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Differentiation and Delineation of LADA from Type 2 Diabetes Mellitus with the Utility of Autoantibodies

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Abstract

Background: Diabetes, especially type 2 diabetes, has become pandemic in India. The emergence of type 2 diabetes has been documented in Asian populations at a young age. Very less work has been done in context to LADA in the Indian population and due to certain characteristics of LADA which phenotypically resemble type 2 diabetes, many LADA patients are often initially misdiagnosed as type 2 diabetic patients. Materials and Methods: The study included 200 diabetic patients between the ages of 18 and 45 years were examined for the study with analysis of GAD 65 and IA2 autoantibodies. Results: The current research population indicated that the prevalence of type 2 diabetes was the greatest (84.5 percent) and LADA (15.5 percent) out of 200 diabetics. The results of autoantibody testing indicated that individuals with LADA had a high level of GAD65 and IA2. Conclusion: According to the present study, both T2DM and LADA tend to influence males more than females, and the adult age of onset (30–40 years) is also quite similar. Additionally, both T2DM and LADA patients exhibited an initial response to the OHA treatment regimen. The LADA patients, on the other hand, had low C-peptide levels and a high level of GAD autoantibodies. As a result, determining C-peptide levels and GAD autoantibodies is strongly suggested for LADA confirmation.

Keywords: T2DM**,** LADA, GAD65, IA2

INTRODUCTION

Diabetes mellitus (DM) is a category of carbohydrate metabolic disorders marked by hyperglycemia and associated macrovascular and microvascular consequences throughout time. Diabetes mellitus is becoming more common in most developed and developing nations, which is cause for great concern [1, 2]. Geographic, environmental, and genetic variables all have a significant influence in the variance of diabetes incidence among all types of diabetes. Despite the fact that diabetes is divided into two basic varieties—type 1 (insulin-dependent) and type 2 (insulin-independent)—there are some types of diabetes that do not fit into either of these categories. One such less well-known and underdiagnosed form of DM appears to afflict people who have many of the symptoms of type 2 diabetes and is associated with a significant risk of insulin dependency development, the condition known as Latent Autoimmune Diabetes in Adults (LADA) [6]. A subset of people with adult-onset autoimmune diabetes do not require insulin therapy at the time of diagnosis and are clinically comparable to patients with type 2 diabetes (T2DM). These individuals, who were originally considered to have T2DM, are now

classified as having latent autoimmune diabetes in adults (LADA) [3-5]. Diabetes onset around the age of 25, clinical presentation masquerading as nonobese type 2 diabetes, and a lack of a family history of type 2 diabetes are the most common features of LADA patients documented. Other features include initial management of hyperglycemia with diet and oral anti-diabetic medicines, rapid development to insulin dependency, and type 1 diabetes signs such as low fasting C-peptide and positive GAD antibodies [7–9]. About 20% of the patients diagnosed with type 2 diabetes may have LADA [10]. Despite the prevalence of LADA, no consistent guidelines exist for testing for islet antibodies in adults with diabetes. A dependable clinical method is necessary to determine whether people with diabetes are at high risk of LADA and require islet antibody testing. [11]. Diabetes, especially type 2 diabetes, has become pandemic in India. The emergence of type 2 diabetes has been documented in Asian populations at a young age. Very less work has been done in context to LADA in the Indian population and due to certain characteristics of LADA which phenotypically resemble type 2 diabetes, many LADA patients are often initially misdiagnosed as type 2 diabetic patients [12]. So, this study was designed to understand the similarities or differences of LADA with other types of diabetes and designing appropriate diagnostic criteria and treatment regimen for such patients.

SUBJECTS AND METHODS:

The study included 200 diabetic patients between the ages of 18 and 45 years who were visiting Diabetic Specialty OPD at MGM Hospital Kamothe. Following the fulfilment of the inclusion criteria, all of them provided written informed permission. The study protocol has been approved by the Institutional Ethical Committee for Human Subjects Research. Patients who did not have diabetes or who were very sick were excluded from the research. Blood (10 mL) was drawn to determine different biochemical markers. The detailed clinical history was taken which included present age, age at onset of diabetes, gender, baseline metabolic index (BMI), type of diabetes, family history of diabetes, if any and the patient's current medication regimen. GAD 65 and IA2 antibodies were identified using an ELISA kit (Immunotag Human ELISA kit). Following the collection of patient information, the data was divided into groups based on the type of diabetes. The mean values for each parameter were computed and compared in two groups. All findings were presented as Mean±SEM or as a percentage. The statistical differences between the groups were evaluated by One Way Analysis of Variance (ANOVA) followed by Tukey's Test by Graphpad Prism 8 statistical tool. $P<0.05$ was deemed statistically significant, while $P<0.001$ was considered extremely significant.

RESULTS:

Results of different parameters evaluated of all the diabetic patients are summarized in Table 1 & 2.

Table 1: Comparative Assessment of different parameters in T2DM and LADA

Parameter		T2DM	LADA
Prevalence (%) (n=200)		84.5 (169)	15.5 (31)
Gender wise Prevalence (%)	Male	53	65
	Female	47	35
Prevalence of different age groups at enrolment	18-25	3.55	19.35
	26-35	37.28	38.71

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(% patients)	36-45	59.17	41.94
BMI range (%patients)	Underweight (Below 18.5)	0	16.13
	Healthy (18.5-24.9)	42.01	51.61
	Overweight (25-29.9)	42.60	16.13
	Obese (Above 30)	15.39	16.13
Family History of Diabetes (% patients)	Present	73.96	58.06
	Absent	26.04	41.94
Treatment Regimen (% patients)	Insulin	1.18	0
	OHA	98.82	70.96
	Insulin+OHA	0	29.04
GAD 65 Antibody		Negative	Positive
IA2 Antibody		Negative	Positive

*Comparative data of different qualitative parameters between T2DM and LADA are presented in the form of percentage; OHA-Oral Hypoglycemic Agents

Table 2: Correlative Evaluation of different parameters inT2DM and LADA

Parameters	T2DM	LADA	P Value
Mean age at onset of diabetes	34.84±6.32	29.87±7.92	**<0.01
Mean BMI (Kg/m^2)	25.9±4.45	24.3±6.14	NS
Mean C-Peptide (ng/ml)	2.62±0.85	1.41±0.31	**<0.01
GAD 65 Antibody	2.39±1.11	8.64±4.38	**<0.01
IA2 Antibody	5.47±1.16	10.44±2.20	**<0.01
HOMA-IR	5.77±2.3	3.94±0.64	**<0.01

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*Comparative data of different quantitative parameters between T2DM and LADA are presented in the form of Mean±SEM (Standard Error Mean/Standard Deviation); Correlation between those type of diabetes carried out by Post HOC Tuckey's One way ANOVA test; ** signified as statistically significant, NS signified as Nonsignificant.

DISCUSSION:

In the literature, the categorization of LADA has been characterised rather controversially [13,14]. Low C-peptide levels and positive GAD antibodies (GADA) in a high percentage of patients before and at the onset of diabetes are the most common features of LADA other common features of LADA include age of patients 35 years, non-obesity, insulin dependency (which occurs more frequently within 1 or 3 years, but can occur later within 10 years), low C-peptide levels, and positive GAD antibodies (GADA) in a high percentage of patients before and at the onset of diabetes [13]. In addition to GADA, additional islet cell-specific antibodies, such as ICA (islet cell antibodies), insulin autoantibodies, and IA-2-A (protein tyrosine phosphatase-like protein IA-2 antibodies), are utilised as predictors in individuals with autoimmune diabetes [15]. The presence of a single positive GADA test is recognised to be an excellent predictor of insulin dependence in adult diabetes patients [16,17], while IA-2-A has also been shown to be a powerful predictor [18]. C-peptide, a measure of residual -cell function, diminishes more slowly in LADA than it does in T1DM. As a result, a link has been shown between the age at which autoimmune diabetes was diagnosed and fasting C-peptide levels [19]. Knowledge of pathophysiology and disease features is critical for implementing national preventive policies and appropriately treating diabetic patients, allowing safe and successful treatments [20]. There is strong evidence that people with LADA should be treated differently from those with type 2 diabetes [21]. According to studies, type 2 diabetes accounts for a significant portion of the diabetic population, accounting for 80–90% of all diabetics [22]. Furthermore, around 20% of individuals diagnosed with LADA may develop type 2 diabetes [23]. The current research population indicated that the prevalence of type 2 diabetes was the greatest (84.5 percent) and LADA (15.5 percent) out of 200 diabetics.

Diabetes prevalence varies by geographical region, ethnicity, genetic, and environmental variables in both men and women. According to worldwide diabetes prevalence surveys, men have a greater diabetes prevalence than women [24]. According to the findings of the current study, diabetes is more frequent in males (55%) than in women (45%). Thus, the findings are consistent with the data provided by *S. Wild* et al and *H. Basavanagowdappa* et al. [24, 25]. Males were shown to have a higher prevalence of type 2 diabetes (53%) than females (47%); similarly, males had a higher incidence of LADA (65%) than females (35%). This implies that males are more likely than females to acquire LADA, but in T2DM, males and females are virtually equally afflicted.

According to studies, the average age of diabetics varies substantially. The present study reported that average age of LADA (33.26 ± 7.01 years) patients was found to be significantly lower than type 2 diabetes (37.20 ± 6.23 years). The average age at start is a crucial determinant in defining the type of diabetes and the treatment plan that will be chosen for the patient. One of the key distinguishing features of LADA, according to data provided by *P. Zimmet* et al, is adult age at onset (>25 years) [7]. The present study showed that the average age at onset of diabetes in patients with LADA (29.87 ± 7.92 years) was significantly lower than patients with type 2 diabetes (34.84 ± 6.32 years) ($P < 0.01$). Further research into the prevalence of diabetes in various age groups indicated that type 2 diabetes was found to be most common in the age group of 36-45 years (59.17%), as well as in the age group of 26-35 years (37.28%), but it was seldom detected in the age group of 18-25 years (3.55%). Similarly, LADA was found to occur most frequently in 36–45 years of age (41.94%) and also in 26-35 years of age (38.71%) but few cases were reported in 18-25 years of age (19.35%). However, when comparing the two groups, it is shown that LADA is nearly always identified in all age groups beginning at the age of 18 as opposed to T2DM, which is more likely to develop beyond the age of 30. The study findings are consistent with the findings of *P. Brahmkshatriya* et al [34].

BMI values of patients with type 2 diabetes revealed that the majority of these individuals (42.60%) were overweight, with a substantial proportion of these

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patients being obese (15.39%). There were a substantial proportion of healthy individuals (42.01%) with T2DM. This suggests that the findings are consistent with the current research from the *American Diabetes Association*, which claims that obesity is one of the primary factors contributing to the development of type 2 diabetes and insulin resistance [27]. The majority of the patients (51.61%) had BMI values comparable to healthy people, indicating that the progressive β-cell death in LADA is inadequate to produce considerable weight loss. According to *B. Mlinar* et al, BMI levels in LADA patients are lower than in type 2 diabetes patients [28]. But in comparison of both the groups of diabetes, the BMI values of LADA (24.3±6.14) and T2DM (25.9±4.45) patients did not show much significant difference.

The influence of a familial history of diabetes (FHD) on LADA is less well understood than that of type 1 and type 2 diabetes [29]. *R Turner* et al and *T Tuomi* et al found that LADA had the same genetic characteristics as type 1 diabetes, including an increased prevalence of HLADQB1 genotypes [30, 31]. According to the findings of a British research by *H. A. Castleden* et al, 33% of individuals with LADA had relatives who have type 2 diabetes. [32]. The results of family history in different types of diabetes revealed no significant differences, but the presence of family history (58.06%) was found in LADA patients, whereas *S Carlsson* et al reported that the presence of family history was an important risk factor for the development of LADA [26]. The notable presence (73.96%) of family history in type 2 diabetes is consistent with the notion that type 2 diabetes is largely genetic in origin.

Majority of enrolled patients in the study with T2DM (98.82%) were treated with oral hypoglycemic agents (OHA) while none of them were on insulin or a combination of insulin and OHA, implying the development of progressive insulin dependence due to impaired insulin secretion via various mechanisms, as reported by *American Diabetes Association* and *G. Biesenbach* et al [27, 33]. Initial response to OHA therapy is one of the key features of LADA patients [7]. In this study, OHA was used to treat the majority of LADA patients (70.96%). A key distinguishing trait for LADA patients would be an early response to OHA with progressive insulin dependence found in people younger than the normal age of onset of type 2 diabetes. Insulin dependence develops over time, with progressive β-cell death, necessitating a multi-therapeutic approach. In accordance with the published literature, a substantial number of LADA patients (29.04%) were found to be using a combination of insulin and OHA [34]. *M Landin Olsson* et al proposed that the observation would aid in the development of an effective therapeutic regimen for LADA patients, namely, that a combined treatment should be prescribed at the time of LADA diagnosis to preserve the remaining β-cell mass, though it is still unknown whether early treatment with insulin is beneficial for the remaining β-cells. [35].

C-peptide is secreted at equimolar quantities with insulin but is not destroyed as quickly. As a result, measuring C-peptide is a useful test for quantifying insulin and, as a result, evaluating β-cell activity. Because LADA is an autoimmune form of diabetes characterised by progressive β-cell destruction, measuring C-peptide levels would be a useful tool for assessing insulin secretion and β-cell function [34]. The C-peptide measurement revealed a significant difference between the two groups, with low levels of C-peptide in LADA patients (1.4 ± 0.31 ng/mL) compared to individuals with type 2 diabetes (2.62 ± 0.85 ng/mL) ($P < 0.01$). This is consistent with the findings of *P Zimmet* et al [7]. Many additional studies have found that LADA (also known as Ab positive type 2 diabetes) individuals had lower C-peptide levels than Ab negative type 2 diabetic patients [36-38]. In both situations, low C-peptide levels indicate insulin insufficiency caused by autoimmune cell death. Patients with type 2 diabetes had increased C-peptide levels, indicating hyperinsulinemia as a result of the compensatory increase in insulin production caused by insulin resistance [34].

The existence of autoantibodies against islet cell antigens in the patients' sera, which is prevalent in both type 1 diabetes and LADA, demonstrates the immunological evidence. These antigens consist of glutamic acid decarboxylase 65 kDa (GAD65) and insulinoma-associated antigen (IA2) [39]. As a result, estimating GAD autoantibodies can be a useful diagnostic sign for LADA and, in certain cases, IA2. GAD autoantibody levels over 5.0 IU/mL showed the presence of GAD autoantibodies, while IA2

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autoantibody levels above 7.0 IU/mL indicated the presence of IA2 autoantibodies, whereas values below this indicated the absence of autoantibodies. The results of autoantibody testing indicated that individuals with LADA had a high level of GAD65 and IA2. *A Gottsater* et al and *H Castleden* et al found that the absence of GAD autoantibodies in type 2 diabetes suggests that the illness is not autoimmune [40, 41].

The involvement of insulin resistance in the pathogenesis of LADA is debatable; the degree of insulin resistance in LADA has been reported to be lower than in type 2 diabetes and equivalent to type 1 diabetes [42, 43]. We recently evaluated insulin resistance in LADA and T2DM using the homeostasis model, and T2DM had higher HOMA IR ((5.77±2.3) than LADA (3.94±0.64) (P<0.01). Diabetes develops early in the β-cell-destructive process in LADA due to increased insulin resistance [44].

CONCLUSION:

Patients with T2DM account for the majority of the population, but the frequency of LADA patients is also on the rise. According to the present study, both T2DM and LADA tend to influence males more than females, and the adult age of onset (30–40 years) is also quite similar. Additionally, both T2DM and LADA patients exhibited an initial response to the OHA treatment regimen. The LADA patients, on the other hand, had low C-peptide levels and a high level of GAD autoantibodies. As a result, determining C-peptide levels and GAD autoantibodies is strongly suggested for LADA confirmation. The existence of GAD autoantibodies in LADA suggests that more research into their probable role in the disease's aetiology may be beneficial. Finally, C-peptide levels and GAD autoantibodies determination can be used as confirming diagnostic indicators for LADA patients in a diabetic population. Appropriate identification of LADA would assist to avoid misdiagnosis as type 2 diabetes and would aid in the best management of LADA.

ABBREVIATIONS:

T2DM – Type 2 Diabetes Mellitus

LADA – Latent Autoimmune Diabetes in Adults

GAD65 – Glutamic Acid Decarboxylase 65kDa

IA2 – Insulinoma Associated Antigen

BMI – Body Mass Index

OHA – Oral Hypoglycemic Agents

HOMA IR – Homeostatic Model Assessment Insulin Resistance

DECLARATION:

Ethics approval and consent to participate: Written informed consent was obtained from the subjects, for participating in this study. The study was approved by the Ethics Committee for research on Human Subjects of the MGM Institute of Health Sciences, Navi Mumbai, India.

Consent for publication: The subjects provided written informed consent for the publishing of this study.

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REFERENCES:

1. J. M. Diamond, “Diabetes running wild,” Nature, vol. 357, no. 6377, pp. 362–363, 1992.
2. P. Z. Zimmet, “The pathogenesis and prevention of diabetes in adults: genes, autoimmunity, and demography,” Diabetes Care, vol. 18, no. 7, pp. 1050–1064, 1995.
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. Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, Buzzetti R, et al. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. Diabetes Care 2013;36:908-13.
5. Maddaloni E, Lessan N, Al Tikriti A, Buzzetti R, Pozzilli P, Barakat MT. Latent autoimmune diabetes in adults in the United Arab Emirates:

clinical features and factors related to insulin-requirement. PLoS One 2015;10: e0131837.
6. R. D. Leslie and C. Valeri, "Latent autoimmune diabetes in adults," Diabetes Voice, vol. 48, no. 4, pp. 39–42, 2003.
7. P. Zimmet, R. Turner, D. McCarty, M. Rowley, and I. Mackay, "Crucial points at diagnosis: type 2 diabetes or slow type 1 diabetes," Diabetes Care, vol. 22, supplement 2, pp. B59–B64, 1999.
8. P. Pozzilli and U. Di Mario, "Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabetes off the adult): definition, characterization, and potential prevention," Diabetes Care, vol. 24, no. 8, pp. 1460–1467, 2001.
9. A. Falorni and F. Calcinaro, "Autoantibody profile and epitope mapping in latent autoimmune diabetes in adults," Annals of the New York Academy of Sciences, vol. 958, pp. 99–106, 2002.
10. M. Landin-Olsson, "Latent autoimmune diabetes in adults," Annals of the New York Academy of Sciences, vol. 958, pp. 112– 116, 2002.
11. L. Wolfe, 2006, http://www.isletsofhope.com.
12. Brahmkshatriya PP, Mehta AA, Saboo BD, Goyal RK. Characteristics and Prevalence of Latent Autoimmune Diabetes in Adults (LADA). *ISRN Pharmacol*. 2012; 2012:580202. doi:10.5402/2012/580202.
13. Zimmet P, Turner R, McCarty D, Rowley M, Mackay J. Crucial points at diagnosis. Diabetes Care 1999; 22 [Suppl 2]: B59–B63
14. Monge L, Bruno G, Pinach S et al. Clinically orientated approach increases the efficiency of screening latent autoimmune diabetes in adults (LADA) in a large clinic-based cohort of patients with diabetes onset over 50 years. Diabet Med 2004; 21: 456–458
15. Pietropaolo M, Peakman M, Pietropaolo SL et al. Combined analysis of GAD65 and ICA512 (IA-2) autoantibodies in organ and non-organ-specific autoimmune diseases confers high specificity for insulin-dependent diabetes mellitus. J Autoimmunity 1997; 11: 1–10
16. Kasuga A, Maruyama T, Nakamoto S, Ozawa Y, Suzuki Y. High-titer autoantibodies against glutamic acid decarboxylase plus autoantibodies against insulin and IA-2 predicts insulin requirement in adult diabetic patients. J Autoimmunity 1999; 12: 131–135
17. Schranz DB, Bekris L, Landin-Olsson M et al. Newly diagnosed latent autoimmune diabetes in adults (LADA) is associated with low level glutamate decarboxylase (GAD65) and IA-2 autoantibodies. Hormon Metab Res 2000; 32: 133–138
18. Kanungo A, Sanjeevi CB. IA-2 autoantibodies are predominant in latent autoimmune diabetes adults patients from eastern India. Ann NY Acad Sci 2003; 1005: 390–394
19. Barker A, Lauria A, Schloot N, Hosszufalusi N, Ludvigsson J, Mathieu C, et al. Age-dependent decline of β-cell function in type 1 diabetes after diagnosis: a multi-centre longitudinal study. Diabetes Obes Metab 2014; 16:262-7.
20. Maddaloni E, Pozzilli P. SMART diabetes: the way to go (Safe and Multifactorial Approach to reduce the Risk for Therapy in diabetes). Endocrine. 2014; 46:3–5. doi: 10.1007/s12020-013-0128-3 PMID: 24381129
21. 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. doi: 10.1210/jc.2007-2267 PMID: 18397986
22. R. D. Leslie and C. Valeri, "Latent autoimmune diabetes in adults," Diabetes Voice, vol. 48, no. 4, pp. 39–42, 2003.
23. M. Landin-Olsson, "Latent autoimmune diabetes in adults," Annals of the New York Academy of Sciences, vol. 958, pp. 112– 116, 2002.
24. S. Wild, G. Roglic, A. Green, R. Sicree, and H. King, "Global prevalence of diabetes: estimates for the year 2000 and projections for 2030," Diabetes Care, vol. 27, no. 5, pp. 1047–1053, 2004.
25. H. Basavanagowdappa, A. K. Prabhakar, P. Prasannaraj, K. C. Gurudev, and V. Suma, "Study of prevalence of diabetes mellitus and impaired fasting glucose in a rural population," International Journal of Diabetes in Developing Countries, vol. 25, no. 4, pp. 98–101, 2005.
26. S. Carlsson, K. Midthjell, and V. Grill, "Influence of family history of diabetes on incidence and prevalence of latent autoimmune diabetes of the adult: results from the Nord-Trøndelag health

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study," Diabetes Care, vol. 30, no. 12, pp. 3040–3045, 2007.
27. American Diabetes Association, "Diagnosis and classification of diabetes mellitus," Diabetes Care, vol. 29, 1, pp. S43–S48, 2006.
28. B. Mlinar, J. Marc, A. Janez, and M. Pfeifer, "Molecular mech- ˇ anisms of insulin resistance and associated diseases," Clinica Chimica Acta, vol. 375, no. 1-2, pp. 20–35, 2007.
29. S. Fourlanos, F. Dotta, C. J. Greenbaum et al., "Latent autoimmune diabetes in adults (LADA) should be less latent," Diabetologia, vol. 48, no. 11, pp. 2206–2212, 2005.
30. R. Turner, I. Stratton, V. Horton et al., "UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes," The Lancet, vol. 350, no. 9087, pp. 1288–1293, 1997.
31. T. Tuomi, A. Carlsson, H. Li et al., "Clinical and genetic char- ˚ acteristics of type 2 diabetes with and without GAD antibodies," Diabetes, vol. 48, no. 1, pp. 150–157, 1999.
32. H. A. Castleden, B. Shields, P. J. Bingley et al., "GAD antibodies in probands and their relatives in a cohort clinically selected for Type 2 diabetes," Diabetic Medicine, vol. 23, no. 8, pp. 834– 838, 2006.
33. G. Biesenbach, M. Auinger, M. Clodi et al., "Prevalence of LADA and frequency of GAD antibodies in diabetic patients with end-stage renal disease and dialysis treatment in Austria," Nephrology Dialysis Transplantation, vol. 20, no. 3, pp. 559– 565, 2005.
34. Brahmkshatriya PP, Mehta AA, Saboo BD, Goyal RK. Characteristics and Prevalence of Latent Autoimmune Diabetes in Adults (LADA). *ISRN Pharmacol*. 2012; 2012:580202. doi:10.5402/2012/580202.
35. M. Landin-Olsson, "Latent autoimmune diabetes in adults," Annals of the New York Academy of Sciences, vol. 958, pp. 112– 116, 2002.
36. American Diabetic Association, "Standards of medical care in diabetes-2007," Diabetes Care, vol. 30, 1, no. S4, p. S41, 2007.
37. L. Groop, G. F. Bottazzo, and D. Doniach, "Islet cell antibodies identify latent type I diabetes in patients aged 35–75 years at diagnosis," Diabetes, vol. 35, no. 2, pp. 237–241, 1986.
38. A. Kasuga, T. Maruyama, Y. Ozawa et al., "Antibody to the Mr 65,000 isoform of glutamic acid decarboxylase are detected in non-insulin-dependent diabetes in Japanese," Journal of Autoimmunity, vol. 9, no. 1, pp. 105–111, 1996.
39. M. J. Clare-Salzler, A. J. Tobin, and D. L. O. Kaufman, "Glutamate decarboxylase: an autoantigen in IDDM," Diabetes Care, vol. 15, no. 1, pp. 132–135, 1992.
40. A. Gottsater, M. Landin-Olsson, A. Lernmark, P. Fernlund, and G. Sundkvist, "Islet cell antibodies are associated with β cell failure also in obese adult-onset diabetic patients," Acta Diabetologica, vol. 31, no. 4, pp. 226–231, 1994.
41. R. A. DeFronzo, "Pathogenesis of type 2 (non-insulin-dependent) diabetes mellits: a balanced overview," Diabetologia, vol. 35, no. 4, pp. 389–397, 1992.
42. Behme MT, Dupre J, Harris SB, Hramiak IM, Mahon JL 2003 Insulin resistance in latent autoimmune diabetes of adulthood. Ann NY Acad Sci 1005:374–377.
43. Zinman B, Kahn SE, Haffner SM, O'Neill MC, Heise MA, Freed MI 2004 Phenotypic characteristics of GAD antibody-positive recently diagnosed patients with type 2 diabetes in North America and Europe. Diabetes 53:3193–3200.
44. Ramachandra G. Naik, Barbara M. Brooks-Worrell, Jerry P. Palmer, Latent Autoimmune Diabetes in Adults, *The Journal of Clinical Endocrinology & Metabolism*, Volume 94, Issue 12, 1 December 2009, Pages 4635–4644, https://doi.org/10.1210/jc.2009-1120

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