Type 1 diabetes

The right clinical information, right where it's needed
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<tr>
<td>◊ Type 1 diabetes mellitus is a metabolic disorder characterised by hyperglycaemia due to absolute insulin deficiency.</td>
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<tr>
<td>◊ Patients most often present with a few days or weeks of polyuria, polydipsia, weight loss, and weakness.</td>
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<tr>
<td>◊ Some patients may present with diabetic ketoacidosis.</td>
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<td>◊ Intensive glycaemic control has been shown to decrease the incidence of microvascular and macrovascular complications.</td>
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<tr>
<td>◊ Microvascular complications include retinopathy, nephropathy, and neuropathy.</td>
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<td>◊ Macrovascular complications include coronary artery, cerebrovascular, and peripheral vascular disease.</td>
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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.

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.[3] It is estimated that 1,106,500 people aged 0-19 years have type 1 diabetes worldwide, with 132,600 newly diagnosed cases each year.[4]

In the US from 2011-2012, more than 17,900 people aged under 20 years were newly diagnosed with type 1 diabetes annually (annual rate for new cases about 21 in 100,000).[5] In a study of adults diagnosed with diabetes in the US in 2016 and 2017, type 1 diabetes accounted for 5.6% of cases.[6]

There is significant geographical variation in the incidence of type 1 diabetes. It is more common in Europeans and less common in Asians. Thus, a child in Finland is 40 times more likely to develop type 1 diabetes than a child in Japan and almost 100 times more likely to get the disease than a child in the Zunyi region of China.[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.[3] It affects males and females equally.[3]

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.[13] [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. Among viruses, the strongest associations have been found with human enteroviruses.[15] [16] [17] Among dietary factors, supplementation with vitamin D may be protective.[18] [19] 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.[20] [21] [22] Coeliac disease shares the HLA-DQ2 genotype with type 1 diabetes, and is more common among those with type 1 diabetes.[23] [24] The incidence of type 1 diabetes may also be higher among those with coeliac disease, although a causal relationship is not suggested.[25]

Pathophysiology

Type 1 diabetes usually develops as a result of autoimmune pancreatic beta-cell destruction in genetically susceptible individuals. 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
Type 1 diabetes

Basics

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. 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.

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, 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.

Classification

Types of type 1 diabetes

Autoimmune or classical

- Characterised by absolute insulin deficiency and the presence of antibodies to pancreatic beta cells.

Idiopathic

- Uncommon form that is characterised by absence of antibodies.
- Increased likelihood in patients of African or Asian ancestry and has a strong genetic component.

Presentation of idiopathic type 1 diabetes does not differ from that of autoimmune type 1 diabetes.

The American Diabetes Association has produced a staging system for type 1 diabetes based on clinical features and the presence of autoantibodies. The persistent presence of two or more autoantibodies is an almost certain predictor of clinical hyperglycaemia and diabetes, and the rate of progression is dependent on the age at first detection of antibody, the number of antibodies, the antibody specificity, and the antibody titre. Glucose and glycosylated haemoglobin (HbA1c) levels rise well before the clinical onset of diabetes, making early diagnosis possible. This staging can serve as a framework for future research and screening.
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. [42]
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. When the initial presentation of type 1 diabetes occurs in adulthood, some refer to it as latent autoimmune diabetes in adults (LADA). It is useful to distinguish LADA from type 2 diabetes, because patients with LADA usually require insulin therapy. Features that suggest the presence of LADA rather than type 2 diabetes include two or more of the following: age of onset less than 50 years, acute symptoms, body mass index less than 25 kg/m², and personal or family history of autoimmune disease.[2]

Step-by-step diagnostic approach

Clinical presentation

Type 1 diabetes presents with polyuria, polydipsia, weight loss, generalised weakness, and blurred vision. Some patients present with diabetic ketoacidosis, the acute complication of type 1 diabetes. These patients have symptoms of dehydration and acidosis such as nausea, vomiting, abdominal pain, tachypnoea, tachycardia, and lethargy. Rarely, a patient is diagnosed with type 1 diabetes during routine blood tests. The condition is diagnosed long before its chronic complications have developed.

Diagnosis

Diagnosis can be made on the basis of any of the following:[1]

1. In a symptomatic patient, random plasma glucose of >11 mmol/L (>200 mg/dL)
2. Fasting plasma glucose >6.9 mmol/L (>126 mg/dL)
3. Plasma glucose ≥11 mmol/L (≥200 mg/dL) 2 hours after 75 g oral glucose
4. Glycosylated haemoglobin (HbA1c) ≥48 mmol/mol (≥6.5%).

In an asymptomatic patient, results should be confirmed by repeating the test (from the same sample or in two separate test samples).[1] In symptomatic patients, measurement of plasma glucose if sufficient to diagnose diabetes.[1] Diabetes is the overall diagnostic term applied to people satisfying these criteria, with type 1 and type 2 being further sub-classes based on clinical and/or laboratory criteria.[34]

The diagnosis of type 1 diabetes is often obvious from the clinical presentation, but can be confirmed through additional testing. Low C-peptide levels and presence of one or more autoimmune markers are consistent with a diagnosis of type 1 diabetes.[35] Autoimmune markers include autoantibodies to
glutamic acid decarboxylase (GAD), insulin, islet cells, islet antigens (IA2 and IA2-beta), and the zinc transporter ZnT8.

Elevated plasma or urine ketones in the presence of hyperglycaemia suggests type 1 diabetes, but is occasionally seen at presentation in a patient with type 2 diabetes. As an example, when an obese teenager with a positive family history of type 2 diabetes is found to have high plasma glucose levels on routine blood tests, the diagnosis of type 1 versus type 2 diabetes may not be clear. If C-peptide levels are very low or undetectable relative to the plasma glucose and anti-GAD antibodies are positive in such a patient, a diagnosis of type 1 diabetes can be made.

It is also important to consider monogenic diabetes in the differential for type of diabetes, since this accounts for up to 4% of paediatric diabetes and insulin treatment is inappropriate in these cases.[35] Suspicion should be higher in antibody-negative, ketone-negative paediatric diabetes with a family history of diabetes in multiple generations.[1] The two main forms of monogenic diabetes are maturity-onset diabetes of the young (MODY) and neonatal diabetes. Genetic testing is definitive and can be used to counsel the patient and family members.

[VIDEO: Venepuncture and phlebotomy animated demonstration]

Risk factors

Strong

generical region

- Human leukocyte antigen (HLA) risk profile for type 1 diabetes is widening over time, which may reflect increased environmental influence on susceptible genotypes.[32]
- Geographical variation ranges from 1/100,000 in regions of China to 38/100,000 in Finland.[7]
  Regional variation suggests different contributing risk exposures.[10]

Weak

geneic predisposition

- In one study, concordance for type 1 diabetes was 27.3% in monozygotic twins and 3.8% in dizygotic twins.[30]
- HLA on chromosome 6 thought to contribute to half of the familial basis.[31]
- DR4-DQ8 and DR3-DQ2 present in 90% of children with type 1 diabetes; considered susceptibility genes.[31]
- DR15-DQ6 considered protective.[31]
- Insulin gene on chromosome 11 thought to be second most important susceptibility gene, contributing 10% of genetic susceptibility.[31]
- Several other loci associated with type 1 diabetes under study.[31]

 Infectous agents

- Strongest evidence to date is for human enteroviruses.[15] [16] [17]
dietary factors

- Among dietary factors, supplementation with vitamin D may be protective.[18] [19] 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.[20] [21] [22] There is no consensus about the effect of breastfeeding on risk for type 1 diabetes.[33]

History & examination factors

Key diagnostic factors

presence of risk factors (common)
- Geography is a strong risk factor.

polyuria (common)
- Getting up at night to urinate is typical.

polydipsia (common)
- Getting up at night to drink water is typical.

Other diagnostic factors

young age (common)
- Usually presents in childhood or adolescence. Typical age 5 to 15 years.
- Average age varies in different studies. Incidence increasing in children <5 years old.[36]

weight loss (common)
- Weight loss occurs at onset.

blurred vision (common)
- Occurs with high or fluctuating blood sugar levels.

nausea and vomiting (common)
- Suggest diabetic ketoacidosis.

abdominal pain (common)
- Suggests diabetic ketoacidosis.

tachypnoea (common)
- Suggests diabetic ketoacidosis.

lethargy (common)
- Suggests diabetic ketoacidosis.

coma (uncommon)
- Suggests diabetic ketoacidosis.
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td><strong>random plasma glucose</strong></td>
<td>Confirms diagnosis in the presence of symptoms of polyuria, polydipsia, and unexplained weight loss.[1] ≥11 mmol/L (≥200 mg/dL)</td>
</tr>
<tr>
<td><strong>fasting plasma glucose</strong></td>
<td>Fasting is defined as no caloric intake for at least 8 hours. ≥6.9 mmol/L (≥126 mg/dL)</td>
</tr>
<tr>
<td><strong>2-hour plasma glucose</strong></td>
<td>Plasma glucose is measured 2 hours after 75 g oral glucose load. ≥11 mmol/L (≥200 mg/dL)</td>
</tr>
<tr>
<td><strong>plasma or urine ketones</strong></td>
<td>In the presence of hyperglycaemia suggest type 1 diabetes. medium or high quantity</td>
</tr>
<tr>
<td><strong>HbA1c</strong></td>
<td>Reflects degree of hyperglycaemia over the preceding 3 months. ≥48 mmol/mol (≥6.5%)</td>
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### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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<tbody>
<tr>
<td><strong>fasting C-peptide</strong></td>
<td>C-peptide is a byproduct formed when pro-insulin 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</td>
</tr>
<tr>
<td><strong>autoimmune markers</strong></td>
<td>These include autoantibodies to glutamic acid decarboxylase, insulin, islet cells, islet antigens (IA2 and IA2-beta), and the zinc transporter ZnT8. Presence indicates autoimmune beta-cell destruction. positive</td>
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</table>
# Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| **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. [37]  
• 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. [38]  
• Presents with non-ketotic, non-insulin-dependent diabetes that responds to oral glucose lowering drugs. [39] | • 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. [39] |
| **Neonatal diabetes** | • Diabetes diagnosed under 6 months of age. [1]  
• Usually isolated diabetes in an autosomal dominant pattern of inheritance.  
• Some monogenic causes are characterised by a variety of syndromic features. [40] | • Genetic testing with majority of mutations in the genes encoding the adenosine triphosphate-sensitive potassium channel and the insulin gene. [40] |
| **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. [41]  
• 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. [41] |
| **Type 2 diabetes** | • Typically, signs of insulin resistance (such as | • C-peptide present.  
• Autoantibodies absent. |
### Condition

<table>
<thead>
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<th>Differentiating tests</th>
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<tbody>
<tr>
<td>type 1 diabetes</td>
<td>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.</td>
<td>Testing for C-peptide and autoantibodies usually not required.</td>
</tr>
</tbody>
</table>

### Diagnostic criteria

**American Diabetes Association: criteria for diagnosis of diabetes[1]**

In the absence of unequivocal hyperglycaemia, any of the tests should be confirmed by repeat testing on the same sample or on two separate test samples. Screening tests are generally most applicable to type 2 diabetes.

- Random plasma glucose level ≥11 mmol/L (≥200 mg/dL) in the presence of symptoms of hyperglycaemia; OR
- Fasting plasma glucose ≥6.9 mmol/L (≥126 mg/dL); OR
- Plasma glucose level ≥11 mmol/L (≥200 mg/dL) 2 hours after a 75 g oral glucose load; OR
- HbA1c ≥48 mmol/mol (≥6.5%).
Step-by-step treatment approach

In the short term, insulin is life-saving because it prevents diabetic ketoacidosis, a potentially life-threatening condition. 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. Current guidelines recommend a target HbA1c of <53 mmol/mol (<7%) for adult patients and many children.[1] [35] [43] In the UK, national guidance recommends that patients with type 1 diabetes aim for a target HbA1c level of 48 mmol/mol (6.5%) or lower to minimise the risk of long-term vascular complications.[44] [45] Less stringent goals may be appropriate for 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.[1]

Good glycaemic control in type 1 diabetes requires attention to diet, exercise, and insulin therapy. All three components should be co-ordinated for ideal control. Self-monitoring of blood glucose (SMBG) is a core component of good glycaemic control. Patients on multiple injections daily should consider SMBG before meals, occasionally after meals and at bedtime, and before exercising to assess presence and adequate treatment of hypoglycaemia, and before any task during which hypoglycaemia could have particularly dangerous consequences.[1] Some patients will need to check their blood glucose 6-10 times daily.[46]

As continuous glucose monitoring (CGM) technology continues to improve, the indications for its use are likely to expand.[47] Evidence supports use of CGM for improved glucose control in adults and children.[48] [49] [50] Appropriate use of CGM is when it is targeted at people with type 1 diabetes who have hypoglycaemic unawareness, frequent hypoglycaemia, or continued poor control during intensified insulin therapy, and at those who are willing to use CGM frequently.[1] [51] The limiting factor for tight glycaemic control in type 1 diabetes is hypoglycaemia. Well-controlled blood pressure and lipids, and avoidance of smoking are essential components of cardiovascular risk reduction.

Including technology-based methods, along with individual and group settings are recommended for the delivery of effective diabetes self-management education and support.[1] This approach can be used for adults.[52] as well as children and adolescents.[53]

Diet and exercise

There is no standardised dietary advice that is suitable for all individuals with diabetes.[1] 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. 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.[54] Carbohydrate counting or consistent carbohydrate intake with respect to time and amount may improve glycaemic control. Rapid-acting insulins may make timing of meals less crucial than in the past, but regular meals are still important.

Adults with diabetes are recommended to engage in 150 minutes/week of moderate-intensity aerobic exercise (to 50% to 70% of max heart rate) spread over at least 3 days per week, with no more than 2 consecutive days without exercise.[1] Children and adolescents with diabetes should aim for 60 minutes of moderate- to vigorous-intensity aerobic activity daily and vigorous muscle-strengthening and bone-strengthening activities at least 3 days per week.[35] Patients with type 1 diabetes can safely exercise and manage their glucose levels.[35] [55] Pre-exercise carbohydrate intake and insulin doses can be
Type 1 diabetes

Effectively modified to avoid hypoglycaemia during exercise and sport. Hypoglycaemia can occur up to 24 hours after exercise and may require reducing insulin dosage on days of planned exercise. A carbohydrate snack should be given at the start of exercise if the blood sugar is <5.6 mmol/L (<100 mg/dL).

Clinical judgement should be used in determining whether to screen asymptomatic individuals for coronary artery disease prior to recommending an exercise programme.

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, proliferative or preproliferative retinopathy, or macular oedema. Vigorous exercise may be contraindicated with proliferative or severe preproliferative diabetic retinopathy. Non-weight-bearing exercise may be advisable in patients with severe peripheral neuropathy.

Prolonged sitting should be interrupted every 30 minutes with short bouts of physical activity.

Initiating insulin

Intensive therapy with insulin should be started as soon as possible after diagnosis. 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.

The choice between pump and MDI is based on patient interest and self-management skills, as well as physician preference, as outcomes are generally similar. The insulin pump uses regular or rapid-acting insulin, and provides a basal rate of insulin and delivers mealtime bolus dosing. However, the patient or parent must still measure blood glucose frequently 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 systems (CGMS) and threshold suspend features, and improve HbA1c, while providing greater flexibility. Use of a pump requires a motivated patient with strong family support (for children) and access to practitioners trained in pump therapy.

Using a combination of long- (insulins glargine, detemir, or degludec) or intermediate-acting (NPH) insulin for basal dosing, and rapid- (insulins lispro, aspart, or glulisine) or short- (regular-) acting insulin for bolus dosing, MDI regimens can be designed based on physician and patient preference and modified based on finger-prick data. There is no consensus as to whether insulin analogues are superior to conventional insulins for glycaemic control or reductions in complications.

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 comply with MDI, but it is no longer a first-line recommendation for management because of its lack of flexibility.

Designing a regimen

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 only 10 or 15 units/day. One half of the total dose is given as basal insulin and one half as bolus dosing. The bolus dosing is divided and given before meals. Patients need to self-monitor their blood glucose levels. The insulin doses can be adjusted every 2-3 days to maintain target blood glucose. To achieve an HbA1c <53 mmol/mol (<7%), the pre-meal blood glucose
Type 1 diabetes

Treatment

Goal is 4.4 to 7.2 mmol/L (80-130 mg/dL) and the post-meal blood glucose goal (1-2 hours after starting the meal) is <10.0 mmol/L (180 mg/dL).

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. A simple beginning approach is to use 1 unit of mealtime insulin for every 15 g of carbohydrate in the meal. 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 nutritionist. Using a food diary and 2-hour postprandial blood glucose measurements, the insulin-to-carbohydrate ratio can be adjusted.

A correction dose may be added to the bolus insulin based on the pre-meal blood glucose level. Correction dosing may be calculated as follows when the patient's total daily dose of insulin (TDD) and food intake is stable: 1800/TDD = the predicted point drop in blood glucose per unit of rapid acting insulin. For example, if the TDD is 40 units of insulin, 1800/40 = 45 point drop per unit of insulin.

Example of correction dosing based on pre-meal glucose and above calculation:

- 2.2 to 4.9 mmol/L (45-90 mg/dL): subtract 1 unit from mealtime insulin
- 5.0 to 7.4 mmol/L (91-135 mg/dL): add 0 units of correction insulin
- 7.5 to 9.9 mmol/L (136-180 mg/dL): add 1 unit of correction insulin
- 9.9 to 12.4 mmol/L (181-225 mg/dL): add 2 units of correction insulin
- 12.4 to 14.5 mmol/L (226-270 mg/dL): add 3 units of correction insulin
- 14.5 to 17.3 mmol/L (271-315 mg/dL): add 4 units of correction insulin
- 17.4 to 19.8 mmol/L (316-360 mg/dL): add 5 units of correction insulin
- 19.8 to 22.3 mmol/L (361-405 mg/dL): add 6 units of correction insulin
- >22.3 mmol/L (>405 mg/dL): add 7 units of correction insulin; seek medical assistance.

The number used to calculate the correction dose may be as low as 1500 or as high as 2200. There are no specific guidelines to determine this number. In general, a lower number should be used for obese, insulin-resistant patients, and a higher number should be used for lean, insulin-sensitive patients.

This 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.

Pump therapy utilises a similar concept as basal and bolus dosing and does not require multiple injections of insulin. However, patients still need to monitor their blood glucose from 4-7 times daily. There is some evidence that insulin pump therapy may be associated with improved glycaemic control and lower risk of hypoglycaemia,\[68\] including in children, adolescents, and young adults.\[69\] Because of the monitoring and dose adjustment required, patients selected for pump therapy must be skilled in diabetes self-management and able to manage and troubleshoot the various pump components.\[70\]

The insulin pump uses a subcutaneous insulin injection port. The port is changed every 3 days and may reduce anxiety and help achieve better glycaemic control in selected patients.\[71\] \[72\]

CGMS measure subcutaneous interstitial fluid glucose every 5 minutes. CGMS may be indicated in selected patients with widely fluctuating glucose levels or hypoglycaemia unawareness. A 3-day glucose monitoring system using a CGMS may help the physician adjust insulin doses. Real-time CGMS, worn
by a patient on a regular basis, may help improve glycaemic control.[73] [74] [75] [76] The glucose sensors used in CGMS are not reliable at lower ranges of glucose, and thus do not eliminate the need for fingersticks. Development of these systems is ongoing.[47]

CGMS are also less accurate than traditional capillary blood glucose-monitoring methods. However, they provide information on glucose trends, provide alarms to alert patients to impending hypo- or hyperglycaemia, and reduce episodes of hypoglycaemia.[61] [77] 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 insulin delivery can be determined automatically based on sensed glucose levels. These integrated devices use a computerised control algorithm to create the closed loop insulin delivery system, which functions as an artificial pancreas.[35] [78] In clinical trials, such systems have been shown to reduce the risk of nocturnal hypoglycaemia and to improve glucose control, including in children.[48] [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 and is increasingly reimbursed by insurance providers in the US.

Hypoglycaemia is the most common and potentially most serious side effect of insulin therapy, as it can lead to decreased quality of life, confusion, seizures, and coma. Episodes of hypoglycaemia should be sought at each visit, and efforts made to determine contributing factors, and the ability of the patient to recognise and treat it appropriately.

**Goal not met**

If glycaemic control is not adequate as measured by the HbA1c or by episodes of hypoglycaemia, the patient's nutrition, exercise, and insulin regimen must be re-examined. Children and adolescents may have erratic eating patterns or snack frequently. Consultation with a nutritionist 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 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. If a patient is getting regular insulin, replacing it with rapid-acting insulin may reduce postprandial glucose excursions.

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.

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. Nocturnal hypoglycaemia may result in rebound hyperglycaemia in the morning. The dose of basal insulin should be decreased to prevent nocturnal hypoglycaemia. A bedtime snack is not an effective way of decreasing the risk of nocturnal hypoglycaemia.[81] Alcohol may cause acute hypoglycaemia, but both alcohol and exercise can cause delayed hypoglycaemia (by up to 24 hours).

**Non-insulin treatments**

Pramlintide is indicated as adjunctive treatment in patients with postprandial hyperglycaemia that cannot be controlled with pre-meal insulin alone. For example, it may be useful in a patient with high postprandial glucose, but who develops late hypoglycaemia when pre-meal insulin is increased.
The therapy of people with type 1 diabetes also involves regular eye examinations, foot care, treatment of dyslipidaemia, and blood pressure control.

Adults with type 1 diabetes are at three times the risk of clinical depression compared with those without type 1 diabetes.[82] The prevalence of depression in diabetes is higher in women (28%) compared with men (18%).[83] The risk may also be higher in adolescents, at diagnosis, or when there is a change in disease status.[84] Psychosocial screening and support can help to ameliorate distress and improve the individual’s and family’s capacity for self-care.

Pregnancy

Infants of women with diabetes are at high risk of major congenital malformations and miscarriage.[85] Pre-conception diabetes care reduces this risk.[86] Pre-conception counselling should, therefore, be incorporated in the routine diabetes clinic visit for all women of childbearing potential. Women with type 1 diabetes should use an effective method of contraception until they plan pregnancy. The American Diabetes Association (ADA) recommends that HbA1c should be <48 mmol/mol (<6.5%) before conception if this can be achieved without hypoglycaemia.[1] Women should also be evaluated before pregnancy for retinopathy, nephropathy, neuropathy, and possible cardiovascular disease, which may worsen during or complicate pregnancy.

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. During pregnancy women should be cared for by a multidisciplinary team including a nutritionist, a nurse educator, an endocrinologist, and an obstetrician. All pregnant women require a dilated eye examination soon before or early in pregnancy. Women with diabetes have an increased risk of having infants with neural tube defects compared with the general population,[87] and should take a folic acid supplement prior to and during pregnancy. Statins, angiotensin-converting enzyme inhibitors, and angiotensin-II receptor blockers should be discontinued pre-conception. Intensive insulin treatment with MDI or insulin pump should be started. Commonly used insulins during pregnancy include NPH, detemir, regular, lispro, and aspart.[88] Use of CGM during pregnancy may help in improving glycaemic control and neonatal outcomes.[89]

There are no large randomised trials supporting the safety of insulin glargine in pregnant patients with diabetes. However, insulin glargine has been safely used in many patients during pregnancy. It can be considered second-line to NPH or insulin detemir for basal insulin dosing during pregnancy because there are fewer long-term safety monitoring data. There are few data comparing outcomes for continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes.[90] However, one randomised controlled trial reports better glycaemic outcomes with use of multiple daily injection therapy versus insulin pump therapy.[91] ADA guidelines recommend the following blood glucose targets in pregnant women with pre-existing type 1 diabetes (the same as for gestational diabetes): <5.3 mmol/L (<95 mg/dL) fasting, and either <7.8 mmol/L (<140 mg/dL) 1 hour postprandially or <6.7 mmol/L (<120 mg/dL) 2 hours postprandially, with HbA1c goal individualised <42 mmol/mol (<6%) or up to <53 mmol/mol (<7%) as necessary to prevent hypoglycaemia.[1]

The ADA recommends that all pregnant women with pre-existing type 1 diabetes should consider daily low-dose aspirin starting at the end of the first trimester in order to reduce the risk of pre-eclampsia.[1]
Ongoing comprehensive medical evaluation

Includes assessment of diabetic complications, a psychosocial assessment, and management of comorbid conditions (e.g., autoimmune diseases).[1]

Treatment details 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

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>(summary)</th>
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<tbody>
<tr>
<td>non-pregnant</td>
<td></td>
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<tr>
<td>1st</td>
<td>basal-bolus insulin</td>
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<tr>
<td>adjunct</td>
<td>pre-meal insulin correction dose</td>
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<td>2nd</td>
<td>fixed-dose insulin</td>
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<td>pregnant</td>
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<tr>
<td>1st</td>
<td>basal-bolus insulin</td>
</tr>
<tr>
<td>plus</td>
<td>low-dose aspirin</td>
</tr>
</tbody>
</table>
Treatment options

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.
1st basal-bolus insulin

Primary options

- **insulin glargine**: injected subcutaneously once daily
  - or -
  - **insulin isophane human (NPH)**: injected subcutaneously twice daily
  - or -
  - **insulin detemir**: injected subcutaneously twice daily
  - or -
  - **insulin degludec**: injected subcutaneously once daily
  --AND--
  - **insulin neutral**: injected subcutaneously two to three times daily
  - or -
  - **insulin lispro**: injected subcutaneously pre-meal
  - or -
  - **insulin aspart**: injected subcutaneously pre-meal
  - or -
  - **insulin glulisine**: injected subcutaneously pre-meal

OR

- **pump**: uses regular insulin or insulins lispro, aspart, or glulisine

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 only 10 or 15 units/day. One half of the total dose is given as basal insulin and one half as bolus dosing. The bolus dosing is divided and given before meals. Patients need to self-monitor their blood glucose levels. The insulin doses can be adjusted every 2-3 days to maintain pre-meal and post-meal blood glucose targets.[1]

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...
Type 1 diabetes

### Treatment

<table>
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<th>Ongoing</th>
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<tr>
<td>calculated based on the estimated amount of carbohydrate in the meal and the patient's individual insulin-to-carbohydrate ratio. A simple beginning approach is to use one unit of mealtime insulin for every 15 g of carbohydrate in the meal. 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 nutritionist. Using a food diary and 2-hour postprandial blood glucose measurements, the insulin-to-carbohydrate ratio can be adjusted.</td>
</tr>
</tbody>
</table>

» Reasonable to begin therapy with 2-4 insulin injections daily to cover basal insulin requirements and to cover mealtime insulin needs. Intermediate- or long-acting insulins to cover basal, and short- or rapid-acting to cover mealtime needs, should be used.

» Regular and NPH insulins are less expensive than the insulin analogues. Regular insulin is given about 30 minutes prior to the meal, while rapid-acting insulins (lispro, aspart, or glulisine) can be injected 15 minutes before to shortly after a meal. In children with erratic eating habits, rapid-acting insulins can be given just after the meal. NPH and insulin detemir are injected twice daily while insulin glargine can be injected once daily. The regimen 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.

» Patients with interest and good self-management skills may prefer to use an insulin pump.

adjunct pre-meal insulin correction dose

Treatment recommended for SOME patients in selected patient group

» A correction dose may be added to the bolus insulin based on the pre-meal blood glucose level. Correction dosing may be calculated as follows when the patient’s total daily dose of insulin (TDD) and food intake is stable: 1800/TDD = the predicted point drop in blood glucose per unit of rapid acting insulin. For example, if the TDD is 40 units of insulin, 1800/40 = 45 point drop per unit of insulin.

» Example of correction dosing based on pre-meal glucose and above calculation:
## Treatment

<table>
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<th>Ongoing</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td></td>
<td>» 2.2 to 4.9 mmol/L (45-90 mg/dL): subtract 1 unit from mealtime insulin</td>
</tr>
<tr>
<td></td>
<td>» 5.0 to 7.4 mmol/L (91-135 mg/dL): add 0 units of correction insulin</td>
</tr>
<tr>
<td></td>
<td>» 7.5 to 9.9 mmol/L (136-180 mg/dL): add 1 unit of correction insulin</td>
</tr>
<tr>
<td></td>
<td>» 9.9 to 12.4 mmol/L (181-225 mg/dL): add 2 units of correction insulin</td>
</tr>
<tr>
<td></td>
<td>» 12.4 to 14.5 mmol/L (226-270 mg/dL): add 3 units of correction insulin</td>
</tr>
<tr>
<td></td>
<td>» 14.5 to 17.3 mmol/L (271-315 mg/dL): add 4 units of correction insulin</td>
</tr>
<tr>
<td></td>
<td>» 17.4 to 19.8 mmol/L (316-360 mg/dL): add 5 units of correction insulin</td>
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<tr>
<td></td>
<td>» 19.8 to 22.3 mmol/L (361-405 mg/dL): add 6 units of correction insulin</td>
</tr>
<tr>
<td></td>
<td>» &gt;22.3 mmol/L (&gt;405 mg/dL): add 7 units of correction insulin; seek medical assistance.</td>
</tr>
</tbody>
</table>

The number used to calculate the correction dose may be as low as 1500 or as high as 2200. There are no specific guidelines to determine this number. In general, a lower number should be used for obese, insulin-resistant patients, and a higher number should be used for lean, insulin-sensitive patients.

This 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 amylin analogue

Treatment recommended for SOME patients in selected patient group

### Primary options

|  |
|  |
| » pramlintide: 15-60 micrograms subcutaneously before each meal  |

Synthetic analogue of human amylin, a protein that is co-secreted with insulin by pancreatic beta cells. It reduces postprandial glucose increases by prolonging gastric emptying time, reducing postprandial glucagon secretion, and reducing food intake through centrally mediated appetite suppression.[92]

May be given as an injection before each meal to get more stable glycaemic control. However,
### Ongoing

Insulin treatment must continue in addition to pramlintide.

- At initiation the current pre-meal insulin dose should be reduced by about 50% to avoid hypoglycaemia, and then titrated up.
- Indicated as adjunctive treatment in patients with postprandial hyperglycaemia that cannot be controlled with pre-meal insulin alone. For example, it may be useful in a patient with high postprandial glucose, but who develops late hypoglycaemia when pre-meal insulin is increased.
- Should not be used in a patient with gastroparesis. The most common side effect is nausea, occurring in 28% to 48% of patients. [92]

<table>
<thead>
<tr>
<th>2nd</th>
<th>fixed-dose insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» insulin isophane human/insulin neutral: (50/50, 70/30) injected subcutaneously twice daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» insulin aspart protamine/insulin aspart: (70/30) injected subcutaneously twice daily</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» insulin lispro protamine/insulin lispro: (50/50, 75/25) injected subcutaneously twice daily</td>
<td></td>
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<tr>
<td>OR</td>
<td></td>
</tr>
<tr>
<td>» insulin degludec/insulin aspart: (70/30) injected subcutaneously once or twice daily</td>
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</tbody>
</table>
- Fixed-dose insulin is used when patients are already doing well on a fixed-dose regimen; or cannot manage 3-4 insulin injections daily; or have trouble mixing insulin.

### pregnant

<table>
<thead>
<tr>
<th>1st</th>
<th>basal-bolus insulin</th>
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<tbody>
<tr>
<td><strong>Primary options</strong></td>
<td></td>
</tr>
<tr>
<td>» insulin isophane human (NPH): injected subcutaneously twice daily</td>
<td></td>
</tr>
<tr>
<td>-or-</td>
<td></td>
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<tr>
<td>» insulin detemir: injected subcutaneously twice daily</td>
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</tbody>
</table>
### Ongoing

--AND--

- **insulin neutral**: injected subcutaneously two to three times daily
- **or**
  - **insulin lispro**: injected subcutaneously pre-meal
- **or**
  - **insulin aspart**: injected subcutaneously pre-meal

### Secondary options

- **insulin glargine**: injected subcutaneously once daily

--AND--

- **insulin neutral**: injected subcutaneously two to three times daily
- **or**
  - **insulin lispro**: injected subcutaneously pre-meal
- **or**
  - **insulin aspart**: injected subcutaneously pre-meal

**OR**

- **pump**: uses regular insulin or insulins lispro or aspart

- Blood sugar goals, if able to be achieved without significant hypoglycaemia, are fasting <5 mmol/L (<90 mg/dL), 1-hour postprandial <7.2 to 7.8 mmol/L (<130-140 mg/dL), and 2-hour postprandial <6.7 mmol/L (<120 mg/dL). If these targets result in hypoglycaemia, less stringent targets are appropriate.[1]

- **HbA1c** should be <48 mmol/mol (<6.5%) before conception, if it can be achieved without hypoglycaemia.[1] HbA1c in pregnancy can be monitored monthly.[1]

- Patients should monitor their blood glucose from 4-7 times per day and 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 8-16 weeks before rising throughout the rest of the pregnancy.

- Commonly used insulins during pregnancy include NPH, detemir, regular, lispro, and aspart.[88] Use of CGM during pregnancy may...
help in improving glycaemic control and neonatal outcomes.\[89\] There are no large randomised trials supporting the safety of insulin glargine in pregnant patients with diabetes. However, insulin glargine has been safely used in many patients during pregnancy. It can be considered second-line to NPH or insulin detemir for basal insulin dosing during pregnancy because there are fewer long-term safety monitoring data. There are few data comparing outcomes for continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes.\[90\]

plus low-dose aspirin

Treatment recommended for ALL patients in selected patient group

Primary options

» aspirin: 75-150 mg orally once daily, usual dose 75 mg/day

» The American Diabetes Association recommends that all pregnant women with pre-existing type 1 diabetes should consider daily low-dose aspirin starting at the end of the first trimester in order to reduce the risk of pre-eclampsia.\[1\]
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. 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.

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. 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. 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. 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. 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. 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. Several trials are under way to investigate mono- and combination therapies to arrest inflammation and possibly allow beta-cell regeneration.

Insulin sensitisers

A systematic review suggested that use of metformin in type 1 diabetes reduced insulin requirements but not HbA1c levels after 1 year of follow-up. Further research is indicated to better delineate the potential indications and benefits of this treatment in type 1 diabetes.
Sodium-glucose co-transporter 2 inhibitors

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are oral medications that reduce glucose in an insulin-independent manner, by inhibiting SGLT2 in the proximal renal tubule and blocking glucose reabsorption. They are associated with modest weight loss and blood pressure reduction. SGLT2 inhibitors are approved for use in individuals with type 2 diabetes. Several reports have highlighted the risk of euglycaemic diabetic ketoacidosis in both type 2 and type 1 diabetes.[105] [106] Studies are ongoing to assess safety and efficacy of this class of medications in type 1 diabetes.[1] [107] [108] The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) has approved the selective SGLT2 inhibitor dapagliflozin for use in patients with type 1 diabetes mellitus and a body mass index ≥27 kg/m² as an adjunct to insulin, when insulin alone does not provide adequate glycemic control despite optimal insulin therapy.[109] [110] [111] In March 2019, the CHMP recommended that sotagliflozin, a dual inhibitor of SGLT1 and SGLT2, also be approved for the same indication.[105] [112] [113] [114] [115] However, the US Food and Drug Administration (FDA) rejected approval of sotagliflozin for type 1 diabetes in March 2019. Patients must fulfil requirements to minimise the increased risk of diabetic ketoacidosis with both of these drugs.

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.[116] 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.
**Recommendations**

**Monitoring**

- Glycosylated haemoglobin (HbA1c) should be checked twice yearly in patients who are meeting treatment goal <59 mmol/mol (<7.5%) for patients aged under 18 years with type 1 diabetes and <53 mmol/mol (<7%) for adult patients. It is recommended to check HbA1c every 3 months in patients whose therapy is being modified or who are not meeting the goal. In very old or very young patients and in those with a history of severe hypoglycaemia or limited lifespan, the HbA1c goal can be less stringent.[1] [43]
- Check blood pressure at each visit and treat to a goal of <140/90 mmHg.[1] In older adults, treating to <130/70 mmHg is not recommended.
- For patients who are not on statins, it is recommended to check a screening lipid profile (total cholesterol, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides) in adults with diabetes at the time of first diagnosis, at initial medical evaluation, and then every 5 years thereafter if aged under 40 years (annually may be indicated in some cases). Lifestyle modification should be recommended to all patients with diabetes to improve lipid profile. For patients with atherosclerotic cardiovascular disease, a high-intensity statin should be added to lifestyle therapy. For patients aged 40-75 years without additional atherosclerotic cardiovascular disease risk factors, the American Diabetes Association (ADA) recommends adding a moderate-intensity statin. For patients aged 40-75 years with additional atherosclerotic cardiovascular disease risk factors, the ADA recommends adding a high-intensity statin. Once a patient is taking a statin, LDL cholesterol levels should be assessed 4-12 weeks after initiation of statin therapy, after any change in dose, and on an individual basis (e.g., to monitor adherence and efficacy). If a patient is adherent to statin therapy but not responding, clinical judgement is recommended to determine the need for and timing of lipid panels.[1]
- In the US, initial screening for retinopathy by an ophthalmologist is recommended within 5 years of initial diagnosis of diabetes, and every 2 years after that if no evidence of retinopathy. In the presence of abnormal findings, more frequent follow-up may be indicated (e.g., annually).[1] Recommendations differ in other countries; for example, in the UK, screening for retinopathy is offered at the time of diagnosis and annually to all patients over the age of 12 years.[44] [45] Local guidance should be consulted.
- Yearly screening for increased urinary albumin excretion and serum creatinine to estimate glomerular filtration rate should be done in all patients who have had type 1 diabetes for 5 years or more.[1]
- Screen yearly for distal symmetric polyneuropathy using pin-prick sensation, temperature, and vibration perception (with 128 Hz tuning fork), and 10 g mono-filament pressure sensation at the distal plantar aspect of both great toes and ankle reflexes.
- Symptoms of autonomic neuropathy can be assessed through history (exercise intolerance, constipation, diarrhoea, gastroparesis, bladder or sexual dysfunction, hypoglycaemic autonomic failure) and physical examination (resting tachycardia, orthostatic hypotension).[1]
- Yearly dental examinations are indicated in patients with and without teeth, to control periodontal disease, which both contributes to and exacerbates hyperglycaemia.
- Vaccines should be provided in accordance with age-specific guidelines for the general population, including those for influenza and pneumococcal pneumonia. Hepatitis B vaccine should be provided for unvaccinated adults with diabetes aged 19-59 years, and should be considered for unvaccinated adults with diabetes aged ≥60 years.[1]
- Patients with autoimmune diabetes are more likely to have thyroid disease, coeliac disease, and depression.[43] Physicians should have a low threshold for screening for these conditions.

**Patient instructions**

- The physician should advise the patient and/or carers that it is important to eat a healthy diet and regular meals. Referral to a nutritionist or a dietitian can be helpful in planning a diet.
• Patients should be advised on exercise. They should build up exercise slowly. If the weather is very hot or cold, they could walk at an indoor track or mall. Patients may need to take less insulin or eat a snack before exercise. They should also be advised to check their blood glucose before and after exercising. Any patients with peripheral neuropathy would be wise to perform low-impact exercises such as swimming, bicycling, or arm exercises.

• The physician should help the patient plan how often to check blood glucose. The most likely times would be before each meal and at bedtime. Patients may also check 2 hours after meals and when exercising.

• Patients should usually have an HbA1c performed every 3 months.

• Patients should be advised that hypoglycaemia may occur if they skip a meal, take too much insulin, exercise, or become ill. Alcohol and exercise can cause delayed hypoglycaemia, which may appear even up to 24 hours later. Symptoms should be described, including feeling very hungry, nervous, shaky, sweaty, dizzy, or confused. In order to raise the blood glucose, patients can take glucose tablets or gels, or drink milk or juice, depending on how low the blood sugar falls. Patients should see their physician for adjustment of medication should hypoglycaemia occur. A glucagon kit should be prescribed for emergencies in the case of severe hypoglycaemia or when the patient is unable to drink or eat. Family members and co-workers should be instructed on how to administer this. For children, school and camp staff and caretakers should be educated on how to deal with low blood sugar.

• The American Diabetes Association (ADA) defines level 1 hypoglycaemia as ≥3.0 mmol/L but <3.9 mmol/L (≥54 mg/dL but <70 mg/dL), requiring treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy. Level 2 hypoglycaemia (clinically significant) is defined as <3.0 mmol/L (<54 mg/dL). Level 3 hypoglycaemia (severe) is defined as any low blood glucose level leading to cognitive impairment requiring assistance from another person for recovery.[1]

• Patients should discuss their insulin requirement with their physician prior to skipping any meals (e.g., for a medical test).

• Patients should also be educated on the symptoms of hyperglycaemia, including blurred vision, thirst, frequent urination, or tiredness, and should see their physician immediately if these occur. Patients should also seek medical attention if they develop a fever, cough, dysuria, or wounds on the feet. If patients are sick or if they note a finger-prick >250 mg/dL (>13.9 mmol/L) on two successive pre-meal checks, they should check their urine ketones, and call their physician if the ketones are positive.

• If patients smoke, they should be strongly advised to quit, and offered appropriate treatments as needed.

• The doctor should check patients’ cholesterol and blood pressure and assess for neuropathy regularly.

• Patients should be up to date with their vaccination schedule.

• Patients should be encouraged to discuss any feelings of depression with their physicians so that appropriate treatment can be offered.

• Children can take part in all activities at home or school. Staff members at school or camp should assist with a child’s needs, including checking blood sugars, taking insulin as needed, eating regular meals, and treating any low blood sugars.

• Further information is available at the ADA website. [American Diabetes Association]
Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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</thead>
<tbody>
<tr>
<td>diabetic ketoacidosis (DKA)</td>
<td>short term</td>
<td>high</td>
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</table>

DKA is the classical acute complication of type 1 diabetes, characterised by hyperglycaemia and metabolic acidosis.

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, shortness of breath, abdominal pain, nausea, vomiting, and altered sensorium.

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 1- to 4-hourly monitoring of electrolytes is required. Insulin infusion must continue until ketosis has resolved and a subcutaneous injection of insulin has been given.

Closure of the anion gap will indicate correction of the ketoacidosis.

Potassium repletion is usually indicated because initially apparently normal serum potassium does not reflect true total body depletion.

Treatment with bicarbonate is not indicated except when arterial blood pH is <6.9. Serum phosphorus level is usually low, but does not require replacement unless it is < 1.0 mg/dL (0.323 mmol/L).[125]

<table>
<thead>
<tr>
<th>hypoglycaemia</th>
<th>short term</th>
<th>high</th>
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</table>

The main complication of insulin treatment is hypoglycaemia. The American Diabetes Association defines level 1 hypoglycaemia as ≥3.0 mmol/L but <3.9 mmol/L (≥54 mg/dL but <70 mg/dL), requiring treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy. Level 2 hypoglycaemia (clinically significant) is defined as <3.0 mmol/L (<54 mg/dL). Level 3 hypoglycaemia (severe) is defined as any low blood glucose level leading to cognitive impairment requiring assistance from another person for recovery.[1]

Patients with type 1 diabetes are generally sensitive to insulin.

Therefore, even a slightly higher dose of insulin, decreased food intake, or increased physical activity can lead to hypoglycaemia. Children <6-7 years old may not be aware of hypoglycaemia, necessitating less stringent goals for glucose control.[1] Other risk factors for hypoglycaemia include a prior episode of hypoglycaemia, hypoglycaemic unawareness, autonomic neuropathy, and long duration of diabetes. Alcohol and exercise can cause delayed hypoglycaemia, up to 24 hours after the event.
<table>
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<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
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<tbody>
<tr>
<td>If the patient is able to ingest orally, hypoglycaemia can be treated with 118 mL (4 fluid ounces) of fruit juice or sweetened fluids or glucose tablets (15-20 g of carbohydrate).[1] Blood sugar should be tested and treatment effect apparent in 15 minutes.</td>
<td>long term</td>
<td>high</td>
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<tr>
<td>If oral intake is not possible, glucagon (parenteral or intranasal administration) or intravenous dextrose is required.</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>Patient carers and family members of patients with type 1 diabetes should be educated about the signs and symptoms of hypoglycaemia and taught how to administer oral glucose or glucagon intranasally or as an intramuscular or subcutaneous injection. Unless hypoglycaemia is recurring, the next meal or snack should be eaten and the next dose of basal insulin should be given.</td>
<td>long term</td>
<td>high</td>
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<tr>
<td>Episodic of hypoglycaemia and the possibility of hypoglycaemia unawareness should be assessed at each visit. A strict period of several weeks without hypoglycaemia may improve hypoglycaemic awareness in some patients.</td>
<td>long term</td>
<td>high</td>
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</table>

**Retinopathy**

Retinopathy is the most common microvascular complication of diabetes and its risk is increased at all levels of glycosylated hemoglobin (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%).[118] There is an increased risk of retinopathy in women with pre-existing type 1 diabetes during pregnancy.[1]

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.

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.[1] In advanced disease, photo-coagulation and vitrectomy can be done to prevent blindness.[1] Intravitreal injections of antivascular endothelial growth factors are given for centre-involved macular oedema.[1]

**Diabetic kidney disease**

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%.[126] 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.[127]

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.[1]

Glycaemic control and blood pressure control with an ACE inhibitor or angiotensin-II receptor blocker delays onset and slows progression of disease.[128] [129]

**Peripheral or autonomic neuropathy**

More than 50% of patients will develop neuropathy.[130]
Type 1 diabetes

Follow up

<table>
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<tr>
<th>Complications</th>
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<tbody>
<tr>
<td>Strict glycaemic control prevents onset and delays progression of diabetic neuropathy, which manifests most commonly as distal symmetric polyneuropathy affecting sensory axons.</td>
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<tr>
<td>The duration and extent of hyperglycaemia are the greatest risk factors, although other cardiovascular risk factors probably also contribute.</td>
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<tr>
<td>The other most common types of neuropathy include mononeuropathy, mononeuritis multiplex, polyradiculopathies, and autonomic neuropathy.</td>
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<td>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.[1] For autonomic neuropathy, current treatments for this complication are mostly inadequate. However, symptom management can be considered: for example, compressive stockings for postural hypotension.[1]</td>
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<tr>
<th>cardiovascular disease</th>
<th>long term</th>
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<tr>
<td>Cardiovascular disease is the major cause of death and a major cause of morbidity for patients with diabetes.</td>
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<td>Intensive glycaemic control has been shown to decrease the incidence of macrovascular disease in type 1 diabetes.[121] 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.[122] [131] The cardiovascular disease risk can be further decreased by modification of other cardiovascular risk factors.[132] Lifestyle and behavioural therapy are essential components of treatment.</td>
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<tr>
<td>Hypertension is often secondary to underlying nephropathy in patients with type 1 diabetes. Blood pressure should be treated to &lt;140/80 mm Hg with an ACE inhibitor or angiotensin-II receptor blocker; most patients will require two or three drugs to reach goal. Intensifying antihypertensive therapy to blood pressure targets &lt;140/90 was associated with a lower risk of coronary artery disease in one study.[133] For patients of all ages with diabetes and overt cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. For patients without known cardiovascular disease, individualisation of statin therapy according to their cardiovascular disease risk score is recommended.[134] [ASCVD risk estimator]</td>
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<tr>
<td>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 &lt;1 mmol/L (&lt;40 mg/dL) (&lt;1.3 mmol/L [&lt;50 mg/dL] among women).[1] 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.[1] Monitoring can be every 3 years if LDL &lt;2.6 mmol/L (&lt;100 mg/dL).[1] 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 &lt;10 years.[1]</td>
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**Complications**

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<tr>
<td>All adult patients with diabetes and cardiovascular disease should be treated with aspirin for secondary prevention (75-162 mg/day). Aspirin can be considered for primary prevention for men and women at increased cardiovascular risk, after a comprehensive discussion with the patient on the benefits versus the comparable increased risk of bleeding.[1] All patients should have smoking-cessation counselling and treatment as needed.</td>
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<tr>
<td>Patients aged &gt;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.[135]</td>
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<td>No evidence-based guidelines exist for screening asymptomatic patients for coronary heart disease.[1]</td>
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</table>

**Prognosis**

Untreated type 1 diabetes is a fatal condition due to diabetic ketoacidosis. Poorly controlled 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,[117] [118] [119] [120] [121] and the decreased incidence of macrovascular disease has been shown to persist for up to 30 years.[122] Even a few years of intensive glucose control translate to reduced rates of microvascular and macrovascular complications 10 years later.[118] [123] The American Diabetes Association recommends maintaining glycosylated haemoglobin (HbA1c) <53 mmol/mol (<7%) to prevent complications in most non-pregnant adults with type 1 diabetes, with less stringent goals in children and adolescents.[1]

Overall, cardiovascular disease is the major cause of death and a major cause of morbidity for patients with diabetes. 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.[124]

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

## Europe

### Management of diabetes (SIGN no. 116)
- **Published by:** Scottish Intercollegiate Guidelines Network
- **Last published:** 2017

### Type 1 diabetes in adults: diagnosis and management
- **Published by:** National Institute for Health and Care Excellence
- **Last published:** 2016

### Diabetes (type 1 and type 2) in children and young people: diagnosis and management
- **Published by:** National Institute for Health and Care Excellence
- **Last published:** 2016

## International

### ISPAD clinical practice consensus guidelines 2018
- **Published by:** International Society for Paediatric and Adolescent Diabetes (ISPAD)
- **Last published:** 2018

## North America

### Standards of medical care in diabetes - 2020
- **Published by:** American Diabetes Association
- **Last published:** 2020

### Classification of diabetes mellitus
- **Published by:** World Health Organization
- **Last published:** 2019

### Type 1 diabetes
- **Published by:** Centers for Disease Control and Prevention
- **Last published:** 2019

### Clinical practice guidelines for the prevention and management of diabetes in Canada
- **Published by:** Diabetes Canada
- **Last published:** 2018
## Treatment guidelines

### Europe

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<td>Safer insulin prescribing</td>
<td>National Institute for Health and Care Excellence</td>
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<td>Diabetic foot problems: prevention and management</td>
<td>National Institute for Health and Care Excellence</td>
<td>2019</td>
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<tr>
<td>Community pharmacies: promoting health and wellbeing</td>
<td>National Institute for Health and Care Excellence</td>
<td>2018</td>
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<tr>
<td>Adult type 1 diabetes mellitus: national clinical guideline no. 17</td>
<td>Department of Health (Ireland)</td>
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### Management of diabetes

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### Type 1 diabetes in adults: diagnosis and management

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### Diabetes (type 1 and type 2) in children and young people: diagnosis and management

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### North America

#### Standards of medical care in diabetes - 2020

**Published by:** American Diabetes Association  
**Last published:** 2020

#### Type 1 diabetes

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2019

#### Clinical practice guidelines for the prevention and management of diabetes in Canada

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

#### Diabetes technology: continuous subcutaneous insulin infusion therapy and continuous glucose monitoring in adults

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

#### Clinical practice guidelines for developing a diabetes mellitus comprehensive care plan

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

1. ASCVD risk estimator *(external link)*

2. American Diabetes Association *(external link)*
Key articles


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   Abstract


100. US Food and Drug Administration. FDA approves Afrezza to treat diabetes. Jun 2014 [internet publication]. Full text


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