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## Type 1 diabetes mellitus

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**Abstract** | Type 1 diabetes mellitus (T1DM), also known as autoimmune diabetes, is a chronic disease characterized by insulin deficiency due to pancreatic  $\beta$ -cell loss and leads to hyperglycaemia. Although the age of symptomatic onset is usually during childhood or adolescence, symptoms can sometimes develop much later. Although the aetiology of T1DM is not completely understood, the pathogenesis of the disease is thought to involve T cell-mediated destruction of  $\beta$ -cells. Islet-targeting autoantibodies that target insulin, 65 kDa glutamic acid decarboxylase, insulinoma-associated protein 2 and zinc transporter 8 — all of which are proteins associated with secretory granules in  $\beta$ -cells — are biomarkers of T1DM-associated autoimmunity that are found months to years before symptom onset, and can be used to identify and study individuals who are at risk of developing T1DM. The type of autoantibody that appears first depends on the environmental trigger and on genetic factors. The pathogenesis of T1DM can be divided into three stages depending on the absence or presence of hyperglycaemia and hyperglycaemia-associated symptoms (such as polyuria and thirst). A cure is not available, and patients depend on lifelong insulin injections; novel approaches to insulin treatment, such as insulin pumps, continuous glucose monitoring and hybrid closed-loop systems, are in development. Although intensive glycaemic control has reduced the incidence of microvascular and macrovascular complications, the majority of patients with T1DM are still developing these complications. Major research efforts are needed to achieve early diagnosis, prevent  $\beta$ -cell loss and develop better treatment options to improve the quality of life and prognosis of those affected.

Type 1 diabetes mellitus (T1DM) is a chronic autoimmune disease characterized by increased blood glucose levels (hyperglycaemia), which are due to the insulin deficiency that occurs as the consequence of the loss of the pancreatic islet  $\beta$ -cells<sup>1–4</sup>. T1DM is one of the most common endocrine and metabolic conditions occurring in childhood. In the vast majority of patients (70–90%), the loss of  $\beta$ -cells is the consequence T1DM-related autoimmunity (concomitant with the formation of T1DM-associated autoantibodies); these patients have autoimmune T1DM (also known as type 1a diabetes mellitus). In a smaller subset of patients, no immune responses or autoantibodies are detected, and the cause of  $\beta$ -cell destruction is unknown (idiopathic T1DM or type 1b diabetes mellitus); this type has a strong genetic component<sup>5</sup>. Unless otherwise specified, the term T1DM refers to autoimmune T1DM in this Primer.

T1DM is associated with the appearance of autoantibodies many months or years before symptom onset. These autoantibodies are not thought to be pathogenetic but serve as biomarkers of the development of autoimmunity. Characteristic autoantibodies associated with

T1DM are those that target insulin, 65 kDa glutamic acid decarboxylase (GAD65; also known as glutamate decarboxylase 2), insulinoma-associated protein 2 (IA-2) or zinc transporter 8 (ZNT8)<sup>6–8</sup>. Individuals with specific HLA genotypes (which encode MHC proteins) — that is, HLA-DR and HLA-DQ genotypes (HLA-DR-DQ) — have an increased risk of developing two or more autoantibodies and T1DM<sup>8,9</sup>. The first  $\beta$ -cell-targeting autoantibody to appear during early childhood usually targets insulin or GAD65 (that is, anti-insulin or anti-GAD65 autoantibodies), but these autoantibodies can both be present, whereas it is rare to observe IA-2 autoantibody or ZNT8 autoantibody first<sup>7,8</sup>. What triggers the appearance of a first-appearing  $\beta$ -cell-targeting autoantibody is unclear but is under scrutiny in several studies of children who are being followed-up since birth<sup>6,10–12</sup>.

The pathogenesis of T1DM has been suggested to be a continuum that can be divided into stages that relate to the detection of autoantibodies and progress to  $\beta$ -cell destruction, dysglycaemia and, finally, symptoms associated with hyperglycaemia<sup>13</sup> (FIG. 1). What remains

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to be defined is the aetiology of  $\beta$ -cell-targeted autoimmunity, which probably includes a combination of environmental and genetic factors that trigger or permit the autoimmune response against the  $\beta$ -cells. This event often happens years before the eventual development of dysglycaemia and symptoms. In this Primer, we focus on T1DM — specifically autoimmune T1DM — and consider the aetiology, pathogenesis and subsequent phases of disease progression.

### Epidemiology Symptomatic T1DM

According to the International Diabetes Federation, 8.8% of the adult population worldwide has diabetes<sup>14</sup>. Of all individuals with diabetes, only 10–15% have T1DM; type 2 diabetes mellitus (T2DM) is the most common form. However, T1DM is the most common form of diabetes in children (<15 years of age), and >500,000 children are currently living with this condition globally.

The incidence of T1DM is increasing worldwide and it is estimated that nearly 90,000 children are diagnosed each year<sup>15</sup>. The incidence rate varies markedly between countries<sup>15</sup> (FIG. 2); it is highest in Scandinavian countries, followed by European countries (such as the United Kingdom), North America and Australia. In Asian countries — such as China, Korea and Japan — T1DM is a rare disease. The reason for this variation remains to be fully explained but may be related to genetic susceptibility (for example, the prevalence of HLA genetic risk factors in the population) and environmental and lifestyle factors, possibly including hygiene and childhood infections. In resource-poor countries, T1DM may not be recognized, as the means to make a diagnosis with blood or urinary glucose measurements are still not available. HLA-DR-DQ genotypes vary between countries<sup>16</sup>; T1DM high-risk genotypes that are common to Scandinavia are less common in Asian countries. The risk of developing T1DM in countries such as Mexico is often dependent on European HLA-DR-DQ genotypes<sup>17</sup>. In addition, HLA-DR-DQ haplotypes that are low risk in the country of origin may go on to confer risk in children born to parents who immigrate to a high-risk country such as Sweden<sup>18</sup>. These data support the

view that the risk of developing T1DM is associated with both genetic and environmental factors<sup>19</sup>. Triggers of  $\beta$ -cell-targeted autoimmunity might also vary between countries, given that infections and herd immunity differ, as revealed when comparing  $\beta$ -cell-targeted autoimmunity and T1DM in Finland and Russia<sup>20</sup>. In Russia, children who had a history of several infections had a lesser risk of developing  $\beta$ -cell-targeted autoimmunity than did children who had the same genetic risk but a history of fewer infections.

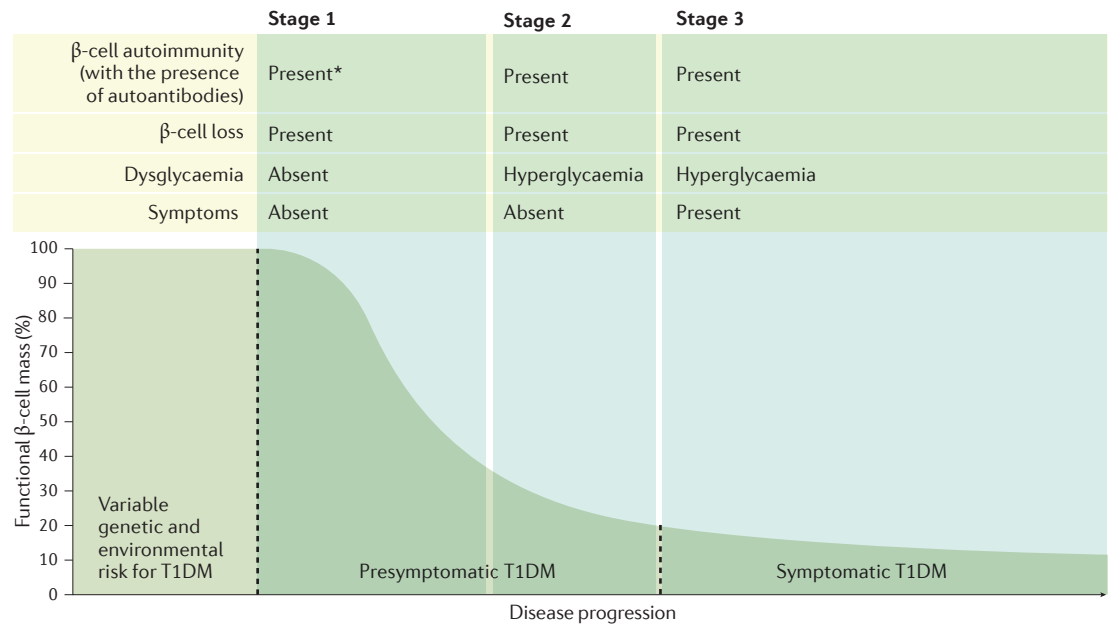
The incidence rate shows a peak at 12–14 years of age (FIG. 3), although recent data indicate that this is the result of earlier diagnosis, particularly in high-incidence countries<sup>21</sup>. Most of these countries are experiencing an increased incidence to the extent that a doubling of new patients <5 years of age is predicted between 2005 and 2020, and such that the incidence in patients 5–15 years of age will rise by 70% during this period<sup>21</sup>. Recent data indicate that T1DM is often diagnosed after 50 years of age<sup>22</sup>. These data are consistent with the finding in the UK Prospective Diabetes Study (UKPDS), that among young adults diagnosed with T2DM, the presence of  $\beta$ -cell-targeting autoantibodies indicates that they have a phenotype consistent with T1DM<sup>23</sup>. In addition, in older adults with T1DM, the presence of  $\beta$ -cell-targeting autoantibodies predicted an increased likelihood that the patients would eventually require treatment with insulin<sup>24–26</sup>. Hence, after the diagnosis of diabetes in adults, the classification of the disease still remains a challenge, as T1DM in adults is often mistaken for T2DM.

Although the incidence rates tend to be similar between boys and girls, it has been observed that the peak for girls precedes that for boys<sup>27,28</sup>. Indeed, the incidence rate increases with age, and the incidence peak is at puberty and is therefore earlier in girls. After the pubertal years, the incidence rate considerably drops in women but remains higher in men up to 29–35 years of age<sup>29</sup>. Thus, at 20 years of age and onwards twice as many men as women are diagnosed with T1DM<sup>30</sup>.

### Presymptomatic T1DM

The identification of autoantibodies (particularly those targeting insulin or GAD65) as biomarkers of pre-symptomatic disease<sup>31</sup> may eventually enable a novel understanding of the pathogenesis and epidemiology of T1DM. Indeed, the majority of individuals with two or more islet-targeting autoantibodies may progress to symptomatic disease<sup>9,13</sup>. However, as screening for islet-targeting autoantibodies is far from established, the epidemiology of T1DM based on current diagnostic criteria will probably remain the hallmark of epidemiology for now.

The risk of progression to stage 3 T1DM (the symptomatic stage; FIG. 1) is associated with the number of autoantibodies detected and the age of seroconversion (that is, the earliest age at which a particular autoantibody is detected) of the first autoantibody, as well as the autoantibody type, affinity and titre<sup>32–34</sup>. In the TEDDY study, the incidence rate of stage 3 T1DM within 5 years of seroconversion was 11%, 36% and 47% in those with one, two and three autoantibodies,



**Figure 1 | Staging of T1DM.** Classically, type 1 diabetes mellitus (T1DM) is classified as either presymptomatic T1DM, which is characterized by a decline in  $\beta$ -cell mass without symptoms, or symptomatic T1DM, at which stage the symptoms of hyperglycaemia (such as polyuria, thirst, hunger and weight loss) become evident. Alternatively, T1DM can be subdivided into three stages: stage 1 is characterized by the presence of autoantibodies and the absence of dysglycaemia; stage 2 is characterized by the presence of both autoantibodies and dysglycaemia; and symptoms only appear at stage 3, which corresponds to symptomatic T1DM. Attempts to stage autoimmune T1DM are useful when enrolling individuals in secondary prevention trials. \* $\beta$ -cell-directed autoimmunity, marked by the presence of autoantibodies targeting  $\beta$ -cell autoantigens, is usually present months to years before the onset of  $\beta$ -cell loss.

respectively<sup>8</sup>. In the DAISY, DIPPP, BABYDIAB and BABYDIET studies, the rate of progression to stage 3 T1DM in 585 high-risk children with multiple islet-targeting autoantibodies was 44%, 70% and 84% at 5, 10 and 15 years of follow-up, respectively<sup>9</sup>. The rate of progression per year seems to be relatively constant at approximately 11% per year over a 10-year time span<sup>35</sup>. Progression is slightly faster in girls than in boys, and in children who developed  $\beta$ -cell-targeting autoantibodies in the first 3 years of life<sup>10,35</sup>. Although the rate of progression is likely to be influenced by some T1DM susceptibility genes, true biomarkers of the rate of progression to stage 2 T1DM are still lacking.

It is generally expected that approximately 0.3–0.5% of children in the general population will develop two or more islet-targeting autoantibodies during childhood<sup>36,37</sup>. The TrialNet study has reported the presence of autoantibodies in approximately 5% of older healthy relatives of patients with T1DM<sup>38</sup>, which indicates that the T1DM high-risk HLA-DR-DQ haplotypes may also increase the risk for  $\beta$ -cell-targeted autoimmunity. However, it cannot be excluded that the shared environment also contributes to the risk of developing a first-appearing islet-targeting autoantibody. In an adult population, the prevalence of GAD65 autoantibody was 1.1% and that of IA-2 autoantibody was 0.8%, whereas the prevalence of insulin autoantibodies decreased with increasing age<sup>39,40</sup>. Studies of children followed from birth have shown that the initial detection of  $\beta$ -cell-targeting autoantibodies usually occurs between 6 and

24 months of age in patients who develop T1DM at an early age (before 5 years of age)<sup>7,8</sup>. Progression from one to more autoantibodies occurs most commonly within 2–4 years of the detection of the first autoantibody<sup>6,9,41</sup>. Whether similar autoantibody progression is true for older patients is not known.

## Mechanisms/pathophysiology

### Aetiology of islet-targeted autoimmunity

**Autoantibodies.** Newborn screening for  $\beta$ -cell-targeting autoantibodies in children who are born into families with a mother or father with T1DM<sup>6</sup>, and in the general population<sup>8–11,42</sup>, has provided a better understanding of when these autoantibodies appear and has enabled analyses of factors — genetic and environmental — that may explain the appearance of the first islet-targeting autoantibody. Although not proven, it is generally thought that the autoantibodies are produced because of continued exposure to  $\beta$ -cell autoantigens.

The first autoantibodies detected usually target insulin or GAD65; the order of appearance of these two autoantibodies is associated with age and genetic differences<sup>7,8</sup>. The peak incidence of insulin autoantibody development is at 1–2 years of age, and this autoantibody usually appears first in children who have the *HLA-DR4-DQ8* haplotype. As the appearance of insulin autoantibodies is rare before 6 months of age, environmental exposures before 1 year of age are likely to be relevant to the aetiology of insulin autoimmunity<sup>4–6</sup>. It is possible that different factors are involved in the

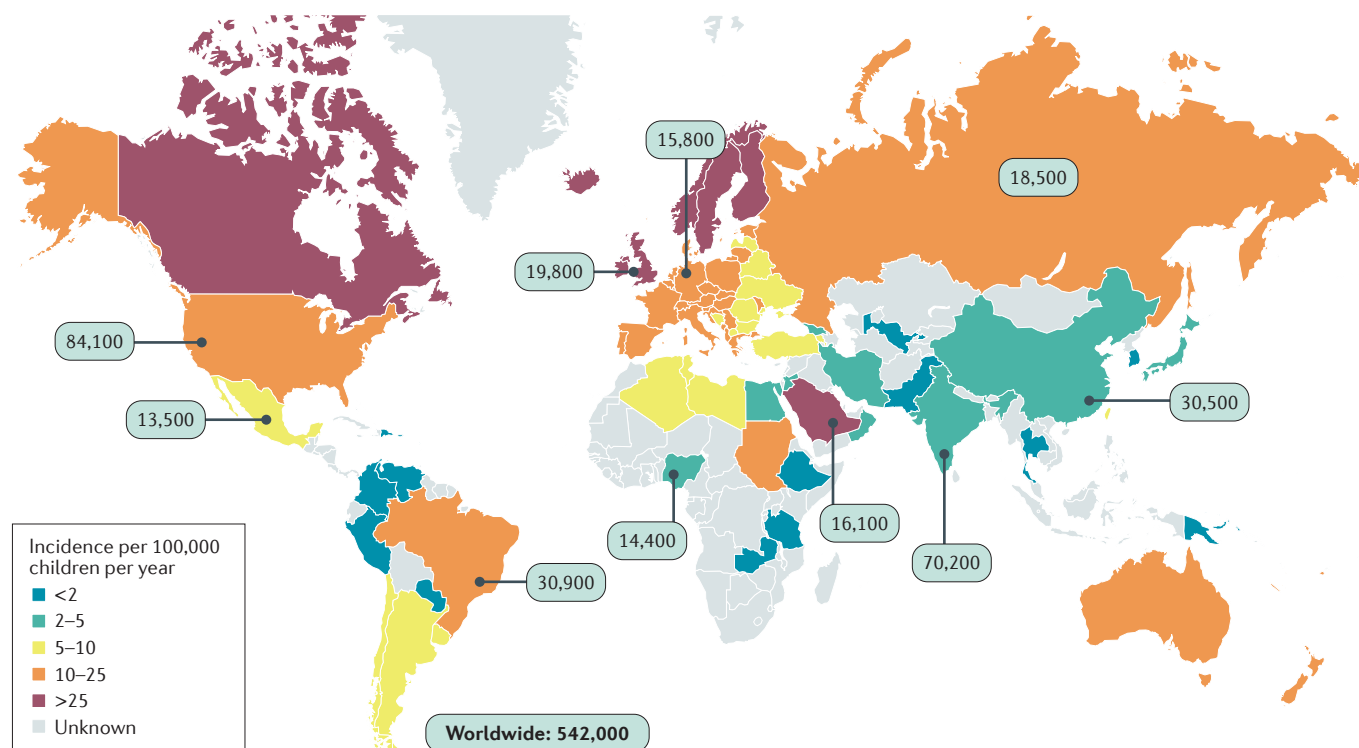


Figure 2 | **The incidence and prevalence of T1DM in children.** The estimated number of new cases of type 1 diabetes mellitus (T1DM) in children (<15 years of age) per 100,000 individuals in 2015. The prevalence of T1DM in the 10 most-affected countries is noted. Data from the International Diabetes Federation (<http://www.diabetesatlas.org/across-the-globe.html>).

aetiology of GAD65 autoantibodies, as children who develop these autoantibodies first are usually >1 year of age and have the *HLA-DR3-DQ2* haplotype<sup>6</sup>. Other autoantibodies can develop after insulin or GAD65 autoantibodies: autoantibodies that target the protein tyrosine phosphatase-like molecules IA-2 and IA-2 $\beta$ , or ZNT8 (REF. 43). These proteins are found in the membrane of secretory vesicles. ZNT8 transports zinc ions from the cytoplasm to the interior of secretory vesicles, but the functions of IA-2 and IA-2 $\beta$  remain to be clarified.

The appearance of IA-2 autoantibody as a second or third autoantibody markedly increases the risk of the individual reaching stage 3 disease<sup>44</sup>. ZNT8 autoantibodies that are specific for three different ZNT8 variants, which have tryptophan, arginine or glutamine at amino acid position 325, seem to appear later during stage 1 and stage 2 (REF. 45). At the time of clinical diagnosis, patients may have ZNT8 autoantibodies that are specific for only one of the variants; the single amino acid at position 325 seemingly dictates the reactivity of the autoantibody against ZNT8 (REF. 46).

**Genetics.** T1DM is a polygenic disease that is influenced by environmental factors. Genetic risk factors are necessary but not sufficient for disease, as their penetrance is low. The concordance rate of T1DM among monozygotic twins is reported to be only 30%, although a recent study that involved long-term follow-up suggested that this percentage might be higher<sup>47,48</sup>.

The major genetic risk factors are the HLA class II haplotypes *HLA-DR3-DQ2* and *HLA-DR4-DQ8* on chromosome 6 (REFS 49–51). The risk of developing  $\beta$ -cell-targeted autoimmunity on the extended HLA-DR-DQ haplotype is complicated by a large number of *HLA-DRB1* alleles in humans. Specifically, on the *HLA-DQ8* haplotype, *HLA-DRB1\*04:01* and *HLA-DRB1\*04:05* are associated with greater susceptibility to T1DM than is *HLA-DRB1\*04:04*, whereas *HLA-DRB1\*04:03* is protective<sup>52–54</sup>. These haplotypes are often associated with insulin autoantibodies<sup>55</sup>, but the extended haplotype *HLA-DRB1\*03:01-DQ2 (HLA-DQA1\*05:01-DQB1\*02:01)* was associated with GAD65 autoantibody<sup>55,56</sup>. These genetic risk factors are common in western populations and have a low penetrance<sup>57,58</sup>, which might explain why many people do not develop islet-targeted autoimmunity or T1DM despite having these T1DM risk factors.

Recent analyses of the first appearance of an islet-targeting autoantibody after birth suggest that the view of genetic risk factors needs to be modified. Although it is well-known that the *HLA-DR4-DQ8* and *HLA-DR3-DQ2* haplotypes are the two major risk factors for T1DM in the western world, these two haplotypes are also the major risk factors for the development of  $\beta$ -cell-targeting autoantibodies<sup>8,9</sup>. As a consequence, HLA-associated risk factors might increase the risk of T1DM development through their association with  $\beta$ -cell-targeting autoantibodies. Moreover, these HLA-associated genetic risk factors are associated with the



type of autoantibody to appear first<sup>59</sup>. Indeed, individuals with the *HLA-DR3-DQ2* haplotype are more likely to develop GAD65 autoantibody as a first  $\beta$ -cell-targeting autoantibody than insulin autoantibodies, whereas individuals with *HLA-DR4-DQ8* are most likely to develop insulin autoantibodies first, but they can develop GAD65 autoantibodies as well<sup>60</sup>. Finally, the age at which autoantibody seroconversion occurs seems to be associated with these haplotypes<sup>8,9</sup>. This finding implies that individuals with these haplotypes have an increased risk of developing autoantibodies at a young age.

In addition, genome-wide association studies (GWAS) in T1DM have revealed >50 non-HLA genetic factors that contribute to T1DM risk<sup>61</sup>, as recently reviewed in REF. 62. The Type 1 Diabetes Genome Consortium made a laudable effort in a large number of patients to confirm that the *HLA-DR-DQ* haplotype is by far associated with the highest risk of developing T1DM but that genetic polymorphisms throughout the genome contribute to risk, although these associations are much weaker than is the *HLA-DR-DQ* association<sup>61,63</sup>. Most, but not all, of these genetic factors are associated with genetic factors that are important to the immune system, whereas only a limited number is associated with the formation of  $\beta$ -cell-targeting autoantibodies<sup>59</sup>. For example, *PTPN22* (which encodes non-receptor protein tyrosine phosphatase type 22, a molecule involved in T cell and B cell responsiveness) and *INS* (which encodes insulin) seem to influence the development of stage 1 T1DM<sup>59,64</sup>. That there are other non-HLA genetic factors associated with autoantibody formation but not with T1DM cannot be excluded. Future investigations will be needed to reveal the extent to which these non-HLA genes contribute to disease pathogenesis in stage 2 and stage 3 T1DM.

*HLA class II and INS polymorphisms* are suggested to influence processes that are involved in thymic immune tolerance and lead to the inadequate deletion of harmful  $\beta$ -cell antigen-reactive T cells or the insufficient generation of T regulatory cells that are specific for  $\beta$ -cell antigens<sup>65,66</sup>. Indeed, some *INS* polymorphisms protect against T1DM development by increasing insulin expression in thymic cells that present self-antigens to newly forming T cells<sup>66</sup>. Many genes that confer susceptibility to stage 1 T1DM are expressed in immune cells, which suggests that the development of stage 1 T1DM is generally influenced by the magnitude and control of the response to immune stimuli, such as those that are encountered during childhood.

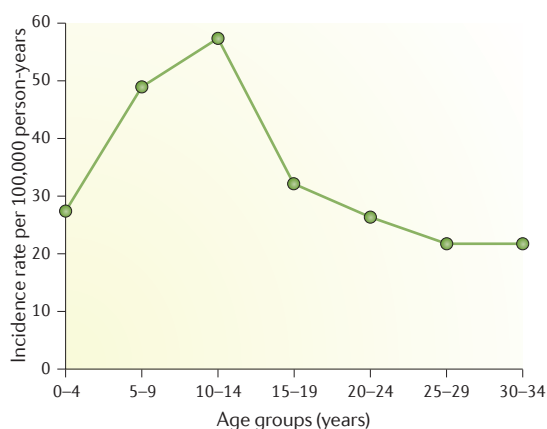
**Environmental factors.** Numerous environmental influences — including viral infections<sup>67–69</sup>, the timing of the first introduction of food<sup>70</sup> and gestational events<sup>71,72</sup> such as gestational infections<sup>73–75</sup> — have been proposed as candidate aetiological factors. The role of gestational events in T1DM risk is, for example, illustrated by the finding that maternal T1DM protects the offspring against the development of insulin autoantibodies in the first year of life<sup>76</sup> owing to increased levels of circulating insulin, which might be associated with improved thymic or peripheral immune tolerance in the

offspring<sup>77</sup>. Validation, along with an understanding of the mechanism or mechanisms by which these factors might influence autoimmunity, is required. Although the additional risk conferred by individual environmental exposures is thought to be small, a combination of events might trigger the appearance of a first islet-targeting autoantibody.

### Pathogenesis

Cognate interactions between T cells and B cells occur that can lead to islet-targeting autoantibody formation<sup>78</sup> (FIG. 4). However, the triggering event is unknown, but the appearance of the first islet-targeting autoantibody reflects autoantigen presentation by dendritic cells and the subsequent responses of autoantigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells. The possibility that the combined occurrence of a virus infection and an environmental exposure event represents a triggering event needs to be explored. Animal research has not been informative, probably because the immune responses of rodents are too different from those of humans. Perturbation by vaccinations or common childhood infections in children followed from birth may be one approach to develop a better understanding of the immune responses that occur in children with the *HLA-DR3-DQ2* and *HLA-DR4-DQ8* haplotypes.

In addition, CD4<sup>+</sup> and CD8<sup>+</sup> T cells that are specific for  $\beta$ -cell autoantigens are detectable in patients with stage 3 T1DM and even in patients with earlier stages of the disease<sup>79,80</sup>. Recent evidence indicates that these T cells preferentially recognize post-translationally modified peptides from  $\beta$ -cells, which suggests that the loss of tolerance to  $\beta$ -cell autoantigens might result from changes to proteins that occur in response to stress within the  $\beta$ -cell<sup>81–85</sup>. The possible role of endoplasmic reticulum stress, and whether protein folding dysfunction is important to the aetiology or progression

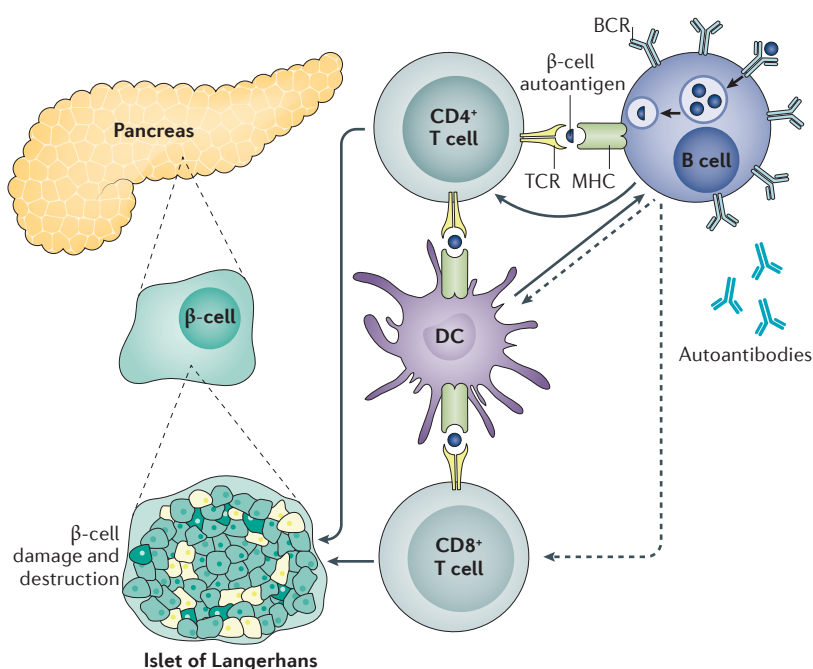


**Figure 3 | Age-specific incidence rates of T1DM.**

The incidence rates of type 1 diabetes mellitus (T1DM) per 100,000 person-years in Sweden by age group. The graph shows the incidence of T1DM in men and women combined, and is based on data from the Prescribed Drug Register; data on insulin prescriptions were used as a proxy for T1DM diagnosis. Adapted with permission from REF. 30, Springer.

of T1DM, needs to be further explored<sup>86,87</sup>. Now that autoantigen-specific and epitope-specific assays for T cells are available<sup>88,89</sup>, they need to be applied in the context of autoantibodies and residual  $\beta$ -cell function to understand the role of T cells and B cells in T1DM progression.

The understanding of the cellular immune response to  $\beta$ -cells in autoantibody-positive patients is limited owing to a lack of available blood samples and pancreatic tissue to study. Spontaneous animal models of diabetes — such as the non-obese diabetic (NOD) mouse and the BioBreeding rat models — are not informative in this respect, as their immunogenetics and pathogenesis differ vastly from those of humans. Screening of pancreatic organ donors shows that insulinitis (that is, inflammation and immune cell infiltration of the islets of Langerhans; FIG. 5) was rare and patchy in individuals with two or more autoantibodies<sup>90–93</sup>. Although, T cell or B cell infiltration was not associated with the presence of  $\beta$ -cell-targeting autoantibodies, the islet cells showed some indication of immune activation, as HLA class I protein expression was increased<sup>94</sup>. Thus, it remains to be determined whether there is chronic low-grade activity of T cell-mediated inflammation in islets or whether there is an acute loss of  $\beta$ -cells owing to the infiltration of inflammatory cells shortly before stage 3 T1DM. In all likelihood, both scenarios are part of the pathogenesis of progression to stage 3 T1DM, given that stage 2 dysglycaemia can be present for >1 year before the onset of symptomatic diabetes.

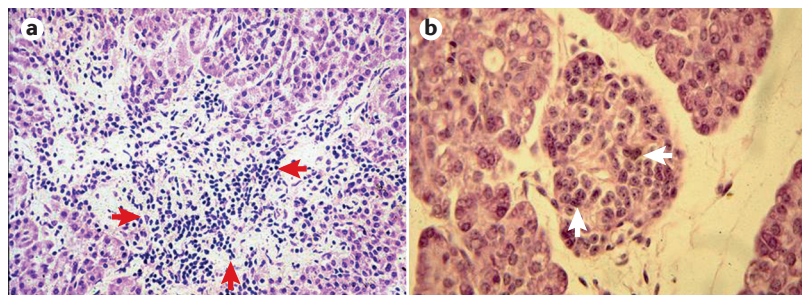


**Figure 4 | Pathogenesis of T1DM.** Type 1 diabetes mellitus (T1DM) is an immune-mediated disease. Activated B cells interact with CD4<sup>+</sup> and CD8<sup>+</sup> T cells, as well as dendritic cells (DCs). Antigen presentation by B cells and DCs drives the activation of  $\beta$ -cell-specific T cells. In addition, the exposure of B cells to  $\beta$ -cell autoantigens leads to the production of islet-targeting autoantibodies, which serve as biomarkers of asymptomatic disease. Dashed arrows indicate the potential interactions between B cells and CD8<sup>+</sup> T cells and between B cells and DCs. BCR, B cell receptor; TCR, T cell receptor.

The progression from stage 1 to stage 2 (FIG. 1) is marked by dysglycaemia, as detected by an oral glucose tolerance test (OGTT)<sup>95,96</sup>, by the loss of first-phase insulin release in an intravenous glucose tolerance test<sup>97</sup> or possibly by a rise in the levels of glycated haemoglobin (HbA1c) within the normal range<sup>98</sup>. Whether the loss of glucose tolerance owing to impaired insulin secretion over time is entirely due to decreasing  $\beta$ -cell mass or also involves dysfunctional  $\beta$ -cells remains to be determined. Areas with  $\beta$ -cells can be seen in the pancreata of patients with stage 3 T1DM, and it is likely the inflammation seen in islets impedes glucose sensing and insulin secretion by  $\beta$ -cells. Many investigators have taken it for granted that the appearance of  $\beta$ -cell-targeting autoantibodies is accompanied by the infiltration of inflammatory cells, but further investigations of children at high risk of developing T1DM who are followed from birth will be needed. Animal models do not fully recapitulate the pathogenesis of the human disease. NOD mice often show pronounced inflammation around the islets (peri-insulinitis) before the onset of hyperglycaemia, and this is characterized by the entry of inflammatory cells into the islets<sup>99</sup>. The pathogenetic process that occurs in NOD mice is not preceded by the presence of autoantibodies, which would indicate  $\beta$ -cell-targeted autoimmunity. By contrast, the  $\beta$ -cells of NOD mice show an endoplasmic reticulum unfolded protein response that may be linked to an inflammatory perturbation<sup>100</sup>. The BioBreeding rat is different from NOD mice, as the  $\beta$ -cell destruction in these rats occurs within 24 hours after a preceding normal blood glucose measurement and without preceding peri-insulinitis, but only in animals that are homozygous for the rat orthologue of *HLA-DQ8* (REFS 101–103).

At clinical onset (stage 3),  $\beta$ -cell-targeted autoimmunity is likely to have occurred for a prolonged period, as indicated by the presence of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, dendritic cells, macrophages and B cells in and around the islets of Langerhans in many, but not all, patients with newly diagnosed T1DM<sup>2,104</sup>. These data are based on observations from samples obtained at disease onset by fine-needle biopsy<sup>105</sup> or by high-risk minimal pancreatic tail resection<sup>106</sup>, and they have confirmed previous data from pancreatic tissue samples from individuals who have succumbed to diabetic keto-acidosis (that is, acidosis due to the breakdown of lipids to ketones as an alternative source of glucose)<sup>2,107,108</sup>. In this setting, the inflammatory lesion does not affect all islets, and the insulinitis process is patchy. Importantly, the volume or mass of islet cells producing glucagon, somatostatin or pancreatic polypeptide remains unaffected at the clinical onset of T1DM<sup>2,104</sup>. At present, there is no explanation of why the  $\beta$ -cells and not the cells that produce glucagon, somatostatin or pancreatic polypeptide are attacked by the immune system. Separate autoantibodies that target human pancreatic cells producing glucagon and those that produce somatostatin have been found in some patients, but further studies of these potentially unique patients are needed<sup>109</sup>.

Although data from the time of clinical onset are limited, major efforts are being made to better understand the inflammatory process that occurs in and around



**Figure 5 | Pancreatic inflammation and insulitis in T1DM.** Histological examination of pancreas tissue after symptom onset (diabetic ketoacidosis) shows very severe insulitis with massive mononuclear cell infiltration in and around the pancreatic islets in one patient (part **a**; red arrows; magnification  $\times 125$ ) and less-severe insulitis only involving dendritic cells in another patient (part **b**; white arrows; magnification  $\times 250$ ). Biopsies were obtained from individuals who carried the *HLA-DR3/4* genotype and succumbed to brain oedema  $<1$  week after symptom onset. Adapted with permission from REF. 108, Springer.

the islets of Langerhans, the presence of dysfunctional  $\beta$ -cells and the possible role of the innate immune system<sup>104,110</sup>. The mechanisms of the well-known ‘honeymoon period’ (that is, the brief period in children during which exogenous insulin requirement is reduced as the pancreas is still able to produce some insulin) after the clinical onset and initiation of insulin therapy are not understood<sup>111</sup>. Whether the insulin therapy has dampened the inflammatory process at the time of clinical onset remains to be determined. It has been speculated that the immunogenicity of the  $\beta$ -cells is reduced after insulin-induced blood-glucose normalization — owing, for example, to reduced GAD65 expression — resulting in the loss of endogenous insulin production<sup>112</sup>.

#### Long-term complications

The complications of chronic diabetes are subdivided into microvascular and macrovascular complications. Microvascular complications include nephropathy, neuropathy and retinopathy, which are specific to diabetes.

Macrovascular complications manifest predominantly as coronary heart disease, but also cerebrovascular disease and peripheral artery disease; these conditions are not specific to diabetes, but people with T1DM are at risk of developing these conditions<sup>113</sup>. It is now recognized that heart failure may also be a complication of diabetes<sup>114–117</sup>. Cognitive function may also be affected by long-term hyperglycaemia<sup>118</sup>. Interventional studies suggest that fluid load and haemodynamics may also be causal in the development of heart failure and sudden cardiac death. Although the observations originate from patients with T2DM, they deserve mention here given the shared high risk of heart failure in patients with T1DM and T2DM<sup>115,119</sup>. In the EMPA-REG trial, the use of a selective sodium/glucose transporter 2 (SGLT2) inhibitor was associated with marked reductions in the frequency of cardiovascular events, including heart failure, and death<sup>120,121</sup>. It is believed that SGLT2 inhibition alters renal sodium and glucose handling in a manner that exerts a diuretic effect and improves renal arteriolar function<sup>122</sup>. The protective effect of SGLT2 inhibition emerged rapidly, as did

the effects of thiazides in the ALLHAT trial<sup>123</sup>, which reported a greater reduction in the risk of heart failure with thiazides than with amlodipine. Hence, it is likely that hyperglycaemia leads to adverse fluid loads and haemodynamic derangements, including a maladaptive renovascular response, which may be alleviated by diuretic agents. Genetic susceptibility and concomitant risk factors (for example, hypertension, dyslipidaemia and smoking) also contribute to the development of complications<sup>124,125</sup>.

Hyperglycaemia predominantly affects the retina, peripheral nerves and renal glomeruli. These cells share an inability to downregulate glucose uptake in the presence of increased levels of extracellular glucose. The pathogenetic effects of hyperglycaemia result from the overproduction of superoxide by the mitochondrial electron transport chain, which results in oxidative stress<sup>124,126,127</sup> (FIG. 6). Retinopathy in T1DM is characterized by impaired blood flow in the retinal vessels, and this stimulates a compensatory proliferation of retinal vessels. The new vessels are fragile and hyperpermeable, features that lead to haemorrhages and the leakage of proteins into the retina. Retinal perfusion diminishes continuously and may ultimately cause blindness.

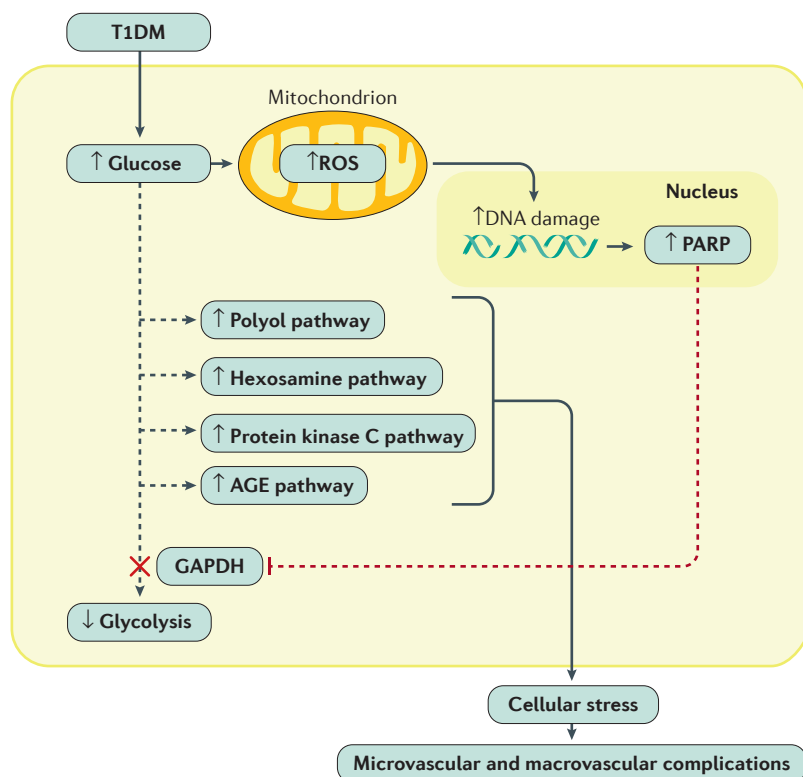
#### Diagnosis, screening and prevention

##### Diagnosis

T1DM is believed to be caused by immune-mediated  $\beta$ -cell destruction that leads to insulin deficiency and hyperglycaemia. Classic symptoms of hyperglycaemia are usually rapid (days to weeks) in onset, particularly in young children, and include polyuria, polydipsia, weight loss, abdominal symptoms, headaches and ketoacidosis<sup>5</sup>. The majority ( $>95\%$ ) of newly diagnosed patients seek medical care owing to the presence of symptoms<sup>128</sup>; a minority are diagnosed by routine glucose screening or through the detection of autoantibodies as a result of enrolment in longitudinal screening programmes.

The 2016 American Diabetes Association (ADA) diagnostic criteria for diabetes mellitus are based on signs of abnormal glucose metabolism, regardless of the diabetes type and the age of onset<sup>129</sup> (BOX 1). Unless unequivocal symptoms of hyperglycaemia are present, the diagnosis should be confirmed by repeated OGTTs. The cornerstones of the diagnosis of T1DM are insulinopenia, T1DM symptoms and evidence of  $\beta$ -cell-targeted autoimmunity. If  $\beta$ -cell-targeting autoantibodies are present, a diagnosis of autoimmune T1DM may be given. If patients have a clinical picture that is consistent with T1DM but no autoantibodies are present, the ADA recognizes a category of idiopathic T1DM. Patients with idiopathic T1DM tend to be older ( $>20$ – $30$  years of age) than those with autoimmune T1DM, are often of African or Asian descent and have a higher body mass index (BMI) than do age-matched individuals with autoimmune T1DM<sup>130</sup>. It is not clear whether patients with idiopathic T1DM have a different underlying pathology, or whether they manifest autoantibodies that are not measured by common assays or autoantibodies that target autoantigens yet to be defined. Patients with neonatal diabetes<sup>131</sup>





**Figure 6 | Mechanisms of hyperglycaemia-induced cellular damage.** An increase in intracellular glucose levels results in oxidative stress and the increased production of reactive oxygen species (ROS), which have many effects, such as causing DNA strand breaks. DNA damage activates poly(ADP-ribose) polymerase (PARP), which then makes polymers of ADP-ribose. These polymers attach to and modify the activity of glyceraldehyde-3-dehydrogenase (GAPDH). Blocking GAPDH leads to a bottleneck in glycolysis, such that glycolytic intermediates are diverted into pathogenetic signalling pathways (dashed arrows). Hyperglycaemia impairs glycolysis, and the consequent accumulation of glycolytic intermediates also inactivates two enzymes that have anti-atherosclerotic effects: namely, endothelial nitric oxide synthase and prostacyclin synthase. AGE, advanced glycation end product; T1DM, type 1 diabetes mellitus.

who may be diagnosed with T1DM but may in fact have rare monogenic forms of diabetes also exist<sup>132,133</sup>. Maturity-onset diabetes of the young may masquerade as T1DM<sup>134</sup>.

In 2006, owing to concerns regarding the lack of standardization of autoantibody assays among various laboratories, the US NIH convened an international committee of experts to ensure standardization of GAD65 autoantibody and IA-2 autoantibody measurements using radiobinding assays on serum or plasma samples<sup>31</sup>. This standardization was a continuation of the preceding preparation of a WHO standard for the detection of autoantibodies that target GAD65 and IA-2 (REF. 135), and represented a considerable step forwards in ensuring the correct classification of autoimmune T1DM<sup>31</sup>. This initiative has enabled the global use of a common standard for the measurement of these autoantibodies.

#### Distinguishing T1DM from T2DM

Distinguishing patients with T1DM from those with T2DM clinically is not always straightforward. Although T1DM is often considered to have an onset in childhood,

adult onset can occur; in these cases, it is frequently mistaken for T2DM. Adults often present with mild symptoms, and it is not always possible to classify patients on the basis of hyperglycaemia alone. The distribution of BMI among children and adults with T1DM is usually similar to that of the general population<sup>136,137</sup>. Thus, approximately 20–40% of children with T1DM are overweight, although they are rarely as overweight or obese as most youths with T2DM. Indeed, the average BMI among children and young adults with T1DM tends to be lower than that of children and young adults with T2DM<sup>138</sup>. Although family history could give an indication of whether an individual has T1DM, patients with T1DM have a threefold greater presence of T2DM in their families than does the general population<sup>139</sup>. Although ketoacidosis is more common in T1DM than in T2DM, approximately 30% of patients in Africa with T2DM may have ketosis at disease onset because of hyperglycaemia-induced  $\beta$ -cell toxicity, which results in very low endogenous levels of insulin and C-peptide (a marker of insulin production)<sup>140</sup>. Thus, C-peptide levels may be low at the time of T2DM diagnosis, and they may be normal during the honeymoon phase of T1DM and, therefore, not helpful for classifying T1DM at onset<sup>141</sup>. Moreover, obese adolescents with a clinical picture suggestive of T2DM can have evidence of autoimmunity<sup>142</sup>. In such situations, terms such as ‘type 1.5 diabetes’, or ‘double’, ‘hybrid’ or ‘mixed’ diabetes have been and continue to be used<sup>143</sup>. Thus, no standard case definitions exist for epidemiological research or surveillance of paediatric diabetes.

The SEARCH for Diabetes in Youth study developed a novel approach to classify diabetes types in children and adolescents (<20 years of age) using the standard ADA classification framework<sup>144</sup>, although this approach is not yet accepted by US or international diabetes organizations as standard practice. On the basis of this study, T1DM is classified as autoimmune diabetes, regardless of the presence of obesity or insulin resistance, whereas T2DM requires the presence of insulin resistance. For the small proportion of patients who may not be able to be classified as proposed above, additional tests may be required. A classification of autoimmune diabetes is based on the presence of at least one islet-targeting autoantibody (GAD65 and IA-2 autoantibodies; it was not feasible to include insulin and ZNT8 autoantibodies). Insulin sensitivity was estimated using clinical variables (namely, waist circumference, HbA1c levels and triglyceride levels) to estimate the glucose disposal rate<sup>145</sup>. Insulin resistance was defined as an insulin sensitivity value below the 25th percentile for individuals without diabetes (12–20 years of age) who were enrolled in the NHANES study<sup>145</sup>.

#### Monitoring long-term complications

T1DM was an inevitably fatal disease before 1922, when insulin therapy was introduced. Insulin therapy diminished the risk of ketoacidosis and alleviated T1DM-associated metabolic abnormalities. Nowadays, people with T1DM still experience substantial morbidity and mortality owing to chronic complications<sup>146</sup>. People

with T1DM are at a twofold to fourfold increased risk of death, which is mainly owing to cardiovascular causes<sup>147</sup>. This translates into an estimated loss of life expectancy at 20 years of age of roughly 12 years relative to those without diabetes<sup>147–149</sup>. Given that the complications are mainly caused by hyperglycaemia, HbA1c is an outstanding marker of long-term glycaemic control and is, therefore, an excellent predictor of complications<sup>150</sup>. Awareness and monitoring of these complications are needed to ensure adequate treatment.

**Microvascular complications.** Diabetic retinopathy, which causes vision loss, has a prevalence of >80% among patients with T1DM<sup>151</sup>. The early stages of retinopathy are characterized by aneurysmatic changes in retinal vessels. Laser photocoagulation is highly effective in restraining these changes, and patients with T1DM should, therefore, be routinely screened using ophthalmological techniques<sup>152</sup>. Furthermore, people with T1DM are at increased risk of macular oedema, cataracts and glaucoma<sup>153</sup>.

Diabetic nephropathy is the leading cause of chronic kidney disease<sup>154,155</sup>. Nephropathy is established when urinary albumin excretion is increased in the absence of other renal conditions. The severity of nephropathy is classified according to the degree of albuminuria. Microalbuminuria is defined as an albumin excretion rate of 30–299 mg per 24 hours. Microalbuminuria may progress to macroalbuminuria (which is defined as an albumin excretion rate of  $\geq 300$  mg per 24 hours). The presence of albuminuria is associated with a high risk of developing serious kidney disease and cardiovascular disease<sup>155</sup>. The relationship between the albuminuria level and the risk of adverse outcomes is a continuum<sup>155–157</sup>. A Danish study showed that roughly one-third of patients with newly diagnosed T1DM develop persistent microalbuminuria within the first two decades from disease onset<sup>158</sup>. In the Swedish National Diabetes Register, which is one of the largest cohorts worldwide, the prevalence of microalbuminuria and macroalbuminuria among patients with T1DM who had no previous history of cardiovascular disease was 9.8% and 4.4%, respectively (mean diabetes duration: 17 years; S.G., unpublished

observations). Approximately 40% of patients progress from microalbuminuria to macroalbuminuria over a period of 10 years<sup>155,159</sup>. However, microalbuminuria may be stable or even regress to normoalbuminuria in treated patients, which is probably the consequence of tight glycaemic control, antihypertensive drugs and statins<sup>160</sup>.

The most common neuropathies in T1DM are peripheral sensorimotor neuropathy and autonomic neuropathy. Peripheral sensorimotor neuropathy is very common and affects peripheral nerves. Autonomic neuropathy affects cardiovascular, genitourinary and gastrointestinal nerves. Cardiovascular effects include exercise intolerance, orthostatic hypotension, a loss of nocturnal decline in blood pressure, silent myocardial ischaemia, resting tachycardia or bradycardia, and reduced heart rate variability<sup>125</sup>. Reduced heart rate variability is an early indicator of cardiovascular autonomic neuropathy, which may affect up to 40% of patients<sup>161</sup>.

**Macrovascular disease.** People with T1DM are at a twofold to eightfold increased risk of cardiovascular disease and death. Macrovascular disease is more aggressive in individuals with T1DM than in controls who do not have diabetes. The pathophysiology underlying this phenomenon has been attributed to vascular alterations. There is little doubt that glucose levels are associated with the risk of macrovascular disease in T1DM; however, evidence from trials and observational studies has demonstrated that it may take many years to notice the effect of glucose levels on macrovascular outcomes<sup>162</sup>. Tight glycaemic control in T1DM may reduce the incidence of cardiovascular disease by 42%<sup>162,163</sup>. Evidence is also accumulating that T1DM confers a very high risk of developing heart failure<sup>114–116</sup>, which may be a consequence of long-term exposure to increased fluid loads secondary to hyperglycaemia<sup>122</sup>. Cardiovascular disease in T1DM is predominantly coronary heart disease, which reflects an accelerated atherosclerotic process<sup>125,164–167</sup>. The excess risk of congenital heart disease in patients with T1DM is roughly threefold in men and sevenfold in women relative to the general population. The excess risk of stroke is equally increased<sup>125,168,169</sup>.

By 65 years of age, the cumulative probability of having a lower-extremity amputation has been reported to be 11% for women and 21% for men with T1DM, which reflects an 85-fold increased risk relative to non-diabetic controls<sup>170</sup>. However, these data are somewhat outdated and may not be representative of contemporary management. It has long been recognized that there are patients who survive for prolonged periods with T1DM and escape complications<sup>171</sup>. These patients often have residual C-peptide production, which is suggestive of surviving  $\beta$ -cells<sup>172</sup>.

### Screening

T1DM is usually diagnosed during stage 3 (FIG. 1), at which point the disease may have progressed to diabetic ketoacidosis, which is a life-threatening condition.

#### Box 1 | The 2016 American Diabetes Association diagnostic criteria for diabetes

Diabetes, including type 1 diabetes mellitus (T1DM), is diagnosed when one or more of following criteria are present<sup>129</sup>:

- A fasting plasma glucose level of  $\geq 126$  mg per dl (7 mmol per l). Fasting is defined as no caloric intake for at least 8 hours.
- A plasma glucose level of  $\geq 200$  mg per dl (11.1 mmol per l) measured 2 hours after a glucose load of 1.75 g per kg (maximum dose of 75 g) via an oral glucose tolerance test (OGTT). Most children and adolescents with T1DM are symptomatic and have plasma glucose concentrations well above this threshold; thus, an OGTT is seldom necessary to diagnose T1DM.
- A glycated haemoglobin (HbA1c) level of  $\geq 6.5\%$ , as measured by an assay that is certified by the National Glycohemoglobin Standardization Program<sup>226</sup>.
- A random venous plasma glucose level of  $\geq 200$  mg per dl (11.1 mmol per l) in a patient with classic symptoms of hyperglycaemia or hyperglycaemic crisis.

Thus, it is crucial that early screening and diagnostic tools are used to identify autoimmunity that is already present during the first years of life and to reduce the risk of serious complications. Screening for stage 2 T1DM (FIG. 1) in individuals with one or more  $\beta$ -cell-targeting autoantibodies is carried out with standard OGTTs and by measuring fasting blood glucose using defined criteria for dysglycaemia<sup>129</sup>. Factors associated with the progression from single to multiple autoantibodies, multiple autoantibodies to dysglycaemia, and dysglycaemia to T1DM have been identified in the TrialNet study<sup>34</sup>.

Screening for autoantibodies in children who were followed from birth was initially done as part of research studies in Finland<sup>173,174</sup>, Germany<sup>6</sup>, Colorado<sup>10</sup>, Sweden<sup>175</sup> and Florida<sup>176</sup>. These initial efforts were subsequently followed by the TEDDY study, in which >440,000 newborn babies were screened for the T1DM high-risk HLA-DR-DQ genotypes<sup>42</sup>. Those with an increased genetic risk were then followed-up and assessed for the presence of islet-targeting autoantibodies. Close follow-up has shown that the prevalence of diabetic ketoacidosis is significantly lower in the children enrolled in these studies, particularly those <2 years of age, than in the general population, as treatment could be started earlier<sup>177,178</sup>.

The Fr1da study in Bavaria, Germany, was initiated in February 2015 and enrolled healthy children 2–5 years of age. The study used a multiplex ELISA (enzyme-linked immunosorbent assay) to screen for autoantibodies (GAD65, IA-2 and ZNT8 autoantibodies) in capillary blood samples<sup>179</sup>. Samples with results >97.5th percentile were retested with reference radiobinding assays. A venous blood sample was also obtained to confirm the autoantibody status of children with two or more autoantibodies. Between February 2015 and November 2015, 26,760 children were screened, 0.39% of whom were found to be positive for two or more autoantibodies. Out of the children who were screened and diagnosed with T1DM, none developed ketoacidosis. The psychological assessment showed that there was no increased distress in the families of the children who were screened<sup>179</sup>.

## Prevention

**Primary prevention.** Several studies have attempted primary prevention of T1DM through diet modification or insulin treatment in children with increased genetic risk before the appearance of islet-targeting autoantibodies. The TRIGR study, which followed 2,159 infants at risk of developing T1DM (based on HLA genotype or on having a first-degree family member with T1DM) for 7 years, did not find a difference between the incidence of islet-targeting autoantibodies in infants who were weaned to hydrolysed (hypoallergenic) formulas and infants who were weaned to conventional formula<sup>180</sup>. Primary prevention using high-dose oral insulin administration was also attempted in newborn babies with an increased genetic risk of developing insulin autoantibody (the Pre-POINT study)<sup>181</sup>. This was a double-blind,

placebo-controlled, dose-escalation, phase I/II clinical multicentre pilot study in 25 children 2–7 years of age who were negative for islet-targeting autoantibodies, had a family history of T1DM and had high-risk HLA genotypes. Daily oral administration of a high dose of insulin, compared with placebo, resulted in an immune response that led to increases in IgG binding to insulin and CD4<sup>+</sup> T cell proliferative responses to insulin without hypoglycaemia, which allowed the authors to conclude that a phase III clinical trial was warranted to test whether oral insulin may indeed prevent the appearance of insulin autoantibody through possible mechanisms of immune tolerance induction<sup>181</sup>. Other studies investigating the effect of adding omega-3 fatty acids to the diets of newborn babies have thus far failed to prevent T1DM<sup>182</sup>.

**Secondary prevention.** Interventions following the appearance of one or more islet-targeting autoantibodies but before symptom onset are termed secondary prevention trials. Secondary prevention trials involving insulin, immunosuppressive drugs (for example, abatacept and teplizumab), alum-formulated GAD65 and nicotinamide are listed in TABLE 1. A post hoc analysis showed that oral insulin administration delayed the onset of T1DM in individuals with high levels of insulin autoantibody<sup>183,184</sup>. The predominant approach of carrying out monotherapy is viewed as a weakness, and combination trials — perhaps a combination of immune tolerance induction and immune suppression or modulation — are likely to be necessary to achieve secondary prevention.

## Management

The management of T1DM requires the tight collaboration of an interdisciplinary team (including physicians, diabetes educators, nurses, dieticians, psychologists and social workers), the patient, and their family and support systems (school or work). The aim is to promote healthy living and glycaemic control in order to prevent severe hypoglycaemia, severe hyperglycaemia and ketoacidosis. Complications of both hyperglycaemia and hypoglycaemia occur in an organ-specific manner; individual guidelines have been created to monitor and treat as necessary<sup>185</sup>.

Management at the onset of disease is markedly different depending on the setting in which patients are diagnosed (for example, if they are treated as in-patients or as out-patients, or if they have reached a state of metabolic decompensation). Indeed, prolonged insulin deficiency resulting in hyperglycaemia and the production of alternative fuel sources (for example, ketones derived from fat) can lead to diabetic ketoacidosis. Furthermore, approximately 30% of children with newly diagnosed T1DM present with diabetic ketoacidosis, which still carries considerable morbidity — patients are affected, for example, by neurological injury from cerebral oedema and by pituitary insufficiency — and even a mortality rate of 0.15–0.3%<sup>186,187</sup>. Immediate treatment, preferably in an intensive care unit, is required. Following initial fluid resuscitation,

Table 1 | Secondary prevention trials in T1DM

| Trial                    | Drug                                       | Phase | n   | Outcome              | ClinicalTrials.gov identifier |
|--------------------------|--|-------|-----|----------------------|-------------------------------|
| <b>Completed studies</b> |  |       |     |                      |                               |
| DPT-1 (REF. 227)         | Subcutaneous insulin                       | III   | 339 | No protective effect | NCT00004984                   |
| DPT-1                    | Oral insulin                               | III   | 400 | No protective effect | NCT00419562                   |
| DIPP (REF. 228)          | Intranasal insulin                         | III   | 264 | No protective effect | NCT00223613                   |
| ENDIT (REF. 229)         | Oral modified-release nicotinamide         | III   | 552 | No protective effect | Not applicable                |
| <b>Ongoing studies</b>   |  |       |     |                      |                               |
| TN07                     | Oral insulin                               | III   | 400 | Ongoing              | NCT00419562                   |
| INIT II                  | Nasal insulin                              | II    | 110 | Ongoing              | NCT00336674                   |
| TN18                     | Intravenous abatacept                      | III   | 206 | Ongoing              | NCT01773707                   |
| TN10                     | Intravenous teplizumab                     | II    | 170 | Ongoing              | NCT01030861                   |
| DiAPREV-IT               | Subcutaneous alum-GAD65                    | II    | 50  | Ongoing              | NCT01122446                   |
| DiAPREV-IT2              | Subcutaneous alum-GAD65 and oral vitamin D | II    | 80  | Ongoing              | NCT02387164                   |
| Fr1da                    | Oral insulin                               | II    | 220 | Ongoing              | NCT02620072                   |
| TEFA                     | Gluten-free diet                           | II    | 60  | Ongoing              | NCT02605148                   |

Alum-GAD65, alum-formulated 65 kDa glutamic acid decarboxylase.

an insulin infusion and hydration with electrolyte replacement are used to correct the severe acidosis and dehydration. In this setting, the initiation of diabetes education is prudent, and must be followed by continued education and close monitoring following patient discharge.

However, for those patients (either symptomatic or asymptomatic) who are diagnosed with T1DM and do not have metabolic decompensation, the debate about the efficacy of initial in-patient versus out-patient management is ongoing. Treatment should be individualized, and the decision based on various factors, including age, location and resources (both those of the institute and those of the patient or family)<sup>188</sup>. Out-patient management achieves many goals, including a reduction in hospitalizations and health care costs, without reducing the quality of care or metabolic control<sup>189,190</sup>. However, lengthy hospital stays are still used worldwide owing to the lack of out-patient resources or to preference. Although difficult to adequately perform, well-controlled head-to-head studies assessing both short-term and long-term outcomes are sparse. One study showed no difference in metabolic control over 2 years among children who were admitted for 1 week versus those admitted for 4 weeks after diagnosis<sup>191</sup>.

### Insulin treatment

**Target levels of HbA1c and glucose.** Management of T1DM in the past two and a half decades since the DCCT study has focused on intensive insulin therapy with the goal of maintaining glucose levels as close to normal as possible and avoiding hypoglycaemia<sup>146</sup>. The DCCT was a landmark study; it showed that intensive glycaemic control was able to maintain a mean HbA1c level of 7.2% (as compared with conventional

management for which the mean HbA1c level was 9.1%), and reduced microvascular complications by 35–76% during the trial and macrovascular complications by 58% during the passive follow-up in the EDIC study<sup>146</sup>. Thus, the benefits of glycaemic control may induce metabolic memory and last for many years<sup>162</sup>. The dramatic difference between treatment groups is attributable not only to multiple daily injections or insulin pump use in the intensive group compared with once-daily or twice-daily insulin injections in the conventional group but also to more-frequent blood-glucose monitoring and contact with health care staff in the intensive group.

The consensus ADA and International Society for Pediatric and Adolescent Diabetes goal for children and adolescents ( $\leq 18$  years of age) is a HbA1c level of  $<7.5\%$ , and different organizations have proposed targets of  $<6.5\%$  or  $<7\%$  in adults<sup>185</sup>. People without diabetes have a HbA1c level of  $<5.7\%$ . Pregnant women should aim for a HbA1c level of  $<6\%$ . The target is  $<7.5\%$  in elderly individuals with T1DM who are living alone and doing their own care, whereas it is  $<8.5\%$  in those living in a nursing home who have limited functioning, mobility or mental capacity<sup>192</sup>. It should be noted that HbA1c levels are also given as mmol per mol, such that  $6.5\%$  is 48 mmol per mol.

Frequent monitoring of blood glucose levels — including before meals, before bed and before exercise — is needed. In addition, testing of blood glucose should be done whenever a low blood glucose level is suspected, after treating low blood glucose levels and before important tasks such as driving. In adults, preprandial capillary blood glucose targets are 80–130 mg per dl (4.4–7.2 mmol per l), and the peak postprandial glucose target is  $<180$  mg per dl ( $<10$  mmol per l). More-stringent or less-stringent targets may be



appropriate for individual patients if these levels can be achieved without considerable hypoglycaemia or adverse events.

**Insulin and insulin analogues.** Exogenous insulin replacement, with frequent capillary blood-glucose monitoring and carbohydrate counting of food (as resources allow), is initiated in all symptomatic patients at diagnosis. Recombinant insulin analogues have mostly supplanted recombinant human insulin formulations. Insulin is given subcutaneously with injection pens or pumps. However, a fully physiological exogenous insulin therapy must be given in such a way that insulin passes first through the liver, similarly to endogenously secreted insulin. Thus, current insulin administration is designed to most closely approximate the normal physiological setting, in which the pancreas continuously secretes a small amount of insulin and produces larger amounts in response to a meal containing carbohydrates. Accordingly, a combination of long-acting and short-acting insulin analogues is now used in the form of multiple daily insulin injections; after stabilization, an insulin pump can be used. Long-acting insulin analogues include insulin detemir, insulin glargine and insulin degludec, which have durations of action of 20–24 hours, 24 hours and 24–42 hours, respectively. Short-acting analogues include insulin aspart, insulin lispro and insulin glulisine, which all have a similar onset of action (15 minutes), a peak effect within 1–2 hours and a duration of action of 4 hours. Other forms of insulin (premixed insulins, insulin isophane and regular human insulin) are available, but these are less physiological than are those listed above; their use can depend on the family situation or on cost. Creating a flexible insulin regimen that is matched to the individual's resources and lifestyle is strongly encouraged.

Technological advances enabling the broader implementation of smaller and better insulin pumps, and continuous glucose monitoring, have hastened progress towards the development of a true artificial pancreas. Although insulin is not a cure, there is hope that the artificial pancreas will greatly improve care and reduce complications and comorbidities until a biological cure is found.

#### Box 2 | Key aspects in the follow-up of children and adolescents with T1DM

- Mental health: screening for depression, anxiety, cognitive impairment, eating disorders, suicide risk, burnout, sleep disorders, social support and connectedness.
- Medical nutrition therapy: provision of information about healthy eating habits, as recommended for all children and adolescents, by a registered dietician alongside continuing weight and height monitoring.
- Physical exercise: 30–60 minutes of moderate physical activity daily, or as much as the patient is able to perform, alongside careful blood-glucose monitoring.
- Community support: camps, meetings and/or groups organized through schools, universities, or local or national organizations.
- Comorbidity screening: thyroid function, urinary albumin levels, blood pressure, lipid profile, retinopathy and dental examination, in addition to screening for coeliac disease and other autoimmune diseases.

**Hypoglycaemia.** The presence of frequent and/or severe hypoglycaemia due to insulin administration can have negative consequences not only physically but also emotionally. Severe hypoglycaemia results in a lack of glucose delivery to the brain and can also directly cause neuronal cell death<sup>193,194</sup>. Hypoglycaemia fear and anxiety — which can be present in patients, as well as parents and/or caregivers — is a common concern that can negatively affect glycaemic control<sup>195</sup>. The treatment of hypoglycaemia with a small amount (15 g) of simple sugar — in the form of juice, candy, glucose gel, glucose tabs or cake icing, for example — should increase the blood glucose level to a safe range but may need to be repeated multiple times, as determined by close self-monitoring of blood glucose levels. The causes of hypoglycaemia include illness, exercise or excessive insulin administration.

#### Other interventions

Aside from insulin therapy, the goals to successful diabetes management include nutritional awareness and healthy food choices to reduce the risk of cardiovascular disease and obesity; vigorous exercise to improve insulin sensitivity, lipid metabolism and blood pressure; and mood assessment and screening to detect depression, anxiety or eating disorders (BOX 2). In addition, frequent self-monitoring of blood glucose levels and/or the use of continuous glucose monitors are vital and have been shown to correlate with improved glycaemic control<sup>196</sup>. Patient empowerment and autonomy are crucial for successful management.

#### Immuno-intervention

Since 1976, there have been a large number of open, uncontrolled interventional studies involving various immunosuppressive agents that aimed to preserve residual  $\beta$ -cell mass in symptomatic patients<sup>197</sup>. In accordance with most prevention trials, none of these studies has been successful thus far. Immune suppression studies with some promise include single-compound trials with cyclosporine (abandoned owing to adverse effects)<sup>198</sup>, azathioprine<sup>199</sup>, monoclonal anti-CD3 antibodies<sup>200,201</sup>, rituximab (anti-CD20)<sup>202</sup> and abatacept<sup>203</sup>. One trial investigating the combination of mycophenolate mofetil (which inhibits T cell and B cell growth) and daclizumab (an anti-IL-2 antibody) also failed<sup>204</sup>, whereas another investigating combination therapy with the mechanistic target of rapamycin (mTOR) inhibitor rapamycin and IL-2 reported an accelerated loss of endogenous residual C-peptide<sup>205</sup>. Immuno-modulation with alum-formulated GAD65 showed initial promise in reducing the loss of C-peptide<sup>206,207</sup> — although the phase III endpoint was not reached<sup>208</sup> — as did an additional TrialNet-conducted phase II study<sup>209</sup>. Although single-compound studies dominate, several combination trials are in progress, along with studies investigating the efficacy of administering haematopoietic stem cells<sup>210</sup>. The rationale to treat patients with haematopoietic stem cells is to induce T regulatory cells, which would supposedly dampen  $\beta$ -cell-targeted autoimmunity<sup>211</sup>.

## Quality of life

### *Diabetes-specific health-related quality of life*

The relentless physical and psychological demands of daily treatment, and the constant anxiety and fear of acute and long-term complications, have a major effect on physical, social and emotional well-being<sup>212</sup>. As T1DM is primarily a self-managed condition<sup>213</sup>, subjective factors — such as the burden borne by self-management and the effect of the disease on role and social functioning are important. Diabetes-related quality of life (QOL) is defined as a multidimensional construct that incorporates an individual's subjective perception of physical, emotional and social well-being, including both a cognitive component (satisfaction) and an emotional component (happiness)<sup>212</sup>.

Health-related QOL (HRQOL) measures the well-being of an individual with respect to physical health. For people without identified medical problems, HRQOL can reflect general health status (that is, physical strength and levels of energy and/or fatigue). For people with a chronic medical condition such as T1DM, HRQOL can include satisfaction with the current status and treatment of the condition; the effect of the condition on physical, social and emotional functioning; and how much one worries about or is distressed by T1DM<sup>214</sup>. A higher T1DM-associated QOL has been shown to predict key diabetes outcomes, including greater adherence to diabetes treatment recommendations and optimal glycaemic control<sup>215–217</sup>, which emphasizes the central role of QOL in diabetes management and control.

As intensive insulin regimens increasingly become the standard of care for people with T1DM, the impact of these regimens on the routines and relationships of patients and their families is increasing<sup>218</sup>. For these reasons, contemporary clinical trials of new diabetes medications and treatment technologies increasingly include patient-reported outcomes, such as HRQOL, in addition to objective health outcomes (for example, HbA1c levels). Furthermore, national and international clinical practice guidelines are increasingly recommending that diabetes care providers use HRQOL instruments<sup>5,219</sup>.

### *Limitations of existing measures*

As clinical trials of new diabetes medications and technologies are increasingly incorporating HRQOL as a primary study outcome<sup>220</sup>, the accurate, reliable and valid measurement of diabetes HRQOL is essential to draw appropriate and meaningful conclusions that can positively influence the treatment of people with diabetes. However, there are three primary limitations of existing measures of T1DM-associated HRQOL. First, existing measures disproportionately emphasize only the negative aspects of HRQOL (such as problems and barriers to optimal HRQOL). Second, current measures do not capture developmentally appropriate (age-specific) topics or issues related to HRQOL at different developmental stages. Third, the content of existing measures often does not reflect contemporary diabetes care regimens and new technologies.

## Outlook

Our understanding of the aetiology and pathogenesis of autoimmune T1DM is undergoing a paradigm shift. The recognition of standardized islet-targeting autoantibodies as strong and reliable biomarkers of the pathogenesis of T1DM has finally made it possible to ask questions about the aetiology of the disease. Studies of T cells and B cells — which have largely been conducted in individuals with newly diagnosed T1DM or at best in those positive for islet-targeting autoantibodies — have suffered from the 'street light effect' (REF. 221), as they study the phenomenon after a substantial loss of  $\beta$ -cells has occurred. Studies during  $\beta$ -cell loss (in antibody-positive individuals) or even before  $\beta$ -cell loss (before seroconversion) should be performed. These analyses of the human immune response will be crucial to the future success of immune tolerance induction or other strategies to prevent  $\beta$ -cell loss. Staging of T1DM pathogenesis (FIG. 1) will help to dissect the progressive chronic autoimmunity associated with  $\beta$ -cell loss, which will enable the design of secondary prevention therapy.

The diagnosis of T1DM in the absence of ketoacidosis and symptoms will be key to a better prognosis, particularly in the very young, while at the same time recognizing that adult-onset T1DM exists<sup>222</sup>. The recognition of disease heterogeneity may be a way to better personalize the treatment of T1DM. In terms of technology, there is currently a healthy competitive market with at least seven different types of insulin pens and a continuous development of needles to suit every body shape. At least six different brands of insulin pumps are being developed, and these have increasing levels of sophistication, including a remote-control feature and the ability to simultaneously perform blood-glucose measurements. Continuous glucose monitors are devices that measure interstitial glucose levels. Finger pricks are no longer necessary, and the devices work 24 hours a day and can include alarms to indicate when glucose levels are too high or too low. Three companies are competing with at least seven different models. Hybrid closed-loop systems that perform continuous glucose monitoring to automatically increase or decrease insulin delivery are under rapid development and have shown promise in reducing hypoglycaemic episodes and reducing HbA1c levels<sup>223,224</sup>. Novel insulin analogues, pumps, pens, continuous glucose monitoring devices and artificial pancreata, in combination with better psychosocial support, are all key ways to improve the life, as well as the QOL, of those already affected by T1DM.

An important next step in the study of diabetes QOL is to develop measures that can be used by diabetes health care providers to tailor their care to individual patients. Developing and validating measures with high clinical utility and strong psychometric properties — including sensitivity to clinically meaningful change and low respondent burden — are of primary importance<sup>225</sup>. With the dramatic increase in the number of new diabetes technologies, measures of diabetes QOL are important both as outcome measures in clinical trials and as measures that can help clinicians to individualize diabetes education and care.

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