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Common autoimmune biomarkers, thyroid hormonal abnormalities, and beta cells dysfunction in patients with latent autoimmune diabetes in adults with type II diabetes mellitus

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ABSTRACT

Aim: Latent autoimmune diabetes in adults (LADA) is autoimmune diabetes with a slow progression characterized by the presence of antibodies associated with Type I diabetes. The present study aimed to assess autoimmune characteristics in patients with LADA in Iran. We attempted to obtain a clear view of autoimmune conditions in LADA among our population.
Methods: This study was sourced from the population-based survey of KERCARDS aiming assessment of cardiovascular risk factors among a great sample of Iranian population who were resident in Kerman, a great province in southern Iran. Among all diabetic patients who were negative for Anti Glutamic Acid Decarboxylase (GAD) antibody test, 120 were selected as the controls and among 80 patients who were positive for this test diagnosed as LADA, the recorded files of 57 patients were complete considered as the cases.
Results: The level of thyroxin is significantly lower in patients with LADA compared with the controls so 73.7% and 45% of patients had normal level of thyroxin, respectively. Also, those with LADA had considerably lower levels of both thyroid peroxydaseantibody (TPO-Ab) and C-peptide when compared with non-LADA group. Using multivariate analyses and with the presence of baseline variables including gender, age, and duration of disease, the diagnosis of LADA was associated with lower serum levels of Anti-TPO, C-peptide, and thyroxin, but not associated with the level of Anti-TTG in serum.
Conclusion: LADA patients may face with lower serum levels of C-peptide and thyroid-specific antibodies indicating insulin therapy requirement and authoimmune fundaments of the disease, respectively.

1. Introduction

Latent autoimmune diabetes in adults (LADA) is autoimmune diabetes with a slow progression characterized by the presence of antibodies associated with Type I diabetes. The main characteristics of the disease consists of the onset of diabetes in older thirties, the presence of antibodies specified to diabetes type 1, not require insulin for six months, and positive Glutamic Acid decarboxylase (GAD) antibody in serum [1–3]. LADA patients have a slowly progressive onset of hyperglycemia associated with clinical symptoms of diabetes type 2 [3–5]. Epidemiologic studies have shown that about 2–12 percent of diabetes include LADA diabetes [5] that is a range of 2.8–10 percent in industrial countries. The etiology of LADA is not completely understood so it is still unclear whether the etiology of diabetes type 1 in children is similar to or different from the etiology of LADA [3]. Recent studies have shown common genetic features of LADA with both diabetes type 1 and type 2 [6,7]. Furthermore, several studies have shown that metabolic diseases such as high blood pressure, obesity and family history of diabetes are associated with an increased

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incidence of LADA [8,9]. Clinically, the diabetes types I and II can be differentiated through phenotypic differences such as age at onset of diabetes, immediate onset of hyperglycemia, presence of ketosis, severity of obesity, presence of other associated autoimmune diseases and also the need for replaced insulin. Also, the main characteristics related to LADA were the manifestation of diabetes below age 50 years; acute symptoms at diagnosis; body mass index <25 kg/m^2; positive personal history of autoimmune disease; and positive family history for autoimmune diseases. There is not a reliable sign for the diagnosis of type II diabetes and in this regard, the absence of markers for type I diabetes is considered as a sign of diabetes type II [8]. The positivity of ICA and GAD autoantibody in 10–30 percent of people with type 2 diabetes reflects the fact that type I diabetes in older diabetic shows type 2 diabetes-like phenotype that is known as LADA [9]. Regarding diagnosis of LADA, the studies have revealed that ICA and IA–IIA antibodies have lower lifetime compared with GAD antibody and the latter antibody has a constant level in the serum, however ICA has higher sensitivity compared with GAD [10,11]. In total, ICAor GAD are better indications of the need for insulin therapy and GAD antibody has been suggested as an appropriate and useful marker for identifying type 2 diabetes patients who require insulin therapy. Despite the presence of some commonalities between type I diabetes and LADA, very few studies have been conducted on the prevalence of autoimmune conditions in LADA. Besides, some studies focused the progression rate of beta cell dysfunction in diabetes. In some studies, deficiency of beta cells within 6 years of diagnosis of diabetes has been reported [12,13], and some studies have mentioned this time as 12 years [14]. The difference in the rate of progression of the disorder can be probably due to the differences in type of antibodies and their titres. In particular, it seems that the lack Islet cell antibody (ICA) can be associated with reducing the progression of beta cell dysfunction [15,16].

The present study aimed to assess autoimmune characteristics in patients with LADA in Iran. In this study, we attempted to obtain a clear view of autoimmune conditions in LADA among our population.

2. Methods

The presence study was sourced from the based population survey of KERCARDS aiming assessment of cardiovascular risk factors among a great sample of Iranian population who were resident in Kerman, a great province in southern Iran. In this survey, 6000 individuals were studied to assess general risk factors for coronary artery disease as well as evaluate nutritional behaviors, lifestyle, and even quality of life status with the purpose of screening and identifying who were predisposed to cardiovascular risk. Among those, 700 patients (11.7%) were diagnosed as diabetes mellitus that 80 (11.4% of diabetics and 1.3% of all subjects) had been revealed to have LADA. The final diagnosis of LADA was based on Anti GAD antibody test (normal range: up to 10 Iu/mL). The study protocol was approved by the Research Ethics Committee of the study hospital and from all patients written consent form was obtained. In the present survey, a serum sample was extracted to measure serum levels of anti-tissue transglutaminase, thyroid peroxidase antibody (TPO-Ab) (normal range: up to 16 Iu/mL), thyroxin (normal range: 5.4–11.7 μg/dL), and thyroid stimulating hormone (TSH) (normal range: 0.34–4.25 mIU/L) using ELISA kits. Also, the level of C_ peptide (normal range: 0.27–1.19 nmol/L) was also measured using RIA to assess beta cells reservation status. The similar measurements were also targeted in diabetic patients who were negative for Anti GAD antibody.

Results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using *t*-test or Non-parametric Mann-Whitney *U*-test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. The multivariate regression model was used to determine main intra-group difference in study variables between the study groups with the presence of confounders. For the statistical analysis, the statistical software SPSS version 16.0 for windows (SPSS Inc., Chicago, IL) was used. *P* values of 0.05 or less were considered statistically significant.

3. Results

Among all diabetic patients who were negative for Anti GAD antibody test, 120 were randomly selected as the controls according to calculated required sample size. Also, among 80 patients who were positive for this test and diagnosed as LADA, the recorded files of 57 patients were complete considered as the cases. In overall, of 177 patients, 63.8% were female. The average age of the patients was 59.26 ± 9.71 years. The cases and control groups were comparable in baseline demographics including distribution of gender and age as well as disease duration. As presented in Table 1, the level of thyroxin is significantly lower in patients with LADA compared with the controls so 73.7% and 45% of patients had normal level of thyroxin, respectively. Also, those with LADA had considerably lower levels of both Anti-TPO and C-peptide when compared with non-LADA group. Tables 2–5 showed univariate and multivariate analyses to determine association of LADA with study parameters. In this regard and with the presence of baseline variables including gender, age, and duration of disease, the diagnosis of LADA was associated with lower serum levels of Anti-TPO, C-peptide, and thyroxin, but not associated with the level of Anti-TTG in serum.

4. Discussion

In first step, we revealed an overall prevalence of 11.4% for LADA among our diabetic population as well as 1.3% in general population that in the range of 2–12% found in all cases of diabetes in adult population [17]. In total, wide range prevalence of this phenomenon reported in studies is strongly affected by lifestyle,

Table 1
Comparing baseline characteristics between the case and control groups.

Characteristics	Total (n = 177)	With LADA (n = 57)	Without LADA (n = 120)	*P*-value
Gender				0.060
Male	64 (36.2)	15 (26.3)	49 (40.8)	
Female	113 (63.8)	42 (73.7)	71 (59.2)	
Age, year	59.26 ± 9.71	58.04 ± 9.60	59.84 ± 9.75	0.250
Age subgroups				0.681
<55 years	61 (34.5)	22 (38.6)	39 (32.8)	
55–64 years	66 (37.3)	19 (33.3)	47 (39.5)	
≥65 years	50 (28.2)	16 (28.1)	33 (27.7)	
Disease duration (m)	63.96 ± 58.68	53.97 ± 48.97	68.64 ± 62.40	0.163
Thyroxin level	12.75 ± 3.55	11.82 ± 3.32	13.21 ± 3.58	0.022
Normal Thyroxin	96 (54.2)	42 (73.7)	54 (45)	<0.001
TSH level	2.92 ± 3.43	2.46 ± 2.04	3.25 ± 4.14	0.201
Normal TSH	153 (86.4)	48 (84.2)	105 (87.5)	0.143
Anti-TPO level	119.70 ± 341.42	91.73 ± 378.78	135.21 ± 319.78	0.046
Normal Anti-TPO	131 (74)	49 (85.9)	82 (68.3)	0.017
Anti-TTG level	21.76 ± 29.47	23.16 ± 21.92	21.08 ± 32.58	0.680
Normal Anti-TTG	76 (42.9)	21 (36.8)	55 (45.8)	0.128
C-peptide level	2.94 ± 1.71	2.66 ± 2.13	3.06 ± 1.51	0.025
Normal C-peptide	166 (93.8)	47 (82.5)	119 (99.2)	<0.001