



Original Research Article

Study to investigate prevalence of latent autoimmune diabetes of adults in type 2 diabetes patients and evaluate characteristics of patients with LADA

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ABSTRACT

Objective: To study prevalence of LADA in type2 diabetes patients and evaluate characteristics of patients with LADA.

Materials and Methods: This is cross-sectional observational study, conducted in a tertiary care hospital in South India; once consultation by physician was over, diabetic patients were screened for study criteria; written informed consent was taken from all participants, who fulfilled study criteria. A written permission has been obtained from Institutional Ethics Committee for the conduct of the study, patients with type 2 diabetes mellitus having age of onset of diabetes greater than 35 years and duration of type 2 diabetes less than 3 years are included in the study and subjects who are requiring insulin within 6 months after diagnosis of diabetes are excluded from the study. Radioimmunoassay is used for detection of auto antibodies to GAD65. LADA is diagnosed by presence of autoantibodies to GAD65. Other laboratory indices done are C-peptide assay, HbA1c, anti-TPO antibodies and lipid profile. Prevalence is calculated for auto antibody positive subjects and characteristics of patients are determined by age, gender, BMI and other laboratory indices.

Results: Out of 100 type 2 diabetes patients included in the study, 30 were diagnosed with LADA. Among these 30 patients with LADA, 84% patients were between 35-50 years of age and 16% were above 50 years of age and 60% were males and 40% were females. 100 % of LADA patients have BMI less than 30, HbA1c greater than 8 is seen among almost all patients of LADA and low c-peptide levels is recorded in all patients with LADA. Anti-thyroid peroxidase antibodies are seen in 93% of patients diagnosed with LADA.

Conclusion: Our study established LADA prevalence of 30% among type 2 diabetes mellitus patients and has shown role of GAD auto antibody in screening for LADA and also tried to evaluate association of age, BMI, higher HbA1c and other autoimmune diseases with LADA. This study helps us in recommending criteria for diagnosis of LADA, screen relatives of LADA patients for immune and metabolic markers to identify high risk individuals.

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1. Introduction

American Diabetes Association (ADA) categorized diabetes mellitus mainly as types 1 and 2 diabetes and others.¹ Type 2 diabetes develops in adult age and is characterized

by insufficient insulin secretion with or without insulin resistance, this form of diabetes does not have autoimmune phenomena and does not require insulin at onset, distinction between type 1 and type 2 diabetes is by presence or absence of islet autoantibodies. If search is done for these autoantibodies in all new cases of diabetes, among non-insulin requiring diabetic subjects at diagnosis, a significant

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minority are islet cell antibody positive.² Less recognized manifestation of diabetes appears to affect adults, known as Latent Autoimmune Diabetes in Adults (LADA). Features of LADA are onset of diabetes at ≥ 40 years of age, clinical presentation as non-obese type 2 diabetes, unlikely to have family history of type 2 diabetes, initial control of hyperglycaemia with diet and oral antidiabetic agents, evolution to insulin necessity within months, and some features of type 1 diabetes such as low fasting C-peptide and positive Glutamic acid decarboxylase (GAD) auto antibodies.^{3–5}

Hyperglycaemia in type 1 diabetes is end result of interaction between susceptible genes and abnormal immune response to beta cells after exposure to some environmental factors.⁶ It is speculated that in case of LADA, qualitative and quantitative exposure to such factors is less pronounced, there are several common features between LADA and type 1 diabetes, including T-cell insulinitis and low residual beta cell function.⁷ In very young, linear and rapid progression beta cell function is likely to occur, whereas in adolescent, longer prodrome followed by acute precipitating factor is more common.⁸

In LADA, it is speculated that multiple events may hit beta cells in genetically susceptible subjects, leading to decline of beta cell function, age at diagnosis influences amount of beta cell mass left.⁹ LADA has several features of classic type 1 diabetes in addition to islet cell antibody positivity, including high rates of HLA-DR3 and DR4.^{10–13} Adults with non-insulin requiring diabetes, positive for Glutamic acid decarboxylase (GAD) or islet cell cytoplasmic antibodies (ICA) require insulin treatment significantly earlier after diagnosis than ICA negative patients.^{14,15}

Type of autoantibodies to islet cell antigens distinguish between acute-onset type 1 diabetes and LADA because GAD antibodies and ICA indicate slow disease progression, whereas Insulinoma associated antigen-2 (IA-2) antibodies is associated with acute onset clinical phenotype.¹⁶ Patients with LADA share insulin resistance with type 2 diabetic patients but display more severe defect in maximally stimulated beta cell capacity.¹⁷

A wide variation has been described in prevalence of LADA depending on markers chosen to define and characteristics of patients like newly diagnosed or previously diagnosed. Worldwide studies identified some 10–20% of non-insulin requiring diabetic patients with ICA and GAD antibodies.¹⁸ GAD antibodies appeared to have higher sensitivity I predicting insulin dependence than Islet cell antibodies ICA.¹⁹

GAD antibodies are considered as most sensitive marker of LADA as it is predominant autoantibody in primary or in secondary care; e.g., Action LADA study showed that approximately 90% of LADA subjects with diabetes-associated autoantibodies are GADA positive.^{20,21}

GADA can be detected by commercially available radioimmunoassay as well as ELISA. GADA specificity has improved from 94% to 99% from 2010 to 2018 according to the international islet autoantibody standardization program.²²

Patients with high GADA levels tend toward a Type 1 diabetes-like phenotype with lower BMI and lower prevalence of metabolic syndrome.^{23,24} In addition, UKPDS and all other studies found that high GAD antibodies levels were associated with increased risk of insulin requirement.^{25,26}

Various European studies have demonstrated prevalence of LADA ranging from 3 to 10%.^{27–30} Various studies performed in Indians shows prevalence of 25–55% islet auto immunity in type 2 diabetes.^{31–34}

From existing data, it appears that LADA could represent sizeable proportion of diabetic patients. Accurate estimates of prevalence are important not only for correct classification of diabetes and also for developing early intervention strategies. Limited data is available for patients with diabetes in south India; present study is to investigate prevalence and evaluate characteristics of patients with LADA in type 2 diabetes patients.

2. Materials and Methods

This is cross-sectional observational study, conducted in a tertiary care hospital in South India; once consultation by physician was over, diabetic patients were screened for study criteria; written informed consent was taken from all participants, who fulfilled study criteria. A written permission has been obtained from Institutional Ethics Committee for the conduct of the study., patients with type 2 diabetes mellitus having age of onset of diabetes greater than 35 years and duration of type 2 diabetes less than 3 years are included in the study and subjects who are requiring insulin within 6 months after diagnosis of diabetes are excluded from the study.

Diabetes is diagnosed as per American diabetes association (ADA) criteria.³⁵ About 100 diabetic patients attending Internal medicine outpatient are included in study after taking detailed informed consent. Data on age, sex, health status and three generation family history of diabetes is obtained. BMI was calculated based height and weight. Subjects were counselled to come fasting for at least 12 hours for blood sample collection. Radioimmunoassay is used for detection of auto antibodies to GAD65. LADA is diagnosed by presence of autoantibodies to GAD65. Other laboratory indices done are HbA1c, lipid profile, anti-TPO antibodies (anti-thyroid peroxidase antibodies) for other autoimmune association. Prevalence is calculated for GAD auto antibody positive subjects. A value greater than 5.0 IU/mL is considered positive for glutamic acid decarboxylase antibody (GAD). A value greater than 30IU/ml is considered as Anti-TPO positive. A value less

than 0.5 ng/ml is considered as low for fasting c peptide level.

3. Results

Table 1: Showing characteristics of type 2 diabetes mellitus patients included in study

Parameter	Variable	Number of type 2 diabetes patients (out of total 100)	Percentage (%)
Gender	Male	50	50%
	Female	50	50%
Age	35-50 years	50	50%
	51-65 years	50	50%
BMI	<30	35	35%
	>30	65	65%
HbA1c	<8	45	45%
	>8	55	55%
Antithyroid peroxidase antibodies profile	Present	70	70%
	Absent	30	30%
C-peptide	Normal	30	30%
	Abnormal	70	70%
C-peptide	Normal	70	70%
	Low	30	30%

Table 2: Showing characteristics of patients diagnosed with LADA

Parameter	Variable	Number of patients (out of total 30)	Percentage (%)
GAD antibodies	Positive	30	100%
Fasting C-peptide	Low	30	100%
Age	35-50	25	84
	51-65	5	16
Presence of thyroid disease	Yes	28	93%
	No	2	7%
BMI	<30	30	100%
HbA1c	>8	30	100%
Gender	Male	18	60%
	Female	12	40%

3.1. GAD antibodies

Out of 100 type 2 diabetes patients included in the study, 30 patients got GAD autoantibodies positive (>5IU/ml) and they were diagnosed with LADA.

3.2. Gender

Out of 100 type 2 diabetes patients, 50 were females and 50 were males. Out of 30 patients diagnosed with LADA, 60% of patients were males and 40% were females.

3.3. Age

In our study, 50% of patients were above 50 years of age and 50% were between 35-50 years. Out of 30 patients diagnosed with LADA, 84% patients were between 35-50 years and 16% were above 50 years.

3.4. Body mass index

Out of total number of type 2 diabetes patients included in the study, 30 % had BMI of less than 30 and remaining 70 % have BMI of greater than 30. Among patients diagnosed with LADA, 100 % were of BMI less than 30.

3.5. HbA1c

Out of total, 55% of patients have HbA1c greater than 8 and among patients diagnosed with LADA, 100% have HbA1c greater than 8.

3.6. Fasting C- peptide level

Out of total patients, 30% have low c-peptide and remaining 70% have normal c-peptide. Out of patients diagnosed with LADA, 100% of patients have low c-peptide levels (<0.5 ng/ml).

3.7. Other autoantibodies

Anti-thyroid peroxidase antibodies are seen in 70 % of total patients, 93% of patients diagnosed with LADA have anti-TPO positivity.

4. Discussion

From our study, we can propose that minimum age for LADA is above 35 years and prevalence of LADA decreases after 50 years of age, findings in our study are similar to previous study by Carlsson et al.³⁶ that suggested the burden of LADA decreases with increasing age. Minimum age cut-off for LADA varies from 25 to 40 years, based on longitudinal studies of pre-clinical natural history, using metabolic and immune-genetic markers that distinguish LADA from juvenile- onset type 1 diabetes.^{37,38}

Out of 100 type 2 diabetes patients included in study, GAD antibodies are positive in 30 patients; insulin autoantibodies (IAA) and antibodies to tyrosine phosphatase-like insulinoma antigen 2 (IA2) were reported to be infrequent in LADA.^{39,40} However, accurate profile of humoral immunity requires further studies to document prevalence of IAA, IA2 antibodies in different populations of LADA.

Association of other autoimmune diseases with type 1 diabetes, especially autoimmune thyroid disease⁴¹ and coeliac disease⁴² is well-established. In our study, anti-TPO antibodies were positive in 93% of LADA patients.

In our study, 100 % of patients diagnosed with LADA have BMI less than 30. LADA patients are usually lean at diagnosis,¹⁵ similar to children presenting with type 1 diabetes.

Distribution of LADA between males and females with Type 2 Diabetes did not show any major difference, these findings align with other studies that reported LADA to not be influenced by individuals' sex and distribution is even unpredictable among LADA and type 2 diabetes mellitus.⁴³

5. Conclusion

LADA represents a significant component of autoimmune diabetes but, compared with classic type 1 diabetes, is poorly researched. Our study established LADA prevalence of 30% among type 2 diabetes mellitus patients and has shown role of GAD autoantibody in screening for LADA and also tried to evaluate association of age, BMI, higher HbA1c and other autoimmune diseases with LADA. This study helps us in recommending criteria for diagnosis of LADA, screen relatives of LADA patients for immune and metabolic markers to identify high risk individuals. Study calls for well- designed larger longitudinal study to generate strong evidence on association of risk factors associated with LADA.

6. Limitations

Budget and time limitations, which resulted in few numbers of cases with LADA that had inadequate power to draw conclusion of association with risk factors.

7. Source of Funding

None.

8. Conflict of Interest

None.

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