Original Article

Coexistence of Autoimmune Disorders and Type 1 Diabetes Mellitus in Children: An Observation from Western Part of India

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Abstract

Introduction: Type 1 diabetes mellitus (T1DM) is associated with various autoimmune disorders like celiac disease, thyroid disorder, adrenal failure, etc. However, how common is this association in Indian children is not clearly known. **Objective:** To assess the prevalence of other coexisting autoimmune disorders in children with T1DM. **Materials and Methods:** In this cross-sectional study, patients requiring insulin and ketosis-prone diabetic and with history of diabetic ketoacidosis/undetectable fasting C-peptide levels were included. Beside demographic and clinical data, detailed biochemistry evaluations were performed. Celiac disease was diagnosed as per the ESPGHAN diagnostic criteria. ACTH stimulation test was done to confirm the adrenal insufficiency in patients with basal serum cortisol <5 μg/dL. Thyroid function test (TSH) and anti-TPO antibody were assessed in all patients. Screening for other autoimmune disorders was done only when clinically indicated or symptoms or family history was suggestive of presence of such disorder. **Results:** Among 150 patients enrolled, 64.66% were males and mean age was 13.48 ± 3.29 years (range 3–18 years). Mean age at diagnosis of T1DM was 10.0 ± 3.63 years and duration of diabetes was 3.46 ± 3.18 years. The prevalence of antibodies positive against autoimmune diseases was anti-tTG IgA (20.7%), anti-TPO (33.7%), anti-CCP ab (1.3%), and ANA (0.7%). Significantly higher proportion of females had raised anti-TPO antibodies than males (47.2% vs. 25.8%, $P = 0.006$). Celiac disease was most common association (24.8%) followed by hypothyroidism (14.1%) and Grave's disease (3.3%). Significantly higher proportion of females had hypothyroidism than males (25.0% vs. 8.2%, respectively, $P = 0.005$). Prevalence of raised anti-tTG and anti-TPO did not differ significantly by the age ($P = 0.841$ and $P = 0.067$) or duration of T1DM ($P = 0.493$ and $P = 0.399$). **Conclusion:** In this part of country, celiac disease, hypothyroidism, and Graves's disease are common associations in children with T1DM.

Keywords: Autoimmune disorders, celiac disease, thyroid, type 1 diabetes mellitus

Introduction

Type 1 diabetes mellitus (T1DM) is a common autoimmune endocrine disorder of pediatrics population. Autoimmunity and viral infections are the main etiopathological factors implicated in the pathogenesis of T1DM on the background of genetic predisposition.[1] The American Diabetes Association (ADA) classifies T1DM into type 1A (T1DMA) and type 1B (T1DMB).[2] T1DMA is caused by immune-mediated destruction of pancreatic beta cells and is associated with autoantibodies against various components of insulin-producing cells: anti-glutamic acid decarboxylase 65 (anti-GAD 65), anti-islet cell (anti-ICA), anti-tyrosine phosphatase (anti-IA2), and anti-zinc transporter 8 protein (anti-ZnT8). Genetic predisposition, particularly related to some antigens and human leukocyte antigen (HLA) haplotypes in T1DMA is known.[3] On the other hand, T1DMB is a less common form of diabetes not associated with the autoimmune markers against pancreatic beta cells and has no known genetic predisposition.[4]

In Indian context, Kalra *et al.* reported that T1DM was associated with hypothyroidism, and out of 70 patients, 9 patients were hypothyroid, having prevalence of 12.9% in that study population.[5] T1DM is also associated with celiac disease but less frequently than autoimmune thyroid disorders. Prevalence of celiac disease in children and adolescents with T1DM ranges from 5% to 7% as reported by Acerini *et al*.[6] and it is proposed to be responsible for poor metabolic control

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and glycemic variability. Routine screening of autoimmune hypothyroidism and celiac disease at the time of diagnosis of T1DM is recommended by the ADA.[2] Other autoimmune disorders like Graves's disease, pernicious anemia, juvenile rheumatoid arthritis (JRA), and vitiligo are less frequently associated with T1DM.[7] There is relative lack of studies looking at such associations in patients with T1DM in India perticularly in this part of country. Hence, this cross-sectional study was planned to investigate the prevalence of autoimmune disorders like autoimmune thyroid disorders, celiac disease, and other autoimmune disorders in T1DM at a tertiary care teaching hospital in Rajasthan.

Materials and Methods

This study comprised of 150 consecutive children and adolescents with T1DM presenting to the Department of Endocrinology and Metabolism, SMS Medical College, Jaipur, Rajasthan, from August 2016 to December 2017. Patients who required insulin and who were ketosis prone and had history of diabetic ketoacidosis/undetectable fasting C-peptide levels were included in the study. Patients were excluded if they did not require insulin for 3 months or more, had strong family history with mild to moderate hyperglycemia, and not requiring insulin, young T2DM, or maturity onset diabetes of young.

Patients were evaluated with detailed history; age of diagnosis of T1DM; duration of T1DM; and anthropometric data like height, weight, and body mass index (BMI); general and systemic examination (including goitre, features of target organ damage, other endocrinological abnormalities, and autoimmune disorders) findings were recorded. Biochemical parameters including fasting and prandial plasma glucose, glycosylated hemoglobin (HbA1C), urine ketone, serum electrolytes, fasting C-peptide level, thyroid profile, anti-TPO antibody, basal serum cortisol (plasma ACTH and ACTH stimulation, when required), IgA anti-tTG antibody, and total IgE were recorded. All the tests were done on Siemens chemiluminescence method (TSH, FT4, anti-TPO antibody using Siemens ADVIA centaur XPT chemiluminescence method, whereas ACTH and C-peptide level were done on Siemens IMMULITE 1000) using a commercial kit.

Primary hypothyroidism was diagnosed based on raised thyroid stimulating hormone (TSH >5.5 mIU/mL) and low FT4 (<0.89 ng/dL) levels. Anti-TPO levels >60 IU/mL were defined as positive. Goiter was examined and graded as per the WHO grading system.[8]

Estimation of IgA anti-tTG was done using ELISA kits based on solid-phase enzyme immunoassays with a sensitivity of 95% and specificity of 96%. As per the laboratory standard at our institute, anti-TTG level of >15 AU/mL is considered positive and <3 AU/mL is considered negative, whereas level between 3 and 15 is considered as indeterminate. Endoscopic duodenal biopsy was undertaken in patients who had anti-TTG <15 AU/mL with strong clinical suspicion of celiac disease in the form of anemia, short stature, and other features of malnutrition. The diagnosis of celiac disease was made as per the ESPGHAN diagnostic criteria.[9] Biopsy was performed after written informed consent. Severity of the disease was graded histopathologically using modified Marsh classification. A diagnosis of celiac disease was established when the histopathology showed Marsh Grade of 3.[10] ACTH stimulation was performed in patients with basal serum cortisol levels <5 μg/dL. Post-ACTH stimulation, patients with serum cortisol <18 μg/dL were labeled as primary adrenal insufficiency. Screening for other autoimmune disorders was done only when clinically indicated or symptoms or family history suggestive of disorder were present. The study was approved by the Institutional Ethical Screening Committee. Normal ranges considered in various laboratory evaluations were as follows: TSH, 0.42–5.5 mIU/mL; FT4, 0.89–1.72 ng/dL; anti-TPO antibody, <60 U/mL; ACTH, 0–46 pg/mL; C-peptide, 0.9–7.1 ng/mL; and serum cortisol, 5–22.4 μg/dL.

Results

The study sample consisted of 150 patients; out of them, 97 were male (64.66%) and male:female ratio was 1.8:1. Age of the study participants ranged from 3 to 18 years with a mean of 13.48 ± 3.29 years. Age at the diagnosis of T1DM ranged from 2 to 18 years with a mean of 10.0 ± 3.63 years. The duration of diabetes at the time of data collection was 0–12 years with a mean of 3.46 ± 3.18 years. The demographic parameters did not differ significantly in males and females [Table 1]. Prevalence of positivity of antibodies against autoimmune diseases was 33.7% for anti-TPO, 20.7% for anti-tTG IgA, 1.3% for anti-CCP antibody suggesting juvenile rheumatoid arthritis, and 0.7% for ANA [Table 2]. Concomitant positivity of anti-TPO and anti-tTG was found in nine patients (6%). Among patients with positive anti-TPO antibodies, 43% had hypothyroidism. Anti-TPO and anti-tTG antibodies were positive predominantly among females than males (47.2% vs. 25.8%, $P = 0.006$ and 22.6% vs. 19.9%, $P = 0.617$) [Table 2]. Among TTG-positive (20.8%) patients, biopsy was positive in all of them. Among those who had anti-TTG <15 AU but had strong clinical suspicion in the form of short stature, anemia, and other features of malnutrition, duodenal biopsy was done in these patients also and it was positive in 4.0% patients. Therefore, total 24.8% were diagnosed with celiac disease on biopsy.

The sex-wise distribution of the various autoimmune disorders is given in Table 2. Autoimmune hypothyroidism was significantly more prevalent in females than males (25.0% vs 8.2%, $P = 0.005$). Among total hypothyroid patients ($n = 21$, 14.1%), eight were over hypothyroid (TSH >10 mIU/mL) and rest were subclinical hypothyroidism (TSH: >5.5 to <10 mIU/mL and FT4: in normal range). Sex-wise distribution in other disorders like celiac disease (26.9% vs. 23.7%, $P = 0.665$), Grave's disease (5.6% vs. 2.0%, $P = 0.808$), and juvenile RA (3.8% vs 0.0%) was again dominated in females. After ACTH stimulation test, we found two cases of primary adrenal insufficiency. There was one case each of autoimmune

Table 1: Profile of the study patients

Parameters	Total (150)	Male [97 (64.66)]	Female [53 (35.33)]	*P*
Age (years)	13.48±3.29	13.4±3.38	13.36±3.14	0.585
Age at diagnosis (years)	10.0±3.63	9.75±3.6	10.46±3.68	0.245
Duration of diabetes (years)	3.46±3.18	3.61±3.2	3.17±3.16	0.472
HbA1c (%)	12.1±3.4	12.0±3.5	12.3±3.3	0.637
Beginning with ketoacidosis (%)	15 (10.0)	9 (9.3)	6 (11.3)	0.662

hemolytic anemia and vitiligo in female patients only. In addition, two females and three males had short stature and delayed puberty; six females had secondary amenorrhea; one female had history of ADEM (acute demyelinating encephalomyelitis); one male patient had CIDP (chronic inflammatory demyelinating polyneuropathy), and one female had positive ANA. In our study, we did not find any cases of autoimmune thrombocytopenic purpura, alopecia, and myasthenia gravis.

The positivity of anti-TPO was more prevalent in the age group of >10 years and that of anti-tTG antibodies was more prevalent in the age group of <10 years, but statistically not significant [Table 3]. The positivity of antibodies was more prevalent in patients with <5 years of disease [Table 4].

Table 2: Prevalence of autoimmune disorders

Autoimmune disorders	Total (%)	Male (*n*=97)	Female (*n*=53)	*P*
Anti-TPO	50 (33.7)	25 (25.8)	25 (47.2)	0.006
Anti-tTG	31 (20.7)	19 (19.9)	12 (22.6)	0.617
Celiac disease	37 (24.8)	23 (23.7)	14 (26.9)	0.665
Hypothyroidism	21 (14.1)	8 (8.2)	13 (25.0)	0.005
Grave's disease	5 (3.3)	2 (2.0)	3 (5.6)	0.808
Addison's disease	2 (1.3)	1 (1.0)	1 (1.9)	-
Juvenile rheumatoid arthritis	2 (1.3)	0	2 (3.8)	-
ANA	1 (0.7)	0	1 (1.9)	-
Autoimmune hemolytic anemia	1 (0.7)	0	1 (1.9)	-
Vitiligo	1 (0.7)	0	1 (1.9)	-

Table 3: Prevalence of antibodies by age range

Antibodies	Age		*P*
	≤10 years (*n*=27)	>10 years (*n*=123)	
Anti-TPO	5 (18.5)	45 (36.6)	0.067
Anti-tTG	6 (22.2)	25 (20.3)	0.841

Table 4: Relationship between positivity of antibodies and duration of type 1 diabetes mellitus

Antibodies	Duration		*P*
	≤5 years (*n*=114)	>5 years (*n*=36)	
Anti-TPO	40 (35.1)	10 (27.8)	0.399
Anti-tTG	25 (22.0)	6 (16.67)	0.493

Discussion

T1DM is a common endocrine disorder of the childhood or adolescent age group, and mostly present with classical symptoms of polyuria, polydipsia, and polyphagia. It is frequently associated with the various autoimmune disorders like autoimmune thyroiditis, celiac diseases, Grave's disease, etc. Prevalence of T1DM in both males and females varies from 1:1 to 2:1[5,11] and we observed that the prevalence was found to be 1.8:1. Our finding is similar to the observation from Kalra *et al.* who reported M:F ratio of 1.5:1.[11] Low female prevalence of T1DM may be because of poor socioeconomic status of families and probably due to gender discrimination in the developing countries like India.

Among various autoimmune disorders, autoimmune hypothyroidism was the most common endocrine abnormality in T1DM patients. In general population, the prevalence of autoimmune thyroid diseases ranges from 2.9% to 3.2%, whereas in patients with T1DM, it ranges from 19% to 23.4%. Worldwide, the prevalence of autoimmune hypothyroidism in T1DM varies widely and ranges from 10% to 50%.[12]

Ardestani *et al.*[13] found that patients with an elevated TSH and positive anti-TPO antibodies progressed much more frequently to have frank clinical thyroid dysfunction. Jonsdottir *et al.*[14] observed prevalence of 12.3% for anti-TPO antibody with T1DM. This prevalence was higher in diabetic patients with HLA DQA1*0301 and DQB1*0302[15] and in women.[15] However, more recent studies did not prove this association between haplotype HLA DQA1*0301–DQB1*0302 and autoimmune thyroid disease.[14] We found prevalence rates of 33.7% for anti-TPO antibody positivity in our study population of type 1 diabetes mellitus. This prevalence of anti-TPO antibody was more than that reported in the literature, which is probably because of the wide variation of these antibodies, the wider age range of the study population, and the long-duration of the disease. Comparison of the prevalence of anti-TPO antibody according to gender showed higher values for females.

In our study, the prevalence of autoimmune hypothyroidism was found to be 14.1% (8.2% in males and 25% in females), which is nearly similar to the report from Kalra *et al*. (12.9%). It is important to diagnose and treat thyroid disorders to ensure normal growth in pediatric patients.

Celiac disease is an autoimmune enteropathy precipitated by the ingestion of gluten-containing foods (including wheat,

rye, oat, and barley) in genetically predisposed individuals. Celiac disease is frequently associated with T1DM but less frequently than autoimmune hypothyroidism. Various studies demonstrated the higher prevalence of the disease in patients with T1DM.[16,17] T1DM is usually diagnosed before celiac disease, but in 10%–25% cases, celiac disease is diagnosed before T1DM.[17,18] Prevalence of celiac disease in children and adolescents with type 1 diabetes ranged from 5% to 8%.[19]

Van den Driessche *et al.*[20] observed a prevalence of 8%–12% for IgA anti-tTG. Djurić *et al.*[21] found that 7.4% of the patients with T1DM had IgA anti-tTG. Bhadada *et al.*[22] and Tiberti *et al.*[23] observed that the prevalence rates for IgA anti-tTG were 9.2% and 12.8%, respectively, in their studies. Biopsy is considered as a gold-standard procedure for diagnosis of celiac disease. Any patient who has normal anti-tTTG levels (<15 AU/mL) should not disregarded as devoid of celiac disease. In our study, the prevalence of IgA anti-tTG was found to be 20.8%, whereas prevalence of biopsy-proven celiac disease was 24.8%, which is higher in comparison with previous studies. This is important finding in our study that despite being negative on screening test, few patients were positive on biopsy. In our study, duodenal biopsy was performed in anti-tTG-negative patients with strong suspicion of celiac disease on basis of history as we do not have facility of total IgA estimation at our institution. This highlights the utility of duodenal biopsy in anti-tTG-negative patients having strong suspicion of celiac disease on the basis of history and clinical examination.

Grave's diseases may be associated with T1DM as a part of autoimmune polyglandular syndromes (APS). In APS, type II, mutations in the CTLA-4 gene may lead to concomitant presence of Grave's diseases or autoimmune hypothyroidism and T1DM. The prevalence rate of autoimmune thyroiditis varies from 20% to 30%.[11] In our study, the prevalence rate of Grave's disease was 3.3%.

21-Hydroxylase (21-OH) antibodies are seen in about 1.5% of cases of T1DM, of whom 15% developed Addison's disease (AD) during follow-up. The prevalence of AD in T1DM has been reported to be 0.5%. Adrenal and thyroid autoimmunity may coexist in approximately 70% of patients.[24] Screening of 21-OH antibody should be done in T1DM. Patients having positive autoantibodies should be followed for adrenal insufficiency by ACTH stimulation testing. In this study, two (1.33%) patients (one male and one female) had adrenal insufficiency, both clinically and biochemically, although 21-OH autoantibody was not done due to nonaffordability and nonavailability. One female patient had combined features of T1DM, primary hypothyroidism, and adrenal insufficiency, labeled as a case of PGA type 2.

JRA may be rarely associated with T1DM, and it is mostly published as case reports.[25] In our study, two females (1.33%) were found to be having JRA (anti-CCP > 5 U/mL), who were already diagnosed elsewhere for JRA (anti-CCP antibody, normal range: 0.4–5.0 U/mL, ADVIA centaur XPT, Siemens chemiluminescence method).

Vitiligo is an acquired autoimmune disorder leading to loss of melanocytes that results in white spots or leukoderma. Vitiligo may be associated with other autoimmune disorders like T1DM, autoimmune thyroid disorder, celiac diseases, etc. Vitiligo was reported in 6% of T1DM patients.[26] But, we found only one case of vitiligo in our study group. There was one case of autoimmune hemolytic anemia (already diagnosed by a hematologist), although no published reports were found in literature even after extensive search. In our study group, we did not find any patient with autoimmune thrombocytopenic purpura, alopecia, and myasthenia gravis.

Conclusion

This study found a high prevalence of autoimmune hypothyroidism, celiac disease, and other autoimmune disorders especially in female patients with T1DM. It supports previous data which found a wide gender difference in the prevalence of T1DM and unmasks the high prevalence of undiagnosed autoimmune thyroid disorder and celiac disease. This study also emphasizes the importance of total IgA estimation and duodenal biopsy in IgA anti-tTG-negative patients having strong suspicion of celiac disease on the basis of history. In view of relative lack of data on this subject in Indian context, we believe that the study results are important to stimulate generation of more clinical data and further research. Thus, this study reinforces a call to improve the quality of healthcare services, including implementation of universal screening for thyroid dysfunction and celiac disease in children with T1DM.

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Conflicts of interest

There are no conflicts of interest.

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