Review Article:

Organ specific autoimmune disorders in type 1 diabetes mellitus

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ABSTRACT

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease that results in absolute insulin deficiency due to destruction of the pancreatic beta cells. It is frequently associated with other autoimmune diseases like autoimmune thyroid (AIT) disease, celiac disease (CD), Addison's disease (AD), and vitiligo. These diseases, including T1DM are associated with organ specific autoantibodies. These autoantibodies are important as diagnostic markers and detectable antibodies may precede the clinical onset of the disease. These diseases usually occur together in same patient and have shared genetic predisposition. These autoimmune diseases can severely affect clinical management of T1DM. It is possible to screen for these associated diseases by testing for relevant autoantibodies. Earlier detection of organ specific autoimmunity will enable physicians to treat these diseases at an initial stage and can prevent development of full-blown clinical condition.

Key words: *Organ specific autoimmunity, Diabetes mellitus type 1, Autoimmune thyroid disease, Celiac disease, Addison disease*

INTRODUCTION

Type 1 Diabetes Mellitus (T1DM) is an autoimmune disease that results in absolute insulin deficiency due to T-cell mediated destruction of the pancreatic beta cells. T1DM is a model of chronic autoimmune disease, beginning with genetic susceptibility and progressive autoimmunity leading to destruction of β cells.[1]

More than 90% of T1DM is caused by immune mediated reaction. It has strong documented HLA association. At the time of diagnosis, one or more islet cell autoantibodies are detectable.[2] The autoimmune process results in infiltration of pancreatic islets by mononuclear inflammatory cells including auto reactive CD8 + T-lymphocytes- called "insulitis". It causes selective destruction of the β-cells and this process is presumed to be T-cell mediated.

Clinical manifestations of T1DM become overt after loss of more than 80% of viable β-cell mass.[3]

Like other autoimmune conditions, T1DM is frequently associated with other autoimmune diseases like autoimmune thyroid (AIT) disease, coeliac disease (CD), Addison's disease (AD), and vitiligo.[4,5] The prevalence of AIT (Hashimoto's and Graves' disease) is 29%, while CD is seen in 10.1% and AD in <1.6% in patients with T1DM.[5] All these conditions are associated with presence of organ specific antibodies. Risk of autoimmune diseases is increased not only in probands but their relatives also who share the genetic susceptibility. Twenty five percent of first-degree relatives of patients with T1DM patients have AIT and up to 6% have CD.[6] These diseases usually occurring together in same individual and having shared genetic

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predisposition are associated with organ specific autoantibodies. T1DM is associated with Insulin Auto Antibody (IAA), glutamic acid decarboxylase (GAD) antibody and islet cell antigen [ICA]512 (IA2) antibody; AIT with anti thyroid peroxidase (anti TPO) and anti thyroglobulin (anti TG) antibodies; CD with anti tissue trans glutaminase (anti TTG), endomysial autoantibodies (EMA) and AD with anti 21 α hydroxylase auto antibodies.[5] These autoantibodies are important as diagnostic markers of these diseases and detectable antibodies sometimes precede the clinical onset of the disease.

Co-existence of other autoimmune diseases can severely affect clinical management of T1DM especially in children. Earlier detection of organ specific autoimmunity by testing for relevant autoantibodies will enable physicians to treat these diseases at an earlier stage and prevent emergence of full blown clinical picture.

TYPE 1 DIABETES MELLITUS AND ASSOCIATED ORGAN SPECIFIC AUTOIMMUNITY

Genetic factors

Common genetic risk factors have been associated with T1DM, AIT, CD, and AD. The major histo-compatibility complex (MHC) explains their genetic association. In the background of T1DM, CD shows strong association with DR3-DQ2. Homozygosity for DR3-DQ2 in individuals with T1DM carries a 33% risk for the presence of TTG autoantibodies, and 43.3% for AIT.[5] It revealed that the prevalence of transglutaminase autoantibodies was higher in diabetic patients with HLA DQ2 or DQ8 and 32% of DQ2 homozygous patients (22/68) expressed transglutaminase autoantibodies.[7]

In a study which involved families with multiple members affected with T1DM and

Table 1: Reported prevalence of anti-thyroid antibodies in patients with type 1 diabetes mellitus

Study	Place	No. of Patients	Anti TPO No. (%)	Anti TG No. (%)	Anti TPO and/or Anti No. (%) TG
Umpierrez et al[13]	Tennessee	58	18 (31)		
De Block et al[14]	Belgium	399	87 (22)		
Kakleas et al[15]	Greece	144	25 (17.4)	16 (11.1)	
Kordonouri et al[16]	Germany	637	98 (15.4)	92 (14.4)	
Shiva et al[17]	Iran	99	8 (8)	6 (6)	9 (9)
Barker et al[5]	Colorado	814			239 (29)
Jung et al[18]	Korea	73			19 (26)
Riquetto et al[19]	Brazil	233			49 (21)

anti TPO = anti thyroperoxidase; anti TG = anti thyroglobulin

Table 2: Reported prevalence of anti-thyroid antibodies in patients with type 1 diabetes mellitus in India

Study	Place	No. of patients	Prevalence of anti TPO antibody No. (%)	Prevalence of Anti TG antibody No. (%)
Honnamurthy et al[20]	Kerala	75	44 (59)	-
Menon et al[21]	New Delhi	35	19 (54.3)	11 (31.4)
Reddy et al[22]	Tirupati	22	9 (41)	-
Goswami et al[23]	New Delhi	100	35 (35)	-
Dayal et al[24]	Chandigarh	123	23 (18.7)	-

anti TPO = anti thyroperoxidase; anti TG = anti thyroglobulin

AIT, DR3-DQ2 has been shown to be associated with AIT and T1D.[8] A study from New York, involving 55 multiplex families (290 individuals) in which T1D and AITD clustered to identify the joint susceptibility genes for T1DM and AIT. This study conducted tests for linkage and family based associations (transmission disequilibrium test) with four candidate genes; human leukocyte antigen (HLA), cytotoxic T lymphocyte- associated antigen 4 (CTLA-4), insulin variable number of tandem repeats (VNTR) and thyroglobulin. It was observed that the HLA class II locus is responsible for the significant shared risk for T1DM and AIT, and the major HLA haplotype contributing to this association was DR3-DQB1*0201.[9] In presence of T1DM, AD has been associated with the presence of HLA subtype of DR3-DQ2 and DR4-DQ8.[10,11] Individuals with 21α-hydroxylase autoantibodies (21-OHAA) are more likely to have genotype DR3-DQ2, DR4-DR8 with DRB1*0404 when compared with normal subjects or diabetic controls.[11]

Autoimmune thyroid disease

AIT is the most common autoimmune disease in patients with T1DM.[5] Among thyroid disorders, Hashimoto's disease is more frequently associated with T1DM than Graves' disease. The overall prevalence of thyroid disease was found to be 13.4%, and was higher (31.4%) among females.[12] The prevalence of anti-thyroid antibodies in patients with T1DM is shown in Tables 1[5,13-19] and 2.[20-24]

In a multicenter survey[25] done in Germany and Austria that included 17,749 patients with type 1 diabetes, aged 0.1–20 years, antibodies were measured and documented at least once in 7,097 patients. Elevated titres of thyroid autoantibodies (anti TPO and anti TG antibodies) were found in 21.6% of patients.

Table 3: Prevalence of coeliac disease in different studies from various countries

Study	Place	No. of patients	Prevalence of anti TTG antibody No. (%)	Biopsy proven CD* No. (%)
Barker et al[5]	Colorado	814	82 (10.1)	16 (2)
Kakleas et al[32]	Greece	105	9 (8.6)	5 (4.8)
Sharifi et al[33]	Iran	100	8 (8.0)	3 (3)

*Biopsy to prove CD was done only in those who gave consent

Table 4: Prevalence of anti TTG antibodies in different studies from India

Study	Place	No. of patients	Prevalence of anti TTG antibody No. (%)	Biopsy proven CD* No. (%)
Dayal et al[24]	Chandigarh	212	47 (22)	-
Agarwal et al[35]	Rajasthan	101	18 (17.8)	11 (10.9)
Joshi et al[36]	Mumbai	71	11 (15.5)	5 (7.04)
Tandon et al[37]	New Delhi	101	15 (14.9)	-
Joshi et al[38]	Mumbai	86	11 (12.79)	7(8.1)
Bhadada et al[39]	Chandigarh	189	21 (11.1)	21(11.1)
Jacob et al[40]	Kerala	100	8 (8)	3 (3)

*Biopsy to prove CD was done only in those who gave consent.

Patients with these antibodies were older and had a longer duration of diabetes. Serum TSH was higher in patients with thyroid autoimmunity than in those without autoantibodies, and was much higher in patients who were positive for both (anti TPO and anti TG) antibodies.[25] Other studies reported that 21-29% of patients with T1DM have AIT (anti TPO and /or TG ab).[18,19] Studies from Berlin and Iran reported that prevalence of anti TPO and anti TG antibodies among T1DM patients 8%-15.4% and 6%-14.4% respectively.[16,17] Several studies from India also have studied occurrence of anti TPO antibodies in T1DM patients (Table 2).[20-24] Prevalence of autoantibodies in these studies was 18.7%-59%.[20-24] The authors[22] have previously reported a prevalence of 41% of patients with T1DM being positive for anti TPO antibodies. It was noted that patients with goitre were more likely to have anti TPO antibodies.

A cohort of patients with T1DM, recruited originally for DCCT was longitudinally followed for 18 years in Tennessee. There were 33% patients positive for anti TPO antibody at the start of the study and no new cases were detected during follow-up. This study also revealed, hypothyroidism was more common among females and those with anti TPO antibodies had an 18 times higher risk for developing hypothyroidism.[13]

It has been reported that risk for thyroid autoimmunity increased with increasing age, female gender and with long duration of T1DM.[15,25]

Risk of occurrence of AIT is not same in all patients. Increased risk of developing this disease in those who having high serum elevated anti GAD antibodies.[14,15] However, clinical implications of positive antibodies only are not known. Glycaemic control in anti TPO antibody positive patients did not differ much when compared to antibody negative patients.[25]

Several longitudinal studies have stressed the importance of annual screening of thyroid disease in T1DM patients.[12,19]

The best screening for thyroid dysfunction is estimation of TSH. According to American Diabetes Association (ADA), TSH levels should be estimated in all individuals with newly diagnosed T1DM shortly after the stabilization of the metabolic state. If found normal, should be rechecked every 1-2 years especially if the patient develops symptoms of thyroid dysfunction, thyromegaly or abnormal growth rate. Children with T1DM should undergo screening for anti TPO and anti TG antibodies soon after diagnosis.[26]

Coeliac disease

CD is an autoimmune form of enteropathy affecting the small intestine in genetically predisposed children and adults, precipitated by the ingestion of gluten containing foods. It is also known as "coeliac sprue", "gluten sensitive enteropathy" and "non tropical sprue".[27]

Higher incidence of CD in T1DM may be due to presence of shared genetic factors in HLA system.[5] Clinical spectrum of CD is extremely diverse and depends on the age of onset and effectiveness of treatment taken. Development of CD can occur at any age but usually takes place within 5 years of diagnosis of T1DM. Cerutti et al[28] suggested that the highest risk of developing CD in children diagnosed with T1DM was under 4 years of age and the risk was much lower in children of school going age and older children. An epidemiological study from Australia reported that CD is common in young patients with young age of onset of diabetes (< 5years of age) and longer duration of diabetes mellitus.[29]

Barker et al[5] reported that 10.1% of patients with T1DM expressed TTG antibody and highest risk for expression was noted with

DR3-DQ2/DR3-DQ2 HLA genotype. A study from Brooklyn, New York aimed to identify the prevalence of celiac disease in African American children with T1DM, found that even when having high risk HLA genotype for CD, seroprevalence of CD was much lower among African American than among Caucasians.[30]

An Italian cross-sectional multicenter study,[31] that involved 8717 T1DM patients from 31 centers, found that prevalence of EMA anti TTG antibody positivity was 7.2% of these 6.3% subjects showed villous atrophy and were diagnosed as CD, while 0.9%, had normal villous architecture and were classified as potential CD. Prevalence of potential CD among all the celiac seropositive cases was 12.2%.[31] Studies from various other countries reported the prevalence of anti TTG immunoglobulin A (IgA) positivity ranging from 4%-8.6% (Table 3).[5,32-33] In India, prevalence of celiac autoimmunity was reported to be 8%-22% among patients with established T1DM (Table 4).[24,35-40]

A two year follow-up study[41] was done at Barbara Davis Center for Childhood Diabetes to determine the impact of screening-detected celiac disease autoimmunity via IgA anti TTG antibodies in children with T1DM and GFD on growth, bone mineralization, and glycaemic control. It was found that anti TTG antibody positive subjects had consistently lower weight z-scores and higher urine N-telopeptides (a marker of bone turnover) than anti TTG antibody negative subjects, but had similar measures of bone density and diabetes outcomes. TTG antibody positive children who remained on regular diet had lower (IGF-BP3) z-scores (a surrogate marker of growth hormone function) compared with those who reported following a gluten-free diet. Children who continued with high TTG index throughout the study had lower bone mineral density z-scores, serum ferritin and 25-hydroxy vitamin D, compared with the antibody negative group.[41]

A study from university of Toronto compared CD associated with T1DM to CD alone. After following patients for 3 years it was found that CD associated with T1DM represents a distinct and a possibly milder form.[42]

Classical form of CD characterized by chronic diarrhea, fatty stools, malabsorption, somatic developmental delay or behavior disorders is relatively rare in people with T1DM. More frequent is the occult form, periodically asymptomatic, in which symptoms are unstable and uncharacteristic abdominal pain, bloating, diarrhea, constipation, infertility,[43] abnormalities of bone mineralization[44] and psychiatric abnormalities[45] have been reported. The diagnosis of CD requires a high index of suspicion. Subjects can be screened for celiac-associated autoimmunity with EMA or TTG autoantibodies, followed by confirmation with small intestinal biopsy. Screening with anti TTG antibodies has been shown to be highly sensitive in classical symptomatic CD, both in children[46] and adults.[47] A study from Humboldt University[48] suggested that anti TTG antibody positivity is a more sensitive marker than EMA antibody for detection of asymptomatic CD in T1DM.

If only anti TTG IgA estimation is done in CD screening, it may miss some cases, as patients with CD are more prone for IgA deficiency. An Italian multi center study[49] reported that 2.6% of patients with CD had IgA deficiency, 10–16 fold higher than the population in general. The possible way out is to measure serum IgA in the cases before study and perform estimation of IgG-TTG antibodies or IgG against deamidated gliadin peptides in subjects with low serum IgA.

The ADA recommends performing screening for CD with auto antibodies in all patients with T1DM at time of diagnosis of Diabetes, repeated within 2 years, 5 years and in follow-up in anybody with symptoms suggestive of celiac disease. A significant subset of

individuals with T1DM have negative first screen for CD autoimmunity but seroconvert on follow up.[26] Hence patients with T1DM, who have been screened and were found to be negative, still need to evaluate periodically.

Addison's disease

Adrenalitis, followed by complete destruction of adrenal gland results from an autoimmune process and that results in adrenal insufficiency. In developed countries autoimmune adrenalitis is responsible for majority of the cases. A study[50] from Norway reported prevalence of 140 per million in general population and observed common aetiologies were either idiopathic or autoimmune. A study from Sweden found that 21α hydroxylase was major autoantigen in idiopathic AD.[51] In India, a hospital based study[52] found that tuberculosis is the most common cause of AD. Even in idiopathic AD only 21% had 21α hydroxylase antibodies (21-OHAA).[52] A study from[10] Barbara Davis Center for childhood diabetes reported that 1.4% of patients with T1DM individuals expressed 21-OHAA and in follow-up 15% of these individuals developed AD. This study also reported that among patients with T1DM, DR3-DQ2/DR4-DQ8 with DRB1*0404 human leucocyte antigen (HLA) genotype was associated with expression of 21-OHAA. At 2 years of follow-up, individuals homozygous for the major histocompatibility complex class I-related chain A5.1 (MICA5.1) had less AD-free survival compared with those who were not homozygous for MICA5.1.[10] A New Delhi based study found that 2.9% of patients with T1DM were found to have 21-OHAA.[40] The presence of adrenal auto-immunity is known to be associated with thyroid autoimmunity; about 70% of the individuals with 21-OH autoantibodies also express thyroid autoantibodies.[5]

A prospective follow-up study[53] of subjects with adrenal autoantibodies found annual incidence of clinical or subclinical adrenal failure was 19%. They have found that a progression of adrenal insufficiency that begins with elevated plasma renin activity and then progresses to increased ACTH, decreased stimulated cortisol, and eventually abnormalities of fasting cortisol.

OTHER ASSOCIATED AUTOIMMUNE DISEASES

Vitiligo

Vitiligo results from an autoimmune process that results in the loss of the skin pigmentation. It is known to occur with increased frequency in patients with T1DM. In a study from Italy, conducted to document associated skin lesions in DM,[54] it was found that vitiligo was present in 9% of patients with T1DM, compared to 0.8% among patients with T2DM.[55]

Anti parietal cell antibodies and pernicious anaemia

Pernicious anaemia (PA) is another auto-immune disease that is known to be associated with T1DM. It results from autoimmune destruction of gastric parietal cells. Anti parietal cell (APC) antibodies are responsible for autoimmune destruction of gastric parietal cells. One age, sex and ethnicity-matched, case-control study found a significantly higher frequency of APC (13.3%) and PA (4%) when compared to controls. It was also observed that, autoimmunity against gastric parietal cells was associated with other autoimmune diseases.[56]

It was also observed that, APC antibody positive patients, especially who are hypergastrenemic, are a high-risk group for pre malignant lesions and APC antibodies and PA screening was proposed in all patients with T1DM.[55] Kakleas et al,[57] reported that at baseline 7.22% of patients with T1DM had APC antibody and at follow-up, 7.21% had these antibodies. This study also proposed periodic APC autoantibody screening for the
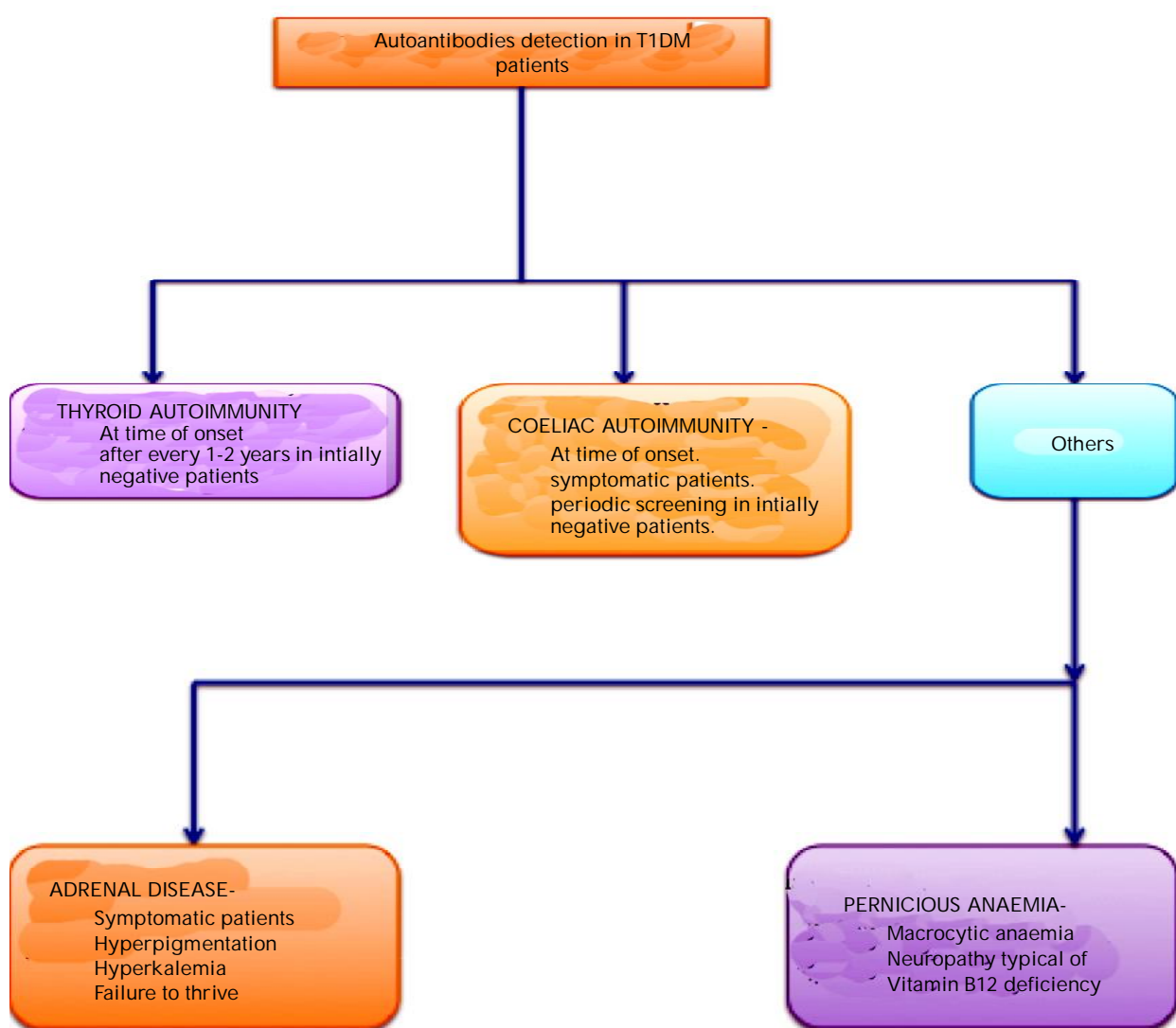
Figure 1: Detection of autoantibodies in T1DM patients

T1DM = Type I diabetes mellitus

early diagnosis and follow-up of gastric autoimmunity especially in patients those with thyroid and/or pancreatic autoimmunity.

T1DM is known to be associated with organ specific autoantibodies. Detection of these antibodies by screening (Figure 1) is very important to prevent development of full-blown disease. Periodic screening is required to detect these autoantibodies. This will help not only for better glycaemic control but also proper wellbeing of the T1DM patients.

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