

Prevalence and clinical profile of celiac disease in children with type 1 diabetes mellitus

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ABSTRACT

Objective: To determine the prevalence of celiac disease (CD) in children with type 1 diabetes mellitus (T1DM) in follow-up in a Tertiary Care Referral Centre in Western India and to describe the clinical features indicative of CD in screened patients of T1DM. **Study Design:** In this single center observational cross-sectional study, 71 children who were diagnosed with T1DM were subjected to screening for CD with tissue transglutaminase antibody testing. Those who tested positive were offered intestinal biopsy for the confirmation of diagnosis. Clinical profiles of both groups of patients were compared and manifestations of CD were delineated. **Results:** The study revealed the prevalence of CD (based on serology) in children with Type 1 diabetes as 15.49%. The prevalence of biopsy-confirmed CD was 7.04%. Of the diagnosed CD patients, one-third were symptomatic at the time of screening while the majority was asymptomatic. The major clinical features indicative of CD were intestinal symptoms, anemia, rickets, and short stature. Autoimmune thyroid disease was prevalent in 29.6% of the patients with T1DM followed by CD. **Conclusions:** The high prevalence of CD in children with Type 1 diabetes emphasizes the need for routine screening programs to be in place for these high-risk populations. The clinical profile of patients with CD further elaborates the indicators of CD and the need to screen for them.

Key words: Celiac disease, children, tissue transglutaminase autoantibodies, Type 1 diabetes mellitus

INTRODUCTION

Owing to a common genetic background and interplay between environmental and immunologic factors, patients with Type 1 diabetes mellitus (T1DM) are at high risk of developing other autoimmune disorders. Studies have shown that 15–30% of patients with T1DM display Hashimoto’s thyroiditis, and celiac disease (CD) is the next in frequency after Hashimoto’s thyroiditis.^[1-4] Various studies have estimated that the prevalence of CD in T1DM varies from 3% to 16%, with a mean prevalence of 8%.^[1]

The clinical picture of CD in T1DM is often silent with the absence of both gastrointestinal and extra-intestinal signs suggestive of gluten-sensitive enteropathy. Untreated CD may be responsible for malabsorption with relevant clinical manifestations (anemia, osteopenia, miscarriages, and liver dysfunction) and increased risk of complications (refractory CD, ulcerative jejunoileitis, and lymphoma). Hence, the International Society for Pediatric and Adolescent Diabetes^[5] recommends that serological screening for CD should be performed in all T1DM patients by means of antibodies to tissue transglutaminase (tTG IgA) at the onset of T1DM. Some authorities have recommended that not only symptomatic cases, but also even potential CD cases (diagnosed by serological testing but asymptomatic) should be kept on a gluten-containing diet with a careful

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clinical and antibody follow-up, since many of them will progress to develop villous atrophy and symptomatic CD on continued gluten exposure.^[1]

Despite the advent of sensitive and specific serologic testing, routine screening for CD in diabetic populations is not a universal practice, especially in resource-limited settings. Though studies outside India^[6-12] have suggested a high prevalence of CD in diabetics, the prevalence has not been extensively studied in India, especially in pediatric diabetic populations.

Furthermore, very few studies have been undertaken to delineate the manifestations of CD in diabetic children, which can be subtle (iron deficiency anemia, failure to thrive) yet can cause significant morbidity.

Therefore, this study was planned to examine the prevalence of CD in children with T1DM and identify the manifestations of CD in these patients.

MATERIALS AND METHODS

Study design and setting

This was a single center observational cross-sectional study of children and adolescents aged 0–18 years diagnosed as T1DM, who were receiving insulin therapy. Children with type 2 diabetes or diabetes due to documented genetic defects in beta cell function or insulin action, pancreatitis, cystic fibrosis, and hemochromatosis were excluded from the study. The study was conducted in the Pediatric Endocrinology Clinic of a Tertiary Care Hospital in the Western India after approval by the Institutional Ethics Committee. Informed consent was taken from the parents as well as children over 7 years of age prior to enrollment in the study. The sample size in the study was 71 patients of Type 1 diabetes. All of these were screened for CD.

Study procedure

Each consenting patient was subjected to serologic testing for tTg IgA enzyme-linked immunosorbent assay (ELISA) using the same method and laboratory (EUROIMMUN anti-tTg IgA ELISA) each time. All patients with positive serologic test results were offered endoscopic intestinal biopsies to confirm CD. The histopathologic diagnosis of CD required jejunal or duodenal biopsy specimens with characteristic CD changes such as partial or complete villous atrophy associated with crypt hyperplasia and a lymphoplasmacytic infiltration in the lamina propria. The staging was done according to the Marsh classification.^[13]

Furthermore, all patients were evaluated for clinico-epidemiologic features of CD at the time of

serologic screening. This included detailed questioning regarding symptoms, physical examination, additional laboratory and radiologic testing, and evaluation for autoimmune thyroid disease (AITD) and glutamic acid decarboxylase antibody positivity. All patients with confirmed CD were recommended to go on a gluten-free diet and were managed appropriately for nutritional deficiencies. At the end of the study, the outcome measures were the prevalence of CD in children with Type 1 diabetes based on serology and histopathology and the prevalence and significance of association of the clinical features of CD.

Statistical methods

The prevalence of CD in T1DM cases was assessed using appropriate statistical methods. For comparisons between tTg IgA positive and tTg IgA negative groups, qualitative data were analyzed in the form of frequency and percentage and the association between discrete variables was assessed using Chi-square test and Fisher's exact test. Quantitative data were represented by mean \pm standard deviation and median.

RESULTS

Out of 71 patients of T1DM, 11 tested positive for tTg IgA. Positive levels were defined as levels above 20 RU/ml. This translated into a prevalence of 15.49% of serology positive patients, irrespective of their symptoms or biopsy results. Out of six patients who consented for and underwent a biopsy, five had changes suggestive of CD, with a prevalence of 7.04% in the screened cohort.

Of the 11 serology positive patients, 54.5% were males and 45% were females. 36% of the serology positive patients were symptomatic at the time of presentation, while the majority (64%) was asymptomatic [Figure 1]. Table 1 depicts the symptomatology of CD patients.

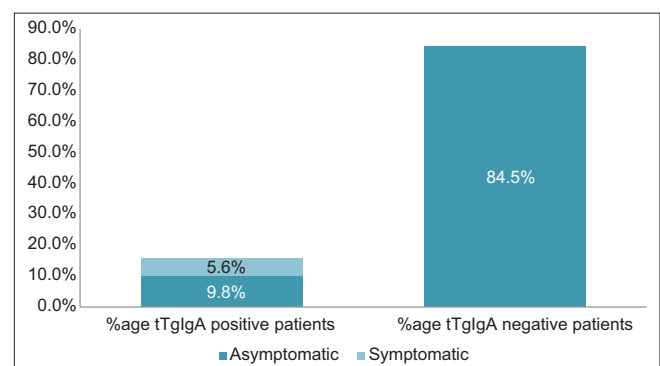


Figure 1: Prevalence of celiac disease in type 1 diabetes (serology) (This figure depicts the prevalence of celiac disease in the screened cohort of Type 1 diabetes patients. While the overall prevalence was 15.49%, the prevalence of asymptomatic celiac disease was 9.8%)

Signs of malnutrition and micronutrient deficiencies

Failure to thrive was defined as weight z-scores of the child falling below -2 for the age and sex, based on Agarwal charts.^[14] Short stature was defined as height for age z-scores ≤ -2 , based on Agarwal charts. Table 2 depicts the frequency of clinical signs in the CD group.

Laboratory features

Anemia was defined as hemoglobin concentration or red blood cell volume below the range of values in the normal population of the same age and sex, based on WHO definitions.^[15]

Hypocalcemia was defined as a serum calcium level of less than 8.5 mg/dL.^[16]

Hypophosphatemia was defined as serum phosphorus levels <3.8 mg/dL (1–3 years), 3.7 mg/dL (4–11 years), and 2.9 mg/dL (12–15 years).^[16]

High alkaline phosphatase was defined as alkaline phosphatase levels above 420 U/L (1–9 years) and above 560 U/L (10–11 years).^[16]

Radiological evidence of rickets/osteoporosis was looked for after obtaining wrist radiographs of all patients. Bone age was calculated for all the patients using the same hand radiographs, based on the Greulich and Pyle bone age atlas. Delayed bone age was defined as a lag of more than 2 years between the bone age and chronologic age.

25 OH Vitamin D levels were measured and were defined to be deficient below 15 ng/ml and insufficient between 15 and 20 ng/ml.^[17]

Thyroid function tests including free T₃, free T₄, and thyroid-stimulating hormone (TSH) as well as thyroid peroxidase (TPO) antibodies were done for all the patients. Overt hypothyroidism was defined as a TSH level of more than 4.5 μ IU/L and a low free T₄ level. Subclinical hypothyroidism was defined as TSH level >4.5 μ IU/L with a normal T₄ or free T₄.^[16] Table 3 depicts the frequency of relevant laboratory features in CD patients.

Intestinal biopsy results

Out of 11 serology positive patients, 6 consented for and underwent duodenal biopsy. Of the 6 patients, 5 had biopsy changes suggestive of CD (Marsh stage 0 $n = 1$, Marsh stage 1 $n = 1$, Marsh stage 2 $n = 1$, and Marsh stage 3 $n = 3$).

Table 1: Frequency of symptoms among CD patients

Symptom	Prevalence %		Significance of association of symptom with CD
	CD serology positive group	CD serology negative group	
Chronic abdominal pain	27	-	Significant ($P=0.0029$)
Chronic diarrhea	27	-	Significant ($P=0.0029$)
Recurrent abdominal distension	36	1.7	Significant ($P=0.00156$)
Failure to gain adequate height	27	10	Not significant ($P=0.138$)
Failure to gain adequate weight	18	6.7	Not significant ($P=0.231$)

CD: Celiac disease

Table 2: Comparison of clinical signs in CD serology positive and negative patients

Clinical sign	Number of patients (prevalence %)		Significance of association with CD
	CD serology positive group	CD serology negative group	
Pallor	6 (54.5)	4 (6.7)	Significant ($P<0.05$)
Rickets	4 (36.4)	8 (13.3)	Not significant ($P=0.08$)
Short stature	2 (18.2)	6 (10)	Not significant ($P=0.60$)
Edema	1 (9.1)	-	Not significant ($P=0.15$)
Hepatomegaly	1 (9.1)	4 (6.7)	Not significant ($P=0.58$)
Pubertal delay	1 (9.1)	-	Not significant ($P=0.15$)

CD: Celiac disease

Table 3: Comparison of laboratory features in CD serology positive and negative patients

Laboratory feature	Number of patients (prevalence %)		Significance of association with CD
	CD serology positive group	CD serology negative group	
Anemia	6 (54.50)	12 (20)	Significant ($P=0.02$)
Radiologic features of rickets	5 (45.40)	8 (13.3)	Significant ($P=0.02$)
Hypophosphatemia	6 (54.50)	8 (13.3)	Significant ($P<0.05$)
Hypocalcemia	1 (9)	1 (1.7)	Not significant ($P=0.28$)
High alkaline phosphatase	5 (45.40)	27 (45)	Not significant ($P=1$)
Delayed bone age	2 (18)	5 (8.3)	Not significant ($P=0.29$)
Vitamin D deficiency	5 (45.50)	27 (45)	Not significant ($P=1$)
Hypothyroidism	3 (36.30)	3 (5)	Not significant ($P=1$)
TPO antibody positivity	6 (54.5)	15 (25)	Not significant ($P=0.07$)

TPO: Thyroid peroxidase; CD: Celiac disease

DISCUSSION

This study concluded that the prevalence of CD in children with Type 1 diabetes was 15.49% (based on serology). The prevalence of biopsy-confirmed CD was 7.04%. In similar studies conducted in abroad and India, the prevalence

of CD has ranged from 5.5% to 20% based on serology and 1.6% to 16.4% based on histopathology. The mean prevalence of histopathology proven CD based on these studies is 6.18%.^[6-12,18-25] Thus, we reported the prevalence of CD in T1DM close to the world mean prevalence, which is 8–10 times higher than the prevalence reported in the general population.^[26]

Most diabetic children with CD have silent or subclinical forms of the illness and only a small minority (48 of 400 in a recent meta-review) is identified by symptoms.^[27] In the various reports, the number of patients with symptoms and signs differ widely, which probably reflects how carefully these were sought. It is likely that some patients were regarded as asymptomatic when they were not.^[28] In our study, a third of the serology positive patients were symptomatic at the time of screening while the majority (64%) was asymptomatic.

Although intestinal symptoms are classical features of CD, they are more common in children diagnosed within the first 2 years of life. With the shifting of the age at the presentation of the disease later in childhood and with the wider and more liberal use of serological screening tests, extra-intestinal manifestations, without any accompanying digestive symptom, have increasingly been recognized, affecting almost all organs.^[29] Further, at the time of screening, most children do not complain of gastrointestinal disturbances, but failure to thrive and gastrointestinal symptoms may be present, and in some cases may only be recognized in retrospect.^[27]

In our study, intestinal symptoms (chronic diarrhea, chronic abdominal pain, and abdominal distension) indicative of CD were present in a third of the CD patients. Furthermore, there was clustering of all 3 symptoms in 3 out of 4 CD patients who reported this. Among extra-intestinal symptoms, the most common was a failure to gain height, followed by failure to gain adequate weight, and multiple fractures. No significant difference was found in those with or without CD in terms of these complaints.

Failure to thrive

Aktay *et al.*^[30] have reported growth failure in 11.7% of their CD patients. On the other hand, in a study by Westman *et al.*,^[31] it was found that children and adolescents with coexisting T1DM and CD had normal growth, equivalent diabetes control and no differences in energy or nutrient intake compared to matched T1DM controls, despite only a 30% compliance to Gluten free diet. In our study, which evaluated patients using weight for age z-scores (prior to initiation of gluten-free diet), failure to thrive was not a significant clinical feature indicative of CD.

Short stature

Short stature has been reported in about one-third of children with CD in some series^[32,33] but others have reported that it is not a predominant feature.^[34,35] Rossi *et al.*^[36] reported the prevalence of CD among children with short stature as 1.7%. In an Australian study, no significant differences were found between Height z-scores of CD-T1DM patients and T1DM controls.^[37] Bhadada *et al.*^[13] reported that short stature was a manifestation in 52.3% of CD-T1DM patients. In our study, short stature was noted in 18.2% patients in CD patients as opposed to 10% patients in the CD serology negative group. This difference was not statistically significant. This was in contrast to the above cited studies which have reported short stature as the predominant feature of CD in T1DM. The possible explanation for this seeming contradiction was that the 4 patients with short stature in the CD serology negative group were labeled as Mauriac syndrome (triad of hepatomegaly, growth retardation, and cushingoid facies in poorly insulinized type 1 diabetes patients). One patient among the CD group was also suspected to have this syndrome. Thus, one fallacy of our study was that we could not eliminate confounding factors affecting growth like quality of glycemic control giving rise to this syndrome.

Delayed bone age was seen in two short-statured patients out of 11 CD patients (18.2%) while 8.3% of the serology negative patients had delayed bone age. This difference was statistically not significant.

Anemia

Anemia is a frequent finding in patients with CD and may be the presenting feature. Iron deficiency anemia is very common in the setting of CD and has been reported in up to 46% of cases of subclinical CD, with a higher prevalence in adults than children.^[38] In our study, 54.5% of CD patients had anemia as compared to 20% in those without CD, which was found to be statistically significant. Of the CD group, all anemic patients were classified according to the WHO classification into the moderate category, while the anemic patients in the CD serology negative group presented a heterogeneous mix of mild/moderate/severe varieties (11.7%, 6.7%, 1.7%, respectively).

Microcytic anemia was most predominant (66.7% of the anemic patients) in the CD group, indicating it to be due to iron deficiency as a part of CD-malabsorption syndrome.

Metabolic bone disease

Metabolic bone disease in the form of rickets and osteomalacia in children and osteoporosis in adults is a prime feature of CD. The mechanisms postulated are not only malabsorptive-nutritional but also immunoregulatory

in nature.^[39,40] In our study, clinical evidence of rickets was present in 36.4% of CD patients as opposed to 13.3% in the CD serology negative group. We did not find a significant association between clinical evidence of rickets and CD. Overt hypocalcemia was not seen as a major manifestation in those with CD (9.1%). Hypophosphatemia was found to be significantly associated with CD serology positivity (54.5%). Though hypophosphatemia has not been reported previously as a major CD manifestation, its presence assumes significance as a biochemical manifestation of rickets in the CD patients. Radiologic evidence of rickets was another major manifestation of metabolic bone disease due to CD in this study (36.3%).

Despite Vitamin D deficiency being almost equally prevalent in both the groups (45% in both the groups), evidence of rickets and metabolic bone disease was more in the CD group. This could be due to the additional immunoregulatory mechanisms coming into play in patients with both CD and T1DM.

Autoimmune thyroid disease

AITD was detected on the basis of positivity for TPO antibodies in 54.5% among the CD group and 25% among the non-CD group. Overall, the prevalence of AITD in this cohort of type 1 diabetic children was 29.6%. Thus, AITD was the most common autoimmune disease found in our cohort of Type 1 diabetes patients. Overall, the prevalence of overt hypothyroidism was 8.4% while that of subclinical hypothyroidism was 11.26%.

Intestinal biopsy

Intestinal biopsy has been used as the gold standard for the confirmation of CD in all the studies cited, as well as in this study. However, we could biopsy only 6 patients out of 11 as the rest were unavailable either because of attrition (lost to follow-up) or had not given consent to biopsy.

Among the 6 biopsied, 5 had biopsy changes suggestive of CD. Among the 5 not biopsied, 3 had very high tTG IgA levels, which were >10 times the upper normal limit. This was very suggestive of CD in these patients, even though not proven by biopsy.

This is now, especially, significant in the light of the new ESPGHAN guideline,^[41] which no longer holds intestinal biopsy as the gold standard for CD diagnosis. In contrast to the old guidelines, not only Marsh 3 lesions but Marsh 2 lesions are also accepted as compatible with CD. The reasoning behind this is that the histological features in CD may be patchy and, in a small proportion of CD patients, may appear only in the duodenal bulb, and hence can be

missed. Furthermore, these alterations are not specific for CD and may be found in enteropathies other than CD.

Limitations

This study had limitations in terms of a smaller sample size, confounding factors such as glycemic control and nutritional intake and nonassent for intestinal biopsy by some serology positive patients. Furthermore, due to short-term follow-up of the study subjects (6 months–1 year) and attrition of subjects from tTG IgA positive group, we could not compare glycemic control, hypoglycemia, and other diabetes-related complications between the two groups.

CONCLUSION AND CLINICAL IMPLICATIONS OF THE STUDY

- Children with type 1 diabetes and CD often do not have overt gastrointestinal complaints. They may be asymptomatic or may have these subtle manifestations: Iron deficiency anemia (especially, if refractory to therapy), rickets (unresponsive or partially responsive to Vitamin D), failure to thrive, short stature, pubertal delay, and frequent unexplained hypoglycemia episodes. All of these can be easily missed if not looked for. Because of the high prevalence and minimal symptomatology of CD in patients with type 1 diabetes, health care providers should have a low threshold for serologic screening for CD
- Serologic evidence of CD is present in a high percentage of children at the time of diagnosis of Type 1 diabetes. Thus, screening for CD must be part of the standard of care for every newly diagnosed diabetic child
- Dietary management of CD improves symptomatology, prevents hypoglycemia, and decreases the risk of osteopenia and malignant lymphoma.

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Conflicts of interest

There are no conflicts of interest.

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