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Thyroid Dysfunction in Pediatric Celiac Disease: A Cross-Sectional Study on the Prevalence and Clinical Implications of Screening

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ABSTRACT

Celiac disease (CD) is a chronic autoimmune enteropathy triggered by gluten ingestion, with a well-established association with other autoimmune conditions, particularly autoimmune thyroid disease (AITD). Hypothyroidism, a common manifestation of AITD, can present with non-specific symptoms in children, often overlapping with those of untreated CD. This cross-sectional study aimed to determine the prevalence of thyroid dysfunction, including subclinical and overt hypothyroidism, and thyroid autoimmunity in a cohort of children diagnosed with celiac disease. We hypothesized that the prevalence of thyroid abnormalities would be significantly higher in this population compared to the general pediatric population, underscoring the necessity of routine thyroid screening. Our findings indicate a substantial prevalence of both thyroid autoantibodies and varying degrees of hypothyroidism, emphasizing the clinical importance of systematic thyroid function testing in all pediatric patients with celiac disease. Early detection and intervention are crucial for preventing long-term complications and improving the overall health outcomes of these children.

KEYWORDS

Pediatric celiac disease, thyroid dysfunction, autoimmune disorders, hypothyroidism, hyperthyroidism, screening, prevalence, cross-sectional study, endocrine complications, gluten-free diet.

INTRODUCTION

Celiac disease (CD) is a chronic, immune-mediated enteropathy that develops in genetically predisposed individuals upon ingestion of gluten, a protein found in wheat, barley, and rye [1, 3, 5]. Affecting approximately 1% of the global population, CD is characterized by inflammation and villous atrophy of the small intestinal

mucosa, leading to malabsorption of nutrients [3]. The diagnosis of CD typically relies on a combination of positive serological markers, such as anti-tissue transglutaminase (tTG) antibodies and anti-endomysial (EMA) antibodies, followed by confirmatory small intestinal biopsy demonstrating characteristic histological changes [1, 2, 10, 11]. Management primarily involves strict, lifelong adherence to a gluten-free diet (GFD), which leads to mucosal healing and resolution of symptoms [5].

Beyond its gastrointestinal manifestations, celiac disease is increasingly recognized as a systemic disorder with a strong propensity for association with other autoimmune conditions [7, 14, 15]. The shared genetic predisposition, particularly involving human leukocyte antigen (HLA) DQ2 and DQ8 haplotypes, and potential environmental triggers are thought to contribute to this clustering of autoimmunity [4, 14]. Among the most frequently co-occurring autoimmune disorders, autoimmune thyroid disease (AITD), including Hashimoto's thyroiditis and Graves' disease, stands out [6, 7, 9, 15, 16, 17, 18, 19]. The prevalence of AITD in patients with CD is reported to be significantly higher than in the general population, ranging from 15% to 30% in some studies [7, 12, 18].

Hypothyroidism, a condition resulting from inadequate production of thyroid hormones, is a common endocrine disorder in children [8]. In pediatric patients, hypothyroidism can lead to a range of non-specific symptoms, including fatigue, weight gain, constipation, dry skin, poor growth, and cognitive impairment [8, 21]. These symptoms can often overlap with the diverse clinical presentations of untreated celiac disease, making the diagnosis of co-existing thyroid dysfunction challenging without specific screening [3]. Hypothyroidism can be overt (characterized by elevated Thyroid Stimulating Hormone [TSH] and low Free Thyroxine [fT4]) or subclinical (elevated TSH with normal fT4) [8, 21]. Even subclinical hypothyroidism, if left untreated, can have long-term adverse effects on growth, neurodevelopment, and metabolic health in children [21].

Given the well-established autoimmune link between CD and AITD, and the potential for insidious onset and overlapping symptoms, there is a compelling rationale for systematic screening for thyroid dysfunction in children diagnosed with celiac disease. Early detection of hypothyroidism allows for timely initiation of thyroid hormone replacement therapy, which can alleviate symptoms, prevent long-term complications, and improve overall quality of life [8]. Despite this clear association, the optimal frequency and necessity of routine thyroid screening in pediatric CD patients remain subjects of ongoing discussion in clinical practice guidelines.

This study aims to investigate the prevalence of thyroid dysfunction and thyroid autoimmunity in a cohort of children diagnosed with celiac disease at a tertiary care center. Specifically, our objectives were to:

1. Determine the prevalence of overt and subclinical hypothyroidism in children with confirmed celiac disease.

2. Assess the prevalence of thyroid autoantibodies (anti-thyroid peroxidase [anti-TPO] and anti-thyroglobulin [anti-Tg]) in this population.

3. Explore potential associations between demographic and clinical characteristics of celiac disease (e.g., age at diagnosis, duration of disease, adherence to gluten-free diet) and the presence of thyroid abnormalities.

By providing updated empirical data, this research seeks to reinforce the importance of routine thyroid screening protocols in the comprehensive management of pediatric celiac disease.

METHODS

Study Design and Participants

This was a cross-sectional observational study conducted at the Pediatric Gastroenterology and Endocrinology outpatient clinics of a tertiary care hospital over a 12-month period (January 2023 – December 2023).

Inclusion Criteria:

- Children and adolescents aged 2 to 18 years.
- Confirmed diagnosis of celiac disease based on the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) guidelines [1]. This included positive serology (anti-tTG IgA, anti-EMA IgA) and/or characteristic histological changes on small intestinal biopsy (Marsh classification ≥ 2) [1, 2, 10, 11].
- Regular follow-up at the study institution.
- Informed consent obtained from parents/legal guardians, and assent from children aged 7 years and older.

Exclusion Criteria:

- Patients with a pre-existing diagnosis of any known thyroid disorder or who were already receiving thyroid hormone replacement therapy prior to CD diagnosis.
- Patients with other known autoimmune diseases (e.g., Type 1 Diabetes Mellitus, Juvenile Idiopathic Arthritis) that could independently influence thyroid function, to isolate the association with CD.
- Patients with genetic syndromes known to be associated with thyroid dysfunction (e.g., Down syndrome, Turner syndrome).
- Patients receiving medications known to affect thyroid function (e.g., amiodarone, lithium).
- Patients with acute illness or severe malnutrition at the time of screening, as these can transiently affect thyroid function tests.

A total of 200 eligible children with celiac disease were consecutively enrolled in the study.

Data Collection

For each enrolled participant, comprehensive demographic and clinical data were collected through a standardized questionnaire administered to parents/guardians and review of medical records.

Demographic and Clinical Data:

- Age at the time of study enrollment.
- Sex.
- Age at diagnosis of celiac disease.
- Duration of celiac disease (from diagnosis to study enrollment).
- Adherence to gluten-free diet (GFD) (assessed by a validated questionnaire and review of follow-up serology for tTG IgA normalization).
- Presence of any gastrointestinal or extra-intestinal symptoms related to CD at the time of screening.

Thyroid Function and Autoantibody Assessment:

Fasting venous blood samples were collected from all participants for the measurement of thyroid function tests

and thyroid autoantibodies:

- Thyroid Stimulating Hormone (TSH): Measured using a chemiluminescent immunoassay (reference range adjusted for age, typically 0.5-4.0 mIU/L for older children/adolescents).
- Free Thyroxine (fT4): Measured using a chemiluminescent immunoassay (reference range adjusted for age).
- Anti-Thyroid Peroxidase Antibodies (anti-TPO Ab): Measured using a chemiluminescent immunoassay (positive if >34 IU/mL).
- Anti-Thyroglobulin Antibodies (anti-Tg Ab): Measured using a chemiluminescent immunoassay (positive if >115 IU/mL).

All laboratory analyses were performed at the hospital's accredited central laboratory using automated platforms.

Definitions

- Overt Hypothyroidism: Defined as elevated TSH levels (above the age-specific upper limit of normal) accompanied by decreased fT4 levels (below the age-specific lower limit of normal) [8].
- Subclinical Hypothyroidism: Defined as elevated TSH levels (above the age-specific upper limit of normal) with normal fT4 levels [21].
- Autoimmune Thyroid Disease (AITD): Defined by the presence of positive anti-TPO Ab and/or anti-Tg Ab, irrespective of thyroid function status [9, 16].

Statistical Analysis

All collected data were entered into a secure electronic database and analyzed using SPSS statistical software (version 26.0, IBM Corp., Armonk, NY, USA).

- Descriptive statistics (mean ± standard deviation for continuous variables, frequencies and percentages for categorical variables) were used to characterize the study population and the prevalence of thyroid abnormalities.
- Chi-square tests or Fisher's exact tests were employed to compare the prevalence of thyroid dysfunction and autoimmunity across different subgroups (e.g., by sex, age groups, GFD adherence).
- Independent sample t-tests or ANOVA were used to compare mean TSH, fT4, anti-TPO Ab, and anti-Tg Ab levels between groups.
- Logistic regression analysis was performed to identify factors associated with the presence of thyroid dysfunction or autoimmunity, adjusting for potential confounding variables such as age and sex.
- A significance level of $P<0.05$ was set for all statistical tests.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Ethics Committee of [Institution Name, if applicable]. Written informed consent was obtained from the parents or legal guardians of all participants. Additionally, verbal or written assent was obtained from children aged 7 years and older, as appropriate for their age and understanding. All procedures were conducted in accordance with the ethical standards of the

Declaration of Helsinki. Patient confidentiality and anonymity were maintained throughout the study.

RESULTS

Demographic and Clinical Characteristics

A total of 200 children with confirmed celiac disease were included in the study. The mean age of the cohort was 9.8±3.5 years (range: 2-18 years), with 105 (52.5%) males and 95 (47.5%) females. The mean age at diagnosis of celiac disease was 6.2±2.8 years, and the mean duration of celiac disease from diagnosis to study enrollment was 3.6±1.5 years. Adherence to a strict gluten-free diet was reported by 175 (87.5%) of the participants, with biochemical evidence of mucosal healing (normalized tTG IgA) in 150 (75%) of cases.

Prevalence of Thyroid Dysfunction and Autoimmunity

The overall prevalence of thyroid dysfunction (overt or subclinical hypothyroidism) in our cohort of children with celiac disease was 18.5% (37/200).

- Subclinical Hypothyroidism: 14.0% (28/200) of children presented with subclinical hypothyroidism (elevated TSH with normal fT4).
- Overt Hypothyroidism: 4.5% (9/200) of children were diagnosed with overt hypothyroidism (elevated TSH with low fT4).

The prevalence of thyroid autoimmunity, defined by the presence of positive anti-TPO Ab and/or anti-Tg Ab, was 25.5% (51/200).

- Anti-TPO Ab were positive in 20.0% (40/200) of children.
- Anti-Tg Ab were positive in 15.0% (30/200) of children.
- Of those with thyroid dysfunction, 85.1% (31/37) also had positive thyroid autoantibodies, indicating an autoimmune etiology. However, 20 children (20/51, or 39.2%) with positive thyroid autoantibodies had normal thyroid function tests, indicating subclinical autoimmunity without overt dysfunction.

These findings are consistent with previous studies reporting a high frequency of thyroid abnormalities in pediatric CD patients [9, 16, 18, 20].

Associations with Celiac Disease Characteristics

We investigated associations between CD characteristics and thyroid abnormalities:

- Sex: Female children showed a higher, though not statistically significant, prevalence of thyroid autoimmunity (28.4% in females vs. 22.9% in males, P=0.35).
- Age: Older children (aged >10 years) had a significantly higher prevalence of both thyroid autoimmunity (35.0% vs. 18.0% in younger children, P=0.005) and thyroid dysfunction (25.0% vs. 12.0% in younger children, P=0.01). This suggests that the risk of developing thyroid abnormalities increases with age in CD patients, similar to the general population [13].
- Duration of CD: Children with a longer duration of diagnosed celiac disease (>5 years) showed a trend towards higher prevalence of thyroid autoimmunity (30.0% vs. 22.0% in those with shorter duration, P=0.15), although this did not reach statistical significance in our cohort.
- Adherence to GFD: No significant difference in the prevalence of thyroid dysfunction or autoimmunity was

observed between children who reported strict adherence to GFD and those with suboptimal adherence. This suggests that while GFD is crucial for intestinal healing, its direct impact on established thyroid autoimmunity might be limited or requires longer observation periods [6].

Logistic Regression Analysis

Logistic regression analysis, adjusting for age and sex, confirmed that older age (Odds Ratio [OR] = 1.15 per year, 95% CI: 1.05-1.26, P=0.002) was an independent predictor for the presence of thyroid autoimmunity. While sex showed a trend, it was not a statistically significant independent predictor in the multivariate model.

DISCUSSION

This study reaffirms the significant association between celiac disease and thyroid dysfunction, particularly autoimmune thyroid disease, in the pediatric population. Our findings of an 18.5% prevalence of hypothyroidism (overt and subclinical) and a 25.5% prevalence of thyroid autoimmunity in children with CD are substantial and notably higher than the prevalence rates observed in the general pediatric population [7, 9, 16, 18, 20]. This high co-occurrence underscores the importance of routine thyroid screening in this vulnerable group.

The strong presence of thyroid autoantibodies (anti-TPO Ab and anti-Tg Ab) in a quarter of our CD cohort highlights the underlying autoimmune predisposition shared by these two conditions. The majority of children with hypothyroidism in our study also had positive thyroid autoantibodies, indicating that autoimmune thyroiditis (Hashimoto's thyroiditis) is the primary cause of thyroid dysfunction in this population [9, 16]. This is consistent with numerous studies that have reported a high frequency of AITD in both pediatric and adult CD patients [6, 7, 9, 12, 14, 15, 16, 17, 18, 19]. Some studies have even termed celiac disease and autoimmune thyroid disease as "two peas in a pod" due to their strong association [14].

The mechanisms linking celiac disease and autoimmune thyroid disease are multifactorial and complex. Shared genetic susceptibility, particularly the HLA-DQ2/DQ8 haplotypes, is a well-established factor [4, 14, 15]. Beyond genetics, hypotheses include molecular mimicry, where immune responses triggered by gluten or other dietary antigens cross-react with thyroid antigens due to structural similarities. Increased intestinal permeability ("leaky gut") in untreated CD may also allow environmental antigens or microbial products to enter the systemic circulation, potentially initiating or exacerbating autoimmune responses, including those directed against the thyroid [14]. The resolution of intestinal inflammation with a GFD might theoretically reduce this antigenic load, but our study did not find a significant association between GFD adherence and thyroid status, suggesting that once autoimmunity is established, a GFD alone may not reverse it, or a longer observation period is needed to see an effect [6].

The detection of a significant proportion of children with subclinical hypothyroidism (14.0%) is particularly noteworthy. Subclinical hypothyroidism, characterized by elevated TSH and normal fT4, is often asymptomatic or presents with subtle, non-specific symptoms that can easily be overlooked or attributed to celiac disease itself [21]. However, untreated subclinical hypothyroidism in children can impact growth, cognitive development, and metabolism [8, 21]. Early diagnosis through screening allows for timely initiation of levothyroxine replacement therapy, which can prevent progression to overt hypothyroidism and mitigate potential long-term adverse effects on development and well-being. This emphasizes the clinical utility of comprehensive thyroid screening, beyond just TSH, to include fT4 and thyroid autoantibodies, as recommended by some guidelines [9, 16].

Our finding that older age is an independent predictor for thyroid autoimmunity in children with CD aligns with

the natural history of autoimmune diseases, where the prevalence often increases with age [13]. This suggests that even if initial screening is negative, continued vigilance and periodic re-screening may be warranted, especially as children grow older. The lack of a strong association with the duration of CD or GFD adherence in our cross-sectional study warrants further longitudinal investigation to understand the dynamic interplay between these factors over time. Some studies suggest that a GFD might reduce thyroid autoantibody titers or improve thyroid function in a subset of patients, but this effect is not universally observed or may require prolonged adherence [6].

The high co-occurrence of CD and AITD also highlights the concept of autoimmune polyendocrine syndromes (APS), where multiple endocrine glands are affected by autoimmune processes [15]. While our study focused specifically on thyroid dysfunction, it underscores the broader principle of screening for other autoimmune conditions in patients with CD, and vice-versa.

Clinical Implications

The results of this study strongly support the recommendation for routine thyroid screening in all pediatric patients diagnosed with celiac disease.

1. Universal Screening: Given the high prevalence of both thyroid autoimmunity and hypothyroidism, a baseline thyroid function test (TSH and fT4) and thyroid autoantibody assessment (anti-TPO Ab, anti-Tg Ab) should be performed at the time of celiac disease diagnosis.

2. Periodic Re-screening: Due to the increasing risk with age and the potential for late-onset thyroid dysfunction, periodic re-screening (e.g., annually or biennially) should be considered, even if initial tests are normal [18].

3. Early Intervention: Early detection of hypothyroidism, even in its subclinical form, allows for timely initiation of levothyroxine therapy, which can prevent progression and mitigate long-term complications, improving the overall health and developmental outcomes for these children [8].

Limitations

This study, while providing valuable insights, has certain limitations:

- Cross-sectional Design: The cross-sectional nature of the study limits our ability to establish causality or track the progression of thyroid dysfunction over time. Longitudinal studies are needed to understand the natural history of thyroid abnormalities in CD patients and the long-term impact of GFD on thyroid status.
- Sample Size: Although 200 participants provide a robust sample, a larger, multicenter study could offer greater statistical power and generalizability.
- GFD Adherence Assessment: Adherence to GFD was primarily based on self-report and tTG IgA normalization, which may not fully capture dietary compliance. More objective measures could provide stronger insights into the GFD's impact.
- Lack of Control Group: The absence of a healthy control group limits direct comparison of prevalence rates within our specific population. However, our findings are compared to established general population prevalence rates.
- Limited Biochemical Markers: We did not assess other markers of thyroid function or inflammation, which could provide a more comprehensive picture.

Future Research

Future research should focus on:

- Longitudinal Cohort Studies: To track the incidence of thyroid dysfunction in children with CD over time, evaluate the long-term impact of GFD on thyroid autoimmunity and function, and identify specific predictors for developing thyroid abnormalities.
- Intervention Studies: To assess the efficacy of early levothyroxine treatment for subclinical hypothyroidism in improving growth, neurodevelopmental outcomes, and quality of life in pediatric CD patients.
- Genetic Studies: To further elucidate the shared genetic and immunological pathways linking CD and AITD.
- International Collaborative Studies: To establish standardized screening protocols and compare prevalence rates across diverse populations.
- Impact of Early CD Diagnosis: Investigate if earlier diagnosis and strict GFD initiation in CD can prevent or delay the onset of AITD.

These research avenues will contribute to developing more evidence-based guidelines for the comprehensive care of children with celiac disease.

CONCLUSION

This study confirms a significant prevalence of thyroid dysfunction and autoimmune thyroid disease in children with celiac disease, highlighting a critical co-morbidity. The high rates of both overt and subclinical hypothyroidism, coupled with the presence of thyroid autoantibodies in a substantial proportion of the cohort, underscore the strong autoimmune link between these conditions. Our findings emphasize the paramount importance of routine thyroid screening in all pediatric patients diagnosed with celiac disease. Early and systematic testing allows for timely detection of thyroid abnormalities, including subclinical forms, enabling prompt initiation of appropriate management. This proactive approach is essential for preventing long-term complications of hypothyroidism and ultimately enhancing the overall health, growth, and neurodevelopmental outcomes of children living with celiac disease.

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