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Latent Autoimmune Diabetes in Adults (LADA) - Clinical Features

Yuh-Min Song[1,2]

[1]Division of Endocrinology/Metabolism, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation; [2]School of Medicine, Tzu Chi University, Hualien, Taiwan

Abstract

Among the spectrum of different types of diabetes mellitus (DM), latent autoimmune diabetes in adults (LADA) distinguishes itself from the more prevalent type 2 DM (T2DM) by a composite of specific clinical features (onset of diabetes at adult age with non-insulin-therapy as initial regimen, but progresses rapidly to insulin-requiring due to primary failure to oral antidiabetic drugs (OADs) for optimal glycemic control), lower C-peptide levels, and presence of auto-antibodies against antigens derived from pancreatic islets (with antibody against glutamic acid decarboxylase(GAD)-65 having the highest diagnostic accuracy). A correct categorization into LADA at the onset is sometimes challenging because the phenotypic presentations in an adult patient will very likely lead clinicians to prescribing OAD as starting regimen as for patients diagnosed with classic T2DM, especially in the absence of diabetic ketosis/ketoacidosis as initial presentation. Laboratory findings including a low basal (fasting) and/or glucagon-stimulated C-peptide levels can help verify the insulin-dependence state of the patient, and a positive test for GAD-65 antibody may further consolidate the diagnosis of LADA. Early institution of insulin therapy should be considered in order to not only achieve more optimal glycemic control but also preserve and improve β-cell function during the long-term disease course. (J Intern Med Taiwan 2021; 32: 398-410)

Key Words: C-peptide, Glutamic acid decarboxylase antibody, Insulin therapy, Latent autoimmune diabetes in adults

Introduction

Diabetes mellitus (DM) encompasses a spectrum of glucose dysregulation that has been classified into different types for clinical purposes and can also be examined for underlying pathophysiological processes which are critical for the setting of appropriate therapeutic approaches[1,2]. Epidemiological researches in DM have long noted a steady global rising throughout the past three to four decades, and projected a relentless growth due to the significant impact of modern life style on the development and progression of this metabolic disorder[1]. Most patients with diabetes are diagnosed to be type 2 diabetes mellitus (T2DM), with insulin resistance (IR) and impaired function of insulin secretion as underlying pathophysiology, together of which leading to hyperglycemia[3]. Longitudinal follow-up studies have confirmed that optimal glycemic control is critical to reduce diabetes-related

Reprint requests and correspondence：Dr. Yuh-Min Song
Address：Division of Endocrinology/Metabolism, Department of Internal Medicine, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, No. 88, Sec. 1, Fengxing Rd., Tanzi Dist., Taichung City 427, Taiwan.

complications in the long run, with goals requiring continuous striving efforts to achieve by health-care providers concerned with diabetes care[4-6]. However, among T2DM patients who could not reach acceptable or optimal glycemic goals despite usual efforts comprising adequate life-style modification and the use of multiple oral anti-diabetic drugs (OADs), concern should be raised regarding whether the underlying pathophysiology causing hyperglycemia is an unusual one that needs further investigation, with latent autoimmune diabetes in adults (LADA) included in the list of differential diagnoses[7].

Epidemiology of LADA

Before the confirmed diagnosis is given, most LADA patients would have been treated as T2DM for a period of time, usually more than 6 months. On careful review of specific phenotypic presentations that are different from classic T2DM at first diagnosis [lower body mass index (BMI), higher glycated hemoglobin A1c (HbA1c) levels], and by further laboratory tests including a positive test of antibodies against antigens from pancreatic islet cells as well as lower C-peptide (fasting or post-glucagon stimulation) levels (which provide evidences of an underlying autoimmune process leading to the destruction of pancreatic β-cells), the diagnosis of LADA would then be established. Hence, most of the reports on epidemiology of LADA are derived from surveys among population of established DM of adult onset, from which the diagnosis of LADA is supported by combination of presence of specific clinical features and laboratory tests giving evidences of immunological process and impaired pancreatic β-cell function[8]. With this notion in mind, a discussion associating the presence of autoantibodies and distinguishable phenotypic presentations would help taking in a far clearer picture of LADA not only for a correct diagnosis but also the understanding of the scope in prevalence of this specific subtype of diabetes.

In the United Kingdom Prospective Diabetes Study, autoantibodies to islet-cell cytoplasm (ICA) and glutamic acid decarboxylase (GADA) of the 3,672 newly diagnosed T2DM patients were tested to find whether the presence of autoantibodies would characterize a subtype of diabetes and provide better prediction of requirement for insulin therapy after a follow-up of 6 years. The results showed that GADA was detected in 10%, ICA in 6%, and presence of both antibodies in 4% of the population. The ratios of patients having positive GADA and ICA decreased with advancing age at diagnosis. In those patients younger than 35-year-old who were allocated to receive OAD at study entry, 84% of those with GADA and 94% with ICA required insulin therapy by 6 years due to poor glycemic control status; while the rate in those negative for the antibodies were significantly lower at 14% ($p < 0.0001$)[9].

When detected in its single presence, GADA has long been considered to have the highest accuracy in predicting future insulin requirement than other antibodies, hence the most recommended test to do for a confirmatory diagnosis on clinical grounds[10,11].

From a cohort comprising 881 patients younger than 70 years of age who were diagnosed with T2DM after age 40, a cross-sectional study carried out in Italy with purposes of evaluating the prevalence of islet autoimmunity and the associated clinical phenotype in adult-onset diabetes had tested multiple antibodies against islet cell-derived antigens [GADA, protein tyrosine phosphatase IA-2 (IA-2A), and IA-2β/phogrin (IA-2βA)]. The results showed that 58 (6.6%) patients had GADA, 22 (2.5%) had IA-2A, six (0.7%) had IA-2βA. There was also finding of higher proportion of insulin use in patients with higher GADA titer (73.9% in those with > 10 units vs 42.0% in those with ≤ 10 units; $p < 0.007$)[12].

In a multi-national, multi-center study carried

out in Europe, a total of 6,156 consecutive subjects diagnosed with DM within 5 years (age range: 30 - 70 years) of study entry were tested for GADA, antibodies against insulinoma-associated antigen-2 (IA-2A), and zinc-transporter 8 (ZnT8A), along with evaluation of clinical features. Immunological tests revealed 541 (8.8%) having positive GADA in its single presence, but only 57 (0.9%) was positive for IA-2A or ZnT8A. It was concluded that patients with autoimmune diabetes are not rare at a rate of 9.7% in this cohort of adult-onset diabetes and a screening for autoantibodies, notably GADA, is clinically useful to discriminate between these two entities (autoimmunity-related or not) with certainty[13-15].

In a retrospective study carried out in Korean T2DM patients who were diagnosed within 5 years of the assessment, the prevalence of positive GADA was reported to be 4.3% (20/462). Decreased insulin secretory capacity was also noted as reflected by lower fasting C-peptide (FCP) levels when compared with the GADA-negative counterpart (1.2±0.8 ng/mL vs. 2.0±1.2 ng/mL, p=0.004)[16].

A multicenter study carried out in China by Zhou et al. [17] had evaluated 4,880 newly diagnosed diabetes patients within one year of study entry with inclusion criteria as: age ≥ 30 years old, absence of insulin dependence for at least 6 months and ketosis-free after diagnosis. LADA was diagnosed in 5.9% of the study subjects defined by having positive GAD65 autoantibody. Compared with GADA-negative T2DM patients, clinical phenotypes of LADA patients were noted to be leaner, having lower FCP levels and less frequency of metabolic syndrome.

A recently reported study carried out in Egypt had recruited 1,515 patients previously diagnosed as having T2DM between 35- and 70-year-old and divided the cohort into two groups based on presence or absence of GADA. The rate of positive GADA was reported to be 12.8%. Lower FCP level were found in GADA-positive patients, as compared with GADA-negative counterpart (1.3 ± 1.9 vs 2.0 ± 1.7 ng/mL, $p < 0.001$), whereas other phenotypic features did not show significant differences (e.g. age of onset, BMI, glycemic control status, and lipid profile)[18].

The results of epidemiological studies of LADA in adult-onset diabetes (with rates falling between 4% and 13% among different ethnic groups, and around 10% in most researches) heavily rely on the presence of autoantibodies, with GADA the most widely applied and reliable test for diagnosis. Patients who are tested positive with GADA have lower C-peptide levels (fasting or stimulated) than patients without, and the presence of GADA could be an indicator for faster destruction of β-cells and future need of insulin therapy for optimal glycemic control.

Clinical features that help diagnosis of LADA

The first in-depth and systematic investigation into this specific subtype of diabetes sitting between classic T1DM and T2DM was performed more than two decades ago by Tumoi et al.[19,20]. The investigators considered the classification of adult-onset DM can be misled by patients who initially present as T2DM but who later become insulin-dependent for glycemic control. In some of these patients, the pathogenesis could be similar to that in T1DM, namely autoimmune destruction of the pancreatic β-cells. In those 102 patients recruited in their study (> 35 year of age at diabetes diagnosis) who had initially been non-ketotic and non-insulin-dependent for more than 6 months, an insulin-deficient group (n = 33) and a non-insulin-deficient group (n = 69) were classified according to C-peptide levels after a glucagon-stimulation test. Immunological tests showed significantly higher prevalence of GADA in the insulin deficient group [76% (25/33)] than in the non-insulin deficient group [12% (8/69)]. This disorder was soon coined the term “latent autoimmune diabetes in adults (LADA)” by Zimmet.

Although definitions may still differ by various academic societies due to the heterogeneous presentations of this disorder, the following criteria are generally accepted to make a diagnosis of LADA on clinical grounds: (1) ≥ 30 years of age at onset of diabetes; (2) presence of at least one of the four antibodies commonly found in classic T1DM patients (autoantibodies against GAD65, ICA, IA-2, and insulin) which distinguishes LADA from classic T2DM; and (3) insulin independence of treatment for at least more than 6 months since diagnosis, which distinguishes LADA from classic type 1 diabetes[21].

When antibody test is not readily available for a diagnosis, Fourlanos et al.[22] had developed a "LADA clinical risk score" based on five clinical features derived from a retrospective interview with patients (age between 30- and 75-year-old) diagnosed with LADA (n = 102, GADA-positive) and T2DM (n = 111, GADA-negative). Compared with T2DM, patients with LADA were found to have higher frequency of the following features at diagnosis: (1) age of onset < 50 years old; (2) acute symptoms of hyperglycemia (polydipsia, polyuria, and unintentional loss of weight); (3) BMI < 25 kg/m^2; (4) personal history and (5) family history of any autoimmune disease (autoimmune thyroid disease, celiac disease, Addison's disease, vitiligo, rheumatoid arthritis, pernicious anemia, and autoimmune hepatitis). In this study, the authors demonstrated that the presence of at least two clinical features at diagnosis has 90% sensitivity and 71% specificity for detecting LADA, whereas a negative predictive value of 99% was found with a risk score < 2 when each feature was given one-point score for calculation and statistical analysis. (Figure)

In a retrospective electronic-chart review study obtained over a 10-year's period carried out in a single center in Taiwan, a convenient diagnostic tool for LADA was developed based on clinical features that are distinct between patients of LADA and of classical T2DM by Sia et al.[23]. Patients were divided into the case group (GADA-positive, n = 152) and a reference group comprising 358 T2DM patients. At diagnosis of DM, the GADA-positive patients were found to be younger in age, with lower BMI, higher HbA1c, higher high-density lipoprotein cholesterol, and lower total cholesterol and triglycerideslevels, as compared to the T2DM reference group.

However, certain distinctive clinical features lead to tentative diagnosis of LADA and may remind clinicians to order confirmatory laboratory tests including autoimmune antibodies and C-peptide (fasting or stimulated) measurement for differential diagnosis. These features include acute symptoms due to hyperglycemia, leaner body figure, and presence of personal or family history of any autoimmune diseases.

Clinical implicaitons from immunological findings

Discovery of islet cell antibodies in 1974 in the sera of patients with T1DM provided very strong evidence that the β-cell lesion is autoimmune in nature in this group of patients [24,25]. These findings were extended to researches investigating into their clinical implications in patients diagnosed with LADA.

In a nationwide population-based study carried out in Sweden, tests of ICA, GADA or IA-2A were performed in a cohort of newly diagnosed DM patients (n = 764) within 2 years before study entry. With T1DM patients (n = 583) excluded, 47% of T2DM (52/110) and 59% (42/71) of those initially unclassified DM patients were found to have at least one of the 3 antibodies measured. Compared with antibody-negative counterpart, these patients had lower BMI, whereas a higher BMI and FCP levels were noted when compared with 82% of those classic T1DM who were also positive for antibodies (all with p values < 0.001), while no differences were noted in titers of each of the three antibodies between the two latter groups. Follow-up of clini-

cal course for 3 years revealed that the percentage of insulin-requirement among the autoantibody positive patients initially not classified as T1DM increased with time at 83% (1-year), 89% (2-year), and 93% (3-year), while the corresponding figures were 32%, 41%, and 51%, respectively, in those with negative antibodies. When ICA, GADA, IA-2A, BMI and C-peptide were further tested in a multiple logistic regression, only GADA was found to be significantly associated with insulin treatment within

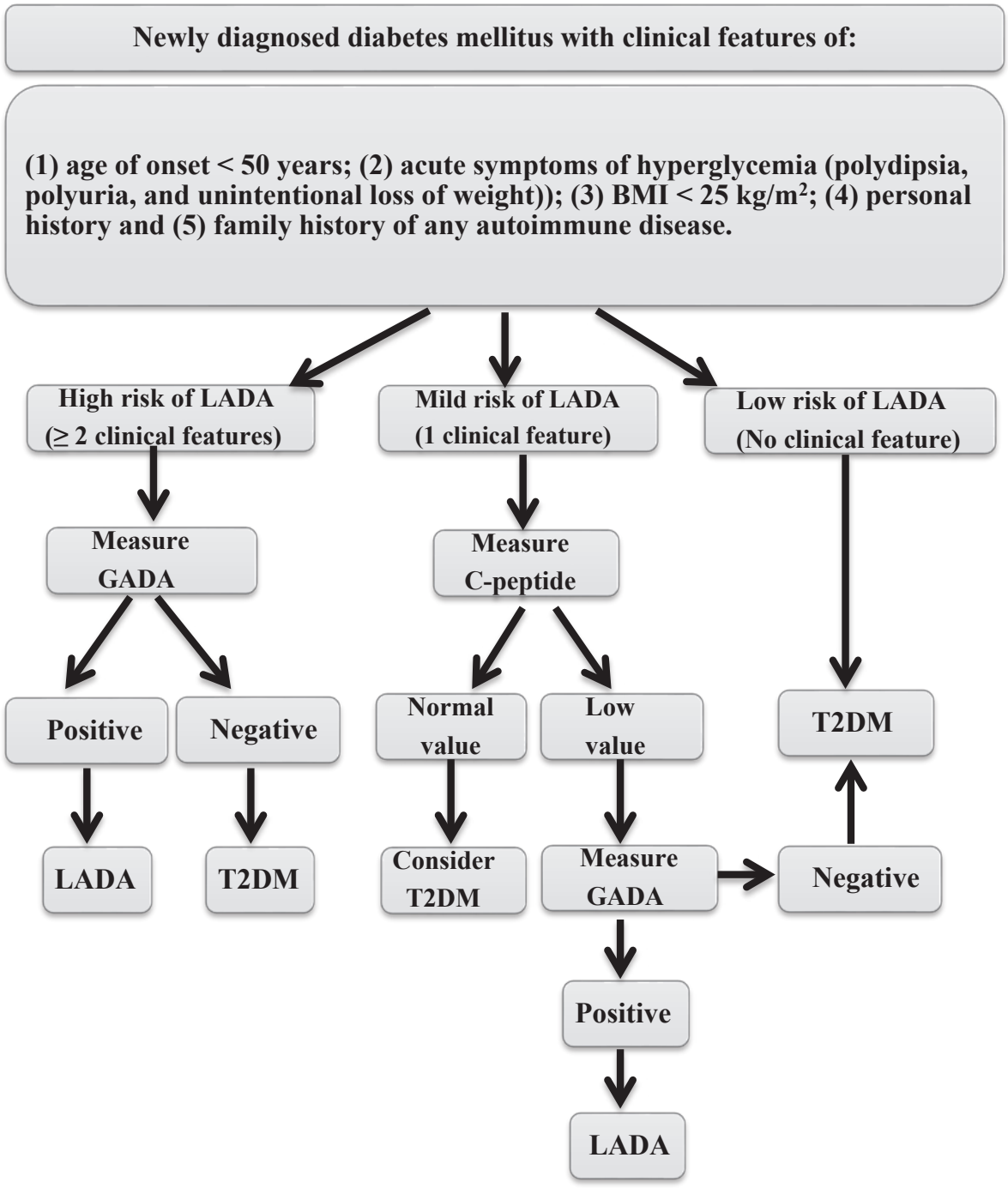

Figure 1: Algorithm for diagnosis of latent autoimmune diabetes in adults (LADA).
BMI, body mass index; GADA, glutamic acid decarboxylase autoantibody; T2DM, type 2 diabetes mellitus.
(Modified from references 8 & 22)

3 years in those patients initially treated with diet or OADs (OR=18.8; 95% CI 1.8-191). It was concluded that, the presence of autoantibodies against islet cell antigens, especially GADA at diagnosis are highly predictive for insulin therapy within 3 years from diagnosis. The presence of autoantibodies provides evidence of an ongoing autoimmune activity directed against pancreatic β-cells with gradual destruction of β-cells function and decrease in endogenous insulin production[26].

In a longitudinal follow-up study carried out in China investigating into the relationship between antibody load and β-cell function in LADA patients diagnosed based on the positive test for GADA, Yang et al.[27] had found that, up to 25% of those LADA patients were noted to have a decrease in FCP levels of more than 50% compared with the baseline values at one-and-half years of follow-up. At two-and-half years, the FCP levels had significantly decreased from baseline, which continuously went down to the end of 6 years' follow-up period. No significant changes of the above parameters were found in those T2DM patients serving as control group. The average percentages of FCP decrement per year in LADA and T2DM patients were significantly different at 15.8% (4.0-91.0%) and 5.2% (-3.5 to 35.5%, $p < 0.001$), respectively. Among LADA patients, there was a negative correlation between the GADA titer and the FCP, indicating an association between the higher titer of GADA and the faster failure rate of islet β-cell function. It was concluded that the decreasing rate of islet β-cell function in LADA is three times that of T2DM patients and, being heterogeneous among LADA patients, the titer of GADA is an important predictor for the progression of islet β-cell function.

In a 7-year longitudinal follow-up study carried out in Italy, a total of 250 patients screened positive for GADA out of 5,330 diagnosed T2DM patients (4.5%) were recruited to investigate the impact of GADA titers along with other clinical features on the future need for insulin therapy. At the end of the 7-year follow-up period, it was found that 56.1% (119/ 212) of LADA patients required insulin therapy. A significantly higher rate of insulin therapy was found among LADA patients having high GADA titer (defined as > 32 arbitrary units) when compared to those having low GADA titer (≤ 32 arbitrary units) and T2DM patients [71.1% (74/104) vs 41.6% (45/108) vs 20.9% (86/412), $p < 0.001$ for both comparisons]. Furthermore, a faster progression to insulin requirement among LADA patients was also noted in those with BMI of ≤ 25 kg/m^2, presence of other autoantibodies including IA-2A and zinc transporter 8, as well as treatment in the first year of diagnosis with sulfonylureas instead of diet and/or insulin sensitizers[28].

In another longitudinal follow-up study carried out in China also with aims of investigating the association between autoimmunity process and β-cell function, a total of 95 study subjects that included 25 high-titer (GADA >180 units/mL) LADA patients, 42 low-titer (GADA <180 units/mL) LADA patients, and 28 T2DM patients (with the latter two groups serving as controls) of similar age, sex, and BMI were clinically followed up for 3 years. Despite similar initial levels, the FCP showed significantly more declining in subjects with high GADA titer (from a mean of 0.49 nmol/L at entry to 0.13 nmol/L at the third year; $p < 0.05$) than those with low GADA titer (from 0.48 to 0.38 nmol/L) or T2DM (from 0.47 to 0.36 nmol/L), with the latter two groups having similar rate of decline. After 3 years, residual β-cell function (defined as FCP > 0.2 nmol/L) was detected in only 42% of those with an initial high GADA titer, compared with 90% in those with a low GADA titer and 97% with T2DM ($p < 0.01$ for both comparisons). It was concluded from this study that, in LADA patients, initial GADA titers identified subjects with different degrees of autoimmunity and disease progression[29].

In a recently published follow-up study carried

out also in China in which 106 LADA patients had been followed-up for 8 years, the pattern of declining and possible determinants of β-cell function were studied on an annual assessment. During the 8-year follow-up period, 29 (28.7%) of the 101 subjects had developed β-cell function failure. A biphasic pattern of C-peptide decline in LADA was found, showing an initial rapid linear progression, which was followed by a stable plateau. Further analysis showed that a discriminatory GADA titer above 173.5 WHO units/mL was the most valuable parameter associated with a higher risk of β-cell function failure. Beta-cell function failure occurred in 71.3% of patients having higher GADA titer, while only 6.2% did in those with lower titer[30].

Higher titers of autoimmune antibodies in LADA patients signify faster destruction of pancreatic β-cells, a risk factor for its earlier failure. Higher clinical vigilance is required to administer timely insulin therapy in order to bring glycemia to optimal control in patients with very low insulin reserve.

Association with other antoimmune endocrine disorders

It has long been acknowledged that patients diagnosed with an autoimmune-related endocrine disorder may have higher risk of harboring another one, as manifesting in autoimmune polyglandular syndrome (APS)[31,32].

In a systematic study carried out in Poland, the presence or not of anti-thyroglobulin (ATG), anti-thyroid peroxidase (ATPO) (for autoimmune thyroid disorders), anti-tissue transglutaminase IgA (ATTA) (for celiac disease), and anti-21-hydroxylase (A21H) (for adrenal insufficiency) antibodies in 70 patients with LADA, 69 with T2DM (all tested negative for GADA, IA2, and anti-insulin antibody), and in 50 healthy controls, were assessed. When compared with healthy control subjects, LADA patients showed a significantly higher rate of ATPO and a trend of higher rate of ATG. A significantly higher rate of ATPO was also noted when compared with T2DM patients. A non-significant higher incidence of newly diagnosed subclinical hypothyroidism (thyroid-stimulating hormone levels > 4.5 mIU/mL) were found in LADA patients [7.14% (5/70)] when compared to T2DM [1.45% (1/69)] and healthy controls [2% (1/50), $p > 0.005$ for both comparisons), while the rates of A21H and ATTA were not different among the three groups[33].

Rare cases of co-existence of LADA with other autoimmune endocrine disorders have been reported recently in the literature. One 47-year-old female patient previously diagnosed with primary adrenal insufficiency whose symptoms of hyperglycemia could only be unmasked after the institution of glucocorticoid therapy was diagnosed to have LADA that was confirmed by presence of GADA and low C-peptide levels. The patient was later diagnosed to also have autoimmune thyroiditis with subclinical hypothyroidism[34]. Another report was on a 49-year-old female patient who had history of Graves' disease was incidentally diagnosed to have diabetes when manifesting prominent symptoms of hyperglycemia. A diagnosis of LADA was later confirmed by positive tests for both GADA and ICA[35]. Although rare in incidence, making a diagnosis of APS in a LADA patient would be a prudent and worthwhile clinical practice by an attentive physician who bears such knowledge in mind, instead of making one by mere serendipity.

Treatment for patients with LADA

With β-cell destruction caused by autoimmune process that leads to significantly impaired secretion of insulin as the major pathophysiology underlying development and progression of LADA, an ideal therapeutic approach would aim not only at obtaining a good metabolic control, but also at protecting residual β-cell mass and function[36].

Insulin therapy

Despite the initial insulin-independence state of LADA at diagnosis, insulin therapy is considered the most optimal treatment modality to begin with. Even in patients of phenotypic T2DM, the presence of islet cell antibody has long been noted to predict future insulin dependence, signifying more rapid loss of β-cell function in the presence of autoimmune process[37]. Furthermore, the destruction of pancreatic β-cells in patients of LADA may progress to a status of insulin deficiency as severe as that encountered in typical T1DM that DKA may develop as the first clinical presentation at diagnosis or as complication of certain physiological stresses (e.g. infections), conditions of which have been presented as case reports in the literature.[38-40]

In a study investigating the therapeutic effect of insulin therapy on both glycemic control and duration of insulin-independence, Kobayashi et al.[41] used a small dose of insulin instead of sulfonylurea (SU) in the early stage of treatment of patients diagnosed with slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM, the specific term for a subtype of DM used in Japanese academic society with clinical presentations similar to LADA but differences in genetic predispositions, and with a prevalence of 3.8% among apparent DM population in Japan)[42-45]. Compared to SU-treated patients, insulin-treated SPIDDM patients showed a significant difference in percentage of increment in C-peptide response (CPR) to 100-gram oral glucose tolerance test (OGTT) that was already seen at the fifth month of treatment and sustained to the study end of 30 months.

In addition to its well-recognized effect on metabolic control, early insulin intervention in LADA patients has a potential benefit in β-cell function preservation than treating with conventional insulin secretagogue.

Sulfonylureas (SU)

In a Japanese study, 60 subjects of adult onset diabetes who were tested positive for GADA and with a duration of ≤ 5 years were equally assigned to an SU group and an insulin group of treatment. Serum CPR to annual OGTT were performed up to a mean of 57 months. The primary endpoint was an insulin-dependent state defined by the sum of serum C-peptide values (∑C-peptide) < 4 ng/mL (1.32 nmol/L) which were derived from measurement obtained from OGTT. The results showed that the proportion of progression to the insulin-dependent state in the insulin group (3/30 = 10%) was lower than that in the SU group (13/30 = 43%; p = 0.003). Longitudinal analysis demonstrated that ∑C-peptide values were better preserved in the insulin group than in the SU group. It was concluded that, compared to SU, insulin intervention to preserve β-cell function is both effective and safe for patients with SPIDDM or LADA[46].

In summary, clinical trials had shown benefits on β-cell function reserve in patients with LADA through insulin administration, an effect that is not observed for insulin secretagogues.

Insulin sensitizers (Thiazolidinediones)

In addition to insulin deficiency caused by the autoimmune-related β-cell destruction in patients with LADA, insulin resistance may also play a role as underlying pathology of hyperglycemia. In a collaborative study carried out between Sweden and Norway, insulin resistance in overweight and obese patients was noted to be associated with increased risk of LADA, in addition to the presence of GADA[47].

In a clinical study carried out in China, the impacts on β-cell function in patients with LADA was compared between insulin therapy alone and combination therapy of rosiglitazone and insulin. Plasma glucose, HbA1c, and FCP were assessed every 6 months. Islet β-cell function was evalu-

ated by FCP, 2-hour PCP after 75-gm OGTT, and ΔCP (ΔCP = PCP-FCP) every 6 months. The results showed that, during the 12-month follow-up period, PCP and ΔCP levels in the combination group stayed steady, while both FCP and PCP levels decreased significantly in the insulin-alone group[48].

In summary, limited clinical data as far had provided evidence that insulin sensitizers may help improve β-cell function in patients with LADA. Well-designed clinical trials are needed to further clarify these findings.

Dipeptidyl peptidase 4-inhibitors (DPP4i)

With the potential of β-cell function preservation observed from use of DPP4i in patients with T2DM[49], their roles in LADA patients has been studied recently in different groups of LADA patients with different DPP4 inhibitors as study drug.

In a single-center study conducted in China, LADA patients of recent diagnosis were randomized to receive either insulin therapy adding 100 mg/day sitagliptin or without sitagliptin, and the β-cell function was assessed every 3-month up to one year. Compared to baseline data, the FCP, 2-hour PCP, and ΔCP (ΔCP = 2 h CP-FCP) levels at 12-month were not different in the insulin-alone group, whereas the parameters of interest were significantly decreased at 12-month in the combination therapy group. It was concluded that β-cell function in LADA patients was maintained when sitagliptin was added to insulin[50].

In a clinical trial originally designed to test the efficacy and safety of linagliptin versus glimepiride in a large population (n = 1,519) of patients diagnosed with T2DM, LADA patients were identified for separate analysis. In this 2-year study, FCP levels increased from baseline at weeks 28, 52, and 104 in those GAD65-positive patients treated with linagliptin, but decreased in the glimepiride-treated counterpart. One of the potential mechanisms may involve a β-cell-protective effect through elevation of endogenous glucagon-like peptide 1 (GLP-1) by DPP4 inhibition[51-53].

The efficacy and tolerability of saxagliptin as well as β-cell function were evaluated in a cohort of T2DM patients (n=2,709) who were subdivided into two groups based on GADA test result. After 24 weeks of treatment, saxagliptin resulted in similar reductions in HbA1c levels for both GADA-positive and GADA-negative patients. Beta-cell function as assessed by Homeostasis Model Assessment-%β (HOMA-B)[54] and PCP area under the curve had increased from baseline in both groups. It was concluded that saxagliptin showed effectiveness in both glycemic control and improving β-cell function in GADA-positive patients[55].

A recently reported clinical trial comparing the therapeutic effects on metabolic control and β-cell function between insulin therapy and DPP4i (sitagliptin) in a group of LADA patients (N = 64) was carried out in a collaborative study between Norway and Sweden[56]. After 21 months of treatment, there were no between-group differences in HbA1c and FCP levels. Compared to baseline assessment, the changes of glucagon-stimulated C-peptide levels showed a trend toward a difference between insulin- and sitagliptin-treated groups, although this trend was not statistically significant (4.4 ± 4.0 μU/mL vs 4.0 ± 2.2 μU/mL, p = 0.06).

In summary, the administration of DPP4i inhibitors had provided evidence from clinical trials of the benefit in β-cell function preservation in patients with LADA.

Glucagon-like peptide-1 receptor agonists (GLP1-RA)

In classic T1DM patients who were overweight, adding liraglutide (one of GLP1-RAs) to existing insulin therapy had shown effective reductions not only in hyperglycemia, but also risk of hypoglycemia as well as insulin dose. Along with findings in animal studies that GLP1-RA was effective in

reducing β-cell apoptosis and promoting β-cell neogenesis, this class of anti-diabetic drug is considered having the potential of preserving β-cell function in patients of LADA[57]. Despite the lack of randomized, controlled trials, a post hoc analysis of data pooled from three randomized phase 3 clinical trials in T2DM patients had demonstrated that, in addition to a significant reduction in HbA1c levels after treatment with dulaglutide up to a 12-month period, β-cell function assessed by HOMA-B in those GADA-positive patients had also shown improvement[58].

In summary, due to limited evidence available as far from randomized, controlled clinical trials, further studies are required to verify the effect of GLP1-RA on the β-cell function in patients with LADA.

Sodium-glucose co-transporter-2 inhibitors (SGLT2i)

Although clinical studies in T1DM as far have mostly shown salutary clinical effects, one major concern of its use is the high risk of euglycemic ketoacidosis that may develop when insulin dose is reduced in the presence of SGLT2i[59,60]. On considering the insulin deficiency status of patients with LADA similar to that in T1DM, the simultaneous use of insulin therapy and SGLT2i would also pose certain risk of ketoacidosis[61-63]. It would be prudent to limit the use of SGLT2i in patients with LADA until strong evidence available from well-designed clinical trials in this specific group of patients[64].

Conclusion

Diabetes mellitus diagnosed at adult age is mostly a disorder of glucose metabolism that is caused by insulin resistance and relative insulin deficiency as underlying pathophysiology, as encountered in classic T2DM patients. However, up to 10% of this population may have distinctive clinical presentations with a more rapid and severe deterioration of the pancreatic β-cells function that are associated with specific genetic and immunological factors, making this subgroup of patients divergent from the classic T2DM patients in decision-making of treatment strategy. The autoimmunity nature causing β-cell destruction and the prolonged time the clinical presentations emerge till adult age give its name "latent autoimmune diabetes in adults (LADA)". With the heterogeneity of underlying pathophysiology (a heterogeneous mixture of insulin deficiency and insulin resistance), comes also an inconsistency of clinical presentations that bring challenges to clinicians to make a correct diagnosis at the first moment. Nevertheless, as time goes by and with the metabolic control not as easily harnessed as for classic T2DM patients, alert clinicians would proceed to making a differential diagnosis among the wide spectrum of glucose dysmetabolism by careful review of the clinical presentations from the outset, checking basal state or stimulated C-peptide levels, ordering a test for the presence of autoantibodies against islet cell-derived antigens (notably GAD antibody), together of which will help make a confirmatory diagnosis of LADA. When diagnosed, it is rational to administer insulin as primary therapy as soon as possible in hopes of achieving an optimal glycemic control and at the same time preserving function of the remaining β-cells. Oral anti-diabetic agents could also be considered adjunctive to insulin therapy with aims to overcome other pathology of LADA, including insulin sensitizers (metformin, thiazolidinediones) for insulin resistance state, and incretin therapies (DPP4 inhibitors) for their abilities of preserving β-cells function and suppressing counter-regulatory effects from glucagon. Insulin secretagogues, like SU are not recommended as standard therapy for LADA patients because of lack of β-cells preservation function compared with insulin. Neither the new class OAD SGLT2 inhibitors are recommended due to higher risk of euglycemic diabetic ketoacidosis when insulin dose might be reduced after their use.

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潛伏性成人自體免疫型糖尿病 - 臨床面相之探討

宋育民

[1]台中慈濟醫院　內分泌新陳代謝科
[2]慈濟大學醫學院醫學系

摘　要

根據流行病學報告，在成年期診斷出糖尿病的族群中，有高達10%的病患可由血液檢查發現可與胰島細胞抗原進行反應的自體抗體，其中以麩胺酸脫羧酶抗體為最常見。在此糖尿病族群，β 細胞被自體免疫作用破壞，其致病生理類似第一型糖尿病患(C-胜肽濃度偏低)，但診斷年齡常落於 > 30歲之成年期，初始時仍可以口服降糖藥物治療，且鮮少以酮酸血症為表徵，又較趨近於第二型糖尿病之臨床表現；因其表象特殊，特被命名為「潛伏性成人自體免疫型糖尿病」。此類糖尿病患有以下特徵：身體質量指數較低，初始之糖化血色素較高，需藉檢驗C-胜肽濃度與麩胺酸脫羧酶抗體來確認其胰島細胞因自體免疫作用而被破壞之證據。治療方式以胰島素療法為首選，臨床實驗顯示胰島素療法不僅適用於血糖控制，且有保存β細胞功能的優勢。其他類口服藥物，如胰島素增敏劑，二肽基肽酶-4抑制劑，研究顯示具正面之臨床效果；然而第二型鈉-葡萄糖轉運蛋白抑制劑則不建議使用，因可能有酮酸血症風險。