludec if there is a particular concern about nocturnal hypoglycaemia; once-daily ultra-long-acting insulin (e.g., insulin degludec) if the patient needs help from a carer or healthcare professional to administer injections.[37] If the patient does not meet their treatment goals with these options, NICE recommends considering

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Ongoing

other basal insulin regimens, taking into account the patient's preferences and comorbidities, risk of hypoglycaemia and diabetic ketoacidosis, and any concerns around adherence.[37]

» NICE recommends analogue rapid-acting insulins as the first-line choice for bolus dosing.[37]

» There is no consensus as to whether insulin analogues are superior to conventional insulins for glycaemic control or reductions in complications.[67][68]

» An initial total daily dose of insulin in adults can be 0.2 to 0.4 units/kg/day. In children, an initial daily dose will be 0.5 to 1.0 units/kg/day, and during puberty the requirements may increase to as much as 1.5 units/kg/day. Often, when first started on insulin, patients with type 1 diabetes will experience a honeymoon period, during which they may require fewer units each day. In general, one half of the total dose is given as basal insulin and one half as bolus dosing.[46] The bolus dosing is divided and given before meals. Basal dose timing varies according to individual patient requirements and the type of insulin used (e.g., insulin detemir is usually given once or twice daily depending on the patient's needs, insulin glargine and insulin degludec are usually given once daily at any time of the day, but preferably at the same time every day). Administration times may vary; check your local guidelines for more information. Patients need to self-monitor their blood glucose levels. In adults, the insulin doses can be adjusted every 2 to 3 days to maintain target blood glucose. Encourage children and young people who are having multiple daily insulin injections to adjust the insulin dose if appropriate after each blood glucose measurement.[35]

» To maintain an HbA1c target of 48 mmol/mol (6.5%) or lower, advise adults with type 1 diabetes to aim for: on waking, a fasting plasma glucose level of 5-7 mmol/L (90-126 mg/dL); before meals at other times of day, a plasma glucose level of 4-7 mmol/L (72-126 mg/dL); after meals, a plasma glucose level of 5-9 mmol/L (90-162 mg/dL) at least 90 minutes after eating; at bedtime, a personalised plasma glucose level that takes into account the timing of their last meal and its related insulin dose, and is consistent with the recommended fasting level on waking.[37]

» Children and young people aged under 18 years should aim for: on waking, a fasting

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Ongoing

plasma glucose level of 4-7 mmol/L (72-126 mg/dL); before meals at other times of day, a plasma glucose level of 4-7 mmol/L (72-126 mg/dL); after meals, a plasma glucose level of 5-9 mmol/L (90-162 mg/dL).[35]

» If the patient drives, ensure they are aware of the relevant local advice on plasma glucose level. In the UK, the Driver and Vehicle Licensing Agency (DVLA) advises to aim for a level of at least 5 mmol/L (90 mg/dL) before driving.[49]

» The simplest approach to covering mealtime insulin requirements is to suggest a range of doses, such as 4 units for a small meal, 6 units for a medium-sized meal, and 8 units for a larger meal. For greater flexibility of carbohydrate content of meals, pre-meal insulin can be calculated based on the estimated amount of carbohydrate in the meal and the patient's individual insulin-to-carbohydrate ratio.

» In adults, a conservative starting approach is to use 1 unit of mealtime insulin for every 15 g of carbohydrate in the meal (bear in mind, however, that the insulin-to-carbohydrate ratio might vary according to local protocols). Patients can use the carbohydrate content per serving listed on food packaging to assess the number of grams in their anticipated meal, but carbohydrate counting is best learned with the help of a dietitian or via a structured diabetes education programme.[37] Using a food diary and 2-hour postprandial blood glucose measurements, the insulin-to-carbohydrate ratio can be adjusted.

» Regimens should be individualised to obtain the best possible glycaemic control.

» A correction dose may be incorporated into the insulin doses based on pre-meal glucose levels.

» An insulin pump (continuous subcutaneous insulin infusion [CSII]) may be considered in some patients for whom MDI regimens are inappropriate or unsuccessful.

» In the UK, NICE recommends an insulin pump as an option for children younger than 12 years for whom MDI therapy is impractical or inappropriate; these patients would be expected to have a trial of MDI therapy at some point between the ages of 12 and 18 years.[69]

» NICE also recommends a pump as a treatment option for those aged 12 years and older whose attempts to achieve target HbA1c levels with an MDI regimen have resulted in disabling

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Ongoing

hypoglycaemia with a significant impact on quality of life; these patients should only continue using a pump if it results in a sustained fall in HbA1c levels and/or a reduction in the frequency of hypoglycaemia episodes.[69]

» The insulin pump has a subcutaneous insulin infusion port which is changed every 3 days. The pump uses short-acting or rapid-acting insulin, and provides a basal rate of insulin and delivers mealtime bolus dosing. However, the patient (or a parent or carer) must still measure blood glucose frequently (in practice, 4-7 times each day) in order to adjust the pump to deliver the appropriate amount of insulin. Insulin pumps may reduce hypoglycaemia, especially when combined with continuous glucose monitoring (CGM) systems and threshold suspend features, and improve HbA1c, while providing greater flexibility.[54] [70] [71] [72] [73] Because of the monitoring and dose adjustment required, use of a pump requires a motivated patient skilled in diabetes self-management and with access to practitioners trained in pump therapy.[74] [75] If the patient is a child, they will need strong family support in place.[74]

» Insulin pumps with glucose sensors integrated into the same unit are called sensor-augmented insulin pumps. Functionality between sensor and pump has been integrated in one available device: a 'closed loop' system. The basal insulin delivery can be determined automatically based on sensor glucose levels. These integrated devices use a computerised control algorithm to create the hybrid closed loop insulin delivery system, which functions as an artificial pancreas.[40] [76] [77] In clinical trials, such systems have been shown to reduce the risk of nocturnal hypoglycaemia and to improve glucose control, including in children.[78] [79] [80] Some models come with smartphone apps that can be used to monitor glucose and insulin dosing. Use of sensors and sensor-augmented pumps is increasing.

» Remind the patient to rotate injection sites within the same body region. The Medicines and Healthcare products Regulatory Agency (MHRA) advises this is to prevent or reduce the risk of developing cutaneous amyloidosis (insulin lipodystrophy) at the injection site which may lead to poor diabetes control caused by lack of insulin absorption due to the amyloid mass.[81]

» Insulin should not be withdrawn from insulin pen devices or cartridges.[37] NHS England warns that the strength of insulin in pen devices

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can vary by multiples of 100 units/mL, whereas insulin syringes have graduations only suitable for calculating doses of standard 100 units/mL. If insulin extracted from a pen or cartridge is of a higher strength than intended, and that is not considered in determining the volume required, it can lead to a significant and potentially fatal overdose.[82]

» Ensure the risk of medication errors with insulins is minimised by prescribing insulins by brand name.[37] There are a number of 'sound-a-like' insulins and, in some cases, multiple different strengths and formulations of each type of insulin.[83]

» In addition, follow local guidance on minimising the risk of medication error with high strength, fixed combination, and biosimilar insulin products.[37] [MHRA: High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error] (https://www.gov.uk/drug-safety-update/high-strength-fixed-combination-and-biosimilar-insulin-products-minimising-the-risk-of-medication-error?UNLID=753360727201648136 2#dose-conversion-when-switching-between-standard-and-high-strength-insulin-products)

adjunct **pre-meal insulin correction dose**

Treatment recommended for SOME patients in selected patient group

» A correction (or adjustment) dose may be added to the bolus insulin based on the pre-meal blood glucose level. In practice, in adults a conservative approach to calculating a correction dose is to assume 1 unit of insulin will lower the patient's blood glucose by 4 mmol/L (72 mg/dL). Correction dosing can also be calculated using the patient's total daily dose of insulin (TDD) if food intake is stable. The correction dose can be added to the patient's mealtime insulin requirement (whether based on general meal size or carbohydrate counting) and given as the total bolus dose.

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: adults: 500 mg orally (immediate-release) once daily for at least one week, followed by 500 mg twice daily for at least one week, then 500 mg three times daily thereafter, maximum 2000 mg/day

MANAGEMENT

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Ongoing

Also available as a modified-release formulation.

» Consider adding metformin to insulin therapy if the patient is an adult with a body mass index (BMI) of 25 kg/m² or above (23 kg/m² or above for people from South Asian and related minority ethnic groups) and wants to improve their blood glucose control while minimising their effective insulin dose.[37] However, the benefits of this approach have been the subject of debate.[89] [90]

» This use is off-label in the UK.

2nd **fixed-dose insulin (adults only)**

» Fixed-dose insulin is used when adult patients are already doing well on a fixed-dose regimen, or cannot manage a multiple daily injection regimen, or have trouble mixing insulin. Various fixed-dose insulin formulations are available; consult your local drug formulary for options.

pregnant

1st **basal-bolus insulin**

Primary options

» insulin isophane human (NPH)
-or-
» insulin detemir
--AND--
» insulin neutral
-or-
» insulin lispro
-or-
» insulin aspart

Secondary options

» insulin glargine
--AND--
» insulin neutral
-or-
» insulin lispro
-or-
» insulin aspart

» National Institute for Health and Care Excellence (NICE) guidelines recommend the following blood glucose targets in pregnant women with pre-existing type 1 diabetes (as long as these are achievable without causing problematic hypoglycaemia): fasting <5.3 mmol/L (<95.4 mg/dL); and 1 hour after meals <7.8

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Ongoing

mmol/L (<140.4 mg/dL); or 2 hours after meals <6.4 mmol/L (<115.2 mg/dL).[95]

» Advise pregnant women with diabetes who are on insulin to maintain their capillary plasma glucose level above 4 mmol/L (72 mg/dL).

» Measure HbA1c levels in all pregnant women with pre-existing diabetes at the booking appointment to determine the level of risk for the pregnancy. Consider measuring HbA1c levels in the second and third trimesters of pregnancy for women with pre-existing diabetes to assess the level of risk for the pregnancy. [95]The level of risk for the pregnancy for women with pre-existing diabetes increases with an HbA1c level above 48 mmol/mol (6.5%).[95]

» Pregnant women should test their fasting, pre-meal, 1-hour post-meal, and bedtime blood glucose levels every day.[95] The pattern should be examined every few weeks early in pregnancy so that nutrition content and timing, exercise patterns, and the insulin doses can be modified to achieve optimal control. Insulin requirements generally increase early in pregnancy, then decrease from about 8 to 16 weeks before rising throughout the rest of the pregnancy.

» Intensive insulin treatment with a multiple daily injection (MDI) regimen or insulin pump is important. Commonly used insulins during pregnancy include isophane (NPH), detemir, neutral, lispro, and aspart.[98] The Continuous Glucose Monitoring in Women With Type 1 Diabetes in Pregnancy Trial (CONCEPTT) showed that use of real-time (RT)-CGM during pregnancy in women with type 1 diabetes was associated with improved glycaemic control and neonatal outcomes compared with women who used only self-monitoring of blood glucose (SMBG).[99] In the UK, NICE recommends offering CGM to all pregnant women with type 1 diabetes. Flash glucose monitoring can be offered to any woman who expresses a clear preference for it and/or is unable to use CGM. [95] [100] The Association of British Clinical Diabetologists has published guidance on the use of diabetes technology in pregnancy.[96]

» NICE recommends isophane insulin as the first-choice for long-acting insulin during pregnancy in diabetes of any aetiology.[95] In practice, in women with type 1 diabetes who are already established on a basal-bolus insulin routine and who have achieved good glycaemic control before pregnancy using a

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Ongoing

long-acting insulin analogue such as detemir or glargine, it may be more appropriate to continue this through pregnancy. There are no large randomised trials supporting the safety of insulin glargine in pregnant patients with diabetes.[101] However, insulin glargine has been safely used in many patients during pregnancy. Limited evidence suggests rapid-acting insulin analogues (aspart or lispro) may be associated with a reduced risk of hypoglycaemia and improved glycaemic control compared with regular human insulin.[95] There are few data comparing outcomes for insulin pump therapy (continuous subcutaneous insulin infusion or CSII) versus multiple daily injections of insulin for pregnant women with diabetes.[102]

adjunct **metformin**

Treatment recommended for SOME patients in selected patient group

Primary options

» metformin: 500 mg orally (immediate-release) once daily for at least one week, followed by 500 mg twice daily for at least one week, then 500 mg three times daily thereafter, maximum 2000 mg/day
Also available as a modified-release formulation.

» Consider adding metformin to insulin therapy during pregnancy (and in the preconception period), when the likely benefits from improved blood glucose control outweigh the potential for harm.[95] This is most likely to be the case in women who have insulin resistance in addition to insulin deficiency and is a recommended consideration if the woman has a body mass index (BMI) of 25 kg/m² or above (23 kg/m² or above for people from South Asian and related minority ethnic groups) and wants to improve their blood glucose control while minimising their effective insulin dose.[37]

» This use is off-label in the UK.

plus **low-dose aspirin**

Treatment recommended for ALL patients in selected patient group

Primary options

» aspirin: 75-150 mg orally once daily

» Advise pregnant women with type 1 diabetes to take aspirin from 12 weeks until the birth of

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Ongoing

the baby.[95] [104] These women are at high-risk of pre-eclampsia.[104]

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Emerging

Immunotherapy

Type 1 diabetes is an autoimmune disease modulated by cytotoxic T cells. Several agents have been studied for treatment of new-onset disease. Non-antigen-specific systemic immunotherapies, including T-cell suppressors (ciclosporin), antiproliferative agents (methotrexate, azathioprine), and anti-thymocyte globulin, have shown a strong tendency to adverse effects. Although ciclosporin use did reduce insulin requirements in the short term, it was associated with nephrotoxicity, and the effect on beta cells waned with treatment cessation. Antigen-specific vaccination with recombinant glutamic acid decarboxylase was shown to increase stimulated C-peptide in patients treated within 3 months of diagnosis.[108] Trials are under way to investigate treatment of type 1 diabetes with dendritic cells, mesenchymal stem cells, cord blood transfusion, and immunomodulators currently approved for use in other diseases, such as granulocyte colony stimulating factor or tumour necrosis factor-alpha inhibitors.[109] [110]

Tepilizumab

One clinical trial of the anti-CD3 monoclonal antibody, teplizumab, in patients with new-onset diabetes shows that the decline in beta-cell function (measured by C-peptide) is slowed and insulin requirements for glycaemic control are reduced.[111] [112] In one study of patients who did not have diabetes, but who were at high-risk (≥2 type 1 diabetes auto-antibodies and dysglycaemia), teplizumab delayed progression to clinical disease.[113] The US Food and Drug Administration has granted teplizumab breakthrough therapy designation for the prevention or delay of clinical type 1 diabetes in at-risk individuals, which may expedite the review process for approval of this drug.

Islet cell transplantation

Islet cells prepared from a donor pancreas are injected into the portal vein.[114] The cells seed in the liver and produce insulin. Patients who undergo this procedure require immunosuppressive therapy afterwards. There is some initial success with this procedure but the long-term results remain disappointing. Even in the best centres, less than 50% of patients are free of insulin requirement at 1 year and only 10% at 5 years.[115] [116] The American Diabetes Association (ADA) recommends that this procedure be performed only within the context of a controlled research study at this time.

Inhaled insulin

In June 2014, the US FDA approved a rapid-acting inhaled insulin. It can be administered before meals and should be used in combination with long-acting insulin. It can cause bronchospasm in patients with asthma and chronic obstructive pulmonary disease, and should not be used if these conditions are present. The most common side effects in a 24-week safety and efficacy trial were hypoglycaemia, cough, and throat infection. Long-term safety data are lacking.[117] Moreover, it is available only in fixed doses of 4 or 8 units. Therefore, dose adjustments can be made only in multiples of 4 which may present difficulty in fine-tuning the dose in patients with type 1 diabetes. More experience is needed before inhaled insulin is routinely prescribed in type 1 diabetes.

Islet cell regeneration

Studies done in mouse models show that from the onset of insulinitis, there is a mass of beta cells within an inflammatory milieu that may be recoverable and serve as a future source of functioning beta cells.[118] Several trials are under way to investigate mono- and combination therapies to arrest inflammation and possibly allow beta-cell regeneration.

Sotagliflozin

Sotagliflozin, an oral sodium-glucose co-transporter 2 (SGLT2) inhibitor, has been approved in Europe as an adjunct to insulin therapy to improve glycaemic control in adults with type 1 diabetes mellitus with a body mass index ≥27 kg/m², who have failed to achieve adequate glycaemic control despite optimal insulin

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therapy. The National Institute for Health and Care Excellence (NICE) recommends sotagliflozin with insulin for this indication.[119] However, sotagliflozin is not yet available in the UK. Sotagliflozin has not been approved in the US; the FDA rejected its approval in 2019. Sotagliflozin has been shown to be safe and effective in clinical trials.[120] [121] [122] [123] [124] However, as with all SGLT2 inhibitors, there is a risk for euglycaemic diabetic ketoacidosis in both type 1 and type 2 diabetes.[120] [125]

Glucagon-like peptide-1 (GLP-1) agonists

GLP-1 is a gut peptide that increases insulin secretion and decreases glucagon secretion in a glucose-dependent manner. In patients with type 2 diabetes, GLP-1 receptor agonists increase levels of GLP-1 and lead to more glucose-dependent insulin secretion, less glucagon secretion, delayed gastric emptying, and increased satiety. The specific advantage of GLP-1 agonists is weight loss, which may be desirable in some patients with type 1 diabetes.[126] The GLP-agonist liraglutide added to insulin improved glucose control in clinical trials with type 1 diabetes, but also increased the risk of both hypoglycaemia and hyperglycaemia with ketosis. Therefore, GLP-1 agonists should not routinely be used in type 1 diabetes.

Patient discussions

Support the patient (and their family members or carers, as appropriate) to develop a good working knowledge of nutrition and how it affects their diabetes.[35] [37]

- There is no standardised dietary advice that is suitable for all individuals with diabetes.[46]
- Individualised nutrition advice should be based on personal and cultural preferences, health literacy and numeracy, access to healthful food choices, and willingness and ability to make behavioural changes. It should also address barriers to change.
- Nutritional recommendations should be modified to take into account: excess weight and obesity, those who are underweight, disordered eating, hypertension and renal failure.[37]
- All patients with diabetes should receive individualised medical nutrition therapy, preferably provided by a registered dietitian who is experienced in providing this type of therapy to diabetes patients.[56]

Carbohydrate counting (with adjustment of insulin dose according to an insulin:carbohydrate ratio) or consistent carbohydrate intake with respect to time and amount may improve glycaemic control. The UK National Institute for Health and Care Excellence (NICE) recommends a low glycaemic index diet to improve blood glucose control in children and young people but does not recommend this approach in adults.[37] [35] Rapid-acting insulins may make timing of meals less crucial than in the past, but regular meals are still important.

Encourage the patient to undertake physical activity on a regular basis.

- Patients with type 1 diabetes can safely exercise and manage their glucose levels.[40] [57] [58] Be aware that in practice many patients find exercise challenging, particularly as acute exercise increases the risk of dysglycaemia.[58] Therefore the patient will need access to ongoing support, education, and input from educators.
- Pre-exercise carbohydrate intake and insulin doses can be effectively modified to avoid hypoglycaemia during exercise and sports.[59]
- Hypoglycaemia can occur up to 24 hours after exercise and may require reducing insulin dosage on days of planned exercise. A carbohydrate snack (10-20g) should be given at the start of exercise if the patient's blood sugar is <5.0 mmol/L (<90 mg/dL).[58]

Bear in mind that people with diabetes might be struggling to manage their diabetes effectively owing to psychological and social challenges; these patients will require an integrated multi-disciplinary approach, including psychologists, psychiatrists and support workers.[88] Specifically consider whether an eating disorder, and associated concerns about body size and weight, might be influencing how the patient uses their insulin.

Advise children (and/or their family members or carers) to routinely perform at least five capillary blood glucose tests every day.[35] More frequent testing will be needed to support safe exercise and during

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intercurrent illness. Encourage any child or young person with type 1 diabetes to carry or wear something (e.g., a bracelet) that alerts people to their diagnosis.[35]

Support adults with type 1 diabetes to check their blood glucose at least 4 times a day.[37] Increase to up to 10 times a day if any of the following apply:[37]

- The patient's agreed HbA1c target is not met
- The frequency of hypoglycaemia episodes increases
- There is a legal requirement to do so (e.g., before driving)
- While the patient is ill
- Before, during, and after sport
- While planning pregnancy, during pregnancy, and while breastfeeding
- If there is any other reason to know blood glucose levels more than 4 times a day (e.g., impaired awareness of hypoglycaemia; high-risk activities).

Bear in mind that additional testing (more than 10 times a day) might be indicated:[37]

- If the patient has impaired awareness of hypoglycaemia
- Depending on the patient's lifestyle (e.g., if they drive for long periods or have a high-risk job).

In practice, most adults with type 1 diabetes are likely to be checking their blood glucose between 4 and 10 times a day.

Advise the patient that hypoglycaemia may occur if they skip a meal, take too much insulin, exercise, or become ill. Alcohol and exercise can cause delayed hypoglycaemia that may appear even up to 24 hours later.

- Symptoms include feeling very hungry, nervous, shaky, sweaty, dizzy, or confused.
- To raise their blood glucose, the patient can take glucose tablets or gels, or drink juice, depending on how low their blood sugar falls.
- The patients should see their physician for adjustment of medication should hypoglycaemia occur.
- Ensure the patient (and/or their family/carers, as appropriate) has a glucagon kit for emergencies, in the case of severe hypoglycaemia or when the patient is unable to drink or eat.
- Severe hypoglycaemia is defined as any low blood glucose level leading to cognitive impairment requiring assistance from another person for recovery.

Advise the patient to discuss their insulin requirement with their physician prior to skipping any meals (e.g., for a medical test).

Ensure the patient is aware of symptoms of hyperglycaemia, including blurred vision, thirst, frequent urination, or tiredness, and that they should see their physician immediately if these occur. They should seek medical attention if they develop a fever, cough, dysuria, or wounds on the feet.

Give the patient clear and individualised oral and written advice ('sick-day rules') about how to adapt management during intercurrent illness.[139][140] This illness plan should include:

- Monitoring blood glucose
- Monitoring and interpreting blood ketones (see below)
- Adjusting their insulin regimen
- Adapting food and drink intake
- How to seek further advice.

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Offer children and young people with type 1 diabetes blood ketone testing strips and a meter. Advise the patient (and/or their family members or carers) to test for ketonaemia if they are ill or have hyperglycaemia.[35]

Consider ketone monitoring (blood or urine) as part of 'sick-day rules' for adults, to facilitate self-management of an episode of hyperglycaemia.[37]

If the patient smokes, give advice on smoking cessation and use of smoking cessation services.[37] If the patient does not smoke, advise them never to start.[37]

Recommend blood pressure management at 135/85 mmHg for adults with type 1 diabetes. If the patient has albuminuria or 2 or more features of metabolic syndrome, recommend blood pressure management at 130/80 mmHg.[37]

Support the patient to engage with technologies that empower them to manage their own condition with remote support as a complement to their usual appointments.

- NICE in the UK recommends offering all patients with type 1 diabetes access to an accredited structured education programme 6 to 12 months after diagnosis.[37] [86]

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Monitoring

Monitoring

The National Institute for Health and Care Excellence (NICE) in the UK recommends a glycosylated haemoglobin (HbA1c) target level of 48 mmol/mol (6.5%) or lower.[37][35]

- A less stringent target may be appropriate for some patient groups including very young children, older adults, people with a history of severe hypoglycaemia, and those with limited life expectancies, advanced microvascular or macrovascular complications, or comorbid conditions.[46]
- If the patient is a child or young person, be aware that a stringent target can cause emotional distress and/or conflict with family members or carers and a compromise may need to be agreed.[35]
- If the patient is an adult, agree an individualised HbA1c aim with them, taking into account factors such as the person's daily activities, aspirations, likelihood of complications, comorbidities, occupation, and history of hypoglycaemia.[37]

Measure HbA1c levels at least:

- Every 3 months in children and young people aged under 18 years[35]
- Every 3 to 6 months in adults.[35]

Monitor:

- For thyroid disease at diagnosis and annually thereafter[35] [37]
- Eye health:
    - By advising children and young people under 18 years of age to have an eye examination by an optician every 2 years[35]
    - With structured eye screening annually in adults[37]
- For diabetic retinopathy via annual screening from 12 years of age[35] [37]
- For moderately increased albuminuria (albumin:creatinine ratio [ACR] 3-30 mg/mmol; 'microalbuminuria') to detect diabetic kidney disease, annually from 12 years of age; use an early-morning urine sample for this.[35] [37] Send the urine sample for estimation of ACR (estimating urine albumin concentration alone is a poor alternative) and measure eGFR at the same time.[37]
- Blood pressure annually from 12 years of age[35] [37]
- Foot health of people at low risk of developing a diabetic foot problem annually[151]
    - Refer people who are at moderate or high risk of developing a diabetic foot problem to your local foot protection service[151]
    - See our topic Diabetic foot complications
- Cardiovascular risk factors in adults annually, including estimated glomerular filtration rate (eGFR) and urine ACR, smoking, blood glucose control, blood pressure, full lipid profile, age, family history of cardiovascular disease, and abdominal adiposity[37]
- For coeliac disease at diagnosis[152]
    - Advise people who have tested negative for coeliac disease that it may present with a wide range of symptoms and they should consult their healthcare professional if any of the symptoms of concern arise or persist.

Advise the patient to have regular dental examinations.[35]

Be alert to the possibility of bulimia nervosa, anorexia nervosa and disordered eating in patients with type 1 diabetes with:[37]

- Over-concern with body shape and weight

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FOLLOW UP

- Low BMI
- Hypoglycaemia
- Suboptimal overall blood glucose control.

Consider an early (or if needed, urgent) referral to local eating disorder services for patients with type 1 diabetes who have an eating disorder.[37]

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Complications

Complications	Timeframe	Likelihood
diabetic ketoacidosis (DKA)	**short term**	**high**

DKA is the classical acute complication of type 1 diabetes, characterised by a biochemical triad of hyperglycaemia, ketonaemia, and metabolic acidosis, with rapid symptom onset. The most common precipitants are missed insulin injections or physiological stresses such as infection or myocardial infarction.

Work-up (e.g., ECG, search for infection) is indicated to detect precipitating factors. In the setting of insulin deficiency, stress hormones including glucagon, cortisol, and catecholamines raise blood glucose levels and stimulate ketogenesis.

Hyperglycaemia and ketosis cause osmotic diuresis leading to dehydration.

Symptoms tend to be due to dehydration and metabolic acidosis and include dry mouth, hyperventilation, abdominal pain, nausea, vomiting, and reduced consciousness.

Blood glucose and ketone levels are high and there is an anion gap metabolic acidosis.

Treatment involves rapid hydration, insulin infusion, and correction of electrolyte imbalance. Hourly monitoring of blood glucose and ketones, and regular monitoring of bicarbonate, potassium, and pH is required. Insulin infusion must continue until DKA has resolved and the patient is eating and drinking. Switch from insulin infusion to subcutaneous insulin when DKA is resolved.

Hyperkalaemia is common but hypokalaemia is an indicator of severe DKA.

Treatment with bicarbonate is not indicated except when venous blood pH is <6.9 and after discussion with a senior consultant.[135]

hypoglycaemia	**short term**	**high**

Hypoglycaemia is the most common and potentially most serious side effect of insulin therapy. It can lead to decreased quality of life; severe hypoglycaemia is a medical emergency which can cause confusion, seizures, and coma. Severe hypoglycaemia is defined as any low blood glucose level leading to cognitive impairment requiring assistance from another person for recovery.

Assess the patient's awareness of hypoglycaemia at each annual review.[37] In adults, use the Gold score or Clarke score.[37]

Episodes of hypoglycaemia occur with different frequency among patients. Patients should check a 3 a.m. blood glucose if there is concern about risk of nocturnal hypoglycaemia. To manage nocturnal hypoglycaemia (symptomatic or detected on monitoring), review the patient's knowledge and self-management skills, current insulin regimen, evening eating habits and previous physical activity.[37] Opt for an insulin type and regimen that is less likely to induce low glucose levels at night.[37] A bedtime snack is not always an effective way of decreasing the risk of nocturnal hypoglycaemia.[87] However, a bedtime snack without insulin (or overnight basal insulin reduced by 20%) is recommended if the patient exercises in the afternoon or evening.[57] Bedtime snacks might also be a suitable approach for patients in hospital.

Alcohol may cause acute hypoglycaemia, but both alcohol and exercise can cause delayed hypoglycaemia (by up to 24 hours).

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FOLLOW UP

Complications	Timeframe	Likelihood

Work with the patient to determine contributing factors, and the ability of the patient to recognise and treat hypoglycaemia appropriately. Advise patients (or parents/carers) that it is important to always have immediate access to a source of fast-acting glucose and blood glucose monitoring equipment so that they can respond quickly to symptoms or signs of hypoglycaemia.[35] [37] Train and equip the patient's family, friends, and/or carers (as appropriate) to give intramuscular glucagon for severe hypoglycaemia in an emergency.[35] [37]

Immediately treat mild to moderate hypoglycaemia in children and young people with oral fast-acting glucose, e.g., 10-20 g (liquid carbohydrate may be easier to swallow than solid). Fast-acting glucose may need to be given in frequent small amounts, because hypoglycaemia can cause vomiting.[35] Recheck the patient's blood glucose levels within 15 minutes (fast-acting glucose should raise blood glucose levels within 5-15 minutes), and give more fast-acting glucose if they still have hypoglycaemia.[35] As the patient's symptoms improve or their blood glucose levels return to normal, give oral complex long-acting carbohydrate to maintain blood glucose levels, unless the child or young person is about to have a snack or meal or having a continuous subcutaneous insulin infusion.[35]

For children and young people with type 1 diabetes who are in hospital, treat severe hypoglycaemia with 10% intravenous glucose if rapid intravenous access is possible. For children and young people with type 1 diabetes who are not in hospital, or if rapid intravenous access is not possible, treat severe hypoglycaemia with intramuscular glucagon or a concentrated oral glucose solution.[35] Do not use oral glucose solution if they have reduced consciousness, because this could be dangerous.[35] Seek senior assistance if the patient's blood glucose levels do not respond or symptoms continue for more than 10 minutes.[35] As symptoms improve or blood glucose levels return to normal, and once the child or young person is sufficiently awake, give oral complex long-acting carbohydrate to maintain normal blood glucose levels. Check blood glucose repeatedly in children and young people who have persistently reduced consciousness after a severe hypoglycaemic episode, to determine whether further glucose is needed.[35]

If the patient is an adult and able to ingest orally, hypoglycaemia can be treated with a fast acting form of glucose.[37] If oral intake is not possible owing to a decreased level of consciousness, glucagon is required.[37] This can be administered intramuscularly (by a family member or friend who has been shown how to do this) or intravenously (by a healthcare professional adept at obtaining intravenous access).[37] The patient should be monitored for response at 10 minutes, and then given intravenous glucose if their level of consciousness is not improving significantly. Once it is safe for the patient to have it, they can be given oral carbohydrate. The patient will need continued observation by someone who has been warned of the risk of relapse.[37]

If hypoglycaemia becomes unusually problematic or frequent, review the possible causes including: inappropriate insulin regimens (incorrect dose distributions and insulin types); meal and activity patterns, including alcohol; injection technique and skills, including insulin resuspension if necessary; injection site problems; possible organic causes including gastroparesis; changes in insulin sensitivity (including drugs affecting the renin–angiotensin system and renal failure); psychological problems; previous physical activity; lack of appropriate knowledge and skills for self-management.[37] Consider referring children and young people with type 1 diabetes for assessment of cognitive function if they have frequent hypoglycaemia or recurrent seizures.

retinopathy	**long term**	**high**

Retinopathy is the most common microvascular complication of diabetes and its risk is increased at all levels of glycosylated haemoglobin (HbA1c) above the non-diabetic range. The incidence is 1 in 100 person-years for a mean HbA1c value of 37 mmol/mol (5.5%) and 9.5 in 100 person-years for a mean HbA1c value of 91 mmol/mol (10.5%).[128] There is an increased risk of retinopathy in women with pre-existing type 1 diabetes during pregnancy.[46]

Twenty years after diagnosis, most patients have evidence of retinopathy. Patients develop microaneurysms, exudates, haemorrhages, angiogenesis, and glaucoma.

Retinopathy is usually asymptomatic until its late stages, so screening is essential.

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Complications	Timeframe	Likelihood

Primary prevention includes strict glycaemic control. Progression of very mild to moderate non-proliferative retinopathy can be delayed through glycaemic, blood pressure, and lipid control.[46] In advanced disease, photo-coagulation and vitrectomy can be done to prevent blindness. Intravitreal injections of antivascular endothelial growth factors are given for centre-involved macular oedema.[46]

diabetic kidney disease	long term	high

Diabetic kidney disease is the most common cause of end-stage renal disease (ESRD) in developed countries. In patients with type 1 diabetes, the annual incidence of microalbuminuria and albuminuria is between 1.3% and 3.8%.[136] In one cohort study, the cumulative risk of ESRD was 2.2% after 20 years and 7.0% after 30 years from the diabetes diagnosis.[137]

The pathogenesis of diabetic nephropathy involves glomerular mesangial sclerosis leading to proteinuria and progressive decline in glomerular filtration. Increased urinary albumin excretion (>30 mg/day) is the earliest sign of disease and a marker of much increased cardiovascular risk. Test yearly in people who have had type 1 diabetes for 5 years or more.[46]

Glycaemic control and blood pressure control with an ACE inhibitor or angiotensin-II receptor blocker delays onset and slows progression of disease.[37] [138] [139] In the UK, the National Institute for Health and Care Excellence (NICE) recommends starting angiotensin-converting enzyme (ACE) inhibitors and, with the usual precautions, titrating to full dose in all adults with type 1 diabetes who have confirmed nephropathy with ACR ≥3 mg/mmol. If ACE inhibitors are not tolerated, NICE recommends substituting angiotensin 2 receptor antagonists. NICE does not recommend combination therapy.[37]

peripheral or autonomic neuropathy	long term	high

More than 50% of patients will develop neuropathy.[140]

Strict glycaemic control prevents onset and delays progression of diabetic neuropathy, which manifests most commonly as distal symmetric polyneuropathy affecting sensory axons.

The duration and extent of hyperglycaemia are the greatest risk factors, although other cardiovascular risk factors probably also contribute.

The other most common types of neuropathy include mononeuropathy, mononeuritis multiplex, polyradiculopathies, and autonomic neuropathy.

Once distal symmetric polyneuropathy is diagnosed, simple inspection should be performed at 3- to 6-month intervals, and referral for podiatric care and special footwear should be made. There are several medications that are particularly effective and may be considered. In the US, Food and Drug Administration-approved medications for diabetic neuropathic pain include pregabalin, duloxetine, and tapentadol. Other treatments that are not approved everywhere for this indication may also be helpful, including tricyclic antidepressants, anticonvulsants, a 5-hydroxytryptamine and noradrenaline (norepinephrine) uptake inhibitor, or capsaicin cream.[46]

For autonomic neuropathy, current treatments for this complication are mostly inadequate. However, symptom management can be considered: for example, compressive stockings for postural hypotension.[46]

cardiovascular disease	long term	high

Cardiovascular disease is the major cause of death and a major cause of morbidity for patients with diabetes.

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FOLLOW UP

Complications	Timeframe	Likelihood

Intensive glycaemic control has been shown to decrease the incidence of macrovascular disease in type 1 diabetes.[131] During the 30-year follow-up of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study, high doses of insulin were associated with a less favourable cardiometabolic risk profile (higher body mass index, pulse rate, triglycerides, lower high-density lipoprotein [HDL] cholesterol), but intensive control continued to have long-term beneficial effects on the incidence of cardiovascular disease in type 1 diabetes.[132] [141]

The cardiovascular disease risk can be further decreased by modification of other cardiovascular risk factors.[142] Lifestyle and behavioural therapy are essential components of treatment.

Hypertension is often secondary to underlying nephropathy in patients with type 1 diabetes. Blood pressure should be treated with an ACE inhibitor or angiotensin-II receptor blocker if >135/85 mmHg (>130/80 if the patient has albuminuria or two or more features of metabolic syndrome).[37] Most patients will require two or three drugs to reach their goal. Intensifying antihypertensive therapy to blood pressure targets <140/90 was associated with a lower risk of coronary artery disease in one study.[143]

For patients of all ages with diabetes and overt cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. For patients of all ages with diabetes and overt cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. For adults with type 1 diabetes without known cardiovascular disease, consider statin treatment for the primary prevention of cardiovascular disease. Specifically, offer statin treatment to those who are older than 40 years, or have had diabetes for more than 10 years, or have established nephropathy, or have other CVD risk factors.[144] Intensive lifestyle therapy and optimal glycaemic control are recommended to decrease cardiovascular risk in patients with triglycerides ≥1.7 mmol/L (≥150 mg/dL) and/or HDL <1 mmol/L (<40 mg/dL) (HDL <1.3 mmol/L [<50 mg/dL] in women).[46] There is no specific low-density lipoprotein (LDL) target.

Children should have a fasting lipid profile once adequate glucose control is achieved if age ≥2 years, with subsequent testing performed at age 9-11 years.[46] Monitoring can be every 3 years if LDL <2.6 mmol/L (<100 mg/dL).[46] The optimal pharmacological treatment of hyperlipidaemia in children has not been clearly defined, although an initial approach to lipid lowering should include modifications to diet and increased exercise. Statins are not approved for children aged <10 years.[46]

All adult patients with diabetes and cardiovascular disease should be treated with aspirin for secondary prevention (75-162 mg/day). Do not offer aspirin for primary prevention in adults with type 1 diabetes.[37] All patients should have smoking-cessation counselling and treatment as needed.

Patients aged >55 years, with or without hypertension, but with cardiovascular disease, dyslipidaemia, increased urinary albumin excretion, or smoking may benefit from an ACE inhibitor to reduce the risk of cardiovascular events.[145]

No evidence-based guidelines exist for screening asymptomatic patients for coronary heart disease.[46]

depression	long term	medium

As a chronic disease, type 1 diabetes may impact on the psychological and psychosocial wellbeing of the patient. Manifestations of this may include diabetes 'burnout' and depression. Adults with type 1 diabetes are at three times the risk of clinical depression compared with those without type 1 diabetes.[146] The prevalence of depression in diabetes is higher in women (28%) compared with men (18%).[147] The risk of psychological adjustment and psychiatric disorders may also be higher in adolescents, at diagnosis, or when there is a change in disease status.[148] [149] [150] Consider seeking the support of a psychologist, preferably within a specialist type 1 diabetes service, if you are concerned.

eating disorders	long term	medium

Be alert to the possibility of bulimia nervosa, anorexia nervosa and disordered eating in patients with type 1 diabetes with over-concern with body shape and weight, low BMI, hypoglycaemia, or sub-optimal overall blood glucose control. Consider an early (or if needed, urgent) referral to local eating disorder services for patients with type 1 diabetes who have an eating disorder.[37]

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Complications	Timeframe	Likelihood
Specifically consider whether an eating disorder, and associated concerns about body size and weight, might be influencing how the patient uses their insulin.[37]		

Prognosis

Untreated type 1 diabetes is a fatal condition due to diabetic ketoacidosis (see our topic Diabetic ketoacidosis). Consistently raised glucose levels in type 1 diabetes is a risk factor for chronic complications such as blindness, renal failure, foot amputations, and heart attacks. Intensive glycaemic control has been shown to decrease the incidence of microvascular and macrovascular disease in type 1 diabetes.[127] [128] [129] [130] [131] The decreased incidence of macrovascular disease has been shown to persist for up to 30 years.[132] Even a few years of intensive glucose control translate to reduced rates of microvascular and macrovascular complications 10 years later.[128] [133] The National Institute for Health and Care Excellence (NICE) in the UK recommends maintaining glycosylated haemoglobin (HbA1c) <48 mmol/mol (6.5%) to prevent complications in most non-pregnant adults with type 1 diabetes.[37] [35] Less stringent targets may be appropriate for some patient groups including children.[46]

Overall, cardiovascular disease is the major cause of death and a major cause of morbidity for patients with diabetes; statin therapy can reduce the risk. One analysis of patients with type 1 diabetes diagnosed before the age of 15 years found that the leading cause of death before the age of 30 years was acute complications of diabetes. After the age of 30 years, cardiovascular disease was predominant, although death attributable to acute complications was still important in this age group.[134]

With careful planning and adequate treatment, most women with type 1 diabetes can have successful pregnancies.

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Diagnostic guidelines

United Kingdom

Type 1 diabetes in adults: diagnosis and management (https://www.nice.org.uk/guidance/ng17)

Published by: National Institute for Health and Care Excellence **Last published:** 2022

Diabetes (type 1 and type 2) in children and young people: diagnosis and management (https://www.nice.org.uk/guidance/ng18)

Published by: National Institute for Health and Care Excellence **Last published:** 2023

Diabetic foot problems: prevention and management (https://www.nice.org.uk/guidance/ng19)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Type 1 diabetes technology: a consensus guideline (https://www.diabetes.org.uk/professionals/position-statements-reports/specialist-care-for-children-and-adults-and-complications/type-1-technology-guidelines)

Published by: Diabetes UK **Last published:** 2019

Community pharmacies: promoting health and wellbeing (https://www.nice.org.uk/guidance/ng102)

Published by: National Institute for Health and Care Excellence **Last published:** 2018

Management of diabetes (SIGN no. 116) (https://www.sign.ac.uk)

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2017

Europe

Adult type 1 diabetes mellitus: national clinical guideline no. 17 (https://www.gov.ie/en/collection/c9fa9a-national-clinical-guidelines)

Published by: Department of Health (Ireland) **Last published:** 2020

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International

Classification of diabetes mellitus (https://www.who.int/publications-detail/classification-of-diabetes-mellitus)

Published by: World Health Organization **Last published:** 2019

Treatment of diabetes in older adults (https://www.endocrine.org/clinical-practice-guidelines)

Published by: The Endocrine Society **Last published:** 2019

ISPAD clinical practice consensus guidelines 2018 (https://www.ispad.org/page/ISPADGuidelines2018)

Published by: International Society for Paediatric and Adolescent Diabetes (ISPAD) **Last published:** 2018

Diabetes technology: continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults (https://www.endocrine.org/clinical-practice-guidelines)

Published by: The Endocrine Society **Last published:** 2016

Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia: report of a WHO/IDF consultation (https://apps.who.int/iris/handle/10665/43588)

Published by: World Health Organization; International Diabetes Federation **Last published:** 2006

North America

Standards of medical care in diabetes - 2021 (https://professional.diabetes.org/content-page/practice-guidelines-resources)

Published by: American Diabetes Association **Last published:** 2021

Clinical practice guidelines for the prevention and management of diabetes in Canada (https://www.diabetes.ca/health-care-providers/clinical-practice-guidelines?Categories=&SearchText=&Page=1)

Published by: Diabetes Canada **Last published:** 2018

Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan (https://www.endocrinepractice.org/article/S1530-891X(20)35517-8/fulltext)

Published by: American Association of Clinical Endocrinologists, American College of Endocrinology **Last published:** 2015

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Treatment guidelines

United Kingdom

Type 1 diabetes in adults: diagnosis and management (https://www.nice.org.uk/guidance/ng17)

Published by: National Institute for Health and Care Excellence **Last published:** 2022

Diabetes (type 1 and type 2) in children and young people: diagnosis and management (https://www.nice.org.uk/guidance/ng18)

Published by: National Institute for Health and Care Excellence **Last published:** 2023

Using diabetes technology in pregnancy (https://abcd.care/dtn/best-practice-guides)

Published by: Association of British Clinical Diabetologists **Last published:** 2020

Diabetic foot problems: prevention and management (https://www.nice.org.uk/guidance/ng19)

Published by: National Institute for Health and Care Excellence **Last published:** 2019

Type 1 diabetes technology: a consensus guideline (https://www.diabetes.org.uk/professionals/position-statements-reports/specialist-care-for-children-and-adults-and-complications/type-1-technology-guidelines)

Published by: Diabetes UK **Last published:** 2019

Community pharmacies: promoting health and wellbeing (https://www.nice.org.uk/guidance/ng102)

Published by: National Institute for Health and Care Excellence **Last published:** 2018

Management of diabetes (SIGN no. 116) (https://www.sign.ac.uk)

Published by: Scottish Intercollegiate Guidelines Network **Last published:** 2017

Europe

Glucose management for exercise using continuous glucose monitoring (CGM) and intermittently scanned CGM (isCGM) systems in type 1 diabetes (https://www.easd.org/statements.html)

Published by: European Association for the Study of Diabetes; International Society for Pediatric and Adolescent Diabetes **Last published:** 2020

Adult type 1 diabetes mellitus: national clinical guideline no. 17 (https://www.gov.ie/en/collection/c9fa9a-national-clinical-guidelines)

Published by: Department of Health (Ireland) **Last published:** 2018

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International

Precision medicine in diabetes (https://www.easd.org/statements.html)

Published by: European Association for the Study of Diabetes; American Diabetes Association **Last published:** 2020

Diabetes digital app technology: benefits, challenges, and recommendations (https://www.easd.org/statements.html)

Published by: European Association for the Study of Diabetes; American Diabetes Association **Last published:** 2019

Treatment of diabetes in older adults (https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines)

Published by: The Endocrine Society **Last published:** 2019

ISPAD clinical practice consensus guidelines 2018 (https://www.ispad.org/page/ISPADGuidelines2018)

Published by: International Society for Paediatric and Adolescent Diabetes (ISPAD) **Last published:** 2018

Diabetes technology: continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults (https://www.endocrine.org/guidelines-and-clinical-practice/clinical-practice-guidelines)

Published by: The Endocrine Society **Last published:** 2016

North America

Standards of medical care in diabetes - 2021 (https://professional.diabetes.org/content-page/practice-guidelines-resources)

Published by: American Diabetes Association **Last published:** 2021

Clinical practice guidelines for the prevention and management of diabetes in Canada (https://www.diabetes.ca/health-care-providers/clinical-practice-guidelines?Categories=&SearchText=&Page=1)

Published by: Diabetes Canada **Last published:** 2018

Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan (https://pro.aace.com/publications/guidelines)

Published by: American Association of Clinical Endocrinologists, American College of Endocrinology **Last published:** 2015

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Online resources

1. MHRA: High strength, fixed combination and biosimilar insulin products: minimising the risk of medication error (https://www.gov.uk/drug-safety-update/high-strength-fixed-combination-and-biosimilar-insulin-products-minimising-the-risk-of-medication-error?UNLID=753360727201648136 2#dose-conversion-when-switching-between-standard-and-high-strength-insulin-products) *(external link)*

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Key articles

- Norris JM, Johnson RK, Stene LC. Type 1 diabetes-early life origins and changing epidemiology. Lancet Diabetes Endocrinol. 2020 Mar;8(3):226-38. Full text (https://www.clinicalkey.com/#!/content/playContent/1-s2.0-S2213858719304127) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/31999944?tool=bestpractice.bmj.com)
- National Institute for Health and Care Excellence. Diabetes (type 1 and type 2) in children and young people: diagnosis and management. Dec 2020 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng18)
- National Institute for Health and Care Excellence. Type 1 diabetes in adults: diagnosis and management. Jul 2021 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng17)
- National Institute for Health and Care Excellence. Diabetes in pregnancy: management from preconception to the postnatal period. Dec 2020 [internet publication]. Full text (https://www.nice.org.uk/guidance/ng3)

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Treatment recommendations in BMJ Best Practice are specific to patient groups. Care is advised when selecting the integrated drug formulary as some treatment recommendations are for adults only, and external links to a paediatric formulary do not necessarily advocate use in children (and vice-versa). Always check that you have selected the correct drug formulary for your patient.

Where your version of BMJ Best Practice does not integrate with a local drug formulary, you should consult a local pharmaceutical database for comprehensive drug information including contraindications, drug interactions, and alternative dosing before prescribing.

Interpretation of numbers

Regardless of the language in which the content is displayed, numerals are displayed according to the original English-language numerical separator standard. For example 4 digit numbers shall not include a comma nor a decimal point; numbers of 5 or more digits shall include commas; and numbers stated to be less than 1 shall be depicted using decimal points. See Figure 1 below for an explanatory table.

BMJ accepts no responsibility for misinterpretation of numbers which comply with this stated numerical separator standard.

This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

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5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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