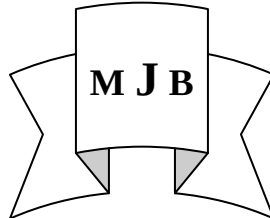


Detection of Latent Autoimmune Diabetes of Adults among Type 2 Diabetic Patients Using Glutamic Acid Decarboxylase Antibodies

Safaa Ali Khudhair

Dept. of Medicine, College of Medicine, Kufa University, Al-Najaf, Iraq.



Abstract

Background: Latent autoimmune diabetes of adults (LADA) is a slowly progressive form of autoimmune diabetes initially managed with diet and oral hypoglycemic agents before becoming insulin requiring. GADA are used for differential diagnosis between LADA and type 2 diabetes.

Objectives: To assess the prevalence of LADA among type 2 diabetic patients using glutamic acid decarboxylase (GAD) antibodies.

Methods: Cross sectional study conducted on 100 patients with primary diagnosis of T2DM, 52 female and 48 male, aged 30-70 years. The GADA test is used for diagnosis of LADA patients.

Results: Out of 100 patients with primary diagnosis of T2DM, 14 patients (14%) were positive for GADA.

Conclusions: LADA patients accounts for 14% of T2DM using GADA assay. Age, sex, and BMI had no significant effect on the prevalence of LADA patients among T2DM.

Key words: GADA, LADA, T2DM.

الخلاصة

الخلفية: مرض السكري ذاتي المناعة الخافي عند البالغين (LADA) يتقدم ببطء تدريجي من مرض السكري ذاتي المناعة ويدار في البداية عن طريق النظام الغذائي وادوية تخفيض داء السكري قبل أن يصبح معتمدا على الأنسولين . وتستخدم حامض الجلوتاميك كربوكسيل (GAD) لتشخيص بين LADA والسكري من النوع ٢.

الأهداف: لتقييم مدى انتشار LADA بين نوع ٢ من مرضى السكري باستخدام الأجسام المضادة لحامض الجلوتاميك كربوكسيل. **الأساليب:** دراسة مقطعية أجريت على ١٠٠ مريض مشخصين ب T2DM, 52 من الذكور و ٤٨ أنثى، الذين تتراوح أعمارهم بين ٣٠-٧٠ عاما. يستخدم اختبار GADA لتشخيص مرضى LADA.

النتائج: كانت النتيجة ايجابية في ١٤ من أصل ١٠٠ من المرضى الذين يعانون من التشخيص الأولي T2DM, **الاستنتاجات:** كانت نسبة المرضى 14% LADA من T2DM باستخدام مقاييس GADA. لم يكن للعمر والجنس، ومؤشر كتلة الجسم تأثير كبير على انتشار LADA عند المرضى الذين يعانون من T2DM.

Introduction

Anti-glutamic acid decarboxylase antibodies (GADA): Glutamate decarboxylase or glutamic acid

decarboxylase (GAD) is an enzyme that catalyzes the decarboxylation of glutamate to γ -Aminobutyric acid (GABA) and CO_2 . GAD uses pyridoxal phosphate as a cofactor. In mammals,

GAD exists in two isoforms encoded by two different genes - Gad1 and Gad2. These isoforms are GAD₆₇ and GAD₆₅ with molecular weights of 67 and 65 kDa, respectively. GAD₆₇ and GAD₆₅ are expressed in the brain where GABA is used as a neurotransmitter, GAD₆₅ is also expressed in the pancreas[1].

Both GAD₆₇ and GAD₆₅ are targets of autoantibodies in people who later develop type 1 diabetes mellitus or latent autoimmune diabetes. Injections with GAD₆₅ has been shown to preserve some insulin production for 30 months in humans with type 1 diabetes[1].

Anti-glutamic acid decarboxylase antibodies were found in the majority of new-onset insulin-dependent diabetic (IDDM) patients and those at risk of the disease. In non-insulin-dependent diabetic (NIDDM) patients, the presence of GADA has led to the suggestion that these patients are perhaps a subset with latent IDDM, (LADA). It has been estimated that 5% of NIDDM patients are LADA subjects with GADA[2-3].

Latent Autoimmune Diabetes of Adults (LADA)

In 1986, Groop et al.[4] reported a subgroup of type 2 diabetic patients who, despite having islet autoantibodies, which showed preserved β -cell function. The type of diabetes in these patients was referred to as latent type 1 diabetes, showing clearly different features from classic type 1 and classic type 2 diabetes. Later, Tuomi et al.[2] and Zimmet et al.[5] launched that the eponym LADA (latent

autoimmune diabetes in adults) had slowly progressive form of autoimmune diabetes initially managed with diet and oral hypoglycemic agents before becoming insulin requiring.

Wroblewski et al.[6] mentioned that the prevalence of LADA patients among age group 40–75 years is 10%, however the prevalence raised to 25% among type 2 diabetic patients younger than 35 years of age[7].

Although controversy exists, the following diagnostic criteria for LADA are suggested: age between 25 and 65 years; absence of ketoacidosis at diagnosis or immediately thereafter, without insulin requirement for 6-12 months; and presence of autoantibodies (especially GADA)[8].

It is important to clarify that obesity does not exclude LADA. Obese type 2-like diabetic patients with islet antibodies show progressive β -cell failure[9].

The objective of this study was to assess the prevalence of LADA among type 2 diabetic patients using GAD antibodies.

Patients and Methods

This is a cross sectional study conducted on 100 patients with primary diagnosis of T2DM aged 30-70 years (56.3 ± 10.7), 52 female and 48 male, in AL-Najaf center for diabetes and endocrine, from April 2010 to April 2011.

The patients were randomly selected, hemoglobin A1c was reviewed for assessment of diabetic control, BMI was

measured, and 5-ml blood sample was collected from each patient for GADA test. ELIZA method was used for detection of GADA.

The average duration of DM was 1-20 years (8.5 ± 5.3). All patients were on oral hypoglycemic agents, patient on insulin therapy are excluded.

t-test has been used for statistical analysis, and p value of < 0.05 considered significant.

LADA patients was 30-68 years (55 ± 11), 8 male and 6 female, BMI was (31.8 ± 3.2) kg/m^2 , and average duration of DM was 1– 8 years. There was no significant effect of age, sex, and BMI on the prevalence of LADA patients. (Table 1).

The control of DM was significantly better in T2DM patients than LADA patients. (Table 2).

Results

The results of this study showed 14 (14%) were positive for GADA. Age of

Table 1 The relation between age, sex, BMI and LADA.

Index		T2DM	LADA	p-value
Age (yrs)	≤ 40	6	3	0.18
	> 40	80	11	
Sex	male	40	8	0.47
	female	46	6	
BMI (kg/m^2)	≤ 30	20	6	0.25
	> 30	66	8	

Table 2 Diabetic control in LADA patients.

Type of DM	Good control $\text{HbA1c} < 7$	Poor control $\text{HbA1c} \geq 7$
T2DM	54	30
LADA	4	10

p-value 0.02

Discussion

The results of this study showed that the prevalence of LADA was 14% among diagnosed T2DM patients aged 30-70 years; this is roughly similar to other studies by Wroblewski et al.[6] who

mentioned a prevalence of 10% among age group 40–75 years. In a series of 256 patients > 25 years, Calsolari MR et al[8] found that 26 (10.2%) were GADA positive. In Korea, Kim CS et al[10] studied the biochemical markers in 647

nonobese patients with type 2 diabetes mellitus and found 10.1% were positive for GADA. Damanhoury LH et al[11] reported the GADA in 8/99 of Saudi Arabian diabetic patients.

Higher prevalence of LADA, with figure of 25% among patients younger than 35 years, had been reported by Borg et al[7], on other hand, Panz et al[12] have investigated the presence of anti-GAD antibodies in different groups of Black South Africans with diabetes and they found 2.5% (2/80) of subjects with type 2 diabetes were anti-GAD-positive. The variation in prevalence of LADA may be due to effect of the population studied, criteria used and antibodies analyzed[8].

There is controversy regarding the effect of age, sex and BMI on the prevalence of LADA. Some authors found the frequency of GADA in diabetes mellitus depends on age at diagnosis and gender[13], and LADA patients are usually thin or of normal weight[14]. Other said that body mass index levels might have rather limited use in connections with latent autoimmune diabetes[15].

The result of this study did not show significant association of LADA with the age, sex and BMI. Similar result reported by Juneja et al[16].

Glycemic control, in the present study, was poor in significant number of GADA positive patient compared to GADA negative patient, probably due to early need of insulin in such patients. Previous study estimated that ~10% of

patients with diabetes may have LADA but are often misdiagnosed and started on oral medications without any improvement in glycemic control[17].

Although not insulin requiring at diagnosis, LADA patients have impaired β -cell function at diagnosis. Hence, insulin treatment is indicated at diagnosis, and the effect of insulin in these patients is most likely against glucose toxicity[18].

Indeed, type 2 diabetic patients without GADA primarily treated with insulin demonstrated better β -cell function 2 years after diagnosis than those primarily treated with glibenclamide[19].

Rosário et al[20] agreed that patients with LADA should be differentiated on the basis of GADA titers and that patients with GADA titers > 20 U/ml benefit from early insulinization.

Conclusion

LADA patients accounts for 14% of T2DM using GADA assay. Age, sex, and BMI had no significant effect on the prevalence of LADA patients among T2DM.

References

1. Ludvigsson J, Faresjö M, Hjorth M, et al. GAD treatment and insulin secretion in recent-onset type 1 diabetes. *N Eng J Med* 2008; 359: 1909–20.
2. Tuomi T, Groop LF, Zimmet PZ, et al. Antibodies to glutamic acid decarboxylase reveal latent diabetes

mellitus in adults with a non-insulin-dependent onset of diabetes. *Diabetes* 1993; 42: 359-362.

3. Niskanen LK, Tuomi T, Karjalainen J, et al. GADAb in NIDDM. Ten-year follow-up from the diagnosis. *Diabetes Care* 1995; 18: 1557-1565.

4. 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 –241.

5. Zimmet PZ, Tuomi T, Mackay IR, et al. Latent autoimmune diabetes mellitus in adults (LADA): the role of antibodies to glutamic acid decarboxylase in diagnosis and prediction of insulin dependency. *Diabet Med* 1994; 11:299 – 303.

6. Wroblewski M, Gottsäter A, Lindgärde F, et al. Gender, autoantibodies, and obesity in newly diagnosed diabetic patients aged 40–75 years. *Diabetes Care* 1998; 21 :250 – 255.

7. Borg H, Arnqvist HJ, Björk E, et al. Evaluation of the new LADA and WHO criteria for classification of diabetes mellitus in young adults people (15–34 yrs) in the Diabetes Incidence Study in Sweden (DISS). *Diabetologia* 2003; 46 :173 –181.

8. Calsolari MR, Rosário PW, Reis JS, et al. Latent autoimmune diabetes of adult or slim type 2 diabetes mellitus. *Arq Bras Endocrinol Metabol.* 2008; 52:315-21.

9. Gottsäter A, Landin-Olsson M, Lernmark Å, et al. Islet cell antibodies

are associated with β -cell failure also in obese adult onset diabetic patients. *Acta Diabeto* 1994; 131 :226 –231.

10. Kim CS, Nam JH, Nam JS, et al. Biochemical characteristics of nonobese type 2 diabetic patients with glutamic acid decarboxylase antibody in Korea. *Metabolism* 2006;55:1107-12.

11. Damanhour L, Dromey JA, Christie MR, et al. Autoantibodies to GAD and IA-2 in Saudi Arabian diabetic patients. *Diabet Med.* 2005 22:448-52.

12. Panz VR, Kalk WJ, Zouvanis M, et al. Distribution of autoantibodies to glutamic acid decarboxylase across the spectrum of diabetes mellitus seen in South Africa. *Diabet Med* 2000; 17:524–7.

13. Lindholm E, Hallengren B, Agardh CD. Gender differences in GAD antibody-positive diabetes mellitus in relation to age at onset, C-peptide and other endocrine autoimmune diseases. *Diabetes Metab Res Rev.* 2004; 20:158-64.

14. Leslie RD, Williams R, Pozzilli P. Clinical review: Type 1 diabetes and latent autoimmune diabetes in adults: one end of the rainbow. *The Journal of Clinical Endocrinology and Metabolism* 2006; 91:1654–9.

15. Landin-Olsson M. Latent autoimmune diabetes in adults. *Annals of the New York Academy of Sciences* 2002; 958: 112–6.

16. Juneja R, Hirsch IB, Naik RG, et al. Islet cell antibodies and glutamic acid decarboxylase antibodies, but not the

clinical phenotype, help to identify type 1(1/2) diabetes in patients presenting with type 2 diabetes. Metabolism 2001; 50:1008 –1013.

17. Nathan, Buse JB, Davidson MB, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy. Diabetes Care. 2006; 29:1963–1972.

18. Gunnar Stenström, Anders Gottsäter, Ekaterine Bakhtadze, et al. Latent Autoimmune Diabetes in Adults. Definition, Prevalence, β -Cell Function,

and Treatment. Diabetes 2005; 54 :68-S72.

19. Alvarsson M, Sundkvist G, Lager I, 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 –2237.

20. Rosário PW, Reis JS, Fagundes TA, Latent autoimmune diabetes in adults (LADA): usefulness of anti-GAD antibody titers and benefit of early insulinization. Arq Bras Endocrinol Metabol. 2007; 51:8-10.