VIA MEDICA
RESEARCH PAPER
ISSN 2450–7458
e-ISSN 2450–8187

Mahdieh Mehranpoor, Malihe Mohammadi, Milad Lagzian
Department of Biology, Faculty of Science, University of Sistan and Baluchestan, Zahedan, Iran

Prevalence and Metabolic Characteristics of Patients with Latent Autoimmune Diabetes in Adults: A Cross-Sectional Study

ABSTRACT

Objective: To evaluate the frequency of autoantibodies to glutamic acid decarboxylase-65 (GADA) and tyrosine phosphatase (IA-2A) in adult patients diagnosed with type 2 diabetes (T2D) and its associated characteristics, in particular those that related to metabolic syndrome.

Materials and methods: In this cross-sectional study, autoantibodies to GADA and IA-2A were measured in 384 adult patients with T2D. Assays for autoantibodies were conducted using ELISA kits. The socio-demographic, clinical, and metabolic characteristics of islet autoantibody-positive and negative participants were then compared. SPSS software was used for data analysis and $p < 0.05$ was selected as a significant level.

Results: Thirty two (8.3%) participants were positive for at least one islet autoantibody. The prevalence of GADA and IA-2A were reported 6.3% and 2.3% respectively, and one patient had both antibodies together. Autoantibody-positive patients were significantly younger ($p < 0.001$), had lower median age at diagnosis ($p = 0.010$), mean body mass index (BMI) ($p = 0.004$), waist circumference (WC) ($p = 0.033$), total cholesterol ($p = 0.020$), triglycerides ($p = 0.041$), C-peptide ($p < 0.001$) and prevalence of metabolic syndrome ($p < 0.001$) and higher fasting blood glucose (FBG) ($p = 0.046$), glycated hemoglobin (HbA1c) levels ($p = 0.035$) and need for insulin therapy ($p < 0.001$) than patients with T2D. Sex distribution, blood pressure levels and family history of diabetes were similar in the two groups.

Conclusions: The prevalence of LADA in the studied population was 8.3%. LADA should be suspected in leaner patients with T2D with worse glycemic control, low C-peptide level and without metabolic syndrome. Antibody screening is recommended to discriminate of LADA and to help better control of glycemic profile.
(Clin Diabetol 2023; 12; 6: 362–369)

Keywords: latent autoimmune diabetes in adults, diabetes mellitus, glutamic acid decarboxylase autoantibody, protein tyrosine phosphatase autoantibody, metabolic syndrome

Introduction

Latent autoimmune diabetes in adults (LADA) is a heterogeneous disease and shares clinical, metabolic and phenotypic features with both type 2 (T2D) and type 1 diabetes (T1D) [1]. LADA characterized by the presence of one or more diabetes-associated autoantibodies, including autoantibodies against glutamic acid decarboxylase (GAD-65), protein tyrosine phosphatase IA-2 (IA-2A), insulin autoantibodies (IAA) and zinc transporter 8 (ZnT8) [2]. Other criteria for diagnosing this complication vary between different studies, mainly according to age at onset and time to insulin initiation [3, 4]. Among various islet cell autoantibodies, GADA represent the most sensitive autoantibody marker with highest prevalence in autoimmune diabetes [2, 4],

Address for correspondence:
Malihe Mohammadi
Phone/Fax: +98 54 33446565
e-mail: mmohammadi@science.usb.ac.ir
Clinical Diabetology 2023, 12; 6: 362–369
DOI: 10.5603/cd.97700
Received: 3.10.2023 Accepted: 6.11.2023
Early publication date: 7.12.2023

This article is available in open access under Creative Common Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, allowing to download articles and share them with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially.

followed by IA-2A which is almost always associated with GADA [4]. In addition to the presence of GADA being recognized as a good predictive marker for insulin dependency among adult patients with T2D [5], IA-2A has also been found to be a strong predictor [6, 7]. Insulin autoantibodies and ZnT8 have also been shown as important autoimmune markers for autoimmune diabetes. IAA occurs in very young children and in some LADA patients [8] and ZnT8, is a pancreatic β-cell secretory granule membrane protein which complement the antibodies created against insulin (IAA), GADA and IA-2A [4]. Patients with latent autoimmune diabetes generally have younger age of onset, lower body mass index (BMI), worse glycemic control and lower prevalence of metabolic syndrome than those with T2D [9, 10] and also are at high risk of progression to insulin dependence [11, 12]. However, some previous studies have shown that phenotypic characteristics and even insulin resistance cannot distinguish LADA patients from T2D [13]. LADA accounts for 4–14% of all patients with diabetes [2]. It is estimated that 7–15% all cases of diabetes are initially misdiagnosed as the wrong subtype of diabetes [1]. This shows the importance of measuring autoantibodies in order to identify autoimmune diabetes [10].

The purpose of the study was to investigate the prevalence of GADA and IA-2A among patients who were initially diagnosed with T2D and to further characterize LADA in Iranian subjects in terms of clinical and metabolic characteristics. The results were compared between participants with LADA to patients with T2D.

Materials and methods

Study participants

This was a cross-sectional study that included 384 patients with T2D over 30 years old, living in urban or rural areas of Birjand city in South Khorasan province, who attended the Imam Reza Hospital and the health centers of this city from October 2019 to October 2020. Diagnosis of T2D in participants were enrolled according to the criteria of the American Diabetes Association [14]. People who had the following characteristics were considered as LADA based on the criteria of Immunology of Diabetes Society: 1) age > 30 years at diagnosis, 2) no need for using insulin for at least 6 months after the initial diagnosis of T2D, 3) and presence of diabetes-associated autoantibodies [15]. Exclusion criteria were age lower than 30 years old, having T1D, showing ketosis at onset of diabetes, acute or chronic inflammatory disease, hepatic diseases and pregnancy. All patients were informed of the nature of the study and gave their written consent. The study protocol was approved by the Local Ethics Committee at each center.

Socio-demographic, clinical, and biophysical characteristics

A full and accurate demographic, biochemical and current medication regimen data were recorded by standardized questionnaire(s) from each participants, and they were specifically asked about onset of disease, history of diabetes in their families and any other underlying disease, such as autoimmune diseases or cancer. Then anthropometric data [weight, height, BMI and waist circumference (WC)] were measured. Height and weight measurement was performed at standard conditions and BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). The patients were categorized as underweight, normal, overweight or obese when their BMI was < 18.5 kg/m^2, 18.5–24.99 kg/m^2, 25.0–29.99 kg/m^2 and ≥ 30 kg/m^2, respectively. Waist circumference was also measured in centimeters, as the smallest horizontal girth between the costal margins and the iliac crest at minimal respiration. The volunteers' blood pressure was measured by a trained physician according to the standard method mentioned previously [16].

Diagnostic criteria for metabolic syndrome

Metabolic syndrome was defined using advised National Cholesterol Education Program — Adult Treatment Panel III criteria, involving achievement of three or more of the following: 1) waist circumference ≥ 90 cm (Asian male) or ≥ 80 cm (Asian female); 2) triglyceride ≥ 1.7 mmol/L (150 mg/dL), 3) HDL cholesterol < 1.04 mmol/L (40 mg/dL) (male) or < 1.30 mmol/L (50 mg/dL) (female), 4) systolic/diastolic blood pressure ≥ 130/85 mmHg and 5) fasting plasma glucose (FBG) ≥ 5.6 mmol/L (100 mg/dL) [17].

Laboratory evaluations

For clinical trials, 10 mL of blood sample was taken from each patient after a minimum 10–12 hours of fasting. The blood samples were collected in cold biochemistry tubes (4°C) at each study site and then transported to the clinical chemistry laboratory. On arrival at the clinical chemistry laboratory, the samples were aliquoted following centrifuge and stored at –20°C until further assessment.

FBG was determined using GOD-POD calorimetric method and glycated hemoglobin (HbA1c) measurement was performed according to the commercial kit protocol (Pars Azmun Co., Iran). Total blood cholesterols and triglycerides (TG) were measured using enzymatic methods (Pars Azmun Co., Iran). Fasting C-peptide level was measured using an ELISA-based commercial kit (Diametra Co., Italy; cat: DKO-077), with an analytical sensitivity of 0.2–10.0 ng/mL. The details of these

Table 1. Clinical and Metabolic Characteristics of Patients with Type 2 diabetes and LADA, mean (± SD) or N (%)

Characteristics	Type 2 diabetes	LADA	P-value
Number (n,%)	352 (91.7%)	32 (8.3%)	
Gender			
Females (n, %)	200 (56.8%)	21 (65.6%)	
Males (n, %)	152 (43.2%)	11 (34.4%)	0.335
Age range [years]	30-70	33-60	0.000
Mean age [years]	53.25 ± 8.04	42.28 ± 6.82	< 0.001
Age at diabetes diagnosis, median [years]	46.53 ± 5.76	39.90 ± 3.22	0.010
Median of disease duration [years]	8.45 ± 4.83	3.12 ± 1.22	0.025
Family history of diabetes (n, %)†	195 (55.4%)	17 (53.1%)	0.804
BMI [kg/m^2]	27.17 ± 3.28	25.48 ± 2.88	0.004
Waist circumference [cm]	92.28 ± 13.66	90.31± 12.84	0.033
Hypertension (n, %)	136 (38.6%)	15 (46.9%)	0.361
Total cholesterol [mg/dL]	190.84 ± 8.75	182.75 ± 11.15	0.020
Triglycerides [mg/dL]	155.24 ± 56.32	139.78 ± 32.33	0.041
FBG [mg/dL]	150.59 ± 12.39	154.97 ± 9.19	0.046
HbA1c [%]	7.87 ± 1.88	9.13 ± 1.72	0.035
C-peptide levels [ng/mL]	1.35 ± 0.45	0.69 ± 0.28	< 0.001
Metabolic syndrome (n, %)	249 (70.7%)	13 (40.6%)	< 0.001
Insulin treatment			
Insulin treatment alone (n, %)	41 (11.7%)	15 (46.9%)	0.023
Insulin treatment with OHA (n, %)	62 (17.6%)	6 (18.7%)	0.073
Insulin treatment alone or with OHA (n, %)	103 (29.3%)	21 (65.6%)	< 0.001

†Is defined as family history of any types of diabetes among first or second-degree relatives
BMI — body mass index; FBG — fasting blood glucose; HbA1c — glycated hemoglobin; LADA —latent autoimmune diabetes in adults; OHA — oral hypoglycemic agents; SD — standard deviation

methods have already been mentioned in previous study [18].

GAD antibodies were determined in all patients using Isletest GAD diagnostic kit (Diametra Co., Italy; cat:DKO-082) with 88.6% sensitivity and 92.3% specificity. Assay for IA-2A was conducted using an ELISA kit (Diametra Co., Italy; cat:DKO-084), with 65.3% sensitivity and 100% specificity. Double measurement was performed only if the result was positive. Based on laboratory results participants who tested positive and negative for the GADA and IA-2A were classified as having LADA and classic T2D, respectively.

Statistical analysis

Statistical analyses were performed using SPSS Version 23 for windows. Data was represented as average ± ± standard deviation (SD) and percentage. The normality of data was checked using the Kolmogorov-Smirnov test. Statistical differences between groups were determined by an independent sample t-test if the data were normally distributed, while a Mann-Whitney U test was used if the data were not normally distributed and p-value < 0.05 was considered as statistically significant.

Ethical approval

This study was carried out in accordance with the Helsinki Declaration principles and approved by the Sistan and Baluchestan University ethics committee, with ethics code of IR.USB. REC.1398.015.

Results

The clinical characteristics of the patients with T2D and LADA are described in Table 1. Among 384 patients participating in this project, 221 (57.6%) women and 163 (42.4%) men were present. The mean ± SD age of the participants was 52.33 ± 8.51 years old. Among all patients diagnosed with T2D, 32 (8.3%) patients had at least one islet autoantibody. Overall GADA and IA-2A were detected in 24 (6.3%) and 9 (2.3%) patients with T2D respectively and only in a 39-years-old men, both autoantibodies to GAD and IA-2 were detected. Among LADA patients, 21 person (65.6%) were women and 11 person (34.4%) were men (p = 0.335). The differences between age at diagnosis of autoimmune subjects and non-autoimmune subjects were statistically significant (p = 0.010) and non-autoimmune patients were older than autoimmune patients (p = 0.001). The

Table 2. Clinical Characteristics of Study Population Based on Type and Number of Positive Autoantibodies, mean (± SD) or N (%)

Characteristics	Single antibody (n = 31)		*P* value	Multiple antibody (n = 1)
	GADA	IA-2A		
Number	23 (71.9 %)*	8 (25.0 %)*		1 (3.1 %)*
Gender				
Females (n, %)	16 (69.6 %)	5 (62.5 %)		0
Males (n, %)	7 (30.4 %)	3 (37.5 %)	0.350	1
Mean age [years]	42.17 ± 7.51	43.00 ± 5.73	0.308	39
Family history of diabetes (n, %)†	12 (52.2 %)	4 (50.0 %)	0.631	yes
BMI [kg/m^2]	25.56 ± 2.88	25.49 ± 3.16	0.804	23.60
Waist circumference [cm]	90.20 ± 10.88	90.01± 11.65	0.732	86.00
Hypertension (n, %)	10 (43.5 %)	4 (50.0 %)	0.530	yes
Total cholesterol [mg/dL]	182.70 ± 9.59	184.63 ± 5.42	0.571	177
Triglycerides [mg/dL]	141.88±37.12	136.45±30.68	0.602	138
FBG [mg/dL]	154.57 ± 10.42	156.75 ± 5.04	0.946	150
HbA1c [%]	9.04±1.67	8.98±1.55	0.061	9.37
C-peptide levels [ng/mL]	0.66 ± 0.29	0.79 ± 0.23	0.113	0.33
Insulin treatment alone or with OHA (n, %)	15 (65.2 %)	5 (62.5 %)	0.756	1

*percentage among LADA patients; †Is defined as family history of any types of diabetes among first or second-degree relatives
BMI — body mass index; FBG — fasting blood glucose; HbA1c — glycated hemoglobin; LADA —latent autoimmune diabetes in adults; OHA — oral hypoglycemic agents; SD — standard deviation

median disease duration was longer in patients with T2D than in LADA patients (p = 0.025). Also the difference between the mean age of GADA positive and IA-2A positive patients was not statistically significant (p = 0.308). The clinical characteristics of study population based on type and number of positive autoantibodies are summarized in Table 2.

Clinical and metabolic characteristics of LADA

The difference in mean BMI values between patients with LADA and T2D (25.48 ± 2.88 kg/m^2 and 27.17 ± ± 3.28 kg/m^2, respectively) was statistically significant (p = 0.004). Also the waist circumference of LADA patients was significantly lower than that of patients with T2D (p = 0.033). The difference between the mean BMI and waist circumference between GADA positive and IA-2A positive patients was not significant (p = 0.804 and p = 0.732 respectively). A family history of diabetes was reported in 53.1% of LADA patient and 55.4% of patients with T2D (p = 0.804). This indicates no significant correlation between family history of diabetes and having GAD or IA-2 antibodies.

The investigation of metabolic characteristics showed that the mean total blood cholesterol and triglycerides level in autoimmune subjects was statistically lower than in those with T2D (p = 0.020 and p = 0.041, respectively), but the prevalence of hypertension between the two groups is not statistically significant (p = 0.361). The prevalence of the metabolic syndrome was significantly lower in the LADA patients (40.6%) than in patients with T2D (70.7%; p < 0.001). In terms of glycemic control, the mean FBG level and HbA1c concentrations were significantly higher in LADA patients than in patients with T2D (p = 0.046 and p = 0.035 for FBG and HbA1c, respectively).

The mean C-peptide level of autoantibody positive volunteers was significantly lower than that in T2D (p < 0.001), but no significant difference was observed between the groups with GADA and IA-2A in mean C-peptide level (p = 0.113).

There was a significant difference between LADA patients and patients with T2D in insulin treatment alone or in combination with other oral hypoglycemic agents (p < 0.001). Also a case who had both GADA and IA-2A received insulin treatment in combination with oral medications. The type of treatment did not show a significant difference between the groups with GADA and IA-2A (p = 0.756).

Discussion

Prevalence

Among 384 patients diagnosed with T2D, 32 patients (8.3%) had positive autoantibodies. Similarly, Szepietowska et al. [19] found the prevalence of autoantibodies in T2D as 8.9%. Previously, the prevalences of LADA in Tianjin in China [20] and in Austria [5] were reported at 9.2% and 9.7%, respectively, which are

nearly in the range reported in this study. However, it is higher than reports from NIRAD Study (4.5%) [21], ADOPT study in North America and in Europe (4.2%) [22] and a study conducted in the UAE (2.6%) [23]. Also the prevalence rate of LADA in this study is lower than the studies that have been conducted in Iran so far [16, 24, 25], which can be a confirmation that even the prevalence of LADA can be different in different regions of each country [17]. In this study GADA were detected in 6.3% patients and IA-2A in 2.3% patients with T2D. Previously Zhou Z. et al. [17] and Zhou J. et al. [26] have reported that the prevalence of GADA in Chinese population was 5.9% and 6.0%, respectively, which is close to the results of the current study. However, various studies have reported the range of GADA to vary between 1.5% and 21% [27–29]. The prevalence of IA-2A in China was 2.4%, which is consistent with the rate obtained in the current study [26], but the prevalence of IA-2A in NIRAD Study and in the UAE was reported to be 0.9%, which is lower than the current study [21, 23]. The main reasons for the difference in the reported rate is due to the racial and ethnic differences and differences in the study design (the selected age range, the number of autoantibodies measured and assay methodology of antibodies) and size of the study population [30, 31].

Baseline characteristics

Compared to patients with T2D, LADA patients showed similar sex distribution, suggesting that there is no gender preference for LADA, which is consistent with the results of the earlier studies [32, 33]. Nevertheless, the results of the two separate studies illustrated that the women are at a higher risk of developing LADA [20, 34], but in some other studies, the prevalence of autoimmune diabetes in men was reported to be higher than in women [35, 36]. The reason for these differences can also be related to demographic characteristics and genetic diversity of populations [27]. The mean age of LADA patients was significantly lower than patients with T2D, which is consistent with the results of previous studies [21, 35]. However, in some other studies, no difference has been reported between the two groups in terms of mean age [10, 24, 27]. Also, the difference in the age at diagnosis between the two mentioned groups was significant, which was consistent with earlier studies [7, 9]. A possible reason could be that β-cell function declines faster in very young patients compared to adolescents and adults. Also, genetic factors have been reported as determinants of age of onset in LADA [3].

The proportions of patients with a family history of diabetes were similar between T2D and LADA patients, which is in agreement with previous studies [17, 27, 37]. However, in some other studies, a significant relationship between family history of diabetes and LADA has been reported [20, 25]. The possible reason for the differences is due to the difference in heredity pattern and racial differences [35]. Both BMI and WC of patients with autoimmune diabetes is significantly lower than T2D, which is supported by earlier reports [3, 15, 19]. However, another study showed that there is no significant difference between MBI and WC between the two considered groups [27]. Also mean BMI values were similar in the GADA and IA-2A positive patients, which is consistent with the results of Maddaloni et al. [23]. It should be noted that the IA-2A positivity is associated with a clinical phenotype more similar to classic T2D and IA-2A is the only autoantibody that showed increased frequency with increasing BMI in patients with T2D [23, 30], but in this study, probably due to the small population studied and the small number of positive IA-2A people, this difference with GADA positive patients was not observed.

Metabolic control and diabetes complications

The result showed that the prevalence of hypertension was similar between patients with T2D and LADA, which is supported by previous studies [22, 24, 29], but some studies have shown that the prevalence of hypertension in patients with T2D is higher than LADA patients [10, 25, 37]. Our data demonstrated that although metabolic syndrome is relatively common in autoimmune diabetes, it is significantly lower than in patient with T2D, which is in agreement with previous studies [3, 9, 17, 22] and is in concordance with observed lower WC, total cholesterol and triglycerides level and high FBG level of LADA patients to T2D subjects. Previously, the UKPDS 70 study reported that LADA patients had a higher FBG, lower total cholesterol and plasma triglyceride levels and less frequency of metabolic syndrome than patients with T2D [38]. However, some studies show that the titer and number of autoantibodies are both related to different metabolic and clinical phenotypes of LADA [2]. In our study, both mean FBG and HbA1c percentage in LADA patients was significantly higher than in T2D, which is consistent with earlier studies [3, 4, 25]. In addition, some studies reported autoantibody-positive patients to have worse glycemic regulation than T2D patients, which can be due to the limited production of endogenous insulin [15, 39]. Another parameter which is significantly lower in LADA patients than patients with T2D, is mean fasting C-peptide level. This result has been "strongly confirmed" by other researchers in several studies [17,19,25,37]. The reason for this might

be an autoimmune-mediated β-cell dysfunction which causes a decrease in the β-cell mass and, as a result, less C-peptide production [3,11]. Therefore, these results can confirm that although insulin resistance may play a role in the pathogenesis of LADA patients, such as T2D, there is a more severe defect in β-cell function [3]. Also no significant difference was observed between mean fasting C-peptide level in GADA and IA-2A positive subjects which was consistent with result of the LADA China Study 5 [36]. Therefore, according to the results of this study, the type of antibody probably does not play a role in the clinical characteristics of LADA patients, but due to the small number of positive antibody samples, these results cannot be generalized.

Diabetes treatment

The results of this study showed that a significantly higher percentage of LADA patients need insulin treatment than patients with T2D. This is because, as discussed in the C-peptide discussion, due to the degradation and inability of pancreatic cells to produce adequate insulin, autoimmune patients should receive exogenous insulin therapy as soon as possible compared to patients with T2D, so that they can have a more moderate metabolism. These results have been confirmed by other studies [15, 34]. Also, only patient with both GADA and IA-2A used insulin therapy for his treatment in combination to oral medications. In T2D patients, the presence of IA-2A in addition to GADA increased the likelihood of insulin requirement [40]. Also, it has been recently shown that the number of antibodies was more important than high titers of GADA for predicting insulin dependence [40]. However, the number of patients with two types of autoantibodies in this study is so small, and more accurate results need to be examined on a larger statistical population.

The strength of this study is that the prevalence of the most common antibody in autoimmune diabetes (GADA) in combination with IA-2A and related metabolic characteristic is evaluated for the first time in a group patients with T2D in eastern Iran. However, this study has some limitations. The first is the relatively small size of subjects studied and **lack of** follow-up. In addition, the clinical parameters of the patients were not compared with the healthy control subjects. Also, the clinical characteristics of LADA patients were not evaluated based on antibody titers. Another issue is that since determinants of the disease can be age-related, classification based on clinical presentation can cause some adults with T1D to be misdiagnosed as T2D, which could affect the final results. Finally, this study did not measure other antibodies, such as zinc-transporter 8 (ZnT8) or insulin autoantibodies (IAA), which are associated with autoimmune diabetes.

Conclusions

The prevalence of LADA based on the positivity of GADA and IA-2A was reported to be 8.3% among T2D, which is within the range reported by most earlier studies. Compared to T2D, LADA patients had worth glycemic control, lower C-peptide level and lower prevalence of metabolic syndrome. They need insulin therapy in a shorter period of time after the onset of the disease and their β-cell function is more severely impaired. This confirms that even a single marker of autoimmunity might lead to different clinical phenotype from that in patients with classic T2D. Therefore the measurement of these autoantibodies is recommended to diagnose LADA patients as soon as possible in order to provide personalized approach to treatment and the preservation of their β-cell functions. Due to the small sample size of the LADA group, the results of the current study cannot be generalized. More epidemiological and clinical studies with a larger sample size and follow-up are needed to better demonstrate the prevalence and increase awareness of latent autoimmune diabetes in adults.

Article information

Data availability statement

Original contributions presented in the study are included in the article.

Ethics statement

All patients were informed of the nature of the study and gave their written consent. This study was carried out in accordance with the Helsinki Declaration principles and approved by the Sistan and Baluchestan University ethics committee, with ethics code of IR.USB. REC.1398.015.

Author contributions

The main idea and development of the project was the responsibility of Dr. Malihe Mohammadi. Mrs. Mahdieh Mehranpoor participated in data extraction and analysis, and Dr. Milad Legzian contributed to writing the discussion and article editing.

Funding

This study was supported by the grant provided by the University of Sistan and Baluchestan, Zahedan, Iran.

Acknowledgments

The authors gratefully acknowledge the financial support for this work that was provided by the University of Sistan and Baluchestan. We thank the patients, diabetes clinic nurses, diabetologists, and general practitioners in Birjand for providing important collaboration to this study and also the Central Laboratory of the Imam-Reza Hospital, Birjand, for the laboratory facilities and the necessary instructions for conducting the laboratory test.

Conflict of interest

The authors declare that there is no conflict of interest.

REFERENCES

1. Wang Z, Zhang J, Xu H, et al. Development and Validation of a Prevalence Model for Latent Autoimmune Diabetes in Adults (LADA) Among Patients First Diagnosed with Type 2 Diabetes Mellitus (T2D). Med Sci Monit. 2021; 27: e932725, doi: 10.12659/MSM.932725, indexed in Pubmed: 34521804.
2. Buzzetti R, Zampetti S, Maddaloni E. Adult-onset autoimmune diabetes: current knowledge and implications for management. Nat Rev Endocrinol. 2017; 13(11): 674–686, doi: 10.1038/nrendo.2017.99, indexed in Pubmed: 28885622.
3. Al-Zubairi T, Al-Habori M, Saif-Ali R. Latent Autoimmune Diabetes in Adults (LADA) and its Metabolic Characteristics among Yemeni Type 2 Diabetes Mellitus Patients. Diabetes Metab Syndr Obes. 2021; 14: 4223–4232, doi: 10.2147/DMSO.S332416, indexed in Pubmed: 34675573.
4. Lampasona V, Petrone A, Tiberti C, et al. Non Insulin Requiring Autoimmune Diabetes (NIRAD) Study Group. Zinc transporter 8 antibodies complement GAD and IA-2 antibodies in the identification and characterization of adult-onset autoimmune diabetes: Non Insulin Requiring Autoimmune Diabetes (NIRAD) 4. Diabetes Care. 2010; 33(1): 104–108, doi: 10.2337/dc08-2305, indexed in Pubmed: 19808923.
5. Biesenbach G, Auinger M, Clodi M, et al. Diabetic Nephropathy Study Group of the Austrian Society of Nephrology. Prevalence of LADA and frequency of GAD antibodies in diabetic patients with end-stage renal disease and dialysis treatment in Austria. Nephrol Dial Transplant. 2005; 20(3): 559–565, doi: 10.1093/ndt/gfh662, indexed in Pubmed: 15671073.
6. Kanungo A, Sanjeevi CB. IA-2 autoantibodies are predominant in latent autoimmune diabetes in adults patients from eastern India. Ann N Y Acad Sci. 2003; 1005: 390–394, doi: 10.1196/annals.1288.065, indexed in Pubmed: 14679098.
7. Kawasaki E, Nakamura K, Kuriya G, et al. Autoantibodies to insulin, insulinoma-associated antigen-2, and zinc transporter 8 improve the prediction of early insulin requirement in adult-onset autoimmune diabetes. J Clin Endocrinol Metab. 2010; 95(2): 707–713, doi: 10.1210/jc.2009-1733, indexed in Pubmed: 20061424.
8. Huang G, Wang X, Li Z, et al. Insulin autoantibody could help to screen latent autoimmune diabetes in adults in phenotypic type 2 diabetes mellitus in Chinese. Acta Diabetol. 2012; 49(5): 327–331, doi: 10.1007/s00592-010-0196-2, indexed in Pubmed: 20473693.
9. Hawa MI, Thivolet C, Mauricio D, et al. Action LADA Group. Metabolic syndrome and autoimmune diabetes: action LADA 3. Diabetes Care. 2009; 32(1): 160–164, doi: 10.2337/dc08-1419, indexed in Pubmed: 18945926.
10. Zaharieva ET, Velikova TV, Tsakova AD, et al. Prevalence of Positive Diabetes-Associated Autoantibodies among Type 2 Diabetes and Related Metabolic and Inflammatory Differences in a Sample of the Bulgarian Population. J Diabetes Res. 2017; 2017: 9016148, doi: 10.1155/2017/9016148, indexed in Pubmed: 28573146.
11. Pieralice S, Pozzilli P. Latent Autoimmune Diabetes in Adults: A Review on Clinical Implications and Management. Diabetes Metab J. 2018; 42(6): 451–464, doi: 10.4093/dmj.2018.0190, indexed in Pubmed: 30565440.
12. Mishra R, Åkerlund M, Cousminer DL, et al. Genetic Discrimination Between LADA and Childhood-Onset Type 1 Diabetes Within the MHC. Diabetes Care. 2020; 43(2): 418–425, doi: 10.2337/dc19-0986, indexed in Pubmed: 31843946.
13. Chiu HK, Tsai EC, Juneja R, et al. Equivalent insulin resistance in latent autoimmune diabetes in adults (LADA) and type 2 diabetic patients. Diabetes Res Clin Pract. 2007; 77(2): 237–244, doi: 10.1016/j.diabres.2006.12.013, indexed in Pubmed: 17234296.
14. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2010; 33 Suppl 1(Suppl 1): S62–S69, doi: 10.2337/dc10-S062, indexed in Pubmed: 20042775.
15. Carlsson S. Etiology and Pathogenesis of Latent Autoimmune Diabetes in Adults (LADA) Compared to Type 2 Diabetes. Front Physiol. 2019; 10: 320, doi: 10.3389/fphys.2019.00320, indexed in Pubmed: 30971952.
16. Mohammadi M, Khaza'i HA. Characteristics and Prevalence of Latent Autoimmune Diabetes in Adults (LADA) in Torbat-e Heydarieh, Iran. Int J Med Lab. 2018; 5(4): 255–263, doi: 10.18502/ijml.v5i4.159.
17. Zhou Z, Xiang Y, Ji L, et al. LADA China Study Group. Frequency, immunogenetics, and clinical characteristics of latent autoimmune diabetes in China (LADA China study): a nationwide, multicenter, clinic-based cross-sectional study. Diabetes. 2013; 62(2): 543–550, doi: 10.2337/db12-0207, indexed in Pubmed: 23086039.
18. Naroei R, Mehranpoor M, Mohammadi M, et al. Prevalence of Islet Cell Autoantibodies in Adult Patients Followed for Type 2 Diabetes Mellitus: A Cross-sectional Study. Int J Basic Sci Med. 2022; 7(1): 41–46, doi: 10.34172/ijbsm.2022.08.
19. Szepietowska B, Głębocka A, Puch U, et al. Latent autoimmune diabetes in adults in a population-based cohort of Polish patients with newly diagnosed diabetes mellitus. Arch Med Sci. 2012; 8(3): 491–495, doi: 10.5114/aoms.2012.29527, indexed in Pubmed: 22852005.
20. Qi X, Sun J, Wang J, et al. Prevalence and correlates of latent autoimmune diabetes in adults in Tianjin, China: a population-based cross-sectional study. Diabetes Care. 2011; 34(1): 66–70, doi: 10.2337/dc10-0488, indexed in Pubmed: 20876205.
21. Buzzetti R, Di Pietro S, Giaccari A, 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(4): 932–938, doi: 10.2337/dc06-1696, indexed in Pubmed: 17392553.
22. Zinman B, Kahn SE, Haffner SM, et al. ADOPT Study Group. Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. Diabetes. 2004; 53(12): 3193–3200, doi: 10.2337/diabetes.53.12.3193, indexed in Pubmed: 15561950.
23. Maddaloni E, Lessan N, Al Tikriti A, et al. Latent Autoimmune Diabetes in Adults in the United Arab Emirates: Clinical Features and Factors Related to Insulin-Requirement. PLoS One. 2015; 10(8): e0131837, doi: 10.1371/journal.pone.0131837, indexed in Pubmed: 26252955.
24. Hossein GM, Maryam S, Saeed E, et al. The prevalence of latent autoimmune diabetes in adults and its correlates in patients with type 2 diabetes in Kerman, Iran [2011]. Diabetes Metab Syndr. 2015; 9(2): 104–107, doi: 10.1016/j.dsx.2014.04.014, indexed in Pubmed: 25470643.
25. Moosaie F, Meftah N, Deravi N, et al. Prevalence of diabetes-associated autoantibodies among patients presenting with type

2 diabetes and related metabolic differences. Prim Care Diabetes. 2021; 15(1): 169–174, doi: 10.1016/j.pcd.2020.07.008, indexed in Pubmed: 32798203.
26. Zhou J, Ma XJ, Bao JQ, et al. Study on prevalence of latent autoimmune diabetes in adults and its relationship with metabolic syndrome. Zhonghua Yi Xue Za Zhi. 2009; 89(18): 1250–1254, doi: 10.3389/fendo.2022.913373, indexed in Pubmed: 19595178.
27. Tam AA, Ozdemir D, Bestepe N, et al. Low rate of latent autoimmune diabetes in adults (LADA) in patients followed for type 2 diabetes: A single center's experience in Turkey. Arch Endocrinol Metab. 2021; 64(5): 584–590, doi: 10.20945/2359-3997000000268, indexed in Pubmed: 34033299.
28. Hwangbo Y, Kim JT, Kim EKy, et al. Prevalence and clinical characteristics of recently diagnosed type 2 diabetes patients with positive anti-glutamic Acid decarboxylase antibody. Diabetes Metab J. 2012; 36(2): 136–143, doi: 10.4093/dmj.2012.36.2.136, indexed in Pubmed: 22540050.
29. Khoshroo M. High Frequency of Multiple Autoantibody Positive LADA in Patients with Type 2 Diabetes Mellitus in Iran Population. International Journal of Pure & Applied Bioscience. 2016; 4(6): 16–26, doi: 10.18782/2320-7051.2387.
30. Pozzilli P, Pieralice S. Latent Autoimmune Diabetes in Adults: Current Status and New Horizons. Endocrinol Metab (Seoul). 2018; 33(2): 147–159, doi: 10.3803/EnM.2018.33.2.147, indexed in Pubmed: 29947172.
31. Laugesen E, Østergaard JA, Leslie RDG, et al. Danish Diabetes Academy Workshop and Workshop Speakers. Latent autoimmune diabetes of the adult: current knowledge and uncertainty. Diabet Med. 2015; 32(7): 843–852, doi: 10.1111/dme.12700, indexed in Pubmed: 25601320.
32. Hernández M, López C, Real J, et al. Preclinical carotid atherosclerosis in patients with latent autoimmune diabetes in adults (LADA), type 2 diabetes and classical type 1 diabetes. Cardiovasc Diabetol. 2017; 16(1): 94, doi: 10.1186/s12933-017-0576-9, indexed in Pubmed: 28750634.
33. Sia HK, Tu ST, Liao PY, et al. A convenient diagnostic tool for discriminating adult-onset glutamic acid decarboxylase antibody-positive autoimmune diabetes from type 2 diabetes: a retrospective study. PeerJ. 2020; 8: e8610, doi: 10.7717/peerj.8610, indexed in Pubmed: 32095379.
34. Löfvenborg JE, Ahlqvist E, Alfredsson L, et al. Genotypes of HLA, TCF7L2, and FTO as potential modifiers of the association between sweetened beverage consumption and risk of LADA and type 2 diabetes. Eur J Nutr. 2020; 59(1): 127–135, doi: 10.1007/s00394-019-01893-x, indexed in Pubmed: 30656477.
35. Brahmkshatriya PP, Mehta AA, Saboo BD, et al. Characteristics and Prevalence of Latent Autoimmune Diabetes in Adults (LADA). ISRN Pharmacol. 2012; 2012: 580202, doi: 10.5402/2012/580202, indexed in Pubmed: 22577577.
36. Xiang Y, Huang G, Shan Z, et al. Glutamic acid decarboxylase autoantibodies are dominant but insufficient to identify most Chinese with adult-onset non-insulin requiring autoimmune diabetes: LADA China study 5. Acta Diabetol. 2015; 52(6): 1121–1127, doi: 10.1007/s00592-015-0799-8, indexed in Pubmed: 26239144.
37. Lee SH, Kwon HS, Yoo SJ, et al. Identifying latent autoimmune diabetes in adults in Korea: the role of C-peptide and metabolic syndrome. Diabetes Res Clin Pract. 2009; 83(2): e62–e65, doi: 10.1016/j.diabres.2008.11.031, indexed in Pubmed: 19166794.
38. Davis TME, Wright AD, Mehta ZM, et al. Islet autoantibodies in clinically diagnosed type 2 diabetes: prevalence and relationship with metabolic control (UKPDS 70). Diabetologia. 2005; 48(4): 695–702, doi: 10.1007/s00125-005-1690-x, indexed in Pubmed: 15729570.
39. Andersen CD, Bennet L, Nyström L, et al. Worse glycaemic control in LADA patients than in those with type 2 diabetes, despite a longer time on insulin therapy. Diabetologia. 2013; 56(2): 252–258, doi: 10.1007/s00125-012-2759-y, indexed in Pubmed: 23096095.
40. Zampetti S, Campagna G, Tiberti C, et al. NIRAD Study Group. High GADA titer increases the risk of insulin requirement in LADA patients: a 7-year follow-up (NIRAD study 7). Eur J Endocrinol. 2014; 171(6): 697–704, doi: 10.1530/EJE-14-0342, indexed in Pubmed: 25213702.