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Adult-onset autoimmune diabetes in 2020: An update

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ABSTRACT

An increasing number of new cases of autoimmune diabetes occur during adulthood. Most are cases of latent autoimmune diabetes in adults (LADA), a form of autoimmune diabetes with older mean age at onset, slower rate of beta-cell loss and longer period of insulin independence after onset when compared with type 1 diabetes. Unfortunately, patients with LADA are often misdiagnosed as having type 2 diabetes, the most frequent form of adult-onset diabetes, and show a sustained poor glycemic control over time. Recent evidence shows that this translates into a significantly increased risk of complications. Therefore, an enhanced awareness of LADA is essential. In this narrative review we aim to provide an update on knowledge about LADA pathophysiology and clinical implications by critically reporting the most recent evidence.

1. Introduction

Autoimmune diabetes is a polygenic multifactorial disorder characterized by the destruction of pancreatic beta cells, on an autoimmune basis, resulting in absolute insulin deficiency [1]. Type 1 diabetes (T1D) is the most aggressive form of autoimmune diabetes and, historically, has been largely considered a disorder of children and adolescents [2]. However, it has been recognized that an increasing number of new autoimmune diabetes cases occur during adulthood. While a small percentage of these cases have a clinical presentation similar to T1D, there is a substantial number of people with an initial clinical diagnosis of type 2 diabetes (T2D), but having detectable serum markers of beta-cell autoimmunity [3–5]. These subjects are affected by a form of autoimmune diabetes called "latent autoimmune diabetes in in adults" (LADA). Even though people with LADA do not require insulin at the time of diagnosis, their clinical features may significantly differ from people with T2D, reflecting a different pathophysiology. LADA is indeed a heterogeneous form of diabetes with a pathogenesis that includes both autoimmune destruction of pancreatic beta cells as well as some degrees of insulin resistance [5]. This heterogeneity is also reflected in its clinical presentation, affecting screening strategies and therapeutic approaches. As a result, patients with LADA are often misdiagnosed and show a sustained worse glycemic control compared to T2D [6,7]. Therefore, an enhanced awareness of LADA features is essential to improve health outcomes of patients with this ambiguous form of adult-onset diabetes. After we published in 2017 a comprehensive narrative review about the current knowledge of adult onset autoimmune diabetes [8], new evidence has been published which could help researchers and clinicians. In this review we aim to provide an update of our above cited 2017 review, discussing about the most recent advancements in the understanding of LADA pathophysiology and clinical implications.

2. Methods

For this narrative review we searched PubMed for original articles published from January 2017 to March 2020 about LADA. The following search strings were used alone or in combination: "LADA", latent autoimmune diabetes"; "genetics"; "therapy"; "vascular complications". Articles resulting from these searches and relevant references cited in those articles were reviewed. Relevant articles published before 2017 were identified through searches in the authors' personal files. Only articles published in English were included.

3. LADA definition

The use of term LADA to identify a form of autoimmune diabetes with later mean age at onset, slower rate of beta-cell loss and longer period of insulin independence if compared to T1D has been only recently discussed also by the American Diabetes Association [9]. The World Health Organization (WHO) classification of diabetes mellitus has also been updated in 2019 to acknowledge LADA, which is defined as "slowly evolving immune-mediated diabetes" among the "hybrid forms" of diabetes [10]. As a form of autoimmune diabetes, LADA shares the same autoantibodies used to identify T1D, such as insulin autoantibody (IAA), glutamic acid decarboxylase antibodies (GADA),

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insulinoma-associated antigen-2 autoantibodies (IA-2A), and zinc transporter-8 autoantibodies (ZnT8A). GADA is the most sensitive antibody for LADA diagnosis [11,12], also informing about LADA clinical phenotype. Indeed, while the mean clinical features of LADA are midway between T1D and T2D, patients with LADA being younger and leaner than those with T2D but older and with higher body mass index and waist to hip ratio than those with T1D [13], there is a large heterogeneity in the clinical presentation of LADA which associates with GADA serum levels and with the number of positive islet autoantibodies [3,13–15]. The broad clinical phenotype makes it difficult to diagnose LADA and screening tools considering different clinical features at diabetes presentation, such as the "LADA clinical risk score" [16], may aid to identify who can benefit the most from GADA measurement. However, there are no universally agreed diagnostic criteria for LADA, and to date the most widely used criteria for diagnosing LADA still reflects those proposed by the Immunology of Diabetes Society (IDS) in 2005: adult age of onset (> 30 years); the presence of any islet autoantibody; and the absence of insulin requirement for at least 6 months after the diagnosis [11]. Based on these criteria, LADA can be identified in 2–12% of patients with a clinical diagnosis of T2D [17]. However, there is an ongoing debate about the IDS diagnostic criteria, which appear to be limited by an arbitrary age cut-off and by a non-specific definition of "insulin requirement". To overcome the latter limit, the evaluation of beta-cell reservoir by measuring C-peptide serum concentrations close to the diagnosis, 6 months and later on the course of the disease could be helpful. In this regard, the urine C-peptide/creatinine ratio may represent a non-invasive practical alternative for the detection of insulin secretion and to differentiate LADA from T1D in routine clinical practice [18], thanks to the stability of C-peptide in urine and the high correlation with serum C-peptide during the mixed-meal tolerance test [19]. While there is no definitive consensus about C-peptide cut-off values to differentiate LADA from T1D, in our opinion random serum C-peptide levels stably ≥0.3 nmol/L or urine C-peptide/creatinine ratio stably ≥0.3 nmol/mmol may be reasonably considered a marker of preserved β-cell function [20,21].

4. What is new in the genetics of LADA

Numerous studies had shown that LADA shares genetic features with both T1D and T2D [22], but studies on LADA, in this respect, were limited to a number of candidate genes that are risk loci in the pathogenesis of T1D and T2D [23,24], hampering the identification of new genes specifically involved in LADA pathogenesis. Similar to T1D, genetic susceptibility to LADA is strongly linked to the human leukocyte antigen (HLA) gene complex (in particular DRB1 and DQB1, with the HLA-DRB1*04-DQB1*0302 and HLA-DRB1*0301- DQB1*0201 haplotypes conferring the highest risk) regulating the immune system [25]. This finding underlines the autoimmune origin of this form of diabetes. In addition, LADA is linked to T1D-associated variants in the protein tyrosine phosphatase non-receptor type 22 (PTPN22), insulin (INS), and SH2B adapter protein 3 (SH2B3) genes, but these associations seem to be restricted to the subset of LADA patients showing a higher autoimmune load as suggested by the presence of more than one positive diabetes autoantibody [26].

An association with the key T2D-associated transcription factor 7-like 2 (TCF7L2) locus has been described in some studies [27,28]. However, this association has been recently questioned in a study describing genetic liability to LADA in one of the largest LADA cohort ever investigated for this purpose [26]. In the same study, genetic risk scores for T1D performed better than genetic risk scores for T2D in distinguishing patients with LADA from controls [26]. Similar results have been subsequently achieved with the first genome-wide association study (GWAS) for LADA, giving important additional information about genetic characteristics of LADA [25]. This study confirms that the genetic basis of LADA can be mainly assimilated to that of T1D, and GADA stratified analysis of LADA patients also shows that the odds ratio of key loci is stronger in LADA cases with the highest GADA levels. However, both the genetic variants predisposing to T1D and the polygenic predisposition to T2D were shown to contribute together to the whole genetic background of LADA. Based on the GWAS results, it has been indeed speculated that the presence of T2D-predisposing variants may modify the risk of developing autoimmune diabetes in subjects who also present an autoimmune susceptibility conferred by some T1D-predisposing variants, leading to the development of LADA [25]. Limits of this GWAS, that should be addressed in the future, include the wide heterogeneity of the LADA cohort enrolled in terms of age, autoantibody measurement, clinical features and diagnostic criteria used to define LADA.

Following on that, a strong interaction between overweight/obesity and high-risk HLA genotypes in relation to the risk of LADA was found, especially in subjects with the DR4/4 genotype [29]. In the same study excess weight was found to interact with TCF7L2 and fat mass and obesity-associated (*FTO*) risk alleles in the promotion of LADA.

Another recent study [30] showed that genetic susceptibility to LADA varies also among ethnicities. DR3 and DR4 alleles were found to be less frequent in East Asian LADA patients compared to Caucasians, while DRB1*0901-DQB1*0303 haplotypes, conferring only a moderate risk, are more common in Asian LADA patients and rare in Caucasians. This may explain the lower prevalence of LADA in East Asians than in Caucasians and the observation that the proportion of LADA patients with low GADA level in China is higher than in Europe (74% vs 49% patients in the low GADA level group respectively).

In addition, two different markers for the MHC class I polypeptide-related sequence A (MICA) gene, namely, the MICA5 and MICA5.1 alleles, have been shown to be associated with T1D and LADA, respectively [31]. However, a conditional analysis within the MHC classes showed that in LADA, differently from childhood-onset T1D, there is no independent effect of MHC class I after conditioning on the leading MHC class II associations, suggesting that the MHC class I association may be a genetic discriminator between LADA and childhood-onset T1D [32].

5. What is new in LADA pathophysiology

LADA represents an "intermediate" form of diabetes between T1D and T2D, characterized by an islet-cell specific autoantibody positivity but a slower β-cells loss than T1D and some metabolic features of T2D [17]. As well as in T1D, insulitis, which is the inflammatory process characterized by the infiltration of immune cells into the pancreatic islets, seems to be the hallmark of the immune mediated beta-cell destruction also in LADA [33]. In autoimmune diabetes, $CD8^+$ cytotoxic T-cells are the most represented infiltrating cells within insulitis and are the main effectors of pancreatic autoimmunity [1]. However, also T $CD4^+$ helper cells, macrophages and B-cells are found in the inflamed pancreatic islets, representing the complex cell-mediated immune pathogenesis of autoimmune diabetes. Briefly macrophages and dendritic cells, which are responsible for presenting beta-cell peptides through major histocompatibility complex (MHC) class II to naive $CD4^+$ T-cells, infiltrate the pancreatic islets and release chemoattractant cytokines such as interleukin (IL)-12. $CD4^+$ T-cells, circulating in the blood and in the pancreatic lymph nodes, are activated by IL-12 and can produce IL-2 which, in turn, activate beta-cell antigen-specific $CD8^+$ cytotoxic T-cells [34].

The confirmation that insulitis occurs in LADA has been initially shown by pancreatic scintigraphy using interleukin 2 (IL-2) radiolabelled with technetium-99m (99mTc), which observed the presence of peripheral blood mononuclear cells (PBMCs) in the pancreas of both T1D and LADA [35]. The first study investigating pancreas pathology in patients with LADA has further confirmed the immune cell-infiltration in the pancreatic islets, with a changed ratio between macrophages and CD8 T-cell towards macrophages [33]. Nevertheless, an increased pancreatic ^{99m}TC-IL-2 uptake has been detected even in autoantibody-

negative (Ab^-) T2D patients, suggesting that a T-cell response may also occur in the absence of the classical markers of pancreatic autoimmunity [36]. This last condition was labelled as T-LADA [37], and seems to be characterized by a more rapid β-cell functional decline than T2D [38], despite the absence of the known islet autoantibodies. Indeed, while routinely LADA is diagnosed by detecting islet autoantibodies, these are only markers and not the effectors of β-cell destruction, which is mainly caused by islet antigen-specific $CD4^+$ and $CD8^+$ T cells. Nowadays it is possible to identify and distinguish T-LADA ($Ab^- T^+$) from classic T2D ($Ab^- T^-$) using enzyme-linked immunospot (ELISPOT) assay, a promising technique allowing to detect antigen-reactive T cells and their cytokine response [39]. It is well known that the pathogenesis of autoimmune diabetes is mediated by pro-inflammatory cytokines, of which interleukin-17 (IL-17) is playing an emerging role, together with interferon gamma (IFN-γ) [40,41]. Badal et al. demonstrated LADA peripheral blood mononuclear cells (PBMCs) secrete higher levels of IL-17 in vitro after stimulation with β-cell autoantigens compared to T1D. In this study, a positive correlation between BMI and IL-17 was observed, suggesting that IL-17 might contribute to the low-grade inflammation typical of visceral adiposity in obese subjects and, consequently, to a low-grade autoimmune process causing loss of β-cell function [42]. Similar data were already reported in the Action LADA study, showing that levels of pro-inflammatory cytokines were directly related to some adiposity-related markers, such as BMI, though TNF-α levels were significantly lower in patients with LADA than in those with T2D, but similar to those with T1D [43]. Recently, a new circulating pro-inflammatory biomarker has been detected for a better differential diagnosis between LADA, classical adult-onset T1D and T2D, i.e. soluble levels of the TNF-a 2 receptor (sTNFRII). sTNFRII is a stable protein regulating TNF-α activation in adipocytes, in the context of obesity and insulin resistance [44]. In particular, Castelblanco et al. found that its concentrations gradually increased from T1D to LADA and from LADA to T2D, thus becoming a potential predictor for discriminating LADA from classical adult-onset T1D [45]. Furthermore, sTNFRII plays a key role in the differentiation of activated $CD4^+$ T regulatory cells (Tregs), which are fundamental for maintaining immunological unresponsiveness to self-antigens [46,47]. Consequently, the higher number of Tregs in LADA compared to T1D could explain the milder clinical presentation of the former. Finally, it was observed also a positive correlation between high concentrations of IL-15 and IL-6 with insulin resistance in autoimmune diabetes, including LADA [48], strengthening the hypothesis about the relationship between chronic inflammation, insulin resistance and development of autoimmune diabetes. LADA is indeed characterized by a great phenotypic heterogeneity due to variable degrees of insulin deficiency and insulin resistance. Individuals with LADA tend to have higher BMI than those with T1D. Therefore overweight and obesity are associated with increased risk of LADA, particularly when in combination with family history of diabetes, as illustrated in a Swedish case–control study and the Norwegian HUNT Study [49]. Thus, the development of autoimmunity in patients with LADA could be accelerated by the low-grade inflammation related to visceral adiposity, together with other specific triggers activating autoimmunity against beta-cells. Therefore, people at risk of developing LADA may theoretically benefit by a combination of lifestyle changes as implementing appropriate diet and increasing exercise. However, evidence in this regard are scarce because the small number of studies in this regard were conducted exclusively in Scandinavian populations [50,51]. Furthermore, it is difficult to recognize people at higher risk of developing LADA and no specific recommendations exist for screening relatives of patients with LADA for islet autoantibodies or blood glucose values.

The different pathogenesis of inflammation in LADA could lead to the development of autoimmunity against different antigens. We have elsewhere [8] discussed the first findings from our group demonstrating in patients with LADA, in particular in those with an obese and insulin-resistant phenotype, the existence of autoantibodies against a specific construct of the IA-2 antigen ($IA\text{-}2_{(256\text{-}760)}$), which is different from the construct traditionally recognized by the IA2-A found in T1D ($IA\text{-}2IC_{(605\text{-}979)}$) [52,53]. These autoantibodies have been also recently shown in obese patients with normal glucose tolerance [54]. $IA\text{-}2_{(256\text{-}760)}$ construct has an extracellular N-terminal portion that is more accessible to antigen-presenting cells than the intracellular portion of this protein. This observation may let hypothesize that it can trigger an autoimmune response to unknown self-antigens in the presence of low-grade inflammation, thereby accelerating β-cell loss in obese patients predisposed to autoimmunity. Accordingly, the extracytoplasmatic (EC) $IA\text{-}2EC_{(26\text{-}577)}$ fragment of the IA-2 protein, has also been recently shown as a new epitope (which however overlaps with $IA\text{-}2_{(256\text{-}760)}$) involved in pancreatic autoimmunity in LADA. In particular, autoantibodies against $IA\text{-}2EC_{(26\text{-}577)}$ were found in a subgroup of patients with adult-onset autoimmune diabetes with a “T2D-like” phenotype negative for conventional islet autoantibodies [55], suggesting that the N-terminal region of IA-2 could contribute to the diabetic antigenicity in “T2D-like” patients. In the same line of evidence, antibodies against the central or C-terminal domains of glutamic acid decarboxylase (GAD65) in patients with LADA are prone to be associated with a T1D phenotype and an early need insulin therapy, while antibodies against N-terminal domains are prone to be associated with T2D clinical features [56]. Overall, these findings from independent research groups suggest that different clinical phenotypes of adult-onset autoimmune diabetes may be associated with different epitope spreading (Fig. 1). In addition, also the affinity of islets autoantibodies for their targets has been recently associated to the different clinical phenotypes of LADA. In this regard, electrochemiluminescence assay (ECL) A is a new emerging method for islet autoantibody detection able to discriminate between high-affinity, high risk diabetes-specific antibodies and low-risk, low-affinity antibodies, [57]. Patients who are $ECL\text{-}GAD65^-$, in fact, share a similar T2D phenotype with a slower β-cell loss, whereas patients who are $ECL\text{-}GAD65^+$ show a rapid β-cell dysfunction and require insulin treatment like T1D patients [58].

6. What is new about LADA complications

We have previously highlighted that evidence published up to 2017 about the risk of developing macrovascular and microvascular complications in LADA was very scarce [8]. A systematic analysis of the few studies reporting data about this topic at that time suggested no difference in the prevalence of cardiovascular disease between patients with LADA and those with T2D, independently from diabetes duration. On the contrary, microvascular complications appeared to be rarer in patients with LADA close to diabetes diagnosis, whereas an opposite pattern was suggested later in the disease history [8]. However, those studies were significantly limited by a low sample size, a cross-sectional study design for most of them or a very short follow-up for the few longitudinal studies, and by the lack of data about risk factors possibly explaining the differences found between diabetes types. To confirm these preliminary observations with a stronger evidence, we have recently evaluated the long-term risk of cardiovascular, retinal and renal events in LADA compared to T2D in the large population of adults with a clinical diagnosis of new-onset T2D enrolled in the United Kingdom Prospective Diabetes Study (UKPDS) [6,59]. In the UKPDS, 5102 patients with newly diagnosed T2D were randomized to receive conventional glucose control strategy or to an intensive glucose control strategy and were followed for up to 30-years to ascertain both macrovascular and microvascular outcomes [60]. While all participants were initially thought to be affected by T2D, about 11% resulted positive to at least one diabetes-specific autoantibody [61]. Together with the very long follow-up and the adjudication of all cardiovascular, eye and kidney events, this allowed us to robustly describe the comparative risk of vascular complications in LADA and T2D and the respective risk factors. Participants with LADA had a 27% lower risk of major adverse cardiovascular events compared to T2D, which was however

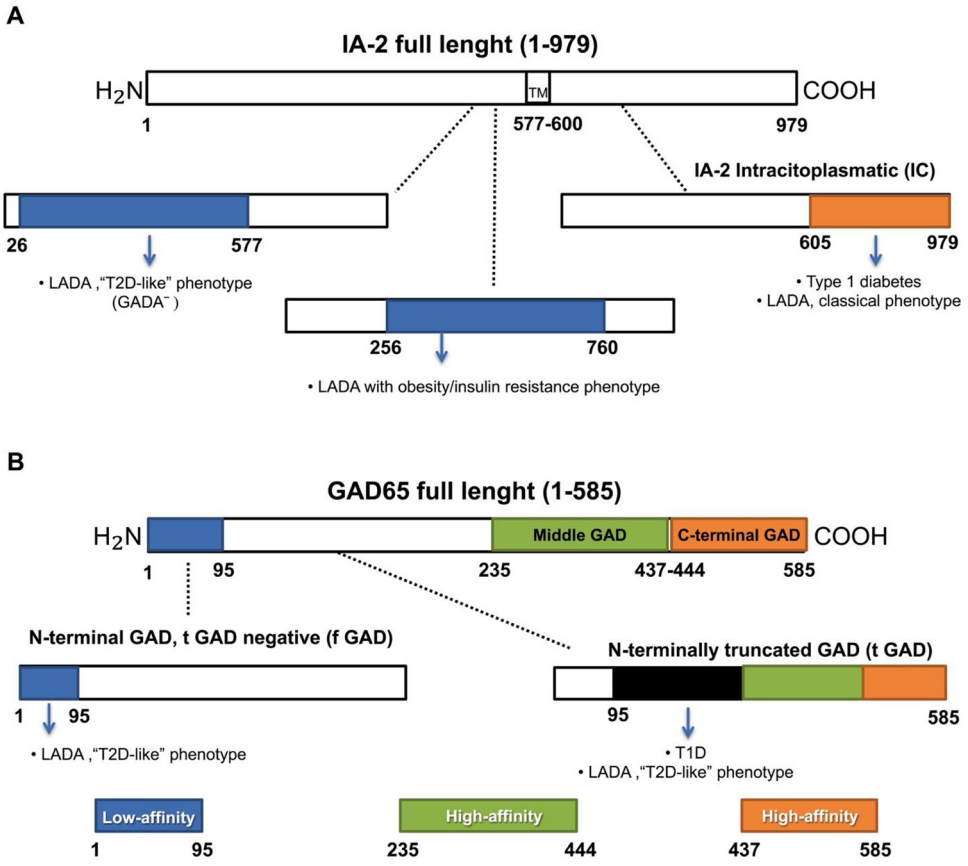

Fig. 1. Epitope spreading differs according to the type of autoimmune diabetes. GAD65 and IA2 are two main self-antigens of autoimmune diabetes, but the construct recognized by the immune system may differ in patients with LADA and in patients with T1D. **A** IA-2 is characterized by different epitopes, which have their own immunoreactivity, linked to various phenotypes of autoimmune diabetes. Immunoreactivity to extra-cytoplasmic portion (N-terminal) appears to be more prone to an autoimmune diabetes with a phenotype similar to T2D (such as LADA), unlike immunoreactivity to intra-cytoplasmic portion (C-terminal) typical of an autoimmune diabetes with the classical T1D-like phenotype. **B** GAD antigen is divided into three constructs, each one with its own immunoreactivity. As well as IA-2, each GAD epitope is associated to a different clinical phenotype. Middle and C-terminal regions have high affinity for GADA and they are associated with a T1D-like phenotype, whereas autoimmunity only against the N-terminal region is more related to a T2D-like phenotype. Antibodies recognizing the N-terminally truncated (95-585) GAD65 epitope are also called t-GADA, whereas autoantibodies recognizing the N-terminal (1-95) GAD65 region are also called f-GADA.
Abbreviations. TM, transmembrane; IA-2, tyrosine phosphatase 2; LADA, Latent Autoimmune Diabetes in Adults; T2D, Type 2 diabetes; GAD65, 65 kDa isoform of glutamic acid decarboxylase GADA glutamic acid decarboxylase antibody.

completely explained by the younger mean age and the more favorable cardiometabolic profile observed in LADA [59]. A time-varying risk was instead found for microvascular complications in the group of patients with LADA, who, compared to patients with T2D, showed a 55% lower adjusted risk for the composite microvascular outcome (renal failure, renal death, blindness in one eye, vitreous haemorrage and retinal photocoagulation) during the first nine years after diagnosis. The lower risk was reversed over time by the sustained poorer glycaemic control observed in people with LADA. They showed a 33% greater adjusted risk than T2D for the same outcome beyond the first 9 years of follow-up. In accordance with the recent GWAS data [25], these UKPDS findings point toward LADA being more close to T1D than to T2D also in terms of complication risk. Indeed, compared to T2D, and similarly to T1D, LADA patients less frequently develop both cardiovascular events, as a consequence of a lower cardiometabolic load, and early microvascular events. However, they experience more difficulties in achieving an optimal glycemic control, as it often happens in T1D, resulting in worse long-term microvascular outcomes. These observations are also in line with Ahlqvist et al. who showed that the cluster of patients with GADA-positive adult-onset diabetes has an unadjusted lower risk of coronary events and a sustained worse glycemic control compared to patients with predominant insulin-resistance, obesity or age-related diabetes [7]. In accordance with the UKPDS findings, also in this case no significant difference in cardiovascular risk was found between diabetes subgroups after adjustment for age and sex.

Overall, the most recent original articles about the risk of developing complications in LADA may have relevant clinical implications. First, they show that measuring diabetes autoantibodies may aid microvascular risk stratification, which is essential for precision medicine. They also emphasize the importance of aggressively tackling traditional cardiovascular risk factors since the diagnosis to keep at the lowest the risk of major cardiovascular events in people with adult-onset autoimmune diabetes. Finally, they show the existence of metabolic memory in LADA, highlighting an early therapeutic window in this group to improve microvascular outcomes by implementing strict glycaemic control.

7. What is new in LADA therapy

As highlighted above, a strict glycaemic control is crucial in LADA. Unfortunately, few novel data have been published since 2017 to better inform clinicians about LADA therapy.

It was already known that sulfonylureas induces a more rapid progression toward beta-cell failure in LADA [62,63], and that early insulin therapy can instead preserve beta-cell function [64]. Further evidence supporting an insulin therapy in LADA comes from a post-hoc analysis of the UKPDS by subgroups of diabetes autoantibodies positive and negative, which showed that early intensive insulin therapy might be associated with protection from cardiovascular death in LADA, but this finding should be evaluated in interventional randomized controlled trials, particularly in light of the cardiovascular benefits that have been observed with some new classes of glucose lowering drugs [59]. Furthermore, despite these evidences, it is still hard to determine the most suitable time to start insulin therapy and the right insulin therapy regimen for patients with LADA.

Some studies had also suggested beneficial effects of drugs acting on the incretin system to protect beta-cell function [65–69]. In this regard, the dipeptidyl-peptidase 4 inhibitor (DPP4i) sitagliptin has been shown to alter the phenotype and the subsets of T cells in LADA, by increasing the protective T helper 2 cells and by decreasing the pathogenic T helper 17 cells, also resulting in an ameliorated glycemic control [70]. However, 21-months treatment of LADA patients with sitagliptin did not result in better endogenous insulin secretion compared to insulin treatment [71]. As well, a small pilot study did not find benefits in

terms of c-peptide when using sitagliptin compared to pioglitazone [72]. On the other hand DPP4i have been hypothesized to be useful if used in combination with other drugs tackling the complex pathophysiology of autoimmune diabetes [73,74]. In this regard, a recent study showed that vitamin D3 in add-on to saxagliptin could maintain pancreatic beta-cell function in LADA [75] probably because vitamin D acts as immunomodulator with consequent beneficial effect of protecting islet β-cell [76]. Potential benefits of glucagon-like peptide 1 receptor agonists (GLP-1RA) in LADA have also been recently evaluated in a post-hoc analysis of the phase three randomized trials AWARD-2, -4 and -5, which were part of the dulaglutide clinical development program in T2D. The study showed that dulaglutide (a once-weekly GLP-1 receptor agonist) significantly reduced HbA1c levels and increased beta cell function markers in LADA patients (GADA positive) [77].

While bariatric surgery has been shown to significantly improve glycemic control in T2D, a recent retrospective study evaluating the effect of Roux-en-Y gastric bypass or of sleeve gastrectomy in ten obese patients with LADA did not show improvement in glycaemic control neither in other cardiometabolic risk factor, despite patients achieved a significant reduction in body weight. Furthermore, about half of the patients experienced diabetic ketoacidosis after surgery [78].

A promising therapeutic option might be the use of sodium glucose cotransporter 2 inhibitors (SGLT2i) for their potential role in β cell regeneration with significant reduction in HbA1c [79,80], but available data are still scarce, and also in this case risk of diabetic ketoacidosis should not be forgotten.

Overall, the heterogeneity of the disease makes it difficult to establish a standardized therapeutic algorithm. Accordingly, physician approaches are also extremely heterogeneous, with current therapies for LADA patients being largely based on the advantages and disadvantages of each drug class experienced in T1D and T2D (Table 1). Insulin is the most frequent therapeutic choice in patients with LADA because of its proven efficacy for both controlling hyperglycemia and preserving beta-cells. However, in some patients showing an insulin-resistant phenotype and with good beta-cell reservoir, insulin, which is associated to increased risk of hypoglycemia and weight gain, may not be the only strategy to choose. These patients may indeed benefit from insulin-sensitizers, such as metformin, which use has been however barely investigated in LADA, or thiazolidinediones, which have anti-apoptotic effects associated to preservation of C-peptide in LADA [81]. Other molecules, such as the above discussed DPP4i, GLP1-RA or SGLT2i, may be used in combination with insulin or insulin-sensitizers based on a personalized approach which consider the specific needs of the single patient. Regular follow-up is crucial for patients with LADA. Therefore, patients with LADA should be reassessed on a regular basis every three-six months to avoid clinical inertia, as suggested for patients with other forms of diabetes [82].

8. Conclusions

Some relevant progresses in the understanding of LADA pathophysiology and clinical implications of LADA have been made very recently (Table 2). While LADA had been thought to be a perfect mixture of T1D and T2D, the most recent studies conducted on large LADA cohorts point toward LADA being a distinct form of T1D. Yet some differences with classical T1D are evident because most people with LADA have the unique features of residual beta-cell function and slow diabetes progression, free from insulin dependence, for years after diabetes diagnosis despite the presence of autoimmunity. Therefore, these findings are extremely relevant in that they give LADA the potential to be a perfect clinical model to understand determinants of the degree and rate of disease progression. While research progresses, however, the clinical problem of how to manage patients with LADA has not yet been solved so far. Aims of ideal therapy should be to achieve an adequate metabolic control, delay or prevent micro and macrovascular complications, and to preserve residual pancreatic beta cells. However, the high heterogeneity of LADA makes it very difficult to identify the optimal therapy for this form of diabetes. Preferable solution could be an individualized approach, with a tailored therapy based on characteristics of each LADA patient.

Contributors

Ernesto Maddaloni contributed to article planning, literature search and manuscript writing.

Chiara Moretti contributed to literature search and manuscript writing.

Carmen Mignogna contributed to literature search and manuscript writing.

Raffaella Buzzetti contributed to article planning and critical revision of the manuscript.

Table 1
Advantages and disadvantages of different therapeutic choices for the management of latent autoimmune diabetes in adults (LADA). Abbreviations: GI, gastrointestinal; DKA, diabetic ketoacidosis; DPP4, dipeptidyl peptidase 4; GLP1, glucagon-like peptide 1; SGLT2, sodium-glucose co-transporter 2.

Therapy	Advantages	Disadvantages
Insulin	- Proven safety and efficacy. - Suppression of autoimmunity. - Possible cardiovascular benefits in LADA.	- Risk of hypoglycemia and weight gain
Metformin	- Low cost. - Useful in LADA with insulin resistance.	- Limited evidence in LADA
Thiazolidinediones	- Potential role in preserving beta cell mass. - Anti-apoptotic effects. - Useful in individuals with high insulin resistance	- Weight gain. - Not effective in lean subjects - Liquid retention
Sulfonylureas	- Low cost	- Risk of hypoglycemia - Exacerbation of autoimmunity - Beta cell function exhaustion
DPP-4 inhibitors	- Immunoregulatory properties. - Potential role in preserving beta cell viability and function.	- Minimal effects on glycemia. - Prospective studies are small and inconclusive.
GLP-1R agonists	- Good effects on HbA1c and on markers of beta cell function.	- GI side effects. - Limited evidence in LADA.
SGLT-2 inhibitors	- Cardiovascular and kidney benefits.	- Increased risk of DKA. - Limited evidence in LADA.
Vitamin D	- Immunomodulatory function. - Protection of islet beta cells.	- Contrasting evidence about its efficacy in diabetes.
Immune intervention	- Preserving c-peptide.	- Limited evidence in LADA. - No immune intervention approved for autoimmune diabetes.

Table 2
Summary box. Main advances in knowledge about LADA from 2017 to 2020 and current gaps in knowledge.

Topic	Knowledge in 2017	Knowledge in 2020	Current gaps in knowledge
LADA definition	2005 IDS definition	2005 IDS definition	Should c-peptide decline be included in the diagnostic criteria of LADA?
Genetics	Genetics of LADA is mid-way between T1D and T2D	The first GWAS in LADA has been performed pointing towards LADA mainly being a form of T1D with lower genetic load.	Candidate genes associated with milder autoimmune response against beta-cell should be searched outside the known regions associated to T1D
	Most studies underpowered and conducted in a single population	The association of TCF7L2 with LADA has been questioned.	
Physiopathology	Pancreatic inflammation showed in LADA by scintigraphy	A pathology study of pancreases from LADA patients is now available showing immune cell-infiltration (CD8+ T-cells and macrophages)	Does the immune cell infiltration differ among the different clinical phenotypes of LADA?
	High and low GADA levels differentiate subtypes of LADA	GADA affinity in addition to GADA levels may differs according to the clinical phenotype	What are the main determinants of the milder autoimmune response in LADA compared to T1D?
	First studies showing epitope spreading may differ between T1D and LADA	Studies from independent groups reinforce the hypothesis of different epitope spreading within IA2 and GAD65 proteins.	What is the role of insulin resistance in LADA pathogenesis?
Complications	Few, underpowered and mostly cross-sectional studies suggesting risk of microvascular complications in LADA may vary according to disease duration.	Long-term longitudinal studies show:	What is the risk of neuropathy?
			Why the risk of microvascular complications is lower in LADA compared to T2D at diagnosis?
		- Lower rates of major cardiovascular events in LADA compared to T2D, which are explained by the better cardiometabolic profile in LADA	What is the impact of novel anti-diabetes drugs on the risk of vascular complications in LADA?
	Macrovascular disease similar to T2D despite differences in metabolic features	- Risk of microvascular complications is lower in LADA compared to T2D at diagnosis but severely affected in the long-term by the worse glycemic control seen in LADA patients	
Therapy	Early insulin therapy is associated with good metabolic control and beta-cell function preservation	Sitagliptin impacts on T-cell subsets in LADA, but failed to show benefits on c-peptide	When is the right time for starting insulin in LADA?
			Should we use metformin in patients with LADA?
			Should all patients with LADA be treated in the same way?
	There is the rationale for testing incretin-base therapy in LADA	Post-hoc analyses of the AWARD trials suggest potential benefits of dulaglutide in LADA	Is the risk of SGLT2i- associated euglycaemic ketoacidosis the same in LADA as in T1D?

Conflict of interest

Dr Maddaloni has received grants from scientific societies supported by Lilly and AstraZeneca and honoraria or consulting fees from Merck-Serono, Pikdare, AstraZeneca, and Abbott. Prof. Buzzetti has received honoraria or consulting fees from Sanofi, Eli Lilly, Abbott, and AstraZeneca. Dr Moretti and Dr Mignogna declare that they have no conflict related to this manuscript.

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