Adult-onset autoimmune diabetes

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Abstract

Adult-onset autoimmune diabetes pathophysiology starts with immune changes, followed by dysglycaemia and overt disease. Adult-onset autoimmune 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 slow-progressing form with late onset, a long period not requiring insulin, and 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 adult-onset autoimmune diabetes aims to prevent complications, and to improve quality 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 adult-onset autoimmune diabetes is challenging. Most of the trials testing disease-modifying therapies for autoimmune diabetes are conducted in people with a 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 adult-onset autoimmune diabetes are needed.

[H1] Introduction

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 a 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[1]. In broad terms, individuals presenting 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 presenting 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 5 different phenotypic groups in which those phenotypes presenting with islet-specific autoantibodies are classified together as severe autoimmune diabetes (SAID)[2]. 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[3].

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 β cell destruction is highly variable, probably due to differential presence of genetic factors and differing severity of the individual autoimmune process[4,5].

Epidemiological studies have highlighted that most patients with AOA diabetes do not require insulin treatment at diagnosis[6,7], 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[1]. 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 understanding and suggestions for future priorities of AOA diabetes, which is too often misdiagnosed.

[H1] Epidemiology

[H2] Prevalence and incidence

The prevalence of T1DM and T2DM has been increasing, with the International Diabetes Federation counting more than 500 million people worldwide living with diabetes in 2021[8]. The global prevalence of T1DM is ~0.1%, 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. i.e. those with LADA, can be initially misclassified as having T2DM. In contrast to the epidemiology of well characterised 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[9]. Nonetheless, current projections show that most new cases of autoimmune diabetes are diagnosed during adulthood[6,10]. 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[11]. Overall, the incidence of adulthood-onset T1DM is higher in Europe, especially in Nordic countries, than in Asia or Africa, and T1DM more prevalent in men than in women[10]. 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 industrialisation associated factors such as pollution and overcrowding, might have a role[12].

A study in a European adult-onset diabetes cohort suggests that non-insulin requiring T1DM, that is LADA, can be up to three-fold more prevalent than insulin-dependent T1DM: 9.7% of patients had autoimmune diabetes and most of these (odds ratio 3.3) were initially non-insulin dependent[6]. Other 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[2,6,7] . These individuals, reclassified as having LADA, account for 2-11% of the whole population with T2DM, with frequencies varying by region **(FIG.2)**.

Two factors constrain the epidemiological data available . First, the error to assume that those presenting with diabetic ketoacidosis **(Box 1)** have T1DM might be as high as 50% and can especially occur in adult-onset cases[13,14]. Second, immune markers of T1DM lack specificity. For example,

using glutamic acid decarboxylase (GAD) serum autoantibody (GADA) detection essays 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[15]. 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, e.g. GAD N-terminal truncation, or using high affinity assays, e.g. electrochemiluminescence and bridging-type ELISA[16-18]. 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 celiac disease and autoimmune gastritis) develop more frequently in T1DM than in T2DM[19], which has also been confirmed in LADA[20,21].

[H2] Risk factors for LADA

About half of inheritable childhood-onset T1DM is attributed to variation in human leukocyte antigen (HLA) alleles but, in adult-onset cases, that heritability is much lower with lower twin concordance rates, lower high-risk HLA heterozygosity, lower HLA Class I risk and higher frequency of protective HLA alleles[5,22]. As a result, although genetic risk scores have been developed to aid the discrimination between T1DM and T2DM[23], the altered and reduced genetic risk in adult-onset T1DM has not been shown to be predictive[24]. 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 has increased substantially. By implication, non-genetic factors may be common to both forms of diabetes[25,26]. A Norwegian study indicated a strong effect of a family history of diabetes as a risk factor for LADA[25]. The presentation of LADA was associated with increased bodyweight, 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[27,28]. Metabolic syndrome, a proxy for insulin insensitivity and overweight, can be identified in ~85% of cases with T2DM and in ~40% of those with adult-onset T1DM[29]. 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[30].

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

In addition, in one study, a healthy lifestyle (BMI <25 kg/m², moderate-to-high physical activity, a healthy diet, no smoking and moderate alcohol consumption) was found to have a possibly positive effect on the risk of LADA development as well as on T2DM presentation; BMI <25 kg/m² conferred the largest risk reduction for both LADA and T2DM[28]. These important observations may potentially provide guidance for preventive measures in future interventional trials.

[[H1] Mechanisms/pathophysiology

The pancreas comprises an exocrine portion consisting of acinar cells, which secrete digestive enzymes (amylase, digesting 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[34]. These islands comprise 70% of β-cells, which secrete insulin and amylin, glucagon-secreting α-cells,), somatostatin-secreting δ-cells, ghrelin-secreting ε-cells and PP cells, which secrete pancreatic polypeptide.

In addition to active insulin, β-cells secrete C-peptide, a peptide that is cleaved from the larger molecule pro-insulin and used to measure endogenous production of insulin. In autoimmune diabetes, β-cells are the predominantly affected cell type, undergoing damage by the immune system, although other endocrine and exocrine cells may also be affected[35].

[H2] 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[36]. 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 interact with environmental factors, but the precise contribution of the components of this interaction, and the nature of this interaction is not fully understood. This period is followed by dysglycaemia and finally symptomatic diabetes, when β-cell function is insufficient to maintain glucose metabolism, leading to symptoms of diabetes. In this model, relating to staging of autoimmune diabetes[36], 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, rather than a precise cut off that would be designated T1DM.

[H2] Islet pathology

In individuals with either T1DM or T2DM, pancreatic mass is reduced[37]. 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[37], the I^2 measure of heterogeneity between studies assessing pancreatic volume by ultrasonography, CT and MRI is large, and quantification of the reduction varies between 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+2.5 cm^3), compared with control individuals (69.6+2.2 cm^3). However, this reduction was less than in individuals with classic adult-onset T1DM (47.7+2.7 cm^3)[38] . A post mortem study of pancreas pathology in individuals diagnosed with T2DM found reduced β cell mass in those positive for islet autoantibodies or HLA genotypes HLADR3 or HLADR4 (high risk for autoimmune diabetes) compared with those negative for autoantibodies[39]. These observations suggest a 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 insulitis. Insulitis is defined as lesions with ≥15 $CD45^+$ cells, indicating the presence of haematopoietic cells and inflammation, immediately adjacent to islet endocrine cells in a minimum of 3 islets[40]. Insulitis is uncommon in people presenting with AOA diabetes and was reported in only 29% of those aged 15-40, studied within a month of diabetes onset[34]. Even in younger individuals presenting with T1DM, the pathological manifestation of insulitis is heterogeneous and there is a distinct difference in both frequency and type of $CD45^+$ immune cells found in the islets of individuals <7 years of age presenting with T1DM compared with older individuals. The $CD45^+$ immune cells in those with T1DM are $CD8^+$ cytotoxic T cells and $CD20^+$ B cells, although other immune cell types, such as macrophages, dendritic cells and $CD4^+$ T cells, have also been observed. $CD8^+$ T cell cytotoxicity can take a number of forms, including direct damage of insulin-producing cells and indirect damage due to the production of inflammatory cytokines, which include IFN-γ, TNF-α, IFN-α and IL1-β, and induction of apoptosis; however, it is not clear in humans which mode of death is most prominent. The role of the $CD20^+$ 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[41] in those presenting at <7 years of age compared with those > 13 years of age, who generally have more insulin-containing islets and less insulitis. However, even for those who have had T1DM for many years, some islets may not be affected. This heterogeneity, where there may be greater numbers of insulin-containing islets and also fewer islet that display insulitis is more pronounced in older individuals. The presence of insulitis and greater loss of insulin within the islets occurs suggests immune destruction of the β 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 insulitis[35]and demonstrates not only that β-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 interleukin 2 (IL-2) radiolabeled with technetium-99m (99mTc) confirmed that activated T cells infiltrate the pancreas in those with LADA, indicating the presence of insulitis in both T1DM and LADA[42]. In addition, heterogeneous islet infiltration with predominantly $CD8^+$ T cells and macrophages was observed in pancreas samples of individuals with LADA, similar to individuals with older age onset T1DM[43]. Of note, a T cell response may also occur in the absence of the classic islet autoantibody markers of pancreatic autoimmunity[44]. This condition, termed T-LADA, seems to be characterized by a more rapid β-cell functional decline than T2DM, despite the absence of known islet autoantibodies[45]. Indeed, although LADA is routinely diagnosed by detecting islet autoantibodies, these are markers of immune activity only and not the effectors of β-cell destruction, which is mainly caused by islet antigen-specific $CD4^+$ and $CD8^+$ T cells.

In addition, pancreatic tissue from individuals with T1DM shows evidence of enteroviral infection[46,47], as well as increased expression of MDA5, a viral sensor in α-cells and β-cells of the pancreas[48]. 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.

[H2] Autoantibodies

Islet autoantibodies act as immune activity markers and their detection can help to distinguish an autoimmune from a non-autoimmune type of diabetes. Islet autoantibodies detected with standardized assays include GAD autoantibodies (GADA), tyrosine phosphatase IA2 antibodies (IA2-A), zinc transporter isoform 8 autoantibody (Znt8A), and insulin autoantibody (IAA)[1]. Individuals with higher levels of GADA show a greater loss of insulin secretory capacity and present with clinical features similar to childhood T1DM, such as a higher prevalence of other autoimmune disorders[49-51]. 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 recognising middle and COOH-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 NH2-terminal reactive GADA[52]. Similarly, immunoreactivities against different IA2 protein domains characterize distinct LADA phenotypes: IA2-A 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[53].

[H2] 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 $CD8^+$ cytotoxic cells are a major subset of T cells that can damage islet β cells, recognising a number of target antigens within the islet β cells that include proinsulin and GAD **(Fig. 4)**. Autoreactive T cells are deleted in the thymus via central tolerance processes, as they recognise self-antigens that are strongly presented in the thymus, which trigger T cell apoptosis[54]. However, if T cells recognise the self-antigens poorly, they may not be deleted but 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 MHC molecules, they can become activated and cause damage[54]. Furthermore, autoreactive T cells may respond to post-translationally modified self-antigens, representing neoantigens that are not presented in the thymus. T cells may recognise these neoantigens as foreign and become activated, possibly causing autoimmunity. These post-translational modifications are potentially linked to β cell stress[55]. This has been shown for forms of T1DM with a rapid onset and might also occur in slower-onset autoimmune process. However, in addition to $CD8^+$ cytotoxic cells, regulatory T (Treg) 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 Treg cells have been intensively studied, as many T1DM susceptibility loci that include *IL2, CTLA4, IL10, PTPN2* and *IL2RA* could influence effector T cells as well as Treg cells[56-58]. In one subset of $CD25^{hi}CD4^+$ Treg cells originating in the thymus, the transcription factor FOXP3 is used as a marker of $CD4^+$ Tregs. Using multiparameter flow cytometric analysis to define Tregs, there is no clear evidence that Treg frequency is changed in T1DM[59]. Rather, the evidence suggests that Treg function is reduced[59], and that effector T cells are also less suppressible[60]. Fewer studies have been done in

individuals classified as having LADA. In a Swedish study, people with LADA treated with diet and oral hypoglycaemic agents had increased peripheral blood $CD4^+$ T cells expressing various levels of CD25 and the activation marker CD69, together with FOXP3[61]. This finding contrasts with an earlier small study indicating downregulation of FOXP3, shown by qPCR[62]. 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) inhibitors, 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 (TH1) and RORC (TH17), both transcription factors in inflammatory cells[63]. Alterations in Treg function have not been tested to understand whether this is different in individuals who have slower onset autoimmunity compared with individuals who have T1DM.

[H2] Gut microbiota

Various studies have examined gut microbiota in different types of diabetes, revealing differences in gut microbiota species in different geographical areas[64] Focusing on the functions of bacteria rather than their identity might, therefore, provide more useful insights. Analysis of gut microbiota in Chinese individuals diagnosed as having LADA, as distinct from those with T1DM and T2DM, revealed differences in the structure and composition of the gut microbiota[65]. Specifically, metagenomic analysis, the study of the structure and function of the genetic material of bacteria, indicated a number of enterobacterial coabundance groups in the gut microbiota which differ among diabetes types. The investigators also studied sequences of the bacteria. They demonstrated that there were different abundances of these groups of the microbiota, and also that there were differences in the biochemical and metabolic pathways used. These included downregulation of amino acid (valine, leucine and isoleucine) degredation, 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 (SCFA) was noted in LADA individuals, even more than found in people with T1DM and T2DM[65]. These SCFA reduce chronic inflammation, pancreatic autoimmunity, strengthen gut barriers and alter intestinal hormones; notably, they also improve glucose metabolism and insulin sensitivity[66]. 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[67]. Much additional information has been obtained from The Environmental Determinants of Diabetes in the Young

(TEDDY) samples, in which high-risk individuals from 6 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, in order to document environmental, genetic microbial, immunological contributors to T1DM develepment[67]. Weak associations were observed for some bacteria. However, more important were the loss of functionally protective properties, also relating to fermentation and synthesis of SCFA 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[68]. 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[69]. 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.

[H2] Immunotherapy-related autoimmune diabetes

Considerable improvement in clinical outcomes in cancer patients have been observed with immune checkpoint inhibitors that include programmed cell death protein-1 (PD-1) inhibitors (such as Nivolumab or Pembrolizumab), programmed death-ligand 1 (PD-L1) inhibitors (such as Atezolizumab, Avelumab or Durvalumab), and cytotoxic T cell-associated protein 4 (CTLA-4) inhibitors (such as Ipilimumab). However, an increase in immune-mediated adverse events has occurred, including diabetes associated with PD-1 or PD-L1 inhibitor use[70]. The presentation of diabetes includes fulminant T1DM and diabetic ketoacidosis, occurring with life-threatening illness and deaths[71]. 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[72]. It is not clear why these immune-related adverse events only occur in some patients but underlying genetic susceptibility to autoimmune diseaseand the composition of the host microbiota may be contributory[73]. 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[73]. 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.

[H1] Diagnosis, screening and prevention

[H2] Clinical features

The clinical presentation of AOA diabetes varies depending on insulin dependence at clinical onset of disease and β-cell loss rate over time (rapid vs slowly progressive autoimmune diabetes). Anthropometric indices reported in individuals with LADA vary between ethnic groups and specific clinical features, such as overweight and obesity, [74]. In most studies, people with LADA have a lower prevalence of metabolic syndrome components (overweight or obesity, waist-to-hip ratio, hypertension and dyslipidaemia) than those with classic T2DM, but higher than in T1DM patients [6,7,75,76]. An intermediate level of β-cell dysfunction has been found in LADA compared with those who have T1DM, T2DM and/or MODY[76-79] **(FIG 1)**. This intermediate clinical status was evident in European cohorts and confirmed in a large study from the United Arab Emirates [6,7,77,80,81]. However, differences between adults with diabetes testing positive or negative for GADA were less pronounced in other studies including different cohorts, such as drug-naïve individuals or Asian populations.[82,83]. In this regard, the LADA China study indicated that clinical features varied less between islet cell antibody-negative individuals than between those who were antibody-positive[83]. Similarly, a study from Singapore including a transethnic comparator from Germany showed that, in contrast to Asians individuals, Europeans with diabetes, testing GADA- and/or IA2-A-positive, had a lower mean BMI compared with antibody-negative participants[84]. Mixed phenotypic features have also been reported in a studys from Nigeria, West Africa[85]. Population-based studies reporting incident diabetes cases have better defined the phenotypic spectrum of people with AOA diabetes, confirming that GADA-positive 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-negative patients[86,87]. C-peptide reserve was more compromised in people with LADA compared with those with T2DM, but people with LADA were less insulin resistant[87]. Studies from Scandinavia emphasized diabetogenic lifestyle factors, such as higher BMI, smoking, and lower level of physical activity, in association with LADA[2,26,33,88]. 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 β-cell functional parameters than patients with T1DM, independent of BMI [78]. An enhanced rate of functional decline of β-cells is indeed a common clinical feature of LADA compared with T2DM, even though the high variability of the β-cell destruction in longitudinal studies was seen in conjunction with insulin resistance[25,77,81,89,90]. 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 two times faster in GADA-positive than GADA-negative individuals with T2DM[81,91]. In addition, poorer glycaemic control with higher HbA1c levels was in LADA compared with T2DM in the same cohort[77,92,93]. 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[94].

Overall, individuals with LADA have a clinical phenotype differing 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[81,92]. Furthermore, time trends of specific features need to be taken into consideration, such as the obesity epidemic and the continuous change of lifestyle risk factors[6,74].

[H3] Interplay of immunological and clinical feature

Clinical heterogeneity due to islet cell autoantibody 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 low GADA levels[20,49,83,95]. Compared 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, a 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[49]. Similarly, the PTPN22 risk genotype was also associated with high GADA concentrations in patients with LADA[96]. Conversely, the transcription factor 7 like 2 (*TCF7L2*) risk allele for T2DM was associated with low, rather than high, GADA levels[90,97].

Similarly, differences in clinical features associated with IA-2A recognized epitopes were observed. IA-2A directed against the construct IA-2 (256-760)[98-100] are more frequently found in people with LADA testing negative for GADA and who show a phenotype resembling classic T2DM, with higher BMI and waist circumference, and lower rates of progression towards an insulin-dependent state. Of note, the simultaneous positivity to two or more autoantibodies (for example both GADA and IA-2A) is associated with a more rapid progression towards insulin therapy and a clinical phenotype

more similar to younger onset T1DM, that is,[low BMI and low prevalence of other cardiometabolic conditions, such as hypertension or dyslipidemia[7]. 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[101]. In addition, adult-onset diabetic patients positive for both GADA and IA-2A had lower waist circumference and higher fasting glucose levels than those positive for both GADA and ZnT8A[102].

[H2] Classification and diagnosis

Misclassification of the diagnosis of classic adult-onset T1DM is rare but, as it always requires insulin *ab initio* and frequently presents with metabolic acidosis, 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 islet cell autoantibody; and absence of insulin requirement for at least 6 months after diagnosis[103].

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[104,105].

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" with often features of metabolic syndrome, presence of GADA as a single autoantibody and greater retained β-cell function[106]. However, the 2019 WHO classification did not provide conclusive criteria, due 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[92]. 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-month intervals to reflect the functional β-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, IA-2A, ZnT8A, and tetraspanin 7 autoantibodies less frequent) and by evaluating β-cell function[92].

, The most recent 2022 ADA recommendations for classification and diagnosis of diabetes includes LADA in T1DM, due to the autoimmune nature of β-cell destruction[1]. 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.

[H2] 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 it is also true for other diabetes subtypes presenting in adulthood[107]. 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[92,107,108]. Consequently, LADA and MODY are likewise misdiagnosed as different T2DM subtypes[109,110]. To stratify 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 β-cell reserve at diabetes onset as well as during follow-up, and presence or absence of the various islet-cell autoantibodies.

[H1] 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 of people living with the disease. Clinical guidance for managing AOA diabetes has been provided by recent international consensus statements[92,111], 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 β-cell dysfunction in people with AOA diabetes.

[H2] 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 based on 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 [111]. Both personalized medical nutrition therapy and physical activity

programs 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 [112-114]. 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[115-117]. This translates, clinically, into improvements of blood glucose control, weight loss in overweight or obese individuals, reduction of cardiovascular risk factors, and decreased morbidity and mortality[118,119]. Nonetheless, 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[111]. Thus, it is recommended that all people with autoimmune diabetes should engage in physical exercise on most days and they should refer for individualized medical nutrition therapy provided by nutritionists with proven skills in providing diabetes-specific nutritional advice[111].

[H2] Insulin therapy

Insulin therapy is the most straightforward therapeutic choice in patients with AOA diabetes, as it augments low levels of endogenous insulin caused by the autoimmune destruction of pancreatic islets, with proven efficacy for controlling hyperglycaemia, preventing diabetic ketoacidosis and preserving β-cells[111]. 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 β-cell function for decades **(FIG.3)**[77,120]. In the latter cases, some clinical features (GADA levels, presence of multiple pancreatic autoantibodies, age at onset and BMI) may help predict the progression towards an insulin-dependent state[7,50]. However, there is a lack of data from randomized, controlled trials with sufficient length of follow-up to draw conclusions about the optimal time for starting insulin therapy. In this regard, measurement of C-peptide concentration, which reflect endogenous insulin secretion capacity, may aid in the decision to start insulin in people with AOA diabetes **(FIG.5)**[121]. In the LADA expert consensus report, three broad categories of C-peptide levels 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 values in the 'grey area' ≥0.3 and ≤0.7 nmol/L, in which a modified ADA/EASD algorithm for T2DM is recommended considering insulin in combination with other therapies to modulate β-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 [92]. Importantly, a systematic review showed that insulin therapy provides better metabolic control than sulphonylurea treatment, 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 β cells (mean HbA1c difference -1.3% (95% CI -2.4 to -0.1; P = 0.03)[122]. In addition, insulin was found to maintain pancreatic β-cell function better than sulphonylureas in most studies included in the systematic review[122]. 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[123], 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)[92]. 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 ≥0.3 nmol/L[92].

The main adverse effects associated with insulin therapy are hypoglycemia, body weight gain and skin reactions, such as local inflammation and lipodystrophies. Hypoglycemia is the most worrisome adverse event of insulin therapy, associated with increased morbidity and mortality[124]. The risk of hypoglycemic events is particularly high in people with T1DM because α cell dysfunction often associates with β cell dysfunction, ultimately resulting in an impaired glucagon response to low blood glucose levels[125]. Thus, education of patients on managing insulin doses, correct insulin administration technique, strict self-monitoring of blood glucose values and efficacious correction of hypoglycemic 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[126,127].

[H2] 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 β cell reserve of the patient[92]. Although there is agreement about the importance of avoiding sulphonylureas in people with LADA due to an increased risk of hypoglycemia[128] and worse metabolic control and acceleration of β-cell loss[122], other agents may be considered, such as insulin-sensitizers, drugs acting on the incretin system, amylin analogs 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-

hyperglycemic therapy other than insulin in people with LADA should be considered individually and will often be *off-label* prescriptions.

[H3] Insulin sensitizers

As the prevalence of overweight and obesity in people with autoimmune diabetes is increasing[129], insulin resistance is also rapidly becoming an important issue. Insulin resistance has always been considered a key pathological finding among adults with LADA[77,81]. Metformin is the most commonly prescribed insulin-sensitizer worldwide and has been shown to improve insulin sensitivity also in youth with T1DM[130]. 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)[131]. 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 working as peroxisome proliferator-activated receptor (PPAR) gamma agonists[132]. Two studies tested rosiglitazone in people with slowly progressive autoimmune diabetes, suggesting a potential benefit of thiazolidinediones in preserving β cell function[133,134]. 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 edema and weight gain, and with the known limited efficacy of thiazolidinediones in lean patients[135]. Another small study in ten patients with LADA showed a faster disease progression in those treated with pioglitazone alone compared with those treated with metformin alone[136].

[H3] 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 showing their metabolic and cardiovascular benefits[137]. As incretin hormones were shown to reduce apoptosis of human β cells *in vitro*[138], GLP1-RAs were hypothesized to ameliorate or preserve endogenous insulin secretion in people with autoimmune diabetes. In a phase 2 trial in adults with new onset autoimmune diabetes and residual β cell function, liraglutide slowed β cell decline when used in combination with anti-IL-

21, but no benefits were found with liraglutide alone[139]. In a randomized 52-week phase 2 trial using albiglutide in newly diagnosed AOA diabetes, no appreciable preservation of β cell function was observed[140].

Nonetheless, GLP1-RAs might still improve metabolic control in people with LADA, as suggested by a pooled post-hoc analysis of the AWARDS-2, -4 and -5 trials showing that dulaglutide was as effective in reducing HbA1c values in participants with adult-onset diabetes testing positive for GADA as in those testing negative[141]. Of note, insulin-treated patients were excluded from AWARDS-2 and -5, and patients on >3 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 glycemic 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[142]. In summary, GLP1-RA may be an attractive opportunity for aiding the treatment of people affected by LADA, especially for those with a certain amount of residual βcell function.

CD26/Dipeptidyl-peptidase 4 inhibitors (DPP4i)

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 DPP-4, the enzyme responsible for the degradation of GLP1 and GIP[143]. Due to the potential effects of incretin hormones on β cell survival, gliptins have been tested in LADA with both the aims of preserving β cells and ameliorating glycemic 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[144-146]. Data about a potential role for DPP4i in preserving β cell viability and function are conflicting. Small clinical trials from China suggest that sitagliptin may maintain β cell function over time[147,148], altering the predominant phenotype and the balance of different T cell subsets[63]. Similarly, saxaglitpin was associated with improvements of markers of β cell function alone or in combination with Vitamin D3[145,149]. 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[150].

[H3] Sodium-glucose Cotransporter 2 inhibitors (SGLT2i)

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 hypothesis that these drugs might help in ameliorating the metabolic control also in people with autoimmune diabetes. Since the DEPICT and the InTandem clinical trials program showed improvements of glycemic control associated with the use of dapagliflozin and sotagliflozin, respectively, in adjunct to insulin in adults with T1DM[151-153], both drugs were approved by the EMA as adjunctive therapy in addition to insulin for the treatment of people with T1DM and a BMI ≥27 Kg/m^2 and uncontrolled blood glucose. The Pharmaceutical and Medical Devices Agency (PMDA) in Japan also approved dapagliflozin and ipragliflozin[154] for the treatment of people with T1DM in adjunct to 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 has also been 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[155]. The risk-benefit ratio associated with the use of SGLT2i in people with T1D can be improved by careful patient selection and education, use of lower SGLT2i drug doses, avoiding drastic reduction of insulin doses and use in the subgroup of patients with BMI ≥27Kg/m^2 [156,157]. Thus, although no clinical trials have been specifically designed and 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 β cells and are more often affected by concomitant overweight or obesity.

[H3] Pramlintide

The amylin analog pramlintide suppresses glucagon secretion and delays gastric emptying, resulting in benefits on glycemic control and body weight[158]. 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.

[H2] Immune modulatory drugs

Several immune-modulatory drugs, including non-antigen-specific immunomodulators (such as CTLA-4 immunoglobulin, IL-1 and IL-6 receptor antagonist, anti-TNF-alpha, 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[159,160].

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 β cell loss and the higher prevalence of residual endogenous insulin production often seen in people with adult-onset, compared to young-onset, autoimmune diabetes could make AOA diabetes an attractive setting for immune-modulatory drugs. In a small phase 2 placebo-controlled immune-intervention trial conducted in individuals with LADA, GAD-alum was used to induce immune-tolerance in GADA-positive non–insulin requiring patients, showing a good safety profile with evidence of a beneficial effect on β cell function[161]. Another phase 2 trial suggests that the tyrosine kinase inhibitor imatinib could help in preserving βcell function in adults with recent onset T1DM, although questions related to the ideal dose, duration of therapy and safety remain to be resolved[162].

[H1] Quality of life

Health Related Quality of Life (QoL) 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 healthcare 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)[163,164]. 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[165,166]. 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 glycemic control and lower socioeconomic status[165-167].

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[168]. 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[168]. Individuals with insulin-treated LADA have a worse average weighted impact score compared with corresponding non-insulin-treated T2DM patients. 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 a primary education) and former smoking also had a negative effect on the average weighted impact score[168].

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 T2DM patients[168]. Perception of increased hyperglycemia frequency was found to be higher in the LADA group (87.5%) than in the T2DM group (53.9%) and, surprisingly, the T1DM group too (71%; $p < 0.001$ and $p=0.039$, respectively). Comparing insulin-treated subgroups, people with LADA treated with insulin had a higher hyperglycemia frequency perception than those who had T1DM ($p=0.04$) and those who had insulin-treated T2DM ($p=0.05$) [168]. The higher blood glucose values often translate to an increased risk of complications, especially microvascular[169,170], which in turn may have QoL implications **(Box 2)**.

[H1] 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 β-cell destruction under the category T1DM, other societies propose different definitions to reflect the slower disease progression often observed in AOA diabetes[106,171]. In fact, the 2020 international consensus on LADA found it challenging to define categorical immunogenetic and phenotypic features of LADA[92]. 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 due 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 false-positive T2DM patients 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[15]. 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[172]. A similar finding was made in a population in China: where those with high levels of GADA had poorer β-cell function and fewer diabetic complications than those with low GADA levels, who were similar to T2DM patients, except that they were prone to develop ketosis more frequently[173]. In a Japanese population, an inverse correlation of metabolic syndrome with increasing GADA quartile was observed[174]. 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 utilizing both autoantibodies and C-peptide[92]. Autoantibodies with standardized assays include GADA, IA2-A, insulin autoantibody, and ZnT8A, with GADA being the most prevalent autoantibody among adults, even in China where GADA is less dominant[175]. High levels or the presence of more than one autoantibody increases the likelihood of autoimmunity[15]. 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 IA 2-A 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 titer thresholds, or only testing in higher prevalence populations by restricting testing to those with clinical features suggestive of T1DM[15]. 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-A), and genetic risk score is under development (https://www.diabetesgenes.org/t1dt2d-prediction-model/)[176]. 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[177,178]. In patients diagnosed as having T2DM, measurable T cell responses are associated with lower stimulated[177] and fasting[178] C-peptide levels. However, T cell reactivity in autoantibody negative individuals is unexpectedly high[177,178], indicating that further work is required to elucidate the underlying mechanisms of these associations.

Compared with pediatric 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 need 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[179], 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 pediatric 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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Competing interests

RB declares consulting for Sanofi, Novo Nordisk and Eli Lilly; and receiving honoraria for speaker bureaus from AstraZeneca and Abbott.

JG declares consulting for Vertex Pharmaceuticals Inc., Dompé farmaceutici and Avotres Inc.

EM declares consulting for Merck KGaA and PikDare; and receiving honoraria as speaker from Abbott.

RDL, FSW, BOB declare no competing interests.

BOXES

BOX 1. Diabetic ketoacidosis.

Diabetic ketoacidosis (DKA) is a preventable, acute and life-threatening complication of diabetes which occurs in case of absolute or relative insulin deficiency[180]. The heterogeneous rate of β cell loss in people with adult-onset autoimmune (AOA) diabetes translates into different risks of DKA between adults presenting with a classical T1DM onset (high DKA risk) and those affected by LADA[181,182], 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 about the higher risk of DKA occurrence in AOA diabetes than in T2DM, 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 healthcare, low socioeconomic status, female sex, ethnicity, poor metabolic control, low self-management skills, omission of insulin therapy, psychiatric disorders, infections, alcohol and drug abuse[111,181]. In general, however, the risk of DKA decreases with older age at onset[183].

Box 2. Chronic complications

Chronic complications that may affect people with adult-onset autoimmune (AOA) diabetes resemble those with type 2 diabetes, 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 LADA and those with T2DM was found in a systematic analysis[77]. A more recent study showed that a slightly better cardiometabolic profile observed in LADA compared to T2DM translates into a lower incidence of cardiovascular events[123]. 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[77,170,2] 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[170], 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 UKPDS study, the largest longitudinal study with the longest follow-up comparing microvascular complications between LADA and T2DM, only few microvascular events were kidney events[170]. 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[184,185]. 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[186,187]. No solid data comparing prevalence and features of diabetic foot between LADA and T2DM have been published so far.

Figure Legends

Figure 1: The adult-onset diabetes spectrum

In people with adult onset-autoimmune (AOA) diabetes clinical and pathogenetic features of classical 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 (AAb) are similar to those with classic T1DM, whereas those with low GADA concentrations and/or multiple islet AAb are similar to those with T2DM It should be noted that MODY, which also may be diagnosed during adulthood, was not included in the figure because it most frequently occurs during the first decades of life and because it encompasses several different types of diabetes with monogenic causes differing in clinical features, and being itself a heterogenous group of diabetes subtypes.

Figure 2. Frequencies of islet-specific autoantibodies in adults with a clinical diagnosis 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 (T2DM) testing positive for islet-specific autoantibodies, mainly glutamic acid decarboxylase serum autoantibody (GADA). Of note, these finding 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[6,7,49,75,82-85,95,188-198]

[a]Frequencies reported in small studies with a sample size <500 participants.

Figure 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 β-cell function, which occurs during a pre-symptomatic period characterized by detectable immune changes and

normoglycemia (stage 1). When the percentage of residual functional β-cell mass is too low to maintain blood glucose values within normal ranges a period of asymptomatic dysglycemia (stage 2) starts. As the loss of β-cell capacity continues, exogenous insulin becomes necessary for survival . This insulin-dependent state, 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 β- cell loss differs among individuals. In people with classical type 1 diabetes mellitus (T1DM), the progression from the presymptomatic stages (1 and 2) to stage 3 is so rapid that in most cases the asymptomatic dysglycemia is often undiagnosed, whereas latent autoimmune diabetes in adults (LADA) is characterized by longer presymptomatic stages, which enable diagnosis of dysglycemia 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 β-cell function and will not need insulin treatment (LADA non-insulin dependent).
Stages 1, 2 and 3 in the figure refer to classical T1DM. Adapted from Ref.[36]

Figure 4. Model for pathogenesis of autoimmune diabetes.

[1. Genetic factors can lead to defective central and peripheral tolerance. Defective central tolerance allows naïve islet-reactive $CD4^+$ and $CD8^+$ 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 and 3. Environmental factors (such as viral infections or altered commensal bacteria) could activate 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 Islets of Langerhans. 4. In the pancreas, several possible mechanisms could lead to the death of β cells including a natural process of tissue remodelling, viral infection and endoplasmic reticulum stress due to high metabolic demand for insulin. Moreover, cytokines produced by infiltrating cells that include macrophages (IL1β and TNF)can contribute to apoptosis. Furthermore, damage of β cells may occur related to β cell production of IFNα priming them further for immune cell destruction. These events can lead to apoptosis of β-cells which releases β cell antigens. 5. Antigens released from apoptotic β cells are uptaken by dendritic cells, which migrate to the pancreatic lymph node. 6. Dendritic cells present β cell antigens to naïve $CD4^+$ T cells in the pancreatic lymph node leading to activation of several possible helper (Th) subsets including Th1, Th2, Th17 and Treg. Dendritic cells also cross-present

antigens to $CD8^+$ T cells in the pancreatic lymph node. 7. $CD4^+$ cells can help B cell production of autoantibodies targeting β cell proteins. $CD4^+$ cells may also assist in activation of $CD8^+$ T cells. 8. Activated T and B cells traffic to the islets of Langerhans. 9. $CD8^+$ cytotoxic T cell infiltration can induce lysis of β cells presenting self-antigen, via secretion of perforin, the apoptotic Fas–FasL pathway and inflammatory cytokines. 10. $CD4^+$ Th1 cells secrete pro-inflammatory cytokines IFNγ and TNF which could induce β cell death and stimulate macrophages to produce reactive oxygen species, TNF and IL1β. These may augment β cell death.

Figure 5. Diagnostic and therapeutic algorithm for LADA

After diabetes diagnosis, islet autoantibodies (AAb) 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 <0.3nmol/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 ≥0.3-≤0.7nmol/L, who might benefit from an early introduction of basal insulin, especially if HbA1c is >9%. In these patients, GLP1-RA or SGLT2i may be suggested in a second therapeutic step, especially in the presence of established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD). In this regard, the use of SGLT2i should be considered with caution in people with latent autoimmune diabetes in adults (LADA) because of the increased risk of diabetic ketoacidosis found in studies of type 1 diabetes mellitus (T1DM)[a]. Of note, formal regulatory approval for non-insulin therapy in LADA 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 hyperglycemic episodes.

[b]In alphabetical order; preference for one drug instead of another should be based on clinical judgment. Adapted from Ref [92].

Figure 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

Tables

Table 1: Broad clinical features of diabetes subtypes

Features	LADA	Classic or true T2DM	Classic young-onset T1DM	Classic adult-onset T1DM	Carriers of mono-genic variants
Age at diagnosis	>30 years#	Adulthood	<20 years	>20 years	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 T2DM	Increased	Absent	Absent or increased	Absent or increased
HDL-cholesterol levels	Normal	Low	Normal	Normal	Normal
Islet cell antibodies	Positive#	Negative	Positive	Positive	Negative
GADA	Positive	Negative	Positive	Positive	Negative
Presence of multiple islet cell autoantibodies**	Rarer than T1DM	Negative	Common	Common	Negative
Insulin-requirement at disease onset	None#	None	Yes	Yes	None
Partial remission phase ##	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***
C-peptide at diagnosis	Decreased but detectable	Positive or highly positive	Low or negative****	Low or negative	Positive
Non-fasting C-peptide	≤300 pmol/L or 300-600 pmol/L, needs follow-up quantification	≥600 pmol/L	≤300 pmol/L	≤300 pmol/L	300-600 pmol/L
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 Vit. B12 deficiency	Increased	Rate of background population	Increased	Increased	Rate of background population
Microvascular complications at diagnosis	Lower rate than T2DM	Can be already present	Absent	Absent	Absent
Risk of microvascular complications during follow-up	Increased compared with T2DM (UKPDS data)	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 CVD risk to T2DM	Increased	Increased	Increased	Variable, dependent on gene variant

#) predefined main IDS criterion/predefined component of LADA; clinical criteria presented are not categorial. BMI: wide-ranging level of indices can be seen in almost all DM subtypes, including LADA, T1DM and T2DM.
##) Partial remission (PR), a period experienced by patients with autoimmune diabetes soon after diagnosis, characterized by transient recovery of islet β cell function resulting in low insulin requirements (less than 0.5 units/kg of body weight per day) and improved glycaemic control (HbA1c between 7% [53 mmol/mol] and 6% [42 mmol/mol])[199,200] *) Compared with typical T2DM cases; **) Multiple islet-cell specific antibodies include ICA, IA-2A, ZnT8, tetraspanin 7 autoantibodies and insulin-autoantibodies in particular in young-onset T1DM; ***) in cases with HNF1A - and HNF4A-variants, progressive pancreatic β-cell dysfunction; ****) using standard C-peptide assays.