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Original Article

Pathology Section

Prevalence of Autoantibodies and HLA DR, DQ in Type 1 Diabetes Mellitus

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ABSTRACT

Introduction: Type I diabetes Mellitus (T1DM) is caused by autoimmune destruction of β-cells of pancreas. Two forms of T1DM are known called as 1A (autoimmune) and 1B (idiopathic).

Aim: Aim was to study the prevalence of Anti-TTG IgA, Anti-TPO, GADA, ZnT8 and IA-2 autoantibodies and HLA DR and DQ genes and its diagnostic value in T1DM.

Materials and Methods: Thirty four T1DM patients, 59 type 2 diabetes mellitus (T2DM) patients and 28 healthy controls were included in study. Antibodies levels were estimated by ELISA and HLA typing was performed by SSP-PCR method.

Result: The prevalence of various autoantibodies in T1DM were Anti-TTG 14.7%, Anti-TPO 17.65%, GADA 38.23%, ZnT8 11.76% and IA-2 5.88%. Only GADA and ZnT8 were significantly positive in T1DM. GADA (66.67%) and ZnT8 (33.33%) positivity was more in patients below 15 years age while levels of other antibodies were higher after 15 years age. All autoantibodies were detected in higher frequency in T1DM than in T2DM and controls.

HLA DR and DQ typing showed highly significant increase in DRB1*0301 (61.76%, p=0.00) and DQB1*0201 (64.71%, p=0.00) in T1DM. Subjects with HLA DRB1*0301 and DQB1*0201 had 80-100% positive prevalence of GADA, ZnT8, IA-2, Anti-TTG and Anti-TPO autoantibodies.

Conclusion: Combination of GADA antibody with DRB1 and DQB1 estimation improved diagnosis of T1A than insulin antigen specific antibodies alone.

Keywords: Type 1 Diabetes, Type 2 Diabetes, Autoantibody, HLA-DR alleles, HLA-DQ alleles

INTRODUCTION

Type I Diabetes Mellitus (T1DM) is caused by autoimmune destruction of beta cells (β-cell) of the pancreas. It represents 10 % cases of the total DM. Prevalence of Type I DM varies from country to country. The lowest incidence in the general population is less than 1 of 100,000 in China while in Finland its incidence is high 40 per 100,000 populations [1]. The incidence of T1DM is increasing worldwide at a rate of 3% [2]. Genetic susceptibility, environmental triggers and epigenetic changes alter the immune system. In T1DM pancreatic β-cell destruction leads to insulin deficiency [3]. Two forms of T1DM are found, the first one is called as T1A which results from cell mediated autoimmune attack on β-cells [4]. Another variant T1B is named as idiopathic. It is less frequent, has no known causes, occurs mostly in individual of Asian and African descents, who have varying degree of insulin deficiency between sporadic episodes of ketoacidosis [5].

Genetic susceptibility is present in T1A [6,7]. In addition to genetic susceptibility, environmental triggers and epigenetic changes also contribute to disease susceptibility. All these together leads to β-cell destruction [3]. Abnormal activities of T cell mediated immune response leads to inflammation of islet (insulitis) by predominantly CD8 T cells and stimulate β-cell to produce β-cell antigen specific autoantibodies [7]. Autoantibodies to insulin (IAA), Glutamic acid decorboxylase (GADA), and Protein tyrosine phosphatase (IA-2) are present in T1A. The presence of one or more types of these autoantibodies may precede the clinical onset in T1A by years. Progressive destruction of β-cells leads to clinical onset of overt T1A [8].

There is no evidence to suggest that these antibodies have a role in pathogenesis of T1A. Insulitis affects few islets and is present in only one third of the case of overt T1A. Hence, studies argue about the role of T cell mediated immune response (IR) in T1A [9].

HLA locus contributes as much as 50% of the genetic susceptibility to T1DM [10]. Among HLA in upto 50% cases susceptibility is contributed to HLA DR and DQ [11]. Most frequent genetic risk factors are DRB1*0301-DQB1*0201, DRB1*0301-DQA1*0501-DQB1*0201 and DRB1 *0401- DQB1*0302 [12]. Other studies reported most frequent disease associated alleles to be DRB1*0301, 0401 and DQA1*0301 [13]. In contrast, DRB1*1501-DQB1*0602 haplotype is most common protective factor [12,13].

Besides HLA, several other candidate genes like CTLA-4, PTPN-22, IL-2RA1 are also associated with increased risk of T1DM [14]. T1A is very frequently associated with some autoimmune diseases like Celiac disease [15] and autoimmune thyroid disease [16,17].

AIM

Aim of the present study was to assess the prevalence of GADA, IA-2 and ZnT8 antibodies and HLA DRB1 and DQB1 gene in patients with T1DM and also to predict the type of T1DM. Another Aim of study was also to see the association of Celiac disease and autoimmune thyroid disease with both types of DM.

MATERIALS AND METHODS

Thirty four patients withT1DM and 59 patients with T2DM were enrolled from the outpatient department (OPD) of Department of Endocrinology, Banaras Hindu University, Varanasi during the period 2012-2014. All patients had hyperglycemia. Twenty eight healthy controls were included in the study. The study was approved by the institutional ethics committee. An informed consent was obtained from all subjects.

About 2 ml blood was collected in EDTA for HLA studies by PCR and 5ml blood was taken in plain vial for autoantibodies analysis. Various types of kits were used for autoantibodies analysis.

- Anti-Glutamic acid decorboxylase (GADA) antibody was done by ELISA kit of Medizym, Germany. The Cut-off point was 5.0 IU/ml.

- Protein Tyrosine phosphatase (IA-2) antibody was done by ELISA kit of Elisa RSR, UK. The Cut-off point was 7.5 U/ml.
- Zinc transporter 8 (ZnT8) antibodies was done by ELISA kit of Diametra, Italy. The Cut-off point was15.0AU/ml.
- Anti tissue transglutaminase (Anti-TTG) IgA antibody was estimated by ELISA kit of D-Tek Co., Belgium. The cut-off point was 50 IU/ml.
- Anti thyroid peroxidase (anti-TPO) antibody was estimated by ELISA kit of Phadia Diagnostics Co., Germany. The cut-off point was 60 IU/ml.

HLA DRB1and DQB1 Genotyping

Genomic DNA was extracted by phenol- chloroform method. HLA DRB1and DQB1 genotyping was done by BAG Health Care Germany, supplied by Shiva Scientific, Delhi and kit was based on Sequence Specific Probes -PCR method (SSP-PCR). The data analysis was done by Sequence Compilation and Rearrangement Evaluation (SCORE) software and interpretation worksheet provided by manufacturers.

STATISTICAL ANALYSIS

All data were analysed using Statistical Package for Social Sciences (SPSS, Chicago, Illinos, USA), version 16. Pearson's Chi-square and relative risk test were used to compare differences between the frequencies as per the requirement. A p-value <0.05 was considered significant for all analysis.

RESULTS

Total 34 cases of T1DM, 59 cases of T2DM and 28 healthy controls were included for study. It was found that GADA Ab was positive in 38.23% in T1DM, 1.69% in T2DM and it was not seen in controls. ZnT8 Antibody was positive only in 4 cases (11.76%). Out of these, two cases were also positive for GADA Ab. IA-2 Ab was detected in only two cases (5.88%) and out of this one case was also positive for GADA Ab. ZnT8 Ab and IA-2 Ab were not seen in T2DM and Control. Anti-TTG IgA Ab was found in 14.70% T1DM, 10.17% T2DM and 7.14% in Control while Anti-TPO Ab was detected in 17.65% cases of T1DM, 5.08% T2DM and 14.28% of Control. Although all autoantibodies were more common in T1DM but only GADA was statistically significant as compared to control [Table/Fig-1].

Correlation of various autoantibodies with age of the patients revealed that the insulin antigen specific antibodies, GADA and ZnT8 Ab positivity were highest in children below 15 years (66.67% and 33.33%) thereafter it declined. Whereas IA-2 Ab was positive at the higher age (above 25 years) in T1DM and other autoantibodies like Anti-TTG IgA Ab (0.0% vs. 28.57%) and Anti-TPO Ab (16.67% vs. 26.31%) increased after 15 years of age and were less frequent below 15 years [Table/Fig-2].

Correlation of various autoantibodies with the sex of the patients showed that all autoantibodies were more positive in females as compared to males. However, the significant relationship was observed only for ZnT8 Ab [Table/Fig-3].

Correlation of autoantibodies with duration of disease revealed that GADA Ab positivity was low (29.17%) below 2 years duration while between 2 to 4 years and more than 4 years duration positivity were high (60%). Contrary to GADA Ab, Anti-TPO Ab and ZnT8 Ab were more positive between 1.5 to 4 years duration. IA-2 Ab was positive in more than 4 years disease duration. Only IA-2 Ab gave significant positive correlation with duration of disease more than 4 years [Table/Fig-4].

Group	No.	GADA Ab	ZnT8 Ab	IA-2 Ab	Anti-TtG IgA Ab	Anti-TPO Ab
A. T1DM	34	13(38.23%)	4 (11.76%)	2 (5.88%)	5 (14.70%)	6 (17.65%)
B. T2DM	59	1 (1.69%)	0	0	6 (10.17%)	3 (5.08%)
C. Control	28	0	0	0	2 (7.14%)	4 (14.28%)
A vs C	X^2 value	13.546	3.521	1.702	0.877	0.128
	p	0.000	0.061	0.192	0.349	0.720
B vs C	X^2 value	0.480	-	-	0.208	2.173
	p	0.488	-	-	0.648	0.140
A vs B	X^2 value	22.522	7.253	3.547	0.426	3.894
	p	0.000	0.007	0.060	0.514	0.048

[Table/Fig-1]: Autoantibodies in Diabetes Mellitus and Healthy Control.

Age (Year)	No.	GADA Ab positive	ZnT8 Ab positive	IA-2 Ab positive	Anti-TtG IgA AbPositive	Anti-TPO Positive
T1DM						
≤15	6	4(66.67%)	2 (33.33%)	0	0	1(16.67%)
15.1-25	19	7(36.84%)	2 (10.53%)	0	3(15.79%)	5(26.31%)
25.1-40	7	2(28.57%)	0	1(14.28%)	2(28.57%)	0
>40	2	0	0	1(50%)	0	0
X^2 value	3.584	3.917	9.487	2.470	2.915	
p	0.310	0.271	0.023	0.481	0.405	
T2DM						
40.1-50	18	1(5.56%)	0	0	0	3(16.67 %)
50.1-60	21	0	0	0	4(19.04%)	0
>60	20	0	0	0	2 (10%)	0
X^2 value	2.317	-	-	3.850	7.199	
p	0.314	-	-	0.146	0.027	

[Table/Fig-2]: Correlation of Autoantibodies with Age of the DM Patients (T1DM & T2DM).

Group	No.	GADA positive	ZnT8 Ab positive	IA-2 Ab positive	Anti-TtG IgA AbPositive	Anti-TPO Positive
T1DM						
Female	13	5(38.46%)	4(30.76%)	1(7.69%)	2(15.38%)	3(23.07%)
Male	21	8(38.09%)	0	1(4.76%)	3(14.28%)	3(14.28%)
X^2 value		0.0004	7.323	0.126	0.008	0.427
p		0.983	0.007	0.724	0.930	0.513
T2DM						
Female	45	0	0	0	1(2.22%)	0
Male	14	0	0	0	5 (35.71%)	3(21.43%)
X^2 value		-	-	-	13.111	10.159
p		-	-	-	0.000	0.001

[Table/Fig-3]: Correlation of Autoantibodies with Sex of the DM Patients (T1DM and T2DM).

Group	No.	GADA positive	Znt8 Ab positive	IA-2 Ab positive	Anti-TtG IgA AbPositive	Anti-TPO Positive
T1DM						
<2 year	24	7(29.17%)	4(16.67)	0	4(16.67%)	6 (25%)
2-4	5	3(60%)	0	0	1(20%)	0
>4	5	3(60%)	0	2(40.0%)	0	0
X^2 value		2.842	1.889	12.325	1.047	3.036
p		0.242	0.389	0.002	0.592	0.219
T2DM						
<2 year	15	0	0	0	0	0
2-4	0	0	0	0	0	0
>4	44	0	0	0	6 (13.64)	3(6.82%)
X^2 value		-	-	-	2.277	1.078
p		-	-	-	0.131	0.299

[Table/Fig-4]: Correlation of Autoantibodies with Duration of Disease in DM Patients (T1DM and T2DM).

HLA DRB1 Typing in T1DM showed that 61.76% patients had DRB1*0301 which was highly significant as compared to controls (5%) and T2DM (10%). DQB1 typing revealed that 64.71% patients of T1DM were positive for DQB1*0201 allele, while only 10% healthy controls had this allele. This was also significant (p=0.000). Comparison of HLA DQ antigen in T1DM and T2DM shows that DQB1*0201 was found in 64.71% patient of T1DM and 30% patients of T2DM which was statistically significant (p=0.023). Although DQB1*0501, DQB1*0601 and DQB1*0602 were more in T2DM but statistically it was not significant [Table/Fig-5].

Correlation of the DRB1* allele with GADA Ab revealed that 84.62% of GADA Ab positive cases were DRB1*0301 positive. About 84.62% GADA Ab positive cases had DQB1*0201 and 53.85% had DQB1*0501. ZnT8 positivity (100%), Anti-TtG (80%) and Anti-TPO positivity (100%) was also high in DQB1*0201 positive patients. Similarly in DRB1*0301 positive ZnT8 (100%), IA-2 (100%), Anti-TtG (80%) and Anti-TPO positivity (100%) were also high as compared to other DQ typing [Table/Fig-6].

GADA was negative in two positive cases of the ZnT8 and one case of IA-2. In 6 cases, all GADA, IA-2 and ZnT8 antibodies and

Group		A		B		C		A vs C		B vs C		A vs B	
		T1DM (n=34)		T2DM (n=20)		Control (n=20)		RR	p value	RR	p value	RR	p - value
DRβ Typing		No.	%	No.	%	No.	%						
1.	DRβ1*0101	1	2.94	0	0	0	0	1.606	1.000	---	1.000	1.606	1.000
2.	DRβ1*0301	21	61.76	2	10	1	5	2.35	0.000	0.649	1.000	2.177	0.000
3.	DRβ1*0401	6	17.65	1	5	1	5	1.439	0.239	1.000	1.000	1.439	0.239
4.	DRβ1*0403/6	3	8.82	1	5	2	10	0.948	1.000	1.370	1.000	1.210	1.000
5.	DRβ1*0701	12	35.29	6	30	4	20	1.295	0.356	0.750	0.716	1.091	0.771
6.	DRβ1*0901	0	0.00	1	5	1	5	0.000	0.370	1.000	1.000	0.000	0.370
7.	DRβ1*1101	1	2.94	3	15	1	5	0.788	1.000	0.474	0.605	0.379	0.138
8.	DRβ1*1104	1	2.94	0	0	0	0	1.588	1.000	---	1.000	1.588	1.000
9.	DRβ1*1201	0	0.00	1	5	1	5	0.000	0.370	1.000	1.000	0.000	0.370
10.	DRβ1*1301	1	2.94	0	0	2	10	0.515	0.548	0.000	2.111	1.588	1.000
11.	DRβ1*1310	3	8.82	2	10	0	0	1.645	0.287	2.111	0.487	0.948	1.000
12.	DRβ1*1404	5	14.71	2	10	9	45	0.493	0.024	0.293	0.031	1.158	1.000
13.	DRβ1*1501/1502	12	35.29	11	55	11	55	0.735	0.254	1.000	1.000	0.735	0.254
14.	DQβ1*0201	22	64.71	6	30	2	10	2.292	0.000	1.714	0.235	1.702	0.023
15.	DQβ1*0202	2	5.88	0	0	0	0	1.627	0.525	---	1.000	1.627	0.525
16.	DQβ1*0301	2	5.88	4	20	1	5	1.063	1.000	1.750	0.342	0.500	0.179
17.	DQβ1*0302	9	26.47	3	15	7	35	0.855	0.549	0.529	0.273	1.240	0.500
18.	DQβ1*0303	3	8.82	2	10	2	10	0.948	1.000	1.000	1.000	0.948	1.000
19.	DQβ1*0304	2	5.88	0	0	0	0	1.625	0.525	---	1.000	1.625	0.525
20.	DQβ1*0501	18	52.94	15	75	14	70	0.773	0.262	1.138	1.000	0.716	0.151
21.	DQβ1*0601	8	23.53	9	45	8	40	0.731	0.23	1.107	1.000	0.670	0.133
22.	DQβ1*0602	1	2.94	2	10	2	10	0.515	0.548	1.000	1.000	0.515	0.548
23.	DQβ1*0609	1	2.94	0	0	0	0	1.588	1.000	---	1.000	1.588	1.000

[Table/Fig-5]: Correlation of DR and DQ with T1DM, T2DM and Control.

Group	Type I DM (n=34)		GADA Ab Positive cases (n=13)		ZnT8 AbPositive cases (n=4)		IA-2 Ab Positive cases (n=2)		Anti-TtG IgA Ab Positive cases (n=5)		Anti-TPO Ab Positive cases (n=6)		Control (n=20)	
DRβ Typing	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
DRβ1*0101	1	2.94	0	0	0	0	0	0	0	0	0	0.00	0	0
DRβ1*0301	21	61.76	11	84.62	4	100	2	100	4	80	6	100	1	5
DRβ1*0401	6	17.65	1	7.69	0	0	2	100	1	20	1	16.67	1	5
DRβ1*0403/6	3	8.82	2	15.38	1	25	0	0	0	0	1	16.67	2	10
DRβ1*0701	12	35.29	2	15.38	0	0	0	0	1	20	1	16.67	4	20
DRβ1*0901	0	0	0	0	0	0	0	0	1	20	0	0.00	1	5
DRβ1*1101	1	2.94	0	0	0	0	0	0	0	0	0	0.00	1	5
DRβ1*1104	1	2.94	0	0	0	0	0	0	0	0	0	0.00	0	0
DRβ1*1201	0	0	0	0	0	0	0	0	0	0	0	0.00	1	5
DRβ1*1301	1	2.94	0	0	0	0	0	0	0	0	0	0.00	2	10
DRβ1*1310	3	8.82	0	0	0	0	0	0	0	0	0	0.00	0	0
DRβ1*1404	5	14.71	2	15.38	0	0	0	0	0	0	1	16.67	9	45
DRβ1*1501	10	29.41	3	23.08	1	25	0	0	1	20	0	0.00	11	55
DRβ1*1502	2	5.88	0	0	0	0	0	0	0	0	0	0.00	11	55
DQβ1*0201	22	64.71	11	84.62	4	100	1	50	4	80	6	100	2	10
DQβ1*0202	2	5.88	0	0	0	0	0	0	0	0	0	0.00	0	0
DQβ1*0301	2	5.88	0	0	0	0	0	0	0	0	0	0.00	1	5
DQβ1*0302	9	26.47	5	38.46	2	50	2	100	2	40	3	50.00	7	35
DQβ1*0303	3	8.82	0	0	0	0	0	0	0	0	0	0.00	2	10
DQβ1*0304	2	5.88	1	7.69	0	0	0	0	0	0	0	0.00	0	0
DQβ1*0501	18	52.94	7	53.85	2	50	1	50	3	60	3	50.00	14	70
DQβ1*0601	8	23.53	2	15.38	0	0	0	0	0	0	0	0.00	8	40
DQβ1*0602	1	2.94	0	0	0	0	0	0	0	0	0	0.00	2	10
DQβ1*0609	1	2.94	0	0	0	0	0	0	0	0	0	0.00	0	0

[Table/Fig-6]: Correlation of DR and DQ with Autoantibodies.

HLA DRB1*0301 were negative but DQB1*0201 was positive. After comparing individual and combined test we found that if GADA and HLA DRB1 and DQB1 are done then 76.47% cases can be diagnosed as T1DM while if only autoantibodies are done then 47.06% cases can be diagnosed [Table/Fig-7].

Test	Positive		Negative	
	No.	%	No.	%
GADA	13	38.24	21	61.76
ZnT8	4	11.76	30	88.24
IA-2	2	5.88	32	94.12
GADA+ZnT8	15	44.12	19	55.88
GADA+ZnT8+IA-2	16	47.06	18	52.94
GADA+DRB1	19	55.88	15	44.12
GADA+DRB1+DQB1	26	76.47	8	23.53

[Table/Fig-7]: Sensitivity of individual and Combined test for diagnosis of T1DM.

DISCUSSION

Autoantibodies to pancreatic antigen are a diagnostic hallmark for T1DM. In our study, we found low sensitivity of GADA, ZnT8 and IA-2 antibodies. Only 47.06% patient had either alone or combination of these antibodies. Commonest antibody detected in our series was GADA (38.23%). Western literature had reported that about 85-90% newly diagnosed T1DM have GADA and or IA-2 or ZnT8 or IAA [18-21]. Verge et al., reported that 70% patients of T1DM have GADA and addition of IA-2 antibody increases sensitivity to 80% positivity while Gurau et al., found that of GADA is positive in 68.5% only [21,22]. A study conducted in Saudi children also found high positivity of GADA (73.3%), followed by ICA 512 Ab (41%) and 27.3% cases had both antibodies [23]. Chan et al., in China found that GADA was found in only 31% of insulin deficient T1DM [24]. Our observation is more or less similar to Chinese study and we also found low prevalence of GADA (38.46%) in T1DM. Prevalence of GADA in Indian T1DM has been low. A study conducted from Northern India [25] on T1DM patient showed GADA positivity in only 41.2 %, but in these series IA-2 positivity was high (20.6%) as compared to our finding (5.88%).

GADA is associated with younger age of onset [24]. We also had similar findings. About 66.67% patients under 15 years, 36.84% patients between 15-25 years and only 22.22% patients between 25-40 years were GADA positive. Like GADA, ZnT8 was also detected in patients below 15 years, whereas IA-2 was detected in the age between 25 and 45 years.

Western literature also reports higher prevalence of ZnT8Ab in T1DM. Wenglan et al., reported that 63% newly diagnosed T1DM and 3 % healthy control and 3% T2DM have ZnT8 Ab [26]. Contrary to it, we found very low prevalence of ZnT8 Ab (11.76%) in T1DM. The prevalence of autoimmune thyroid disease in many diabetic patients varies from 3-50% [27]. In present study anti-TPO antibody was positive in 17.65% patient of T1DM and it was more positive in females (23.07%) as compared to males (14.28%). Contrary to our study, other workers [28] found high anti-TPO Ab in female (73%) than male (44.7%) in T1DM patients. This is because they had evaluated anti-TPO Ab in GADA positive cases, whereas we analysed the same in all T1DM cases. More or less similar to our studies some series have reported anti-TPO Ab positivity in 20-30% patient of T1DM [29,30].

Another common disease associated with T1DM is celiac disease (CD). Prevalence of CD in T1DM varies from 1.7 to 17% [17,22,31,32]. CD is 20 times more common in T1DM than the control population [33,34]. In our study, we found the prevalence of Anti-TTG IgA Ab in 14.7% cases of T1DM which was higher than other Indian studies [35] that found Anti-TTG IgA Ab in only 8% T1DM patient and 2% healthy controls.

T1DM is a polygenic disease, but HLA antigen (DRB1 and DQB1) contributes to genetic susceptibility and autoimmune response. The HLA haplotype that are most frequently associated with susceptibility to T1DM are DRB1*0301-DQB1*0201, DRB1*0301-DQA1*0501-DQB1*0201 and DRB1 *0401-DQB1*0302 [12]. In addition to it, Erlich et al., also reported DRB1*0404-DQA1*0301-DQB1*0302, DRB1*0801-DQA1*0401-DQB1*0402 haplotypes [36].

Most of the studies in India found increased frequency of DRB1*0301 and DQB1* 0201 in T1DM [37]. Present study also found significant increase in DRB1*0301 (64.71%) and DQB1*0201 (61.76%) in patients of T1DM. DRB1*0301 and DQB1*0201 together were detected in 80% T1DM. Like our study DRB1*0301 and DQB1*0201 were found in increased frequency in Taiwan [38], Yemenites of Jewish population [39], Northern Spain [40], Europe [41] and USA [36] in T1DM patient.

Some of the studies have also found increased susceptibility to DRB1*0401 in T1DM [36,42,43]. In the present study we also found an increased frequency of DRB1*0401 but statistically it was not significant. Rani et al., from India also did not find significant association with DRB1*0401 in T1DM. [37].

DRB1*1404/05, DRB1*1501/02 were less prevalent in patients but only DRB1*1404 was significantly reduced in patients. Similar to our study Erlich et al., also reported these two alleles act as protective allele for T1DM [36].

In our study, we observed that DQB1*0601 is more frequent in control as compared to T1DM (40% Vs 23.53%) but statistically it was non-significant. Similar to our study, other earlier workers [36,44] also found negative association of DQB1* 0601 with T1DM.

We found positive correlation of GADA with DRB1*0301 and DQB1*0201. About 84.62% GADA positive cases had DRB1*0301 and 84.62% GADA positive cases had DQB1*0201. Similar to our study Manan et al., also reported that 81% DRB1*0301, 68.75% DQB1*0201, 62.5% DRB1*0405, 43.75% DQB1*0302, and 43.7% DRB1*03/04 positivity in GADA positive cases [23]. One study from USA [36] also has reported significant association of GADA with DQB1*0201.

All IA2 positive patients had DRB1*0301, 0401, DQB1*0302 and 50% had DQB1* 0201 and 0501 whereas in ZnT8 positive cases all had DRB1*0301 and DQB1*0201, and 50% had DQB1*0302 and 0501. Similar to our findings other workers [23,45,46] also found strong association of ICA512 and ZnT8 Ab with DRB1 0301 and DQB1*0201.

CONCLUSION

From our study, we conclude that for diagnosis of T1DM, GADA antibody is the most superior autoantibody. Its sensitivity is low hence, it should be combined with HLA DRB1 and DQB1 typing so that more than 76.47% cases of T1A can be diagnosed. Study also shows that cell mediated immune response is more important in pathogenesis of T1DM than humoral response.

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