Editorial

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Latent Autoimmune Diabetes in Adults: Autoimmune Diabetes in Adults with Slowly Progressive β-cell Failure

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Type 1 diabetes (T1D) is caused by interactions of genetic predisposition, immunologic triggers, and environmental events leading to autoimmune-mediated pancreatic β-cell destruction and insulin deficiency, although some subjects show lack of autoantibodies to pancreatic islets. Regarding the time lag of complete β-cell mass loss in T1D, simple or unique patterns may not be identified, with some individuals progressing for more than several years. Contrary to T1D, type 2 diabetes (T2D), irrelevant of autoimmune-mediated β-cell destruction, is a heterogeneous disorder characterized by insidious onset and insulin resistance with relative insulin secretory dysfunction. Clinically, some diabetic patients exhibit autoimmune antibodies without insulin requirement. This biphasic type of diabetes is a special form of diabetes that is clinically similar to the early stage of T2D and pathophysiologically defined as a disorder of the autoimmune-mediated progressive β-cell dysfunction. To clarify different features from T1D and T2D, Zimmet [1] introduced the eponym "latent autoimmune diabetes of adults" (LADA) to describe this subgroup of adult phenotypic T2D patients positive for autoantibodies. Based on the natural history of LADA, in which secretory β-cell dysfunction is prominently aggravated depending on the presence of antibodies seen in T1D, Stenstrom et al. [2] suggested LADA is not always a latent disease. Therefore, autoimmune diabetes in adults with slowly progressive β-cell failure might be a more adequate concept. The Immunology of Diabetes Society (IDS) has proposed criteria to standardize the definition of LADA: 1) ≥35 years of age, 2) positive for at least 1 of the 4 antibodies commonly seen in T1D patients; islet cell autoantibodies (ICA), anti-glutamic acid decarboxylase (anti-GAD), Insulinoma-associated protein-2 antibodies (IA-2A), and insulin autoantibodies (IAA), and 3) not requiring insulin therapy within the first 6 months after diagnosis [3].

Regarding the genetic and immunologic characteristics in LADA, subjects with LADA show a type of difference from patients with T1D. First, compared with T1D, susceptibility genes are much less prevalent, but protective genes are more prevalent in LADA [4]. HLA alleles associated with T1D susceptibility are HLA DR3, DR4, and DQB1*0201 and 0302, while the alleles associated with T1D protection are DR2 and DQB1*0301 and 0602 [5,6]. These differences may partially explain the relatively late onset of LADA. Second, there are several differences in autoantibodies between T1D and LADA. Compared with T1D, anti-GAD and ICA are much more common than IAA, IA-2A, and zinc transporter 8 (ZnT8) antibodies in subjects with LADA [7,8]. GAD is a neuronal enzyme involved in the synthesis of the neurotransmitter gamma-aminobutyric acid. Anti-GAD is seen not only in a variety of autoimmune neurologic disorders including stiff-man syndrome, autoimmune cerebellitis, brain stem encephalitis etc., but also

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in autoimmune T1D. In clinical practice, anti-GAD is not only an important serological marker of predisposition to T1D but also the major pancreatic islet antibody for diagnosing T1D [9]. Of the anti-GAD subclasses, the IgG4 subclass is more frequent in LADA than in T1D [10]. T1D and LADA also show different epitope specificity for anti-GAD. The middle or COOH-terminal portion of GAD was recognized by more than 90% of sera from T1D compared with only 65% of LADA patients. In contrast, 20% of LADA patients' sera bound to the NH2-terminal portion of GAD, compared with 5% of T1D patients [11].

There are many controversial issues regarding prevalence of LADA. In previous epidemiological studies, LADA accounted for 2% to 12% of all cases of diabetes [1,8,12]. Some studies suggested that LADA accounts for approximately 10% of the patients initially diagnosed as T2D [13,14]. Despite several studies on the prevalence in the Korean population [15-17], controversy still remains on the accurate prevalence. Most studies tested for anti-GAD only when the patients were suspected to have T1D. Recently, Hwangbo et al. [18] reported a 4.3% prevalence of LADA in newly-diagnosed Korean T2D subjects regardless of their clinical characteristic at the time of presentation. Though Hwangbo et al. [18] indicated that 4.3% prevalence of anti-GAD positivity was similar to that in Japan, they did not thoroughly review the well-designed trials studying the prevalence of LADA in Korea, where a recent-onset T2D Korean National Diabetes Program cohort showed a 4.4% prevalence by the positivity of circulating autoantibodies to pancreatic islet cell antigens (GAD, IA-2, and ZnT8) [19], as well as 5.1% to 5.3% prevalence in a single center trial [20,21]. Another limitation of the study conducted by Hwangbo et al. [18] is that the authors only evaluated for the anti-GAD, and not other autoantibodies such as ICA, IA-2A, and IAA. Based on the data, the prevalence of LADA in Korea may be around 5% in T2D. However, the ambiguity in diagnosis criteria in previous studies such as age (more than 30 or 35 years), antibodies (ICAs and anti-GAD, IA-2A, and IAA in IDS criteria, or anti-GAD, IA-2A, anti-ZnT8 in European NIRAD LADA group criteria), and period of insulin independence after diagnosis did not come to a conclusive answer regarding prevalence and incidence.

Regarding the β-cell secretory dysfunction in LADA, several studies have reported the presence of a single autoantibody and/or lower anti-GAD titer is associated with older age, a slower rate of disease progression, and lower risk of insulin dependency. In contrast, the presence of multiple autoantibodies and/or higher anti-GAD titer is associated with younger age, a faster rate of disease progression, and higher risk of insulin dependency [10,22]. Similar to the above-mentioned results, Hwangbo et al. [18] reported that high anti-GAD titer showed significantly lower C-peptide level and was more likely to require insulin treatment. A well-designed 12-year prospective study [23] showed diabetic subjects with multiple islet antibodies (ICA, anti-GAD, IA-2A) are more prone to deteriorate in insulin secretory resulting in β-cell failure within 5 years, whereas patients with only anti-GAD or only ICA mostly develop β-cell failure after 5 years. Though Hwangbo et al. [18] were unable to observe the natural course of the β-cells, a prospective 36-month multicenter study in Korean diabetic subjects showed 7.7% subjects with LADA were dependent on insulin within 3 years, but true insulin dependency evidenced by multiple antibody positivity was not high and did not increase in Korean subjects [19]. Considering the characteristics of Korean patients with T2D, whose secretory β-cell dysfunction is a major contributing factor to the development and aggravation of hyperglycemia [24,25], a large scale nationwide prospective study is warranted to verify the meaning of autoantibody positivity to pancreatic islets and the natural course of β-cell secretory dysfunction in LADA.

Another controversy on subjects with LADA may be the relevance of metabolic syndrome. As described previously, T2D, irrelevant of autoimmune-mediated β-cell destruction, has a heterogeneous pathophysiology characterized by insulin resistance with relative insulin secretory dysfunction, but LADA is an autoimmune diabetes in adults with slowly progressive β-cell failure. Regarding islet autoantibodies in metabolic features, LADA patients with multiple autoantibodies and/or a high titer of anti-GAD showed a higher risk of β-cell dysfunction and presence of other autoimmune disorders, but a lower prevalence of metabolic syndrome in Western populations [22]. Hwangbo et al. [18] could not find differences in the metabolic syndrome and its components including HOMA-IR between subjects with anti-GAD positive and subjects with anti-GAD negative, and suggested LADA in the Korean population might be different from LADA in the Caucasian population. However, Lee et al. [20] showed that low C-peptide level and absence of metabolic syndrome were variables independently associated with the diagnosis of LADA.

Due to the ambiguous pathophysiology and clinical characteristics of LADA, no specific guideline for treatment of LADA

has been established. The primary defect in autoimmune diabetes is loss of insulin secretion. Insulin secretory capacity in LADA has been recognized as between T1D and T2D [23]. LADA patients have a faster decline in C-peptide levels compared with patients with T2D [23,26], whereas a slower rate of decline compared with adult T1D [27]. Several Japanese studies demonstrated insulin treatment showed better preservation of β-cell function compared with sulfonylurea in ICA-positive and anti-GAD-positive phenotypic T2D subjects [28]. Anti-inflammatory therapy that slows progression of β-cell destruction could be another option. Thiazoledinediones also might be of value in the treatment of LADA, because of the anti-inflammatory effect, as well as improving insulin sensitivity. LADA patients treated with rosiglitazone were reported to have greater β-cell preservation compared with a group of LADA subjects treated with insulin alone during a 3-year follow-up [29]. Recently, antigen-specific immunomodulation has been reported as potential treatment choice, such as GAD vaccine [30].

LADA is not a rare disease, and many subjects are still underdiagnosed. Without awareness, a correct diagnosis of LADA is not easy. Earlier correct diagnosis of LADA could help clinicians and patients to manage ongoing β-cell dysfunction. A large scale nationwide study to examine the natural course and clinical characteristics of subjects with LADA in Korean subjects is essential to preserve β-cell function in subjects with LADA.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Zimmet PZ. The pathogenesis and prevention of diabetes in adults: genes, autoimmunity, and demography. Diabetes Care 1995;18:1050-64.
2. Stenstrom G, Gottsater A, Bakhtadze E, Berger B, Sundkvist G. Latent autoimmune diabetes in adults: definition, prevalence, beta-cell function, and treatment. Diabetes 2005;54 Suppl 2: S68-72.
3. Naik RG, Brooks-Worrell BM, Palmer JP. Latent autoimmune diabetes in adults. J Clin Endocrinol Metab 2009;94:4635-44.
4. Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nissen M, Ehrnstrom BO, Forsen B, Snickars B, Lahti K, Forsblom C, Saloranta C, Taskinen MR, Groop LC. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 1999;48:150-7.
5. Greenbaum CJ, Schatz DA, Cuthbertson D, Zeidler A, Eisenbarth GS, Krischer JP. Islet cell antibody-positive relatives with human leukocyte antigen DQA1*0102, DQB1*0602: identification by the Diabetes Prevention Trial-type 1. J Clin Endocrinol Metab 2000;85:1255-60.
6. Vandewalle CL, Decraene T, Schuit FC, De Leeuw IH, Pipeleers DG, Gorus FK. Insulin autoantibodies and high titre islet cell antibodies are preferentially associated with the HLA DQA1*0301-DQB1*0302 haplotype at clinical type 1 (insulin-dependent) diabetes mellitus before age 10 years, but not at onset between age 10 and 40 years. The Belgian Diabetes Registry. Diabetologia 1993;36:1155-62.
7. Cervin C, Lyssenko V, Bakhtadze E, Lindholm E, Nilsson P, Tuomi T, Cilio CM, Groop L. Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes. Diabetes 2008;57:1433-7.
8. Juneja R, Hirsch IB, Naik RG, Brooks-Worrell BM, Greenbaum CJ, Palmer JP. Islet cell antibodies and glutamic acid decarboxylase antibodies, but not the clinical phenotype, help to identify type 1(1/2) diabetes in patients presenting with type 2 diabetes. Metabolism 2001;50:1008-13.
9. Vianello M, Tavolato B, Giometto B. Glutamic acid decarboxylase autoantibodies and neurological disorders. Neurol Sci 2002;23:145-51.
10. Hillman M, Torn C, Thorgeirsson H, Landin-Olsson M. IgG4-subclass of glutamic acid decarboxylase antibody is more frequent in latent autoimmune diabetes in adults than in type 1 diabetes. Diabetologia 2004;47:1984-9.
11. Hampe CS, Kockum I, Landin-Olsson M, Torn C, Ortqvist E, Persson B, Rolandsson O, Palmer J, Lernmark A. GAD65 antibody epitope patterns of type 1.5 diabetic patients are consistent with slow-onset autoimmune diabetes. Diabetes Care 2002; 25:1481-2.
12. Kobayashi T, Tamemoto K, Nakanishi K, Kato N, Okubo M, Kajio H, Sugimoto T, Murase T, Kosaka K. Immunogenetic and clinical characterization of slowly progressive IDDM. Diabetes Care 1993;16:780-8.
13. Abiru N, Takino H, Yano M, Kawasaki E, Yamasaki H, Yamaguchi Y, Akazawa S, Nagataki S. Clinical evaluation of non-insulin-dependent diabetes mellitus patients with autoantibodies to glutamic acid decarboxylase. J Autoimmun 1996;9:683-8.

14. Niskanen LK, Tuomi T, Karjalainen J, Groop LC, Uusitupa MI. GAD antibodies in NIDDM: ten-year follow-up from the diagnosis. Diabetes Care 1995;18:1557-65.
15. Kim CS, Park J, Cho MH, Park JS, Nam JY, Kim DM, Ahn CW, Cha BS, Lim SK, Kim KR, Lee HC. Frequency of anti-GAD antibody in non-obese, adult-onset type 2 diabetes in Korea and clinical and biological characteristics according to anti-GAD antibody. J Korean Diabetes Assoc 2004;28:66-74.
16. Ko KS, Hong SK, Lee KU, Kim NH, Choi DS, Ihm SH, Park SW, Kim CH, Byun DW, Suh KI, Chang HC, Rhee BD. The frequency of ICA and anti-GAD antibody in Korean IDDM and NIDDM patients. J Korean Diabetes Assoc 1998;22:312-9.
17. Oh JH, Yoon JS, Won KC, Lee HW. Antibodies to GAD and ICA in type 2 DM with secondary failure of oral hypoglycemic therapy. J Korean Diabetes Assoc 2007;31:402-9.
18. Hwangbo Y, Kim JT, Kim EK, Khang AR, Oh TJ, Jang HC, Park KS, Kim SY, Lee HK, Cho YM. Prevalence and clinical characteristics of recently diagnosed type 2 diabetes patients with positive anti-glutamic acid decarboxylase antibody. Diabetes Metab J 2012;36:136-43.
19. Park Y, Hong S, Park L, Woo J, Baik S, Nam M, Lee K, Kim Y; KNDP collaboratory Group. LADA prevalence estimation and insulin dependency during follow-up. Diabetes Metab Res Rev 2011;27:975-9.
20. Lee SH, Kwon HS, Yoo SJ, Ahn YB, Yoon KH, Cha BY, Lee KW, Son HY. Identifying latent autoimmune diabetes in adults in Korea: the role of C-peptide and metabolic syndrome. Diabetes Res Clin Pract 2009;83:e62-5.
21. 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. Epub 2010 Oct 16. DOI: 10.1007/s00592-010-0228-y.
22. van Deutekom AW, Heine RJ, Simsek S. The islet autoantibody titres: their clinical relevance in latent autoimmune diabetes in adults (LADA) and the classification of diabetes mellitus. Diabet Med 2008;25:117-25.
23. Borg H, Gottsater A, Fernlund P, Sundkvist G. A 12-year prospective study of the relationship between islet antibodies and beta-cell function at and after the diagnosis in patients with adult-onset diabetes. Diabetes 2002;51:1754-62.
24. Kim DJ, Lee MS, Kim KW, Lee MK. Insulin secretory dysfunction and insulin resistance in the pathogenesis of korean type 2 diabetes mellitus. Metabolism 2001;50:590-3.
25. Rhee SY, Woo JT. The prediabetic period: review of clinical aspects. Diabetes Metab J 2011;35:107-16.
26. Torn C, Landin-Olsson M, Lernmark A, Palmer JP, Arnqvist HJ, Blohme G, Lithner F, Littorin B, Nystrom L, Schersten B, Sundkvist G, Wibell L, Ostman J. Prognostic factors for the course of beta cell function in autoimmune diabetes. J Clin Endocrinol Metab 2000;85:4619-23.
27. Hosszufalusi N, Vatay A, Rajczy K, Prohaszka Z, Pozsonyi E, Horvath L, Grosz A, Gero L, Madacsy L, Romics L, Karadi I, Fust G, Panczel P. Similar genetic features and different islet cell autoantibody pattern of latent autoimmune diabetes in adults (LADA) compared with adult-onset type 1 diabetes with rapid progression. Diabetes Care 2003;26:452-7.
28. Kobayashi T, Maruyama T, Shimada A, Kasuga A, Kanatsuka A, Takei I, Tanaka S, Yokoyama J. Insulin intervention to preserve beta cells in slowly progressive insulin-dependent (type 1) diabetes mellitus. Ann N Y Acad Sci 2002;958:117-30.
29. Yang Z, Zhou Z, Li X, Huang G, Lin J. Rosiglitazone preserves islet beta-cell function of adult-onset latent autoimmune diabetes in 3 years follow-up study. Diabetes Res Clin Pract 2009;83:54-60.
30. Wherrett DK, Bundy B, Becker DJ, DiMeglio LA, Gitelman SE, Goland R, Gottlieb PA, Greenbaum CJ, Herold KC, Marks JB, Monzavi R, Moran A, Orban T, Palmer JP, Raskin P, Rodriguez H, Schatz D, Wilson DM, Krischer JP, Skyler JS; Type 1 Diabetes TrialNet GAD Study Group. Antigen-based therapy with glutamic acid decarboxylase (GAD) vaccine in patients with recent-onset type 1 diabetes: a randomised double-blind trial. Lancet 2011;378:319-27.