

FREQUENCY OF HYPOTHYROIDISM IN CHILDREN WITH CELIAC DISEASE: A CROSS-SECTIONAL STUDY AT A TERTIARY CARE HOSPITAL IN PAKISTAN

Original Research

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ABSTRACT

Background: Celiac disease (CD) is an autoimmune disorder characterized by an immune-mediated response to gluten, leading to intestinal mucosal damage and various systemic complications. Among its extraintestinal manifestations, thyroid dysfunction is a significant concern, with studies indicating an increased risk of hypothyroidism in CD patients. The interplay between chronic inflammation, genetic predisposition, and delayed diagnosis contributes to the high prevalence of autoimmune thyroid diseases in affected individuals. Despite global evidence supporting this association, data on pediatric populations, particularly in resource-limited settings, remain scarce.

Objective: This study aimed to determine the prevalence of hypothyroidism in children with CD and assess its association with demographic and clinical factors.

Methods: A cross-sectional study was conducted at the Pediatric Department of a tertiary care hospital in Pakistan from September 1, 2023, to November 30, 2024. A total of 196 children aged 2–12 years with a confirmed diagnosis of CD were enrolled. Diagnosis was established through serological markers, including anti-tissue transglutaminase (anti-tTG) and anti-endomysial antibodies (EMA), with histopathological confirmation where available. Demographic data, nutritional status, and clinical history were recorded. Thyroid function was assessed through anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-TG), free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) levels. Statistical analysis was conducted using SPSS v.26, with a p-value <0.05 considered significant.

Results: The study population included 102 females (52.0%) and 94 males (48.0%), with the majority aged 6–10 years (42.9%), followed by 1–5 years (29.6%) and 11–15 years (27.6%). Nutritional assessment revealed that 82 children (41.8%) were underweight, 92 (46.9%) had a normal BMI, and 22 (11.2%) were overweight/obese. Hypothyroidism was diagnosed in 42 children (21%), while 154 (79%) remained euthyroid. A significantly higher prevalence was observed in younger children aged 1–5 years (40.9%, $p = 0.048$) and those with underweight status (50.0%, $p = 0.012$). A family history of thyroid disease was also significantly associated with hypothyroidism ($p = 0.014$). However, no significant associations were found with gender ($p = 0.728$), duration of CD ($p = 0.112$), dietary adherence ($p = 0.129$), or comorbidities such as type 1 diabetes and iron deficiency anemia ($p > 0.05$).

Conclusion: The study highlights a notable prevalence of hypothyroidism in children with CD, emphasizing the need for routine thyroid function screening in this high-risk population. Younger age, underweight status, and a family history of thyroid disease emerged as significant risk factors. Early detection and strict dietary adherence may help mitigate the risk of thyroid dysfunction. Further longitudinal studies are needed to explore the underlying mechanisms and to establish effective screening and management protocols.

Keywords: Celiac disease, children, hypothyroidism, pediatric screening, prevalence, thyroid disorders, thyroid function

INTRODUCTION

Celiac disease (CD) is a complex autoimmune disorder that has gained increasing recognition as one of the most common chronic conditions affecting children globally, with a prevalence estimated between 0.5% and 1% across different populations. It results from an immune-mediated reaction to gluten, a protein found in wheat, barley, and rye, leading to progressive damage to the small intestinal mucosa. This damage manifests as villous atrophy, impairing nutrient absorption and resulting in a wide spectrum of clinical presentations, ranging from asymptomatic cases to severe gastrointestinal symptoms and systemic complications such as malnutrition. While the presence of the HLA-DQ2 or HLA-DQ8 haplotypes is a necessary genetic prerequisite for disease development, these genetic markers are found in approximately 30% of the general population, indicating that additional genetic and environmental factors play a critical role in disease onset (1). The pathogenesis of CD is influenced by a complex interplay between genetic susceptibility and environmental triggers such as gluten exposure. Beyond HLA-associated risk, non-HLA genetic loci, including CELIAC2 (5q31-33) and CELIAC3 (2q33), have been implicated in the immune dysregulation underlying the disease (2). Despite advances in understanding these genetic contributors, the precise mechanisms remain incompletely elucidated, presenting challenges in predicting disease development in at-risk individuals. The chronic immune activation in CD extends beyond the gut and is associated with an increased risk of various autoimmune disorders, particularly autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves' disease. Research has demonstrated that individuals with CD have a markedly higher prevalence of thyroid disorders, with some studies suggesting rates up to ten times greater than in the general population (3). Notably, Ventura et al. observed that CD patients often exhibit elevated thyroid autoantibodies, which tend to normalize upon adherence to a strict gluten-free diet, supporting the hypothesis that ongoing gluten exposure may exacerbate systemic autoimmune responses, including those targeting the thyroid gland (4).

The association between CD and thyroid dysfunction in Pakistan mirrors international trends, with reports indicating a higher prevalence of autoimmune thyroiditis in individuals with CD compared to the general population. A large-scale meta-analysis estimated the prevalence of autoimmune thyroiditis at approximately 5.2% in individuals with CD (5). However, regional variations in genetic predisposition, delayed diagnosis, and prolonged gluten exposure due to dietary patterns may contribute to slightly higher prevalence rates observed in Pakistani cohorts. As awareness of CD has grown in Pakistan, improvements in diagnostic capabilities, including serological testing and endoscopic biopsy, have led to a notable increase in diagnosed cases and a better understanding of associated autoimmune conditions (6). Historically underdiagnosed in South Asia, CD is now recognized as a significant public health concern, with recent studies suggesting its prevalence may reach 1% in specific high-risk groups (7). This rising recognition underscores the need for systematic evaluation of associated autoimmune complications, including hypothyroidism, to enable early diagnosis and appropriate management. Despite the well-documented link between CD and thyroid disorders, limited local data exists on the burden of hypothyroidism among pediatric CD patients in Pakistan. Given the potential consequences of undiagnosed thyroid dysfunction on growth, development, and overall health, identifying its prevalence within this population is crucial. This study aims to assess the frequency of hypothyroidism in children with CD at a tertiary care hospital in Pakistan, providing valuable insights into its burden and emphasizing the importance of timely screening and intervention in this high-risk group.

METHODS

This cross-sectional study was conducted at the Pediatric Department of Combined Military Hospital, Kharian, from September 1, 2023, to November 30, 2024. The study population comprised children diagnosed with celiac disease (CD) who were receiving treatment at the hospital's medical department. Participants were recruited from both outpatient and inpatient settings to ensure a comprehensive representation of pediatric CD cases. Children aged 2 to 12 years with a confirmed diagnosis of CD were eligible for inclusion. The diagnosis was established based on elevated serological markers, including anti-tissue transglutaminase (anti-tTG) antibodies and/or anti-endomysial antibodies (EMA). In cases where available, histopathological confirmation through small bowel biopsy was also utilized, with characteristic findings such as villous atrophy and crypt hyperplasia serving as diagnostic criteria. To eliminate potential confounding factors, children with pre-existing thyroid disorders diagnosed before their CD diagnosis were excluded. Additionally, those with incomplete or missing medical records, including absent serological or biopsy data, and children whose families declined

participation or withdrew consent were not included. Participants with chronic illnesses known to independently impact thyroid function, such as chronic kidney disease or systemic lupus erythematosus, were also excluded to maintain the integrity of the study findings.

The sample size was determined based on a reported prevalence of 15% for anti-thyroid antibodies among CD patients, as observed in prior studies. Using an online sample size calculator, a total of 196 participants were estimated to achieve a 95% confidence level with a 5% margin of error, ensuring sufficient statistical power for meaningful analysis. A convenience sampling technique was employed to recruit participants. Demographic and clinical data, including age, gender, and medical history, were recorded at enrollment. Blood samples were collected for the assessment of thyroid autoantibodies, specifically anti-thyroid peroxidase (anti-TPO) and anti-thyroglobulin (anti-TG) antibodies, using a manual enzyme-linked immunosorbent assay (ELISA) technique. Compliance with a gluten-free diet was retrospectively evaluated by reviewing anti-tTG IgA levels recorded six months after dietary initiation, with levels exceeding ten times the upper limit of normal indicative of non-compliance. In cases where autoimmune thyroiditis was identified, thyroid function was assessed through measurements of free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) levels. Ethical approval for the study was obtained from the Institutional Review Board (IRB) of the hospital. Written informed consent was secured from the parents or legal guardians of all participants, while verbal assent was obtained from children aged seven years and above, ensuring adherence to ethical research practices. Data were analyzed using SPSS version 26. Categorical variables, including age, gender, and thyroid status, were expressed as frequencies and percentages. The chi-square test was applied to compare categorical variables, with a p-value of <0.05 considered statistically significant.

RESULTS

The study included 196 children diagnosed with celiac disease, with the majority aged between 6–10 years (42.9%), followed by those younger than 5 years (29.6%) and those aged 11–15 years (27.6%). Females (52.0%) slightly outnumbered males (48.0%). Regarding nutritional status, 41.8% of the children were underweight, while 46.9% had a normal body mass index (BMI), and 11.2% were classified as overweight or obese. The majority had been diagnosed with celiac disease for 1–3 years (44.9%), while 23.5% had a disease duration of less than one year and 31.6% for more than three years. Strict adherence to a gluten-free diet was reported by 68.4% of participants, whereas 31.6% showed partial or non-adherence. A family history of thyroid disease was present in 22.4% of cases. The most common comorbidities were iron deficiency anemia (46.9%) and type 1 diabetes mellitus (19.4%), while 33.7% of the children had no associated comorbidities. Among the study participants, 42 children (21%) were diagnosed with hypothyroidism, while 154 (79%) were euthyroid. This indicates that approximately one in five children with celiac disease had concurrent hypothyroidism, underscoring the importance of routine thyroid function screening in this population.

A significant association was observed between hypothyroidism and younger age groups, with 40.9% of children aged 1–5 years affected compared to 26.3% in the euthyroid group ($p = 0.048$). Hypothyroidism was also significantly more prevalent among underweight children (50.0%) compared to those with a normal BMI (40.9%) or overweight/obese status (9.1%) ($p = 0.012$). A positive family history of thyroid disease was significantly associated with hypothyroidism, with 36.4% of affected children reporting a family history compared to 18.4% in the euthyroid group ($p = 0.014$). However, no statistically significant association was observed between hypothyroidism and gender ($p = 0.728$), duration of celiac disease ($p = 0.112$), dietary adherence ($p = 0.129$), or the presence of comorbidities such as type 1 diabetes mellitus or iron deficiency anemia ($p > 0.05$).

Table: Demographic and Clinical Characteristics of Study Population (n=196)

Characteristic	Frequency (n)	Percentage (%)
Age Group (Years)		
>5	58	29.6
6–10	84	42.9
11–15	54	27.6
Gender		
Male	94	48.0
Female	102	52.0
Body Mass Index (BMI)		
Underweight (<5th percentile)	82	41.8
Normal weight (5th–85th)	92	46.9
Overweight/Obese (>85th)	22	11.2
Duration of Celiac Disease		
<1 year	46	23.5
1–3 years	88	44.9
>3 years	62	31.6
Dietary Adherence		
Strict adherence	134	68.4
Partial/non-adherence	62	31.6
Family History of Thyroid Disease		
Yes	44	22.4
No	152	77.6
Presence of Comorbidities		
Diabetes Mellitus Type 1	38	19.4
Iron Deficiency Anemia	92	46.9
None	66	33.7

Table: Association of Presence of Hypothyroidism with Demographic and Clinical Characteristics (N=196)

Characteristic	Hypothyroid (n=44)	Euthyroid (n=152)	p-value
Age Group (Years)			0.048*
1–5	18 (40.9%)	40 (26.3%)	
6–10	20 (45.5%)	64 (42.1%)	
11–15	6 (13.6%)	48 (31.6%)	
Gender			0.728
Male	22 (50.0%)	80 (52.6%)	
Female	22 (50.0%)	72 (47.4%)	
Body Mass Index (BMI)			0.012*
Underweight (<5th percentile)	22 (50.0%)	60 (39.5%)	
Normal weight (5th–85th)	18 (40.9%)	74 (48.7%)	
Overweight/Obese (>85th)	4 (9.1%)	18 (11.8%)	
Duration of Celiac Disease			0.112
<1 year	14 (31.8%)	32 (21.1%)	
1–3 years	18 (40.9%)	70 (46.1%)	
>3 years	12 (27.3%)	50 (32.9%)	
Dietary Adherence			0.129
Strict adherence	26 (59.1%)	108 (71.1%)	
Partial/non-adherence	18 (40.9%)	44 (28.9%)	
Family History of Thyroid Disease			0.014*
Yes	16 (36.4%)	28 (18.4%)	
No	28 (63.6%)	124 (81.6%)	
Presence of Comorbidities			0.129
Diabetes Mellitus Type 1	12 (27.3%)	26 (17.1%)	
Iron Deficiency Anemia	22 (50.0%)	70 (46.1%)	
None	10 (22.7%)	56 (36.8%)	

*= P< 0.05

Association of Hypothyroidism with BMI in Celiac Disease Patients

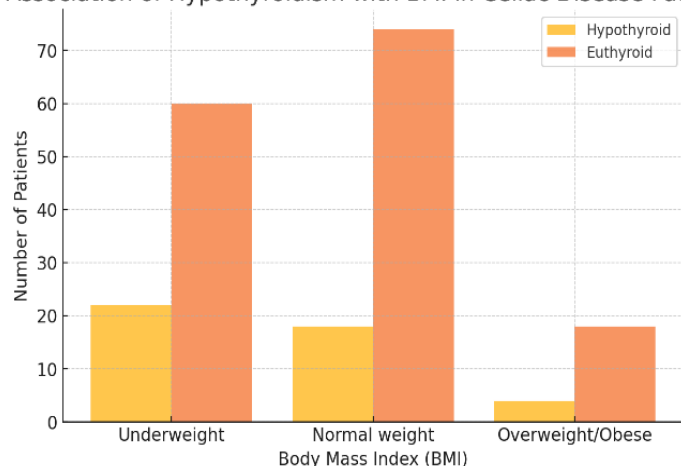


Figure 1 Association of Hypothyroidism with BMI

Prevalence of Hypothyroidism in Celiac Disease Patients

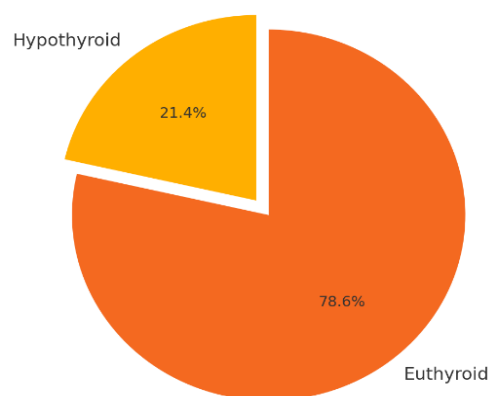


Figure 2 Prevalence of Hypothyroidism in Celiac Disease

DISCUSSION

The current study aimed to determine the prevalence of hypothyroidism in children with celiac disease at a tertiary care hospital. Celiac disease is a chronic autoimmune disorder with a highly variable clinical presentation, often leading to delayed diagnosis and underreporting. The findings of this study revealed a hypothyroidism prevalence of 21%, which is notably higher than the 10–15% reported in European studies, suggesting the influence of genetic predisposition, environmental factors, and healthcare disparities in different regions. The increased prevalence aligns with global evidence indicating an elevated risk of thyroid dysfunction among individuals with celiac disease, emphasizing the need for routine thyroid screening in this population (11). A systematic review identified an odds ratio of 3.06 for thyroid disease among celiac disease patients compared to the general population, reinforcing the global predisposition of this group to thyroid dysfunction (12). Another study from Northern Sardinia reported thyroid disorders in 15.4% of celiac disease patients, demonstrating consistency in findings despite regional variations (13). The elevated prevalence of hypothyroidism observed in this study may be attributed to delayed diagnosis and suboptimal adherence to a gluten-free diet, as noted in 31.6% of participants. Previous research has shown that delayed diagnosis of celiac disease can extend autoimmune activation, increasing the risk of secondary autoimmune disorders, including thyroid dysfunction. A study demonstrated a significant delay in celiac disease diagnosis, particularly among asymptomatic individuals, with an average diagnostic lag of over a decade, highlighting the challenges in timely disease recognition (14). Poor dietary compliance, commonly observed in resource-limited settings, has been implicated in the persistence of chronic inflammation and increased autoimmunity, further contributing to thyroid dysfunction (15). This suggests that both timely diagnosis and strict adherence to a gluten-free diet play a critical role in mitigating autoimmune complications.

The findings of this study also align with limited local data that support the association between celiac disease and thyroid dysfunction. A study conducted in Pakistan reported a strong association between celiac disease and thyroid disorders in adult populations, emphasizing the need for early screening and management strategies. However, some studies have reported even higher prevalence rates, with one study documenting hypothyroidism in 41.3% of the sample (16). Differences in methodologies, sample sizes, and diagnostic criteria may contribute to the variability in reported prevalence across studies. The predominance of female patients in this study is consistent with previous findings suggesting a gender predisposition in autoimmune diseases, including celiac disease, though some studies indicate no substantial gender disparities in thyroid dysfunction among celiac disease patients (17). The association between hypothyroidism and younger age groups (1–5 years) suggests that early-onset celiac disease may involve a more pronounced autoimmune response. Literature reviews and multicenter studies have reported similar findings, reinforcing the need for early screening and tailored management strategies for younger children at risk of developing thyroid dysfunction (18,19). The significant association between hypothyroidism and underweight status further supports the hypothesis that nutritional deficiencies, common in celiac disease, may contribute to autoimmune thyroid disorders. While some studies have linked obesity in celiac disease patients to an increased risk of thyroid autoimmunity, other research suggests that deficiencies in iodine and selenium, prevalent in undernourished populations, may

exacerbate the risk of thyroid dysfunction (20,21,22). The interplay between malnutrition and autoimmune thyroiditis requires further investigation, particularly in settings where nutritional deficits are prevalent.

A family history of thyroid disease was significantly associated with hypothyroidism, observed in 36.4% of hypothyroid cases compared to 18.4% in the euthyroid group. This supports genetic studies identifying familial clustering of autoimmune disorders, indicating a shared genetic predisposition (17,23,24). The role of genetic counseling and family-wide screening in identifying at-risk individuals is crucial for the early detection and prevention of thyroid dysfunction among children with celiac disease. Interestingly, dietary adherence did not show a statistically significant association with hypothyroidism in this study. Variations in compliance assessment methods, the retrospective nature of data collection, and socioeconomic barriers to accessing gluten-free products may have influenced this outcome. Cultural and financial constraints in resource-limited settings often impact dietary adherence, reducing the effectiveness of dietary interventions in mitigating autoimmune complications. While this study provides valuable insights into the association between hypothyroidism and celiac disease in pediatric populations, several limitations must be considered. The cross-sectional design limits causal inference, and the reliance on retrospective dietary adherence data may introduce recall bias. Additionally, the sample size, though statistically adequate, may not fully capture regional variations in prevalence. Future studies should incorporate prospective longitudinal designs to assess the long-term impact of dietary adherence on thyroid function. Further research exploring the role of specific nutritional deficiencies in the pathogenesis of thyroid dysfunction among celiac disease patients would be beneficial in understanding underlying mechanisms.

CONCLUSION

The study underscores a strong association between hypothyroidism and celiac disease in children, emphasizing the need for routine thyroid function screening in this high-risk population. The findings highlight key contributing factors, including younger age, underweight status, and a family history of thyroid disease, which may further predispose pediatric patients to thyroid dysfunction. Given the challenges of delayed diagnosis and dietary noncompliance, particularly in resource-limited settings, early detection and proactive management strategies are crucial in mitigating long-term autoimmune complications. These insights reinforce the importance of an integrated approach to care, ensuring timely intervention and improved health outcomes for children with celiac disease.

AUTHOR CONTRIBUTIONS

Author	Contribution
Waseem Ahmed*	Substantial Contribution to study design, analysis, acquisition of Data
	Manuscript Writing
	Has given Final Approval of the version to be published
Muhammad Tariq Nadeem	Substantial Contribution to study design, acquisition and interpretation of Data
	Critical Review and Manuscript Writing
	Has given Final Approval of the version to be published
Sadia Naz	Substantial Contribution to acquisition and interpretation of Data
	Has given Final Approval of the version to be published
Farooq Ikram	Contributed to Data Collection and Analysis
	Has given Final Approval of the version to be published
Abdullah Akram	Contributed to Data Collection and Analysis
	Has given Final Approval of the version to be published
Abdul Samad	Substantial Contribution to study design and Data Analysis
	Has given Final Approval of the version to be published
Sher Afgan Raisani	Contributed to study concept and Data collection
	Has given Final Approval of the version to be published

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