Latent Autoimmune Diabetes in Adults: Current Status and New Horizons

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Autoimmune diabetes is a heterogeneous disease which can arise at any age. Subjects with adult-onset autoimmune diabetes who do not necessitate insulin-therapy for at least 6 months after diagnosis are demarcated as having latent autoimmune diabetes in adults (LADA). This condition is more heterogeneous than young-onset autoimmune diabetes and shares clinical and metabolic characteristics with both type 2 and type 1 diabetes. Patients with LADA are considered by having highly variable β-cell destruction, different degrees of insulin resistance and heterogeneous titre and pattern of islet autoantibody, suggesting different pathophysiological pathways partially explaining the heterogeneous phenotypes of LADA. To date the heterogeneity of LADA does not allow to establish *a priori* treatment algorithm and no specific guidelines for LADA therapy are available. These subjects are mostly treated as affected by type 2 diabetes, a factor that might lead to the progression to insulin-dependency quickly. A personalised medicine approach is necessary to attain optimal metabolic control and preserve β-cell function to decrease the risk of long-term diabetes complications. Recent data concerning the use of oral antidiabetic agents as dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 receptor agonists indicate up-and-coming results in term of protect C-peptide levels and improving glycaemic control. This review summarises current knowledge on LADA, emphasising controversies regarding its pathophysiology and clinical features. Moreover, we discuss data available about novel therapeutic approaches that can be considered for prevention of β-cell loss in LADA.

Keywords: Islet cell; Autoantibodies; Diabetes mellitus, type 1; Diabetes mellitus, type 2; C-peptide; B-cell function; Insulin; Insulin resistance; Latent autoimmune diabetes in adults

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an autoimmune disease derived from the selective destruction of insulin-secreting β-cells leading to requirement of insulin therapy [1]. This condition occurs in most cases during childhood or adolescence; however, some patients experience onset in adulthood [2]. A proportion of subjects with adult-onset autoimmune diabetes does not require insulin-therapy at the time of diagnosis and are clinically similar to patients with type 2 diabetes mellitus (T2DM). These patients, who were initially thought to be affected by T2DM, are defined as having latent autoimmune diabetes in adults (LADA) [3-5], a form of autoimmune diabetes, distinct from T1DM that shows an older age of onset and slower progression towards insulin requirement [6-8].

To diagnose LADA, the Immunology of Diabetes Society has established three main criteria including: (1) adult age of onset (>30 years); (2) presence of any islet cell autoantibody; and (3)

absence of insulin requirement for at least 6 months after diagnosis [9]. However, the definition of LADA remains controversial and an open debate regarding these diagnostic criteria still exists. Thus, patients defined as having LADA are characterized by genetic, phenotypic, and immunological heterogeneity, highly variability of the β-cell destruction's rate and different degrees of insulin resistance and autoimmunity, likely due to differences in genetic and immune factors [10-12]. Moreover, the great heterogeneity of LADA makes it difficult to determine an *a priori* algorithm for treatment. A personalised therapy for LADA should be implemented [13].

This review summarizes and discusses current knowledge about LADA, emphasizing the differences from both T1DM and T2DM. In addition, we examine the results of recent studies about novel therapeutic approaches that could prevent β-cell loss in LADA.

EPIDEMIOLOGY

Most epidemiological studies suggest that adult-onset autoimmune diabetes is not rare as previously reported (Table 1) [5,13-17]. Indeed, data collected from Italian registries show that the incidence of T1DM in subjects aged 30 to 49 years is similar to that of adolescents aged 15 to 19 years [18]. According to these data, studies among Caucasians from Northern Europe reported that approximately 40% of T1DM cases occur in people older than 30 years of age [2] and that the real incidence of this condition in subjects aged 15 to 34 years is up to three times higher than previously reported [19]. Data reported in LADA show that this is the most frequent form of adult-onset autoimmune diabetes and may account for 2% to 12% of all cases of diabetes in adult population [20]. Moreover, multicentre studies carried out in Europe, Asia, and North America, reported that 4% to 14% of patients diagnosed with T2DM are positive for T1DM associated autoantibodies which are diagnostic for LADA [4,5,21-29]. However, the prevalence of LADA seems to vary between different countries and populations, probably due to differences in study design and inclusion criteria, as well as different life-style and ethnicity. In Action LADA, a European multicentre study that evaluated over 6,000 adult-onset diabetes patients, the overall frequency of islet cell autoantibody positivity was reported in 9.7% of subjects with T2DM, even though consistent differences between patients living in North and South Europe were found, ranging between 4% and 10%. In accordance with these data, the NonInsulin Requiring Autoimmune Diabetes (NIRAD study) found a cumulative frequency of positivity for autoantibodies (glutamic acid decarboxylase [GAD] and/or protein tyrosine phosphatase [IA-2]) in 5% of

Table 1. Epidemiology of LADA [13]

Study	Country	Type of study	No. of sample size	Age range, yr	Autoantibody	Frequency of autoantibody positivity, %
UKPDS 25	United Kingdom	Clinical based	3,672	25–65	GAD and/or ICA	12
BOTNIA	Finland	Registry based	1,122	28–83	GAD and/or IA-2	9.3
Ehime study	Japan	Clinical based	4,980	>20	GAD	3.8
ADOPT	USA, Europe	Clinical based	4,357	30–75	GAD and/or IA-2	4.2
NIRAD	Italy	Clinical based	5,330	30–75	GAD and/or IA-2	4.5
HUNT	Norway	Population based	1,134	≥20	GAD	10
Tianjin	China	Population based	8,109	≥15	GAD	9.2
Maioli et al. (2010) [14]	Italy (Sardinia)	Clinical based	5,568	35–70	GAD	4.9
Action LADA	Europe	Clinical based	6,810	30–70	GAD and/or IA-2, ZnT8	9.7
LADA China	China	Clinical based	5,324	≥20	GAD	5.9
Maddaloni et al. (2015) [5]	United Arab Emirates	Clinical based	17,072	30–70	GAD and/or IA-2	2.6
Lee et al. (2009) [16]	Korea	Clinical based	1,370	47–62	GAD and/or IA-2	5.1
Park et al. (2011) [17]	Korea	Population based	884	44–60	GAD and/or IA-2, ZnT8	4.4
Roh et al. (2013) [15]	Korea	Clinical based	323	29–63	GAD	5.3

Adapted from Buzzetti et al., with permission from Springer Nature [13].

LADA, latent autoimmune diabetes in adults; UKPDS, United Kingdom Prospective Diabetes Study; GAD, glutamic acid decarboxylase; ICA, islet cell; IA-2, protein tyrosine phosphatase; NIRAD, NonInsulin Requiring Autoimmune Diabetes; ZnT8, islet-specific zinc transporter isoform 8.

Italian patients with T2DM [25]. Similar results emerge from studies carried out in Asia. In the multicentre China study a frequency of 5.9% was reported [30], whereas data in the Korean population show a prevalence ranging between 4.4% and 5.3% [15]. Regarding African-American, Hispanic, and Arab populations, recent studies have highlighted a lower prevalence of adult-onset autoimmune diabetes among these populations [5,31].

PATHOGENESIS

The spectrum of adult-onset diabetes involves all three forms of diabetes (T1DM, T2DM, and LADA) without defined parameters. The distribution of pathological factors, such as autoimmunity, insulin sensitivity and β-cell function, along a continuous line distinguishes categories of diabetes mellitus (Fig. 1) [13, 28,32]. When compared with classical T1DM, LADA appears like the other extreme of the autoimmune diabetes spectrum, whereby genetic susceptibility, autoimmune response and non-insulin-necessity presentation constitute a mild form of autoimmune diabetes with pathological features closer to those of T2DM than to those of adult T1DM, which is more similar to classical T1DM [13].

Genetic features
Data available on genetic susceptibility suggest that LADA shows a lower genetic component [10,11,33] than T1DM. In particular, the human leukocyte antigen (HLA)-DRB1*04-

DQB1*0302 and HLA-DRB1*0301-DQB1*0201, which are very common in young-onset T1DM and decrease in frequency with the increasing age at disease onset, are less frequent in LADA than in adult-onset T1DM [25,34]. Similar findings have been observed for the Cyst1858Thr single-nucleotide polymorphism in the protein tyrosine phosphatase nonreceptor 22 (PTPN22) gene and the insulin variable number tandem repeat (INS VNTR) I/I genotype expression [34,35]. Otherwise, the frequency of the cytotoxic T-lymphocyte–associated antigen 4 (CTLA4) Ala49Gly polymorphism in exon 1 has been shown not to be associated with the age of onset of T1DM, suggesting a similar role in LADA susceptibility [36].

Another study carried out in Swedish and Finnish populations, showed that the frequency of T2DM associated CT/TT genotypes rs7903146 in the transcription factor 7 like 2 (TCF7L2) gene was increased in LADA subjects as in T2DM subjects [37], as well as genetic similarities with T1DM have been observed related to HLA, INS VNTR, and PTPN22 [38]. These results suggest that patients with LADA may share genetic features with both T1DM and T2DM which further supports the concept that LADA is an admixture of the two major types of diabetes [38].

However, it should be noted that most of these studies have investigated genes previously associated with young-onset T1DM or T2DM [10,39-42]. Further studies are needed to better characterize the genetic susceptibility of LADA in order to establish preventive strategies as well as allow safe and effective therapies [43].

Autoimmunity
In T1DM activated T-cells to islet-cell proteins characterize the lymphomononuclear cell infiltration in the endocrine pancreas (insulitis), causing the progressive loss of insulin-secreting β-cells. On the other hand, islet cell autoantibodies seem to be an epiphenomenon rather than pathogenic factors in β-cells destruction, though their detection in plasma helps to diagnose autoimmune diabetes.

As a form of autoimmune diabetes, LADA is characterized by islet-cell specific autoantibody positivity and similar cell-mediated immune response although impairment of β-cells is slower than in classical T1DM [6-8]. Specifically, a recent study observed presence of insulitis by pancreatic scintigraphy using interleukin 2 (IL-2) radiolabelled with technetium-99m (^{99m}Tc) and contrast-enhanced magnetic resonance imaging, providing evidence for the presence of activated mononuclear cells in the pancreas of LADA subjects, particularly within 1 year of initia-
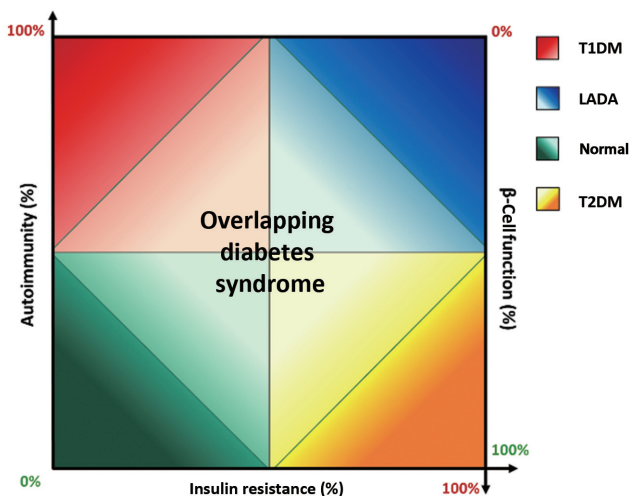

Fig. 1. Pathogenetic features and their relation to define diabetes. T1DM, type 1 diabetes mellitus; LADA, latent autoimmune diabetes in adults; T2DM, type 2 diabetes mellitus [32].

tion of insulin therapy, similar to T1DM at diagnosis [44]. Moreover, increased pancreatic ^{99m}TC-IL-2 uptake has been found in a subgroup of autoantibody-negative diabetic subjects, suggesting that insulitis may occur even in absence of islet-cell autoantibodies [45].

C-peptide, a marker of residual β-cell function, declines slower in LADA than in T1DM. Thus, a positive correlation between age at diagnosis of autoimmune diabetes and fasting C-peptide levels has been reported [46]. Indeed, LADA subjects show higher stimulated C-peptide values al all time-points following a mixed-meal tolerance than subjects with classical T1DM [12].

Islet-cell autoantibodies detectable in subjects with LADA are the same used to identify T1DM. Glutamic acid decarboxylase autoantibody (GADAs) is the most sensitive marker in both adult-onset T1DM and LADA, whereas insulin autoantibodies, protein tyrosine phosphatase IA-2 (IA-2A) and islet-specific zinc transporter isoform 8 (ZnT8) autoantibodies, which are detectable in younger T1DM patients, are positive only in a small percentage of LADA patients [47]. In the Action LADA study, 68.6% of subjects screened for diabetes-associated autoantibodies were positive for GADA only, 5% positive for IA-2A only and 2.3% positive for ZnT8A only, whereas at least two autoantibody types were found in 24.1% patients [4].

To sum up and as previously mentioned, LADA shows halfway pathological features between T1DM and T2DM. In a recent Italian work, it has been suggested that different pathophysiological could explain the heterogeneous phenotypes of LADA [13]. Based on this model, in patients with moderate genetic susceptibility to T1DM, specific immunological factors can trigger an autoimmune process against islet cell antigens marked by the appearance of GADAs leading to β-cell apoptosis and insulin deficiency. On the other hand, in obese subjects

with genetic susceptibility to T2DM, the low-grade inflammation, typical of visceral adiposity, might trigger a low-grade autoimmune process marked by IA-2 autoantibodies positivity, causing loss of β-cell function and an impairment of insulin secretion (Fig. 2).

Clinical features and relation with islet autoantibody profile

LADA shares clinical and metabolic features with T2DM and T1DM as part of a continuum of variable severity of immune and metabolic dysfunction [48], described as "end of the rainbow" (Tables 2, 3) [8].

Metabolic syndrome and its components (blood pressure, lipid profile, waist-hip ration) are less prevalent in LADA patients than in those with T2DM, both in Caucasians and non-Caucasians subjects [5,16]. Nevertheless, this assumption changes when LADA patients are compared with patients with T1DM. The BOTNIA study [22] demonstrated that components of metabolic syndrome have a higher prevalence in LADA than in classical T1DM. Similar results emerge from the Action LADA project [49]. Another study, carried out in Spain, showed that adiposity parameters, blood pressure and triglyceride levels are more elevated in LADA than in T1DM but lower than in T2DM [50]. Similarly, data collected among a cohort of subjects with LADA in the United Arab Emirates showed higher body mass index (BMI), waist circumference, systolic blood pressure and glycated hemoglobin (HbA1c) values [5]. On the other hand, Swedish and Norwegian registers report that overweight and obesity are associated with increased risk of LADA [37], particularly in combination with family history for diabetes. However, as previously discussed, LADA is characterized by a great phenotypic heterogeneity, witnessed by variable degrees of in-
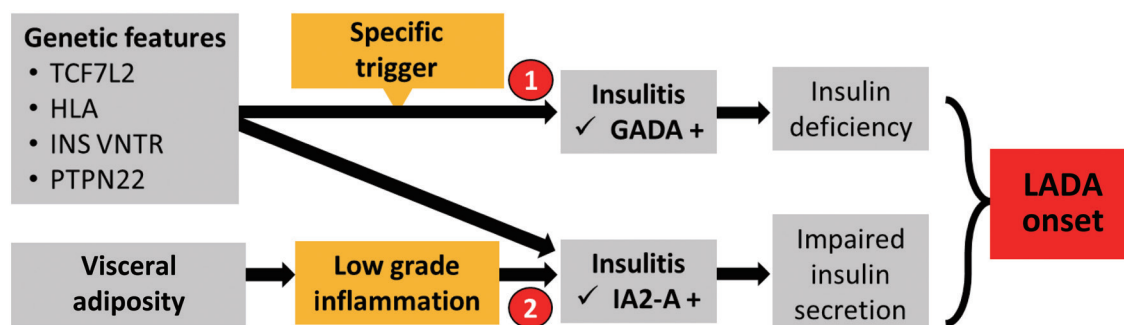

Fig. 2. Potential pathological pathways of latent autoimmune diabetes in adults (LADA). Modified from Buzzetti et al., with permission from Springer Nature [13]. TCF7L2, transcription factor 7 like 2; HLA, human leukocyte antigen; INS VNTR, insulin variable number tandem repeat; PTPN22, protein tyrosine phosphatase nonreceptor 22; GADA, glutamic acid decarboxylase autoantibody; IA-2A, protein tyrosine phosphatase IA-2.

sulin resistance and insulin insufficiency.

Recent evidence shows that the titre of antibody positivity, especially GADA, can influence clinical characteristics of subjects with LADA [14,25,28]. The NIRAD study [25] demonstrated the presence of a "bimodal distribution" of GADA titre in LADA sub-classifying two distinct forms of the disease. Patients with high GADA levels, typed as LADA 1, show more similar phenotypic features with T1DM (lower C-peptide levels, lower BMI, more ketosis prone) than with T2DM, whereas patients with low GADA titre, typed as LADA 2, are less ketosis

Table 2. Differences in Clinical and Genetic Features between LADA and T2DM

	LADA	T2DM
Age at diagnosis	>30 Years	Adulthood (rarely before)
Family history of diabetes	Negative or positive	Frequently positive
HLA susceptibility	Increased	Mild increased
Onset	Subclinical (rarely acute)	Silent/subclinical
Rate of long-term complications at diagnosis	Low	High
Risk of acute complications at diagnosis	Low	Mild increased
C-peptide levels at diagnosis	Decreased but still detectable	Normal to increased
Autoimmunity	Mild increased	Absent
Ketosis	Rare	Rare
Insulin resistance	Increased/no change	Increased
β-Cell function	Decreased	Increased or normal
Insulin requirement	>6 Months after diagnosis	Absent or years after diagnosis
Body mass index	Normal (rarely overweight or obese)	Overweight or obese
Cardiovascular risk	Increased	Increased
Lipid profile	Normal to hypertriglyceridemia	Frequently hypertriglyceridemia and/or hypercholesterolemia

LADA, latent autoimmune diabetes in adults; T2DM, type 2 diabetes mellitus; HLA, human leukocyte antigen.

Table 3. Differences in Clinical and Genetic Features between LADA and T1DM

	LADA	T1DM
Age at diagnosis	>30 Years	Childhood/adolescence (rarely in adulthood)
Family history of diabetes	Negative or positive	Negative or positive
HLA susceptibility	Increased	Importantly increased
Onset	Subclinical (rarely acute)	Acute
Rate of long-term complications at diagnosis	Low	Low
Risk of acute complications at diagnosis	Low	Increased
C-peptide levels at diagnosis	Decreased but still detectable	Non detectable (rarely decreased)
Autoimmunity	Mild increased	Importantly increased
Ketosis	Rare	Rare
Insulin resistance	Mild increased	Absent (rarely increased)
β-Cell function	Decreased (−)	Loss of function
Insulin requirement	>6 Months after diagnosis	At diagnosis
Body mass index	Normal (rarely overweight or obese)	Normal (or underweight)
Cardiovascular risk	Increased	Increased
Lipid profile	Normal to hypertriglyceridemia	Normal (especially)

LADA, latent autoimmune diabetes in adults; T1DM, type 1 diabetes mellitus; HLA, human leukocyte antigen.

and dyslipidemia prone as compared with LADA 1, but possess higher frequency of obesity, hypertension, dyslipidemia, and cardiovascular diseases. Similar results have been found in a Korean population where GADA levels showed a negative correlation with age of onset, total cholesterol, triglycerides, BMI, fasting and stimulated C-peptide, whereas a positive correlation was found with HbA1c and high density lipoprotein cholesterol [15]. The existence of two distinct subgroups of patients affected by LADA has been substantiated by genetic studies. PTPN22 risk genotype has been associated with a high GADA titre [51], whereas some but not all studies, have found an association between a lower GADA titre and the TCF7L2 risk allele for T2DM [52]. In addition, a higher frequency of other organ-specific autoantibodies (against thyroid peroxidase, steroid 21-hydroxylase, tissue, tissue transglutaminase, and parietal cell) was detected in patients with high GADA levels, highlighting a more extensive autoimmune process in this subpopulation than in those with a lower GADA titre [53]. Accordingly, several studies have testified an inverse relationship between GADA titre and C-peptide levels [54], as well as more pronounced traits of insulin deficiency were described in patients with higher GADA titre [25]. Another interesting finding concerns the relationship between clinical phenotypes of LADA and specific GADA binding patterns. Action LADA 12 [55] demonstrated an association between presence of N-terminally truncated GAD65 autoantibodies and the clinical phenotype of T1DM in patients with LADA. This may have important practical implications given the relatively large number of adult patients who are screened for GADA, both for diabetes classification and risk prediction for insulin therapy.

Even the number of islet autoantibodies in LADA appears to be associated with the intensity of autoimmune response. Indeed, the United Kingdom Prospective Diabetes Study (UKPDS) group and the NIRAD group, have noted that the number of islet cell autoantibodies was directly proportional to the intensity of autoimmune response, predicting more sever insulin insufficiency [21,47,56].

Not only the titre, but also different patterns of antibody positivity could influence clinical features of LADA patients. In a cohort of approximately 17,000 subjects affected by LADA, the positivity for IA-2A only was associated with a clinical phenotype more similar to T2DM, whereas subjects positive for both IA-2A and GADA were more similar to T1DM [5]. Other authors observed that IA-2A was the only autoantibody that showed increased frequency with increasing BMI in patients affected by T2DM [57]. However, conflicting data have been reported. In the Action LADA 7 patients positive for at least two autoantibodies compared with those positive for a single antibody did not show relevant differences in demographic or clinical parameters [4]. Moreover, mixed results about the correlation between GADA titre and length of insulin-free period have been reported [14,22,54,58].

NATURAL HISTORY OF LADA

To date, only few data related to the development of late diabetic complications have been reported in patients with LADA.

Microvascular complications

There are only few studies related to the occurrence of microvascular complications (nephropathy, retinopathy, neuropathy) in LADA and controversial results have been reported, partly due to a substantial heterogeneity regarding disease duration of study's subjects. Limited to patients with a short disease duration, microvascular complications in LADA appear to be less frequent than in patients affected by T2DM. In particular, the Fremantle Diabetes Study [59], showed less frequency of microalbuminuria in patients with a recent diagnosis of LADA than in those with T2DM. In addition, in the same study an association between GADA positivity and a reduced risk of developing microalbuminuria during a follow-up period (<5 years) was found. In a study among Chinese subjects [60], it was observed that the onset of nephropathy and retinopathy is less common in patients with a recent diagnosis (<5 years) of LADA than in those affected by T2DM. However, these findings could be explained by the fact that subjects with T2DM are usually diagnosed later than subjects with LADA, being chronically expose to hyperglycaemia which may ultimately lead to microvascular complications. Thus, studies evaluating patients with a disease duration >5 years did not find differences between LADA and T2DM with respect to the prevalence of nephropathy or retinopathy, as well as no association was found between GADA positivity and rate of microvascular complications [61-63]. However, the BOTNIA study [64] observed that patients with a disease duration >5 years had an increased risk of retinopathy; in addition, the rate of neuropathy appears more prevalent in LADA than in T2DM [59,62,64,65].

Macrovascular complications

A lower risk of macrovascular complications—including coronary heart disease, stroke, peripheral artery disease—could be postulated on the basis of the healthier metabolic profile of pa-

tients with LADA respect to those with T2DM. However, current data showed similar cardiovascular outcomes in LADA and T2DM. In the BOTNIA study [64] no statistically significant differences were found in respect to coronary heart disease, stroke, overall mortality, and cardiovascular mortality between LADA and T2DM. Similar results emerged from other independent studies. The Fremantle Diabetes Study [59] did not evidenced different rate of cardiovascular disease and mortality in LADA versus T2DM, while the HUNT2 study observed similar increase of cardiovascular risk in patients positive for GAD antibodies and in those who were negative, compared to non-diabetic patients [66]. Altogether, these results suggest that different pathogenetic mechanisms might modulate the onset of macrovascular complications in LADA, regardless of the metabolic profile.

Fracture risk

Impaired bone metabolism and increased risk of fractures have been observed in both T1DM and T2DM [67], partly due to reduction of bone formation. A recent cross-sectional study [68], showed that bone resorption is reduced in both LADA and T2DM compared to non-diabetic subjects whereas circulating sclerostin—which is an antagonist of the osteoblastic bone formation—is increased in T2DM only, probably due to the association between sclerostin levels and metabolic syndrome which is more prevalent in T2DM than in LADA. However, these data suggest that pathways involved in bone metabolism differ between these two types of diabetes and further studies are needed to clarify the pathogenesis of bone impairment and explore the potential role of sclerostin on bone fragility associated with diabetes.

TREATMENT OF LADA

To date, no specific guidelines for treatment of subjects affected by LADA have been published. Therefore, these subjects are mostly treated as affected by T2DM resulting in rapid progression to an insulin-dependent state [13], especially in patients who present with clinical and biochemical features closer to T1DM than T2DM [5,69]. In addition, a correct therapeutic strategy for LADA patients should aim to the preservation of residual β-cell function as well as improvement of glucometabolic control, in order to reduce the risk of long-term complications. Maintenance of β-cell function, as demonstrated by the Diabetes Control and Complication Trial, is indeed associated with a reduction of long teen diabetic complications [70].

Sulphonylurea

A small randomized controlled trial, carried out in Japan, compared glibenclamide with insulin treatment in subjects affected by LADA. Results showed worsening metabolic control and progressive deterioration of β-cell function as measured by significant reduction of stimulated C-peptide ratio after 30 months follow-up in patients treated with sulphonylurea [71]. Similar results have been reported in the Tokyo study [72], a multicenter, randomized, nonblinded clinical study that evaluated 4,089 noninsulin-dependent LADA patients with a 5-year or shorter duration of diabetes. In this study Maruyama et al. [72] demonstrated that the progression rate to insulin-dependency in the sulphonylurea group was higher than that in the insulin group, and C-peptide during the oral glucose tolerance test was more preserved in patients undergoing insulin therapy. Altogether, these data suggest that sulphonylurea should not be used as first-line therapy in patients with LADA.

Insulin therapy

There insulin treatment is essential in all patients with complete β-cell loss and represents the most straightforward therapy for replacing missing endogenous insulin secretion [13]. However, subjects with a recent diagnosis of LADA are characterized by some degree of preservation of β-cell function as shown by higher C-peptide levels, and progress slower to absolute insulin dependency. Nevertheless, consistent data from randomized clinical trials highlight the importance of an early initiation of insulin therapy in LADA regardless of presence of some endogenous insulin secretion. The rationale behind this approach is to improve metabolic control while protecting β-cell function.

Even though the pathophysiological basis of the protective effect of insulin therapy is not well known, several preclinical studies showed that therapy with exogenous insulin would support β-cell function, reducing the hyperglycaemic stress [73] and decreasing severity of insulitis [74]. Other studies suggest the promotion of T helper 2 immunity and activation of insulin-specific regulatory T-cells mediated by the exposure to exogenous insulin [75,76]. Moreover, a suppression of autoreactive T-cells through local release of regulatory cytokines has been suggested in patients treated with insulin [77].

Preservation of β-cell function: next frontiers in LADA therapy

An intervention intended to preserve β-cell function should be pursued in patients with LADA. Recent immune-intervention trials have achieved promising results in term of preserving

stimulated C-peptide levels and improving glycaemic control [78-80]. However, some drugs currently used for treatment of T2DM might be considered in LADA.

Dipeptidyl peptidase 4 (DPP-4) inhibitors represent a class of oral antidiabetic agents frequently used in T2DM which have been shown to preserve β-cell function and reduce insulitis in patients with T2DM as well as in mouse models of autoimmune diabetes [81-83], suggesting that they might be a valuable treatment option in LADA. A recent randomized-controlled study conducted in China [84] has observed that treatment with sitagliptin in addition to insulin preserved C-peptide concentration better than insulin alone in patients with LADA over a 1-year period. Similarly, sitagliptin improved glycaemic control in adults with T1DM [85]. Furthermore, Johansen et al. [86] have reported that another DPP-4 inhibitor, linagliptin, attenuated decline of C-peptide in LADA patients over a 2-year study period. In a *post hoc* analysis of data pooled from five randomized, placebo-controlled studies [87], saxagliptin was effective in lowering blood glucose levels and well tolerated in GADA-positive patients. Moreover, compared with placebo saxagliptin appeared to increase C-peptide levels at 24 weeks follow-up.

Other interesting findings come from our study of a *post hoc* analysis investigating treatment with dulaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1RA) [88] in patients with T2DM among whom there were some GAD antibody positive patients. The effectiveness of dulaglutide in subjects with LADA was indicated by reduction of HbA1c and increase of β-cell function, without affecting the rate of hypoglycaemia over 1-year observation period. This study is the first to indicate that dulaglutide is an effective anti-hyperglycaemic treatment in T2DM patients positive for GAD antibodies. Taking together these data highlight the potential long-term effects of DPP-4 and GLP-1RA in patients with LADA. However, further studies with larger cohort and longer treatment duration are needed to assess whether these therapies translate into a reduced progression to insulin dependence and diabetic complications [87].

CONCLUSIONS

Adult-onset autoimmune diabetes is a heterogeneous disease with clinical and metabolic features ranging from classical T1DM with onset from childhood to adult age, to LADA. When defined according to the criteria proposed by the Immunology of Diabetes Society, LADA also is characterized by significant degree of heterogeneity, encompassing different clinical phenotypes, ranging from prevalent insulin resistance to prevalent insulin deficiency associated with severe or mild markers of autoimmunity [47]. However, mid-way features between T1DM and
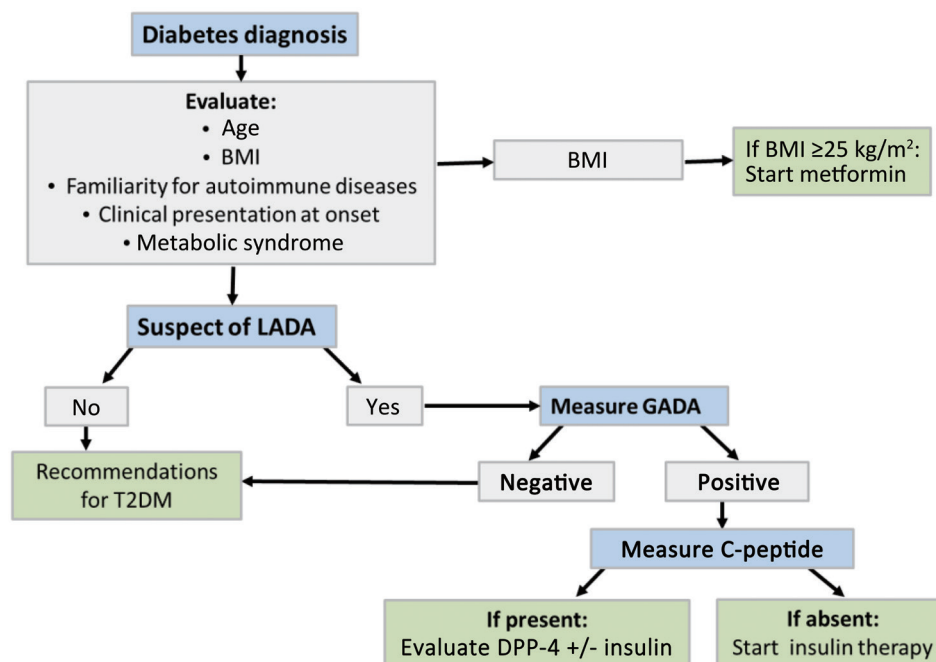

Fig. 3. Algorithm for diagnosis and therapy of latent autoimmune diabetes in adults (LADA). BMI, body mass index; T2DM, type 2 diabetes mellitus; GADA, glutamic acid decarboxylase autoantibody; DPP-4, dipeptidyl peptidase 4.

T2DM are recognised in patients affected by LADA. The titre of antibody positivity [14,25,28], especially GADA, as well as the recognition of different patterns of autoantibody positivity [5] can influence the clinical features of LADA and may be useful for diabetes classification and prediction of risk for insulin therapy.

Epidemiological studies show that LADA is a prevalent form of diabetes and may account for 2% to 12% of all cases of diabetes in adult population [20]. Moreover, 4% to 14% of patients diagnosed with T2DM are positive for T1DM associated autoantibodies which are diagnostic for LADA [4,5,14,21-29]. For this reason, when diagnosing diabetes in adult age, a diagnosis of LADA should be always considered, especially when clinical features are suggestive of this form of diabetes.

To date, an *a priori* algorithm for treatment of LADA does not exist [13]. However, a personalized medicine approach is requested to achieve optimal metabolic control and preserve β-cell function, which is associated with a lower risk of occurrence of long-term diabetes complications.

In this regard, several data showed that insulin treatment, as well as DPP-4 agents, can sustain residual β-cell function [81-88]. Insulin therapy (basal), at low dose can be prescribed to LADA patients with DPP-4 as an additional weapon, whereas sulphonylurea may hasten insulin dependency and should not be used as first-line therapy for patients with LADA (Fig. 3).

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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