

## Editorial

# Latent Autoimmune Diabetes in Adults (LADA) in Recent Clinical Practice

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Diabetic patients have been increasing and this tendency has become a medical and social problem worldwide.<sup>1</sup> There are some types of diabetes, in which the prevalence of type 2 diabetes mellitus (T2DM) has been higher without requiring insulin treatment. On the other hand, type 1 diabetes mellitus (T1DM) has acute onset due to virus infection. Under such circumstances, there is a disease that has been clinically important in recent years. It is Latent autoimmune diabetes in adults (LADA).

As to LADA, there are both clinical and immunological characteristics between T2DM and T1DM. The genesis of T1DM has been the autoimmune destruction of islet  $\beta$ -cells in the pancreas. There are some major anti-islet autoantibodies, such as glutamic acid decarboxylase autoantibody (GADA), and T1DM shows a high prevalence of GADA.<sup>2,3</sup>

When positive GADA is observed in the patient with T2DM, the patient does not require insulin treatment during the early stage, but the patient may become insulin-dependent status within a few years. This subtype of diabetes has been called LADA mainly in Europe and North American region.<sup>4</sup> In contrast, in Japan and the Asian region, it has been called slowly progressive insulin-dependent (type 1) diabetes mellitus (SPIDDM),<sup>5</sup> and/or LADA.<sup>6</sup>

The characteristic point of LADA would be a conceptual phenotype that exists between conventional T1DM and T2DM. Recently, there has been some clinical issues and challenges for LADA.<sup>7</sup> They include the prevention of progressive  $\beta$ -cell failure by dipeptidyl peptidase-4 (DPP-4) inhibitors, Glucagon-like peptide-1 (GLP-1) analogs, metformin, and insulin.<sup>8</sup> Furthermore, there was an investigation of islet cells and exocrine pancreatic tissues in the pancreas for LADA which were positive for GADAs and islet cell antibody (ICA).<sup>9</sup>

LADA is characterized for its rather less intensive autoimmune situation and its broad clinical features.<sup>10</sup> Patients with LADA are initially insulin independent at early stages and can be checked by examination of islet-cell autoantibodies. Then, it is rather difficult to diagnose LADA in the usual clinical setting. Probably, there are lots of cases of LADA which would exist in the large group of T2DM with higher misdiagnosis rate.

As a matter of fact, the screening test for ICAs would be necessary for the patients with newly diagnosed as T2DM. Unless this exam of antibodies is performed, a gradual decrease in the ability of insulin secretion may be found later after years.<sup>10</sup> Consequently, LADA may show slower decreased pancreas function compared with that of T1DM. Furthermore, patients with LADA can prepare the pathophysiological changes in advance a few years later, with the adequate therapeutic approach of diabetic treatment.

LADA has been characterized for the presence of specific autoantibodies for the islet cells. It includes GADA and IA-2 antibodies.<sup>11</sup> This type is often diagnosed as T2DM at an early stage, but a few years later its diabetic status will develop to the degree similar to T1DM. This situation has been as rather popular in adulthood as in childhood.<sup>11</sup> Thus, there is a possibility of misdiagnosis between T2DM and LADA just after the diagnosis of diabetes. These patients are defined as LADA which has been one of the subtypes of autoimmune diabetes.<sup>12</sup> Its specific points would be more heterogeneous than T1DM in a young person and slower changes to  $\beta$ -cell failure for years with necessary treatment of insulin.<sup>13</sup>

From the guidelines of the Immunology of Diabetes Society (IDS), a patient with LADA has been defined by i) adult age of onset usually more than 30-years, ii) insulin independence at

onset for at least 6-months, iii) positive results for islet-cell autoantibodies.<sup>13</sup> In contrast, there have much discussion and controversy concerning the definition of LADA. It is rather difficult to show clear diagnostic guidelines at present. Consequently, the various situation of LADA includes heterogeneous matters in phenotypic, immunological and genetic features. These phenomena probably come from the variability of autoimmunity, insulin resistance and pancreatic  $\beta$ -cell impairment rate.<sup>14</sup>

In clinical practice, LADA has been sometimes unnoticed among patients with T2DM. Its incidence may be supposed to be about 5-10% of misdiagnosis rate.<sup>11</sup> Actually, it is recommended to order the measurement of the blood C-peptide value and autoantibody examination such as GADA in the patients with newly diagnosed as T2DM. It is necessary to make confirmation the diagnosis whether there is the possibility of LADA or not.<sup>15</sup> It is indeed that it cost some expense for the detecting GADA antibody, but it is crucial to be checked at the early stages of diagnosis. Obtaining the data for GADA antibody, prevention for  $\beta$ -cells failure and other clinical diabetic disorder for the future can be prepared in advance.<sup>16</sup>

According to the study on GADA in 32 patients with LADA, 59% of them showed positive results for the measurement of GADA-ELISA method.<sup>17</sup> Patients with positive ELISA had significantly lower insulin secretion, suggesting the presence of more cytotoxic GAD epitopes. Consequently, measuring the value of GADA may predict the ability of insulin secretion in patients with LADA.

In the action LADA study, the majority of subjects showed positive for GADA, while only 24.1% of subjects were positive for at least two autoantibody types.<sup>18</sup> There are some controversies concerning the pathogenesis of LADA, which has not been clarified yet. A recent study revealed a significant association between Islet cell antigen 512 (IA-2) positivity and increased body mass index (BMI).<sup>19</sup> It may suggest two possibilities in obese or lean subjects for LADA. One is persisting low-grade inflammation with genetic susceptibility to T2DM in obese people, and another is specific immunological involvement with genetic susceptibility to T1DM in lean people.<sup>16</sup>

Formerly, T1DM has been thought of as a childhood disease. In the last decade, however, about 30% of T1DM cases have been diagnosed after 30-years-old by statistical investigations.<sup>15</sup> Thus, T1DM onset in adults becomes an important matter at present. From various studies, the incidence rate of adult-onset autoimmune diabetes has been different in countries and ethnicity. It is rather higher in North Europe than American, Latino, and Asia.<sup>12,20</sup> The prevalence of LADA has been reported as follows: 2.6% in the United Arab Emirates, 3.2% in India, 4.4%-5.3% in Korea, 5.7% in China, 7.0-14.0% in North Europe.<sup>20,21</sup> In these studies, however, there have been various differences in study design, method, and criteria, where we have to compare the data of incidence and prevalence from a different area in the world.

In summary, LADA has been recently found in various

areas. When the patient is diagnosed as LADA, autoantibodies and the clinical course should be carefully monitored. The pathogenesis for LADA has been gradually elucidated and the development of future research is expected.

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