What is type 1 diabetes?

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Abstract

Type 1 diabetes mellitus (T1DM) is a chronic disease characterized by hyperglycaemia secondary to absolute insulin deficiency. It is the result of T cell-mediated autoimmune destruction of the insulin-producing β-cells that reside in the islets of Langerhans. T1DM is associated with circulating autoantibodies to β-cell antigens. It results from an interplay between genetic and environmental factors. The autoimmune process can start in infancy, and the rate of autoimmune β-cell destruction varies widely between individuals. Therefore the disease has a variable duration of prodrome before the patient presents with symptoms of T1DM. The classic clinical presentation of T1DM is an acute onset of symptoms caused by rapid β-cell failure: weight loss, polyuria, polydipsia and risk of ketoacidosis. Although T1DM is the most common form of dysglycaemia in children and young adults, it can present at any age. Indeed, in some records 40% of cases present after age 30 years. The clinical presentation in adults can be less acute, and there is potential for diagnostic confusion. The long preclinical prodrome raises the possibility of intervention to delay or prevent the clinical onset of disease.

Keywords Aetiology; autoantibody; autoimmunity; classification; diagnosis; epidemiology; immunology; MRCP; type 1 diabetes

Key points

- A diagnosis of type 1 diabetes mellitis (T1DM) is supported by evidence of an autoimmune pathogenesis and by insulin deficiency
- T1DM can be diagnosed at any age, although it is more common in younger age groups, and it has a spectrum of presentation that depends on the rate of β-cell destruction
- Diagnostic confusion can occur between type 1 and type 2 diabetes, leading to inappropriate treatment decisions

Introduction

Type 1 diabetes mellitus (T1DM), formerly known as insulin-dependent diabetes mellitus, is a chronic disease characterized by hyperglycaemia secondary to absolute insulin deficiency.[1] T1DM is caused by an autoimmune destruction of insulin-producing β-cells in the pancreatic islets of Langerhans. This has metabolic consequences, ranging from the classical triad of weight loss, polyuria and polydipsia, to ketoacidosis. A genetic predisposition coupled with environmental factors has been implicated in the pathogenesis of T1DM.

Although not routinely screened for, T1DM can be predicted using a combination of autoantibodies, genetic markers and tests of β-cell function. This raises the possibility of intervening to prevent autoimmune β-cell destruction, and thus the clinical onset of T1DM.

Epidemiology of T1DM

T1DM affects approximately 400,000 people in the UK and 20 million people worldwide. It accounts for 5–10% of all cases of diabetes mellitus. Although most common in childhood and adolescence, T1DM can present at any age.

The annual incidence of T1DM in children <14 years of age varies 600-fold globally, with Asian countries, such as China, reporting a low incidence, and European countries, such as Finland, reporting the highest incidence. In the UK, the incidence of childhood T1DM is 24.5 per 100,000 per year.

In Europe, the incidence has been increasing by approximately 4% per year since 1989. The rise has been particularly marked in children <5 years of age. In the UK, it is predicted that the number of children <15 years old with TIDM will increase from 22,000 in 2010 to 33,300 in 2020. This rapid increase strongly suggests that environmental factors play a role in the aetiology of T1DM.

Pathology of T1DM

T1DM is characterized by autoimmunity to β-cell proteins, a number of which have now been identified (Table 1 and Figure 1).

Measuring circulating autoantibodies to these proteins is clinically useful because it allows us to confirm a diagnosis of T1DM where there is uncertainty.[2] Adult patients tend to have higher levels of glutamic acid decarboxylase (GAD) autoantibodies, and children tend to have higher levels of insulin autoantibodies. However, not all patients with T1DM are antibody-positive. Therefore although a positive value is helpful, a negative value does not necessarily exclude a diagnosis of T1DM. Assays for these autoantibodies are available through most UK pathology laboratories. Measuring autoantibodies is also helpful because they pre-date and predict a diagnosis of T1DM. They can thus also be used in a research setting to identify people for T1DM prevention trials (see below).

Insulitis is infiltration of the pancreatic islets by immune cells (Figure 2). These are predominantly T and B lymphocytes, macrophages and dendritic cells. Of these, it is believed that the T cells play a crucial role in initiating the autoimmune process as the transfer of single T cell clones causes T1DM in animal models

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Frequency of autoantibodies to β-cell proteins targeted by the autoimmune response in T1DM

Islet autoantibodies	Frequency
glutamic acid decarboxylase	85%
IA2	55%
Insulin	50%
ZnT8	50%
Any autoantibody	*90%*

Frequencies of autoantibodies are based on data for white Caucasian adults.

Table 1

of this condition. In a normally functioning immune system, several complementary mechanisms eliminate islet reactive T cells or control their activity. It is thought that T1DM results from the failure of one or more of these immune mechanisms.

Genetic contribution to the development of T1DM

There is strong clustering of T1DM in some families. The risk of T1DM when neither parent has T1DM is 1 in 250, rising to 1 in 50–100 if the mother has the disease, and to 1 in 10 if both the mother and a sibling have T1DM. These findings support a genetic contribution to the development of T1DM.

The human leucocyte antigen (HLA) region on chromosome 6p21 confers about half the genetic risk of T1DM. The strongest association is with HLA class II DR and DQ loci, which encode cell surface receptors that present antigens to T cells. Haplotypes DR4-DQ8 and DR3-DQ2 are most strongly associated with T1DM. In white Caucasian with T1DM, 93% carry either a DR3 or a DR4 allele, or both. Those carrying these two alleles together are at highest genetic risk.

Genome-wide association studies have identified >40 loci associated with T1DM, explaining about 80% of its hereditability.

Location of β-cell proteins targeted by the autoimmune response in T1DM

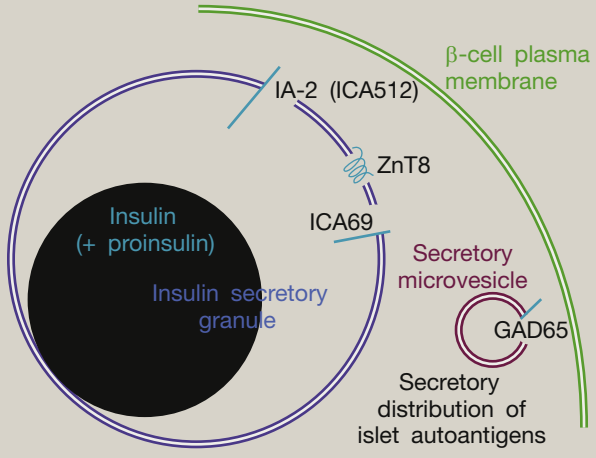

Figure 1

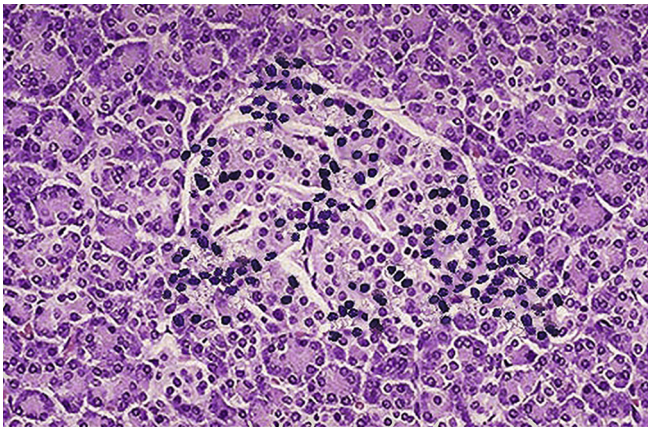

Figure 2 Insulitis: the human islet (centre) is infiltrated by T and B lymphocytes, macrophages and dendtritic cells in type 1 diabetes mellitis.

These loci include the variable number of tandem repeats near the insulin gene (*INS-VNTR*), cytotoxic T lymphocyte-associated protein-4 (*CTLA4*), and protein tyrosine phosphatase non-receptor-type 22 (*PTPN22*). These genes all encode for proteins involved in pathways related to the key interaction between antigen-presenting cells and T cells.

Environmental contribution to the development of T1DM

Evidence that environmental factors play a role in the development of T1DM derives from three observations:

- The concordance rate for the development of T1DM in monozygotic twins is considerably less than 100% despite their shared genetic susceptibility.
- Incidence rates in young children are rising too rapidly to be explained by changes in the population gene pool.
- Studies of migrants from low-incidence regions to parts of the world where the incidence is high have found that immigrants assume the higher risk of their adopted country within a single generation.

Environmental contributions to the development of T1DM are under investigation and are the subject of clinical trials (see below). These potential contributions include childhood viral infections, lack of exposure to childhood infections, early exposure to cows milk or gluten, vitamin D deficiency and obesity.

Natural history of T1DM

Progression to T1DM is marked by loss of the first-phase insulin response to intravenous glucose or an oral meal challenge (Figure 3). By the time of diagnosis, 80–95% of β-cells have been destroyed. Once this point has been reached, patients are dependent on daily insulin administration for life.

Shortly after diagnosis, 60% of adults with T1DM experience a period of partial remission, or 'honeymoon', characterized by low insulin requirements and good glycaemic control. This honeymoon period is attributed to two factors: partial recovery of β-cell function, and correction of insulin sensitivity.[3] Both decline with increased duration of T1DM, bringing the honeymoon period to a natural close. On average,

the honeymoon period lasts 9 months, but this can extend to more than 5 years.

Presentation of T1DM

T1DM classically presents in lean children or adolescents with an acute onset of polyuria, polydipsia, weight loss or ketoacidosis. However, it can present more insidiously in adults and without pathognomonic osmotic symptoms or ketoacidosis, reflecting a relatively slow rate of β-cell destruction. These adults can be initially misclassified and treated as having type 2 diabetes (T2DM), but they usually require insulin treatment within months of their initial diagnosis.

The term latent autoimmune diabetes in adults (LADA) is sometimes used to describe adults with autoantibody-positive diabetes, who are initially non-insulin requiring, but later progress to insulin dependency. In white populations approximately 10% of those initially diagnosed with T2DM in fact have antibody positive autoimmune disease. This figure is lower in Asian populations.

Adult-onset T1DM can present with ketoacidosis, but one should bear in mind that T2DM can also present with ketoacidosis. In ketosis-prone T2DM, seen particularly in Afro-Caribbean individuals, a transient acute reduction in insulin secretion can lead to ketoacidosis. This can result in misdiagnosis of T2DM as T1DM, and inappropriate long-term insulin treatment.

Diagnosing T1DM

The diagnosis of diabetes relies on establishing dysglycaemia. This can be through:

- an elevated concentration of glycated haemoglobin (HbA_{1c}; >48 mmol/mol or >6.5%), repeated if there are no diabetes-associated symptoms. HbA_{1c} can be normal in early T1DM, and this should not be as the sole diagnostic test for dysglycaemia
- an elevated fasting (≥7 mmol/litre) or random (≥11.1 mmol/litre) blood glucose, repeated if there are no diabetes-associated symptoms.

Once diabetes has been diagnosed, it is usually straightforward to differentiate between T1DM and T2DM through a history, examination and testing for ketones.[4]

In some patients, however, the diagnosis is not straightforward. Given the rise in obesity, more young adults are developing T2DM. Conversely, many adults with T1DM are obese. There is therefore potential for diagnostic confusion, but the correct diagnosis is important because the treatments for T1DM and T2DM are different.

Where there is diagnostic confusion, it can be useful to measure relevant antibodies (glutamic acid decarboxylase, IA-2, islet cell, zinc transporter ZnT8; Table 1), bearing in mind that a negative test does not necessarily exclude a diagnosis of T1DM. Furthermore, testing of circulating C-peptide can be useful

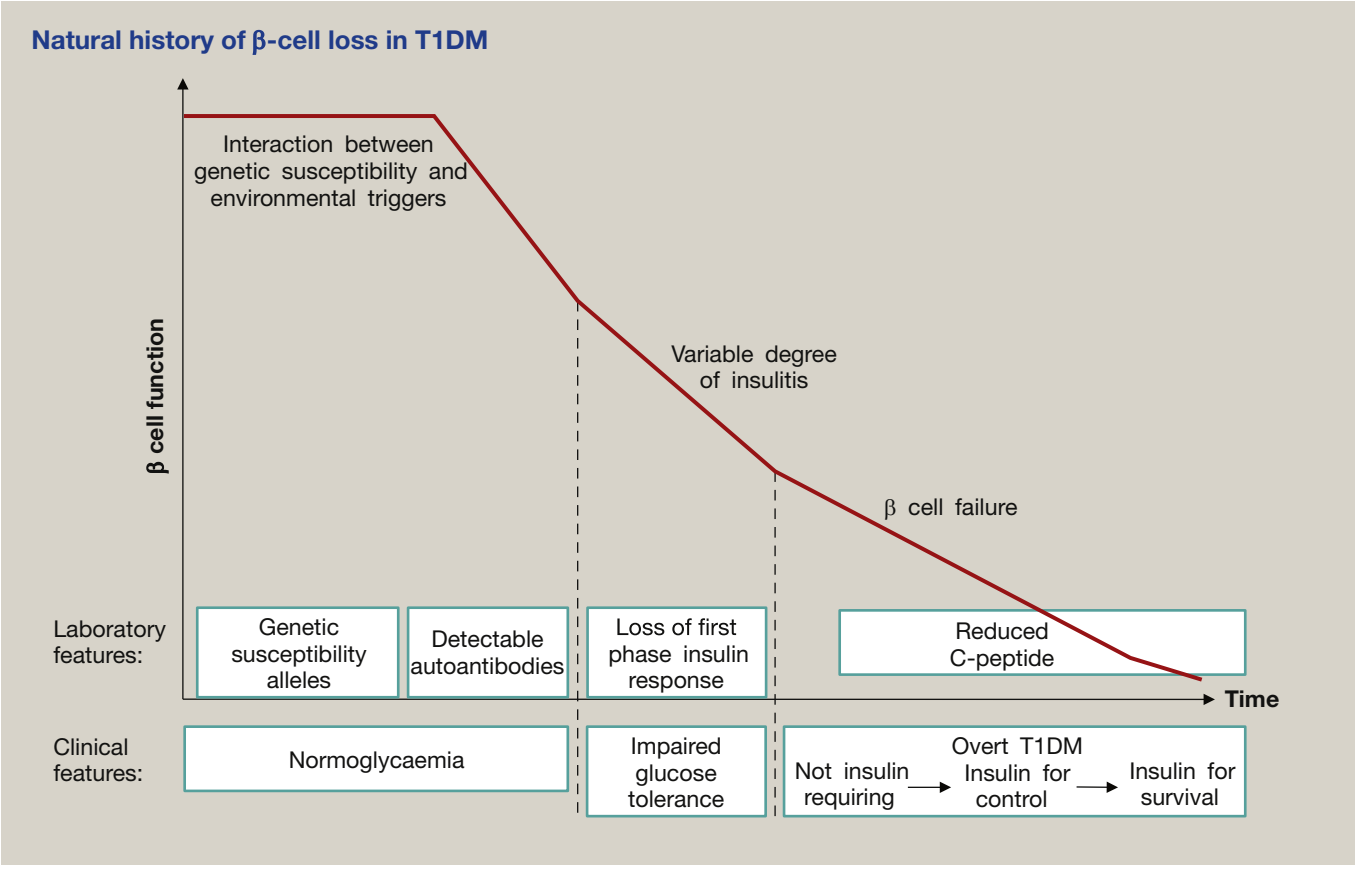

Figure 3

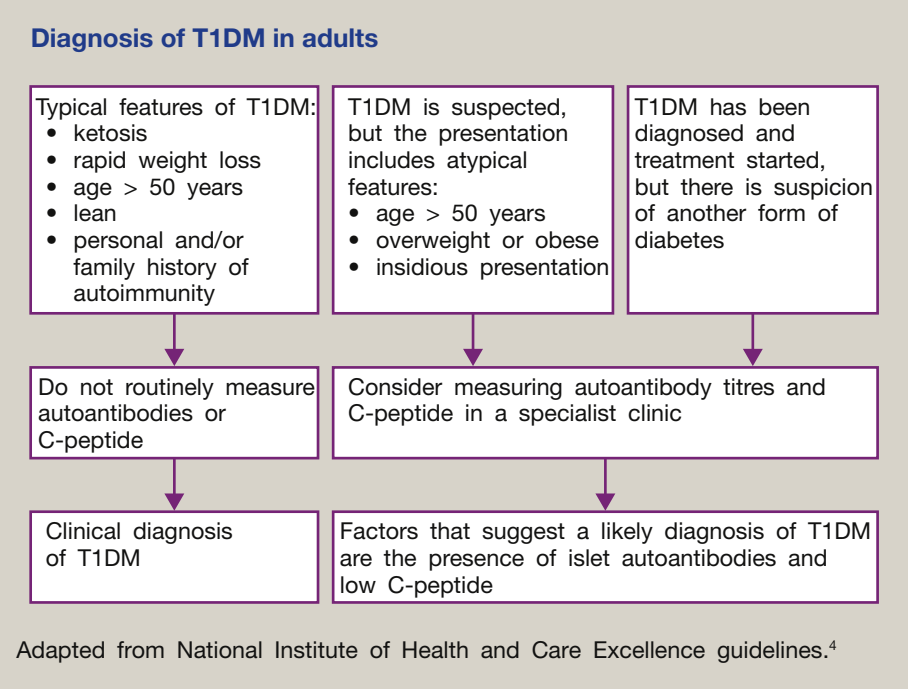

Figure 4

(Figure 4). C-peptide is a by-product formed when insulin is cleaved, and is a more accurate measure of insulin production than is measuring insulin itself. The caveat here is that patients with newly diagnosed T1DM continue to have some residual C-peptide, and therefore a 'normal' value also does not necessarily exclude a diagnosis of T1DM. Measuring C-peptide several years after diagnosis can, however, be useful in differentiating between T1DM and T2DM, although by this time an incorrect diagnosis and treatment will have been established.

Towards prevention of T1DM

T1DM has a long pre-clinical prodrome before β-cell failure and metabolic decompensation occur. Individuals at risk of developing T1DM can be accurately identified using a combination of autoantibodies, markers of genetic susceptibility and tests of β-cell function. This has led to clinical trials attempting to prevent or delay the onset of T1DM (Table 2). In addition, clinical trials have been undertaken in new-onset T1DM, when there is still significant residual β-cell function. These trials have aimed to preserve residual β-cell function. Although these patients still need to inject insulin, residual β-cell function is associated with improved glycaemic control and fewer complications.

The autoimmune disease process can potentially be modified by manipulating environmental exposures that trigger autoimmunity, or by modulating the autoimmune process. To date, no agent or intervention has resulted in the prevention or delay of T1DM, or in a sufficient preservation of β-cell function to warrant its use in routine clinical practice.[5]

One reason for limited success may be that most trials have relied predominantly on manipulating a single pathway, whereas

Examples of prevention trials in T1DM

Type of trial	Population	Intervention	Comments
Primary prevention	Genetically at-risk individuals, before onset of autoimmunity	Intranasal insulin	PINIT (Primary Intranasal Insulin Trial) is investigating whether giving intranasal insulin to children aged 1—7 years genetically at risk of T1DM delays the appearance of autoantibodies
Secondary prevention	Autoantibody-positive individuals, after onset of autoimmunity but before onset of dysglycaemia	Anti-CD3 monoclonal antibody	CD3 is a T cell surface marker. Anti-CD3 alters the activity of T cells in a manner that may prevent autoimmune activation. It has been successfully used to preserve residual β-cell function in trials of new-onset T1DM
Tertiary prevention	Individuals with new-onset T1DM, after onset of dysglycaemia but while significant β-cell function persists	Exercise	Physical exercise reduces insulitis and prevents diabetes in animal models of T1DM. This may work through better regulation of islet reactive T cells

Table 2

the pathogenesis of T1DM is multifactorial. Success may therefore require a combination approach, and one that is individualized to patients. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 40-year-old man presented with a 1-month history of 3 kg weight loss, polyuria and polydipsia. He had a strong family history of type 2 diabetes.
On clinical examination, his body mass index was 31 kg/m^2.

Investigations

- Fasting plasma glucose 9.8 mmol/litre (3.0–6.0)

Which test would you do next in order to differentiate which type of diabetes he has?

A. HbA_{1c}
B. C-peptide
C. Glutamic acid decarboxylase (GAD) autoantibodies
D. Genetic susceptibility alleles
E. Insulin autoantibodies

Question 2

The prevalence of type 1 diabetes is increasing in many countries.

What is the best evidence that this is caused by environmental factors?

A. Identical twins have similar incidence rates
B. Increased migration has occurred from high-prevalence counties to low-prevalence countries
C. Migrant families acquire the prevalence rates of their new countries
D. Changes are occurring in the population gene pool
E. The increase is largely in the over-20s age group

Question 3

A 24-year-old man presented with weight loss and tiredness. Three months previously, he had been found to have diabetes. His father had autoimmune thyroid disease. The man had initially been treated with metformin, and gliclazide was later added.
On clinical examination, he had lost 5 kg in weight.

Investigations

- Random capillary glucose 11 mmol/litre (3.0–6.0)
- Capillary ketones 1.5 mmol/litre (<0.6)
- HbA_{1c} 69mmol/litre (20–42); 8.5% (4.0–6.0)
- GAD autoantibody titre >2000 U/ml (<5)

What is the most appropriate additional treatment?

A. Liraglutide
B. Intravenous insulin
C. Pioglitazone
D. Sitagliptin
E. Subcutaneous insulin