ORIGINAL ARTICLE

Latent Autoimmune Diabetes of Adults in Latakia, Syria

Al-Farwi AA[a], Khayat MI[a], Muhsen Al-Mehri M[b]

[a] Department of Laboratory Medicine and [b]Endocrinology Division, Tishreen University, Latakia, Syria

This study aimed at assessing the frequency of latent autoimmune diabetes of adults (LADA) and its laboratory and clinical characteristics at the Diabetic Center of Latakia, Syria.

Materials and Methods: Based on glutamic acid decarboxylase autoantibodies positivity, a population of 254 type 2 diabetic males and females, aged 35 to 75 years, were subdivided and studied in terms of the laboratory and clinical characteristics. Results: Glutamic acid decarboxylase autoantibodies (GADAs) were positive (GADA+) in 45 diabetic patients versus 209 type 2 diabetics with GADA negative (GADA-). In both subgroups, GADA+ and GADA-, no significant differences were observed in terms of anthropometric and clinical features except for body mass index (BMI) which was significantly lower in GADA+ subgroup (27.6±4.8 vs. 29.8±5.9; P= 0.02). Significant poor glycemic control was detected in terms of fasting blood sugar (FBS) (221.6±77.9 vs 182±66.7; P=0.001), glucosuria (60% vs. 41.6%; P=0.025), and ketonuria (22.2% vs. 3.8%; P<0.0001) in LADA patients (GADA+) versus type 2 diabetic patients (GADA-). By subdividing the studied sample into tertiles of type 2 diabetes, GADA- <5 IU/ml , GADA+ ≤50 IU/ml, and GADA+ >50 IU/ml, the tertile with high GADA titers (>50 IU/ml) presented significantly low BMI (P=0.012) and c-peptide levels (P<0.002) in comparison with type 2 and GADA≤ 50 IU/ml tertiles. Conclusion: Overall the prevalence of LADA was 17.7% in the type 2 diabetics studied. LADA patients showed similar laboratory and clinical features as type 2 diabetics, except for low BMI levels and poor glycemic control.

Correspondence: Aiman Ahmad Al-Farwi, Department of Laboratory Medicine, Tishreen University, Latakia, Syria

E-mail: myownlab@yahoo.com

Key Words: LADA, Type 2 diabetes, GADA, C-peptide, BMI

Received: 28.04.2010 **Accepted**: 03.08.2010

Introduction

In 1977, Irvine and others outlined a subset of type 2 diabetics, which were positive for islet cell autoantibody (ICA) and failed to respond to sulphonylurea treatment[1]. Later on, autoimmune diabetes of adults was reported in 1986[2], leading to ongoing arguments in terms of its nomenclature, classification, and management. The name of latent autoimmune diabetes of adults (LADA) was launched[3] after discovering circulating glutamic acid decarboxylase autoantibodies (GADAs) in 1990[4]. Since then, many eponyms (Table 1) were introduced to state the disease criteria in terms of slow progressive rather than rapid onset type1 diabetes in adults[22, 28-30].

Although LADA shares some clinical, immune, and genetic similarities with type 1 diabetes[16,22,30-32], it is still a crucial issue that[25, 33-37] is not only misclassified as type 2 diabetes[12-13,16,31,38], but is sometimes presented with incompatible criteria of type 1 diabetes[12, 39]. Therefore, considering the lack

of standard clinical features, LADA needs to be identified carefully.

Overall, the positivity of at least one circulating autoantibody such as ICA, GADA, protein tyrosine phosphatase autoantibody (IA-2), or insulin autoantibody (IAA) against pancreatic islet β-cell antigens is enough to define LADA. GADA has been confirmed to be a sensitive autoimmune marker to diagnose LADA[3,10,13,27,31,38,40-43] and epidemiological data have demonstrated that the prevalence of LADA, based on GADA positivity, ranged from 2.8% to 16% in type 2 diabetics[10,13,18, 31, 38, 41]. According to GADA titers, not only was LADA was subdivided into two clinically distinct subgroups of patients[17, 18,27], but it also mirrored the progression to absolute or relative insulin deficiency[13,17,18,22,31,38,41,43]. The need for early insulinization proved to protect or delay islet β-cell deterioration[26,31,42,43]). Plasma c-peptide was reported to reflect the degree of endogenous insulin secretion by islet β-cell [19,28,40,43,44] and to fall more rapidly in type 1 rather than in LADA[22, 44].

This paper aims to determine the prevalence of LADA in Latakia based on the positivity of GADAs among type 2 diabetic patients, and investigates further the clinical and laboratory characteristics of LADA based on GADA titers.

Table 1. Eponyms for latent autoimmune diabetes of adults based on the first article that utilized this terminology

Eponym	Year
Slowly progressive insulin-dependent diabetes mellitus (SPIDDM)[5]	1984
Type 1.5 diabetes/ Type 1 1/2 diabetes[6]	1985
Latent type 1 diabetes[2]	1986
Progressive insulin-dependent diabetes mellitus (PIDDM)[7]	1992
Latent autoimmune diabetes in adults[3]	1993
Autoimmune diabetes in adults (ADA)[8]	1996
Slow-onset insulin-dependent diabetes mellitus[9]	1997
Slowly progressive type 1 diabetes[10]	1998
Latent-onset type 1 diabetes[1]	1999
Antibody-positive non-insulin-dependent diabetes[11]	1999
Slowly progressing autoimmune type 1 diabetes[12]	1999
Type 2 diabetes with glutamic acid decarboxylase antibodies[13]	1999
Slow type 1 diabetes[14]	1999
Slow onset autoimmune diabetes[15]	2000
Slowly progressing autoimmune diabetes[15]	2000
Autoimmune diabetes not requiring insulin at diagnosis[16]	2001
Latent autoimmune diabetes of adults –type 1 and –type 2 [17-18]	2001
Slowly progressive β-cell failure[19]	2001
Slowly progressive autoimmune diabetes in adult patients[20]	2001
Antibody-positive phenotypic type 2 diabetes with obesity[21]	2003
Slowly progressive adult-onset type 1 diabetes[22]	2003
Latent autoimmune diabetes of adulthood[23]	2003
Type 2 with islet cell autoimmunity[24]	2004
Adult-onset latent autoimmune diabete[18]	2004
Autoimmune diabetes in adults with slowly progressive b-cell failure (ADASP)[25]	2005
Antibody-positive slowly progressive type 1 diabetes[26]	2005
Non insulin requiring autoimmune diabetes (NIRAD)[27]	2007

Materials and Methods

Patients:

A group of 254 (equally divided in gender) type 2 diabetics, aged 35 to 75 years enrolled in the diabetic center of the National Health Services of Latakia, were recruited in this study during the period of January 2008 to February 2009[12-13,16-17,22,24-25,30,38,41]. Each patient was provided with the date and a pre-analytical preparation notice for an interview. Seventeen patients were excluded from the study and the exclusion criteria were malignancy, autoimmune diseases, known abnormal thyroid function at the time of the study, use of NSAIDS or acetylsalicylic acid, or infections in the previous two weeks before the start of the study; in addition, patients with type 1 diabetes requiring insulin after 6 months of diagnosis were also excluded[13,22,25,34]. Ninety-three diabetic patients (36.6%) of our cohort were insulin treated. A hundred and forty-five patients were on oral hypoglycemic drugs while 16 patients were on a diet; some of them refused to have treatment. These subgroups of patients were studied in terms of the clinical characteristics, biochemical laboratory assessment, and determination of GADAs concentrations.

Clinical assessment:

The recruited patients visited the Diabetic Center frequently (every 2 months) for general clinical evaluation. All patients were examined by the same endocrinologist and newly diagnosed patients were referred to the related clinics for further assessment of the diabetic complications. Personal and clinical characteristics (Table 3) of type 2 GADA- subgroup were compared with misdiagnosed type 2 GADA+ subgroup (LADA) in terms of gender, age, duration of diabetes (in years), body mass index (BMI), and family history of diabetes. Also, diabetic complications including peripheral neuropathy, retinopathy, cardiovascular disease, and peripheral vascular disease in both subgroups (type 2 GADA- patients versus GADA+ diabetics) were assessed according to the Diabetics Center records. Nephropathy evaluation was done by laboratory tests (urea, creatinine, and Macro- or Micro- proteinuria) and hypertension was considered abnormal if a subject took antihypertensive drugs or had blood pressure >140/90 mmHg. Metabolic syndrome was evaluated for each subject according to the World Health Organization (WHO) 1999 criteria[29].

Biochemical laboratory methods:

After a 12-hour overnight fasting, plasma heparin samples were used for all tests except LDL-C and HBA1c for which we used serum for LDL-C and plasma EDTA for HGBA1c. The amount of the anticouagulants are international standards for 5ml tubes. Samples were drawn after interviewing patients between 8 and 10 am at the diabetic center of Latakia. In addition, a morning midstream urine specimen was collected from every patient for chemical urinalysis (protein, glucose, ketones, and microalbuminuria) according to the pre-analytical notice that was given to each patient previously. The blood and urine analysis were run in the department of Laboratory Medicine at Al-Assad Hospital of Latakia. Glucose, cholesterol (total, High density lipoprotein (HDL-C), and Low density lipoprotein (LDL-C), triglycerides, urea, and creatinine (modified kinetic Jafe' method) were tested by enzymatic methods while HbA1c was analyzed by ion exchange chromatographic method. HDL and LDL cholesterol were precipitated by phosph-otungstate/magnesium and polyvinyl sulp-hate/polyethyleneglycol methods, respe-ctively. Normal and abnormal controls were run with every tested sample for all the above mentioned tests, and all the above mentioned materials were commercially supplied by BioSystems S. A., Spain. Microalbuminuria was determined by turbidimetric latex method (BioSystems S. A.) and albuminuria

levels >20 mg/L were considered microalbuminuria, according to WHO 2002 criteria[45]. Ketones, glucose, and protein in urine were tested using urine strip tests (Analyticon® Biotechnologies AG). Urine controls level 1 and level 2 were applied in each run (DiaSys Diagnostic Systems GmbH). C-peptide (ng/mL) was tested by two-site immunoluminometric assay (DiaSorin S. P. A, Italy).

Determination of GAD65 autoantibodies: Glutamic acid decarboxylase 65 (GAD65) autoantibodies were tested on the serum samples using enzyme immunoassay method and the kits were supplied commercially by Medipan Diagnostica, Germany. The manufacturer's reference value of ≥ 5.0 IU/mL was considered positive with 92.3 % sensitivity and 98.6 % specificity. The commercial assay was calibrated against the WHO reference preparation National Istitute of Biological Standards and Control (NIBSC) 97/550 and the concentration was, therefore, expressed in IU/ml. The threshold for positivity (≥ 5.0 units/mL) was further confirmed in our laboratory as the 96.6th percentile from a healthy control group (n =48) according to WHO criteria; only normal subjects with normal glucose tolerance test were included in this study.

Statistical analysis

The results are statistically expressed as mean ± standard deviation (SD). Differences between GADA- versus GADA+ subgroups were analyzed with Student t-test (continuous variables) and $\chi 2$ test (dichotomous variables). One way ANOVA was used to show the differences of c-peptide and BMI variables according to subgroups of diabetics with GADA- <5 IU/mL (type 2), GADA+ ≤50 IU/mL, or GADA+ >50 IU/mL. Level of significance was 0.05.

Results

This study showed that GADA+ was prevalent in 45 (17.7 %) patients out of 254 type 2 diabetics. In Table 2 the clinical comparison of GADA+ patients (n=45) versus individuals with GADA- (n=209) showed that there were no significant differences with respect to personal, anthropometric and clinical features including gender, age at diagnosis, family history for diabetes, and disease duration with the exception of BMI which was significantly lower in the GADA+ subgroup compared with results of the GADA- subgroup (27.6±4.8 vs. 29.8±5.9; P=0.02). Furthermore, no difference was noticed with respect to the metabolic syndrome and the clinical complications of diabetes in both GADA- and GADA+ subgroups, although the frequency of metabolic syndrome and the family history of diabetes were high (> 50%) in both subgroups, GADA+ and GADA- diabetics (Table 2).

Table 2. Personal and clinical characteristics of patients without Glutamic acid decarboxylase autoantibodies versus those with Glutamic acid decarboxylase autoantibodies diabetics mis-diagnosed as having typen 2 diabetes

Variable	GADA-*	GADA+
	n(209)	n(45)
Gender; F/M (%)	48.8/51.2	55.6/44.4
Age (years)	52.8±9.9	54.0±9.8
Duration of diabetes (years)	8.1±7.1	9.9±6.7
Body mass index (kg/m2)	29.8±5.9	27.6±4.8†
Family History of diabetes (%)	66	51.1
Neuropathy (%)	39.7	44.4
Retinopathy (%)	17.7	15.5
Nephropathy (%)	3.35	2.2
Hypertension (%)	30.6	20
Cardiovascular disease (%)	12	17.7
Peripheral vascular disease (%)	3.35	0
Metabolic syndrome (%)	64.6	62.2

*Glutamic acid decarboxylase autoantibodies, continuous variables are presented with mean±SD, †P=0.02

Comparing blood and urinary laboratory tests (table 3) showed significant laboratory differences in terms of the glycemic control variables such as FBS, glucosuria, and

ketonuria between GADA- and GADA+ subgroups. The FBS was significantly higher in the GADA+ diabetics (221.6±77.9) than in GADA- subgroup (182±66.7), (P=0.001). However, there no differences were observed in HBA1c, c-peptide, lipids (total cholesterol, triglycerides, HDL-C, LDL-C) in male and female with respect to the presence or absence of GAD autoantibodies. Urinary tests showed that glucosuria and ketonuria were significantly different between GADA+ and GADA- subgroups with P=0.025 and P<0.0001, respectively.

Table 3. Laboratory results of patients without Glutamic acid decarboxylase autoantibodies versus those with glutamic acid decarboxylase autoantibodies diabetics misdiagnosed as having type 2 diabetes

Variable	GADA^{-}* n (209)	GADA^{+} n (45)	P value
Fasting blood glucose (mg/dL)	182±66.7	221.6±77.9	0.001
HBA1c (%)	7.4±1.3	7.7±1.3	ns†
C-peptide (ng/mL)	1.7±1.1	1.6±0.9	ns
Total Cholesterol (mg/dL)			
females	223±49.3	228.3±51.7	ns
males	205.4±43.9	203.8±41.3	ns
Triglycerides(mg/dL)			
female	193.9±97.2	178.6±112	ns
male	181.7±123.3	185.1±122.1	ns
High density lipopro1tein cholesterol(mg/dL)			
female	38.1±11.2	42.6±16.21	ns
male	31.2±8.9	29.6±8.4	ns
Low density lipoprotein cholesterol (mg/dL)			
female	137.4±34.1	150.5±41.8	ns
male	134.1±39.7	136.1±36.6	ns
Urine (% positivity)			
Protein	8.6	8.9	ns
Glucose	41.6	60	0.025
Ketones	3.8	22.2	<0.0001

* Glutamic acid decarboxylase autoantibodies; † non significant; continus variables are presented with mean±SD

Based on GADA levels, the studied sample was further subdivided into tertiles of type 2 ,GADA- <5 IU/mL, GADA+ ≤50 IU/mL, and GADA+ >50 IU/mL. As seen in figure 1, there were significantly lower c-peptide concentrations between the

subgroups (P =0.002), diabetic patients with GADA+ >50 IU/mL had significantly lower c-peptide concentrations in comparison to those detected in the type 2 and GADA+ ≤50 subgroups.

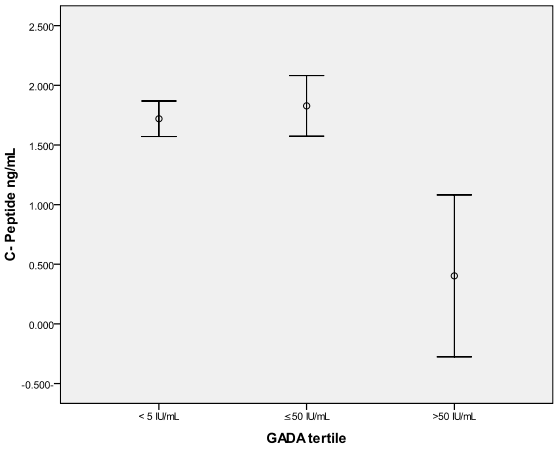

Fig. 1. C-peptide concentrations (ng/mL) in tertiles of diabetic patients with type 2, GADA+ ≤50 IU/mL, and GADA+ >50 IU/mL (CI 95%).

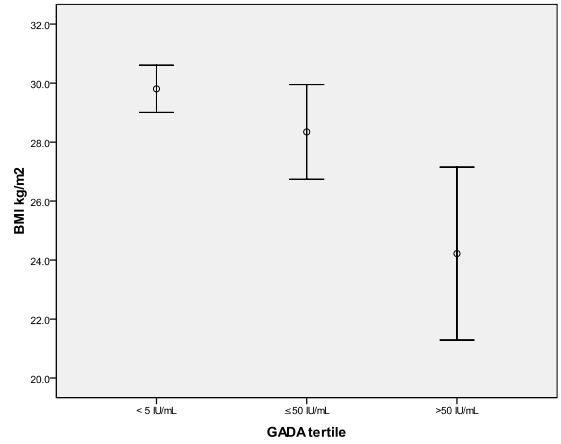

Fig. 2. Body mass index (kg/m2) values in tertiles of diabetics with type 2, GADA+ ≤50 IU/ml, and GADA+ >50 IU/mL (CI 95%)

Also, as seen in figure 2, BMI in the subgroup of GADA+ >50 IU/mL was significantly lower than that found in type 2 patients (p=0.012). However, no significant differences were detected between GADA+ ≤50 IU/ml subgroup and both of type 2 and GADA+ >50 IU/ml subgroups.

Discussion

Based on GADA positivity, the findings of this study showed that 17.7% of type 2 diabetic patients, aged 35 to 75 years, were diagnosed as having LADA. The prevalence of LADA in Latakia was higher than that observed by extensive studies in Europe and North America that reported LADA in less than 10% of the type 2 diabetics studied[31, 41]. Moreover, the classification of LADA is further emphasized in this study by islet cell autoantibody screening in agreement with WHO and American Diabetic Association reports[28,29] rather than the clinical judgment in the subgroup of misdiagnosed type 2 diabetics.

In LADA subjects, the clinical presentation ranged across the classical features of type 1 and type 2 diabetes, in agreement with other studies[17,18] in relation with the GADA titers. Regardless of BMI, the clinical picture in our cohort illustrated that GADA+ patients (n=45) have similar clinical features as classical GADA- type 2 diabetes, with no significant differences in terms of gender, age at diagnosis, family history for diabetes, and disease duration. Isomaa and his colleagues[12] reported no significant differences in terms of the clinical complications of diabetes between LADA and type 2 subjects. Different studies reported that the metabolic syndrome was significantly different in LADA with type 2 diabetics regardless of GADA titers[12-13,18-19, 27,38,41,46]. Our results showed no significant differences between LADA patients and GADA- type 2 diabetic patients; nonetheless, more than 50% of patients in both subgroups have metabolic syndrome parameters. However, the majority of our cohort with high GADA titers (>50 IU/mL) had lower frequencies of metabolic syndrome components, in agreement with data reported by other studies[12-13, 18-19, 27].

In agreement with several previous studies[3,13,17-18,22, 27, 31], the findings concerning BMI presented significantly lower levels in LADA versus type 2 diabetic subjects, but in both subgroups patients were overweight or obese, which could be related to the high prevalence of obesity worldwide[47]. Fourlanos et al showed that using BMI as a single variable to identify LADA resulted in 30% sensitivity, since LADA patients were overweight or obese[48]. However, patients with high GADA levels (> 50 IU/ml) were found to present with normal or lean weight, in comparison with type 2 diabetics similar to those seen in classical type 1 diabetes[22,17,27, 42,49].

In comparison with GADA- type 2 subjects, LADA patients metabolically presented with poorly controlled glycemia, estimated by significantly observed high levels of FBS, glucosuria, and ketonuria; some of these were treated with oral hypoglycemic drugs, especially those who showed advanced stages of β-cell failure. Many researchers agree on commencing insulin early with GADA+ subjects[13,19,31,39, 42]. Early diagnosis of LADA based on detecting GADA and c-peptide will help to preserve insulin secretory capacity by β-cell. Turner and his colleagues noticed that almost 50% of LADA patients required insulin after 6 years[31] while others showed that better glycemic control was accomplished with the insulinization of GADA+ diabetic subjects between from 2 to 4 years after diagnosis[50, 51]. Based on c-peptide in patients with GADA+ >50 IU/mL, the data presents significant low levels of c-peptide and shows complete deterioration of islet β-cell in comparison with type 2 and GADA+ ≤50 IU/ml subgroups in which both showed relatvely more preserved β-cell funtion.

In conclusion, it seems that LADA is a prevalent public health problem in Syria and it has to be considered at the national level in terms of islet β-cell autoimmune screening. LADA patients showed similar laboratory and clinical features as type 2 diabetics with the exception of low BMI levels and poor glycemic control.

Acknowledgements

Dr. Nada Shiek Yousef and all the academic staff at the Diabetic Center of National Health Services in Latakia for their excellent technical assistance; Mrs. Roula Alkattib and Mrs. Kafa Ahmad for their laboratory technical assistance at Al-Assad Teaching Hospital in Latakia; Dr Imad Abo Assali who has kindly contributed to my study with c-peptide controls level 1 and 2, and Dr. Mouhannad Hassan and the Faculty of Medicine at Tishreen University for its sponsorship.

References

1. Irvine WJ, McCallum CJ, Gray RS, Duncan LJ. Clinical and pathogenic significance of pancreatic-islet-cell antibodies in diabetics treated with oral hypoglycemic agents. Lancet 1977: 1025-7.
2. Groop LC, Bottazzo GF, Doniac D. Islet cell antibodies identify latent type 1 diabetes in patients aged 35–75 years at diagnosis. Diabetes 1986; 35: 237-41.
3. Tuomi T, Groop LC, Zimmet PZ, Rowley MJ, Knowles W, Mackay IR. Antibodies to glutamic acid decarboxylase reveal latent autoimmune diabetes mellitus in adults with a non-insulin-dependent onset of disease. Diabetes 1993; 42: 359-62.
4. Baekkeskov S, Aanstoot HJ, Christgau S, Reetz A, Solimena M, Cascalho M, et al. Identification of the 64K autoantigen in insulin-dependent diabetes as the GABA-synthesizing enzyme glutamic acid decarboxylase. Nature 1990; 347: 151-6.
5. Kobayashi T, Sawano S, Sugimoto T, Itoh T, Kosaka K. Risk factors of slowly progressive insulin-dependent (type I) diabetes mellitus. J Steroid Biochem 1984; 20: 1488.
6. No authors listed. Insulin-dependent? Lancet 1985; 2: 809-10.
7. Harris M, Zimmet P. Classification of diabetes mellitus and other categories of glucose intolerance. In: Alberti K, De Fronzo R, Keen H, Zimmet P, editors. International Textbook of Diabetes Mellitus. Chichester: John Wiley & Sons Ltd, 1992. p. 3-18.

8. Björk E, Berne C, Kämpe O, Wibell L, Oskarsson P, Karlsson FA. Diazoxide treatment at onset preserves residual insulin secretion in adults with autoimmune diabetes. Diabetes 1996; 45: 1427-30.
9. Lohmann T, Sessler J, Verlohren HJ, Schröder S, Rötger J, Dãhn K, et al. Distinct genetic and immunological features in patients with onset of IDDM before and after age 40. Diabetes Care 1997; 20: 524-9.
10. Seissler J, de Sonnaville JJ, Morgenthaler NG, Steinbrenner H, Glawe D, Khoo-Morgenthaler UY, et al. Immunological heterogeneity in type I diabetes: presence of distinct autoantibody patterns in patients with acute onset and slowly progressive disease. Diabetologia 1998; 41: 891-7.
11. Juneja R, Palmer JP. Type 1 1/2 diabetes: myth or reality? Autoimmunity 1999; 29: 65-83.
12. Isomaa B, Almgren P, Henricsson M, Taskinen MR, Tuomi T, Groop L, et al. Chronic complications in patients with slowly progressing autoimmune type 1 diabetes (LADA). Diabetes Care 1999; 22: 1347-53.
13. Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, et al. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes 1999; 48: 150 -7.
14. Zimmet P, Turner R, Mc Carty D, Rowley M, Mackay I. Crucial points at diagnosis: type 2 diabetes or slow type 1 diabetes. Diabetes Care 1999; 22: 59-64.
15. Carlsson A, Sundkvist G, Groop L, Tuomi T. Insulin and glucagon secretion in patients with slowly progressing autoimmune diabetes (LADA). J Clin Endocrinol Metab 2000; 85:76–80.
16. Pozzilli P, Di Mario U. Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabetes of the adult): definition, characterization, and potential prevention. Diabetes Care 2001; 24: 1460-7.
17. Lohmann T, Kellner K, Verlohren HJ, Krug J, Steindorf J, Scherbaum WA, et al. Titre and combination of ICA and autoantibodies to glutamic acid decarboxylase discriminate two clinically distinct types of latent autoimmune diabetes in adults (LADA). Diabetologia 2001; 44: 1005-10.
18. Li X, Zhou ZG, Huang G, Yan X, Yang L, Chen XY, et al. Optimal Cutoff Point of Glutamate Decarboxylase Antibody Titers in Differentiating Two Subtypes of Adult-Onset Latent Autoimmune Diabetes. Ann N Y Acad Sci 2004; 1037: 122-6.
19. Borg H, Gottsäter A, Landin-Olsson M, Fernlund P, Sundkvist G. High levels of antigen-specific islet antibodies predict future beta-cell failure in patients with onset of diabetes in adult age. J Clin Endocrinol Metab 2001; 86: 3032-8.
20. Schernthaner G, Hink S, Kopp HP, Muzyka B, Streit G, Kroiss A. Progress in the characterization of slowly progressive autoimmune diabetes in adult patients (LADA or type 1.5 diabetes).Exp Clin Endocrinol Diabetes 2001; 109 Suppl 2: S94-108.
21. Palmer JP, Hirsch IB. What's in a name: latent autoimmune diabetes of adults, type 1.5, adult-onset, and type 1 diabetes. Diabetes Care 2003; 26: 536-8.
22. Hosszufalusi N, Vatay A, Rajczy K, Prohaszka Z, Pozsonyi E, Horvath L, et al. 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.
23. Behme MT, Dupre J, Harris SB, Hramiak IM, Mahon JL. Insulin resistance in latent autoimmune diabetes of adulthood. Ann N Y Acad Sci 2003; 1005: 374-7.
24. Barinas-Mitchell E, Pietropaolo S, Zhang YJ, Henderson T, Trucco M, Kuller LH, et al. Islet cell autoimmunity in a triethnic adult population of the Third National Health and Nutrition Examination Survey. Diabetes 2004; 53: 1293-302.
25. Stenström G, Gottsäter A, Bakhtadze E, Berger B, Sundkvist G. Latent autoimmune diabetes in adults: definition, prevalence, beta-cell function, and treatment. Diabetes 2005; 54: 68-72.
26. Matsumoto M, Satou S. Small doses of insulin may prevent the decrease of intrinsic insulin secretion in anti-GAD, ICA and IA-2 antibody-positive slowly progressive type 1 diabetes. Journal of the Japan Diabetes Society 2005; 48: 257-61(Japanese).
27. Buzzetti R, Di Pietro S, Giaccari A, Petrone A, Locatelli M, Suraci C, et al. Non Insulin Requiring Autoimmune Diabetes Study Group.. High Titer of Autoantibodies to GAD Identifies a Specific Phenotype of Adult- Onset Autoimmune Diabetes. Diabetes Care 2007; 30: 932-8.
28. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997; 20: 1183-97.
29. World Health Organization, editor. Report of a WHO Consultation. Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. World Health Organization, Department of Noncommunicable Disease Surveillance: Geneva; 1999.
30. Rosário PW, Reis JS, Amim R, Fagundes TA, Calsolari MR, Silva SC, et al. Comparison of Clinical and Laboratory Characteristics Between Adult-Onset Type 1 Diabetes and Latent Autoimmune Diabetes in Adults. Diabetes Care 2005; 28: 1803-4.
31. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, et al; UK Prospective Diabetes

Study (UKPDS) Group. cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. Lancet 1997; 350: 1288-93.
32. Horton V, Stratton I, Bottazzo GF, Shattock M, Mackay I, Zimmet P, et al. Genetic heterogeneity of autoimmune diabetes: age of presentation in adults is influenced by HLA DRB1 and DQB1 genotypes (UKPDS 43). UK Prospective Diabetes Study (UKPDS) Group. Diabetologia 1999; 42: 608-16.
33. Palmer JP, Hampe CS, Chiu H, Goel A, Brooks-Worrell BM. Is latent autoimmune diabetes in adults distinct from type 1 diabetes or just type 1 diabetes at an older age? Diabetes 2005; 54: 62-7.
34. Fourlanos S, Dotta F, Greenbaum CJ, Palmer JP, Rolandsson O, Colman PG, et al. Latent autoimmune diabetes in adults (LADA) should be less latent. Diabetologia 2005; 48: 2206-12.
35. Gale EA. Latent autoimmune diabetes in adults: a guide for the perplexed. Diabetologia 2005; 48: 2195-9.
36. Leslie RD, Williams R, Pozzilli P. Clinical review: Type 1 diabetes and latent autoimmune diabetes in adults: one end of the rainbow. J Clin Endocrinol Metab 2006; 91: 1654-9.
37. Groop L, Tuomi T, Rowley M, Zimmet P, Mackay IR. Zimmet. Latent autoimmune diabetes in adults (LADA)- more than a name. Diabetologia 2006; 49: 1996-8.
38. Römkens 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.
39. Takeda H, Kawasaki E, Shimizu I, Konoue E, Fujiyama M, Murao S, 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.
40. Borg H, Gottsater A, Fernlund P, Sundkvist G. A 12-year prospective study of the relationship between islet antibodies and β-cell function at and after diagnosis in patients with adult-onset diabetes. Diabetes 2002; 51: 1754-62.
41. Zinman B, Kahn SE, Haffner SM, O'Neill MC, Heise MA, Freed MI; ADOPT Study Group. Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. Diabetes 2004; 53: 3193-200.
42. Rosário PW, Reis JS, Fagundes TA, Calsolari MR, Amim R, Silva SC, et al. Latent Autoimmune Diabetes in Adults (LADA): Usefulness of Anti-GAD Antibody Titers and Benefit of Early Insulinization. Arq Bras Endocrinol Metabol 2007; 51: 52-8.
43. Maruyama T, Tanaka S, Shimada A, Funae O, Kasuga A, Kanatsuka A, et al. Insulin intervention in slowly progressive insulin-dependent (type 1) diabetes mellitus. J Clin Endocrinol Metab 2008; 93: 2115-21.
44. Palmer JP, Fleming GA, Greenbaum CJ, Herold KC, Jansa LD, Kolb H, et al. C-peptide Is the Appropriate Outcome Measure for Type 1 Diabetes Clinical Trials to Preserve {beta}-Cell Function: Report of an ADA Workshop. Diabetes 2004; 53: 250-64.
45. Reinauer H, Home PD, Kanagasabapathy AS, Heuck CC; World Health Organization, editors. Laboratory Diagnosis and Monitoring of Diabetes Mellitus. World Health Organization: Geneva; 2002.
46. Hawa MI, Thivolet C, Mauricio D, Alemanno I, Cipponeri E, Collier D, et al; Action LADA Group. Metabolic syndrome and autoimmune diabetes: action LADA 3. Diabetes Care 2009; 32: 160-4.
47. Abelson P, Kennedy D. The obesity epidemic. Science 2004; 304: 1413.
48. Fourlanos S, Perry C, Stein MS, Stankovich J, Harrison LC, Colman PG. A clinical screening tool identifies autoimmune diabetes in adults. Diabetes Care 2006; 29: 970-5.
49. Maruyama T, Oak S, Shimada A, Hampe CS. GAD65 autoantibody responses in Japanese latent autoimmune diabetes in adult patients. Diabetes Care 2008; 31: 1602-7.
50. Alvarsson M, Sundkvist G, Lager I, Henricsson M, Berntorp K, Fernqvist- Forbes E, et al. Beneficial effects of insulin versus sulphonylurea on insulin secretion and metabolic control in recently diagnosed type 2 diabetic patients. Diabetes Care 2003; 26: 2231-7.
51. Alvarsson M, Sundkvist G, Lager I, Henricsson M, Berntorp K, Fernqvist-Forbes E, et al. Effects of insulin vs. glibenclamide in recently diagnosed type 2 diabetic patients. Diabetologia 2004; 47: A56 (Abstract).