DOI：10.6314/JIMT.202104_32(2).02 內科學誌 2021：32：83-97

Latent Autoimmune Diabetes in Adults: The Current Understanding and Challenge

Kuo-Bin Tseng

Division of Endocrinology and Metabolism, Department of Internal Medicine, E-DA Cancer Hospital, Kaohsiung, Taiwan

Abstract

Latent autoimmune diabetes in adults (LADA) is the most prevalent form of adult-onset autoimmune diabetes and probably the most prevalent form of autoimmune diabetes in general. It shares clinical and metabolic features with both type 2 diabetes mellitus (T2DM) and type 1 diabetes mellitus (T1DM). Patients with LADA may initially be diagnosed incorrectly as having T2DM based on their age, particularly if they have risk factors for T2DM such as a strong family history or obesity. The diagnosis of LADA is typically based on the finding of hyperglycemia together with the clinical impression that β-cell failure rather than insulin resistance (IR) is the main cause; detection of a low C-peptide and raised antibodies against the islets of Langerhans support the diagnosis. Highly variable β-cell destruction, different degrees of IR and heterogeneous titer and pattern of islet autoantibody, suggesting different pathophysiological pathways partially explaining the heterogeneous phenotypes of LADA. The decline in β-cell function progresses much faster in LADA than in T2DM, presumably because of the ongoing autoimmune assault in LADA, and therefore necessitates insulin therapy much earlier in LADA than in T2DM. The existence of heterogeneous phenotypes in LADA makes it difficult to establish an a priori treatment algorithm, and therefore, an individualized pharmaceutical therapy is required to preserve residual β-cell function and attain optimal diabetic control to decrease the risk of long-term diabetic complications in patients with LADA. This article aims to give an overview of the current understanding and gaps in knowledge regarding epidemiology, clinical and metabolic features, genetics, immunology, complications and therapeutic strategy of LADA and summarize an update on results from recent studies on the treatment of the disease. (J Intern Med Taiwan 2021; 32: 83-97)

Key Words: Latent autoimmune diabetes in adults, Insulin, Islet autoantibodies, Residual β- cell function, Randomized clinical trials, Treatment

Introduction

The American Diabetes Association "The Standards of Medical Care in Diabetes-2019" classifies diabetes into T1DM, T2DM, gestational diabetes mellitus, and specific types of diabetes due to other causes, not including LADA[1]. Three main criteria has been proposed by the Immunology of Diabetes Society (IDS) to diagnose LADA: 1. age at diagnosis ≥ 30 years; 2. positive for circulating islet autoantibodies; and 3. non-insulin requirement for at least 6 months after diagnosis[2]. However, these diagnostic criteria for LADA diagnosis remains controversial and debatable. For example, the age and treatment requirements seem arbitrary in nature. Patients younger than 30 years old may

Reprint requests and correspondence：Dr. Kuo-Bin Tseng
Address：Division of Endocrinology and Metabolism, Department of Internal Medicine, E-DA Cancer Hospital, No.1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan

present with a slowly-progressive form of autoimmune diabetes that is indistinguishable from older patients with LADA[3]. Thus, only the presence of islet autoantibodies (IAA) is an objective requirement. The characteristics of LADA include humoral autoimmunity, gene and phenotype heterogeneity, embracing a variety of insulin resistance (IR) and β-cell autoimmunity; this heterogeneity is likely due to different pathological mechanisms[4]. It is difficult to establish a standardized treatment due to the great heterogeneous phenotypes in LADA, and therefore, an individualized therapeutic approach is necessitated[5]. This article aims to give an overview of current knowledge and summarize an update on results from recent studies on the treatment of LADA.

Epidemiology

The prevalence of LADA exists considerably difference among different population groups in the world[6-23]. Probably, this is due to differences in inclusion criteria and study design, as well as different lifestyle and ethnicity. For examples, two Chinese studies reported 5.9% and 9.2% prevalence of LADA, respectively[6,7], whereas studies from Korea show a prevalence ranging between 4.1 and 5.3%[8,9]. In Japan, the prevalence is 3.8%[10]. In India, the prevalence from epidemiological studies are sparse[11-13]. The European studies show a prevalence ranging between 3% and 12%[14-18]. High prevalence has been reported in Middle Eastern ranging from 12.1 to 31%[19,20] with the exception of 2.6% prevalence of that in a large clinical-based study[21]. In Africa, available data reported the prevalence are estimated 6 to 12%[22,23]. Regarding North America and Hispanic populations, recent studies have revealed a lower prevalence among these populations[24,25].

In most of these studies, LADA is diagnosed by IDS three main criteria[1]. However, trends across different populations in the diagnosis of LADA differ even between regions within a given country, particularly between clinical-based and population-based studies. Take China as an example, frequency of LADA was highest in the northeast (7.1%), which has the highest latitude and coldest climate, and lowest in the southwest (4.0%)[7]. Similar results emerge from Spanish studies, showing that the north has a lower prevalence of LADA compared to the south (5.6-7.2% vs 10.9-14.7%, respectively)[26]. This discrepancy might be attributed partly to sample size; however, environmental factors and genetics might influence LADA prevalence. Regarding the Indian prevalence of LADA, controversial results have been shown[12,13] , which may be regarded as resulting from aspects of study differential such as age of onset/diagnosis, demographics of the studied subjects, and methods used to measure glutamic acid decarboxylase antibody (GADA) and/or islet antigen 2 antibody (IA-2A)/islet cell antibody. Moreover, the definition of these autoantibodies positive are not apparent and different studies may apply different cut-off points. Considerably, few studies suggested high prevalence of LADA which involved subjects from a specific subgroup of the population who were non-obese, younger age, and early diabetic diagnosis with higher probability of LADA[12,13]. Such results could not actually reflect the population prevalence of LADA in India.

The dynamic changes in autoantibody status is still not sufficiently understood, but time-varying anti-idiotypic antibodies possibly may interfere in diabetes-associated autoantibodies assays[27]. It should be noted that the unexplored field of percentage of the affected with transient autoantibodies, in whom most of otherwise features of LADA are presented except autoantibody negative. Take Scandinavia of adult-onset diabetes as an example, in a recent large cohort study, of which 6.4% was diagnosed LADA, but 17.5% presented with similar features including insulin deficiency but were GADA negative[28].

Clinical and metabolic features

When compared to T1DM, the frequency and the components of the metabolic syndrome (MS) are more prevalent in LADA[15,29]. However, this assumption changes when T2DM are compared with LADA[7,29]. For example, a cohort study in the United Arab Emirate suggested that LADA patients have higher waist circumference, body mass index (BMI), glycated hemoglobin (HbA1c) and systolic blood pressure as compared with T1DM patients[21]. By comparison with T2DM, LADA tend to younger at diagnosis, lower waist-hip ratio and BMI and lower rate of hypertension, but a more decreased lower C-peptide secretion as well as an increased likelihood of insulin requirement[7,17,18,29]. Thus, LADA usually has a more rapid progression to a deficient insulin secretion state that manifests frequently to be prone to diabetic ketoacidosis and the earlier requirement of insulin treatment[3].

It has been suggested that the GADA titers are associated with a requirement for early insulin therapy or the deterioration of β- cell function in a prospective or cross-sectional study of Caucasians[14,15]. Subjects with high GADA titers are susceptible to have more prominent traits of impairment of insulin secretion and a profile of more severe autoimmunity resulting in higher HbA1c, lower BMI and a lower prevalence of MS and its components that are more marked and more similar to T1DM, patients being younger age of onset, leaner with a high risk of the requirement for insulin therapy, whereas subjects with low GADA titers are more comparable to those with T2DM[7,15,17,18]. However, there exist a certain number of patients with high GADA titers who sustain non-insulin dependent for many years although high circulating GADA levels are one of important markers to predict future insulin requirement[30]. Therefore, there exists overlapping for these clinical parameters among groups of patients to make it impossible to accurately identify adult-onset autoimmune diabetes in subjects presenting with T2DM based on clinical features alone[2,15].

There are debates about the influence of IR in the pathophysiology of LADA[31]. The known MS parameters such as waist and triacylglycerides associated with MS in T2DM were not associated with increased IR in LADA[31]. The high-density lipoprotein cholesterol was higher in LADA than GADA-negative diabetes subjects and was unexplainably associated with IR among LADA[31]. However, the current knowledge of LADA is unsuccessful to capture IR, an extraordinary pathogenic mechanism and a therapeutic target in this type of autoimmune diabetes. Formal investigation of IR indicates that LADA is less insulin sensitive than healthy, but its insulin sensitivity is comparable with or more than that of T2DM and depends upon BMI[32].

It remains ambiguous how LADA has association with the progressive decline of insulin secretory capacity. Therefore, it is recommended not to manage diabetes on the basis of current knowledge of LADA alone. Chemokines and adhesion molecules have also been shown to be associated with diabetes progression[33]. For example, compared to T1DM, cytokines [interleukin-6, lipocalin 2, and high-sensitivity C-reactive protein (hs-CRP)] were higher in Chinese LADA[34].

Genetic features

The genetic investigation of autoimmune-assault diabetes in patients who progress to the disease during adulthood could explain the etiology of this delayed-onset autoimmunity and impact its further management. It has been shown that the frequency of human leukocyte antigen (HLA) susceptibility alleles are increased in subjects with LADA[35], but regardless of whether there are mysterious differences for specific alleles between LADA and T1DM is controversial[35]. Later, many studies have already conducted an investigation of the associa-

tion of the major histocompatibility complex region with LADA, particularly HLA class genes[15,36]. Take Chinese patients as an example, as for European patients, HLA-DQ genetic analysis revealed markedly lower frequency of diabetes-susceptibility haplotypes in both T2DM (47.1%) and control (43.2%) than in LADA (63.9%) patients[7].

The insulin gene has been recognized as a susceptibility locus for developing autoimmune diabetes in children as well as in adulthood. The magnitude of the insulin gene variable number of tandem repeats (*INS* VNTR) effect size in LADA does not suggest differing appreciably from that seen in T1DM[37]. LADA subjects demonstrate decreased frequency of the CT/TT genotypes in the PTPN22 gene compared with T1DM subjects, although more than in control subjects[38]. A recent systematic review has demonstrated that cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) and protein tyrosine phosphatase non-receptor type 22 (PTPN22) are potential risk factors for LADA[39]. Moreover, the fat mass and obesity-associated (FTO) gene has also been recognized to be associated with LADA as well as T2DM[40].

Previously, variation in the transcription factor 7-like 2 (TCF7L2) gene suggested strong association of T2DM[41]. However, it has been observed that common genetic variants of susceptibility in the TCF7L2 only associate with GADA antibody titer in T2DM and LADA, where the higher it is, the weaker the association[42]. Similar results arise from study in the FTO gene[40]. The TCF7L2 common variants gene could give assistance to make distinction between autoimmune and non-autoimmune diabetes in young but not in middle-aged subjects with diabetes[43].

LADA is also related with increase in the frequency of common variants in solute carrier family 30 (zinc transporter), member 8 (SLC30A8)[44], which converts into code of zinc transporter 8 (ZnT8), and the obesity-associated variant of FTO[40,44]. As such, those observations demonstrate that the heterogeneous genes in LADA are associated with varying degree of activity of autoimmune, which suggest that it may be a representative from genetic admixture of T1DM and T2DM. Aiming whole-genome exome sequencing or exome sequencing at Genome-wide association studies are left to be carried out in patients with adult-onset autoimmune in large cohorts to clarify whether such genetic admixture is characterizes as a part of an autoimmune continuum or just a distinct disease syndrome.

Immunological features

LADA presents activation of peripheral blood mononuclear cells, particularly within one year of the beginning of insulin treatment, resembling T1DM at onset[45]. Importantly, it has been showed that a small group of patients presented with autoantibody-negative phenotypic T2DM display an autoimmune T-cell response, implying that an inflammation of the islets of Langerhans might occur without the presence of autoantibodies in islet[46].

To date, it is suggested that GADA are the most sensitive and prevailing antibodies in adult-onset diabetes[7,15,18]. Compared to those with high GADA titers, subjects with low GADA titers had less prominent traits of insulin deficiency and a profile of less severe autoimmunity resulting in lower HbA1c, higher BMI, a higher prevalence of MS and its components[47]. Other investigations didn't suggest such a frequency distribution with two modes of GADA titers [15]. These significant discrepancies may reflect that different populations have different characteristics of LADA[7]. Subjects with high-titer GADA are likely to have high-affinity GADA, suggesting a shorten preservation of residual β-cell function[48].

IA-2 is an intrinsic membrane protein of secretory granules which is expressed in insulin-producing pancreatic β-cells[49]. IA-2A are almost always present in combination with other islet cell autoantibodies in autoimmune diabetes. Evidence has

shown that IA-2A positivity persists up to a few years after onset but decreases rapidly thereafter, unlike GADA, which might increase with age[50]. Thus, IA-2A could be used to identify LADA, while screening for IA-2A in older subjects is less useful since the diagnostic sensitivity for LADA (2~4%) is much lower[50].

ZnT8 is also an islet β-cell secretory granule membrane protein identified as an autoantigen in T1DM[51]. It has suggested that the identification of ZnT8 autoantibodies (ZnT8A) based on IA-2A and GADA could improve LADA diagnostic sensitivity in Chinese patients[52]. The concentrations of the ZnT8A arginine variant represent higher concentrations of stimulated C-peptide after onset of T1DM and during follow-up[53]. Thus, the associations between stimulated C-peptide levels and ZnT8A a few months after onset might have crucial clinical implications with respect to individualized insulin treatment and implementary clinical intervention trials designed to preserve and regenerate β-cell function. Different from GADA, ZnT8A, which are capable of being detected in younger subjects with T1DM, are positive only in a small percentage of subjects with LADA[54].

LADA or T1DM patients have similar changes in systemic concentrations of cytokines, adhesion molecules and chemokines[55]. In China, study has suggested heterogeneity of altered cytokine levels among all three primary types of diabetes[34]. Moreover, it reported lower adiponectin but higher hs-CRP in LADA when compared to T1DM[34]. Studies have also suggested that methylated DNA levels are modified in $CD4^+$ T cells from LADA patients, which may progress to disease onset and development by changing the expression of autoimmune-associated genes[56].

Complications

The long-term consequences of LADA with regard to microvascular complications remain poor understood. Earlier studies of LADA that have compared with either T1DM or T2DM the risk of microvascular complications were restricted to small sample sizes, different ethnic groups, heterogeneous metabolic control, unclear definition of LADA and diabetic duration, the last of which was the most important variable factor. Cross-sectional studies suggest that LADA tend to have worse glycemic control than T2DM[57]. One explanation could be that there remains a priori treatment algorithm strategy unestablished for LADA[58]. The longitudinal and observational Fremantle Diabetes Study suggested that microalbuminuria was more frequent in patients with T2DM than in those with a recent diagnosis of LADA[59]. GADA positivity was found to reduce 62% risk of microalbuminuria development for a period of follow-up less than 5 years[59]. This study also suggested that nephropathy complicating LADA behaved more like T1DM than T2DM, but the reasons for the discordance with neuropathy and retinopathy were unclear. Similar results were carried out in Chinese study[60]. These discrepancies might be accounted for by the fact that LADA patients as usual are diagnosed early than T2DM patients, being likely long-term affected by hyperglycemia which might eventually contribute to microvascular complications. The prevalence of retinopathy and nephropathy were comparable in subjects between T2DM and LADA when duration is more than 5 years[57,60] and did not differ between the frequency of microvascular events and GADA positivity[61].

Earlier studies suggested that no significant differences were found between T2DM and LADA concerning the prevalence of macrovascular complications[57,59,60], cardiovascular mortality[57,59], and overall mortality[59]. Later, cardiovascular disease outcomes in LADA have been investigated by several studies. A cross-sectional study showed that carotid atherosclerosis was more frequent in LADA compared with T2DM and T1DM[62]. Conversely, a

retrospective Chinese study reported that a comparable frequency of carotid atherosclerosis was found between LADA and T2DM[60]. It was reported that LADA patients had a comparable risk of acute myocardial infarction to that of T2DM patients for a period of follow-up less than 4 years, whereas heart failure rates tended to be increased (hazard ratio 1.51) in LADA patients[59]; however, the number of subjects was small, and no stratification by sex was presented. A small study reported that patients with T2DM had a numerical more incidence of coronary damage than patients with LADA (19.7% vs. 11.5%), whereas the incidence of peripheral vascular disease (27.1% vs. 30.8%) seemed rather similar between the two groups. However, patients with LADA had lower cerebrovascular incidents than patient with T2DM (19.2% vs. 34.9%; $p < 0.01$)[63]. Those recognizable differences in macrovascular complications between T2DM and LADA could be attributed to interactions between susceptible β-cells_genetically with numbers of factors, including susceptibility to environmental influences, IR, and inflammation/immune dysregulation[64].

Treatment

Although different recommendations have existed in the management of patients with T2DM and T1DM, no priori treatment algorithm in the management of subjects with LADA has been established so far. As a result, subjects with LADA are currently regarded as affected by subjects with T2DM resulting in progression rapidly to an insulin dependency[5], particularly in subjects who have presented with biochemical and clinical features getting close to T1DM than T2DM[21,65]. To date, several intervention trials have been conducted to investigate different therapeutic strategies of LADA (Table 1).

Lifestyle modifications

Diet therapeutic strategy is no difference in patients between LADA and T1DM. Obese patients with LADA receive benefit of increased levels of physical activity and restriction in calorie consumption[66]. The Nord-Trøndelag health study reported that overweight, physical inactivity and increased age are as strong risk factors for LADA[67]. These findings suggest IR playing a role in the pathogenesis of LADA and provide important public health implications since they convey the concept that LADA to a large extent is influenced by environmental factors and hence preventable.

Insulin sensitizers

Although IR is more prominent in T2DM than LADA, it does a clinical characteristic of LADA. Metformin has been investigated in an experimental diabetes of autoimmune animal model; however, it did not change the lymphocytic infiltration as well as the clinical trajectory of disease in the pancreatic islets of the non-obese diabetic mouse[68], demonstrating that metformin does not affect the pathogenic process resulting in β-cell destruction. A case report showed that metformin could maintain intrinsic insulin secretion capacity for five years in a patient with LADA[69]. Although only one case report is not enough to arrive at a firm conclusion, this case implies that metformin might be a choice of treatment for LADA when the residual β-cells function are maintained. To date, no large and long prospective studies have investigated metformin for treatment of LADA[70].

A pilot study comparing insulin alone versus rosiglitazone plus insulin suggested that rosiglitazone plus insulin may maintain pancreatic β-cell function in subjects with LADA[71]. However, this study did not clarify the effect of monotherapy of TZD. Similarly, another study showed that rosiglitazone combined with insulin wherever or not maintain pancreatic β-cell function in patients with LADA after 3 years[72]. However, a randomized control trial comparing pioglitazone with metformin

Table 1. Studies investigating the efficacy of pharmacological therapies to LADA

Drugs tested	Study design	Study population	Conclusions	Refs
Metformin	Case report	1 participant with NIDDM. Positive for GAD autoantibodies.	Insulin independence was maintained with metformin for five years.	69
Rosiglitazone with insulin versus insulin alone	Randomized, open-label study	23 participants with LADA, fasting C-peptide levels > 0.3 nmol/L	After 12 and 18 months, measures of β-cell function stayed steady in rosiglitazone combined with insulin group but decreased more in the insulin-alone group.	71
Rosiglitazone versus sulfonylureas and rosiglitazone with insulin versus insulin alone	Randomized, open-label study	54 participants with LADA. Rosiglitazone group versus sulfonylureas group (GAD autoantibodies < 175 U/mL and fasting C-peptide levels > 0.3 nmol/L). Insulin group versus rosiglitazone plus insulin group (GAD autoantibodies ≥ 175 U/mL or GAD autoantibodies < 175 U/mL and fasting C-peptide levels ≤ 0.3 nmol/L).	Rosiglitazone combined with insulin wherever or not preserved β-cell function in LADA patients after 3 years.	72
Pioglitazone versus metformin	Randomized, open-label study	10 participants with T2DM Positive for GAD autoantibodies. Disease duration:0~9 years (mean 3.2 years)	Pioglitazone may accelerate the disease course of slowly progressive type 1 diabetes.	73
Glibenclamide (SU) with insulin versus insulin	Randomized, open-label study	14 participants with T2DM Positive for ICA and GAD autoantibodies	The insulin-alone group had better fasting glucose and also improved the markers of autoimmunity than the SU plus insulin group. Exclusion of glibenclamide in the treatment of ICA+ partially decreases specific autoimmunity against endocrine pancreatic cells and improves metabolic control. No differences found for GAD autoantibodies and fasting C-Peptide between the groups.	74
Glibenclamide (SU) versus insulin	Pilot randomized, open-label study	10 participants with NIDDM. Positive for ICAs	The SU group had worsening metabolic control and a progressive deterioration of β-cell function as measured by serum C-peptide response within 6 and 12 months but improved significantly in the insulin group.	75
SU versus insulin	Multicenter, randomized, nonblinded clinical study (the Tokyo study)	60 participants with NIDDM. Positive for GAD autoantibodies. Disease duration ≤ 5 years	After a mean follow-up of 57 months, the insulin group had a lower rate of progression to an insulin-dependent state. The C-peptide values was more preserved in participants undergoing insulin treatment. The high GADA titers subgroup treated with SU had the greatest proportion participants for progression to insulin dependence.	76
Glimepiride (SU) versus Linagliptin (DPP-4 I)	Prespecified exploratory analysis of a double-blind, randomized, controlled study	118 participants with LADA Positive for GAD autoantibodies.	Participants treated with linagliptin increased fasting C-peptide levels from baseline at weeks 28, 52 and 104 but decreased in participants treated with glimepiride. No differences in metabolic control found.	77
Sitagliptin with insulin versus insulin alone	Randomized, open-label control study	30 participants with LADA	LADA participants treated with sitagliptin and insulin maintained β-cell function by comparison with insulin alone.	79

(continued)

Table 1. Studies investigating the efficacy of pharmacological therapies to LADA (Continued)

Drugs tested	Study design	Study population	Conclusions	Refs
Saxagliptin	Post-hoc analysis of pooled data from five randomized, placebo-controlled, 24-week phase III studies	133 participants, positive for GAD autoantibodies (98 in the saxagliptin group and 35 in the placebo group)	Saxagliptin was effective in lowering blood glucose levels and generally well tolerated in GAD autoantibody -positive participants. Saxagliptin seems to improve β-cell function in GAD autoantibody- positive participants.	80
Sitagliptin versus pioglitazone	Pilot randomized, open-label controlled study	14 participants with LADA Positive for GAD autoantibodies.	Sitagliptin may be more effective in preserving the β-cell function for at least 4 years in participants with LADA.	81
Exenatide or Liraglutide (GLP-1 RA)	Longitudinal observational study	620 participants with T2DM commencing a GLP1-RA Positive for GAD/IA-2 autoantibodies (N=520)	Participants with GAD or IA2 autoantibody positive had a non-significant reduction in the adjusted mean HbA1c change -4.6 mmol/mol, which was lower than the reduction observed in participants with antibody-negative. Participants with antibody-positive had a 17% reduction in insulin dose (versus 40% in participants with antibody-negative).	82
GLP-1 RA (dulaglutide)	Post-hoc analysis of data pooled from 3 randomized phase III trials on T2DM	123 (dulaglutide), 44 (glargine), 18 (sitagliptin) participants positive for GAD autoantibodies. Duration of diabetes at enrolment: 6.1-10.9 years (mean)	Among those treated with dulaglutide, HbA1c was reduced after 3, 6 and 12 months (vs baseline) in GADA positive and GADA negative participants. Levels of HbA1c were reduced to a similar extent in dulaglutide and glargine treated GADA positive participants, while in GADA negative participants a more pronounced decrease was found with dulaglutide vs. glargine. Compared to treatment with sitagliptin, dulaglutide decreased HbA1c more effectively in GADA positive as well as in GADA negative participants.	83
Insulin versus diet with or without OHA (metformin and/or SU)	Randomized, open-label study	37 participants with NIDDM Positive for GAD autoantibodies or ICAs	Early insulin treatment in LADA leads to better preservation of metabolic control and was safe. Superior preservation of C-peptide could not be significantly demonstrated. Only baseline level of C-peptide significantly influenced C-peptide level after 3 years.	85
Insulin versus sitagliptin, both add-ons to metformin	Randomized treatment study on LADA. Clinical Trial Registration Number: NCT01140438	30 (insulin) and 31 (sitagliptin) participants with LADA	Early insulin treatment may be advantageous in LADA but does not protect against an autoimmune assault on β cells.	86
Insulin versus. insulin + saxagliptin versus. insulin + saxagliptin + vitamin D3 (NCT02407899)	Multicenter, open-label, randomized controlled trial	300 (estimated) participants with LADA	The main purpose is to evaluate whether saxagliptin (and vitamin D3) with insulin therapy can better protect islet β cell function than insulin alone. Data from 104 weeks of intervention are presently analyzed.	87

Abbreviations: GAD, glutamic acid decarboxylase; ICA, islet-cell autoantibody; GLP-1 RA, glucagon-like peptide 1 receptor agonist; IA-2, islet antigen 2; LADA, latent autoimmune diabetes in adults; NIDDM, non-insulin-dependent diabetes mellitus; DPP-4 i, Dipeptidyl peptidase-4 inhibitors; OHA, oral hypoglycaemic agent; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; HbA1c, glycated hemoglobin.

in patients with LADA suggested that pioglitazone may accelerate the disease course of LADA during a follow-up period, more than 48 months[73]. To clarify whether pioglitazone could affect the disease course of LADA or not, more prospective and interventional studies are needed for further exploration.

Sulfonylureas

Sulfonylureas (SU) stimulate insulin release from the pancreatic β cells. It is reasonable to speculate that SU in LADA would actually accelerate the progressive deterioration in β cells and shorten starting time of insulin therapy, and this hypothesis has been confirmed by several studies [66,74-77]. In Japan, two randomized controlled trial (RCT) investigated the therapeutic effects between glibenclamide and insulin in subjects affected by LADA. The first trial was a small pilot RCT investigating glibenclamide versus insulin treatment[75]. After a 30-month follow-up, glibenclamide suggested making metabolic control worse and a gradual decline in β-cell function with almost 40% reduction from baseline as measured by serum-stimulated C-peptide ratio. The second trial evaluated sixty non-insulin dependent and positive GADA diabetic patients within 5 years of diabetic duration[76]. This study suggested that the SU group had higher rate of progression to insulin-dependence compared to the insulin group, and C-peptide levels got more preserved during the oral glucose tolerance test in subjects experiencing insulin intervention. Moreover, the greatest proportion patients for progression to insulin dependence were the high GADA titers subgroup receiving SU treatment. A small study compared glimepiride with linagliptin suggested that the decline rate of C-peptide levels may have accelerated in glimepiride group over a 2-year disease trajectory in patients with LADA[77]. It was difficult to compare these studies since there was a greater amount of heterogeneity among studies design, selection criteria, follow-up durations, ethnicity, and different outcome parameters. Therefore, there is no strong clinical evidence to support SU as a first line treatment for LADA.

Incretins

It was suggested that LADA has higher DPP-4 activity expression when compared with both T1DM and T2DM[78]. Thus, DPP-4 activity may be a primary predictive factor to determine type of diabetes. A small double-blind RCT showed that DPP-4 inhibitors, linagliptin, may have attenuated the C-peptide declined rate over a two year disease trajectory in LADA[77]. An open-label RCT showed that β-cell function may be preserved in recent-onset LADA patients treated with sitagliptin at the 12-month follow-up[79]. Interestingly, a post hoc analysis of pooled data from five RCTs suggested that saxagliptin seems to improve β-cell function in GADA-positive subjects, while a longer course for treatment may be warranted to give evidence to factuality of this finding[80]. A recent open-label RCT in Japan has observed that sitagliptin treatment may be more effective to protect β-cells function from decline than insulin treatment for at least 4-year period in patients with LADA, probably through the immunomodulatory effects of DPP-4 inhibitors[81]. Altogether, those trials suggested that DPP-4 inhibitors may be effective to preserve β-cell function in LADA as a class effect and a suitable candidate in intervention and/or prevention of LADA trials.

More recently, an investigation of the GLP-1 receptor agonists (GLP-1RAs) exenatide or liraglutide was conducted for 6 months in subjects with LADA, suggesting the adjusted mean level of HbA1c not significantly reduced, which was higher than the reduction observed in antibody-positive subjects[82]. Moreover, those who presented severe insulin deficiency with antibody positive for IA-2 or GADA also had significantly lower impact of glucose response to GLP-1RAs treatment[82]. Another GLP-1 RA study in LADA suggested dulaglutide favorable

effect on glycemic control[83].

In summary, these studies emphasize the long-term prospective effects of DPP-4 inhibitors and GLP-1RAs in LADA. However, more large-scale cohort and long-term course of treatment studies are necessary to investigate whether these therapeutic approaches are effective to alleviate rapidly progressed to insulin dependent state and reduce long-term complications of diabetes in LADA.

Insulin therapy

To date, one of the main challenges regarding the therapeutic strategies of LADA is whether the introduction of early insulin treatment is really necessary for this form of autoimmune diabetes. Since LADA presents with a non-insulin requiring disease at diagnosis and the current therapeutic strategy is to reduce the risk of progression toward insulin requirement. Thus, initiating early insulin therapy in LADA seems somehow paradoxical. Of course, the rationale behind this strategy is to preserve residual β-cell function while improving metabolic control.

Insulin instead of SU treatment was more desirable to preserve or reverse β-cell function in LADA[76]. Moreover, in subgroup analysis, insulin has been suggested to be very effectively approach for LADA with high GADA titers and maintained β-cell function at baseline[76]. Many studies concluded a general recommended treatment with insulin in LADA, however, the evidence has not been convincing, as concluded by the 2011 Cochrane review[84]. A study with 3-year follow-up suggested that early initiation with insulin management not only results in more effective control of metabolism, but also was well-tolerated and safe in LADA[85]. However, superior of preserving C-peptide levels did not be significantly demonstrated. Several studies suggested that patients with LADA progress towards an insulin-dependent state being different based on biochemical and metabolic features[21,14,65].

The optimal insulin regimen in LADA remains unclear. Given that early rapid decline in insulin secretion capacity progresses in LADA, multiple-dose insulin replacement therapy may be helpful. However, from a practical viewpoint, initiating multiple doses of insulin injection may be difficult in patients with LADA, especially if their blood sugar are within reasonable elevation. In such patients, injection with a long-acting insulin for blood sugar control could be a good alternative[70,76]. Recently, in a Swedish-Norwegian RCT, LADA patients on metformin were randomized to add-on treatment with either insulin or the DPP4-inhibitor sitagliptin during an intervention period of 21 months[86]. This study suggests that early initiation of insulin therapy may be beneficial in LADA but does not protect β-cells from an autoimmune assault. An ongoing multicenter, open-label RCT in China investigates saxagliptin and vitamin D3 protective efficacy in patients with LADA who were previously treated with insulin[87]. Data from 104 weeks of intervention are presently analyzed. Altogether, the studies done until now on early insulin treatment in LADA and benefits in preserving β-cells function still show discrepancies and future large-scale studies of insulin treatment are needed to elucidate the uncertainties.

Immune modulation

Since an progressive autoimmune assault of β-cells results in LADA, immunomodulatory therapy may be a good alternative to provide the progression control of autoimmune disease by inducing tolerance. However, most immune intervention trials in autoimmune diabetes as far have either failed to preserve β-cell function successfully or have met an obstacle but have nevertheless shown only a transient effect[88-91]. It is apparent that extremely effective prevention against the progressive decline in β-cell function remains an obscure target. Therapeutic strategy established for the interactions between β-cells and immune system

represent an effective alternative but translation of the basic science in this field to clinical trials is challenging. Much has been learned over the past decades with the dramatic growth in clinical trials of autoimmune diabetes but much more remains to be done.

Conclusions

The challenge of how to define and diagnose LADA has resulted in numerous debates and literatures regarding whether LADA is a distinct but heterogeneous clinical entity or just a variant of T1DM. The lack of clear clinical features make it difficult to distinguish LADA from T2DM. The long-term consequences of LADA in terms of microvascular and macrovascular complications remain largely unknown. To date, no standard treatment guidelines is established for LADA since its pathogenesis and nature history remains not well understood. The main therapeutic approach in the management of LADA is to preserve β-cells function and prolong insulin independency as possible by offering an effective control of metabolism and improving the nature history of the disease. There is no strong evidence for or against the use of metformin in LADA, although SUs are positively discouraged. TZD may potentially be beneficial to LADA, but more prospective and interventional studies are needed to confirm it as a good therapeutic option. DPP-4 inhibitors may be effective as a class effect in LADA. GLP-1RAs have no potential beneficial effects on HbA1c reduction as well as glycemic response in LADA. Immunomodulatory agents may be a good alternative to provide the progression control of autoimmune diabetes, but most immune intervention trials failed to demonstrate their beneficial effects in LADA. Insulin seems the cornerstone of management of LADA. Current knowledge from clinical treatment studies in LADA does not represent a solid foundation for an official treatment strategy for LADA patients. Obviously, further high-quality studies are necessary to investigate various features of this form of autoimmune disease and to establish the best therapeutic strategy, which, if successful, may also be helpful to prevent progression to an insulin-dependent state in younger individuals who have increased susceptibility to T1DM.

References

1. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2019. Diabetes Care 2019; 42 (Suppl 1): S13-28.
2. Fourlanos S, Dotta F, Greenbaum CJ, et al. Latent autoimmune diabetes in adults (LADA) should be less latent. Diabetologia 2005; 48: 2206-12.
3. Naik RG, Brooks-Worrell BM, Palmer JP. Latent autoimmune diabetes in adults. J Clin Endocrinol Metab 2009; 94: 4635-44.
4. Hernandez M, Mollo A, Marsal JR, et al. Insulin secretion in patients with latent autoimmune diabetes (LADA): halfway between type 1 and type 2 diabetes. Action LADA 9. BMC Endocr Disord 2015; 15: 1-6.
5. Buzzetti R, Zampetti S, Maddaloni E. Adult-onset autoimmune diabetes: current knowledge and implications for management. Nat Rev Endocrinol 2017; 13: 674-86.
6. Qi X, Sun J, Wang J, et al. Prevalence and Correlates of Latent Autoimmune Diabetes in Adults in Tianjin, China: A population-based cross-sectional study. Diabetes Care 2011; 34, 66-70.
7. Zhou Z, Xiang Y, Ji L, et al. Frequency, Immunogenetics, and Clinical Characteristics of Latent Autoimmune Diabetes in China (LADA China Study): A Nationwide, Multicenter, Clinic-based Cross-sectional Study. Diabetes 2013; 62: 543-50.
8. Park Y, Hong S, Park L, et al. LADA prevalence estimation and insulin dependency during follow-up. Diabetes Metab Res Rev 2011; 27: 975-9.
9. Roh MO, Jung CH, Kim BY, Mok JO, Kim CH. The prevalence and characteristics of latent autoimmune diabetes in adults (LADA) and its relation with chronic complications in a clinical department of a university hospital in Korea. Acta Diabetol 2013; 50:129-34.
10. Takeda H, Kawasaki E, Shimizu I, et al. Clinical, autoimmune, and genetic characteristics of adult-onset diabetic patients with GAD autoantibodies in Japan (Ehime Study). Diabetes Care 2002; 25: 995-1001.
11. Katulanda P, Shine B, Katulanda GW, et al. Diabetes mellitus among young adults in Sri Lanka—role of GAD antibodies in classification and treatment: the Sri Lanka Young Diabetes study. Diabetologia 2008; 51: 1368-74.
12. Chandni R, Paul BJ, Udayabhaskaran V, Ramamoorthy KP. A study of non-obese diabetes mellitus in adults in a tertiary care hospital in Kerala, India. Int J Diabetes Dev C 2013; 33: 83-5.
13. Shrivastav A, Mukhopadhyay S, Chowdhury S. Prevalence

of latent autoimmune diabetes in young, non-obese, adult onset diabetes patient with poor response to oral insulin secretagogues. Diabetologia 2015; 58: S248-9.
14. Turner R, Stratton I, Horton V, et al & UK Prospective Diabetes Study (UKPDS) Group. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. The Lancet 1997; 350: 1288-93.
15. Tuomi T, Carlsson A, Li H, et al. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 1999; 48: 150-7.
16. Bosi E, Garancini MP, Poggiali F, Bonifacio E, Gallus G. Low prevalence of islet autoimmunity in adults diabetes and low predictive value of islet autoantibodies in the general adult population of northern Italy. Diabetologia 1999; 42: 840-4.
17. Radtke MA, Midthjell K, Nilsen TIL, Grill V. Heterogeneity of patients with latent autoimmune diabetes in adults: linkage to autoimmunity is apparent only in those with perceived need for insulin treatment: results from the Nord-Trondelag Health (HUNT) study. Diabetes Care 2009; 32: 245-50.
18. Hawa MI, Kolb H, Schloot N, et al. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: action LADA 7. Diabetes Care 2013; 36: 908-14.
19. Arikan E, Sabuncu T, Ozer EM, Hatemi H. The clinical characteristics of latent autoimmune diabetes in adults and its relation with chronic complications in metabolically poor controlled Turkish patients with Type 2 diabetes mellitus. J Diabetes Complications 2005; 19: 254-8.
20. AL-Hasnawi SMJ, AL-Jiboury SA. Prevalence of Latent Autoimmune Diabetes of Adult (LADA) among Type 2 Diabetes Mellitus (DM 2) in Karbala. Kufa Journal for Nursing sciences 2015; 5: 138-45.
21. Maddaloni E, Lessan N, Al Tikriti A, Buzzetti R, Pozzilli P, Barakat MT. Latent autoimmune diabetes in adults in the United Arab Emirates; clinical features and factors related to insulin-requirement. PLoS One 2015; 10: e0131837.
22. Otieno CF, Huho AN, Omonge EO, Amayo AA, Njagi E. Type 2 diabetes mellitus: clinical and aetiologic types, therapy and quality of glycaemic control of ambulatory patients. East Afr Med J 2008; 85: 24-9.
23. Ipadeola A, Adeleye JO, Akinlade KS. Latent autoimmune diabetes amongst adults with type 2 diabetes in a Nigerian tertiary hospital. Prim Care Diabetes 2015; 9: 231-6.
24. Lerman I, Granados J, Aguilar-Salinas C, et al. Baja prevalencia de autoinmunidad (anticuerpos anti GAD+) en pacientes adultos con diabetes tipo 2 de inicio temprano. Rev Endocrinol Nutr 2010; 18: 170-5.
25. Barinas-Mitchell E, Pietropaolo S, Zhang YJ, et al. Islet cell autoimmunity in a triethnic adult population of the Third National Health and Nutrition Examination Survey. Diabetes. 2004; 53: 1293-302.
26. Soriguer-Escofet F, Esteva I, Rojo-Martinez G, et al. Prevalence of latent autoimmune diabetes of adults (LADA) in Southern Spain. Diabetes Res Clin Pract 2002; 56: 213-20.
27. Hampe CS, Hall TR, Ågren Å, Rolandsson O. Longitudinal changes in epitope recognition of autoantibodies against glutamate decarboxylase 65 (GAD65Ab) in prediabetic adults developing diabetes. Clin Exp Immunol 2007; 148: 72-8.
28. Ahlqvist E, Storm P, Käräjämäki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol 2018; 6: 361-9.
29. Mollo A, Hernandez M, Marsal JR, et al. Latent autoimmune diabetes in adults is perched between type 1 and type 2: evidence from adults in one region of Spain. Diabetes Metab Res Rev 2013; 29: 446-51.
30. Ishii M, Hasegawa G, Fukui M, et al. Clinical and genetic characteristics of diabetic patients with high-titer (> 10,000 U/ml) of antibodies to glutamic acid decarboxylase. Immunol Lett 2005; 99: 180-5.
31. Salem SD, Saif-Ali R, Muniandy S, Al-Hamodi Z, Ismail IS. Comparison of adults with insulin resistance (IR) in latent autoimmune diabetes versus IR in glutamic acid decarboxylase antibody-negative diabetes. Ann Acad Med Singapore 2014; 43: 107-12.
32. Tripathy D, Carlsson AL, Lehto M, Isomaa B, Tuomi T, Groop L. Insulin secretion and insulin sensitivity in diabetic subgroups: studies in the prediabetic and diabetic state. Diabetologia 2000; 43: 1476-83.
33. Herder C, Baumert J, Thorand B, et al. Chemokines as risk factors for type 2 diabetes: results from the MONICA / KORA Augsburg study, 1984–2002. Diabetologia 2006; 49: 921-9.
34. Xiang Y, Zhou P, Li X, et al. Heterogeneity of altered cytokine levels across the clinical spectrum of diabetes in China. Diabetes Care 2011; 34: 1639-41.
35. Naik RG, Palmer JP. Latent autoimmune diabetes in adults (LADA). Rev Endocr Metab Disord 2003; 4: 233-41.
36. Desai M, Zeggini E, Horton VA, et al. An association analysis of the HLA gene region in latent autoimmune diabetes in adults. Diabetologia 2007; 50: 68-73.
37. Desai M, Zeggini E, Horton VA, et al. The variable number of tandem repeats upstream of the insulin gene is a susceptibility locus for latent autoimmune diabetes in adults. Diabetes. 2006; 55: 1890-4.
38. Cervin C, Lyssenko V, Bakhtadze E, et al. Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes. Diabetes. 2008; 57: 1433-7.
39. Dong F, Yang G, Pan HW, et al. The association of PTPN22 rs2476601 polymorphism and CTLA-4 rs231775 polymorphism with LADA risks: a systematic review and meta-analysis. Acta Diabetol 2014; 51: 691-703.
40. Pettersen E, Skorpen F, Kvaloy K, Midthjell K, Grill V. Genetic heterogeneity in latent autoimmune diabetes is linked to various degrees of autoimmune activity: results from the Nord-Trondelag Health Study. Diabetes 2010; 59: 302-10.
41. Zhang C, Qi L, Hunter DJ, et al. Variant of transcription factor 7-like 2 (TCF7L2) gene and the risk of type 2 diabetes in large cohorts of US women and men. Diabetes 2006; 55: 2645-8.

42. Andersen MK, Sterner M, Forsen T, et al. Type 2 diabetes susceptibility gene variants predispose to adult-onset autoimmune diabetes. Diabetologia 2014; 57: 1859-68.
43. Bakhtadze E, Cervin C, Lindholm E, et al. Common variants in the TCF7L2 gene help to differentiate autoimmune from non-autoimmune diabetes in young (15-34 years) but not in middle-aged (40-59 years) diabetic patients. Diabetologia 2008; 51: 2224-32.
44. Lundgren VM, Andersen MK, Isomaa B, Tuomi T. Family history of type 1 diabetes affects insulin secretion in patients with 'type 2'diabetes. Diabet Med 2013; 30: e163-69.
45. Signore A, Capriotti G, Chianelli M, et al. & Action LADA Group. Detection of Insulitis by Pancreatic Scintigraphy With 99mTc-Labeled IL-2 and MRI in Patients With LADA (Action LADA 10). Diabetes Care 2015; 38: 652-8.
46. Brooks-Worrell BM, Reichow JL, Goel A, Ismail H, Palmer JP. Identification of autoantibody-negative autoimmune type 2 diabetic patients. Diabetes Care 2011; 34: 168-73.
47. Buzzetti R, Di Pietro S, Giaccari A, et al. High titer of autoantibodies to GAD identifies a specific phenotype of adult-onset autoimmune diabetes. Diabetes Care 2007; 30: 932-8.
48. Huang G, Yin M, Xiang Y, et al. Persistence of glutamic acid decarboxylase antibody (GADA) is associated with clinical characteristics of latent autoimmune diabetes in adults: a prospective study with 3-year follow-up. Diabetes Metab Res Rev 2016; 32: 615-22.
49. Solimena M, Dirkx Jr R, Hermel JM, et al. ICA 512, an autoantigen of type I diabetes, is an intrinsic membrane protein of neurosecretory granules. The EMBO J 1996;15: 2102-14.
50. Decochez K, Tits J, Coolens JL, et al. High frequency of persisting or increasing islet-specific autoantibody levels after diagnosis of type 1 diabetes presenting before 40 years of age. The Belgian Diabetes Registry. Diabetes Care 2000; 23: 838-44.
51. Wenzlau JM, Juhl K, Yu L, et al. The cation efflux transporter ZnT8 (Slc30A8) is a major autoantigen in human type 1 diabetes. Proc Natl Acad Sci USA 2007; 104:17040-5.
52. Huang G, Xiang Y, Pan L, Li X, Luo S, Zhou Z. Zinc transporter 8 autoantibody (ZnT8A) could help differentiate latent autoimmune diabetes in adults (LADA) from phenotypic type 2 diabetes mellitus. Diabetes Metab Res Rev 2013; 29: 363-8.
53. Andersen MLM, Vaziri-Sani F, Delli A, et al. Association between autoantibodies to the Arginine variant of the Zinc transporter 8 (ZnT8) and stimulated C-peptide levels in Danish children and adolescents with newly diagnosed type 1 diabetes. Pediatr Diabetes 2012; 13: 454-62.
54. Lampasona V, Petrone A, Tiberti C, et al. Zinc Transporter 8 Antibodies Complement GAD and IA-2 Antibodies in the Identification and Characterization of Adult-Onset Autoimmune Diabetes. Diabetes Care 2010; 33: 104-8.
55. Strom A, Menart B, Simon MC, et al. Cellular interferon-γ and interleukin-13 immune reactivity in type 1, type 2 and latent autoimmune diabetes: action LADA 6. Cytokine 2012; 58: 148-151.
56. Li Y, Zhao M, Hou C, et al. Abnormal DNA methylation in CD4+ T cells from people with latent autoimmune diabetes in adults. Diabetes Res Clin Pract 2011; 94: 242-8.
57. Isomaa B, Almgren P, Henricsson M, et al. Chronic complications in patients with slowly progressing type 1 diabetes (LADA). Diabetes Care 1999; 22: 1347-53.
58. Brophy S, Davies H, Mannan S, Brunt H, Williams R. Interventions for latent autoimmune diabetes (LADA) in adults. Cochrane Database Syst Rev 2011(9): CD006165.
59. Myhill P, Davis WA, Bruce DG, Mackay IR, Zimmet P, Davis TME. Chronic complications and mortality in community-based patients with latent autoimmune diabetes in adults: the Fremantle Diabetes Study. Diabet Med 2008; 25: 1245-50.
60. Lu J, Hou X, Zhang L, et al. Associations between clinical characteristics and chronic complications in latent autoimmune diabetes in adults and type 2 diabetes. Diabetes Metab Res Rev 2015; 31: 411-20.
61. Hawa MI, Buchan AP, Ola T, et al. LADA and CARDS: a prospective study of clinical outcome in established adult-onset autoimmune diabetes. Diabetes Care 2014; 37:1643-9.
62. Hernández M, López C, Real J, et al. Preclinical carotid atherosclerosis in patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes and classical type 1 diabetes. Cardiovasc Diabetol 2017; 16: 94-94.
63. Romkens TE, Kusters GC, Netea MG, Netten PM. Prevalence and clinical characteristics of insulin-treated, anti-GAD-positive, type 2 diabetic subjects in an outpatient clinical department of a Dutch teaching hospital. Neth J Med 2006; 64: 114-8.
64. Schwartz SS, Epstein S, Corkey BE, Grant SF, Gavin JR, Aguilar RB. The time is right for a new classification system for diabetes: rationale and implications of the β-cell–centric classification schema. Diabetes Care 2016; 39: 179-86.
65. Zampetti S, Campagna G, Tiberti C, et al. High GADA titer increases the risk of insulin requirement in LADA patients: a 7-year follow-up (NIRAD study 7). Endocrinology, 2014; 171: 697-704.
66. Davis TME, Wright AD, Mehta ZM, et al. Islet autoantibodies in clinically diagnosed type 2 diabetes: prevalence and relationship with metabolic control (UKPDS 70). Diabetologia 2005; 48: 695-702.
67. Carlsson S, Midthjell K, Tesfamarian MY, Grill V. Age, overweight and physical inactivity increase the risk of latent autoimmune diabetes in adults: results from the Nord-Trøndelag health study. Diabetologia 2007; 50: 55-8.
68. Beales PE, Giorgini A, Annovazzi A, Signore A, Parlapiano C, Pozzilli P. Metformin does not alter diabetes incidence in the NOD mouse. Horm Metab Res 1997; 29: 261-3.
69. Hirata T, Shimada A, Morimoto J, Maruyama T. Slowly progressive type 1 diabetes treated with metformin for five years after onset. Intern Med 2013; 52: 2635-7.
70. Cernea S, Buzzetti R, Pozzilli P. β-cell protection and therapy for latent autoimmune diabetes in adults. Diabetes Care 2009; 32(suppl 2): S246-52.
71. Zhou Z, Li X, Huang G, et al. Rosiglitazone combined with insulin preserves islet β cell function in adult-onset latent autoimmune diabetes (LADA). Diabetes Metab Res Reviews

2005; 21: 203-8.
72. Yang Z, Zhou Z, Li X, Huang G, Lin J. Rosiglitazone preserves islet β-cell function of adult-onset latent autoimmune diabetes in 3 years follow-up study. Diabetes Res Clin Pract 2009; 83: 54-60.
73. Shimada A, Shigihara T, Okubo Y, Katsuki T, Yamada Y, Oikawa Y. Pioglitazone may accelerate disease course of slowly progressive type 1 diabetes. Diabetes Metab Research Reviews 2011; 27, 951-3.
74. Cabrera-Rode E, Perich P, Diaz-Horta O, et al. Slowly progressing type 1 diabetes: persistence of islet cell autoantibodies is related to Glibenclamide treatment. Autoimmunity 2002; 35: 469-74.
75. Kobayashi T, Nakanishi K, Murase T, Kosaka K. Small doses of subcutaneous insulin as a strategy for preventing slowly progressive beta-cell failure in islet cell antibody-positive patients with clinical features of NIDDM. Diabetes 1996; 45: 622-6.
76. Maruyama T, Tanaka S, Shimada A, et al. Insulin intervention in slowly progressive insulin-dependent (type 1) diabetes mellitus. J Clin Endocrinol Metab 2008; 93: 2115-21.
77. Johansen OE, Boehm BO, Grill V, et al. C-peptide levels in latent autoimmune diabetes in adults treated with linagliptin versus glimepiride: exploratory results from a 2-year double-blind, randomized, controlled study. Diabetes Care 2014; 37: e11-2.
78. Duvnjak L, Blaslov K, Lovrenčić MV, Ćuća JK. Persons with latent autoimmune diabetes in adults express higher dipeptidyl peptidase-4 activity compared to persons with type 2 and type 1 diabetes. Diabetes Res Clin Pract 2016; 121: 119-26.
79. Zhao Y, Yang L, Xiang Y, et al. Dipeptidyl peptidase 4 inhibitor sitagliptin maintains β-cell function in patients with recent-onset latent autoimmune diabetes in adults: one year prospective study. J Clin Endocrinol Metab 2014; 99: E876-80.
80. Buzzetti R, Pozzilli P, Frederich R, Iqbal N, Hirshberg B. Saxagliptin improves glycaemic control and C-peptide secretion in latent autoimmune diabetes in adults (LADA). Diabetes Metab Res Rev 2016; 32: 289-96.
81. Awata T, Shimada A, Maruyama T, et al. Possible long-term efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, for slowly progressive type 1 diabetes (SPIDDM) in the stage of non-insulin-dependency: an open-label randomized controlled pilot trial (SPAN-S). Diabetes Ther 2017; 8: 1123-34.
82. Jones AG, McDonald TJ, Shields BM, et al Markers of β-cell failure predict poor glycemic response to GLP-1 receptor agonist therapy in type 2 diabetes. Diabetes Care 2016; 39: 250-7.
83. Pozzilli P, Leslie RD, Peters AL, et al. Dulaglutide treatment results in effective glycaemic control in latent autoimmune diabetes in adults (LADA): A post-hoc analysis of the AWARD-2,-4 and-5 Trials. Diabetes Obes Metab 2018; 20: 1490-8.
84. Brophy S, Davies H, Mannan S, Brunt H, Williams R. Interventions for latent autoimmune diabetes (LADA) in adults. Cochrane Database Syst Rev 2011.
85. Thunander M, Thorgeirsson H, Törn C, Petersson C, Landin-Olsson M. β-Cell function and metabolic control in latent autoimmune diabetes in adults with early insulin versus conventional treatment: a 3-year follow-up. Eur J Endocrinol 2011; 164: 239-45.
86. Halsl I, Grill V, Fiskvik FH, et al. Favorable effects of insulin treatment for latent autoimmune diabetes in adults do not outweigh autoimmunity-induced decline in insulin release during 21 months of intervention.
https://easddistribute.manage.com/from.storage? image=4iBH9mRQm 1kfeEHULC2CxmsX94 Hlv_Ny_e7OEBP-0s4269WM3qcypA9bkz1WS3MPa0 (2018).
87. US National Library of Medicine. ClinicalTrials.govhttps://clinicaltrials.gov/ct2/show/NCT02407899 (2018).
88. Buzzetti R, Cernea S, Petrone A, et al. & DiaPep Trialists Group. C-peptide response and HLA genotypes in subjects with recent-onset type 1 diabetes after immunotherapy with DiaPep277: an exploratory study. Diabetes 2011; 60: 3067-72.
89. Schloot NC, Cohen IR. DiaPep277® and immune intervention for treatment of type 1 diabetes. Clin Immunol 2013; 149, 307-16.
90. Zhang Y, Lu S, Alahdal M, et al. Novel mutant P277 peptide VP to ameliorate atherogenic side-effects and to preserve anti-diabetic effects in NOD mice. Exp Cell Res 2018; 371, 399-408.
91. Agardh CD, Cilio CM, Lethagen Å, et al. Clinical evidence for the safety of GAD65 immunomodulation in adult-onset autoimmune diabetes. J Diabetes Complications 2005; 19: 238-46.

成年隱匿型自體免疫糖尿病：當前的認知與挑戰

曾國賓

義大癌治療醫院 內科部內分泌暨新陳代謝科

摘　要

成年隱匿型自體免疫糖尿病乃是成人發作型自體免疫糖尿病中盛行率最高的一種疾病，並且可能在自體免疫糖尿病中大體上也是盛行率最高的一種型式。它同時擁有第一型和第二型糖尿病在臨床和代謝方面的特徵。成年隱匿型自體免疫糖尿病起初可能會被誤診斷為第二型糖尿病基於患者的年紀之故，特別是當他們有第二型糖尿病的危險因子時，譬如有強烈的糖尿病家族史或體型肥胖。通常成年隱匿型自體免疫糖尿病的診斷是由於高血糖的發現，同時有胰島細胞衰竭而不是胰島素阻抗為主要病因的臨床臆斷；檢測到低量的C-胜肽鍊胰島素(C-peptide)和胰臟蘭氏小島(islets of Langerhans)抗體的產生則有助於該疾病的診斷。高度多面性胰島細胞的破壞、不同程度的胰島素阻抗和異質性力價(heterogeneous titer)以及胰島細胞自體抗體的型式，暗示不同的病生理學路徑並不能夠完全地可以解釋成年隱匿型自體免疫糖尿病的異質性表現型(phenotypes)。胰島細胞衰竭的程度，在成年隱匿型自體免疫糖尿病的進展會比第二型糖尿病較快上許多，推測可能與進行中的自體免疫攻擊有關，因此啟動胰島素治療的時程，在成年隱匿型自體免疫糖尿病的時間會比在第二型糖尿病還要快上許多。由於成年隱匿型自體免疫糖尿病存在的異質性表現型，因此要建立一個事先治療的流程是有困難的，所以對於成年隱匿型自體免疫糖尿病的患者，需要個別化的治療方式以保存殘存的胰島細胞功能以達到良好的血糖控制進而減少長期糖尿病併發症的風險。本文旨在闡述當前我們對於成年遲發型自體免疫糖尿病整體性的認知，並討論當前其在流行病學、臨床和代謝型態、遺傳學、免疫學、併發症及治療方法在知識上的分歧，並概括更新關於最近研究在成年遲發型自體免疫糖尿病治療方面的結果。