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Commentary

Celiac disease & type 1 diabetes: A double burden

Type 1 diabetes mellitus (T1DM) and celiac disease (CD) are both relatively common T-cell-mediated autoimmune disorders prevalent in children[1]. T1DM occurs due to the destruction of pancreatic islet β-cells, leading to severe insulin deficiency and hyperglycaemia, while CD results from damage to the intestinal epithelium resulting in characteristic abdominal symptoms, and multiple extra-intestinal consequences. The two disorders have considerable genetic overlap and the frequency of CD is increased in patients with T1DM. The co-occurrence of these two disorders worsens the prognosis of T1DM. The diagnosis of CD necessitates life-long avoidance of gluten-containing foods (such as wheat and barley) and compliance is difficult, especially since patients with T1DM already have dietary restrictions. Hence, making an accurate diagnosis of CD is essential.

CD is triggered by the ingestion of gluten-containing foods, and the disease is ameliorated by the removal of gluten from the diet. It occurs in individuals with a genetic predisposition for the disorder, with the homozygous HLA DR3-DQ2 haplotype conferring the highest risk[2]. The DR3-DQ2 haplotype, along with DR4-DQ8, also increases predisposition to T1DM. Gliadin peptide, present in gluten-containing foods, enters through the intestinal epithelium into the lamina propria where deamidation by tissue transglutaminase (tTG) increases its immunogenicity. Gliadin is presented by antigen-presenting cells, leading to release of pro-inflammatory cytokines from T-cell. This leads to infiltration of the intestinal epithelium with lymphocytes and, finally, villous atrophy and hyperplasia of crypt cells[1]. The role of tTG antibodies in the pathogenesis of the CD is still not clear.

CD is present in 0.5-1 per cent of the general European population. However, its frequency is considerably increased in patients with T1DM (3-16%)[1,3,4]. Manifestations of CD in individuals with T1DM may include gastrointestinal symptoms, such as diarrhoea and abdominal pain, or extra-intestinal manifestations such as weight loss, poor glycaemic control (especially hypoglycaemia), anaemia, short stature, delayed puberty and low bone density[1]. A significant proportion of patients with CD may be asymptomatic. Because patients with T1DM may have mild or no features of CD, the disease may be overlooked for many years.

CD is preceded by different antibodies in the serum, including against tTG, deamidated gliadin and endomysium. Most commonly measured is the immunoglobulin A (IgA)-tTG antibody, which has high sensitivity and specificity for untreated CD[3-5]. On the basis of antibody positivity and intestinal biopsy findings, a spectrum of CD can be defined[1,6]. Symptomatic patients with IgA-tTG antibody and characteristic findings on intestinal biopsy are classified as classical CD and should be managed with gluten withdrawal. Patients who are asymptomatic but have tTG antibody in serum and intestinal biopsy changes are known as silent CD. These patients have been shown to benefit from gluten withdrawal. In contrast, varying titres of tTG antibody may be present in asymptomatic patients without any intestinal mucosal lesions (potential CD)[7,8]. The course and prognosis of potential CD is not well defined and gluten withdrawal is still controversial[7,8].

CD should be tested in all symptomatic patients of T1DM and those at high-risk of developing the disorder, *e.g.* having a first-degree relative with CD. However, due to the high frequency of CD, and the fact that many patients are asymptomatic, it has been recommended that all T1DM patients should be screened[9,10]. Screening for CD is recommended at diagnosis of T1DM and after two and five years[9,10]. In children, this schedule will identify nearly three-fourths of patients with CD[3,4]. Further screening after five years is recommended for patients who have

suggestive clinical features or with a family history of CD[9]. Most commonly, IgA antibodies against tTG are measured, along with total serum IgA, which should be normal. In case IgA levels are low, IgG-tTG or IgG-deamidated gliadin antibody can be measured. If tTG antibody is elevated, most society guidelines recommend a duodenal biopsy to confirm the diagnosis of CD[9,10]. The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) guidelines for CD in all children has recommended that a biopsy may not be necessary in symptomatic children with very high titres of IgA-tTG antibody (>10 times normal), if another test such as IgA-endomysial antibody is also positive[11]. HLA typing for DQ2/DQ8 is also recommended for these patients. However, the guidelines by the Indian Council of Medical Research state that diagnosis of CD should not be based on serology alone[6]. In asymptomatic children with T1DM who are antibody positive, a biopsy should be performed to confirm the diagnosis of silent CD[10].

In Indian patients with T1DM, a variable frequency of seropositivity of tTG antibody and CD has been reported. The frequency was reported to be higher in patients of north Indian origin (tTG antibody 11-34%; CD 3.8-13.5%) compared with a study from southern India (tTG antibody 5%)[12-14]. The reason for this is not clear, but it may be due to the differences in frequency of genetic susceptibility loci or environmental factors such as the age of initiating gluten-containing foods in infancy.

Kaur *et al*[15] in this issue studied the utility of five different commercial tTG ELISA kits with different antigen epitopes for determining antibody prevalence of CD. In addition, the frequency and clinical features of a spectrum of patients with overt and potential CD were determined. Two groups of patients with T1DM, *viz*. those with overt symptoms of CD (n=50) and asymptomatic patients (n=100), were studied. All symptomatic T1DM patients were positive for IgA-tTG antibodies and had intestinal biopsy changes confirming CD. Except for a kit which utilized native tTG antigen, all other kits detecting antibodies against recombinant IgA-tTG had acceptable sensitivity in symptomatic patients. In contrast, on testing T1DM patients without clinical features of CD, the frequency of antibody-positive patients was low (0-4%) using IgA-tTG antibody kits. Somewhat surprisingly, when an assay for detecting both IgA-tTG and IgG-tTG antibodies was used, the antibody positivity rate was increased to 37 per cent. Duodenal biopsies performed in five of 37 patients with antibody showed non-specific changes. In addition, HLA-DR and DQ alleles and clinical features did not differ between groups. During a follow up of two years, no patients with IgG-tTG antibody developed features of CD. On the basis of these data, the authors concluded that potential CD was frequent in their T1DM patients, when using an assay for detecting both IgA-tTG and IgG-tTG.

This well-designed and detailed study provides useful information. First, ELISA kits based on the detection of recombinant IgA-tTG antibody had high sensitivity, and were more or less equally effective in diagnosing CD in symptomatic T1DM patients. Because a multitude of kits were used for the diagnosis of CD, their data provides general guidelines for choosing appropriate kits for screening for antibodies. Second, the high occurrence of CD in symptomatic T1DM children reiterates the importance of prompt antibody testing for the disorder in this group of patients. However, it was surprising that all symptomatic patients with T1DM were positive for IgA-tTG antibodies and had a characteristic altered intestinal histology. This is because many features of CD, such as anaemia, short stature and even abdominal complaints, may also occur in many other unrelated conditions and are not specific. Third, regarding potential CD, the authors stated that more than one-thirds of asymptomatic T1DM patients had IgG-tTG antibodies and fit into this category[15]. However, such a high frequency of IgG-tTG antibody has rarely been reported previously in CD patients with normal total IgA levels[16]. In addition, the characteristics of this group of potential CD patients were also not well defined. Intestinal biopsy could only be done in a small proportion of antibody-positive patients and was non-diagnostic. Detailed HLA-DR and DQ alleles and clinical features also did not differ between potential CD and antibody-negative patients. No patient with potential CD became symptomatic during a follow up of two years. Hence, while the finding of a large sub-group of T1DM with potential CD is interesting, it requires re-confirmation in a separate cohort of children while using different assays for IgG-tTG antibody.

How does this study improve our knowledge and what are those aspects of CD which require further study? The current study reiterates that patients with T1DM and characteristic symptoms are likely to have CD and require gluten-free diet. In addition,

prevalence and prognosis of potential CD needs to be further defined on prospective studies. In view of the reported wide variation in the prevalence of CD in north and south India, a multicentric study with standardized protocols needs to be conducted in patients with T1DM. Finally, different aspects of gluten-free diet and its assessment in the Indian context, including acceptability of various dietary interventions, need another study. With the availability of high-quality data on different aspects of CD in Indian children with T1DM, specific guidelines for its diagnosis and management should be feasible.

***Conflicts of Interest*:** None.

Eesh Bhatia
Department of Endocrinology, Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow 226 014, Uttar Pradesh, India
ebhatia@sgpgi.ac.in

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