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Celiac Disease Among Patients with Type 1 Diabetes Mellitus

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ABSTRACT

The prevalence of celiac disease (CD) in type-1 diabetes mellitus (T1DM) may vary depending on the region, genetic background, and screening practices. **Objectives:** To determine the frequency of CD in patients with T1DM. **Methods:** This cross-sectional study was conducted at the Outpatient Department and Pediatric Ward of Children's Hospital and Institute of Child Health, Multan, Pakistan, from February 2024 to July 2024. The inclusion criteria were children aged 2-18 years with type 1 diabetes mellitus (T1DM). Anti-transglutaminase assessment for the diagnosis of CD was performed, and it was deemed positive if the serum anti-tissue transglutaminase IgA antibody level was ≥100 IU/mL or the histopathology of the intestinal biopsy specimen was consistent with Marsh category 3 or higher. Data analysis was performed using IBM-SPSS Statistics, version 26.0. **Results:** The mean age was 9.03±3.6 years. There were 57(58.2%) children who were male. Fifty-two (53.1%) children belonged to middle-class families. A positive family history of T1DM, autoimmune thyroiditis, and CD was noted in 46 (46.9%), 10 (10.2%), and 6 (6.1%) cases, respectively. The diagnosis of CD was confirmed in 20 (20.4%) children with T1DM. There were 4 (20.0%) and 2 (10.0%) patients with positive CD who had a positive family history of autoimmune thyroiditis and CD, respectively. **Conclusions:** The frequency of celiac disease was high among children with type 1 diabetes mellitus. The utility of anti-tTG evaluation is a non-invasive diagnostic tool for the screening of CD and can be utilized for the early diagnosis of CD in children with T1DM.

INTRODUCTION

Type 1 diabetes mellitus (T1DM) is an immune-related disease characterized by a deficiency or absence of the insulin hormone as a result of T-cell-mediated decay of β-cells of the pancreas [1, 2]. Recent epidemiological data reveal the incidence of T1DM is around 15/100,000 [3]. T1DM is associated with various autoimmune diseases, and it is believed that 15-30% of patients with T1DM also have an autoimmune thyroid disease, 5-10% have autoimmune gastritis, and 4-9% have celiac disease (CD) [4]. Data from the developed world have shown a very low prevalence of CD in T1DM [5]. CD is a disorder with an underlying genetic (the main involved gene is HLA-DQ2-8) and inflammatory etiology, resulting from an immune response to gluten present in barley, wheat, and rye, and when these are ingested, they alter the small intestine [6]. Both T1DM and CD share a strong genetic predisposition through HLA-DR3/DQ2 and HLA-DQ8 haplotypes, and these molecules present autoantigens to CD4+ T cells, leading to β-cell destruction in T1DM and gluten-driven intestinal inflammation in CD. This overlap explains their frequent coexistence and supports routine CD screening in T1DM patients [7]. The prevalence of CD is estimated to be around 0.5% in the general population [4]. CD is two times more prevalent among the female population, while the

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prevalence of CD in T1DM is 5-7 times higher [8]. Children with T1DM are at higher risk of autoimmune thyroiditis and also have an increased susceptibility to celiac disease, as both are influenced by environmental triggers, including HLA haplotypes. A study from the Islamic Republic of Iran done in 2013 to document the prevalence of CD as 6.8% in T1DM [9]. The elevated prevalence of CD among children is owing to an overlap in the genetic tendency of both disorders awarded by the HLA-DR3/DQ2-8 [2]. The typical presentation of CD consists chiefly of gastrointestinal symptoms related to malabsorption, e.g., loose stools, failure to gain weight, and height [10]. Children are screened for IgA and IgG anti-tissue transglutaminase (anti-tTG) antibodies present in serum, and diagnosis is usually confirmed by a small gut biopsy [11,12]. Data also show that underlying CD is related to a high risk of symptomatic high blood sugar and that the administration of a gluten-free diet (GFD) with normalization of the gut mucosa may decrease its frequency [13]. Researchers have highlighted the importance of diagnosing and managing CD in asymptomatic children with T1DM [14]. If unrecognized, the underlying CD in patients with T1DM may lead to erratic glucose control and poor linear growth (height and weight) due to ongoing malabsorption. The prevalence of CD in T1DM varies across regions due to genetic factors, dietary habits, and differences in screening protocols. In some areas, routine serological testing detects more cases, while selective or symptom-based screening leads to underdiagnosis. Given the lack of standardized local practices, this study aimed to determine the frequency of CD in children with T1DM to help guide early diagnosis and improve management strategies. Although celiac disease (CD) is recognized as a common autoimmune comorbidity in children with type 1 diabetes mellitus (T1DM), reported prevalence varies widely across regions due to differences in genetic background, environmental exposures, and screening strategies. In Pakistan, limited local data exist regarding the true burden of CD among pediatric T1DM patients, and routine screening practices are not standardized. This lack of region-specific evidence creates uncertainty in clinical decision-making and may lead to underdiagnosis. Therefore, determining the local frequency of CD in children with T1DM is essential to guide screening policies and optimize patient care. This study aims to provide valuable insights for clinicians, policymakers, and caregivers in tailoring care for children with T1DM who may also have CD. Therefore, this study aimed to determine the frequency of CD in children with T1DM.

METHODS

This cross-sectional study was conducted at the Outpatient Department and Pediatric Ward of Children's Hospital and Institute of Child Health, Multan, Pakistan, from February 2024 to July 2024. The study commenced after obtaining approval from the institutional ethical review committee (Letter No. ERC/2023/36). A sample size of 98 patients was calculated using the standard single-population proportion formula: $n=Z2\times p\times(1-p)/d2$; where Z = 1.96 (corresponding to a 95% confidence level), p=0.068 (expected prevalence of CD in T1DM = 6.8%) [9], and d = 0.05 (margin of error). The inclusion criteria were children of both genders, aged 2-18 years, with T1DM. The exclusion criteria were patients with other comorbidities, like other types of diabetes, chronic liver disease, chronic lung disease, tuberculosis, immunosuppressive disorders, congenital heart diseases, or hematological disorders. T1DM was labeled by the presence of any one or more of the following: i) fasting levels of plasma glucose≥126 mg/dL (7.0 mmol/L), ii) random levels of plasma glucose≥200 mg/dL (11.1 mmol/L), iii) HbA1c≥6.5% [2]. T1DM diagnosis was confirmed from existing medical records, where fasting glucose, random glucose, or HbA1c had already been performed at the time of initial diagnosis. Non-probability consecutive sampling technique was used. All of the study patients were subject to informed and written consent from their parents/guardians after they were informed of the objective, safety, and data secrecy. For children above 7 years of age, verbal assent was also sought in line with ethical guidelines for paediatric research. Once the patients were recruited, demographic data regarding age, gender, and duration of DM were recorded. A 5 ml venous blood sample was collected, and an anti-tTG assessment was done. If the index of suspicion was high and tTG was not suggestive, the patients underwent endoscopic intestinal biopsy, and specimens were sent for histopathology. The patients were classified as having CD, positive or negative. It was deemed positive if the serum anti-tissue transglutaminase IgA antibody level was≥100 IU/mL [5] or the histopathology of the intestinal biopsy specimen was consistent with Marsh category 3 or higher. The Marsh classification is a histopathological grading system for CD, ranging from early mucosal changes to advanced villous atrophy. Marsh I indicates increased intraepithelial lymphocytes, Marsh II adds crypt hyperplasia, while Marsh III (a–c) represents progressive villous atrophy of mild, moderate, or severe degree. A diagnosis of CD in this study was confirmed when biopsy findings were consistent with Marsh III or higher, reflecting clinically significant disease relevant to pediatric patients with T1DM. Age was grouped into early childhood (2–6 years), middle childhood (7–12 years), and adolescence (13–18 years). Socioeconomic status was classified based on monthly household income: low (<30,000 PKR), middle (30,000–70,000 PKR), and high (>70,000 PKR). Family history of T1DM or other autoimmune

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disorders (e.g., thyroid disease) was recorded as present or absent based on parental reporting. Data collection was carried out on a specific, predesigned proforma. Data was analyzed using "IBM-SPSS Statistics" version 26.0. The quantitative variables, which included age and duration of disease (T1DM), were presented as mean and standard deviation (SD), or median and interquartile range (IQR) (depending upon the normal distribution of data, checked by the Shapiro-Wilk test). For the qualitative variables such as gender, family history of T1DM (yes/no), family history of other autoimmune disorders, i.e., thyroid (yes/no), and the outcome, i.e., CD (yes/no), frequency and percentage were calculated. The effect modifiers like gender, age, socioeconomic status of the parents, age at diagnosis with T1DM, age at the time of diagnosis of CD, family history of T1DM, and family history of other autoimmune disorders, were dealt with through stratification. As the data were stratified with respect to CD status (present/absent), associations between categorical variables (e.g., gender, age groups, socioeconomic status, family history, and HbA1c categories) and CD were assessed using the chi-square / Fisher's exact test. A p-value ≤0.050 was considered statistically significant.

RESULTS

Of all 98 children, the mean age was 9.03±3.6 years, with ages ranging between 2.5 to 15 years. Male and female contributions were 57 (58.2%) and 41 (41.8%) children, respectively. In our study, the median duration of the disease (T1DM) was calculated to be 2 years (IQR: 2-5), with a minimum and maximum duration of 0.5 years and 8 years. There were 52 (53.1%) children who belonged to middle-class families. A positive family history of T1DM, autoimmune thyroiditis, and CD was noted in 46 (46.9%), 10 (10.2%), and 6 (6.1%) cases, respectively (Table 1).

Table 1: Characteristics of Patients (N=98)

Characteristics		Frequency (%)
Gender	Boys	41 (41.8%)
	Girls	57 (58.2%)
Age (years)	2-5	42 (42.9%)
	5-15	56 (57.1%)
Age at Diagnosis of T1DM (Years)	<5	32 (32.6%)
	5-10	53 (54.1%)
	>10	13 (13.3%)
Parental Socioeconomic Status	<30,000 PKR	35 (35.7%)
	30,000-70,000 PKR	52 (53.1%)
	>70,000 PKR	11 (11.2%)
Family History of Autoimmune T1DM	Yes	46 (46.9%)
	No	52 (53.1%)
Family History of Autoimmune Thyroiditis	Yes	10 (10.2%)
	No	88 (89.8%)
Family History of CD	Yes	6 (6.1%)
	No	92 (93.9%)
HbA1c (%)	≤7.5	31 (31.6%)
	>7.5	67 (68.4%)

When comparing children with and without CD, no statistically significant associations were observed with gender (65.0% vs. 56.4% females, p=0.487), age group (60.0% vs. 56.4% in 5–15 years, p=0.772), or age at T1DM diagnosis (70.0% vs. 50.0% for 5–10 years, p=0.232). Socioeconomic status also showed no significant association (p=0.412), though CD was more frequent in the middle-class group (65.0% vs. 50.0%). A positive family history of T1DM was less common in CD patients (30.0% vs. 51.3%, p=0.088), while family history of autoimmune thyroiditis was relatively higher (20.0% vs. 7.7%, p=0.104). Family history of CD showed no significant difference (10.0% vs. 5.1%, p=0.4175). Glycemic control measured by HbA1c also did not differ significantly (≤7.5%: 30.0% vs. 32.1%, p=0.860) (Table 2).

Table 2: Association of the Characteristics of Children with CD

Characteristics		Celiac Disease		p-Value
		Yes (n=20)	No (n=78)	
Gender	Boys	7 (35.0%)	34 (43.6%)	0.487
	Girls	13 (65.0%)	44 (56.4%)	
Age (Years)	2-5	8 (40.0%)	34 (43.6%)	0.772
	5-15	12 (60.0%)	44 (56.4%)	
Age at Diagnosis of	<5	5 (25.0%)	27 (34.6%)	0.232
	5-10	14 (70.0%)	39 (50.0%)	
	>10	1 (5.0%)	12 (15.4%)	
Socioeconomic Status (Rupees Per Month)	<30,000 PKR	6 (30.0%)	29 (37.2%)	0.412
	30,000-70,000 PKR	13 (65.0%)	39 (50.0%)	
	>70,000 PKR	1 (5.0%)	10 (12.8%)	
Family History of TIDM	Yes	6 (30.0%)	40 (51.3%)	0.088
	No	14 (70.0%)	38 (48.7%)	
Family History of Autoimmune Thyroiditis	Yes	4 (20.0%)	6 (7.7%)	0.104
	No	16 (80.0%)	72 (92.3%)	
Family History of CD	Yes	2 (10.0%)	4 (5.1%)	0.417
	No	18 (90.0%)	74 (94.9%)	
HbA1c (%)	≤7.5	6 (30.0%)	25 (32.1%)	0.860
	>7.5	14 (70.0%)	53 (67.9%)	

DISCUSSION

The frequency of celiac disease (CD) in T1DM in this study was 20.4%, which is considerably higher than global estimates. Craig *et al.*, analyzing 52,721 young T1DM patients across 3 continents, reported a biopsy-proven CD prevalence of 3.5% [15]. A recent meta-analysis by Karimzadhagh *et al.*, found that globally, about 1 in 16 individuals with T1DM are affected by CD, with a higher prevalence in Asia and the Middle East (≈1 in 12) [16]. Several factors may explain the comparatively higher frequency in

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this study. The selection bias cannot be ruled out, as this study was conducted at a tertiary care center where children with more severe or complicated diseases may be overrepresented. Regional genetic predisposition, particularly the high prevalence of HLA-DR3/DQ2 and DQ8 haplotypes in South Asian populations, may contribute to the increased risk. Environmental influences, such as dietary gluten exposure, early childhood infections, and differences in screening practices, may also play a role. These considerations highlight the need for routine and systematic screening for CD in children with T1DM, especially in regions with a potentially higher genetic and environmental risk. Early diagnosis and management can prevent complications like malabsorption, poor glycemic control, and impaired growth. The present findings contrast with those of Albatayneh *et al.*, who reported that among 138 patients, CD was positive in 6.5% [17]. Some researchers have reported that the occurrence of T1DM is rapidly rising in the pediatric age group, with a stated rise of 3% on an annual basis [18, 19]. So, with this rise, an overall rise in the prevalence of CD is also expected, which warrants measures for the timely identification and management of CD in this set of patients. CD is a female-dominant disorder and is almost three times more prevalent among the female population [19]. This study noted that the proportion of females in CD was 65.0% versus 56.4% without CD in T1DM. According to Wedrychowicz *et al.*, the occurrence of CD was significantly higher in girls (13.9%) than in boys (4.9%) with T1DM, and this correlates well with the present findings [20]. In this study, the mean age was 9.03±3.6 years in children with CD, which is relatively similar to what a recent study by Andari and colleagues reported as 8.28 years [21]. This study showed that the median duration of T1DM in children was 2 years, with a range of 6 months to 8 years. Honar *et al.*, demonstrated a significant association between disease duration and positive tTG findings, with the mean duration being markedly longer in antibody-positive patients (3.0 ± 0.8 years vs. 1.0 ± 0.4 years, p=0.04), suggesting that longer duration of T1DM increases the likelihood of developing CD [22]. Vajravelu *et al.*, in a large cohort of 9,180 patients with T1DM, reported that female gender and younger age at T1DM diagnosis were strong predictors of subsequent CD development, indicating robust associations with these demographic factors [23]. Unal *et al.*, analyzing 779 T1DM patients, revealed that serological evaluation and follow-up monitoring are advised instead of biopsy evaluation for the confirmation of CD [24]. Laitinen *et al.*, in a cohort study of 850 children aged up to 17 years, concluded that screening for CD should be done in every T1DM patient, as children who had screening for CD were less symptomatic than those who were tested after they had symptoms [25].

A study from Finland showed that the young patients with a +ve family history of other autoimmune disorders had a high level of islet cell auto-antibodies (p=0.003), and the HLA DR3 DQ2 haplotype in the children was linked with CD in the complete family (p<0.001), but not with a raised prevalence of immune diseases generally [26]. Routine screening for CD using anti-tTG in children with T1DM can enable early diagnosis, reducing complications associated with undiagnosed CD. Anti-tTG evaluation is a non-invasive, cost-effective tool that can be integrated into routine care for high-risk populations like T1DM patients. Early diagnosis and management of CD can improve growth, nutritional status, and overall quality of life in children with T1DM [24, 25]. The findings of this research support the need for standardized screening protocols for CD in T1DM patients, promoting better long-term health outcomes. Single-center study setting and a modest sample size were some of the limitations of this study, so our findings need further verification. Studies should also be planned to evaluate the clinical impact of CD on T1DM. As this was a cross-sectional study, causal relationships between T1DM and CD could not be established. A prospective cohort design would provide stronger evidence regarding temporal and causal associations, and future studies in this setting should consider such an approach.

This study has certain limitations, including its single-center design and relatively small sample size, which may restrict the generalizability of the findings. The cross-sectional nature also limits the ability to establish temporal or causal relationships between T1DM and CD. Additionally, long-term clinical outcomes following CD diagnosis were not assessed. Future multicenter, longitudinal studies with larger cohorts are needed to evaluate risk factors, monitor disease progression, and assess the impact of early CD screening on glycemic control and growth outcomes in children with T1DM.

CONCLUSIONS

The frequency of CD was high among children with T1DM. The utility of anti-tTG evaluation is a non-invasive diagnostic tool for the screening of CD and can be utilized for the early diagnosis of CD.

Authors' Contribution

Conceptualization: MJ
Methodology: ML, NQ, MI
Formal analysis: MJ, FJ
Writing and Drafting: MJ, MS, MF, MI, FJ
Review and Editing: MJ, MS, MF, MI, FJ, ML, NQ

All authors approved the final manuscript and take responsibility for the integrity of the work

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Conflicts of Interest

All the authors declare no conflict of interest.

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