Management of Latent Autoimmune Diabetes in Adults: A Consensus Statement From an International Expert Panel

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A substantial proportion of patients with adult-onset diabetes share features of both type 1 diabetes (T1D) and type 2 diabetes (T2D). These individuals, at diagnosis, clinically resemble T2D patients by not requiring insulin treatment, yet they have immunogenetic markers associated with T1D. Such a slowly evolving form of autoimmune diabetes, described as latent autoimmune diabetes of adults (LADA), accounts for 2–12% of all patients with adult-onset diabetes, though they show considerable variability according to their demographics and mode of ascertainment. While therapeutic strategies aim for metabolic control and preservation of residual insulin secretory capacity, endotype heterogeneity within LADA implies a personalized approach to treatment. Faced with a paucity of large-scale clinical trials in LADA, an expert panel reviewed data and delineated one therapeutic approach. Building on the 2020 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus for T2D and heterogeneity within autoimmune diabetes, we propose "deviations" for LADA from those guidelines. Within LADA, C-peptide values, proxy for β-cell function, drive therapeutic decisions. Three broad categories of random C-peptide levels were introduced by the panel: *1*) C-peptide levels <0.3 nmol/L: a multiple-insulin regimen recommended as for T1D; *2*) C-peptide values ≥0.3 and ≤0.7 nmol/L: defined by the panel as a "gray area" in which a modified ADA/EASD algorithm for T2D is recommended; consider insulin in combination with other therapies to modulate β-cell failure and limit diabetic complications; *3*) C-peptide values >0.7 nmol/L: suggests a modified ADA/EASD algorithm as for T2D but allowing for the potentially progressive nature of LADA by monitoring C-peptide to adjust treatment. The panel concluded by advising general screening for LADA in newly diagnosed non–insulin-requiring diabetes and, importantly, that large randomized clinical trials are warranted.

Both type 1 diabetes (T1D) and type 2 diabetes (T2D) are complex heterogeneous diseases with a highly variable clinical course given that not all patients fit into the current binary classification. A substantial subgroup of patients, mostly with onset in adulthood, share several characteristics of both T1D and T2D as described over 30 years ago (1–3). These patients are considered to have a slowly progressive form of autoimmune diabetes with serum immune markers of T1D but not requiring insulin at diagnosis. Such patients identified as having latent autoimmune diabetes of adults (LADA) account for 2–12% of all patients with diabetes, with considerable variability according to ethnicity, type of autoantibody used for screening (most often autoantibody against glutamic acid

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decarboxylase [GADA]), and method of ascertainment (primary care shows lower rates than secondary care) (4–12). LADA is part of the autoimmune diabetes spectrum, encapsulated by the term T1D, but with marked differences in endophenotypes across the spectrum (13). LADA, also called type 1.5 diabetes, is a global phenomenon with an estimated 6 million people with this condition in China (10). Higher disease rates are reported in Northern Europe and regions of China (7–14%) compared with African American and Hispanic individuals (14–16).

Notwithstanding the widespread recognition of LADA, there are no guidelines for its management. An international group of experts convened a meeting to address this issue. The following report consists of three sections: *1*) identifying subjects with LADA, *2*) reviewing current therapeutic options, and *3*) presenting the group's proposal for management of LADA.

LADA is a well-recognized form of diabetes; however, there are no guidelines for its management. The panel concluded that there is a need for defining a strategy for the management of LADA.

Identifying Subjects With LADA

Adult-onset diabetes (>30 years at diagnosis), presence of diabetes-associated autoantibodies, and absence of insulin requirement for at least 6 months after diagnosis are the key current diagnostic criteria for LADA (Table 1). None of these criteria are categorical; given that LADA is clinically and metabolically a hybrid of T1D and T2D, it is challenging to define categorical immunogenetic and phenotypic features (17–20). Notably, a similar type of slowly progressive form of autoimmune diabetes can also be found in young-onset cases called latent autoimmune diabetes in the young (LADY) (21), reflecting a wide latitude for the variable age at diagnosis. Few studies compare LADA with T1D presenting at similar ages (9,22). Andersen et al. (22) showed that even those LADA patients with higher GADA levels (highest quartile) had better insulin secretion and higher BMI than those with adult-onset (>35 years) T1D, whereas in a cross-sectional study, GADA-positive patients started on insulin between 1 and 6 months post-diagnosis (considered T1D) could not be distinguished phenotypically from patients with LADA (9). Furthermore, GADA positivity may be transient before clinical diabetes develops (23). Importantly, considering the heterogeneity of LADA, for the clinician it is not possible to be certain that any given patient does or does not have LADA without estimating diabetes-associated autoantibodies. However, some anamnestic and clinical features may help the clinician identify likely LADA patients, including age <50 years, family and/or personal autoimmunity, BMI <25 kg/m^2, and acute symptoms at onset (24). A clinical diagnostic model has recently been developed on cross-sectional data to identify need for insulin and low C-peptide within 3 years (considered T1D) or not (considered T2D) based on five parameters including age at diagnosis, BMI, GADA and tyrosine phosphatase (IA-2) autoantibodies (IA-2A), and T1D genetic risk score (25). This model provides an area under the receiver operating characteristic curve (ROC AUC) of 0.90 (clinical features only) to 0.97 (all five parameters) with low prediction error, but it only applies to European-origin patients aged between 18 and 50 years at diagnosis and, being cross-sectional, is not predictive.

Table 1—Broad characteristics of LADA*

- Age >30 years**
- Family/personal history of autoimmunity
- Reduced frequency of metabolic syndrome compared with T2D—lower HOMA, lower BMI, lower blood pressure, and normal HDL compared with T2D
- No disease-specific difference in cardiovascular outcomes between these patients and those with T2D
- C-peptide levels decrease more slowly than in T1D
- Positivity for GADA as the most sensitive marker; other autoantibodies less frequent (ICA, IA-2A, ZnT8A, and tetraspanin 7 autoantibodies)
- Non–insulin requiring at onset of diabetes

*None of these features categorically define LADA. **Limited data on older patients with higher probability of T1D in younger patients.

Characteristics of LADA

i) Phenotypical Features

Data obtained from all major studies including the UK Prospective Diabetes Study (UKPDS) (4) and the Botnia study (5) show that the autoantibody frequency (GADA) in patients diagnosed with T2D is higher in younger patients compared with older patients (e.g., in UKPDS from 34% when aged 25–34 years to 7% in older patients aged 55–65 years). On average, patients with LADA, compared with those with antibody-negative T2D, are younger at diabetes diagnosis with lower BMI and have a personal or family history of autoimmune diseases. Metabolic syndrome tends to have a similar or higher frequency in LADA compared with adult-onset T1D (5,22,26), but compared with autoantibody-negative T2D patients, LADA patients show a lower frequency, with lower HOMA of insulin resistance index (HOMA-IR) and blood pressure (BP) and less diabetic dyslipidemia (5,9). However, there is considerable heterogeneity, with some patients having a T1D phenotype (without metabolic syndrome) while others are indistinguishable from T2D (with metabolic syndrome) (22,27). Although patients with LADA have less major cardiovascular risk factors, i.e., they are leaner, with better lipid and BP profiles, there is no difference in cardiovascular outcomes in them compared with T2D patients after adjustment for traditional cardiovascular risk factors (28,29).

In a post hoc analysis of UKPDS, LADA subjects at diabetes onset have a lower risk of microvascular complications that becomes higher secondary to worse glycemic control compared with T2D subjects. This suggests that the optimization of glycemia may prevent later risk of these complications (30).

C-peptide levels decrease more slowly in LADA than in T1D, and this marker may be used to stage LADA patients according to their residual β-cell function and progression

toward insulin requirement (27,31–33). The risk of progression to insulin deficiency is variable, depending on age at diagnosis, autoantibody level, and presence of multiple islet autoantibodies (4,5,9,10,34).

ii) Autoantibodies

GADA is considered the most sensitive marker of LADA as it is the predominant autoantibody, whether in Europe or China, and in primary or in secondary care; e.g., the Action LADA study showed that approximately 90% of LADA subjects with diabetes-associated autoantibodies are GADA positive (9,15). GADA can be detected by commercially available radioimunoassays as well as ELISA.

GADA specificity has improved from 94% to 99% from 2010 to 2018 according to the international islet autoantibody standardization program (35).

Patients with high GADA levels tend toward a T1D-like phenotype with lower BMI and lower prevalence of metabolic syndrome (7,22,26). In addition, UKPDS and all other studies found that high GADA levels were associated with an increased risk of insulin requirement (4,34).

Importantly, a fraction of autoantibody-positive cases could have false positive autoantibodies either through assay variation or limited predictive power for insulin dependence (36), reducing the predictive value of any given autoantibody. Increasing the autoantibody assay specificity and enriching the population under study for LADA will increase the positive predictive value.

It follows that some patients with GADA will have T2D and should be treated as such, a dilemma circumvented, in part, by placing more emphasis on C-peptide levels.

Other autoantibodies target different IA-2 epitopes (IA-2A), insulin (IAA), the islet-specific zinc transporter isoform 8 (ZnT8A), and tetraspanin 7, while other GADA epitopes are less frequent in LADA (15,16,37–41). A recent study (40) found that individuals with LADA, positive for N-terminally truncated GADA, have a clinical phenotype more similar to classical T1D and a higher odds ratio for early progression to insulin therapy compared with patients positive for the full-length GADA. This may have important practical implications for prediction of risk for insulin therapy. The autoantibody that recognizes the IA-2_{IC} epitope is most utilized for the diagnosis of young-onset T1D at diagnosis and identifies LADA with a sensitivity and specificity of approximately 30% and 100%, respectively. Autoantibodies against the IA-$2_{(256–760)}$ fragment were shown to be a reliable marker of LADA with a sensitivity and specificity of 40% and 97%, respectively (37).

Diabetes-associated autoantibody positivity is predictive for progression both to non–insulin-dependent diabetes (23,42,43) and especially to future insulin dependency after the diagnosis of diabetes, e.g., UKPDS found at least 50% of LADA patients required insulin treatment 6 years post-diagnosis (4,25). However, not all patients in UKPDS and in other studies required insulin, even after 10 years from diagnosis. An important feature of LADA is the increased risk of other organ-specific autoantibodies and autoimmune diseases. GADA are predictive of thyroid autoimmunity (7,36,44,45), while IA-2 autoantibodies confer a high risk of celiac disease–associated autoimmunity in China (15). Moreover, in LADA, high GADA levels are strongly associated with thyroid autoimmunity and inversely related to the serum cytokine profile (44,45).

iii) Genetic Susceptibility

The shared genetic susceptibility of LADA and T1D includes polymorphisms within the HLA *DQB1* and *DRB1* genes and within the insulin and protein-tyrosine-phosphatase nonreceptor 22 (*PTPN22*) genes (19); all these gene polymorphisms and the Src homology 2-B (*SH2B3*) gene were identified in a recent large well-powered genome-wide association study (46). On the other hand, in relatively small studies, LADA was associated with the strongest T2D variant transcription factor 7–like 2 (*TCF7L2*) (47–49), especially in overweight cases (50), but not in the genome-wide association study or in a Chinese study, the latter potentially due to ethnic differences (46,51). Moreover, class I genes (HLA-A and HLA-B) are not associated with LADA, whereas they are strongly associated with childhood-onset T1D (52). Application of gene risk scores may assist stratification of rates of progression to insulin dependency in patients with diabetes-associated autoantibodies and help identify cases likely to have false positive autoantibodies (25).

Treatment of Patients With LADA: Overview of Current Approaches

By definition, LADA patients have functioning β-cells at diagnosis indicating that it is imperative to implement therapeutic strategies targeted to improve metabolic control but also to preserve the insulin-secreting capacity (53). To make a proposal for treatment of LADA, the panel reviewed current clinical trial data and reiterated the conclusions of the Cochrane Review regarding lack of good-quality, large-scale, controlled trials with long-term follow-up (54). As mentioned earlier, the criteria used to define LADA are shown in Table 1. Of note, our proposal only applies to patients who initially were considered not to need insulin.

Hypoglycemic Agents

Insulin Sensitizers (Metformin, Thiazolidinediones). The majority of LADA patients are clinically diagnosed as having T2D and treated initially with metformin before they are identified as having LADA. The panel concluded that although there is little evidence for the use of metformin, there is no evidence against its use. Metformin can increase insulin sensitivity in T1D (55) without evidence that it could improve long-term glycemic control; in addition, it might reduce weight, LDL cholesterol levels, and the risk of atherosclerosis progression (56). Results from ongoing clinical trials, investigating the effects in LADA patients of monotherapy/adjunct metformin on metabolic control, β-cell function, and tolerability, will provide more evidence on the precise role of metformin.

In a small study ($n = 23$ patients), thiazolidinediones (TZD), when combined with insulin, preserved β-cell function in LADA, although the study needs to be replicated (57).

In a four-arm, randomized trial performed in 54 Chinese subjects, LADA patients were assigned to either sulfonylurea (SU) ($n = 14$) or rosiglitazone ($n = 15$) therapy if GADA was <175 units/mL and fasting C-peptide was >0.3 nmol/L. While fasting C-peptide was not different between the two groups, C-peptide levels post–oral glucose and delta C-peptide were higher with rosiglitazone as compared with the SU group after 18 months and up to 36 months ($P < 0.05$ for all comparisons) (58).

Data Quality Assessment
- Limitations Coherence: Moderate
- Relevance: Moderate
- Adequacy: Minor
- **Overall: Low**

The panel concluded that there is limited evidence supporting the use of metformin and few studies using TZD, so the efficacy of both compounds appears inconclusive. For TZD, the potential risk of atypical bone fractures, macular edema, and weight gain could be a limitation to the use of these compounds.

Insulin. While therapy with insulin is essential in all cases with undetectable C-peptide, patients diagnosed with LADA have, by definition, residual β-cell function and, in general, slow progression toward insulin dependency. A major question is whether insulin therapy should be the initial treatment for LADA (59). There are no data from large randomized, controlled trials with sufficient length of follow-up to draw a conclusion. A Japanese randomized trial comparing insulin ($n = 30$) with an SU ($n = 30$) over a 5-year period showed significantly better integrated C-peptide response with insulin. Thus, in the insulin-treated group, progression to insulin-requiring diabetes was lower compared with SU ($P = 0.003$) (60). On the other hand, Thunander et al. (61) concluded that early insulin treatment for LADA did not lead to preservation of β-cell function ($n = 37$), although it was well tolerated and resulted in better metabolic control (in the control group but not in the insulin-treated group, HbA_{1c} increased significantly at 36 months compared with baseline [$P = 0.006$], while C-peptide decline was progressive, irrespective of age, sex, BMI, HbA_{1c} values, and autoantibody levels). Interestingly, UKPDS found that 11.6% of patients were autoantibody-positive and that they tended to require insulin treatment sooner, irrespective of other allocated therapy (4,62). The data available, although limited, indicate that insulin intervention is effective for metabolic control in LADA patients. However, it remains to be established whether insulin should be administered at an early stage of the clinical disease or whether it is the optimal therapy regardless of the stage of the disease process. Further studies are needed to clarify the impact of insulin therapy and the optimum time for intervention.

Data Quality Assessment
- Limitations Coherence: Moderate
- Relevance: High
- Adequacy: Moderate
- **Overall: Moderate**

The panel concluded that insulin intervention is effective and safe for LADA patients; however, it still remains to be established whether insulin should be administered in the early stages of LADA, especially when substantial residual β-cell function is present.

Sulfonylureas. As with previous agents discussed, there is limited evidence to suggest the efficacy of SU in subjects with LADA (19). In a multicenter, randomized, nonblinded clinical study, Japanese patients with LADA, randomized to insulin or glibenclamide ($n = 30$ in each group), were followed for up to 5 years. During follow-up, the SU group had worse metabolic control and a more rapid decline in C-peptide level compared with the group treated with insulin ($P = 0.005$) (63). More recently, a post hoc exploratory analysis of a small subgroup of LADA patients ($n = 38$), enrolled in a randomized, controlled trial comparing glimepiride and linagliptin ($n = 21$ linagliptin, $n = 17$ glimepiride) at 28 weeks as add-on therapy to metformin in T2D, revealed that despite similar glycemic efficacy, fasting C-peptide at 28, 52, and 104 weeks decreased in patients treated with glimepiride. Conversely, an increase in C-peptide level was observed in those subjects treated with linagliptin; the difference between groups was significant at 28 and 58 weeks ($P < 0.01$ for all comparisons) (64). As previously described, in a four-arm pilot, randomized, controlled trial performed in 54 Chinese subjects with LADA, comparison of 3-year follow-up data between subjects treated with SU ($n = 14$) showed a lower delta C-peptide as well as C-peptide after 2-h 75-g glucose load compared with patients treated with rosiglitazone ($n = 15$) ($P < 0.05$ for all comparisons), with no differences in glycemic control (58). Overall, the current data are inconclusive, but it cannot be excluded that treatment of LADA with SU results in a decreased insulin secretion. SU are not therefore recommended for the treatment of LADA, nor are they generally recommended as first-line therapy for T2D.

Data Quality Assessment
- Limitations Coherence: Moderate
- Relevance: High
- Adequacy: Minor
- **Overall: Moderate**

The panel concluded that sulfonylureas are not recommended for the treatment of LADA, as deterioration of β-cell function as a consequence of this treatment cannot be ruled out.

Dipeptidyl Peptidase 4 Inhibitors. Small clinical trials with dipeptidyl peptidase 4 inhibitors (DPP-4i) in patients with LADA suggest that this class of hypoglycemic agents

might improve glycemic control and preserve β-cell function with a good safety profile compared with placebo, glimepiride, and pioglitazone (64–66). In a post hoc analysis of pooled data from five randomized, placebo-controlled studies ($n = 2,709$), saxagliptin improved β-cell function as assessed by HOMA2 of β-cell function and postprandial C-peptide from baseline in both GADA-positive ($n = 98$) and GADA-negative subjects ($n = 1,849$) (67). A recent study (68) compared the outcome of glucagon-stimulated C-peptide tests after 21-month treatment with either insulin or sitagliptin in GADA-positive LADA patients ($n = 64$) without any clinical indication for insulin treatment less than 3 years from diagnosis. The metabolic control during intervention did not differ between the two treatment arms, and post-intervention β-cell function was similar in the insulin- and sitagliptin-treated patients. Of note, the stimulated C-peptide response deteriorated significantly more in the group with high GADA level compared with the group with low level regardless of the treatment. Another small study ($n = 30$) found that sitagliptin, as an add-on treatment to insulin, had a beneficial effect on C-peptide decline compared with insulin alone (65).

Moreover, a recent trial evaluated the effect of saxagliptin in combination with vitamin D3 in subjects with LADA with promising results (69). Although these studies have several limitations (i.e., post hoc analyses, small sample size, short periods of follow-up, interstudy heterogeneity), DPP-4i agents represent a potential therapeutic alternative for effective management of LADA.

Data Quality Assessment
- Limitations Coherence: Moderate
- Relevance: High
- Adequacy: Moderate
- **Overall: Moderate**

The panel concluded that DPP-4i may improve glycemic control in LADA patients with a good safety profile. Larger randomized studies are warranted to prove that DPP-4i might preserve C-peptide secretion.

Sodium–Glucose Cotransporter 2 Inhibitors. Sodium–glucose cotransporter 2 inhibitors (SGLT2i) improve glycemic control without hypoglycemia and are currently used for the management of T2D. Although no interventional studies have been conducted in LADA patients, international, multicenter, randomized clinical trials in over 5,000 T1D patients confirm the efficacy and safety of adding SGLT2i to existing insulin regimens (70–77). One SGLT2i, dapagliflozin, has been recently approved by the European Medicines Agency for use in adults with T1D with BMI of at least 27 kg/m^2 who failed to achieve adequate glycemic control despite optimal insulin therapy. However, in the U.S., the use of SGLT2i in T1D still remains off-label. The approval was based on data from phase III DEPICT clinical program (70). SGLT inhibition confers additional benefits in terms of HbA_{1c} reduction, reduced glucose variability, small reduction in weight, and reduced total daily insulin doses without increasing the risk of hypoglycemia. However, there is an increased risk of ketoacidosis, often not associated with hyperglycemia, especially in patients not overweight (BMI <27 kg/m^2). This feature is of special importance in those LADA patients with medium to low C-peptide levels and not on insulin, considering their increased risk of developing insulin deficiency. Treatment with SGLT2i might mask the signs of progression to insulin deficiency (often presenting as postprandial hyperglycemia) and yet increase the risk of ketoacidosis; therefore, patients should be advised to monitor for ketosis, i.e., measure ketonemia and ketonuria regularly, even daily, as recommended (78), and to discontinue SGLT2i prior to scheduling surgical procedures or exposure to metabolically stressful conditions associated with potential symptoms or signs of ketoacidosis.

Data Quality Assessment
- Limitations Coherence: Low
- Relevance: High
- Adequacy: Low
- **Overall: Moderate**

The panel concluded that the approved use of SGLT2i in both T2D and selected T1D patients, in particular those overweight, suggests that they may be promising agents in LADA. However, no studies have been performed in LADA and attention should be paid to ketoacidosis in patients with medium to low C-peptide.

Glucagon-Like Peptide 1 Receptor Agonists. Glucagon-like peptide 1 receptor agonists (GLP-1RA) reduce hyperglycemia (with low rates of hypoglycemia), reduce and maintain weight control, and may suppress appetite, reduce food intake, and slow gastric emptying. A post hoc analysis of pooled data from three randomized phase III trials (AWARD-2, -4, and -5; patients with GADA assessment) indicated that dulaglutide is effective in reducing HbA_{1c} in LADA patients. Dulaglutide treatment resulted in a comparable decrease in HbA_{1c} values in GADA-negative (-1.09%) and GADA-positive (-0.94%) patients at 1 year post-diagnosis, and it appears to be slightly more effective in LADA patients with low autoantibody levels compared with those with high autoantibody levels (79). However, as expected, there was a reduced glycemic response to GLP-1RA analogs (exenatide/liraglutide) in a small patient group ($n = 19$) with diabetes-associated autoantibodies and low fasting C-peptide levels (≤ 0.25 nmol/L) (80). Large-scale, prospective, randomized trials with long-term follow-up are required to confirm the efficacy of GLP-1RA in preserving metabolic control and delaying progression to insulin dependence in LADA.

Data Quality Assessment
- Limitations Coherence: Low
- Relevance: High
- Adequacy: Moderate
- **Overall: Moderate**

The panel concluded that GLP-1RA have shown beneficial results in terms of improving metabolic control in LADA patients unless C-peptide levels are very low. These drugs are approved in T2D and in insulin-treated patients, but more evidence is required in patients with LADA.

Immune Intervention

There is only one immune intervention study in LADA patients. Alum-formulated recombinant GADA (GAD-alum) was used in a small phase 2 study that was placebo-controlled with dose escalation in GADA-positive non–insulin-requiring patients ($n = 47$), who received subcutaneous injections of GAD-alum in different doses (81). The primary outcome was safety as assessed by neurological tests, medication use, and β-cell function evaluated over 5 years, representing the end of the trial (82). No severe study-related adverse events occurred during the 5-year follow-up, and active treatment was not associated with increased risk of starting insulin treatment compared with placebo. After 5 years, fasting C-peptide levels declined in the placebo group compared with the two highest dose intervention groups. The authors concluded that in this small study, the primary outcome of safety was achieved, with evidence of a beneficial effect on β-cell function. A more extensive trial is required before such treatment can be recommended and is currently under way.

Data Quality Assessment

- Limitations Coherence: Low
- Relevance: Moderate
- Adequacy: Low
- **Overall: Low**

The panel concluded that current data on immune intervention in LADA are very limited, and more extensive phase 2 studies are required before drawing any conclusions.

Lifestyle Modifications

LADA is associated with factors that favor insulin resistance and T2D, including low birth weight, overweight/obesity, physical inactivity, smoking, and consumption of sweetened drinks (12). The role of obesity and insulin resistance as risk factors for LADA is abundantly documented (83). It may therefore be possible to treat LADA by a combination of lifestyle changes much as is done in T2D. Among these, medically assisted weight loss if necessary, increased physical activity, and cessation of smoking should be promoted. Thus, intervention studies examining the role of lifestyle factors in the development of LADA are necessary, as our current knowledge is hampered because the small number of studies were conducted exclusively in Scandinavian populations (83).

Quality Assessment

- Limitations Coherence: Low
- Relevance: High
- Adequacy: Low
- **Overall: Moderate**

The panel concluded that lifestyle modifications are important in treatment of T2D. Intervention studies examining the role of weight reduction and physical activity in the development of LADA are required.

Proposal for Management of LADA

Diagnostic Challenges in LADA

The panel agreed that to effectively identify patients affected by LADA, all newly diagnosed T2D patients should be screened for GADA positivity (immune marker with the highest sensitivity) to allow for a rapid diagnosis and implementation of an appropriate therapy and follow-up of progressing β-cell failure. This approach may be costly, but the one-off cost of GADA measurement (currently around €5 or $6) is justified.

As they become available, new cost-effective bioassays detecting autoantibodies targeting other islet autoantigens (in addition to GADA) should be considered to diagnose LADA. If, however, economic issues represent an obstacle, at least one of the following clinical factors should be sought to select patients in whom to measure GADA: family history of T1D or autoimmune diseases (84), normal/slightly

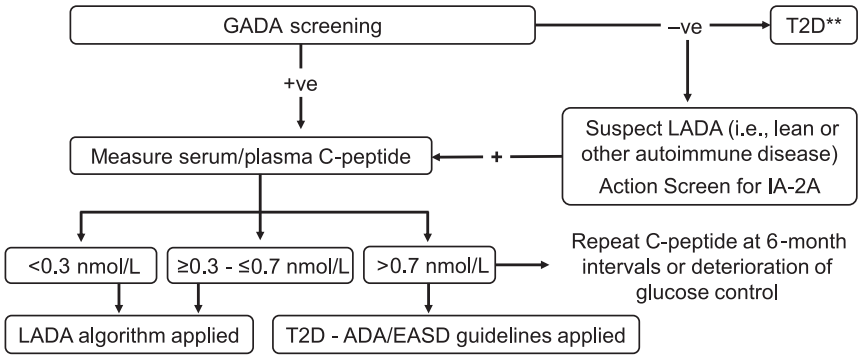

Figure 1—Algorithm for LADA diagnostic pathway based on autoantibody screening and C-peptide levels at diagnosis (to be used when financial restriction does not apply). **Consider also pancreatitis or monogenic diabetes.

overweight BMI (<27), young age at onset (<60 years), and poor metabolic control. If patients are GADA positive, they are managed according to Fig. 1. If there is a strong suspicion of LADA in a GADA-negative individual, other islet autoantibodies (e.g., ICA or IA-2A, ZnT8A) should be assayed. GADA-negative (autoantibody-negative), likely T2D, patients are managed according to Fig. 1. Although elevated levels of GADA have been associated with a greater risk of insulin requirement compared with low levels, GADA levels cannot be used in clinical practice for therapeutic choice because it is difficult to set a threshold to discriminate between high and low levels, bioassays are semiquantitative, and there is variation in GADA levels between different laboratories.

The panel recommends measurement of serum (plasma) C-peptide levels as a proxy for insulin secretion in islet-cell related autoantibody–positive patients (85). In sampling for C-peptide evaluation, the concomitant measurement of blood glucose levels should be done to ensure that it is between 80 and 180 mg/dL to avoid the effect of abnormally low or high glucose values. C-peptide can be measured in samples collected at fasting, random time points, or postprandially. The data on fasting C-peptide is supported by two recent prospective studies (in Europe and China) with results consistent with our current proposal (67,86) The mixed meal tolerance test has been considered the gold standard to measure postprandial C-peptide, but it cannot be performed routinely in clinical settings. However, many clinical laboratories have applied the mixed meal tolerance test values (87) for C-peptide measured 2 h after a random meal, although this has not been yet standardized. C-peptide assays are commercially available, inexpensive, and widely accessible (Fig. 1).

By definition, LADA patients have detectable C-peptide at diagnosis, which, in general, decreases more slowly than in T1D patients (depending on the genetic characteristics) (88) and more rapidly than in T2D patients. Similarly, in case of treatment failure, C-peptide measurement should be repeated to identify progression to insulin deficiency and the need for insulin treatment.

C-peptide measurement should drive the decision-making process for the choice of LADA treatment. Three broad categories of C-peptide levels were suggested by the panel:

- **C-peptide levels <0.3 nmol/L:** a multiple-insulin regimen is recommended. If this occurs at diagnosis, then patients can be considered to have T1D and approved national/international guidelines for T1D can be followed thereafter.
- **C-peptide levels ≥0.3 and ≤0.7 nmol/L:** defined by the panel as the "gray area" where a modified American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) algorithm for T2D is recommended (Figs. 2 and 3). The modification consists of avoiding the use of hypoglycemic drugs that may have an effect in deteriorating β-cell function.
  Insulin in combination with other therapies to control/prevent diabetic complications should be considered. The advantages/disadvantages and even dangers of

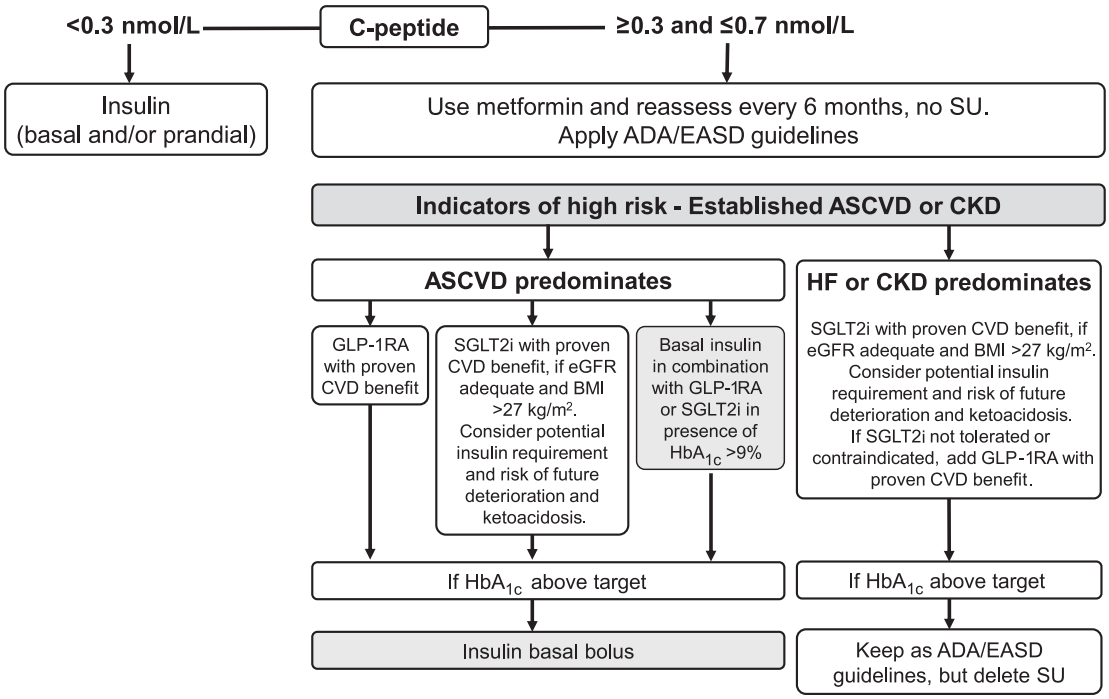

Figure 2— Algorithm for glucose-lowering medications in LADA patients with C-peptide <0.3 mmol/L or with C-peptide ≥0.3 and ≤0.7 nmol/L. ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; HF, heart failure.

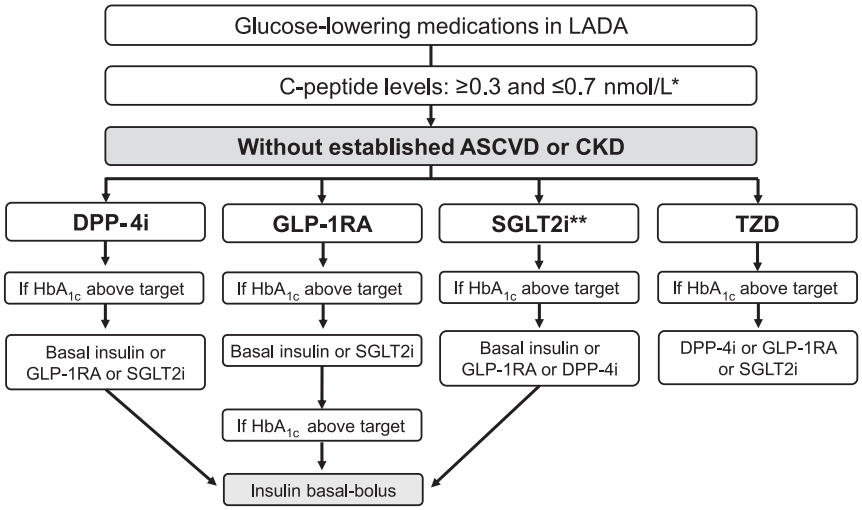

Figure 3—Algorithm for glucose-lowering medications in LADA patients with C-peptide levels ≥0.3 and ≤0.7 nmol/L without established ASCVD (atherosclerotic cardiovascular disease) or CKD (chronic kidney disease). *Deviation from ADA/EASD T2D algorithm. **Increased risk of diabetic ketoacidosis, especially in patients with BMI ≤27.

using certain classes of agents need to be taken into account when prescribed alone. Follow-up of patients in this C-peptide category should take place at least every 6 months. Note that many adult-onset T1D patients have C-peptide levels in this range at diagnosis, so patients with marked hyperglycemia may need to be started on insulin with frequent review.

- **C-peptide levels >0.7 nmol/L:** suggests using a slightly modified ADA/EASD algorithm for T2D, notably the only difference being that LADA patients should be followed with repeated C-peptide measurements if there is a deterioration of glucose control; some of these cases will have false positive autoantibodies and therefore be true T2D.

Personalized Therapy for LADA and the ADA/EASD Guidelines

The overall objective of a personalized approach for the management of LADA is to achieve good metabolic control and preserve β-cell function.

The clinical guidelines for the management of hyperglycemia in T2D do not take into account the diverse metabolic phenotypes of LADA. The 2020 ADA/EASD guidelines for T2D do not suggest any specific treatment for LADA, which constitutes a significant fraction of patients with adult-onset diabetes (89). The panel felt it was important to provide recommendations for the management of these patients in clinical practice. Our proposal for LADA is defined on the basis of deviations/variations from the ADA/EASD algorithm for T2D driven by the measurement of C-peptide for evaluating β-cell function. Each "deviation" for LADA patients from the ADA/EASD T2D guidelines is outlined (Figs. 1–3). The use of metformin and/or insulin elicited much discussion among the panel, but it was concluded that they both have a role. Importantly, for personalized therapy, the first step is to establish the fundamental disease characteristics before deciding on a therapeutic path; we appreciate that, likely as not, estimating C-peptide and diabetes-associated autoantibodies will be done infrequently in the average clinic. Metformin is recommended in GADA-positive patients (in particular those who are obese) who cannot be "controlled" with diet alone. The addition of other hypoglycemic agents such as incretin-based therapy (GLP-1RA or DPP-4i), TZD, and SGLT2i may confer some additional advantages, e.g., weight loss, cardiovascular/renal protection (Figs. 2 and 3).

Key Knowledge Gaps/Future Perspectives

Patients identified as having LADA account up to 12% of all patients with diabetes attending clinics.

Our proposal embodies an attempt at making both general and specific recommendations for LADA, on the basis of its descriptive and functional features. These recommendations offer a personalized, multidimensional, and integrated guide for the physician to facilitate the management of LADA.

The identification and treatment of LADA poses significant challenges for the physician. The faculty outlined some key points for future action, including *a*) screening for LADA, *b*) personalized medicine, *c*) need for more randomized controlled comparative trials with hypoglycemic agents, *d*) further investigation of immune therapy, *e*) large-scale long-term studies in different patient populations, *f*) quality of life/lifestyle issues, *g*) studies including patients of different ethnic origin, *h*) nature/quality of autoantibody assays (GADA, IA-2, etc.), and *i*) cost-benefits balance of measuring GADA autoantibodies and serum C-peptide.

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