

# Slowly Progressive Type 1 Diabetes Mellitus: Current Knowledge And Future Perspectives

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**Abstract:** Slowly progressive type 1 insulin-dependent diabetes mellitus (SPIDDM), sometimes referred to as latent autoimmune diabetes in adults (LADA), is a heterogeneous disease that is often confused with type 1 and type 2 diabetes. As a result, there were few diagnostic criteria for this disorder until 2012, when the Japan Diabetes Society established criteria that could be used in clinical practice. A primary question is whether pathologic markers for type 1 or type 2 diabetes are present in the pancreas of patients with SPIDDM, because the phenotype of SPIDDM is similar to both type 1 and type 2 diabetes. Recent studies clarified pathologic findings in the pancreas of patients with SPIDDM, which included T-cell-mediated insulinitis, a marker of type 1 diabetes; pseudoatrophic islets (islets specifically devoid of beta cells), another hallmark of type 1 diabetes; and a lack of amylin (ie, islet amyloid polypeptide) deposition to the islet cells, a pathologic marker of type 2 diabetes. In terms of preventing the loss of beta-cell function in patients with SPIDDM, several studies have shown that some drugs, including dipeptidyl peptidase-4 inhibitors, are effective. There is an increased need for early diagnosis of SPIDDM to preserve beta-cell function. This review presents updated findings on the pathogenesis and immunologic findings of the affected pancreas, diagnostic markers, risk factors for progression of beta-cell dysfunction, epidemiology, clinical features, diagnostic strategies, prevention strategies, and clinical options for patients with SPIDDM.

**Keywords:** slowly progressive type 1 diabetes mellitus; SPIDDM, latent autoimmune diabetes in adults; LADA, insulinitis, PanIN, GAD antibody

## Introduction

Slowly progressive type 1 insulin-dependent diabetes mellitus (SPIDDM),<sup>1-4</sup> sometimes referred to as latent autoimmune diabetes in adults (LADA),<sup>5,6</sup> is the most prevalent clinical subtype of type 1 diabetes mellitus in Japan.<sup>3</sup> In terms of nomenclature, SPIDDM is not always synonymous with LADA. This is because SPIDDM includes patients with any age of onset of diabetes (AOD), whereas LADA restricts the AOD to adults. Additionally, genetic differences potentially influence the different clinical phenotypes.<sup>7,8</sup> The term SPIDDM is used in this review when the reported cases meet the diagnostic criteria for SPIDDM set by the Japan Diabetes Society<sup>9</sup> and/or when the authors of the manuscripts cited used SPIDDM in their reports.<sup>1-4</sup>

Both SPIDDM and LADA are characterized by late age at onset; progressive beta-cell failure, which is associated with an initial non-insulin-requiring state and an ultimate insulin-dependent state over several years, and persistent islet cell autoantibodies, including glutamic acid decarboxylase autoantibodies (GADAb) and islet cell antibodies (ICAs).<sup>1-4,9,10</sup> SPIDDM and LADA are conceptual phenotypes between

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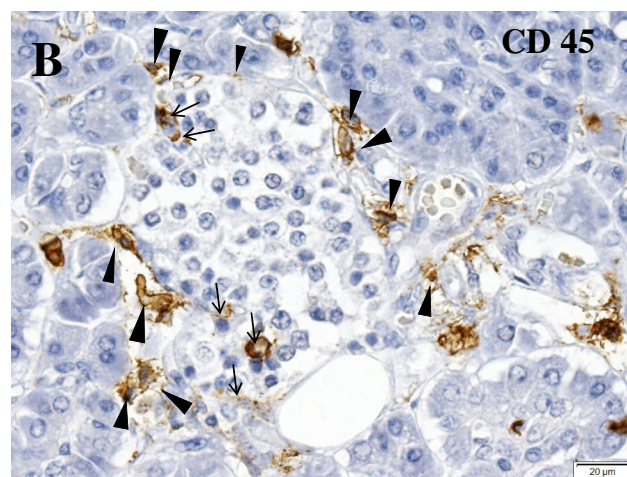
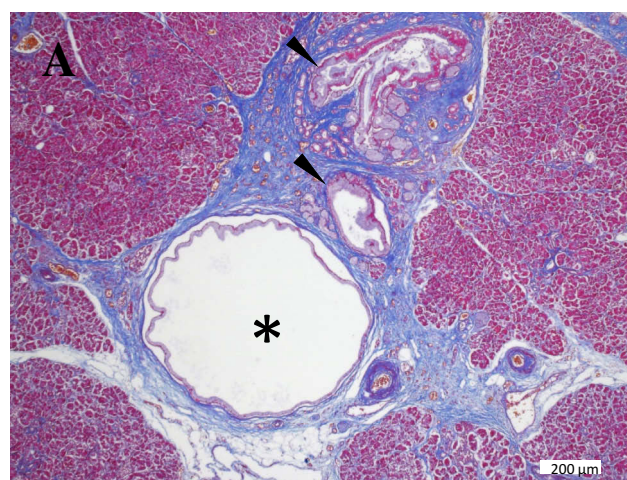
classic acute-onset type 1 diabetes (AT1D) and type 2 diabetes (T2D), and the term “Type 1.5” diabetes was also proposed to describe these disorders.<sup>6</sup> Because of the wide range of clinical phenotypes and the overlap between features of type 1 diabetes (T1D) and T2D, diagnostic criteria that could be used in routine clinical practice were not established until recently. In 2012, the Japan Diabetes Society organized a nationwide Research Committee on Type 1 Diabetes and established diagnostic criteria for SPIDDM.<sup>9</sup> These criteria are helpful in recruiting subjects for intervention trials aimed at preventing progressive beta-cell failure using various pharmacologic options, such as insulin, metformin, dipeptidyl peptidase-4 (DPP4) inhibitors, and/or glucagon-like peptide 1 analogs. The most challenging clinical issue is how to intervene before beta-cell failure in patients with SPIDDM.<sup>11–14</sup>

This review presents updated findings on the pathogenesis and immunologic findings of the affected pancreas, diagnostic markers, risk factors for progression of beta-cell dysfunction, epidemiology, clinical features, diagnostic strategies, prevention strategies, and clinical options for patients with SPIDDM.

## Pathogenesis And Immunologic Findings Of The Pancreas In Patients With SPIDDM

It is unclear whether beta-cell-specific inflammation of islet cells (insulinitis), a pathologic marker of T1D, or amylin (islet amyloid polypeptide [IAPP]) deposition, a specific marker of T2D, are present in the pancreas of patients with SPIDDM. This lack of clarity occurs because the phenotype of SPIDDM is similar in part with both T1D and T2D. Similarly, it is unclear whether pancreatic exocrine inflammation occurs in the pancreas of patients with SPIDDM. Radiologic changes seen on a ductogram of the pancreas showed the presence of chronic pancreatitis-like dilatation, narrowing of pancreatic ducts, and atrophy of exocrine pancreas in patients with SPIDDM.<sup>15,16</sup> Shimada et al<sup>17</sup> reported the presence of CD4<sup>+</sup> T-cell dominant islet inflammation in a patient with GADAb-positive, non-insulin dependent diabetes in the early stage of SPIDDM. In a study using pancreatic scintigraphy with interleukin-2 radiolabeled with <sup>99m</sup>Tc (<sup>99m</sup>Tc-IL-2) and contrast-enhanced magnetic resonance imaging, pancreatic accumulation of <sup>99m</sup>Tc-IL-2 was detected in patients with LADA.<sup>18</sup> Furthermore, <sup>99m</sup>Tc-IL-2 uptake was inversely correlated with duration of disease ( $r = 0.7$ ;  $P = 0.03$ ). Systematic pathologic examination of the pancreas of patients with SPIDDM is warranted to resolve the many questions regarding the role of

pancreatic inflammation and amylin-positive amyloid deposition in this disorder.<sup>4</sup> Between 1982 and 2014, we obtained pancreatic tissue during autopsies of patients with various types of diabetes including SPIDDM, fulminant T1D (FT1D), acute-onset type 1 diabetes (AT1D), autoimmune pancreatitis, and T2D.<sup>15,19</sup> The pancreatic ducts of cases with SPIDDM showed marked pancreatic intraepithelial neoplasia (PanIN lesions) (Figure 1A).<sup>20,21</sup> PanIN lesions are precancerous pancreatic ductal changes with Kras mutations, which are characterized by tall columnar cells and significant mucinous secretions. Secreted mucin-rich content sometimes builds up around pancreatic ducts and blocks the secretion of pancreatic digestive enzymes. As a result, leaked/digestive enzymes



**Figure 1** Characteristic features of the pancreas in patients with SPIDDM. **(A)** Pancreatic intraepithelial papillary neoplasia (PanIN) lesion frequently observed in the patients with SPIDDM. Azan staining. PanIN lesion of pancreatic ducts (arrowheads) is associated with an atrophied, fibrous pancreatic lobe (stained blue), a dilated pancreatic duct (asterisk) and extensive mononuclear cell infiltration. **(B)** Insulinitis in a patient with SPIDDM. CD45 (leukocyte common antigen) + mononuclear cells (MNCs) are infiltrated around (arrowheads) and into the islet cells (arrows). Most of the CD45<sup>+</sup> cells are CD8<sup>+</sup> T cells and CD68<sup>+</sup> macrophages. Aida K, Fukui T, Jimbo E, et al. Distinct inflammatory changes of the pancreas of slowly progressive insulin-dependent (Type 1) Diabetes. *Pancreas*. 2018;47(9):1101–1109.<sup>21</sup>

cause cell necrosis and acute inflammation and ultimately lead to obstructive chronic pancreatitis. Pancreatic ducts that are obstructed by mucous plaque become dilated and cystic.<sup>20,21</sup> Our previous report<sup>16</sup> showed that the dilated and narrowed portions of pancreatic ducts in patients with SPIDDM are linked to three different pathological changes. First, distinct pathologic changes of the pancreas in patients with SPIDDM include persistent insulinitis with preserved beta cells (Figure 1B), major histocompatibility complex (MHC) class I hyper-expression of the islet cells, and exocrine pancreatic inflammation related to PanIN lesions.<sup>20,21</sup> Chronic inflammatory milieu due to obstructive chronic pancreatitis induces the release of self-antigens from islet cells and the exocrine pancreas and enhance MHC class I expression of beta cells. These inflammatory conditions attract autoreactive T cells to islet beta cells with resulting insulinitis, a definitive finding in patients with T1D.<sup>22</sup> Second, the presence of pseudoatrophic islet cells (islet cells devoid of beta cells), another hallmark of T1D,<sup>22</sup> has been noted in all cases of SPIDDM. This pathologic finding indicates that beta cells are specifically destroyed through an immunologic mechanism, despite extensive exocrine pancreatic inflammation. Third, IAPP amyloid deposition to the islet cells, a pathologic marker of T2D,<sup>23</sup> was not observed in the pancreas of patients with SPIDDM, suggesting that the mechanism(s) of beta-cell failure in SPIDDM is/are not the same as in T2D, despite transient clinical phenotypes similar to T2D in patients with SPIDDM. As outlined in Figure 1A, “PanIN lesions are associated with an atrophied, fibrous pancreatic lobe”. Fibrosis in the exocrine pancreas may alternatively be referred to as desmoplastic reaction and it is a result of the activation of the pancreatic stellate cells (PSC) with subsequent extracellular matrix (ECM) production and deposition (Figure 1A). Interestingly it was reported that chronic hyperglycaemia itself may activate PSCs, induce ECM production and therefore may potentially contribute to the development of this pathology.<sup>24</sup> Furthermore, Carstensen et al reported that patients with T1DM are at higher risk for pancreatic cancer development, independently from the exogenous insulin dose applied, which potentially also raises a role for chronic hyperglycaemia in the neoplasia risk development.<sup>25</sup>

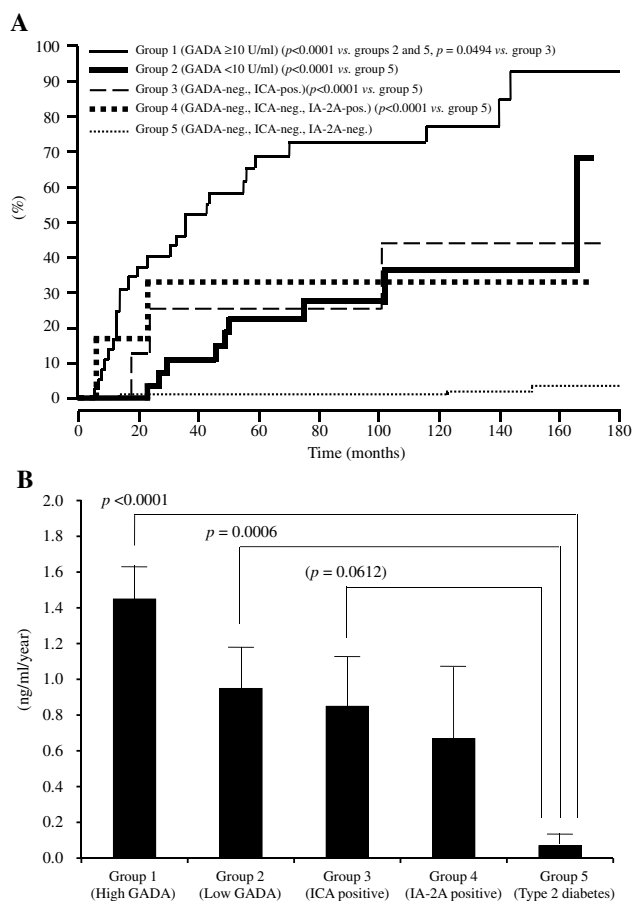
## Diagnostic Markers, Strategies And Criteria Of SPIDDM

### Diagnostic Markers: Islet Cell Autoantibodies

Five islet autoantibodies such as GAD antibody, insulin-associated antigen 2 (IA-2), insulin autoantibodies (IAA),

zinc transporter 8 antibodies (ZnT8) and ICA have been detected in patients with LADA. Among these autoantibodies, GADAb is the most common and sensitive marker in patients with SPIDDM and adult-onset AT1D.<sup>26–30</sup> In addition, GADAb autoantibodies persist for a long time after disease onset and are not influenced by age at onset. In contrast, the four other islet cell autoantibodies are negatively associated with age at onset. In a Japanese nationwide survey conducted between April 2004 and December 2009, the frequency of patients with SPIDDM among patients with T2D was 10%.<sup>31</sup> Patients with SPIDDM showed a significantly higher frequency of GADAb than IA-2Ab or IAA and showed the highest frequency of single positive autoantibodies among GADAb, IA-2Ab, and IAA than patients with AT1D.<sup>31</sup> In the Action LADA 7 study, 598 of 6156 patients (9.8%) had any islet cell autoantibody present, and GAD, IA-2, and ZnT8 autoantibodies were identified in 8.8%, 2.3%, and 1.8%, of patients, respectively.<sup>32</sup> In that study, 144 of 598 (24.8%) patients had two or more islet cell autoantibodies present.

The association between GADAb titers and further progression of beta-cell dysfunction was studied with a large number of patients with diabetes without insulin treatment for up to 15 years (from 1995 to 2005) using a well-standardized GADAb assay from the Diabetes Antibody Standardization Program 2005.<sup>33</sup> Subjects did not require insulin and had a disease duration between 6 months and 5 years. Subjects were divided into those with a high titer of GADAb ( $10 \geq \text{U/mL}$ ), a low titer of GADAb ( $<10 \text{ U/mL}$ ), and GADAb-negative T2D. GADAb-positive subjects progressed to the insulin-dependent stage during the follow-up period (Figure 2A). The progression rate was significantly higher in GADAb-positive groups and IA-2Ab or ICA-positive groups than in those with T2D (Figure 2B). GADAb antibodies were a risk factor for insulin-dependency irrespective of titer (hazard ratio [HR]: 4.69–11.21), age of onset  $<45$  years (HR: 2.18), BMI  $<22 \text{ kg/m}^2$  (HR: 2.40), fasting C-peptide  $<1.0 \text{ ng/mL}$  at entry (HR: 4.61), and independent autoantibodies of ICA and IA-2 from GADAb (HR: 3.05–3.90). In contrast, Murao et al<sup>34</sup> reported that thyroid autoantibodies, including anti-thyroglobulin antibody (TgAb) or anti-thyroid peroxidase antibody (TPOAb), were independent risk factors for beta cell failure. The association between islet cell autoantibodies and the deterioration of beta-cell function is described later.



**Figure 2 (A)** Longitudinal changes of patients who progressed from the non-insulin-requiring stage to an insulin-dependent stage (IDS) in five study groups. IDS is defined as the state when integrated values of serum C-peptide levels at 0, 30, 60, 90, and 120 min during a 100-g oral glucose tolerance test (sigma C-peptide) reach <5 ng/mL. **(B)** Reduction rate of sigma C-peptide in group 1 (patients with GADAb titer  $\geq 10$  AU/mL [ $\geq 180$  WHO U/mL]), group 2 (patients with GADAb titer <10 AU/mL [ $< 180$  WHO U/mL]), group 3 (patients without GADAb and with islet cell antibodies [ICA]), group 4 (patients without GADAb or ICA antibodies and with insulin-associated antigen 2 antibodies [IA-2A]), and group 5 (patients with T2D without GADAb, ICA, or IA-2A antibodies).

**Note:** Copyright © 2015. Japan Diabetes Society. Reproduced from Tanaka S, Okubo M, Nagasawa K, et al. Predictive value of titer of GAD antibodies for further progression of beta cell dysfunction in slowly progressive insulin-dependent (type 1) diabetes (SPIDDM). *Diabetol Int.* 2016;7(1):42–52.<sup>33</sup>

Patients with LADA, especially with high GADAb titers, have been shown to have other organ-specific autoantibodies such as thyroid peroxidase (TPO), antiparietal cells, or tissue transglutaminase antibodies.<sup>35,36</sup> In particular, more than 20% of the patients with LADA had positive TPO antibodies<sup>35,36</sup> suggesting the need for general screening for TPO antibodies in all patients with LADA.

Several, but not all, studies showed bimodal distribution of GADAb in patients with SPIDDM or LADA, suggesting the presence of two distinct forms of the disease in the ~1/10th of patients who are antibody positive at all.<sup>32,35,37–39</sup> Compared with the low GADAb titer group, the high GADAb titer group

was younger, had a higher HbA1c level, lower BMI, lower prevalence of metabolic syndrome and its components, higher prevalence of other autoantibodies including IA-2 and TPO antibodies, and higher prevalence of high/moderate human leukocyte antigen (HLA) risk genotypes; these findings suggest a greater similarity to AT1D.<sup>35,36,38,39</sup> However, these findings cannot rule out the possibility that patients with early-phase AT1D were erroneously included in the study population.<sup>35,36,38,39</sup>

In addition to the GADAb titer, antibody-binding epitopes of GADAb are associated with the clinical phenotype of diabetes.<sup>40–43</sup> For example, the binding of GAD65Ab with N-terminal 83 residues was shown to be inversely correlated with the period in which insulin was not required.<sup>42</sup> The associations between GADAb titer or antibody-binding epitopes and beta-cell function are described later.

Positive findings for IA-2 antibodies have different clinical meanings in patients with LADA. Patients with positive findings for IA-2 alone have a clinical phenotype more similar to T2D, whereas patients with positive findings for both IA-2 and GADAb have a clinical phenotype more similar to AT1D.<sup>44</sup> The NIRAD study analyzed IA-2 epitope immunoreactivity and showed that the IA-2<sub>(256–760)</sub> antibodies represent a new sensitive marker for the study of the humoral IA-2 immunoreactivity in patients with LADA.<sup>45</sup> In addition, the frequency of IA-2<sub>(256–760)</sub> antibodies increased with increasing BMI, whereas the frequency of GAD and intracytoplasmic (IC) IA-2<sub>IC(605–979)</sub> antibodies decreased with increasing BMI.<sup>46</sup> However, the clinical utility of IA-2 antibodies is questionable because the prevalence of these antibodies differs by country.<sup>47,48</sup>

## Diagnostic Strategies

Theoretically, all patients with newly diagnosed diabetes, and in particular T1D, should be tested for GADAb autoantibodies because: 1) epidemiologic studies indicate that 2% to 10% of patients with newly diagnosed diabetes show positive findings, which may indicate the presence of SPIDDM, 2) the prevalence of SPIDDM is increasing, and 3) some intervention strategies to slow or stop the decline in beta-cell function that occurs with SPIDDM are available (described below). There is, however, no recommendation to test islet cell autoantibodies, including GADAb, in all patients with newly diagnosed diabetes; this lack of recommendation is likely due to the high costs of testing. The American Diabetes Association's "Standards of Medical Care in Diabetes 2019" recommends screening for a panel of autoantibodies only in children and adolescents with overweight/obesity in

whom the diagnosis of T2D is being considered, in the setting of a research trial, and in first-degree family members of a proband with T1D.<sup>49,50</sup>

In most clinical settings, islet cell autoantibodies are generally tested only when SPIDDM is suspected. In Japan, the costs for measuring GADAb, IA2Ab, and ICA autoantibodies are covered by the life insurance system.

In addition to patients with newly diagnosed diabetes, there may be a need to test for islet cell autoantibodies in patients diagnosed with T2D who have poor glycemic control. This is because some case reports showed that islet cell autoantibodies became positive in patients with T2D in whom findings were previously negative.<sup>51</sup>

## Diagnostic Criteria Of SPIDDM

Due to the great heterogeneity of SPIDDM or LADA among different ethnic groups and geographic areas, common diagnostic criteria are not specific and may lead to false-positive findings. Recently, the Japan Diabetes Society established diagnostic criteria for SPIDDM<sup>9</sup> (Table 4). On the other hand, the Immunology of Diabetes Society (IDS) established diagnostic criteria for LADA in 2005.<sup>52</sup> The IDS criteria require; 1) Adult age at onset of diabetes, 2) the presence of circulating islet autoantibodies and 3) lack of a requirement for insulin for at least 6 months after diagnosis. These two criteria are similar in the requirements for positive islet autoantibodies and insulin independency at onset. However, there are at least three differences between these criteria. First, unlike LADA criteria, age of onset of SPIDDM is not restricted to populations older than 35 years.<sup>4,6</sup> Second, the Japan Diabetes Society cutoff criteria for duration from the onset of diabetes to insulin-dependency was established based on comparisons with patients with AT1D:<sup>53</sup> For patients with AT1D, the duration from onset of diabetes to the insulin-requiring state was <3 months. A diagnosis of SPIDDM can only be made after a 3-month period in which no insulin is required. Third, only GADAb and/or ICA are applied for islet autoantibodies in the Japan Diabetes Society criteria whereas all kinds of islet cell autoantibodies are applied in the Immunology of Diabetes Society criteria.

## Genetics

LADA is reported to share genetic features with both AT1D and T2D, although it is more similar to AT1D<sup>54–58</sup> (Table 1). In a population-based study assessing the association between family history of T1D or T2D and LADA, both family history of T1D and T2D were associated with

an increased risk for LADA. However, compared with a family history of T2D, a family history of T1D was more strongly associated with higher GADAb antibody levels, lower C-peptide levels, and a lower prevalence of low-risk HLA genotypes.<sup>54</sup> In another study that compared the frequencies of several genes associated with AT1D or T2D among patients with LADA, AT1D, T2D, and healthy controls, the frequencies of AT1D-associated genes were higher in patients with LADA compared with patients with T2D or controls, and the frequencies of T2D-associated genes increased to the same extent in patients with LADA or T2D compared with controls.<sup>55</sup>

## Human Leukocyte Antigen (HLA)

In a Japanese population, HLA-DQ haplotypes were examined in patients with AT1D and SPIDDM.<sup>3</sup> In patients with AT1D, three haplotypes, DQA1\*03:01-DQB1\*04:01-DRB1\*04:05 (DR4), DQA1\*03:01-DQB1\*03:02-DRB1\*08:02: (DR8), and DQA1\*03:01-DQB1\*03:03-DRB1\*09:01 (DR9) showed an increased prevalence, whereas only DQA1\*03:01-DQB1\*04:01-DRB1\*04:05 (DR4) was significantly increased in patients with SPIDDM. Additionally, DQA1\*01:03-DQB1\*06:01-DRB1\*15:02 (DR2) was decreased in both AT1D and SPIDDM. These results indicate that SPIDDM is related to specific susceptible and protective HLA genotypes, but fewer susceptible HLA genotypes, including increased HLA-DR4 and decreased DR2, are associated with SPIDDM compared with AT1D. We also studied nationwide data from the Japan Diabetes Society involving the increased number of subjects with SPIDDM, AT1D, and FT1D and confirmed previous results.<sup>59</sup> That is, a high proportion of patients with AT1D had four types of susceptible haplotype combinations, HLA-DR4/4, -DR9/9, -DR4/9, and -DR4/8, whereas patients with SPIDDM had only two susceptible haplotype combinations, HLA-DR4/4 and DR4/8. These results suggest that the differences in number of susceptible genes influence DR-beta, DQ-alpha, and DQ-beta heterodimer expression encoded by DRB1, DQA1, and DQB1 genes and determine the rate of beta-cell damage in patients with AT1D and SPIDDM. In other words, the number of T1D-related HLA haplotypes determines the clinical subtype of T1D (AT1D or SPIDDM). Another characteristic feature of SPIDDM is a lack of association with class I HLA: HLA-A24.<sup>3</sup> HLA-A24 is associated with complete destruction of beta-cell function in patients with AT1D.<sup>15</sup> The lack of association of HLA-A24 with complete destruction of beta cells in patients with SPIDDM may be related to a gradually progressive clinical course and preserved beta-cell function in this disorder.

**Table 1** Genes Associated Or Not Associated With SPIDDM Or LADA

	Gene	dbSNP ID (Rs Number)	Association	Odds Ratio (95% CI)	Comparator	Reference
<b>HLA</b>	DR3	2187668	Positive	3.37 (2.92–3.90)	Healthy subjects	57
	DR4	660,895	Positive	3.34 (2.94–3.81)	Healthy subjects	57
	DQA1*0301-DQB1*0401-DRB1*0405 (DR4)	N/A	Positive	2.9 (N/A)	Healthy subjects	3
	DQA1*0103-DQB1*0601-DRB1*1502 (DR2)	N/A	Protective	0.08 (N/A)	Healthy subjects	3
	DQA1*0301-DQB1*0302-DRB1*0802 (DR8)	N/A	No association	N/A	Healthy subjects	3
	DQA1*0301-DQB1*0303-DRB1*0901 (DR9)	N/A	No association	N/A	Healthy subjects	3
	DQA1*05_DQB1*0201_DRB1*0301	N/A	Positive	2.65 (1.93–3.65)	Healthy subjects	61
	DQA1*03_DQB1*0401_DRB1*0405	N/A	Positive	2.02 (1.48–2.76)	Healthy subjects	61
	DQA1*03_DQB1*0303_DRB1*0901	N/A	Positive	1.61 (1.34–1.93)	Healthy subjects	61
	DQA1*03_DQB1*0303_DRB1*0803	N/A	Protective	1.61 (1.34–1.93)	Healthy subjects	61
	DQA1*0601g_DQB1*0301_DRB1*1202	N/A	No association	N/A	Healthy subjects	61
	DQA1*0101g_DQB1*0502_DRB1*1401	N/A	No association	N/A	Healthy subjects	61
	DQA1*03_DQB1*0303	N/A	Positive	N/A	Healthy subjects	39
	DQA1*03_DQB1*0401	N/A	Positive	N/A	Healthy subjects	39
	DQA1*05_DQB1*0201	N/A	Positive	N/A	Healthy subjects	39
	DQA1*05_DQB1*0201	N/A	Positive	N/A	T2D subjects	39
	DQA1*0102_DQB1*0602	N/A	Protective	N/A	T2D subjects	39
	DQA1*05_DQB1*0201_DRB1*0301	N/A	Protective	0.55 (0.42–0.72)	AT1D subjects	61
	DQA1*03_DQB1*0401_DRB1*0405	N/A	No association	N/A	AT1D subjects	61
	DQA1*03_DQB1*0303_DRB1*0901	N/A	No association	N/A	AT1D subjects	61
	DQA1*0601g_DQB1*0301_DRB1*1202	N/A	Positive	2.79 (1.71–4.57)	AT1D subjects	61
	DQA1*0101g_DQB1*0502_DRB1*1401	N/A	Positive	8.19 (2.47–27.12)	AT1D subjects	61
	DQB1*0401-DRB1*0405 (DR4)	N/A	Positive	2.5 (N/A)	Healthy subjects	59
	DQB1*0303-DRB1*0901 (DR9)	N/A	Positive	1.9 (N/A)	Healthy subjects	59
	DQB1*0601-DRB1*1502 (DR2)	N/A	Protective	0.14 (N/A)	Healthy subjects	59
	DQB1*0302-DRB1*0802	N/A	No association	N/A	Healthy subjects	59
	DQB1*0602-DRB1*1501	N/A	No association	N/A	Healthy subjects	59
	DQB1 *0201_DRB1 *0301	N/A	Positive	3.08 (2.32–4.12)	Healthy subjects	60
	DQB1 *0302_DRB1 *0401	N/A	Positive	2.57 (1.80–3.73)	Healthy subjects	60
	DQB1 *0602_DRB1 *1501	N/A	Protective	0.21 (0.13–0.34)	Healthy subjects	60
	DQB1 *0602_DRB1 *1501	N/A	Protective	N/A	Healthy subjects	64
	DQB1 *0301_DRB1 *1101(04)	N/A	Protective	0.25 (0.12–0.48)	Healthy subjects	60
	DQB1	9273368-A	Positive	3.115 (2.855–3.398)	Healthy subjects	63
	DQB1	1049107	Protective	0.27 (0.13–0.56)	Healthy subjects	59
	DQB1*0401_DRB1*0405	N/A	Positive	N/A	Healthy subjects	64
	DQB1 low risk	N/A	Positive	2.26 (1.17–4.36)	Healthy subjects	65
	DQB1 moderate risk	N/A	Positive	3.49 (1.15–10.61)	Healthy subjects	65
	DQB1 high risk	N/A	Positive	3.92 (1.12–13.79)	Healthy subjects	65
	DQB1	9273368-A	Positive	2.439 (2.222–2.676)	T2D subjects	63
	DQB1 *0302/*02, 0302/X	N/A	Positive	N/A	T2D subjects	62
DQB1	9273368-A	Protective	0.335 (0.256–0.385)	AT1D subjects	63	
DOB	2071554	Protective	0.28 (0.15–0.54)	Healthy subjects	59	
A24	N/A	No association	N/A	Healthy subjects	3	
<b>CTLA4</b>	49 GG	N/A	Positive	5.93 (2.21–15.86)	Healthy subjects	65
	49 AG	N/A	Positive	2.74 (1.12–6.69)	Healthy subjects	65
	AG	N/A	Positive	2.47 (1.27–4.81)	Healthy subjects	66
	AA	N/A	Protective	0.40 (0.20–0.80)	Healthy subjects	66

(Continued)

Table 1 (Continued).

	Gene	dbSNP ID (Rs Number)	Association	Odds Ratio (95% CI)	Comparator	Reference
	G>A	3087243	Protective	0.75 (0.68–0.83)	Healthy subjects	57
	N/A	N/A	No association	N/A	Healthy subjects	58
	CT60	3087243	No association	N/A	T2D subjects	62
<b>PTPN22</b>	1858 C>T	2476601	Positive	1.7 (1.1–2.7)	Healthy subjects	55
	1858 C>T	2476601	Positive	1.717 (1.539–1.915)	Healthy subjects	63
	1858 C>T	2476601	Positive	1.77 (1.53–2.06)	Healthy subjects	57
	1858 C>T	2476601	Positive	N/A	Healthy subjects	55
	1858 C>T	2476601	No association	N/A	Healthy subjects	69
	1858 C>T	2476601	Positive	N/A	T2D subjects	62
	1858 C>T	2476601	Positive	1.529 (1.380–1.693)	T2D subjects	63
	A>C	6679677	Positive	1.469 (1.427–1.510)	Healthy subjects	58
	1123 G>C	2488457	No association	N/A	Healthy subjects	69
	2740 C>T	1217412	No association	N/A	Healthy subjects	69
	T>C	478582	No association	N/A	Healthy subjects	57
	G>C	45450798	No association	N/A	Healthy subjects	57
<b>INS</b>	VNTR T>A	689	Positive	1.265 (1.234–1.296)	Healthy subjects	58
	VNTR AA	689	Positive	1.7 (1.2–2.6)	Healthy subjects	55
	VNTR T>A	689	Positive	1.483 (1.363–1.613)	Healthy subjects	63
	VNTR A>T	689	Protective	0.47 (0.42–0.54)	Healthy subjects	57
	VNTR T>A	689	positive	1.473 (1.352–1.605)	T2D subjects	63
	VNTR A/T	689	No association	N/A	T2D subjects	62
	VNTR	3842755	Positive	1.6 (1.1–2.5)	Healthy subjects	55
	VNTR	N/A	Positive	2.34 (1.25–4.38)	Healthy subjects	65
<b>Vitamin D receptor Interleukin 2 receptor</b>	BB genotype	N/A	Positive	N/A	Healthy subjects	71
	A>G	12722495	Protective	0.70 (0.58–0.83)	Healthy subjects	57
	IL-2 receptor-alpha (IL2RA)(CD25)	706778	No association	N/A	Healthy subjects	72
	IL-2 receptor-alpha (IL2RA)(CD25) IL2RA	3118470 N/A	No association No association	N/A N/A	Healthy subjects Healthy subjects	72 58
<b>TCF7L2</b>	CT/TT	7903146	Positive	1.5 (1.2–1.9)	Healthy subjects	55
	T	7903146	Positive	1.44 (1.18–1.77)	Healthy subjects	73
	T/C	7903146	No association	N/A	Healthy subjects	58
	T/C	7903146	Protective	N/A	T2D subjects	58
	GT/TT	12,255372	Positive	1.5 (1.1–1.9)	Healthy subjects	55
	G>T	12,255372	No association	N/A	Healthy subjects	57
<b>ZMIZ1 SH2B3</b>	A	12571751	Positive	1.35 (1.15–1.60)	Healthy subjects	73
	C/G	7310615	Positive	1.284 (1.193–1.383)	Healthy subjects	63
	C/G	7310615	Positive	1.240 (1.151–1.336)	T2D subjects	63
	A>G	3184504	Positive	1.35 (1.22–1.50)	Healthy subjects	57
	C/T	3184504	Positive	1.24 (1.151–1.336)	T2D subjects	63
	G/A	17696736	Positive	1.277 (1.250–1.304)	Healthy subjects	58
<b>PFKFB3</b>	C/T	1983890	Positive	1.16 (1.14–1.32)	Healthy subjects	63
<b>TNF</b>	N/A	1800610	Positive	2.17 (1.51–3.11)	Healthy subjects	59
<b>MHC</b>	A/G	9272,346	Positive	1.455 (1.427–1.483)	Healthy subjects	58
<b>HNFA</b>	G/C	12427353	Positive	1.291 (1.256–1.326)	Healthy subjects	58

(Continued)

Table 1 (Continued).

	Gene	dbSNP ID (Rs Number)	Association	Odds Ratio (95% CI)	Comparator	Reference
<b>STAT4</b>	G>T	7574865	Positive	1.23 (1.09–1.39)	Healthy subjects	57
<b>STAT</b>	N/A	N/A	No association	N/A	Healthy subjects	58
<b>ERBB3</b>	C>A	2292239	Positive	1.20 (1.08–1.33)	Healthy subjects	57
<b>CLEC16A</b>	A>G	12708716	Protective	0.83 (0.75–0.93)	Healthy subjects	57
	N/A	N/A	No association	N/A	Healthy subjects	58
<b>SMARCE1</b>	N/A	7221109	Protective	N/A	AT1D subjects	58

**Abbreviations:** dbSNP ID, The Single Nucleotide Polymorphism Database; CI, confidence interval; HLA, human leukocyte antigen; CTLA4, cytotoxic T lymphocyte-associated antigen 4; PTPN22, protein tyrosine phosphatase, non-receptor 22 gene; INS, insulin gene; VNTR, variable number of tandem repeats; TCF7L2, transcription factor 7 like 2; ZMIZ1, zinc finger MIZ-type containing 1, SH2B3, SH2B adaptor protein 3; PFKFB3, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase; TNF, tumor necrosis factor; MHC, major histocompatibility complex; HNF1A, HNF1 homeobox A; STAT4 signal transducer and activator of transcription 4; ERBB3, erb-b2 receptor tyrosine kinase 3; CLEC16A, C-type lectin domain containing 16A; SMARCE1, SWI/SNF related, matrix associated, actin-dependent regulator of chromatin, subfamily e, member 1; T2D, type 2 diabetes; AT1D, acute type 1 diabetes.

There is an independent and racial association between LADA and HLA haplotypes and susceptible genes associated with AT1D in the Caucasian population. The primary susceptible haplotypes in Caucasian patients with LADA were DRB1 0301\_DQB1 0201, and DRB1 0401\_DQB1 0302, whereas DRB1 1501\_DQB1 0602 had a protective effect.<sup>60</sup> The frequencies of these HLA haplotypes, however, were lower than those seen in patients with AT1D<sup>37,61</sup> and the frequency of HLA-DQB1 risk genotypes and alleles was significantly lower compared with patients with AT1D diagnosed after the age of 35.<sup>62</sup> In the genome-wide association study (GWAS) of LADA, the authors reported the attenuation of the key type 1-associated HLA haplotype (HLA-DQB1, rs9273368-A) frequencies in LADA.<sup>63</sup> In addition, the frequency for AT1D protective haplotypes was significantly higher in Caucasian patients with LADA compared with patients with AT1D.<sup>61</sup>

The association between HLA haplotype and SPIDDM or LADA is also seen in Asian patients. In a study of LADA in a Chinese population, HLA diabetes-susceptible haplotypes were more frequent in patients with LADA (63.9%) compared to patients with T2D (47.1%) and controls (43.2%), whereas HLA diabetes-protective haplotypes was less frequent in patients with LADA (22.8%) compared to patients with T2D (33.3%) and controls (32.7%).<sup>39</sup> The contribution of HLA-DRB1-DQA1-DQB1 loci to LADA susceptibility, however, differs from that in Caucasian patients with LADA.<sup>61</sup>

The presence of AT1D susceptibility or protective HLA haplotypes is associated with clinical characteristics

in patients with LADA.<sup>35,37,64</sup> The prevalence of high or moderate HLA-risk genotypes was associated with high GADAb titers<sup>35,39</sup> and younger age at disease onset,<sup>64</sup> whereas protective HLA haplotypes are associated with older age at onset of diabetes, high BMI, resistance to insulin-deficient state, low titer of GADAb, and low frequency of other organ-specific autoantibodies.<sup>64</sup> In another study, DR3 was associated with positive findings for GADAb, but absence of IA-2A, and DR4 was associated with positive findings for IA-2A.<sup>57</sup>

### Cytotoxic T Lymphocyte-Associated Antigen 4 (CTLA4)

Several studies showed an association between CTLA4 and LADA,<sup>57,65,66</sup> whereas Andersen et al showed that CTLA4 was associated only with AT1D.<sup>62</sup> In the 1990s, Van der Auwera et al showed that the presence of a G-containing CTLA4 genotype confers a moderate but significant increased relative risk for insulin-dependent diabetes mellitus that is independent of age.<sup>67</sup> That study suggested a weak association between CTLA4 and LADA. In a Japanese population with SPIDDM and other subtypes of T1D, a G-containing genotype was poorly associated with T1D but was associated with autoimmune thyroid disease complicated with T1D.<sup>68</sup> In a study of a Caucasian population, Cosentino et al showed that the heterozygous A/G genotype was significantly more frequent among 80 patients with LADA (69%) than among 85 healthy subjects of similar age and geographic location (47%).<sup>66</sup>



## Protein Tyrosine Phosphatase, Non-Receptor 22 Gene (PTPN22)

A systematic and trans-rational association and linkage study including 1690 Japanese samples, 180 Korean samples, and 472 Caucasian samples demonstrated that the minor allele of a single-nucleotide polymorphism (SNP) at nucleotide position 1858 (rs2476601, +1858C>T) was associated with AT1D in Japanese and Caucasian populations.<sup>69</sup> In the Japanese population, we can identify five novel SNPs, but not the +1858C>T SNP. Of these two frequent SNPs, -1123G>C, and +2740C>T were in strong linkage disequilibrium (LD) with a combined group consisting of subjects with AT1D and SPIDDM. The -1123G>C promoter SNP was associated with AT1D but not SPIDDM in the Japanese population (odds ratio [OR] = 1.42, 95% confidence interval [CI] = 1.07–1.89,  $P=0.015$ ). This association was also observed in Korean patients with T1D (Mantel–Haenszel  $\chi^2 = 6.543$ ,  $P = 0.0105$ , combined OR = 1.41, 95% CI = 1.09–1.82). Furthermore, the affected family-based control (AFBAC) association test and the transmission disequilibrium analysis of multiplex families of European descent from the British Diabetes Association (BDA) Warren Repository indicated that the association was stronger for -1123G>C compared to +1858C>T,<sup>69</sup> suggesting a weak predisposition for SPIDDM associated with the PTPN22 polymorphism.

In contrast, a Caucasian population of patients with LADA showed an increased frequency of PTPN22 risk genotypes and alleles compared with patients with T2D, whereas the frequency was significantly lower compared with patients with AT1D diagnosed after age 35.<sup>62</sup>

## Insulin Gene (INS)

In a Caucasian population, LADA was independently associated with a variable number of tandem repeats in the insulin gene (INS VNTR).<sup>55,57,65</sup> The AA genotype of rs689, referring to the class I allele in INS VNTR, was increased in both patients with classic AT1D and patients with LADA compared with control subjects<sup>55</sup> and in Japanese patients with T1D including SPIDDM.<sup>70</sup> Similar association with INS rs689 and LADA in case subjects of European ancestry versus population control subjects was found in GWAS.<sup>63</sup>

## Vitamin D Receptor

Vitamin D receptors are expressed on T cells and affect cytokine responses. The BB genotype was higher in patients with SPIDDM and AT1D than in controls.<sup>71</sup>

## Interleukin-2 Receptor-Alpha (IL-2R alpha) Gene

IL-2R alpha genes are expressed on regulatory T cells. We found a strong association with IL-2R alpha genes in patients with AT1D, but not in those with SPIDDM or FT1D.<sup>72</sup>

## Transcription Factor 7 Like 2 (TCF7L2)

An association between LADA and *TCF7L2*, a known risk allele for T2D, has been reported,<sup>55,57,73,74</sup> but findings remain inconclusive.<sup>57</sup>

## Zinc Finger MIZ-Type Containing 1 (ZMIZ1)

One previous report showed that variants in the *ZMIZ1* (rs12571751,  $p = 4.1 \times 10^{-5}$ ) loci was strongly associated with LADA.<sup>73</sup>

## SH2B Adaptor Protein 3 (SH2B3)

Two GWAS results showed independent association between *SH2B3* rs7310615 and LADA.<sup>58,63</sup> In addition, Mishra et al showed that *SH2B3* signal remained strongly associated and had stronger OR in the restricted subset of GADA+ IA2A+ LADA cases (OR = 1.48;  $P = 5.93 \times 10^{-6}$ ) compared with whole LADA cases (OR = 1.277;  $P = 1.10 \times 10^{-5}$ ).<sup>58</sup>

## 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3 (PFKFB3)

In the recently published GWAS of LADA, the authors reported a novel signal at the known type 1 diabetes locus harboring *PFKFB3*, encoding a regulator of glycolysis and insulin signaling in T2D and inflammation and autophagy in autoimmune disease.<sup>63</sup>

## Risk Factors For Progression Of Beta-Cell Dysfunction In SPIDDM

There are five risk factors for loss of beta-cell function in patients with SPIDDM or LADA: 1) numbers of autoantibody for pancreatic beta-cell (multiple antibodies), 2) high GADAb titer, 3) lower BMI, 4) HLA and 5) sulfonylurea treatment after diagnosis.

## Number Of Autoantibodies

Several longitudinal studies have shown that patients with SPIDDM or LADA with multiple islet autoantibodies are likely to show a more rapid progression to insulin-dependency, suggesting that the number of positive islet cell

autoantibodies reflects the intensity of the autoimmune response to islet cell damage.<sup>26,28,75–77</sup> In Japanese patients with SPIDDM, GADAb-positive and ICA-positive findings lead to insulin-dependency in 100% of patients during 5 years, whereas only 47% of the population with GADAb-positive findings alone progressed to insulin-dependency 5 years after diagnosis.<sup>10</sup>

In the UKPDS 25, GADAb-positive findings alone or both GADAb- and ICA-positive findings lead to the need for insulin therapy for 52% and 68% of patients older than 45, respectively.<sup>26</sup>

## High GADAb Titer

Patients with SPIDDM or LADA with a high GADAb titer have an increased risk for insulin dependency compared with patients with a low GADAb titer (<10 AU/mL: <180 U/mL according to the World Health Organization [WHO] standard samples).<sup>26,35,78</sup> In our long-term, follow-up Japanese study (mean follow up, 107 months), 65% of patients with a high GADAb titer ( $\geq 10$  AU/mL:  $\geq 180$  WHO U/mL according to WHO standard samples) progressed to insulin dependency, whereas 24% of patients with a low GADAb titer (<180 WHO U/mL) patients progressed to insulin dependency (Figure 2A).<sup>33</sup> Notably, the reduction rate of serum C-peptide response to oral glucose was significantly faster in the high and low GADAb titer groups than in patients with T2D (Figure 2B). In the NIRAD 7 study, 71.1% of patients with a high GADAb titer progressed to insulin dependency, compared with 41.6% of patients with a low GADAb titer and 20.9% of patients with T2D ( $P < 0.0001$  for both).<sup>76</sup> However, these studies used different GADAb cut-off values. The use of a standardized GADAb titer cut-off value is needed to determine the accuracy of GADAb titers for predicting the progression to beta-cell dysfunction.<sup>79</sup>

## Lower BMI

Lower BMI (<22 kg/m<sup>2</sup>) is an independent risk factor for progression to insulin-dependency in patients with SPIDDM who do not require insulin.<sup>33</sup> The NIRAD study showed that a BMI <25 kg/m<sup>2</sup> can identify patients with LADA who will require insulin therapy within 4 years of diagnosis.<sup>38</sup> A low BMI is related to decreased pancreatic digestive function, as evidenced by a small atrophic exocrine pancreas<sup>80</sup> and low serum levels of pancreatic enzymes in patients with SPIDDM.<sup>81</sup> In addition, Japanese individuals with SPIDDM and the T1D-risk HLA (DRB1\*04:05-DQB1\*04:01) haplotype had a lower BMI.<sup>82</sup> Caucasian patients with LADA with a T1D-risk HLA (HLA DR3/4) had a lower BMI than those

without the risk HLA phenotype.<sup>83</sup> Taken together, the findings of exocrine pancreatic failure in patients with SPIDDM and HLA genes associated with SPIDDM may indicate that HLA genes are related to extensive exocrine advanced pancreatic failure in patients with reduced BMI and SPIDDM.

## HLA

In a multivariate analysis, Maioli et al showed that HLA DRB1-DQB1 genotypes in patients at high risk for AT1D had a significant effect on disease progression within 4 years of diagnosis.<sup>38</sup>

## Sulfonylurea Treatment After Diagnosis

In the NIRAD study, treatment with a sulfonylurea in the first year after diagnosis of diabetes was associated with faster progression to insulin dependency.<sup>76</sup> In a Tokyo study, patients randomly assigned to a sulfonylurea treatment group had a faster progression to insulin dependency compared with patients treated with insulin.<sup>11</sup>

## Epidemiology

AT1D is the most common type of diabetes in children and adolescents. However, LADA is more common than AT1D in patients older than 30 years who develop diabetes.<sup>32,44</sup> A large body of evidence shows that the prevalence of SPIDDM or LADA varies from 2% to 10% (Table 2).<sup>26,32,35,37–39,44,64,84–88</sup> This variation is due to several factors such as ethnicity, country, types of autoantibodies assessed, assay methods, sample age, or study type (clinical, registry, or population based). In Japan, the prevalence of SPIDDM ranges from 4% to 10% among patients tentatively diagnosed with non-insulin requiring diabetes in a referral hospital-based study (Table 2).<sup>31</sup> In general, the prevalence of SPIDDM or LADA is similar in Europe, northern America, and Asia. It is noteworthy that the incidence of SPIDDM or LADA in Asian countries, including Japan, is similar to that in northern Europe. In contrast, the annual incidence of AT1D in Japan is extremely low (2/10<sup>4</sup>). The comparable incidence of LADA with a Caucasian population may suggest that environmental factors rather than a genetic predisposition have a larger influence on the occurrence of SPIDDM or LADA.

## Clinical Features Of SPIDDM Or LADA Compared With AT1D And T2D

Table 3 shows clinical characteristics of SPIDDM or LADA compared with AT1D and T2D. These three

Table 2 Prevalence Of Islet Cell Autoantibody Positivity Among Patients With Diabetes

Author (Study), Year	Region	Location	AA Positivity (%)	Sample Size (n)	Type Of Study	Measured AA	Refs
Takeda et al (Ehime study), 2002	Asia	Japan	3.8	4980	Clinical-based study	GAD	64
Lee et al, 2009		Korea	5.1	1370	Clinical-based study	GAD, IA-2	84
Qi et al, 2011		China	9.2	8109	Population-based study	GAD	85
Zhou et al (LADA China study), 2013		China	5.9	4880	Clinical-based study	GAD	39
Turner et al (UKPDS 25), 1997	Europe	U.K.	12	3672	Clinical-based study	GAD, ICA	26
Tuomi et al (Botnia study), 1999		Finland	9.3	1122	Population-based study	GAD, IA-2, ICA	37
Bosi et al (Cremona study), 1999		Italy	2.8	2076	Population-based study	GAD, IA-2	86
Zinman et al (ADOPT), 2004		Europe, US, Canada	4.2	4357	Clinical-based study	GAD	87
Buzzetti et al (NIRAD study), 2007		Italy	4.5	4250	Clinical-based study	GAD, IA-2	35
Radtke et al (HUNT study), 2009		Norway	10.1	1049	Population-based study	GAD	88
Maioli et al, 2010		Italy	4.9	5568	Clinical-based study	GAD	38
Hawa et al (Action LADA 7), 2013		Europe	9.7	6156	Clinical-based study	GAD, IA-2, ZnT8	32
Maddaloni et al, 2015	Middle Eastern	United Arab Emirates	2.6	17,072	Clinical-based study	GAD, IA-2	44

Abbreviations: LADA, latent autoimmune diabetes in adults; ADOPT, A Diabetes Outcome Progression Trial; NIRAD, Non-Insulin Requiring Autoimmune Diabetes; UKPDS, United Kingdom Prospective Diabetes Study; HUNT, Nord-Trøndelag Health; AA, autoantibody; GAD, glutamic acid decarboxylase; IA-2, tyrosine phosphatase IA-2; ZnT8, zinc transporter 8; ICA, islet-cell antibody.

subtypes of diabetes, however, form a continuum of varying severity in terms of immune and metabolic dysfunction,<sup>89</sup> and the clinical characteristics of SPIDDM or LADA are extremely broad.

Asian patients with LADA have a lower BMI compared with Caucasian patients with LADA. In a joint collaborative project between Italy and Korea, Caucasian patients with LADA had a significantly higher BMI than Asian patients with LADA ( $27 \pm 5.1 \text{ kg/m}^2$  versus  $25.3 \pm 3.3 \text{ kg/m}^2$ , respectively,  $p < 0.01$ ) although the mean age and HbA1c values were nearly identical.<sup>90</sup> Similar lower BMI values were observed in the study from Japan and China.<sup>39,64</sup>

Among patients with SPIDDM or LADA, there are some differences in clinical characteristics between high-GADAb titer patients and low-GADAb titer patients.<sup>26,39,87</sup> Compared with patients with low GADAb titers, patients with high GADAb titers had more prominent traits of insulin deficiency and more severe autoimmunity, resulting in higher A1C levels, lower BMI, and a lower prevalence of metabolic syndrome and its components.

### Mirco/Macro Complications

To date, the risk of micro and macrovascular complications in patients with SPIDDM or LADA compared with patients with AT1D, patients with T2D, or healthy controls are not well known, as almost all studies are cross-sectional or statistically underpowered.

In terms of microvascular complications, a few studies showed a lower prevalence of diabetic kidney disease in patients with LADA compared with patients with T2D. For example, the Fremantle Diabetes Study showed that microalbuminuria was less frequent both at baseline and during follow-up in the LADA subgroup with relatively shorter duration of disease compared with the GAD antibody-negative patients after adjustment for other risk factors.<sup>91</sup> A Chinese study showed that the prevalence of diabetic retinopathy and diabetic nephropathy was significantly lower in patients with LADA compared with patients with T2D.<sup>92</sup> These findings could be explained by the fact that patients with T2D may go undiagnosed for a longer period than patients with SPIDDM or LADA and thus be more likely to experience complications of chronic hyperglycemia.<sup>93,94</sup> No study has shown statistically significant differences in the prevalence of neuropathy between patients with LADA and T2D after adjusting for several risk factors, although some studies showed a numerically higher prevalence of neuropathy in patients with LADA.<sup>91,95-97</sup> A study assessing nerve conduction

**Table 3** Clinical Characteristics Of SPIDDM Compared With AT1D And T2D

	AT1D	SPIDDM	T2D
Age at diagnosis	Childhood to adolescence	Any age	Adulthood
Onset	Acute	Intermediate	Slow
Acute complications (e.g. ketosis) at diagnosis	Frequently	Rare	Rare
Micro/macro-vascular complications at diagnosis	Rare	Rare	Sometimes
Family history of diabetes	Sometimes	Sometimes	Frequently
Family history of autoimmune disease	Frequently	Frequently	Rare
Autoimmunity	Severely increased	increased	no change
Other autoimmune disease	Frequently	Frequently	Rare
HLA	Strongly associated	Associated	Not associated
BMI	Low to normal	Normal to high	High
Mets or its components	Rare	Sometimes	Frequently
Beta cell function	Severely decreased	Decreased	No change or increased
Decline in beta cell function	<3 months	>3 months	>years

**Abbreviations:** AT1D, acute-onset type 1 diabetes; SPIDDM, Slowly progressive type 1 (insulin-dependent) diabetes mellitus; T2D, type 2 diabetes mellitus; HLA, human leukocyte antigen; BMI, body mass index; Mets, metabolic syndrome.

**Table 4** Diagnostic Criteria For Slowly Progressive Insulin-Dependent Type 1 Diabetes Mellitus (2012)

Requirements
<ol style="list-style-type: none"> <li>1. Presence of glutamic acid decarboxylase antibodies (GADAb) and/or islet cell antibodies (ICA) at some time during the disease course</li> <li>2. Absence of ketosis or ketoacidosis at onset (or diagnosis) of diabetes mellitus and no need for insulin treatment to correct hyperglycemia immediately after diagnosis</li> </ol> <p>Determination: "Slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM)" should be diagnosed if the conditions described in 1 and 2 above are met</p>
Notes
<ol style="list-style-type: none"> <li>1) As the course progresses, insulin secretory capacity gradually decreases, and insulin therapy becomes necessary more than 3 months after onset (or diagnosis) of diabetes mellitus, and insulin dependence frequently develops</li> <li>2) In the field of pediatrics, at the time diabetes mellitus is diagnosed, insulin treatment at low doses (0.5 U/kg body weight) is sometimes started immediately. Even in the field of internal medicine, if GADAb-positive findings are confirmed, patients are sometimes started immediately on insulin therapy, in consideration of preventing decreased insulin secretion</li> <li>3) GADAb and/or ICA sometimes become negative during the disease course in many cases</li> <li>4) In rare cases with GADAb and/or ICA, insulin dependence does not develop until 10 years and more after onset (or diagnosis) of diabetes mellitus, because of extremely gradual or no change in insulin secretory capacity, irrespective of the titer of GADAb and ICA</li> </ol> <p>a Because there is insufficient evidence for insulinoma-associated antigen-2 antibodies (IA-2Ab), insulin autoantibodies (IAA), or zinc transporter 8 antibodies (ZnT8Ab), the presence of these antibodies was excluded from the required diagnostic criteria</p> <p>b This limitation does not apply when soft drink ketosis (ketoacidosis) has occurred at onset of diabetes mellitus</p>

parameters showed more frequent peripheral nerve dysfunction in patients with LADA compared with patients with T2D in limited subgroups.<sup>92</sup>

The prevalence of macrovascular disease in patients with SPIDDM or LADA is similar to that of patients with T2D but higher than in healthy individuals.<sup>91,98</sup> Theoretically, patients with SPIDDM may have lower macrovascular complications compared with patients with T2D because patients with SPIDDM have a better lipid profile, lower blood pressure, and lower BMI. On the other hand, patients with SPIDDM have worse glycemic

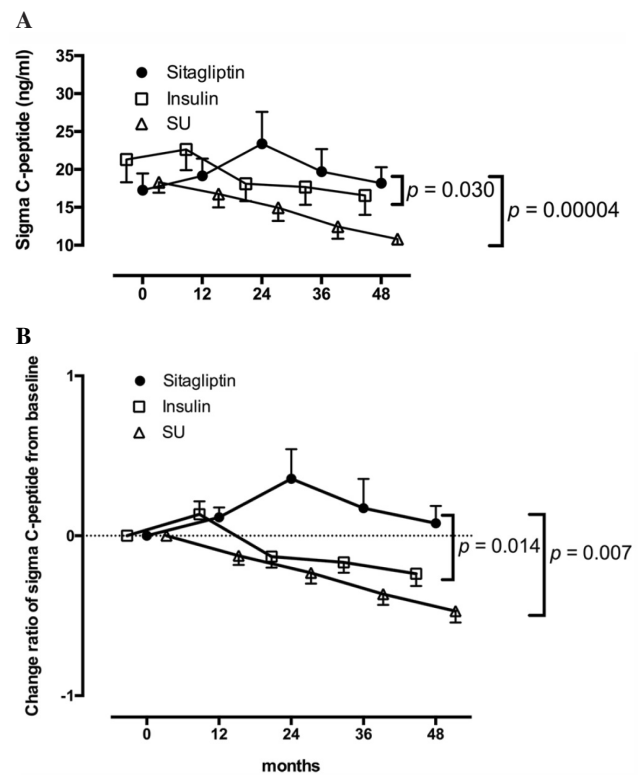
control compared with patients with T2D due to reduced beta-cell function and a higher risk for hypoglycemia due to the greater number of patients treated with insulin. In a follow up to the HUNT study, increased risks for all-cause mortality (HR, 1.55), cardiovascular disease (1.87), and ischemic heart disease (2.39) were observed in patients with LADA compared with individuals without diabetes. Patients with T2D had similarly high risks compared with those without diabetes.<sup>98</sup> The Fremantle Diabetes Study showed that GADAb-positive patients with LADA had a similar prevalence and incidence of coronary heart disease

and cerebrovascular disease and cardiac and all-cause mortality compared with the GADAb-negative patients.<sup>91</sup>

## Prevention Strategies And Clinical Options For SPIDDM

Preservation of beta-cell function is the principal treatment strategy for SPIDDM or LADA. In SPIDDM, residual beta-cell function is particularly important for the prevention of diabetic complications<sup>99,100</sup> because beta cells have been shown to be preserved in patients with SPIDDM even after 10 years.<sup>15</sup> Our prospective study, published in 1996,<sup>101</sup> demonstrated that small doses of insulin before the pre-insulin requiring stage of SPIDDM were associated with seroconversion of ICA from positive to negative findings, suggesting that some kind of immunologic modulation is associated with low insulin doses. An extended multicenter, randomized, non-blinded clinical study (Tokyo study) of 60 GADAb-positive non-insulin requiring patients with diabetes for  $\leq 5$  years reported that patients treated with insulin early showed greater preservation of the C-peptide response than patients treated with a sulfonylurea.<sup>11</sup> In addition, a low-GADAb titer and preserved C-peptide response at entry were independent markers for the effective prevention of insulin dependency. In our case report, changes in treatment from insulin to an alpha-glucosidase inhibitor resulted in increases in the GADAb titer, suggesting that activation of an immunologic assault to beta cells may contribute to the development of SPIDDM.<sup>102</sup> The Nationwide study demonstrated that seroconversion of GADAb from negative to positive and an increase in HbA1c level in patients with T2D occurred more frequently in non-insulin-treated patients.<sup>51</sup> A meta-analysis recommended early insulin treatment instead of sulfonylureas as being preferable to preserve residual beta-cell function in patients with LADA.<sup>103</sup>

DPP-4 inhibitors are effective in preventing loss of beta-cell function for long-term periods in patients with SPIDDM or LADA.<sup>14</sup> It was reported that the fasting serum DPP-4 activity independently from the ICA or GAD status was increased in patients with T1DM in 2011.<sup>104</sup> Subsequently others found that DPP-4 inhibitors are effective in preventing loss of beta-cell function for long-term periods in patients with SPIDDM or LADA. Our 4-year, open-label, randomized control trial (SPAN-S study) demonstrated that sitagliptin treatment was more potent than insulin treatment at preventing beta-cell deterioration in patients with SPIDDM (Figure 3).<sup>14</sup> In this study, we compared our present data with those in the Tokyo Study as a historical control. This study



**Figure 3** Longitudinal changes in the C-peptide response to the oral glucose tolerance test for 48 months in patients treated with sitagliptin in the Tokyo study. Patients with 48 months of follow-up are shown. Data are expressed as the mean  $\pm$  SEM. In both the  $\Sigma$ C-peptide values (**A**) and change ratios from baseline (**B**), a repeated-measures analysis of variance revealed a significant interaction between time and treatment assignment (sitagliptin or insulin;  $p = 0.030$  and  $p = 0.014$ , respectively) as well as between time and treatment assignment (sitagliptin or sulfonylurea;  $p = 0.00004$  and  $p = 0.007$ , respectively) in the longitudinal changes.

**Note:** Reproduced from Awata T, Shimada A, Maruyama T, et al. Possible Long-Term Efficacy of Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor, for Slowly Progressive Type I Diabetes (SPIDDM) in the Stage of Non-Insulin Dependency: An Open-Label Randomized Controlled Pilot Trial (SPAN-S). *Diabetes Ther.* 2017;8(5):1123-1134. Creative commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.<sup>14</sup>

indicated that treatment by sitagliptin significantly influenced the longitudinal changes of the C-peptide responses to the oral glucose tolerance test with a more increased direction than insulin and sulfonylurea. Additional studies have also reported preservation of beta cell function in patients with SPIDDM or LADA treated with DPP-4 inhibitors, including sitagliptin for 1 year,<sup>13</sup> linagliptin,<sup>105</sup> and saxagliptin.<sup>106</sup> The possible mechanisms for the effect of DPP-4 inhibitors may be related to findings in NOD mice models in which DPP-4 inhibitors decrease CD4<sup>+</sup> T cell migration<sup>107</sup> and increase CD4<sup>(+)</sup>CD25<sup>(+)</sup>FoxP3<sup>(+)</sup> regulatory T cells.<sup>108</sup>

Candidates for combination treatment for preserving beta cell function in SPIDDM include metformin,<sup>12</sup> which changes gut microbiota profiles, and pioglitazone, although results are inconclusive.<sup>109,110</sup>

## Conclusion

Prevention of slowly progressive beta-cell failure in patients with SPIDDM is a promising target for intervention. Addressing the unique inflammatory changes associated with PanIN lesions of the pancreatic duct in patients with SPIDDM may also be an attractive target to slow or stop the progression of beta-cell dysfunction in these patients.

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## Disclosure

The authors report no conflicts of interest in this work.

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