

Optimal Cutoff Point of Glutamate Decarboxylase Antibody Titers in Differentiating Two Subtypes of Adult-Onset Latent Autoimmune Diabetes

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ABSTRACT: The optimal cutoff point of glutamate decarboxylase antibody (GAD-Ab) titers for differentiating two latent autoimmune diabetes (LADA) subtypes remains unclear. One hundred and forty-five GAD-Ab-positive patients screened from phenotypic type 2 diabetes were diagnosed as LADA. The clinical features were compared among LADA patients with different GAD-Ab titers. The receiver-operating characteristic (ROC) curve was used to evaluate the diagnostic value of GAD-Ab titers and to define the optimal cutoff point. The heterogeneity of clinical features in LADA could be discriminated by five GAD-Ab titers, with maximal differences at the titer of 175 U/mL. The ROC curve analysis showed that the optimal cutoff point for discriminating two LADA subtypes was at the titer of 175 U/mL, with sensitivity and specificity of 54.5% and 92.1%, respectively. These findings demonstrated that the two clinically distinct subtypes of LADA can be optimally discriminated by the GAD-Ab titers.

KEYWORDS: GAD antibody; latent autoimmune diabetes in adults; subtypes; titer

INTRODUCTION

The clinical and immunological heterogeneity in LADA has recently been identified.^{1,2} Based on the presence of ICA and/or GAD-Ab titers, Lohmann defined two LADA subtypes—LADA-type 1 and LADA-type 2—in which the differentiation of high or low GAD-Ab titers was arbitrary. In view of this, as well as the technically difficult standardization for ICA measurement, we set out to explore the diagnostic role of GAD-Ab titer alone and the optimal cutoff point of GAD-Ab titers for discriminating the two LADA subtypes.

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METHODS

Patients with classic T1DM ($n = 130$), GAD-Ab positive LADA ($n = 145$), and GAD-Ab negative T2DM ($n = 145$) were age-, sex-, and duration-matched and were enrolled for the study with informed consent. LADA was screened in the Second Xiangya Hospital with GAD-Ab.³ The Metabolic Syndrome (MS) was diagnosed according to the working definition proposed by WHO.⁴ Insulin deficiency was defined as serum fasting C-peptide RIA <300 pmol/L. GAD-Ab was tested as previously described.⁵ The cutoff point of GAD-Ab titer of 20 U/mL or higher, defined as positive, was determined according to the 99.5% upper limit of 188 healthy controls. The sensitivity and specificity of the GAD-Ab assay in our lab were 82% and 98%, respectively, evaluated in the Third Diabetes Autoantibody Standardization Program (DASP2003).

RESULTS

Clinical Heterogeneity of LADA Could Be Differentiated by Diverse GAD-Ab Titer Cutoff Points

We divided LADA patients into high- and low-titer subgroups by different GAD-Ab titers of 50, 110, 175, 230, and 290 U/mL to analyze the heterogeneity of clinical features in LADA. As shown in TABLE 1, the features of the low-titer LADA subgroup were similar to those of T2DM, except that BMI was smaller and more cases were combined with insulin deficiency; while the high-titer subgroup had significantly more clinical features representing insulin deficiency (such as C-peptide level and proportions of insulin deficiency) than did the T2DM group.

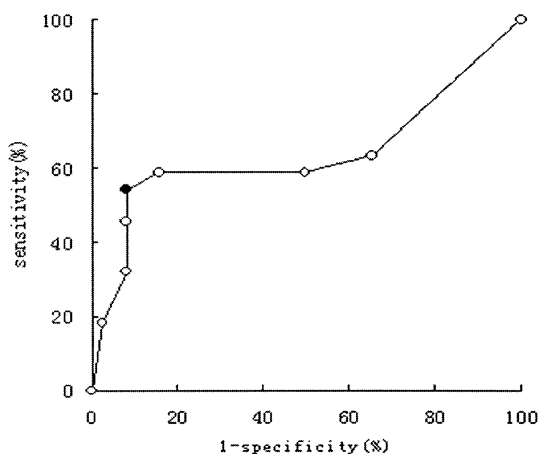


FIGURE 1. ROC curves for the GAD-Ab titer diagnosing two LADA subgroups. The value of the GAD-Ab titer for diagnosing insulin deficiency and the metabolic syndrome. The *black dot* at the upper left is at the titer of 175 U/mL, with sensitivity and specificity of 54.5% and 92.1%, respectively.

TABLE 1. Clinical features of LADA patients divided by different GAD-Ab titers

	Onset age (year)	BMI (kg/m ²)	FCP (pmol/L)	ID (%)	MS (%)
T1DM (n = 130)	23.0 ± 13.9	19.3 ± 3.3	125.0 (0–421.5)	90.3	17.0
T2DM (n = 145)	49.9 ± 12.8*	23.6 ± 3.1*	630.0 (138.0–4500.0)*	10.3*	52.1*
LADA (n = 145)	49.6 ± 13.1*	21.6 ± 3.3**	507.5 (37.0–2720.5)**	29.8**	52.0*
1) GAD-Ab ≥ 50 U/mL (n = 84)	49.0 ± 14.4*	21.0 ± 3.2**&	468.8 (37.0–1658.0)**	33.3**	47.3*
20 ≤ GAD-Ab < 50 U/mL (n = 61)	50.5 ± 11.2*	22.5 ± 3.4**	538.4 (42.0–2720.5)*	25.0*	57.8*
2) GAD-Ab ≥ 110 U/mL (n = 55)	47.2 ± 15.2*	20.2 ± 2.7**&	328 (37.0–1544.0)**&	46.8**&	36.1**&
20 ≤ GAD-Ab < 110 U/mL (n = 90)	51.2 ± 11.4*	22.5 ± 3.4**	623.2 (42.0–2720.5)*	18.9*	60.9*
3) GAD-Ab ≥ 175 U/mL (n = 49)	46.1 ± 15.2**&	19.9 ± 2.6**&	301.5 (37.0–1544.0)**&	50.0**&	30.0**&
20 ≤ GAD-Ab < 175 U/mL (n = 96)	51.4 ± 11.5*	22.6 ± 3.3**	628.0 (42.0–2720.5)*	19.0*	61.4*
4) GAD-Ab ≥ 230 U/mL (n = 45)	47.4 ± 15.0*	20.1 ± 2.6**&	331 (37.0–1544.0)**&	47.4**&	33.3*
20 ≤ AD-Ab < 230 U/mL (n = 100)	50.7 ± 12.1*	22.4 ± 3.4**	622.3 (42.0–2720.5)*	21.7*	58.9*
5) GAD-Ab ≥ 290 U/mL (n = 41)	47.4 ± 15.2*	20.1 ± 2.6**&	346.6 (50.7–1544.0)**&	44.1**	39.1*
20 ≤ GAD-Ab < 290 U/mL (n = 104)	50.5 ± 11.9*	22.3 ± 3.4**	589.2 (37.0–2720.5)*	24.1**	55.8*

NOTE: Data are shown as mean ± SD or median (min-max). Compared with classic T1DM * P < 0.01; compared with T2DM #P < 0.01; comparisons between different LADA subgroups &P < 0.01. ID, insulin deficiency; FCP, fasting C peptide; MS, metabolic syndrome.

When the two LADA subgroups, divided respectively by GAD-Ab cutoff points, were compared, we found that their clinical features could be discriminated by all five cutoff points except 50 U/mL, with the best divider being the GAD-Ab titer of 175 U/mL (TABLE 1).

Optimal Cutoff Point of GAD-Ab Titer in Differentiating Two LADA Subtypes

The value of GAD-Ab titers was evaluated for diagnosing the existence of insulin deficiency without MS (representing LADA-type 1 who are more insulin deficient) and the combination of MS without insulin deficiency (representing LADA-type 2 who are more insulin resistant). The ROC curve was made to define the optimal cutoff point of GAD-Ab for discrimination of two LADA subgroups. As was shown in FIGURE 1, the optimal point, GAD-Ab titer of 175 U/mL, was at the upper left of the curve, with an AUC (area under curve) of 0.79 ± 0.07 (95% Confidence Interval: 0.65–0.93).

DISCUSSION

In accordance with the studies,^{1,2} our results showed that the severity of insulin deficiency and insulin resistance differed in LADA patients with diverse GAD-Ab titers. The high-titer LADA subgroup was in an intermediate status between classic T1DM and T2DM, which possessed characteristics of “classical LADA” and could be referred to as LADA-type 1.¹ Clinical features of the low-titer LADA subgroup were similar to those of T2DM, which might be referred to as LADA-type 2.¹ The clinical features between the two LADA subgroups divided by diverse GAD-Ab titers were all different—that is, LADA-type 2 was intermediate between T2DM and LADA-type 1, while LADA-type 1 was intermediate between classic T1DM and LADA-type 2. Therefore, we could deduce that diabetes presents as a continuum spectrum and the extent of insulin deficiency and insulin resistance changes gradually between classic T1DM and T2DM. LADA patients, with medium insulin deficiency and insulin resistance, fell between classic T1DM, who were dominantly insulin deficient and T2DM who were more insulin resistant.^{3,6}

In this study, the ROC curve showed that GAD-Ab titer of 175 U/mL was the optimal cutoff point for discriminating insulin deficiency and metabolic syndrome in LADA patients. The diagnostic value of GAD-Ab with a higher specificity and lower sensitivity may be due to the following reasons: (1) to some extent, insulin resistance also coexists in LADA-type 1 patients, as does insulin deficiency in LADA-type 2 patients;^{1,7} (2) the insulin deficiency in LADA-type 1 is not as severe as that in classic T1DM;⁶ and (3) LADA patients preserve islet beta cell function during the first 3–5 years after diagnosis.² Identifying the heterogeneity of LADA with GAD-Ab titers has important implications in understanding its autoimmune pathogenesis and guiding its diagnostics and therapeutics. LADA patients with high or low GAD-Ab titer may require different treatment strategies.

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