



## Diagnosis and management of type 1 diabetes in adults

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### Abstract

Autoimmune destruction of the pancreatic beta cells leads to onset of type 1 diabetes (T1D). Although T1D can occur at any age, 85% of patients are diagnosed under the age of 20. Patients usually present with typical features of thirst, polyuria, weight loss and hyperglycaemia, with or without ketosis. In adults, symptoms are similar to those in children but there is a wider differential diagnosis. Autoimmune diseases cluster together because of a common susceptibility genotype, due to mutations in HLA genes. The presence of certain other autoimmune diseases, in the patient or relatives, is highly suggestive of an autoimmune cause of diabetes. Patients with T1D who are commenced on insulin usually have resolution of their presenting symptoms and regain any weight lost. In those with typical features including young age at diagnosis, personal or family history of immune diseases, positive ketones and positive antibodies (either high titre or multiple positive antibodies), there is little doubt that the diagnosis is T1D and insulin treatment will be lifelong. If patients continue to lose weight, pancreatic disease, i.e. pancreatic cancer or chronic pancreatitis, should be suspected. All patients should be offered a structured education programme of proven benefit within 6-12 months of diagnosis. The updated NICE guidelines have moved away from suggesting capillary blood testing for most patients to recommending continuous glucose monitoring for all patients.

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# Diagnosis and management of type 1 diabetes in adults


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## New type 1 diabetes


**Presenting features may include:**

- Polydipsia
- Polyuria
- Weight loss
- Age < 50
- BMI <25
- Personal or family history of autoimmune disease
- Hyperglycaemia
- Positive ketones (blood or urine)
- HbA1c can be normal



**Differential diagnosis:**

- Type 2 diabetes
- Pancreatic disease
- Other forms of diabetes



**Start Insulin without delay**

**How** should diagnosis be confirmed?

**How** should patients be assessed?

**What** are the goals of management?



**AUTOIMMUNE DESTRUCTION OF THE PANCREATIC BETA CELLS LEADS TO ONSET OF TYPE 1 DIABETES (T1D).**

Although the majority of people developing T1D are children, with 85% of patients being diagnosed under the age of 20,<sup>1</sup> T1D can occur at any age. A study from the UK Biobank showed that 74% of people diagnosed with diabetes under the age of 30 had T1D while in those aged 31-60, only 4% had T1D.<sup>1</sup>

**DIAGNOSIS**

Patients usually present with typical features of thirst, polyuria, weight loss and hyperglycaemia with or without ketosis and diagnosis is straightforward. In adults, symptoms are similar to those in children but there is a wider differential diagnosis.

The revised NICE guidelines, updated earlier this year, suggest that patients presenting with hyperglycaemia should be diagnosed with T1D on clinical grounds bearing in mind that they are

likely to have one or more of:

- Ketosis
- Rapid weight loss
- Age under 50
- BMI under 25
- A personal or family history of autoimmune disease<sup>2</sup>

Only very low levels of insulin are required to inhibit lipolysis and ketone formation although this can be enhanced during intercurrent severe illness by adrenaline, cortisol and glucagon.<sup>3</sup> The presence of ketones in blood or urine is therefore strongly supportive of diabetes being T1D. While only around 11% of patients with new onset T1D present with diabetic ketoacidosis,<sup>1</sup> lower levels of ketones (in blood or urine) are common and helpful in making the correct diagnosis. Ketones also occur during starvation, in patients on a low carbohydrate 'keto-diet', and in people with type 2 diabetes (T2D) who are on SGLT2 inhibitors or who have ketosis-prone T2D, usually seen in people of Afro-Caribbean descent.

Although weight loss is considered a typical feature of T1D, it can occur in any form of diabetes and there is little evidence that weight loss or BMI are discriminatory in distinguishing T1D from T2D.<sup>4</sup> The onset of diabetes with significant weight loss, particularly in older people should raise the possibility of pancreatic cancer.<sup>5</sup>

Age is a strong predictor of diabetes type at the point of diagnosis.<sup>1,4</sup> In people aged 30 and under, T2D is far less common although T1D needs to be distinguished from monogenic diabetes.<sup>1</sup> Both T1D and T2D occur in genetically susceptible individuals due to a combination of multiple gene variances and environmental factors. Monogenic diabetes describes types of diabetes caused by a single gene mutation. Most forms are inherited in an autosomal dominant manner although mitochondrial diabetes is inherited only through the maternal line. Monogenic forms of diabetes often manifest in young adults.

Studies using age under 30 as a »

predictor of T1D show sensitivity of 57-84% and specificity of 72-88%. Using a cut-off of 45 years lowers sensitivity and specificity to 65% and 67% respectively.<sup>4</sup>

Autoimmune diseases cluster together due to a common susceptibility genotype, now known to be due to mutations in human leukocyte antigen (HLA) genes.<sup>6</sup> Around 9.8% of patients with T1D also have hypothyroidism, 4.5% have coeliac disease, 4.3% have gastric autoimmunity, 2.4% have vitiligo, 1.3% have hyperthyroidism and 0.2% have Addison's disease.<sup>7</sup> Although patients with T2D also have an increased risk of hypothyroidism, this is mainly seen in those over the age of 65.<sup>8</sup> The presence of these autoimmune diseases in the patient or relatives is highly suggestive of an autoimmune cause of diabetes. Absence of acanthosis nigricans and hypertension have also been shown to be predictive of T1D in those presenting with new diabetes.<sup>4</sup>

The NICE guidelines suggest measuring diabetes specific autoantibodies in patients diagnosed with T1D but not C-peptide or the use of a genetic risk score.<sup>2</sup>

The presence of antibodies directed against the pancreatic islet cells is helpful in confirming the autoimmune nature of the diabetes. While insulin autoantibodies are more likely to be positive in children, GAD antibodies, IA2 antibodies and ZnT8 antibodies are more helpful in assessing adults.<sup>9</sup> Of all the known autoantibodies, anti-GAD has the highest frequency in adults with T1D.<sup>10</sup> Anti-GAD and anti-IA2 antibodies tend to decrease with time after diagnosis<sup>9</sup> so early testing is important. False-positive results can occur so NICE recommends testing for at least two different antibodies.<sup>2</sup> Patients with diabetes who are positive for multiple autoantibodies nearly all have T1D.<sup>9</sup> High titres of autoantibodies are also highly predictive of T1D.<sup>10</sup>

C-peptide is co-secreted with insulin and levels thus provide a marker of insulin production. While high levels suggest insulin resistance and are helpful in diagnosing T2D, levels are often still positive at diagnosis of T1D, falling with time. They are not therefore helpful at diagnosis of T1D but can be helpful at least three years later when levels will be low.<sup>10</sup> NICE recommends that C-peptide can be measured in antibody-negative patients where classification of diabetes remains uncertain.<sup>2</sup>

As T1D has a strong genetic disposition, use of genetic risk scores based on determination of multiple known predisposing genes has the

### Box 1

#### A hundred years of insulin therapy

This year marks the centenary of the first use of insulin to treat type 1 diabetes (T1D). Leonard Thompson, a 14-year-old boy dying of ketoacidosis, was famously the first patient to be treated with insulin extracted from bovine pancreas. Commercial insulin production began within a year.<sup>11</sup> Since then countless numbers of lives have been saved. This year's updates to the NICE guidelines on diagnosis and treatment of type 1 diabetes<sup>2</sup> are timely in this 100th anniversary year.

potential to transform the diagnosis of T1D.<sup>1</sup> However, although available, these are not yet in routine clinical practice and not recommended at present by NICE.<sup>2</sup>

#### REVISITING INITIAL DIAGNOSIS

Patients with T1D who are commenced on insulin usually have resolution of their presenting symptoms and regain any weight lost. In those with typical features including young age at diagnosis, personal or family history of immune diseases, positive ketones and positive antibodies (either high titre or multiple positive antibodies), there is little doubt that the diagnosis is T1D and insulin treatment will be lifelong.

In patients without such strong features of T1D, the development of other features of metabolic syndrome such as hypertension, hyperlipidaemia or gout may raise the question of T2D. In addition, patients who wish to stop their insulin may request further testing for confirmation of diagnosis. After at least three years of diabetes, C-peptide measurement can be helpful.<sup>10</sup> Continuation of insulin therapy is recommended if this is < 300 pmol/L.<sup>10</sup>

If patients continue to lose weight, pancreatic disease, i.e. pancreatic cancer or chronic pancreatitis, should be suspected. If patients aged over 40 develop jaundice, they should be referred using the two-week wait pathway for suspected pancreatic cancer while other compatible symptoms such as abdominal pain or diarrhoea should prompt a CT scan to exclude pancreatic cancer.<sup>12</sup>

Patients under the age of 30 with a family history of diabetes but no history of other autoimmune disease may have a monogenic form of diabetes. This accounts for 1-5% of all diabetes. Most patients have a form of maturity onset diabetes of the young (MODY) but other forms include mitochondrial diabetes and lipodystrophy.<sup>13</sup> Patients with negative antibodies and a compatible family history should have C-peptide measured and, if detectable, investigated for possible monogenic diabetes.

#### ASSESSMENT

The management of T1D can be complex and a full assessment is required to ensure that patients are able to:

- Receive an appropriate insulin regimen
- Undertake blood glucose monitoring and interpret the results
- Reduce the risk of hypoglycaemia
- Eat well
- Drive safely
- Reduce the risk of long-term complications
- Reduce the risk of adverse pregnancy outcomes

At diagnosis, in addition to standard history and examination, assessment should include a review of social, cultural, educational and lifestyle factors, psychological wellbeing, social and family support and attitudes to medications.<sup>2</sup>

Anyone diagnosed with T1D who drives must inform the DVLA and their insurance company. Patients must check their blood sugar before driving and only drive if it is over 4 mmol/L.

All patients should be offered a structured education programme of proven benefit within 6-12 months of diagnosis.<sup>2</sup> The programme with the best evidence is DAFNE (Dose Adjustment For Normal Eating). This was introduced in the UK in 2002 and has been shown to reduce HbA<sub>1c</sub> by around 11 mmol/mol, reduce the risk of hypoglycaemia and improve quality of life.<sup>14</sup> Many secondary care diabetes teams run local programmes such as BERTIE based on DAFNE principles with similar proven outcomes<sup>15</sup> or with online versions for patients who cannot attend in person (see Useful information box, p26).

NICE continues to recommend all people diagnosed with T1D be treated with a basal bolus insulin consisting of twice daily Levemir and a short-acting analogue insulin for meals.<sup>2</sup> Although twice daily Levemir has been shown to reduce HbA<sub>1c</sub> better than twice daily long-acting human insulin, evidence of benefits over once daily long-acting analogue insulins are absent.<sup>16</sup> NICE concedes that once daily insulin glargine

# key points

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### Autoimmune destruction of the pancreatic beta cells

leads to onset of type 1 diabetes (T1D). Although T1D can occur at any age, 85% of patients are diagnosed under the age of 20. Patients usually present with typical features of thirst, polyuria, weight loss and hyperglycaemia, with or without ketosis. In adults, symptoms are similar to those in children but there is a wider differential diagnosis.

### Autoimmune diseases cluster together because of

a common susceptibility genotype, due to mutations in HLA genes. Around 9.8% of patients with T1D also have hypothyroidism, 4.5% coeliac disease, 4.3% gastric autoimmunity, 2.4% vitiligo, 1.3% hyperthyroidism and 0.2% Addison's disease. Although patients with type 2 diabetes also have an increased risk of hypothyroidism, this is mainly seen in those over 65. The presence of these autoimmune diseases, in the patient or relatives, is highly suggestive of an autoimmune cause of diabetes.

### Patients with T1D who are commenced on insulin usually

have resolution of their presenting symptoms and regain any weight lost. In those with typical features including young age at diagnosis, personal or family history of immune diseases, positive ketones and positive antibodies (either high titre or multiple positive antibodies), there is little doubt that the diagnosis is T1D and insulin treatment will be lifelong. If patients continue to lose weight, pancreatic disease, i.e. pancreatic cancer or chronic pancreatitis, should be suspected.

**The management of T1D can be complex and a full assessment is required to ensure that patients are able to receive an appropriate insulin regimen; undertake blood glucose monitoring and interpret the results; lower the risk of hypoglycaemia, long-term complications and adverse pregnancy outcomes; eat well and drive safely. All patients should be offered a structured education programme of proven benefit within 6-12 months of diagnosis. The programme with the best evidence is DAFNE which has been shown to reduce HbA<sub>1c</sub> by around 11 mmol/mol, reduce the risk of hypoglycaemia and improve quality of life.**

**The updated NICE guidelines have moved away from previous guidance suggesting capillary blood testing for most patients with continuous glucose monitoring (CGM) for selected patients to recommending CGM for all patients who will accept it. Studies have shown benefits of CGM in reducing hypoglycaemia (particularly severe or nocturnal) and glycaemic variability; and achieving target HbA<sub>1c</sub>.**

**Hypoglycaemia is the main barrier to good glycaemic control. NICE recommends agreeing with the patient an HbA<sub>1c</sub> target that does not lead to problematic hypoglycaemia. The risk of hypoglycaemia is increased by excessive insulin dose; reduced food intake; exercise; alcohol; recent change in weight, fitness or renal function; recent hypoglycaemic episodes and reduced hypoglycaemic awareness.**

can be used if the person has a strong preference for once daily basal insulin and once daily insulin degludec can be used if there is nocturnal hypoglycaemia or insulin needs to be administered by a third party.<sup>2</sup>

### GLUCOSE MONITORING

The new NICE guidelines<sup>2</sup> have moved away from previous guidance suggesting capillary blood testing for most patients with continuous glucose monitoring (CGM) for selected patients to recommending CGM for all patients who will accept it. CGM can be either in the form of real time CGM (rtCGM) or intermittently scanned CGM (isCGM or 'flash' glucose monitoring e.g. FreeStyle Libre). This change was brought about by a number of studies showing benefits of CGM in reducing hypoglycaemia, particularly severe or nocturnal hypoglycaemia, reducing glycaemic variability and achieving target HbA<sub>1c</sub> although no difference in quality of life measures was found.<sup>17</sup>

CGM should be initiated and monitored by 'a team with expertise in its use'.<sup>2</sup> For many this will mean the secondary care team. GPs and practice nurses can access online training to learn how to use CGM and interpret the results (see Useful information box, p26). Data available from CGM includes mean glucose, estimated HbA<sub>1c</sub>, glycaemic variability and risk indices for high and low glucose. It also categorises time as percentages in range as well as above or below range.

A recent consensus is that for most people with T1D, time in range (TIR) should be at least 70% while time below range (TBR) should be less than 4%. For older individuals the recommendation is for TIR above 50% and TBR less than 1%. When trying to optimise control, TBR should be tackled first.<sup>18</sup>

All people with diabetes using CGM still need to have access to traditional capillary blood glucose testing meters and prescription of lancets and strips in case of CGM failure or where blood sugars are changing rapidly.<sup>2</sup>

For patients who prefer to continue with capillary blood glucose testing, minimum recommended testing remains at four times per day (before meals and at bedtime) up to a maximum of ten times per day where the HbA<sub>1c</sub> target has not been met, where hypoglycaemia is a problem, for driving, during intercurrent illness or for sport.<sup>2</sup>

Their repeat prescriptions should be reviewed to ensure that they have enough lancets and testing strips to perform the required number of tests.

### MANAGEMENT

In 1993 the landmark DCCT trial showed that tight blood glucose control reduced the risk of complications<sup>19</sup> and the focus of management moved to preventing disability from blindness, renal failure, painful neuropathy and amputation. However, the same study showed that tight control tripled the risk of severe hypoglycaemia.<sup>19</sup>

Current treatment aims to achieve tight control of blood glucose without hypoglycaemia thus leading to better quality of life.

Generally, an HbA<sub>1c</sub> target of less than 48 mmol/mol is recommended based on risks of long-term complications.<sup>2</sup> Although the individual with diabetes may benefit from this in terms of quality of life, it also has significant cost implications.

Managing long-term complications accounts for 80% of the costs of managing diabetes.<sup>20</sup> A recent model suggested that reducing HbA<sub>1c</sub> to 53 mmol/mol for all people with T1D where it was 69 mmol/mol or more would reduce chronic complications from 6.8 to 1.2 and diabetic ketoacidosis from 14.5 to 1.0 events per 100 person-years saving the NHS just over a billion pounds over five years.<sup>20</sup>

However, it has long been recognised that hypoglycaemia is the main barrier to good glycaemic control.<sup>21</sup> NICE therefore recommends agreeing with the individual an HbA<sub>1c</sub> target that does not lead to problematic hypoglycaemia.<sup>2</sup>

Factors that increase the risk of hypoglycaemia include excessive insulin dose; reduced food intake; exercise; alcohol; recent change in weight, fitness or renal function; recent hypoglycaemic episodes and reduced hypoglycaemic awareness.<sup>21</sup>

Unlike in T2D,<sup>22</sup> NICE does not recommend a decision aid for patients with T1D when agreeing target HbA<sub>1c</sub>. However, many of the same criteria exist including older age and comorbidities as well as hypoglycaemia risk and these should be discussed with the individual. Hypoglycaemia caused by incorrect insulin dose for the amount of food eaten, exercise taken, and the effects of alcohol can be minimised by good education including refresher courses.<sup>14</sup>

The use of CGM which alerts the patient at the onset of hypoglycaemia minimises the degree of hypoglycaemia and the time spent with a low blood glucose.<sup>17</sup> However, even with this technology, those who have very active jobs or those that require driving or operating complex machinery may choose a higher HbA<sub>1c</sub> target. >>

**CONCLUSION**

T1D is not always straightforward to diagnose and clinicians should remain alert to the possibilities of T2D, pancreatic disease and monogenic diabetes. However, as the consequence of missing a diagnosis of T1D can be ketoacidosis and death, if there is any doubt about the diabetes classification, insulin should be initiated while investigations proceed. Insulin therapy may be initiated in primary care or a same day referral to secondary care may be made.

Treatment options should aim for the best quality of life for the patient. This includes, at the current time, to reduce the risk of hypoglycaemia and allow the patient to eat what and when they choose, to be as active as they desire and to participate in their chosen career. It also includes thinking ahead to prevent complications and reduced quality of life in the future. The introduction of CGM for almost all patients with T1D should help them get these two priorities balanced.

**Competing interests:** None

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**Useful information**

**For patients**

Structured education programmes  
**DAFNE**  
<https://dafne.nhs.uk>

**BERTIE**

[www.bertieonline.org.uk](http://www.bertieonline.org.uk)

**For healthcare professionals**

Online course on continuous glucose monitoring for primary care  
[www.edendiabetes.com/education-blog/e-learning](http://www.edendiabetes.com/education-blog/e-learning)

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