Prevalence of Latent Autoimmune Diabetes of Adult (LADA) among Type ٢ Diabetes Mellitus (D.M.٢) in Karbala

انتشار السكري المناعي الذاتي المتأخر الحدوث للبالغين بين السكري من النوع الثاني في كربلاء

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الخلاصة:
الهدف : هدف الدراسة هو تحديد انتشار السكري المناعي الذاتي المتأخر الحدوث للبالغين بين مجموعة مرضى السكري من النوع الثاني المشخصين سريريا.
المنهجية : تم تسجيل ٢٨٠ مريض سكري من النوع الثاني في هذه الدراسة ولقد تم تجميعهم من استشارية السكري في مشفى الحسين التعليمي في كربلاء للفترة من حزيران للعام ٢٠١٣ ولغاية كانون الثاني من العام الحالي ٢٠١٤ ولقد ضمنت المعلومات التالية في الاستفهام السريري لكل مريض:المعلومات الشخصية،التاريخ العائلي،نوع السكري،نوع العلاج،تحليل السكر في الدم قبل الإفطار،الهيموكلوبيين السكري،مؤشر كتلة الجسم،مدة المرض والمضاعفات الحاصلة بسبب السكري. النتائج حللت إحصائيا باحتساب نسبة السكري المناعي الذاتي المتأخر الحدوث للبالغين عند مرضى السكري من النوع الثاني واختبار مربع كاي.
النتائج : انتشار السكري المناعي الذاتي المتأخر الحدوث للبالغين عند مرضى السكري من النوع الثاني كان مساويا ل ١٢.١٪. إضافة إلى وجود فرق معنوي في التاريخ العائلي، ،تحليل السكر في الدم قبل الإفطار،الهيموكلوبيين السكري،مؤشر كتلة الجسم وفترة مرض السكر
الاستنتاج : تقدير نسبة او انتشار السكري المناعي الذاتي المتأخر الحدوث للبالغين سريريا هي اقل بكثير من واقعها الصحيح وعمر المريض يجب أن لايعتمد كوسيلة للتفريق بين أنواع السكري.
التوصيات : اعتماد تحليل المضادات الذاتية للأنسولين عند كل المرضى في بداية الإصابة بالسكري.

Abstract:
Objective: the aim of the study is to determine the prevalence of LADA among group of clinically diagnosed type ٢ diabetes mellitus.
Methodology: sample size equal to ٢٨٠ patients with type ٢ D.M. were subjected in this study, participating patients were consecutively recruited from Diabetes outpatient clinic in AL-Hussein Teaching Hospital in Karbala from June, ٢٠١٣ through January, ٢٠١٤. A clinical questioner containing personal data, family history, type of diabetes, type of treatment, FBS, HA١C, BMI, diabetes duration& complications of diabetes. For analysis of data Prevalence of LADA among D.M.٢ cases was calculated as the proportion of LADA cases in the D.M.٢ cases. The Chi square test ($X^٢$) was used to assess the significance (P-value) of differences in frequencies of categorical variables.
Results: prevalence of LADA among D.M.٢ patients was ١٢.١٪. A significant difference in family history, BMI, FBS, HA١C and duration of D.M was found between the studied groups.
Conclusion: The prevalence of LADA is clinically underestimated among D.M٢ patients and age of onset of diabetes should no longer be considered as a valid way to differentiate diabetes.
Recommendation: the study recommends screening for islet cell autoantibodies as GAD٦٥ for all patients with diabetes at onset or beginning of disease.
Key word: GAD٦٥, LADA, diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a group of metabolic diseases in which a patient has increase blood sugar, because the pancreas does not secret enough insulin, or unresponsiveness of cells to the insulin that is produced [(١)]. Diabetes mellitus is categorized into general categories: type١, type٢, gestational diabetes and other specific types. The specific types are group of a few dozen individual causes [(١)].Type ٢ diabetes is characterized by impaired β-cell function and may be accompanied with changes of the immune system [(٢)]. Latent autoimmune diabetes in adults (LADA) or Type ١.٥ diabetes has some clinical features of type ٢ diabetes & shows immunological abnormalities similar to those in type

١ diabetes, such as glutamic acid decarboxylase antibody (GADA) [٣].So far it is not understood why disease progression in LADA is slower than in type ١ diabetes despite the immunological similarities. Insulin secretion was reported to be intermediate in LADA compared with type ١ and type ٢ diabetes, whereas metabolic syndrome was similar in type ١ diabetes and LADA [٤].

Type ١.٥ diabetes is usually diagnosed after the age of ٣٥ years and there is no immediate requirment for insulin therapy [٥]. Approximately ١٠٪ to ٣٠٪ of adults with type ٢ diabetes test positive for autoantibodies, depending on the age and ethnicity of the study group [٦]. The immune-mediated destruction of beta-cells in type ١.٥ diabetics leads to insulin dependency more rapidly than in type ٢ diabetes, but the more attenuated genetic and immune factors associated with type ١.٥ diabetes as compared with type ١ diabetes lead to an older age at onset and a slower progression to insulin dependency [٧].The Clinical characteristics predictive of type ١.٥ diabetes include: Age < ٥٠ years, acute symptoms of hyperglycemia (polydypsia, polyuria, or unintentional weight loss), body mass index < ٢٥ kg per m², family history of autoimmune disease (thyroid disorders, celiac disease, type ١ diabetes, rheumatoid arthritis or any other form autoimmune disorder), personal history of autoimmune disease (thyroid disorders, celiac disease, type ١ diabetes, rheumatoid arthritis or any other form of autoimmune disorder). The presence of at least two of these clinical features (LADA risk score ≥ ٢) was found to have ٩٠ % sensitivity and ٧١ % specificity for identifying diabetic patients affected by type ١.٥ diabetes. Patients with one or no feature were unlikely to have LADA [٨].

Type ١.٥ diabetes and type ٢ diabetes populations can be distinguished from each other based on clinical features, but a large degree of overlap exists between the two types of diabetes. Hence, the use of immunogenetic markers, in particular the measurement of autoantibodies, remains the gold standard for identifying type ١.٥ diabetic patients. Identification of these patients is clinically relevant to their management as the early use of insulin resulted in β-cell preservation in several pilot studies [٩]. Type ١.٥ diabetes is diagnosed by the presence of pancreatic auto-antibodies, such as glutamic acid decarboxylase (GAD) antibodies in an adult initially presenting with non-insulin dependent diabetes [١٠].

PATIENTS AND METHOD

A ٢٨٠ individual were enrolled in this study at the period from June, ٢٠١٣ through January, ٢٠١٤. All patients were selected randomly from Diabetes outpatient clinic in AL-Hussein Teaching Hospital in Karbala; these patients were clinically diagnosed as type ٢ D.M, ١٣٥ males &١٤٥ females with age range from ٣٠-٧٣ years, and duration of disease between ١ month -٢٥ years. Descriptive variables of patients included: name, age, gender, type of diabetes, type of treatment (insulin, OHD, diet or mixed), FBS, HA١C, BMI, complications they were suffered due to D.M. and duration of disease. Serum samples were taken from all patients and subjected to ELISA analysis by GAD٦٥ ELISA kits (CUSABIO BIOTECH CO., LTD. USA) which is a solid phase enzyme immunoassay based on the sandwich technique, in which two monoclonal antibodies are directed against separated antigenic determinants on the GAD٦٥ molecule.

RESULTS

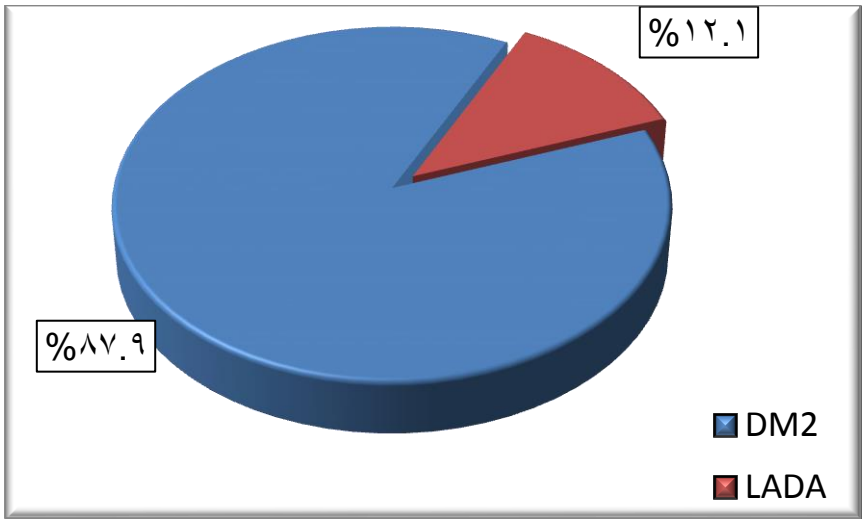

Figure١. Prevalence of LADA among ٢٨٠ D.M.٢ cases

Figure ١ shows that out of the ٢٨٠ patients with type II D.M., ٣٤ had LADA, GAD٦٥ positive this giving a prevalence of LADA among D.M.٢ patients equal to (١٢.١٪).

Table١. Comparison of baseline characteristics of LADA and DM٢ cases

Variable		DM٢ No.=٢٤٦		LADA No.=٣٤		Statistics
		No.	%	No.	%	
Age (years)	≤ ٣٠	٤٠	١٦.٣	١	٢.٩	
	٣١ – ٤٠	٤٤	١٧.٩	٣	٨.٨	X^2= ٧.٨
	٤١ – ٥٠	٥٠	٢٠.٣	٨	٢٣.٥	P= ٠.١٠
	٥١-٦٠	٧٢	٢٩.٢	١٥	٤٤.١	NS
	> ٦٠	٤٠	١٦.٣	٧	٢٠.٦	
Gender	Male	١٢٥	٥٠.٨	١٤	٤١.٢	X^2= ٠.٧٦
	Female	١٢١	٤٩.٢	٢٠	٥٨.٨	P= ٠.٣٨ NS
Family history	Positive	٢١١	٨٥.٨	٢١	٦١.٨	X^2= ١٠.٥
	Negative	٣٥	١٤.٢	١٣	٣٨.٢	P= ٠.٠٠١ Sig
BMI (kg/m^2)	Normal (١٨ - ٢٤.٩)	٢٣	٩.٣	١١	٣٢.٤	X^2= ١٤.٩
	Overweight (٢٥ - ٢٩.٩)	١٧٩	٧٢.٨	١٨	٥٢.٩	P= < ٠.٠٠١
	Obese (>=٣٠)	٤٤	١٧.٩	٥	١٤.٧	Sig
FBS (mg/dl)	Mean ± SD	٢٦٥ ± ٨٠		٢١٨ ±٧٩		٠.٠٠١ Sig
HA١C (%)	Mean ± SD	٩.٣ ± ١.٣		٨.٣ ± ١.٢		< ٠.٠٠١ Sig
Duration of DM (years)	< ٥	٥٤	٢١.٩	١٦	٤٧.١	X^2= ١٧.٤
	٥ – ٩	٣٩	١٥.٩	٥	١٤.٧	P= < ٠.٠٠١
	١٠ – ١٤	١٢٠	٤٨.٨	٥	١٤.٧	sig
	≥١٥	٣٣	١٣.٤	٨	٢٣.٥	
	Mean ± SD	١٠.٤ ± ٣.٢		٩.١ ± ٥.٣		
Type of treatment	With Insulin	٥٣	٢١.٥	٨	٢٣.٥	X^2=٠.٣
	Without Insulin	١٩٣	٧٨.٥	٢١	٦١.٨	P= ٠.٦١ NS
Complications	Positive	٩٤	٣٨.٢	٧	٢٠.٦	X^2= ٣.٣
	Negative	١٥٢	٦١.٨	٢٧	٧٩.٤	P= ٠.٠٧

	NS

The comparison of baseline characteristics of studied groups as it shown in table ١ revealed:

A significant differences in family history (P=٠.٠٠١); Positive family history was more frequent in D.M.٢ than LADA cases; ٢١١ (٨٥.٥٪) vs. ٢١ (٦١.٨٪), respectively.

A highly significant difference in BMI; D.M.٢ cases were more likely to be overweight and obese than LADA cases, (P<٠.٠٠١).

A highly significant difference in mean FBS and HA١C, D.M.٢ cases had higher mean FBS (٢٦٥ ± ٨٠) mg/dl higher mean HA١C (٩.٣٪ ± ١.٣٪) than LADA cases (the mean FBS was ٢١٨±٧٩, and the mean HA١C was (٨.٣٪ ± ١.٢٪)

Duration of D.M. was highly significant longer in D.M.٢ group than LADA group, (P<٠.٠٠١).

No significant differences had been found in age, gender, type of treatment or complications in between both groups, in all comparison , P>٠.٠٥.

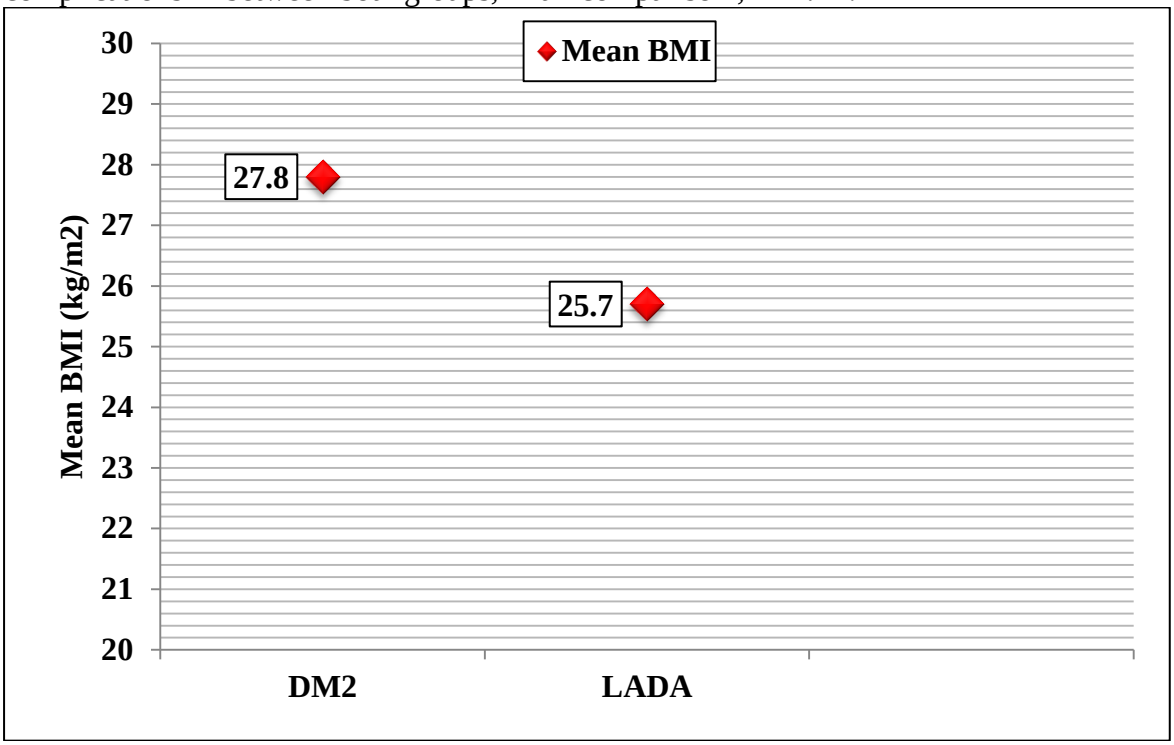

Figure٢. Comparison of mean BMI values of studied group

The mean BMI of D.M.٢ group was ٢٧.٨± ٣.٦ kg/m^{٢}, of LADA group was ٢٥.٧±٣.٥, it had been significantly found that patients in D.M.٢ group had the higher BMI value than LADA.

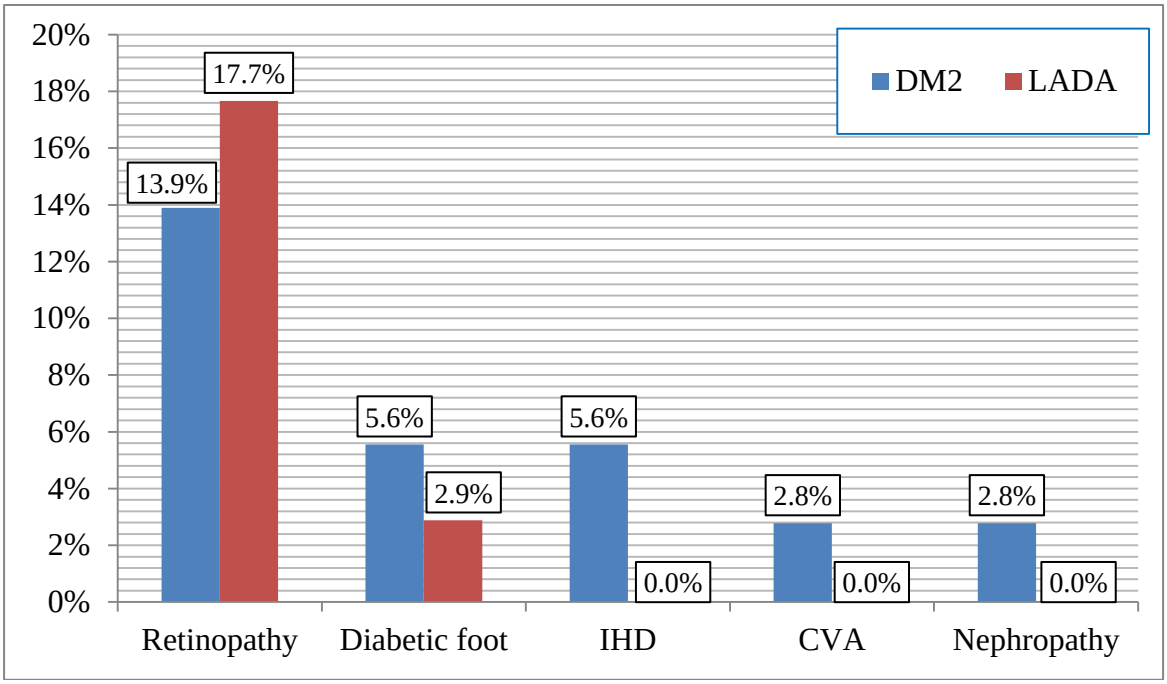

Figure٣. Proportional distribution of complications in DM٢ and LADA groups

LADA cases have ١٧.٧٪ retinopathy and ٢.٩٪ diabetic foot.

DISCUSSION

LADA is not a rare disease, and many subjects are still under diagnosed. Without awareness, a correct diagnosis of LADA is not easy. Adults with LADA may initially be diagnosed as having type ٢ diabetes based on their age, particularly if they have risk factors for type ٢ diabetes such as a strong family history or are obese.٨٠٪ of persons initially diagnosed with type ٢ but test positive for GAD progress to insulin dependency within ٦ years (some sources say between ٣–١٢ years after diagnosis) [١١].

Our study shows that from the ٢٨٠ diabetic patients, there were (٣٤) GADA positive, the prevalence of LADA was ١٢.١٪. This result is in line with what was obtained by Olufunmilayo study [١٢] who report prevalence rate equal to ١٤٪, also reports from Ghana where documented prevalence rates for LADA amongst people being managed for type ٢ DM was ١٣.٥٪ [١٣] and the study of Lutale et al., showed a level of islet cell positivity ٧.٣٪ [١٤]. However other studies done in Korea found lower prevalence rate of LADA ٤.٣٪ [١٥] & ٤.٧٪ [١٦]. Seissler and Scherbaum demonstrated the relative high frequency of this form of diabetes (approximately ٢٠٪) among type ٢ diabetic patients in the age range ٢٥-٤٤ years. This difference could be attributed to the difference in population ethnicity and age of onset of the disease [١٧].

Regarding demographic characteristics of the studied groups, although no significant difference in age between LADA & D.M.٢ Majority of the subjects with LADA in this study were in ٤١–٥٠, ٥١-٦٠ & >٦٠ age categories (٣٠/٣٤ cases) and less than ١١.٧٪ were in other age categories. This observation suggests that LADA increases with increasing age decade, confirming result observed by Olufunmilayo study [١٢] & Carlson et al. study [١٨] that older age was an important risk factor for LADA as for Type ٢ DM and this may suggest a potential role for insulin resistance in the pathogenesis of LADA. Similarly Chinese study found that the prevalence of LADA slowly increased with age up to ٦٠ years and was high in individuals aged ٥٠–٥٩ years [١٩].

Our study shows that the presence of LADA is non sex specific although the higher percentage (٥٨.٨٪) of patients positive for antiGAD autoantibodies in this study were

females, this may be due to the fact that autoimmune diseases are more common in females than males and the logical cause for this difference would be the sex hormones, females might respond more to conventional antigens due to sex hormones. This goes with other studies as Olufunmilayo study who found (٦٤٪) of subjects positive for antiGAD autoantibodies were females [١٢] & same result was clarified by Qi et al. [١٩].

A highly significant difference in BMI between LADA & D.M.٢ cases; D.M.٢ cases were more likely to be overweight and obese than LADA cases this is due to insulin resistant in those patients. This finding is similar to what was obtained by Genovese et al. as they concluded that, LADA patients are non obese in contrast to those who are actually type ٢ DM as they are mostly obese with BMI >٣٠ [٢٠]. Although ٥٢.٩٪ of LADA patients are overweight in our study, this may be due to the fact that they have low levels of insulin & improper treatment with oral hypoglycemic drugs. The proportion of overweight among subjects with LADA in this study was higher than those in normal weight category and this suggests insulin resistance as possible contributory factor in the pathogenesis of LADA amongst our patients. The mean BMI of our study LADA patients was ٢٥.٧ kg/m², which is lower than that of Western studies (٢٧.٥ to ٣٢ kg/m²), [٢١] . This result is in agreement with report done by Yul Hwangbo in Korea that found mean BMI was ٢٥.٣ kg/m² [١٥] and this may be explained due to different features related to different ethnic groups.

Significant positive family history for D.M.٢(٨٥.٨٪), although high percent of LADA (٦١.٨٪) have positive family history for type ٢ D.M., Olufunmilayo study reveal that ٣٩٪ of LADA patients have positive family history for type ٢ D.M. [١٢].

Duration of diabetes was highly significant longer in GAD negative than LADA group; this goes with studies done in Korea & Nigeria where longer duration of disease reported in D.M.٢ [١٥; ١٢].

Regarding insulin treatment ٢٣.٥٪ of LADA patients were already on insulin at the time of the study for glycaemic control, although statistically result is not significant. Other studies found that ١٥٪, ٣٧٪ of LADA cases were on insulin treatment at study time [١٥; ١٢] respectively, and this may be due to autoimmune destruction of the β-cells which has been reported to be present at diagnosis of diabetes in LADA patients [٦].

A higher proportion of subjects with LADA had evidence of microvascular complications of diabetes namely retinopathy while D.M.٢ cases had more macrovascular complications. The foregoing would suggest that macrovascular complications were more frequent in D.M.٢ patients, while LADA subjects manifest predominantly microvascular complications especially retinopathy. The poor indices of long term glycemic control in LADA may account for the observed higher percentage of LADA subjects with evidence of microvascular DM complications. This is in agreement with finding of study from Turkey [٢٢], Reports from Western Finland [١٩] & study of Olufunmilayo [١٢].

A highly significant difference in mean FBS and HA١C, D.M.٢ cases had higher mean FBS (٢٦٥ ± ٨٠) mg/dl & higher mean HA١C (٩.٣٪ ± ١.٣٪) than LADA cases, although LADA cases still have high level of FBS & HA١C (the mean FBS was ٢١٨±٧٩, and the mean HA١C was (٨.٣٪ ± ١.٢٪).This result is similar to Olufunmilayo study who revealed mean HA١C equal to ٨.٤±١.٨ in LADA patients [١٢]. In Yul Hwangbo report HA١C mean was ٨±٢.٤ for LADA cases versus ٧.٥±١.٦ for D.M.٢ cases, FBS mean ١٤٧.٣±٤٣.١ for LADA versus ١٣٥.٨±٤١.٣ for D.M.٢ cases [١٥], these differences in results in comparison to our study may be due to different patient's education, dietary habits & self care.

CONCLUSION:

١. The prevalence of LADA is clinically underreported among D.M٢ patients and age of onset of diabetes should no longer be considered as a valid way to differentiate diabetes.
٢. Patients with LADA who are characterized by autoimmunity to pancreatic beta cells show a clinical phenotypic with anthropometric features that are similar to type ١diabetic patients & differed from those clinically observed in patients with type ٢ DM.
٣. LADA increases with increasing age decade.
٤. D.M.٢ patients were more obese & overweight than LADA patients due to insulin resistant in those patients.

RECOMMENDATION:

١. Screening for islet cell autoantibodies should be done at onset of diabetes by simple & reliable test to confirm the autoimmune nature of disease.
٢. Type ٢ diabetic patients with clinical criteria of LADA patients should be screened for GADA as they considered as marker for autoimmunity to confirm the diagnosis of autoimmune diabetes in those patients for appropriate diabetic management, to predict insulin dependency & to prevent future complications due to poor glycemic control.

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