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PREVALENCE OF GAD AND IA2 ANTIBODIES IN CLINICALLY DIAGNOSED YOUNG INDIAN TYPE 2 DIABETES INDIVIDUALS WITH AGE OF ONSET OF DIABETES LESS THAN 35 YEARS

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ABSTRACT

Objectives: To determine the prevalence of GAD 65 and insulinoma associated protein 2 auto antibodies in clinically diagnosed type 2 diabetes with age of onset less than 35 years. **Materials and methods:** 381 patients were randomly selected from patients with age of onset of diabetes less than 35 years attending the outpatient department of Karnataka institute of endocrinology and research Bangalore over a period of 2 years. A fasting and post prandial blood sample was taken for estimation of plasma glucose by hexokinase method. HBA1C was measured by the high-performance liquid chromatography method using the Bio-rad Variant 2 turbo analyzer. Diagnosis of diabetes was made by using criteria of fasting plasma glucose ≥126 mg/dl and HBA1c ≥6.5%. GAD 65 and IA 2 antibodies were estimated using ELISA methods. **Results:** Age of onset of all type 2 diabetes subjects is less than 35 years. 34.6% and 60.6% of the subjects were in the age group of 20 to 30 and 31-40 years, 72.4% were males. Newly diagnosed subjects were 17.3%, duration of diabetes 1 to 5 years in 63.8% and 6 to 10 years in 14.2% of type 2 diabetes subjects. Consanguinity was present in 26.2% of subjects. BMI was 18.5 to 24.9 in 54.3% and 25 to 29.9 in 38.1% of subjects. Antibody positivity was detected in 29 (7.61%) of 381 subjects studied. GAD antibody positive in 22 (6.04%), IA 2 antibody positive in 5(1.3%) and 2(.52%) were positive for both antibodies in clinically diagnosed type 2 diabetes subjects. The clinical variables of age, BMI, waist circumference, hip circumference SBP, DBP, FPG, PPPG, HBA1C and fasting C-peptide were statistically similar between antibody positive and negative groups studied. **Conclusions:** Antibody positivity was detected in 29 (7.61%) of 381 subjects studied. GAD antibody positive in 22 (6.04%), IA 2 antibody positive in 5(1.3%) and 2(.52%) were positive for both antibodies in clinically diagnosed type 2 diabetes subjects. So if we test GAD antibodies in Indian type 2 diabetes subjects we can detect many LADA patients. It is not necessary to test other antibodies which will save lot of money when we do a large population or clinic based multicentre studies. Immunomodulator therapy in antibody positive type 2 diabetes subjects may help to reduce beta call destruction.

KEYWORDS: GAD antibodies, IA2 antibodies, C-Peptide.

INTRODUCTION

Type 2 diabetes in youth has increased enormously in India and in addition the incidence of even type 1 diabetes is increasing in youth. So there are some patients who have mixed features. Given the obesity epidemic, many youth with type 1 diabetes are either overweight or obese at diagnosis[1,2], making it difficult for clinicians to distinguish between type 1 and type 2 diabetes based on weight alone. The classic criteria for distinguishing between two major types of diabetes (i.e., age at onset and weight) are increasingly blurred; it is absolutely necessary to develop better methods of diabetes classification in youth.

A hallmark of autoimmune involvement in T2DM is the presence of circulating autoantibodies. Consistent evidence of islet cell autoimmunity in T2DM patients was reported in 1997 by Turner et al.[3] Glutamic acid decarboxylase (GAD) and islet cytoplasm auto antibodies were identified in 12% of over 3,000 T2DM patients aged between 25 and 65 years, recruited in UKPDS trial centers. In fact, evidence on the presence of circulating auto antibodies in type2 diabetes mellitus in adults has gradually emerged since the late 1970s.[4,5]

The largest cohort examined for diabetes-associated autoantibodies included over 6,000 consecutive adult-onset diabetic patients and revealed that the prevalence of adult-onset autoimmune diabetes in Europe was 9.7%. GAD autoantibodies were detected in most of these cases, with only a small subset of patients presenting other auto antibodies.[6] Patients aged 30-70 years were

designated with LADA if they were autoantibody-positive and did not require insulin treatment for >6 months after diagnosis. Overall, LADA was more prevalent than adult-onset T1DM, i.e. autoantibody-positive patients who required insulin treatment <6 months after diagnosis, with an odds ratio of 3.3.[6]

LADA is a distinct clinical entity, encompassing phenotypic features of T2DM and immunological similarities to T2DM, which have been extensively reviewed.[7] The genetic background of patients with LADA shares features of both T1DM and T2DM.[8]

Autoantibodies against β cells imply ongoing immune-mediated β-cell destruction, therefore these patients require insulin therapy earlier during disease progression compared to autoantibody-negative patients with T2DM.[9] Consequently, the prevention of β-cell destruction is imperative for these patients.

Adults in the UK Prospective Diabetes Study (UKPDS) who had positive GAD-65 antibodies and physician-diagnosed type 2 diabetes, oral treatment failed significantly more rapidly than in those without autoimmunity (94 vs. 14% at 6 years) (10). These and other studies suggest that there are clinically significant differences between autoantibody positive and negative type 2 diabetes.

The incidence of type 2 diabetes is increasing in youth of all ethnic origins, the importance of determining the effectiveness of treatment options is very important. This study examines islet autoimmunity in youth who were considered by diabetologists to have type 2 diabetes based on their clinical features. Clinical and laboratory differences between islet antibody-positive and antibody-negative participants at screening were studied.

Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made, **Assumptions: 1.**Dependent variables should be normally distributed, 2.Samples drawn from the population should be random, Cases of the samples should be independent.

Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis) on metric parameters. Leven`s test for homogeneity of variance has been performed to assess the homogeneity of variance. A t-test is a statistical test that is used to compare the means of two groups. It is often used in hypothesis testing to determine whether a process or treatment actually has an effect on the population of interest, or whether two groups are different from one another with the null hypothesis (H_0) is that the true difference between these group means is zero and the alternate hypothesis (H_a) is that the true difference is different from zero.

Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups, Non-parametric setting for Qualitative data analysis. Fisher Exact test used when cell samples are very small.

Significant figures
+ Suggestive significance (P value: 0.05<P<0.10)
* Moderately significant (P value: 0.01<P ≤ 0.05)
** Strongly significant (P value: P≤0.01)

Statistical software: The Statistical software namely SPSS 22.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS

Age of onset of all type 2 diabetes subjects is less than 35 years. 34.6% and 60.6% of the subjects were in the age group of 20 to 30 and 31-40 years, 72.4% were males. Newly diagnosed subjects were 17.3%, duration of diabetes 1 to 5 years in 63.8% and 6 to 10 years in 14.2% of type 2 diabetes subjects. Consanguinity was present in 26.2% of subjects. BMI was 18.5 to 24.9 in 54.3% and 25 to 29.9 in 38.1% of subjects. (Table 1-6)

Table 1: Age distribution of patients studied.

Age in Years	No. of Patients	%
<20	13	3.4
20-30	132	34.6
31-40	231	60.6
>40	5	1.3
Total	381	100.0

Mean ± SD: 31.29±5.56

Table 2: Gender distribution of patients studied.

Gender	No. of Patients	%
Female	105	27.6
Male	276	72.4
Total	381	100.0

Table 3: Age at onset-distribution of patients studied.

Age at onset	No. of Patients	%
10-20	38	10.0
21-30	197	51.7
31-40	146	38.3
Total	381	100.0

Mean ± SD: 28.19±5.17

Table 4: Duration-distribution of patients studied.

Duration	No. of Patients	%
New	66	17.3
1-5 Yr	243	63.8
6-10 Yr	54	14.2
11-15 Yr	13	3.4
16-20 Yr	5	1.3
>20 Yr	0	0.0
Total	381	100.0

Table 5: H/O Consanguinity-distribution of patients studied.

H/O Consanguinity	No. of Patients	%
No	281	73.8
Yes	100	26.2
Total	381	100.0

Table 6: BMI-distribution of patients studied.

BMI	No. of Patients	%
<18.5	19	5.0
18.5-24.9	207	54.3
25.0-29.9	145	38.1
>30.0	10	2.6
Total	381	100.0

Mean ± SD: 24.26±3.13

Antibody positivity was detected in 29 (7.61%) of 381 subjects studied. GAD antibody positive in 22 (6.04%), IA-2 antibody positive in 5(1.3%) and 2(.52%) were positive for both antibodies in clinically diagnosed type 2 diabetes subjects. (Table7)

Table 7: Group-distribution of patients studied.

Group	No. of Patients	%
Antibody negative	352	92.4
Antibody positive	29	7.61
Total	381	100.0

The clinical variables of age, BMI, waist circumference, hip circumference were statistically similar between antibody positive and negative groups studied. (Table 8)

Table 8: Comparison of clinical variables according to Antibody positive and negative of patients studied.

Variables	Antibody positive	Antibody negative	Total	P Value
Age	30.66±4.76	31.35±5.63	31.3±5.57	0.518
Age at onset	27.22±5.11	28.27±5.18	28.19±5.18	0.294
BMI	24.76±2.96	24.22±3.15	24.26±3.14	0.379
Waist circumference	89.45±8.69	86.62±8.8	86.84±8.82	0.097+
Hip circumference	93.52±7.21	92.25±6.6	92.35±6.64	0.325

The clinical variables of SBP, DBP, FPG, PPPG, HBA1C and fasting C-peptide were statistically similar between antibody positive and negative groups studied. (Table 9)

Table 9: Comparison of clinical variables according to Antibody positive and negative of patients studied.

Variables	Antibody positive	Antibody negative	Total	P Value
SBP (mmhg)	123.1±15.5	125.89±16.62	125.67±16.53	0.384
DBP (mmhg)	75.52±11.92	81.88±35.82	81.39±34.62	0.342
FPG	184.97±70.2	190.02±75.07	189.64±74.63	0.726
PPG	271.03±102.1	282.84±114.98	281.94±113.97	0.592
HbA1C	8.89±2.37	9.97±5.24	9.89±5.08	0.271
Fasting C-peptide	3.11±1.44	2.84±1.54	2.86±1.53	0.367

Macroalbuminuria was present in 7.1% of antibody negative and 3.4% of antibody positive type2 diabetes. Macroalbuminuria was two times more common in antibody negative than antibody positive type 2 diabetes subjects. (Table 10)

Table 16: Albuminuria-Frequency distribution of type 2 diabetes subjects in two groups studied.

Albuminuria	Antibody positive	Antibody negative	Total
<30	21(72.4%)	253(71.9%)	274(71.9%)
30-300	7(24.1%)	74(21%)	81(21.3%)
>300	1(3.4%)	25(7.1%)	26(6.8%)
Total	29(100%)	352(100%)	381(100%)

DISCUSSION

Our results emphasize the importance of determining islet autoantibodies in all youth and young adults thought to have type 2diabetes. Young people with clinically diagnosed type 2 diabetes and unrecognized islet autoimmunity may develop metabolic decompensation with rapid onset of a requirement for insulin. Knowledge of the presence of autoimmunity in overweight and obese young people with diabetes can help in initiation of early insulin therapy to avoid this preventable morbidity. All young people with type 2 diabetes should be instructed about the signs and symptoms of severe insulin deficiency and the importance of seeking prompt medical attention.

Future studies of antibody-positive adolescents and young adults with clinical features of type 2 diabetes are needed to determine their clinical course and optimal treatment regimens. It will be important to determine whether early insulin therapy or other treatment approaches will be effective in preserving residual β-cell function in these youth. In antibody positive type 2 diabetes we have to avoid sulfonylureas which increase the progression of beta cell destruction. So use of low dose insulin and DPP4inhibitors can sustain beta cell function in LADA.

Manifestations of autoimmunity are detectable in numerous pathologic conditions, which do not fall under the category of autoimmune diseases. Type 2 diabetes (T2DM) is one such example. Sustained research over the last 30 years has challenged the stereotypical view that T2DM is solely a metabolic disease by identifying autoimmunity as an overlapping features of type1diabetes (T1DM) and T2DM, which leads to impaired insulin secretion in β cells and promotes hyperglycemia.[11]

This is a unique study as both GAD and IA 2 antibodies were measured in young type 2 diabetes. There are few studies in India measuring only GAD antibodies. There are no studies published in India measuring both GAD and IA2 antibodies in type 2 diabetes. The IA 2 antibody kit is also not widely available in India. So this study has been compared with international studies in this table below. The following are the different studies from various countries. There is variation of antibody positivity in different ethnic groups. Studies from UK, Europe, Finland and Norway show higher positivity rate when compared to India, Japan, Korea, UAE and China.

Study	Country	Type of study	No. of sample size	Age range, yr	Autoantibody	Frequency of autoantibody positivity, %
UKPDS 25	United Kingdom	Clinical based	3,672	25–65	GAD and/or ICA	12
BOTNIA	Finland	Registry based	1,122	28–83	GAD and/or IA-2	9.3
Ehime study	Japan	Clinical based	4,980	>20	GAD	3.8
ADOPT	USA, Europe	Clinical based	4,357	30–75	GAD and/or IA-2	4.2
NIRAD	Italy	Clinical based	5,330	30–75	GAD and/or IA-2	4.5
HUNT	Norway	Population based	1,134	≥20	GAD	10
Tianjin	China	Population based	8,109	≥15	GAD	9.2
Maioli et al. (2010)	Italy (Sardinia)	Clinical based	5,568	35–70	GAD	4.9
Action LADA	Europe	Clinical based	6,810	30–70	GAD and/or IA-2, ZnT8	9.7
LADA China	China	Clinical based	5,324	≥20	GAD	5.9
Maddaloni et al. (2015)	United Arab Emirates	Clinical based	17,072	30–70	GAD and/or IA-2	2.6
Lee et al. (2009)	Korea	Clinical based	1,370	47–62	GAD and/or IA-2	5.1
Park et al. (2011)	Korea	Population based	884	44–60	GAD and/or IA-2, ZnT8	4.4
Roh et al. (2013)	Korea	Clinical based	323	29–63	GAD	5.3
Present study	Bangalore India	Clinic based	381	<35	GAD and IA 2	7.61

Longitudinal studies show that GAD autoantibodies and IA-2 autoantibodies remain positive for up to 12 years, although IA-2 autoantibodies decrease more rapidly with disease progression, while GAD autoantibodies tend to remain high even when C-peptide secretion becomes undetectable.[12] The present study detect antibody positivity in 29 (7.61%) of 381 subjects studied. GAD antibody positive in 22 (6.04%), IA 2 antibody positive in 5(1.3%) and 2(.52%) were positive for both antibodies in clinically diagnosed type 2 diabetes subjects. So if we test GAD antibodies in Indian type 2 diabetes subjects we can detect many LADA patients. It is not necessary to test other antibodies which will save lot of money when we do a large population or clinic based multicentre studies.

LADA clinical risk score was formulated by Spiros Fourlanos in a retrospective study titled a clinical screening tool identifies autoimmune diabetes in adults.[13] LADA clinical risk score includes clinical

features like age of onset<50 years; acute symptoms of hyperglycemia; BMI < 25 kg/sqmt; personal history of autoimmune disease; family history of autoimmune disease as the criteria for diagnosis for LADA. The presence of at least two of these distinguishing clinical features in type 2 diabetes that is LADA risk score ≥2 had 90% sensitivity for identifying LADA. If we use the above LADA clinical risk score the chance of getting antibody positivity increases and we can reduce the cost further in conducting studies. This was demonstrated in our other published study on use of Latent autoimmune diabetes in adults clinical risk score in type 2 diabetes in international journal of medical research and review.[14]

Diabetes development supported combined cellular pathology and insulin resistance has been mirrored by varied terms, like double diabetes, latent autoimmune disorder of the adult (LADA) or the young (LADY) or type1.5 DM. Its nosographic characterization is however a matter of discussion, so several T2DM patients could; go undiagnosed for autoimmune β-cell alterations which can have therapeutic consequences. LADA patients, who are generally defined by age of diagnosis >30 years, presence of circulating islet autoantibodies, and lack of insulin requirement for 6 months after diagnosis, need insulin earlier during disease progression, are likely to respond poorly to oral antidiabetic mediation[15], but they could respond favourably to immunomodulator therapy. However, anti-inflammatory and immunomodulatory therapies have also proven effective in improving the metabolic profile of many T2DM patients, possibly by interfering with autoimmune processes and thereby halting the decline of β-cell function.[16]

Autoimmunity is also each cause and consequence of β-cell dysfunction, imposing in either cases an extra disturbance in aldohexose physiological condition. The prevalence of T2DM is on the increase and if 10% of those patient positive for islet autoantibodies, then testing for islet autoantibodies as a part of the diagnostic assessment in T2DM has relevancy to a large group of adult patients, because it might contribute to the speed of progression to insulin requirement, notably within the absence of gross visceral obesity. Autoantibodies so facilitate distinguish adult patients with T1DM, LADA or T2DM, however conjointly the presence of self-reactive T cells in autoantibody-negative T2DM patients identifies associate pathology that's related to the metabolic dysregulation. Finding an explanation for autoimmune activation in T2DM in future research is definitely a remarkable path value following, because the immunogenic basis of T2DM might not be restricted to chronic inflammation in several patients. The identification of autoimmune aspects in patients with T2DM conjointly depends on winning metabolic management by immunomodulatory treatment that's still to be shown within the long run. Then the right T2DM sub classification has essential therapeutic implications as immunomodulatory regimens would possibly with efficiency to stop or abate reaction destruction of β cells.[17]

The estimation of islet antibodies in more and more type 2 diabetes subjects in future especially GAD antibodies will help to discover immune modulator therapies that can be used in antibody positive diabetes subjects. (LADA)

CONCLUSIONS

Antibody positivity was detected in 29 (7.61%) of 381 subjects studied. GAD antibody positive in 22 (6.04%), IA 2 antibody positive in 5(1.3%) and 2(.52%) were positive for both antibodies in clinically diagnosed type 2 diabetes subjects. So if we test GAD antibodies in Indian type 2 diabetes subjects we can detect many LADA patients. It is not necessary to test other antibodies which will save lot of money when we do a large population or clinic based multicentre studies. Immunomodulator therapy in antibody positive type 2 diabetes subjects may help to reduce beta call destruction.

ABBREVIATIONS

T2DM-Type 2 diabetes mellitus.
T1DM-Type 1 diabetes mellitus.
GAD-Glutamic acid decarboxylase.
IA2-Inuslinoma associated 2.
LADA-Latent autoimmune diabetes in adults.
LADY-Latent autoimmune diabetes in young.
UKPDS-United kingdom prospective diabetes study.
BMI-Body mass index.

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REFERENCES

1. Scott CR, Smith JM, Cradock MM, Pihoker C. Characteristics of youth-onset noninsulin-dependent diabetes mellitus and insulin-dependent diabetes mellitus at diagnosis. Pediatrics, Jul 1, 1997; 100(1): 84-91.
2. Libman IM, Pietropaolo M, Arslanian SA, LaPorte RE, Becker DJ. Changing prevalence of overweight children and adolescents at onset of insulin-treated diabetes. Diabetes care, Oct 1, 2003; 26(10): 2871-5.

3. Turner R, Stratton I, Horton V, Manley S, Zimmet P, Mackay IR, Shattock M, Bottazzo GF, Holman R, UK Prospective Diabetes Study (UKPDS) Group. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. The Lancet, Nov 1, 1997; 350(9087): 1288-93.
4. Irvine WJ, Gray RS, McCallum CJ, Duncan LJ. Clinical and pathogenic significance of pancreatic-islet-cell antibodies in diabetics treated with oral hypoglycaemic agents. The Lancet, May 14, 1977; 309(8020): 1025-7.
5. 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, Feb 1, 1993; 42(2): 359-62.
6. Hawa MI, Kolb H, Schloot N, Beyan H, Paschou SA, Buzzetti R, Mauricio D, De Leiva A, Yderstraede K, Beck-Neilsen H, Tuomilehto J. Adult-onset autoimmune diabetes in Europe is prevalent with a broad clinical phenotype: Action LADA 7. Diabetes care, Apr 1, 2013; 36(4): 908-13.
7. Naik RG, Brooks-Worrell BM, Palmer JP: Latent autoimmune diabetes in adults. J Clin Endocrinol Metab., 2009; 94: 4635-4644.
8. Cervin C, Lyssenko V, Bakhtadze E, Lindholm E, Nilsson P, Tuomi T, Cilio CM, Groop L. Genetic similarities between latent autoimmune diabetes in adults, type 1 diabetes, and type 2 diabetes. Diabetes, May 1, 2008; 57(5): 1433-7.
9. Pozzilli P, Di Mario U. Autoimmune diabetes not requiring insulin at diagnosis (latent autoimmune diabetes of the adult): definition, characterization, and potential prevention. Diabetes care, Aug 1, 2001; 24(8): 1460-7.
10. Zeitler P, Epstein L, Grey M, Hirst K, Kaufman F, T amborlane W, Wilfley D TODAY Study Group, Zeitler P, Epstein L, Grey M, Hirst K, Kaufman F, Tamborlane W, Wilfley D : Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes. Pediatr Diabetes, 2007; **8**: 74–87 CrossRef PubMedWeb of ScienceGoogle Scholar.
11. Wentworth JM, Fourlanos S, Harrison LC. Reappraising the stereotypes of diabetes in the modern diabetogenic environment. Nature Reviews Endocrinology, Sep, 2009; 5(9): 483-9.
12. Borg H, Gottsäter A, Fernlund P, Sundkvist G. A 12-year prospective study of the relationship between islet antibodies and β-cell function at and after the diagnosis in patients with adult-onset diabetes. Diabetes, Jun 1, 2002; 51(6): 1754-62.
13. Fourlanos S1, Perry C, Stein MS, Stankovich J, Harrison LC, Colman PG.A clinical screening tool identifies autoimmune diabetes in adults. Diabetes Care. 2006 May; 29(5): 970-5.
14. R. Anil Kumar, Surekha B Shetty, Lalitha R.Use of Latent autoimmune diabetes in adults clinical risk score in type 2 diabetes. Int J Med Res., Rev., 2017, 5(02):188-193 doi:10.17511/ijmrr. 2017.i02.14.
15. Tuomi T, Carlsson A, Li H, Isomaa B, Miettinen A, Nilsson A, Nissén M, Ehrnström BO, Forsén B, Snickars B, Lahti K. Clinical and genetic characteristics of type 2 diabetes with and without GAD antibodies. Diabetes, Jan 1, 1999; 48(1): 150-7.
16. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease. Nature reviews immunology, 2011; 11(2): 98-107.
17. Itariu BK, Stulnig TM. Autoimmune aspects of type 2 diabetes mellitus-a mini-review. Gerontology, 2014; 60(3): 189-96.