



# Adult-onset autoimmune diabetes

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**Abstract** | Adult-onset autoimmune (AOA) diabetes pathophysiology starts with immune changes, followed by dysglycaemia and overt disease. AOA diabetes can occur as classic type 1 diabetes when associated with severe loss of insulin secretion. More frequently, it is diagnosed as latent autoimmune diabetes in adults, a slowly progressing form with late onset, a long period not requiring insulin, and it is often misdiagnosed as type 2 diabetes. As its clinical presentation varies remarkably and immune markers often lack specificity, it is challenging to classify each case ad hoc, especially when insulin treatment is not required at diagnosis. Proper care of AOA diabetes aims to prevent complications and to improve quality of life and life expectancy. To achieve these goals, attention should be paid to lifestyle factors, with the aid of pharmacological therapies properly tailored to each individual clinical setting. Given the heterogeneity of the disease, choosing the right therapy for AOA diabetes is challenging. Most of the trials testing disease-modifying therapies for autoimmune diabetes are conducted in people with childhood onset, whereas non-insulin diabetes therapies have mostly been studied in the larger population with type 2 diabetes. More randomized controlled trials of therapeutic agents in AOA diabetes are needed.

Diabetes mellitus is a disease characterized by high blood glucose levels. When the disease is associated with severe loss of insulin secretion, it is referred to as insulin dependent, as affected individuals need insulin therapy to survive. Conversely, if the disease is caused by less severe insulin deficiency, affected patients are not dependent on insulin. Disease forms in which certain immune signatures are present, such as peripheral blood islet-specific autoantibodies, are classified as autoimmune diabetes, that is, type 1 diabetes mellitus (T1DM) or, more accurately, type 1A diabetes to distinguish it from idiopathic type 1B diabetes<sup>1</sup>. In broad terms, individuals who present in childhood usually have insulin-dependent T1DM, but may also be affected by monogenic diabetes, known as maturity-onset diabetes of youth (MODY), or even type 2 diabetes (T2DM). Conversely, those who present in adulthood usually have non-insulin-dependent T2DM, but cases of adult-onset autoimmune (AOA) diabetes are also frequent. Adult-onset diabetes has been suggested to encompass five different phenotypic groups in which those phenotypes that present with islet-specific autoantibodies are classified together as severe autoimmune diabetes (SAID)<sup>2</sup>. The distinction between severe insulin deficiency, requiring insulin treatment, and more modest insulin deficiency, treatable by other means, is not always clear, especially in adult-onset diabetes<sup>3</sup>.

Many of the issues surrounding adult-onset diabetes relate to the relationship between T1DM and T2DM in the context of age at onset, blood glucose levels and

insulin deficiency, with lack of clear boundaries that define these major types of diabetes (FIG. 1). For example, although most cases of childhood-onset diabetes are autoimmune diabetes, most cases of autoimmune diabetes, in actual numbers, develop in adulthood. AOA diabetes is much more heterogeneous than young-onset autoimmune diabetes, as the rate of  $\beta$ -cell destruction is highly variable, probably owing to the differential presence of genetic factors and differing severity of the individual autoimmune process<sup>4,5</sup>.

Epidemiological studies have highlighted that most patients with AOA diabetes do not require insulin treatment at diagnosis<sup>6,7</sup>, and these patients are commonly defined as having latent autoimmune diabetes in adults (LADA). In 2022, LADA has been included under the category of T1DM in the diabetes classification proposed by the American Diabetes Association (ADA), although the term retains its own identity, being defined as common and acceptable in everyday clinical practice, raising awareness of individuals at risk of progressing towards requiring insulin therapy<sup>1</sup>. As most studies in AOA diabetes referred to ‘people with LADA’, we retain the term LADA in this Primer when appropriate. The inherent conundrum has implications for this interface between the two major types of diabetes, that is T1DM and T2DM, and how they should be treated in clinical practice.

In this Primer, we discuss the epidemiology, pathogenesis, clinical presentation, diagnosis and management of AOA diabetes, providing a perspective on our current

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understanding and suggestions for future priorities of AOA diabetes, which is too often misdiagnosed.

## Epidemiology

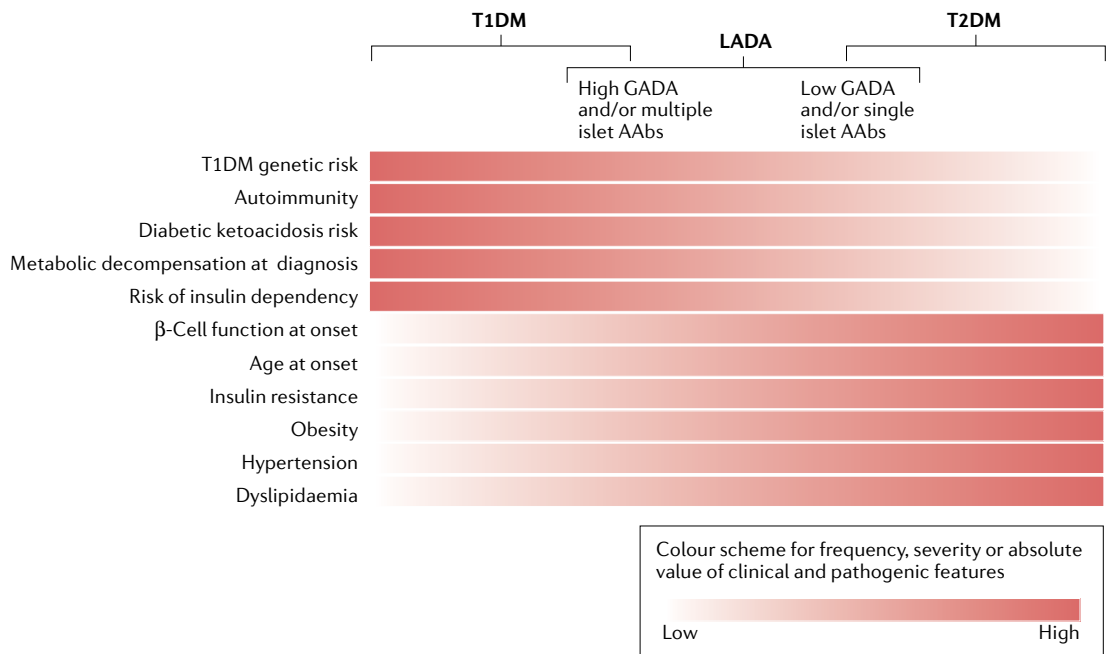
### Prevalence and incidence

The prevalence of T1DM and T2DM has been increasing, with the International Diabetes Federation (IDF) counting more than 500 million people worldwide living with diabetes in 2021 (REF. 8). The global prevalence of T1DM is ~0.1%<sup>8</sup>, likely a marked underestimate given that only classic insulin-dependent T1DM cases were considered and that adults with autoimmune diabetes not requiring insulin at diagnosis, that is, those with LADA, can be initially misclassified as having T2DM. In contrast to the epidemiology of well-characterized childhood-onset T1DM, incidence and prevalence data for AOA diabetes are sparse. Furthermore, only few of the available data derive from population-level studies and they are often limited by small sample sizes and biased by a high risk of misclassification between T1DM and T2DM<sup>9</sup>. Nonetheless, current projections show that most new cases of autoimmune diabetes are diagnosed during adulthood<sup>6,10</sup>. A study in China estimated that adults aged >20 years at diagnosis comprise 65% of all new T1DM cases and there are probably more than 6 million such cases in China<sup>11</sup>. Overall, the incidence of

adulthood-onset T1DM is higher in Europe, especially in Nordic countries, than in Asia or Africa, and T1DM is more prevalent in men than in women<sup>10</sup>. These differences are likely, in part, genetic, given the increased frequency of high-risk disease variants in northern Europe. However, heterogeneity of the distribution of T1DM within countries and data from migration studies indicate that non-genetic factors, including industrialization-associated factors such as pollution and overcrowding, might have a role<sup>12</sup>.

A study in a European adult-onset diabetes cohort suggests that non-insulin-requiring T1DM, that is LADA, can be up to threefold more prevalent than insulin-dependent T1DM: 9.7% of these patients had autoimmune diabetes and most of these (odds ratio 3.3) were initially non-insulin dependent<sup>6</sup>. Epidemiological studies have shown that the autoimmune diabetes markers islet-specific autoantibodies can be found in the peripheral blood of people with an initial diagnosis of T2DM<sup>2,6,7</sup>. These individuals, reclassified as having LADA, account for 2–11% of the whole population with T2DM, with frequency varying by region (FIG. 2).

Two factors constrain the epidemiological data available. First, the error of assuming that those presenting with diabetic ketoacidosis (BOX 1) have T1DM might be as high as 50% and can especially occur in adult-onset cases<sup>13,14</sup>.



**Fig. 1 | The adult-onset diabetes spectrum.** In people with adult-onset autoimmune (AOA) diabetes, clinical and pathogenic features of classic insulin-dependent type 1 diabetes mellitus (T1DM) and of type 2 diabetes mellitus (T2DM) frequently overlap, making it difficult to distinguish between these two types of diabetes. In this regard, most people with AOA diabetes do not require insulin at diagnosis and are commonly defined as having latent autoimmune diabetes in adults (LADA). Several features of LADA are in between those for classic T1DM and T2DM, for example, age at onset, genetic predisposition for T1DM, level of β-cell function, diabetic ketoacidosis risk, risk of progression towards an insulin-dependent state, severity of insulin resistance and prevalence of associated comorbidities (such as obesity, dyslipidaemia and hypertension). Furthermore, LADA is clinically and pathogenetically heterogeneous; people presenting with high glutamic acid decarboxylase serum autoantibody (GADA) concentrations and/or multiple islet autoantibodies (AABs) are similar to those with classic T1DM, whereas those with low GADA concentrations and/or single islet AABs are similar to those with T2DM. It should be noted that maturity-onset diabetes of youth (MODY), which may also be diagnosed during adulthood, was not included in the figure because it most frequently occurs during the first decades of life and is itself a heterogeneous group of diabetes subtypes with monogenic causes, differing in clinical features.

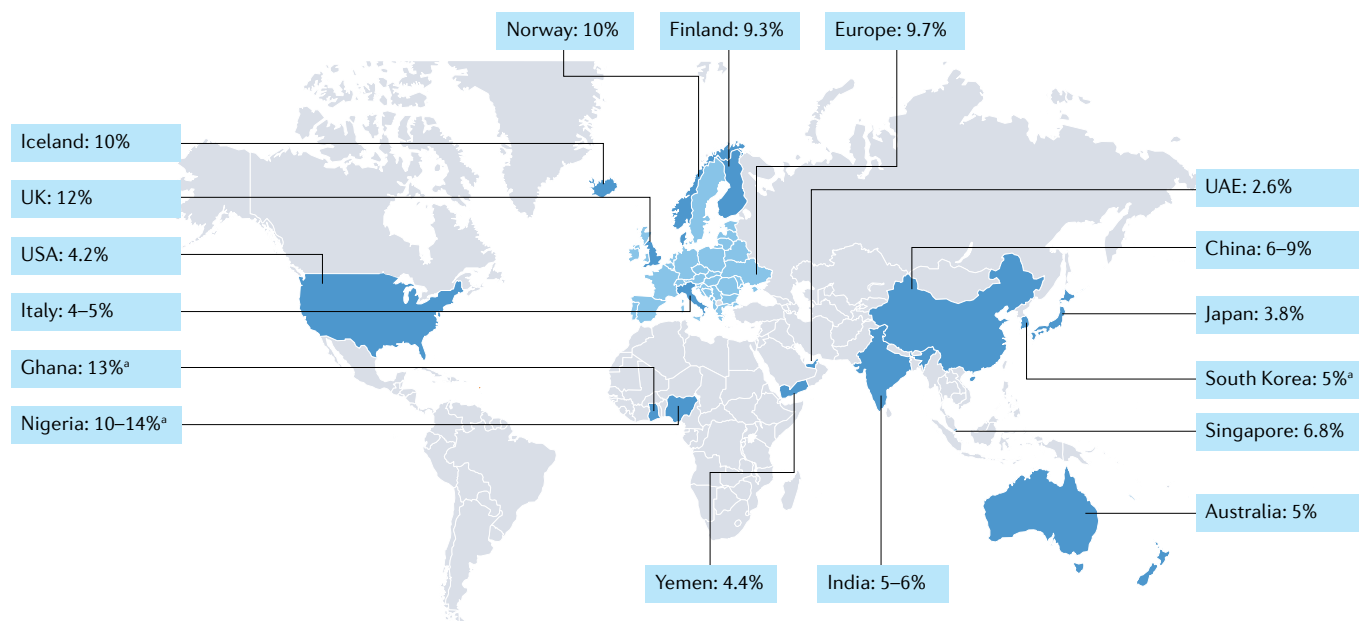


Fig. 2 | **Frequency of islet-specific autoantibodies in adults with a clinical diagnosis of type 2 diabetes mellitus.**

Cross-sectional studies have suggested geographical differences in the proportion of adults with a clinical diagnosis of type 2 diabetes mellitus testing positive for islet-specific autoantibodies, mainly glutamic acid decarboxylase serum autoantibody. Of note, these findings might be due to methodological differences between studies, such as disease duration at the time of autoantibody testing or the assays used for autoantibody measurement. Data from REFS.<sup>6,7,49,75,82–85,95,182–192</sup>. <sup>a</sup>Frequencies reported in small studies with a sample size of <500 participants.

Second, immune markers of T1DM lack specificity. For example, using glutamic acid decarboxylase (GAD) serum autoantibody (GADA) detection assays with 99% specificity in a cohort with adult-onset diabetes in whom the likelihood of T1DM is ~10%, would have a certain rate of false positivity<sup>15</sup>. The more specific the assay, the lower the false positive rate, and various approaches have sought to reduce that false positive rate by modifying the antigen, for example, GAD N-terminal truncation, or using high-affinity assays, for example, electrochemiluminescence and bridging-type enzyme-linked immunosorbent assay (ELISA)<sup>16–18</sup>. Clinicians should be aware of these issues, and additional biomarkers are needed to classify cases (see also section Classification and diagnosis). In this regard, the presence of other organ autoimmune disease might help in identifying people with diabetes with higher probability of presenting with pancreatic autoimmunity. In particular, organ-specific endocrine autoimmunity (such as thyroid or adrenal autoimmunity) and other autoimmune disorders (such as coeliac disease or autoimmune gastritis) develop more frequently in T1DM than in T2DM<sup>19</sup>, which has also been confirmed in LADA<sup>20,21</sup>.

#### **Risk factors for LADA**

About half of inheritable childhood-onset T1DM is attributed to variation in HLA alleles but, in adult-onset cases, that heritability is much lower with lower twin concordance rates, lower high-risk HLA class II genotypes, lower HLA class I risk and higher frequency of protective HLA alleles<sup>5,22</sup>. As a result, although genetic risk scores have been developed to aid the discrimination between T1DM and T2DM<sup>23</sup>, the altered and reduced

genetic risk in adult-onset T1DM has not been shown to be predictive<sup>24</sup>. Thus, genetic risk scores are not widely used in clinical practice in this setting. Genetic susceptibility remains relatively constant in stable populations over a couple of generations, yet the incidence of T1DM and T2DM have increased substantially. By implication, non-genetic factors may be common to both forms of diabetes<sup>25,26</sup>. A Norwegian study indicated a strong effect of a family history of diabetes as a risk factor for LADA<sup>25</sup>. The presentation of LADA was associated with increased body weight, physical inactivity, smoking and low birth weight followed by adult overweight, similar to the risk factors for T2DM development. Of note, the risk of overweight was most prominent in individuals with a family history of diabetes<sup>27,28</sup>. Metabolic syndrome, a proxy for insulin insensitivity and overweight, can be identified in ~85% of individuals with T2DM and in ~40% of those with adult-onset T1DM<sup>29</sup>. Potential links between childhood adiposity and diabetes risk likely reflect stress on insulin secretory networks that maintain glucose homeostasis and glucose disposition and could be, in part, genetic, even for T1DM, given that childhood adiposity genetic variants were positively and causally associated with T1DM risk<sup>30</sup>.

A potential beneficial effect on the autoimmune process by consumption of fatty fish and by moderate alcohol consumption was also seen<sup>27,28</sup>, and processed red meat was associated with increased risk of LADA, whereas no association was found for unprocessed red meat<sup>25,28,31–33</sup>.

In addition, in one study, a healthy lifestyle (BMI <25 kg/m<sup>2</sup>, moderate-to-high physical activity, a healthy diet, no smoking and moderate alcohol consumption)

**Box 1 | Diabetic ketoacidosis**

Diabetic ketoacidosis (DKA) is a preventable, acute and life-threatening complication of diabetes that occurs in cases of absolute or relative insulin deficiency<sup>193</sup>. The heterogeneous rate of  $\beta$ -cell loss in people with adult-onset autoimmune (AOA) diabetes translates into various risks of DKA, between adults presenting with a classic type 1 diabetes mellitus onset (high DKA risk) and those affected by latent autoimmune diabetes in adults (LADA)<sup>194,195</sup>, who are in part protected from DKA by the retention of a certain amount of endogenous insulin secretion. Nonetheless, both patients and physicians should be aware of the higher risk of DKA occurrence in AOA diabetes than in type 2 diabetes mellitus, and should be ready to recognize and address DKA risk factors. Although less studied in adults than in young people, the risk factors include: barriers to health care, low socioeconomic status, female sex, ethnicity, poor metabolic control, low self-management skills, omission of insulin therapy, psychiatric disorders, infections, and alcohol and drug abuse<sup>111,194</sup>. In general, however, the risk of DKA decreases with older age at onset<sup>196</sup>.

was found to have a possibly positive effect on the risk of LADA development as well as on T2DM presentation; BMI  $<25\text{ kg/m}^2$  conferred the largest risk reduction for both LADA and T2DM<sup>28</sup>. These important observations may potentially provide guidance for preventive measures in future interventional trials.

**Mechanisms/pathophysiology**

The pancreas comprises an exocrine portion that consists of acinar cells, which secrete digestive enzymes (amylase, which digests starch, trypsinogen and chymotrypsinogen). Together with ducts they make up 98–99% of the pancreatic tissue. Hormone-secreting endocrine cells found in the islets of Langerhans make up the remaining 1–2% of the pancreas<sup>34</sup>. These islands of endocrine cells comprise 70%  $\beta$ -cells, which secrete insulin and amylin, glucagon-secreting  $\alpha$ -cells, somatostatin-secreting  $\delta$ -cells, ghrelin-secreting  $\epsilon$ -cells and PP cells, which secrete pancreatic polypeptide.

In addition to active insulin,  $\beta$ -cells secrete C-peptide, a peptide that is cleaved from the larger molecule proinsulin and used to measure endogenous production of insulin. In autoimmune diabetes,  $\beta$ -cells are the cell type predominantly affected, undergoing damage by the immune system, although other endocrine and exocrine cells may also be affected<sup>35</sup>.

**Development of autoimmune diabetes**

Autoimmune diabetes develops over a period of months and years before the onset of symptomatic disease. Accordingly, a suggested staging model for T1DM may apply to both those who have LADA and those who have a slower onset of symptomatic diabetes in adulthood<sup>36</sup>. This model (FIG. 3) suggests that there are long pre-symptomatic, normoglycaemic periods in which detectable immune changes occur, which include the generation of anti-islet autoantibodies and autoreactive T lymphocytes. These immune changes occur in individuals who have a genetic predisposition, which

interacts with environmental factors, but the precise contribution of the components of this interaction and the nature of this interaction are not fully understood. This period is followed by dysglycaemia and finally symptomatic diabetes, when  $\beta$ -cell function is insufficient to maintain glucose metabolism, leading to symptoms of diabetes. In this model, relating to staging of autoimmune diabetes<sup>36</sup>, it is conceivable that the presence of fewer predisposing genetic variants for T1DM and more predisposing genetic variants for T2DM may lead to a flattening of the curve in stage 1 and stage 2 of the autoimmune diabetes model, for example, in those who have phenotypic manifestations of diabetes later in life. The possibility then arises not only that immunological changes manifest later but also that the condition progresses more slowly. This heterogeneity would then be explained by different risk factors leading to a continuum of risk, instead of a precise cut-off that would be designated T1DM.

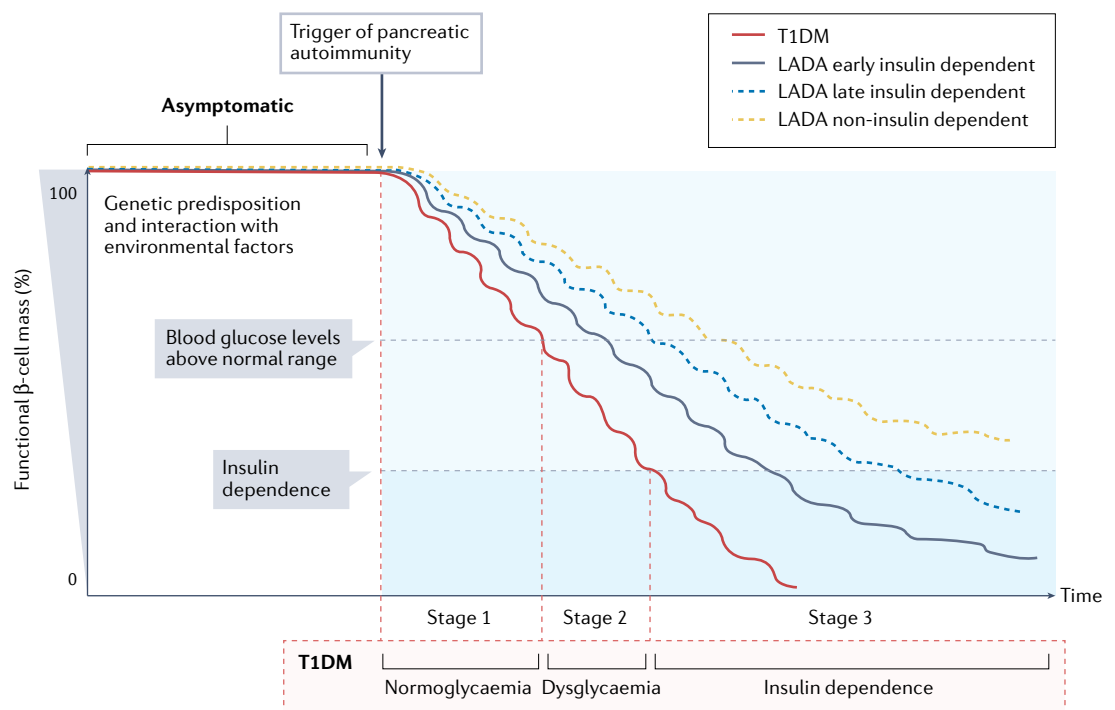
**Islet pathology**

In individuals with either T1DM or T2DM, pancreatic mass is reduced<sup>37</sup>. As the cells that produce insulin and glucagon account for a very small proportion of the total pancreatic mass, it is surprising that the total organ mass has been found to be reduced. In a meta-analysis<sup>37</sup>, the  $P^2$  measure of heterogeneity among studies assessing pancreatic volume by ultrasonography, CT and MRI is large, and quantification of the reduction varies among studies, as it depends on the parameter measured and the method of analysis. A Chinese study in individuals aged 30–75 years revealed by CT that pancreatic volume was reduced in those with LADA ( $55.5 \pm 2.5\text{ cm}^3$ ), compared with control individuals ( $69.6 \pm 2.2\text{ cm}^3$ ). However, this reduction was less than in individuals with classic adult-onset T1DM ( $47.7 \pm 2.7\text{ cm}^3$ )<sup>38</sup>. A post-mortem study of pancreas pathology in individuals diagnosed with T2DM found reduced  $\beta$ -cell mass in those positive for islet autoantibodies or HLA alleles *HLADR3* or *HLADR4* (high risk for autoimmune diabetes) compared with those negative for autoantibodies<sup>39</sup>. These observations suggest loss of both exocrine and endocrine tissue in those with pancreatic autoimmunity. A feature of autoimmune diabetes, not generally seen in T2DM, is the presence of insulinitis. Insulinitis is defined as lesions with  $\geq 15\text{ CD45}^+$  cells, indicating the presence of haematopoietic cells and inflammation, immediately adjacent to islet endocrine cells in a minimum of three islets<sup>40</sup>. Insulinitis is uncommon in people presenting with AOA diabetes and was reported in only 29% of those aged 15–40 years, studied within a month of diabetes onset<sup>34</sup>. Even in younger individuals presenting with T1DM, the pathological manifestation of insulinitis is heterogeneous, and there is a distinct difference in both frequency and type of  $\text{CD45}^+$  immune cells found in the islets of individuals  $<7$  years of age presenting with T1DM compared with older individuals. The  $\text{CD45}^+$  immune cells in those with T1DM are  $\text{CD8}^+$  cytotoxic T cells and  $\text{CD20}^+$  B cells, although other immune cell types, such as macrophages, dendritic cells and  $\text{CD4}^+$  T cells, have also been observed.  $\text{CD8}^+$  T cell cytotoxicity can take several forms, including direct damage of

insulin-producing cells and indirect damage due to the production of inflammatory cytokines, which include interferon- $\gamma$  (IFN $\gamma$ ), tumour necrosis factor (TNF), IFN $\alpha$  and IL-1 $\beta$ , and induction of apoptosis; however, it is not clear in humans which mode of death is most prominent. The role of the CD20<sup>+</sup> B cells is even less clear, as antibodies produced by B cells are not thought to be directly pathogenic. However, B cells also produce cytokines, can present antigens to T cells and seem to be an important part of the immune pathogenesis of T1DM. There are also greater numbers of insulin-deficient islets<sup>41</sup> in those presenting at <7 years of age compared with those >13 years of age, who generally have more insulin-containing islets and less insulinitis. However, even for those who have had T1DM for many years, some islets may not be affected. This heterogeneity, whereby there may be greater numbers of insulin-containing islets and also fewer islets that display insulinitis, is more pronounced in older individuals. The presence of insulinitis and greater loss of insulin within the islets suggests immune destruction of the  $\beta$ -cells and seems to be part

of the spectrum of autoimmune diabetes that has a more aggressive immune pathogenesis in the islets in the young. High-resolution analysis, using single-cell RNA sequencing, has provided new insights into immune cell types involved in insulinitis<sup>35</sup> and demonstrates not only that  $\beta$ -cells show activation of genes that are associated with stress and autophagy but also that ductal cells upregulate genes involved in apoptotic, metabolic and immune responses, indicating the involvement of ductal cells in the immune pathogenesis.

Pancreatic scintigraphy using IL-2 radiolabelled with technetium-99m (<sup>99m</sup>Tc) confirmed that activated T cells infiltrate the pancreas in those with LADA, indicating the presence of insulinitis in both T1DM and LADA<sup>42</sup>. In addition, heterogeneous islet infiltration with predominantly CD8<sup>+</sup> T cells and macrophages was observed in pancreas samples from individuals with LADA, similar to individuals with older-age-onset T1DM<sup>43</sup>. Of note, a T cell response may also occur in the absence of the classic islet autoantibody markers of pancreatic autoimmunity<sup>44</sup>. This condition, termed T-LADA, seems



**Fig. 3 | Model for staging of autoimmune diabetes.** Genetic predisposition to autoimmune diabetes may interact with environmental factors to trigger pancreatic autoimmunity. This pancreatic autoimmunity causes a progressive loss of  $\beta$ -cell function, which occurs during a pre-symptomatic period characterized by detectable immune changes and normoglycaemia (stage 1). When the percentage of residual functional  $\beta$ -cell mass is too low to maintain blood glucose values within normal ranges, a period of asymptomatic dysglycaemia (stage 2) starts. As the loss of  $\beta$ -cell capacity continues, exogenous insulin becomes necessary for survival. This insulin-dependent state (stage 3), if not adequately treated, may be characterized by symptoms of insulin deficiency, such as weight loss, presence of urinary and blood ketones or diabetic ketoacidosis. In adult-onset autoimmune diabetes, the rate of  $\beta$ -cell loss differs between individuals. In people with classic type 1 diabetes mellitus (T1DM), the progression from the pre-symptomatic stages (1 and 2) to stage 3 is so rapid that in most cases the asymptomatic dysglycaemia is undiagnosed, whereas latent autoimmune diabetes in adults (LADA) is characterized by longer pre-symptomatic stages, which enable diagnosis of dysglycaemia in a non-insulin-dependent state. Nonetheless, among people with LADA, some individuals will progress to an insulin-dependent state earlier (LADA early insulin dependent), or later (LADA late insulin dependent), although some people will retain sufficient  $\beta$ -cell function and will not need insulin treatment (LADA non-insulin dependent). Stages 1, 2 and 3 in the figure refer to classic T1DM<sup>36</sup>.



to be characterized by a more rapid  $\beta$ -cell functional decline than T2DM, despite the absence of known islet autoantibodies<sup>45</sup>. Indeed, although LADA is routinely diagnosed by detecting islet autoantibodies, these are markers of immune activity only and not the effectors of  $\beta$ -cell destruction, which is mainly caused by islet antigen-specific CD4<sup>+</sup> and CD8<sup>+</sup> T cells.

In addition, pancreatic tissue from individuals with T1DM shows evidence of enteroviral infection<sup>46,47</sup>, as well as increased expression of MDA5, a viral sensor in  $\alpha$ -cells and  $\beta$ -cells of the pancreas<sup>48</sup>. Given the lag between initiation of autoimmunity and the diagnosis of T1DM, it is not currently possible to prove a causative role. These findings have not been specifically observed in people who had a diagnosis of LADA.

### Autoantibodies

Islet cell autoantibodies (ICAs) act as immune activity markers and their detection can help to distinguish an autoimmune from a non-autoimmune type of diabetes. ICAs detected with standardized assays include GADA, tyrosine phosphatase IA2 antibody (IA2-Ab), zinc transporter isoform 8 autoantibody (Znt8A) and insulin autoantibody (IAA)<sup>1</sup>. Individuals with higher levels of GADA show a greater loss of insulin secretory capacity and present with clinical features similar to those of childhood T1DM, such as a higher prevalence of other autoimmune disorders<sup>49–51</sup>. In addition to GADA levels, the specific GAD epitope recognized by autoantibodies may differ between patients and is related to different clinical features. In studies measuring GADA recognizing middle and C-terminal GAD epitopes, people who have LADA were found to be younger, have lower serum C-peptide levels (indicating lower endogenous insulin production), increased risk of thyroid autoimmunity, higher GADA levels, and are more likely to be insulin treated compared with those with only N-terminal reactive GADA<sup>52</sup>. Similarly, immunoreactivities against different IA2 protein domains characterize distinct LADA phenotypes: IA2-Ab directed against the intracellular epitopes is associated with lower waist circumference, healthier lipid profile (higher HDL-cholesterol and lower triglycerides), lower prevalence of hypertension and higher prevalence of other autoimmune disorders<sup>53</sup>.

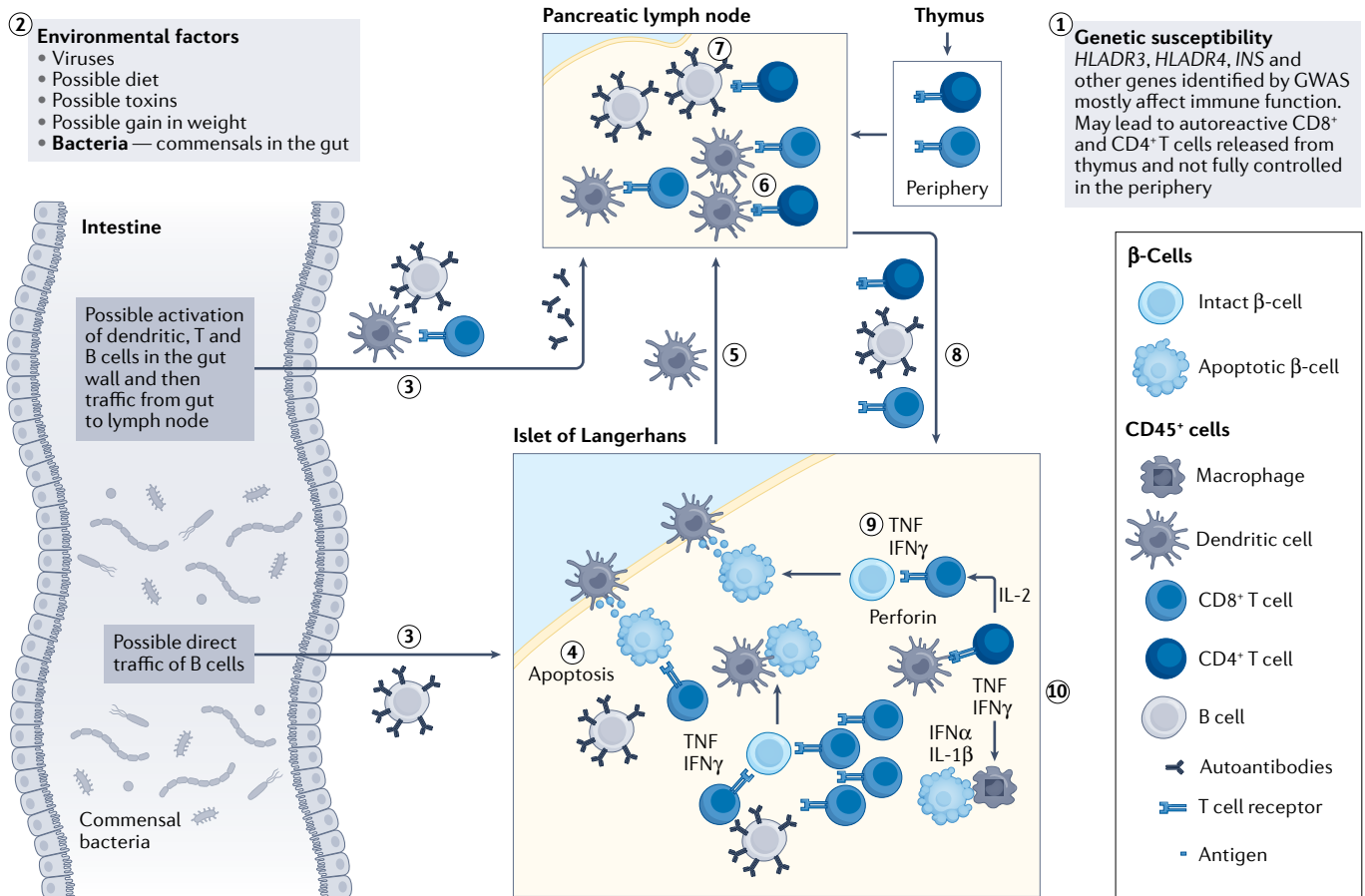
### T lymphocytes

In addition to autoantibodies, other immune manifestations of LADA include the identification of autoreactive T cells, which are reactive to pancreatic autoantigens. Autoreactive CD8<sup>+</sup> cytotoxic cells are a major subset of T cells that can damage islet  $\beta$ -cells, recognizing several target antigens within the islet  $\beta$ -cells that include proinsulin and GAD (FIG. 4). Autoreactive T cells are deleted in the thymus via central tolerance processes, as they recognize self-antigens that are strongly presented in the thymus, which trigger T cell apoptosis<sup>54</sup>. However, if T cells recognize the self-antigens poorly, they may not be deleted but may be released to the periphery. Many autoreactive T cells are weakly reactive to self-antigens, and are not deleted, but when encountering their target antigens, presented by major histocompatibility complex (MHC) molecules, they can become activated and cause

damage<sup>54</sup>. Furthermore, autoreactive T cells may respond to post-translationally modified self-antigens, representing neoantigens that are not presented in the thymus. T cells may recognize these neoantigens as foreign and become activated, possibly causing autoimmunity. These post-translational modifications are potentially linked to  $\beta$ -cell stress<sup>55</sup>. This has been shown for forms of T1DM with a rapid onset and might also occur in a slower-onset autoimmune process. However, in addition to CD8<sup>+</sup> cytotoxic cells, regulatory T (T<sub>reg</sub>) cells also have a role in the regulation of pathogenic cells, and the balance between pathogenic and regulatory cells contributes to the development of autoimmunity. In T1DM, the heterogeneous group of T<sub>reg</sub> cells have been intensively studied, as many T1DM susceptibility loci, including *IL2*, *CTLA4*, *IL10*, *PTPN2* and *IL2RA*, could influence effector T cells as well as T<sub>reg</sub> cells<sup>56–58</sup>. In one subset of CD25<sup>hi</sup>CD4<sup>+</sup> T<sub>reg</sub> cells that originate in the thymus, the transcription factor FOXP3 is used as a marker of CD4<sup>+</sup> T<sub>reg</sub> cells. Using multiparameter flow cytometric analysis to define T<sub>reg</sub> cells, there is no clear evidence that T<sub>reg</sub> cell frequency is changed in T1DM<sup>59</sup>. Instead, the evidence suggests that T<sub>reg</sub> cell function is reduced<sup>59</sup>, and that effector T cells are also less suppressible<sup>60</sup>. Fewer studies have been carried out in individuals classified as having LADA. In a Swedish study, people with LADA treated with diet and oral hypoglycaemic agents had increased peripheral blood CD4<sup>+</sup> T cells expressing various levels of CD25 and the activation marker CD69, together with FOXP3 (REF.<sup>61</sup>). This finding contrasts with an earlier small study indicating downregulation of FOXP3, shown by quantitative PCR<sup>62</sup>. However, function of these cells has not been tested, and caution should be applied to conclusions drawn when studying individuals treated with metformin and dipeptidyl-peptidase 4 (DPP4; also known as CD26) inhibitors (DPP4i), as these may affect T cells. This was shown in a study using sitagliptin in individuals with LADA who demonstrated a reduction in T-bet (T helper 1 (T<sub>H</sub>1)) and RORC (T<sub>H</sub>17), both transcription factors in inflammatory cells<sup>63</sup>. Alterations in T<sub>reg</sub> cell function have not been tested to understand whether this is different in individuals who have slower-onset autoimmunity compared with individuals who have T1DM.

### Gut microbiota

Various studies have examined the gut microbiota in different types of diabetes, revealing differences in gut microbiota species in different geographical areas<sup>64</sup>. Focusing on the functions of bacteria rather than their identity might, therefore, provide more useful insights. Analysis of the gut microbiota in Chinese individuals diagnosed as having LADA, as distinct from those with T1DM or T2DM, revealed differences in the structure and composition of the gut microbiota<sup>65</sup>. Specifically, metagenomic analysis, the study of the structure and function of the genetic material of bacteria, indicated several enterobacterial co-abundance groups in the gut microbiota that differ between diabetes types. The investigators also studied sequences of the bacteria. They demonstrated that these groups of the microbiota differ in abundance, and also that there were



**Fig. 4 | Model for pathogenesis of autoimmune diabetes.** (1) Genetic factors can lead to defective central and peripheral tolerance. Defective central tolerance allows naive islet-reactive CD4<sup>+</sup> and CD8<sup>+</sup> T cells to leave the thymus and migrate to pancreatic lymph nodes. Defective peripheral tolerance alters the function of regulatory T cells, which balance and control potentially pathogenic autoreactive T cells. (2) Environmental factors (such as viral infections or altered commensal bacteria) could activate (3) local T cells and B cells. Activation of T cells and B cells may also occur in the gut. This activation enables their trafficking to pancreatic lymph nodes, or, in the case of activated B cells, trafficking directly to the islets of Langerhans. (4) In the pancreas, several possible mechanisms could lead to the death of  $\beta$ -cells, including a natural process of tissue remodelling, viral infection and endoplasmic reticulum stress owing to high metabolic demand for insulin. Moreover, cytokines produced by infiltrating cells that include macrophages (IL-1 $\beta$  and tumour necrosis factor (TNF)) can contribute to apoptosis. Furthermore, damage of  $\beta$ -cells may occur related to  $\beta$ -cell production of

interferon- $\alpha$  (IFN $\alpha$ ) priming them further for immune cell destruction. These events can lead to apoptosis of  $\beta$ -cells, which releases  $\beta$ -cell antigens. (5) Antigens released from apoptotic  $\beta$ -cells are taken up by dendritic cells, which migrate to the pancreatic lymph node. (6) Dendritic cells present  $\beta$ -cell antigens to naive CD4<sup>+</sup> T cells in the pancreatic lymph node, leading to activation of several possible T helper (T<sub>H</sub>) cell subsets including T<sub>H</sub>1, T<sub>H</sub>2, T<sub>H</sub>17 and T<sub>reg</sub> cells. Dendritic cells also cross-present antigens to CD8<sup>+</sup> T cells in the pancreatic lymph node. (7) CD4<sup>+</sup> cells can help B cell production of autoantibodies that target  $\beta$ -cell proteins. CD4<sup>+</sup> cells may also assist in activation of CD8<sup>+</sup> T cells. (8) Activated T and B cells traffic to the islets of Langerhans. (9) CD8<sup>+</sup> cytotoxic T cell infiltration can induce lysis of  $\beta$ -cells presenting self-antigen, via secretion of perforin, the apoptotic FAS–FASL pathway and inflammatory cytokines. (10) CD4<sup>+</sup> T<sub>H</sub>1 cells secrete pro-inflammatory cytokines IFN $\gamma$  and TNF, which could induce  $\beta$ -cell death and stimulate macrophages to produce reactive oxygen species, TNF and IL-1 $\beta$ . These may augment  $\beta$ -cell death. GWAS, genome-wide association study.

differences in the biochemical and metabolic pathways used. These included downregulation of amino acid (valine, leucine and isoleucine) degradation, as well as downregulated fatty acid biosynthesis in individuals with LADA, compared with healthy control individuals. Furthermore, other metabolic pathways for amino acid, cofactors and vitamins were downregulated in LADA compared with T2DM. However, the presence or absence of GADA and varying medication regimens were also associated with the microbial differences. A decrease in bacteria that produce short chain fatty acids (SCFAs) was noted in individuals with LADA, even more than that found in people with T1DM or T2DM<sup>65</sup>. These SCFAs reduce chronic inflammation,

pancreatic autoimmunity, strengthen gut barriers and alter intestinal hormones; notably, they also improve glucose metabolism and insulin sensitivity<sup>66</sup>. Although these data show correlative rather than causative associations, these observations confirm findings from studies focused on the development of T1DM that have mainly been performed in children, in which it has been possible to identify individuals at high genetic risk and follow birth cohorts<sup>67</sup>. Much additional information has been obtained from The Environmental Determinants of Diabetes in the Young (TEDDY) samples, in which high-risk individuals from six geographical regions were followed from 3 months of age, collecting monthly stool samples together with information on diet, medications,

childhood illnesses and other aspects of life experience, to document environmental, genetic microbial, immunological contributors to T1DM development<sup>67</sup>. Weak associations were observed for some bacteria. However, more important was the loss of functionally protective properties, also relating to fermentation and synthesis of SCFAs in the commensal gut flora, which were lost in those at risk of T1DM who seroconverted to anti-islet autoantibodies. In Chinese individuals with T2DM, a wide range of functional characteristics of the gut microbiome included increased markers of membrane transport of sugars and branched chain amino acids among others, but a decrease in bacterial chemotaxis, biosynthesis of the SCFA butyrate and metabolism of cofactors and vitamins<sup>68</sup>. A study of European women who had T2DM, impaired or normal glucose tolerance, indicated broadly similar results of microbial functions and included enrichment for bacteria involved in glycerolipid metabolism and synthesis of fatty acids<sup>69</sup>. Thus, despite the noted differences, reduction or loss of SCFA-synthesizing bacteria was common in all groups, which may be a key environmental feature influencing both metabolism and immunity.

#### **Immunotherapy-related autoimmune diabetes**

Considerable improvement in clinical outcomes in patients with cancer has been observed with immune checkpoint inhibitors, which include programmed cell death protein 1 (PD1) inhibitors (such as nivolumab or pembrolizumab), programmed cell death 1 ligand 1 (PDL1) inhibitors (such as atezolizumab, avelumab or durvalumab) and cytotoxic T cell-associated protein 4 (CTLA4) inhibitors (such as ipilimumab). However, an increase in immune-mediated adverse events has occurred, including diabetes associated with PD1 or PDL1 inhibitor use<sup>70</sup>. The presentation of diabetes includes fulminant T1DM and diabetic ketoacidosis, occurring with life-threatening illness and deaths<sup>71</sup>. Of note, the fact that these phenomena have been observed in older individuals might be due to these medications being used for cancers in older patients<sup>72</sup>. It is not clear why these immune-related adverse events only occur in some patients but underlying genetic susceptibility to autoimmune disease and the composition of the host microbiota may be contributory<sup>73</sup>. Although some instances of diabetes development have occurred in individuals with pre-existing islet autoantibodies, in others, autoantibodies developed only after treatment or autoantibodies have not been found at all<sup>73</sup>. Rather than a new type of diabetes, these instances may represent an extreme alteration of the regulatory immune cell balance in individuals who have a predisposition to autoimmunity.

#### **Diagnosis, screening and prevention**

##### **Clinical features**

The clinical presentation of AOA diabetes varies depending on insulin dependence at clinical onset of disease and  $\beta$ -cell loss rate over time (rapid versus slowly progressive autoimmune diabetes). Anthropometric indices reported in individuals with LADA vary among ethnic groups and specific clinical features, such as overweight and obesity, reveal time trends in view of the unabated

obesity epidemic<sup>74</sup>. In most studies, people with LADA have a prevalence of metabolic syndrome components (overweight or obesity, high waist-to-hip ratio, hypertension and dyslipidaemia) that is lower than that of people with classic T2DM, but higher than in patients with T1DM<sup>67,75,76</sup>. The level of  $\beta$ -cell dysfunction in LADA is in between T1DM and T2DM<sup>76–79</sup> (FIG. 1). This intermediate clinical status was evident in European cohorts and was confirmed in a large study from the United Arab Emirates<sup>5,7,77,80,81</sup>. However, differences between adults with diabetes testing positive or negative for GADA were less pronounced in other studies including different cohorts, such as drug-naive individuals or Asian populations<sup>82,83</sup>. In this regard, the LADA China study indicated that clinical features varied less between islet cell antibody-negative and antibody-positive individuals compared with what was observed in non-Asian studies<sup>83</sup>. Similarly, a study from Singapore that included a transethnic comparator from Germany showed that, in contrast to Asian individuals, Europeans with diabetes, testing GADA<sup>+</sup> and/or IA2-Ab<sup>+</sup>, had a lower mean BMI compared with antibody-negative participants<sup>84</sup>. Mixed phenotypic features have also been reported in a study from Nigeria, West Africa<sup>85</sup>. Population-based studies reporting incident diabetes cases have better defined the phenotypic spectrum of people with AOA diabetes, confirming that GADA<sup>+</sup> individuals with incident diabetes have a higher frequency of acute symptoms, a lower BMI, a lower waist circumference and are younger at the time of diagnosis than GADA<sup>-</sup> patients<sup>86,87</sup>. C-peptide reserve was more compromised in people with LADA compared with those with T2DM, but people with LADA showed less insulin resistance<sup>87</sup>. Studies from Scandinavia emphasized diabetogenic lifestyle factors, such as higher BMI, smoking and lower level of physical activity, in association with LADA<sup>2,26,33,88</sup>. In addition, in a cross-sectional study from Germany, people with LADA had higher insulin sensitivity indices than matched patients with T2DM and presented with better  $\beta$ -cell functional parameters than patients with T1DM, independently of BMI<sup>78</sup>.

An enhanced rate of functional decline of  $\beta$ -cells is indeed a common clinical feature of LADA compared with T2DM, even though the high variability of the  $\beta$ -cell destruction in longitudinal studies was seen in conjunction with insulin resistance<sup>25,77,81,89,90</sup>. In a large, long-term, observational, population-based study (Genetics of Diabetes Audit and Research in Tayside Study (GoDARTS)), similar to the UK Prospective Diabetes Study (UKPDS), the rate of metabolic deterioration was found to progress twice as quickly in GADA<sup>+</sup> as in GADA<sup>-</sup> individuals with T2DM<sup>81,91</sup>. In addition, poorer glycaemic control with higher glycated haemoglobin (HbA1c) level was found in LADA compared with T2DM in the same cohort<sup>77,92,93</sup>. In the interventional Action to Control Cardiovascular Risk in Diabetes (ACCORD) study, aiming for intensive glycaemic control to lower cardiovascular disease risk, lower levels of C-peptide and islet autoantibody positivity predicted the risk of severe hypoglycaemia during intensification of diabetes treatment, indicating glucose instability as an additional clinical feature of LADA<sup>94</sup>.



Overall, individuals with LADA have a clinical phenotype that differs from that observed in people with classic T2DM and young-onset as well as adult-onset T1DM and MODY (TABLE 1). However, the reported differences need to be carefully considered, as there may be potential bias in study designs, namely selection of more severe clinical cases in centre-based surveys versus individuals identified in population-based studies. In addition, these studies are often limited by small sample sizes. Consequently, generalizability of diabetes-variant specific anthropometric indices may not be helpful for clinical decision making<sup>81,92</sup>. Furthermore, time trends of specific features such as the obesity epidemic and the continuous change in lifestyle risk factors need to be taken into consideration<sup>6,74</sup>.

#### *Interplay of immunological and clinical features.*

Clinical heterogeneity due to ICA levels is also found in LADA. The NIRAD study and others highlighted a bimodal distribution of GADA levels that identified two subpopulations, those with high and those with low GADA levels<sup>20,49,83,95</sup>. In comparison with individuals with LADA who had low GADA levels, those with high levels had more prominent traits of insulin deficiency and a profile of more severe autoimmunity, higher levels of HbA1c, lower BMI and a lower prevalence of metabolic syndrome. Differences in clinical and biochemical features were substantiated by genetic studies showing that the frequencies of HLA genotypes, in particular, the *DR3-DQ2* haplotype but not *DR4-DQ8*, decreased linearly from high to low GADA concentrations<sup>49</sup>. Similarly, the *PTPN22* risk genotype was also associated with high GADA concentrations in patients with LADA<sup>96</sup>. Conversely, the transcription factor 7 like 2 (*TCF7L2*) risk allele for T2DM was associated with low, rather than high, GADA levels<sup>90,97</sup>.

Similarly, differences in clinical features associated with IA2-Ab recognized epitopes were observed. IA2-Ab directed to the construct IA2(256–760)<sup>98–100</sup> is more frequently found in people with LADA who test negative for GADA and who show a phenotype that resembles classic T2DM, with higher BMI and waist circumference, and lower rates of progression towards an insulin-dependent state. Of note, simultaneous positivity to two or more autoantibodies (for example, both GADA and IA2-Ab) is associated with more rapid progression towards insulin therapy and a clinical phenotype more similar to that of younger-onset T1DM, that is, low BMI and low prevalence of other cardiometabolic conditions, such as hypertension or dyslipidaemia<sup>7</sup>. ZnT8As were more common and more persistent in patients with LADA compared with those with adult-onset T1DM, but their presence was not associated with specific clinical characteristics<sup>101</sup>. In addition, patients with adult-onset diabetes who were positive for both GADA and IA2-Ab had lower waist circumference and higher fasting glucose levels than those positive for both GADA and ZnT8A<sup>102</sup>.

#### **Classification and diagnosis**

Misclassification of the diagnosis of classic adult-onset T1DM is rare as it always requires insulin ab initio and frequently presents with metabolic acidosis, but the diagnosis

and classification of non-insulin-requiring autoimmune diabetes remains a matter of debate. To increase awareness and to harmonize diagnostic procedures, in 2005, the Immunology of Diabetes Society (IDS) established three main criteria of LADA, including adult age of onset (>30 years); presence of any ICA; and absence of insulin requirement for at least 6 months after diagnosis<sup>103</sup>.

Other scientific societies have proposed different nomenclature and diagnostic criteria. For example, the Japan Diabetes Society considers “slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM)” for the condition in which the main diagnostic criteria are the presence of GADA and/or ICA at some time during the disease course, absence of ketosis at onset of DM and no need for insulin treatment to correct hyperglycaemia in the first 3 months after diagnosis. Of note, age of disease onset is not used as a criterion<sup>104,105</sup>.

In the WHO classification of diabetes from 2019, LADA has been described as a hybrid form of diabetes characterized as a “slowly evolving immune-mediated diabetes of adults” often with features of metabolic syndrome, presence of GADA as a single autoantibody and greater retained  $\beta$ -cell function<sup>106</sup>. However, the 2019 WHO classification did not provide conclusive criteria, owing to the controversies around classification of LADA as a separate diabetes entity or as a subtype of T1DM.

In 2020, a consensus statement from an international expert panel confirmed the chief IDS criteria for LADA<sup>92</sup>. The panel selected additional measures, such as reduced frequency of metabolic syndrome features in LADA, in addition to lack of disease-specific cardiovascular outcomes compared with classic T2DM. The panel highlighted the quantification of C-peptide serum or plasma levels at baseline and repeated measurements at 6-monthly intervals to reflect the functional  $\beta$ -cell reserve. According to the panel's view, therapeutic response can be predicted by measuring autoantibody levels to various islet cell autoantigens (GADA as the most sensitive marker; other ICA, IA2-Ab, ZnT8A and tetraspanin 7 autoantibodies less frequently) and by evaluating  $\beta$ -cell function<sup>92</sup>.

The most recent 2022 ADA recommendations for classification and diagnosis of diabetes include LADA in T1DM, owing to the autoimmune nature of  $\beta$ -cell destruction<sup>1</sup>. The ADA statement pinpoints a key role for C-peptide testing and its potential role in treatment choices. Overall, the definition of LADA remains a matter of debate.

#### **Differential diagnosis of adult-onset diabetes**

One of the complexities in the diagnostic process is the inherent uncertainty in diagnosing the various diabetes entities. This problem is not confined to LADA, but is also true for other diabetes subtypes that present in adulthood<sup>107</sup>. Usually, diabetes onset in adulthood is classified as T2DM, unless an overt insulinopenic phenotype is present, leading almost immediately to the diagnosis of T1DM. However, this diagnostic bias in people who present with adult-onset diabetes leads to a quite remarkable number of misdiagnoses<sup>92,107,108</sup>. Consequently, LADA and MODY are likewise misdiagnosed as different T2DM subtypes<sup>109,110</sup>. To stratify

Table 1 | Broad clinical features of diabetes subtypes

Features	LADA	Classic or true T2DM	Classic young-onset T1DM	Classic adult-onset T1DM	Carriers of monogenic variants
Age at diagnosis (years)	>30 <sup>a</sup>	Adulthood	<20	>20	Before age 25 or adulthood
Symptoms of manifest hyperglycaemia	Absent or subclinical	Absent or subclinical	Common	Common	Absent or subclinical
Risk of acute complications at diagnosis	Absent or low	Absent or low	Increased	Increased	Absent or low
Presence of ketone bodies at diagnosis	Absent	Absent	Present	Present	Absent
Ketoacidosis	Absent at diagnosis, risk in severely insulinopenic subjects during follow-up	Absent at diagnosis, develops rarely in severely insulinopenic subjects during follow-up	Rapid development unless patients receive insulin treatment	Rapid development in subjects with no C-peptide reserve	Absent
Family history of T1DM	Negative or positive	Absent	Negative or positive	Negative or positive	Negative
Family history of T2DM	Negative or positive	Common	Negative or positive	Negative or positive	Positive
BMI	Normal, overweight, rarely obese	Overweight or obese	Underweight or normal	Normal or overweight	Normal
Insulin resistance at diagnosis	Increased, not as pronounced as in T2DM	Increased	Absent	Absent or increased	Absent or increased
HDL-cholesterol level	Normal	Low	Normal	Normal	Normal
Islet cell antibodies	Positive <sup>a</sup>	Negative	Positive	Positive	Negative
GADA	Positive	Negative	Positive	Positive	Negative
Presence of multiple islet cell autoantibodies <sup>b</sup>	Rarer than in T1DM	Negative	Common	Common	Negative
Insulin requirement at disease onset	None <sup>a</sup>	None	Yes	Yes	None
Partial remission phase <sup>c</sup>	No studies available	Absent	Common	Common	Absent
Insulin requirement during follow-up	Around twice as much as T2DM	Lower rate than LADA	Yes	Yes	Rare <sup>d</sup>
C-peptide at diagnosis	Decreased <sup>e</sup> but detectable	Positive or highly positive	Low or negative <sup>f</sup>	Low or negative <sup>f</sup>	Positive
Non-fasting C-peptide (pmol/l)	≤300 or 300–600, needs follow-up quantification	≥600	≤300	≤300	300–600
C-peptide decline at follow-up	Quicker than T2DM, slower than T1DM	Slow	Rapid	Slower than young-onset T1DM	Slow
Thyroid autoimmunity	Increased	Rate of background population	Increased	Increased	Rate of background population
Type A gastritis and vitamin B <sub>12</sub> deficiency	Increased	Rate of background population	Increased	Increased	Rate of background population
Microvascular complications at diagnosis	Lower rate than for T2DM	Can be already present	Absent	Absent	Absent
Risk of microvascular complications during follow-up	Increased compared with T2DM	Increased	Increased	Increased	Variable, dependent on gene variant
CVD risk at diagnosis	Increased	Increased	Rate of background population	Rate of background population	Rate of background population
CVD risk at follow-up	Identical to T2DM	Increased	Increased	Increased	Variable, dependent on gene variant

CVD, cardiovascular disease; GADA, glutamic acid decarboxylase serum autoantibody. <sup>a</sup>Predefined main Immunology of Diabetes Society (IDS) criterion/ predefined component of latent autoimmune diabetes in adults (LADA); clinical criteria presented are not categorical. BMI: wide-ranging level of indices can be seen in almost all diabetes mellitus subtypes, including LADA, type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). <sup>b</sup>Multiple islet cell-specific antibodies include tyrosine phosphatase IA2 antibody (IA2-Ab), zinc transporter isoform 8 autoantibody (ZnT8A), tetraspanin 7 autoantibodies and insulin autoantibodies (IAA), in particular, in young-onset T1DM. <sup>c</sup>Partial remission (PR), a period experienced by patients with autoimmune diabetes soon after diagnosis, characterized by transient recovery of islet  $\beta$ -cell function resulting in low insulin requirements (<0.5 units/kg of body weight per day) and improved glycaemic control (glycated haemoglobin (HbA1c) between 7% (53 mmol/mol) and 6% (42 mmol/mol))<sup>180,181</sup>. <sup>d</sup>In cases with HNF1A and HNF4A variants, progressive pancreatic  $\beta$ -cell dysfunction. <sup>e</sup>Compared with typical cases of T2DM. <sup>f</sup>Using standard C-peptide assays.

individuals with adult-onset diabetes, the following clinical parameters have been shown to be highly relevant: age at diabetes onset, presence of ketone bodies, HbA1c and glucose levels at onset, BMI, C-peptide measurements to quantify  $\beta$ -cell reserve at diabetes onset as well as during follow-up, and the presence or absence of the various ICAs.

### Management

The overall aim of autoimmune diabetes care is to prevent acute and chronic complications, in particular, ketoacidosis (BOX 1), microangiopathy and macroangiopathy (BOX 2), and to improve life expectancy and quality of life (QoL) of people living with the disease. Clinical guidance for managing AOA diabetes has been provided by recent international consensus statements<sup>92,111</sup>, which detail the clinical recommendations for the complex, multidisciplinary and individualized approach needed for the successful treatment of the condition. This Primer provides an overview of the available data on the efficacy and safety of pharmacological and non-pharmacological strategies tested for the treatment of hyperglycaemia and of  $\beta$ -cell dysfunction in people with AOA diabetes.

### Dietary and lifestyle modifications

The cornerstones of any diabetes therapy are following a healthy diet in terms of variety and amount of nutrients, which can be personalized on the basis of individual preferences, and safely engaging in a combination of aerobic and resistance exercise, considering both acute and long-term beneficial effects on blood glucose levels<sup>111</sup>. Both personalized medical nutrition therapy and physical activity programmes improve oxidative stress, glucose and lipid metabolism, and cardiac fitness, as well as act with many other pleiotropic effects on organs that are negatively affected by diabetes<sup>112–114</sup>. Exercise in particular is associated with improvements in insulin sensitivity, which may lead to reduced insulin requirement, better lipid profile and better endothelial function, decreased inflammatory cytokines and improved cardiovascular health<sup>115–117</sup>. This translates, clinically, into improvements in blood glucose control, weight loss in individuals with overweight or obesity, reduction in cardiovascular risk factors, and decreased morbidity and mortality<sup>118,119</sup>. Nonetheless, the literature on the effects of lifestyle modifications in AOA diabetes is limited. However, it can be reasonably hypothesized that avoiding risk factors such as physical inactivity, overweight, sweetened (with caloric sweeteners) beverages, or low consumption of fatty fish, may help in the management of the disease<sup>111</sup>. Thus, it is recommended that all people with autoimmune diabetes should engage in physical exercise on most days and they should be referred for individualized medical nutrition therapy provided by nutritionists with proven skills in providing diabetes-specific nutritional advice<sup>111</sup>.

### Insulin therapy

Insulin therapy is the most straightforward therapeutic choice in patients with AOA diabetes, as it augments the low levels of endogenous insulin caused by the autoimmune destruction of pancreatic islets, with proven

efficacy for controlling hyperglycaemia, preventing diabetic ketoacidosis and preserving  $\beta$ -cells<sup>111</sup>. However, the correct timing for starting insulin therapy may vary considerably depending on the natural course of the disease, as some people experience an absolute insulin deficiency from the clinical onset of the disease, whereas others maintain adequate  $\beta$ -cell function for decades<sup>77,120</sup> (FIG. 3). In the latter cases, some clinical features (GADA levels, presence of multiple pancreatic autoantibodies, age at onset and BMI) may help to predict the progression towards an insulin-dependent state<sup>7,50</sup>. However, there is a lack of data from randomized, controlled trials with sufficient length of follow-up to draw conclusions about the optimal time to start insulin therapy. In this regard, measurement of C-peptide concentration, which reflects endogenous insulin secretion capacity, may aid in the decision to start insulin in people with AOA diabetes<sup>121</sup> (FIG. 5). In the LADA expert consensus report, three broad categories of C-peptide level were introduced by the panel to determine treatment recommendations: C-peptide levels  $<0.3$  nmol/l, which should recommend a multiple-insulin regimen as for T1DM; C-peptide levels in the 'grey area' of  $\geq 0.3$  and  $\leq 0.7$  nmol/l, in which a modified ADA–EASD algorithm for T2DM is recommended considering insulin in combination with other therapies to modulate  $\beta$ -cell failure and limit diabetic complications; C-peptide values  $>0.7$  nmol/l, which may enable the use of a modified ADA–EASD algorithm as for T2DM but considering the potentially progressive nature of LADA by monitoring C-peptide to adjust treatment<sup>92</sup>. Importantly, a systematic review showed that insulin therapy provides better metabolic control than treatment with sulfonylureas, a class of oral anti-diabetes drugs that stimulate insulin release from the pancreas by binding to and closing ATP-sensitive  $K^+$  channels on the cell membrane of  $\beta$ -cells (mean HbA1c difference  $-1.3\%$  (95% CI  $-2.4$  to  $-0.1$ ;  $P=0.03$ ))<sup>122</sup>. In addition, insulin was found to maintain pancreatic  $\beta$ -cell function better than sulfonylureas in most studies included in the systematic review<sup>122</sup>. Data from a post hoc analysis of the UKPDS suggest that early intensive insulin therapy may be associated with early protection from cardiovascular death in LADA<sup>123</sup>, but these findings need to be confirmed in interventional randomized controlled trials. Overall, insulin, alone or in combination, currently remains the main pharmacological intervention for most people with LADA, with multiple daily injections (basal-bolus schemes) required for people with severe insulin deficiency (C-peptide levels  $<0.3$  nmol/l)<sup>92</sup>. To date, no study has specifically investigated whether insulin dosing should differ between LADA and T2DM; thus, insulin titration strategies might follow those suggested in the ADA–EASD algorithm for T2DM, especially in people with C-peptide levels of  $\geq 0.3$  nmol/l (REF.<sup>92</sup>).

The main adverse effects associated with insulin therapy are hypoglycaemia, body weight gain and skin reactions, such as local inflammation and lipodystrophies. Hypoglycaemia is the most worrisome adverse event of insulin therapy, associated with increased morbidity and mortality<sup>124</sup>. The risk of hypoglycaemic events is particularly high in people with T1DM because  $\alpha$ -cell

## Box 2 | Chronic complications

Chronic complications that may affect people with adult-onset autoimmune (AOA) diabetes resemble those seen with type 2 diabetes mellitus (T2DM), even though the rates and timing of presentation may differ.

**Macrovascular complications**

Up to 2017, no difference in the prevalence of cardiovascular disease between people with latent autoimmune diabetes in adults (LADA) and those with T2DM was found in a systematic analysis<sup>77</sup>. A more recent study showed that a slightly better cardiometabolic profile observed in LADA compared with T2DM translates into a lower incidence of cardiovascular events<sup>123</sup>. This suggests that modifiable cardiovascular risk factors should be addressed in LADA as vigorously as in T2DM.

**Microvascular complications**

Data about the prevalence of microvascular complications, such as diabetic retinopathy and nephropathy, in LADA compared with T2DM<sup>2,77,170</sup> suggest that these complications are rarer in autoimmune diabetes close to diabetes diagnosis, whereas an opposite pattern is seen later in the disease history. This is mainly explained by the usually worse metabolic control obtained during the first years after diabetes onset compared with T2DM<sup>170</sup>, which stresses the importance of promptly recognizing and treating the disease to intensively control blood glucose values as soon as possible. Of note, in the UK Prospective Diabetes Study, the largest longitudinal study with the longest follow-up comparing microvascular complications between LADA and T2DM, only a few microvascular events were kidney events<sup>170</sup>. Thus, no solid conclusions about the rate of nephropathy can be drawn.

Very few data about diabetic neuropathies in AOA diabetes exist. Available data confirm that the risk of developing neuropathy varies according to metabolic control and disease duration<sup>197,198</sup>. The prevalence of cardiac autonomic neuropathy, a frequent, life-threatening and often overlooked complication of diabetes, is similar between people with young-onset diabetes and AOA diabetes, but lower than in those with T2DM<sup>199,200</sup>. No solid data comparing prevalence and features of diabetic foot between LADA and T2DM have been published so far.

dysfunction often associates with  $\beta$ -cell dysfunction, ultimately resulting in an impaired glucagon response to low blood glucose levels<sup>125</sup>. Thus, education of patients on managing insulin doses, correct insulin administration technique, strict self-monitoring of blood glucose values and efficacious correction of hypoglycaemic events is a crucial component of insulin therapy. In this regard, adults with T1DM on insulin therapy may benefit from the implementation of carbohydrate counting, which may help to achieve better HbA1c values<sup>126,127</sup>.

**Non-insulin pharmacological therapies**

Pharmacological therapy other than insulin may be used in people with LADA, either alone or in addition to insulin therapy, depending on the  $\beta$ -cell reserve of the patient<sup>92</sup>. Although there is agreement about the importance of avoiding sulfonylureas in people with LADA owing to an increased risk of hypoglycaemia<sup>128</sup> and worse metabolic control and acceleration of  $\beta$ -cell loss<sup>122</sup>, other agents may be considered, such as insulin sensitizers, drugs that act on the incretin system, amylin analogues and gliflozins. Of note, formal regulatory approval for non-insulin therapy in autoimmune diabetes is lacking for many compounds and varies depending on country. Thus, the prescription of anti-hyperglycaemic therapy other than insulin in people with LADA should be considered individually and will often be off-label prescriptions.

**Insulin sensitizers.** As the prevalence of overweight and obesity in people with autoimmune diabetes is increasing<sup>129</sup>, insulin resistance is also rapidly becoming

an important issue. Insulin resistance has always been considered a key pathological finding among adults with LADA<sup>77,81</sup>. Metformin is the most commonly prescribed insulin sensitizer worldwide and has been shown to improve insulin sensitivity also in youth with T1DM<sup>130</sup>. Although the mechanism of action of metformin has not been completely elucidated, it seems to address insulin resistance mainly by inhibiting the mitochondrial respiratory chain in the liver and leading to activation of 5'-adenosine monophosphate-activated protein kinase (AMPK)<sup>131</sup>. No trial has been conducted specifically in people with AOA diabetes, nor has metformin been approved by regulatory agencies for use in autoimmune diabetes. The good safety profile and low cost of metformin, as well as the need to address insulin resistance in an increasing proportion of patients, have led to increasing off-label use of this drug as adjunctive therapy in adults with autoimmune diabetes.

Thiazolidinediones, such as rosiglitazone and pioglitazone, are insulin sensitizers that work as peroxisome proliferator-activated receptor- $\gamma$  (PPAR $\gamma$ ) agonists<sup>132</sup>. Two studies tested rosiglitazone in people with slowly progressive autoimmune diabetes, suggesting a potential benefit of thiazolidinediones in preserving  $\beta$ -cell function<sup>133,134</sup>. However, this observation is limited by the small sample size of the available studies and should be balanced with potential risks of bone fractures, macular oedema and weight gain, and with the known limited efficacy of thiazolidinediones in lean patients<sup>135</sup>. Another small study in ten patients with LADA showed faster disease progression in those treated with pioglitazone alone compared with those treated with metformin alone<sup>136</sup>.

**Glucagon-like peptide 1 receptor agonists.** Glucagon-like peptide 1 receptor agonists (GLP1-RAs) are pharmacological analogues of the incretin hormone GLP1 used for the treatment of T2DM. The relevance of this drug class in the therapeutic algorithm of T2DM has increased because of the strong evidence of its metabolic and cardiovascular benefits<sup>137</sup>. As incretin hormones were shown to reduce apoptosis of human  $\beta$ -cells in vitro<sup>138</sup>, GLP1-RAs were hypothesized to ameliorate or preserve endogenous insulin secretion in people with autoimmune diabetes. In a phase II trial in adults with new onset autoimmune diabetes and residual  $\beta$ -cell function, liraglutide slowed  $\beta$ -cell decline when used in combination with anti-IL-21, but no benefits were found with liraglutide alone<sup>139</sup>. In a randomized 52-week phase II trial using albiglutide in newly diagnosed AOA diabetes, no appreciable preservation of  $\beta$ -cell function was observed<sup>140</sup>.

Nonetheless, GLP1-RAs might still improve metabolic control in people with LADA, as suggested by a pooled post hoc analysis of the AWARDS-2, AWARDS-4 and AWARDS-5 trials, which showed that dulaglutide was as effective in reducing HbA1c values in participants with adult-onset diabetes testing positive for GADA as in those testing negative<sup>141</sup>. Of note, insulin-treated patients were excluded from AWARDS-2 and AWARDS-5, and patients on more than three daily insulin injections were excluded from AWARDS-4, suggesting that results of this post hoc analysis are restricted to people with limited insulin deficiency. Indeed, a reduced glycaemic

response to liraglutide and exenatide was shown in a small sample of people with AOA diabetes ( $n = 20$ ), mostly with low C-peptide levels and on insulin treatment, compared with T2DM<sup>142</sup>. In summary, GLP1-RAs may be an attractive opportunity to aid the treatment of people affected by LADA, especially for those with a certain amount of residual  $\beta$ -cell function.

**CD26/dipeptidyl-peptidase 4 inhibitors.** DPP4i (also known as gliptins) are oral compounds currently approved for the treatment of T2DM. DPP4i act on the

incretin system by reducing the activity of DPP4, the enzyme responsible for the degradation of GLP1 and GIP<sup>143</sup>. Owing to the potential effects of incretin hormones on  $\beta$ -cell survival, gliptins have been tested in LADA with the aims of both preserving  $\beta$ -cells and ameliorating glycaemic control. Sitagliptin, saxagliptin and linagliptin are the three most studied DPP4i in people with LADA. Overall, studies conducted so far show that gliptins are generally well tolerated and, in some cases, effective in lowering blood glucose levels<sup>144–146</sup>. Data about a potential role for DPP4i in preserving  $\beta$ -cell

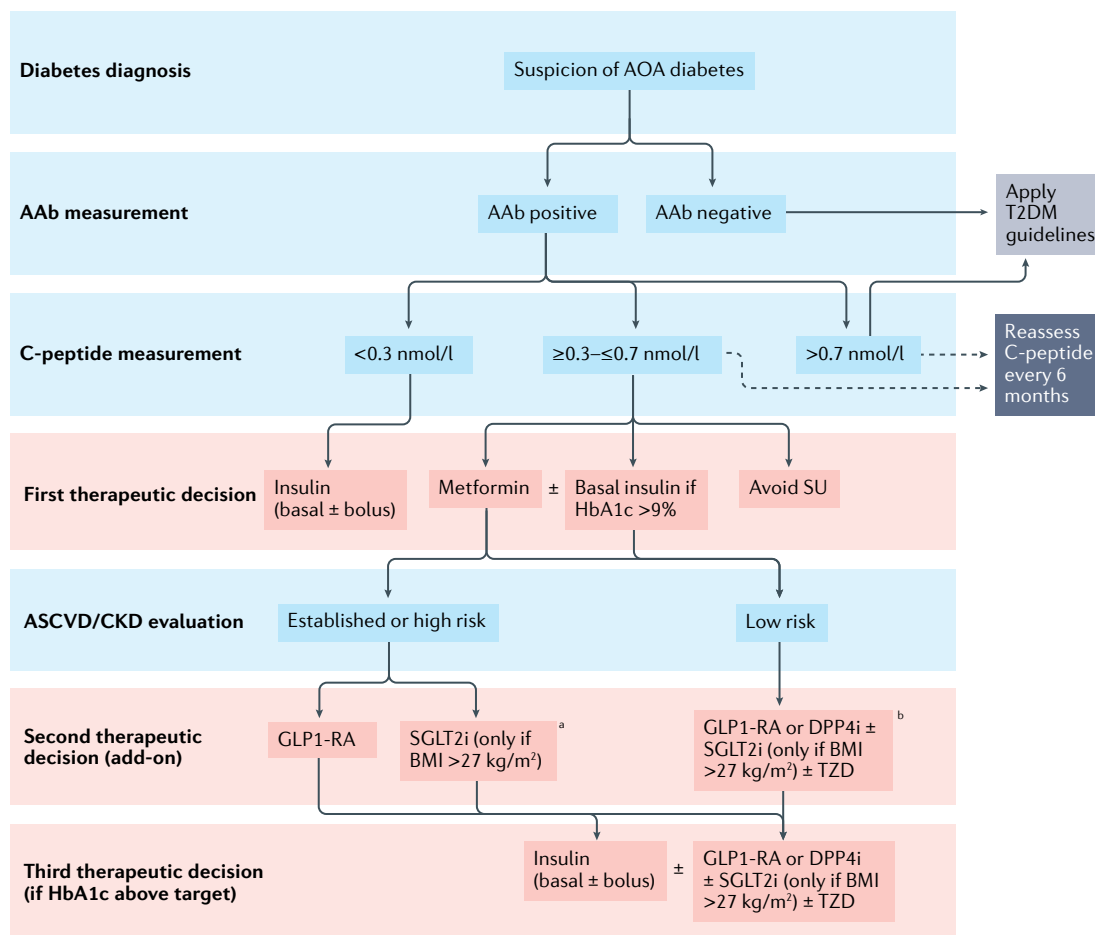


Fig. 5 | **Diagnostic and therapeutic algorithm for LADA**<sup>92</sup>. After diabetes diagnosis, islet autoantibodies (AABs) may be measured in adults with clinical features suspicious of autoimmune diabetes. Measurement of random C-peptide concentration may then aid in the decision to start insulin in people with adult-onset autoimmune (AOA) diabetes. Insulin therapy is essential in all patients with C-peptide levels  $<0.3$  nmol/l, who often require multiple daily insulin injections. Conversely, the decision to start insulin therapy may be delayed in people with C-peptide levels  $>0.3$  nmol/l, who should be periodically reassessed to reconsider insulin requirement. Specifically, in people with AOA diabetes and C-peptide levels  $>0.7$  nmol/l therapeutic strategies may be chosen according to the proposed algorithms for the treatment of type 2 diabetes mellitus (T2DM), while a slightly different algorithm may be used in people with C-peptide levels  $\geq 0.3$  to  $\leq 0.7$  nmol/l, who might benefit from early introduction of basal insulin, especially if glycated haemoglobin (HbA1c) is  $>9\%$ . In these patients, glucagon-like peptide 1 receptor agonists (GLP1-RAs) or sodium–glucose cotransporter 2 inhibitors (SGLT2i) may be suggested in a second therapeutic step, especially in the presence of established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD). DPP4i, dipeptidyl-peptidase 4 inhibitors; SU, sulfonylurea; TZD, thiazolidinedione. <sup>a</sup>In this regard, the use of SGLT2i should be considered with caution in people with AOA because of the increased risk of diabetic ketoacidosis found in studies of type 1 diabetes mellitus (T1DM). Of note, formal regulatory approval for non-insulin therapy in AOA is lacking for many treatments and varies depending on country. Several regimens of insulin therapy can be used when needed. Basal insulin is administered to control hepatic glucose output and ketone production when fasting, whereas insulin bolus doses may be necessary to cover meals and to correct hyperglycaemic episodes. <sup>b</sup>In alphabetical order; preference for one drug instead of another should be based on clinical judgement.



viability and function are conflicting. Small clinical trials from China suggest that sitagliptin may maintain  $\beta$ -cell function over time<sup>147,148</sup>, altering the predominant phenotype and the balance of various T cell subsets<sup>63</sup>. Similarly, saxagliptin was associated with improvements in markers of  $\beta$ -cell function alone or in combination with vitamin D<sub>3</sub> (REFS.<sup>145,149</sup>). By contrast, sitagliptin did not result in better endogenous insulin secretion compared with insulin treatment in a Scandinavian 21-month randomized trial in adults with recent-onset LADA without clinical need for insulin treatment<sup>150</sup>.

**Sodium–glucose cotransporter 2 inhibitors.** Sodium–glucose cotransporter 2 inhibitors (SGLT2i; also known as gliflozins) improve blood glucose concentrations by inhibiting the reabsorption of glucose in the renal proximal tubule, which leads to increased glucose excretion in the urine. Although approved for the treatment of T2DM, the insulin-independent mechanism of action has led to a hypothesis that these drugs might also help in ameliorating metabolic control in people with autoimmune diabetes. As the DEPICT and the InTandem clinical trials programme showed improvements in glycaemic control associated with the use of dapagliflozin and sotagliflozin, respectively, in adjunction with insulin in adults with T1DM<sup>151–153</sup>, both drugs were approved by the EMA as adjunctive therapy in addition to insulin for the treatment of people with T1DM and a BMI of  $\geq 27$  kg/m<sup>2</sup> and uncontrolled blood glucose. The Pharmaceutical and Medical Devices Agency (PMDA) in Japan also approved dapagliflozin and ipragliflozin<sup>154</sup> for the treatment of people with T1DM in adjunction with insulin. However, market authorization of SGLT2i for the treatment of autoimmune diabetes was rejected by the FDA because of an increased risk of diabetic ketoacidosis. In 2021, the EMA-approved indication of dapagliflozin in T1DM was also withdrawn by the pharmaceutical company AstraZeneca because post-approval product information changes for dapagliflozin specific to T1DM were thought to cause confusion among physicians treating patients for other approved indications (T2DM, heart failure and chronic kidney disease), despite there being no new safety or efficacy concerns<sup>155</sup>. The risk–benefit ratio associated with the use of SGLT2i in people with T1DM can be improved by careful patient selection and education, use of lower SGLT2i drug doses, avoidance of drastic reduction of insulin doses and use in the subgroup of patients with BMI  $\geq 27$  kg/m<sup>2</sup> (REFS.<sup>156,157</sup>). Thus, although no clinical trials have been specifically conducted in LADA, gliflozins might be an attractive therapeutic option for people with this form of autoimmune diabetes, who often retain a certain number of functioning  $\beta$ -cells and are more often affected by concomitant overweight or obesity.

**Pramlintide.** The amylin analogue pramlintide suppresses glucagon secretion and delays gastric emptying, resulting in benefits in glycaemic control and body weight<sup>158</sup>. The drug is FDA approved for patients with T1DM and T2DM who receive insulin therapy. As its efficacy has not been separately reported in LADA, no specific recommendations for this group of patients can be made.

### Immunomodulatory drugs

Several immunomodulatory drugs, including non-antigen-specific immunomodulators (such as CTLA4 immunoglobulin, IL-1 and IL-6 receptor antagonist, anti-TNF, anti-CD20 and anti-CD3 monoclonal antibodies, tyrosine kinase inhibitors) and antigen-specific immunotherapies (such as the alum-formulated recombinant GAD, GAD–alum) alone or in combination with other agents, have been tested to improve immune dysregulation and to induce immune tolerance in T1DM<sup>159,160</sup>. Most results from immune intervention trials did not show long-term efficacy in T1DM and, to date, no immunotherapy is available to cure autoimmune diabetes.

The milder rate of  $\beta$ -cell loss and the higher prevalence of residual endogenous insulin production often seen in people with adult-onset, compared with young-onset, autoimmune diabetes could make AOA diabetes an attractive setting for immunomodulatory drugs. In a small phase II placebo-controlled immune intervention trial conducted in individuals with LADA, GAD–alum was used to induce immunotolerance in GADA<sup>+</sup> non-insulin-requiring patients, showing a good safety profile with evidence of a beneficial effect on  $\beta$ -cell function<sup>161</sup>. Another phase II trial suggests that the tyrosine kinase inhibitor imatinib could help in preserving  $\beta$ -cell function in adults with recent-onset T1DM, although questions related to the ideal dose, duration of therapy and safety remain to be resolved<sup>162</sup>.

### Quality of life

Health-related QoL assessment attempts to capture subjective perception and assessment of the individual's health and well-being. To date, QoL assessments in AOA diabetes have been limited. Fortunately, QoL instruments are increasingly being included in new trials evaluating diabetes interventions as they may be used in health-care policy and coverage decisions. Tools that have been applied to the adult-onset population include the Audit of Diabetes-Dependent Quality of Life (ADDQoL-19) questionnaire and the Diabetes Treatment Satisfaction Questionnaire (DTSQ)<sup>163,164</sup>. QoL in all forms of diabetes may depend on many sociodemographic and clinical factors. Complications related to the disease, treatment modalities — in particular insulin use — and the co-occurrence of obesity may considerably lower the QoL in patients with diabetes<sup>165,166</sup>. Multiple studies in broad T1DM populations, including paediatric T1DM, have observed that QoL and treatment satisfaction are lower with increasing age, female sex, lower education level, insulin treatment and obesity, presence of diabetic comorbidities, poorer glycaemic control and lower socioeconomic status<sup>165–167</sup>.

Important in understanding QoL is treatment satisfaction, a subjective measure that assesses one's experience of treatment including ease of use, adverse effects and efficacy. Treatment satisfaction is also influenced by demographic characteristics such as age, educational level and income<sup>168</sup>. In those characterized as having LADA, hypertension, longer disease duration and a larger waist circumference have been associated with lower diabetes-specific treatment satisfaction QoL<sup>168</sup>.

Diagnosis	Natural history	Pathophysiology	Interventions
<ul style="list-style-type: none"> <li>Improved assays of autoimmunity</li> <li>Evaluation of <math>\beta</math>-cell capacity</li> <li>Better classification models and decision support tools</li> <li>Appropriate screening and/or diagnosis and health-care provider awareness</li> </ul>	<ul style="list-style-type: none"> <li>Cohorts with more definitive diagnosis and less misclassification</li> <li>Studies in racially diverse groups</li> <li>Evaluations of <math>\beta</math>-cell capacity and stress</li> <li>Understanding risks and burdens of complications</li> </ul>	<ul style="list-style-type: none"> <li>Mechanistic studies of aetiology</li> <li>Mechanistic studies of complications</li> <li>Phenotype–genotype studies</li> </ul>	<ul style="list-style-type: none"> <li>Disease-modifying therapies</li> <li>Effect of non-insulin therapies</li> <li>Post-diagnosis education and support</li> </ul>

**Fig. 6 | Priorities to address gaps in understanding of adult-onset autoimmune diabetes.** Adult-onset autoimmune (AOA) diabetes is a heterogeneous disease. This heterogeneity is likely a result of different pathological mechanisms, which have implications for treatment. Several gaps remain in accurate diagnosis and treatments for AOA diabetes, and knowledge of the natural history and underlying pathophysiology of this disease.

Individuals with insulin-treated LADA have a worse average weighted impact score compared with corresponding non-insulin-treated patients with T2DM. To determine the average weighted impact score, the impact of diabetes on each domain is weighted according to the importance of the domain to the patient's QoL. The presence of diabetic retinopathy, longer disease duration, lower education level (less than primary education) and former smoking also had a negative effect on the average weighted impact score<sup>168</sup>.

People with LADA, diabetic retinopathy and insulin treatment had a lower QoL than any other combination of diabetes type, retinopathy status and insulin treatment. Furthermore, insulin-treated LADA patients who did not have diabetic retinopathy had a lower QoL than non-insulin-treated patients with T2DM<sup>168</sup>. Perception of increased hyperglycaemia frequency was found to be higher in the LADA group (87.5%) than in the T2DM group (53.9%) and also, surprisingly, than in the T1DM group (71%;  $P < 0.001$  and  $P = 0.039$ , respectively). Comparing insulin-treated subgroups, people with LADA treated with insulin had a higher perception of hyperglycaemia frequency than those who had T1DM ( $P = 0.04$ ) and those who had insulin-treated T2DM ( $P = 0.05$ )<sup>168</sup>. The higher blood glucose values often translate to an increased risk of complications, especially microvascular<sup>169,170</sup>, which in turn may have QoL implications (BOX 2).

### Outlook

AOA diabetes likely encompasses different endotypes with phenotypes ranging from classic rapidly progressing T1DM with onset in adult life to LADA. There are many gaps in our understanding of AOA diabetes and the selection of optimal treatment approaches (FIG. 6). The absence of unambiguous, standardized definitions of subtypes such as LADA is one of the most vexing problems. Although the ADA does not formally recognize LADA as a specific type of diabetes, but instead includes all forms of diabetes mediated by autoimmune  $\beta$ -cell destruction under the category T1DM, other societies propose different definitions to reflect the slower disease progression often observed in AOA diabetes<sup>106,171</sup>. In fact, the 2020 International Consensus on LADA found it challenging to define categorical

immunogenetic and phenotypic features of LADA<sup>92</sup>. With different definitions used in the literature, defining potentially different subgroups makes it difficult to compare the results of various studies of adult-onset diabetes owing to the differences in inclusion criteria and the heterogeneity of the phenotypes of those enrolled.

The measurement of only one autoantibody, using assays with low specificity in populations with low prevalence of autoimmune diabetes, can lead to patients with T2DM who test false positive for the autoantibody being grouped with those who have true autoimmune diabetes. This could result in misleading findings of an intermediate phenotype by combining two populations with very different phenotypes rather than the existence of a true intermediate phenotype<sup>15</sup>. Findings for such a hypothesis include a study that reported a more T1DM-like phenotype in a German population with multiple autoantibodies and an inverse correlation between number of antibodies and markers of metabolic syndrome<sup>172</sup>. A similar finding was made in a population in China, in which those with high levels of GADA had poorer  $\beta$ -cell function and fewer diabetic complications than those with low GADA levels, who were similar to patients with T2DM, except that they were prone to develop ketosis more frequently<sup>173</sup>. In a Japanese population, an inverse correlation of metabolic syndrome with increasing GADA quartile was observed<sup>174</sup>. Standardization of definitions, implementation of a diagnostic decision tree and other improvements in the diagnostic approach to subtypes of AOA diabetes should greatly improve classification among adult-onset subtypes of diabetes. Classification could be aided by using both autoantibodies and C-peptide<sup>92</sup>. Autoantibodies with standardized assays include GADA, IA2-Ab, IAA and ZnT8A, with GADA being the most prevalent autoantibody among adults, even in China where GADA is less dominant<sup>175</sup>. High levels or the presence of more than one autoantibody increase the likelihood of autoimmunity<sup>15</sup>. These autoantibodies have all been well characterized for disease prediction in young-onset T1DM, but the relative role in diagnosis and prognostic value of ZnT8A and insulin autoantibody in AOA diabetes has not yet been thoroughly studied.

In addition, different GADA and IA2-Ab assays may skew towards different epitope reactivities, which has implications in identifying affected individuals. False positive results with autoantibody assays can occur and are reduced by using higher-specificity assays, such as N-terminally truncated GADA, using higher titre thresholds or only testing in higher prevalence populations by restricting testing to those with clinical features suggestive of T1DM<sup>15</sup>. It remains unclear how best to screen for autoimmunity in adults diagnosed with diabetes, and the clinical implications of identifying such individuals have not yet been elucidated either.

A prediction model for diabetes classification that combines clinical features, islet autoantibody test results (GADA and IA2-Ab), and genetic risk score is under development<sup>176</sup>. However, it is currently only applicable to patients aged 18–50 years at diagnosis and of white European origin.

Most commonly, autoimmunity is identified in diabetes using autoantibodies, but T cell assays may provide information to further define individuals with adult-onset diabetes<sup>177,178</sup>. In patients diagnosed as having T2DM, measurable T cell responses are associated with lower stimulated<sup>177</sup> and fasting<sup>178</sup> C-peptide levels. However, T cell reactivity in autoantibody-negative individuals is unexpectedly high<sup>177,178</sup>, indicating that further work is required to elucidate the underlying mechanisms of these associations.

By comparison with paediatric studies of T1DM, few large studies of AOA diabetes have been conducted. Most AOA diabetes studies have focused on North America, Europe and China. Thus, racial and ethnic diversity in the study of AOA diabetes needs to be increased. Large, well-defined cohorts are needed to better understand the subtypes, natural history, disease burden and complications of this disease.

Finally, specific studies of disease-modifying therapies in AOA diabetes are required. As disease progression

tends to be more rapid in young individuals with T1DM<sup>179</sup>, it is believed to be easier to show response to immune interventions in young individuals, as the effect of the change should be large compared with placebo, over a relatively short period of time. This has diminished interest in studying interventions in AOA diabetes, and this population is often used to show safety before initiating paediatric diabetes studies, instead of performing the large and long studies in the adult population that would be required to clearly demonstrate benefit. Even in these studies, inclusion is often restricted to the subset of individuals treated with exogenous insulin. Similarly, non-insulin diabetes therapies have mostly been studied in the larger, more readily recruited, T2DM populations. Although autoantibody-positive subgroup analysis has occasionally been reported from these large T2DM trials, more randomized controlled comparative trials of therapeutic agents in AOA diabetes are still required.

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#### Author contributions

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#### Competing interests

R.B. declares consulting for Sanofi, Novo Nordisk and Eli Lilly; and receiving honoraria for speaker bureaux from AstraZeneca and Abbott. J.G. declares consulting for Vertex Pharmaceuticals, Inc., Dompé farmaceutici and Avotres, Inc. E.M. declares consulting for Merck KGaA and PikDare; and receiving honoraria as speaker from Abbott. R.D.L., F.S.W. and B.O.B. declare no competing interests.

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