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Research Article

Prevalence and Characteristics of Hypothyroidism in Pediatric Celiac Disease Patients in King Abdulaziz Medical City, Saudi Arabia

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Abstract

Background: Celiac disease (CD) is an autoimmune disorder that is characterized by an inappropriate immune response when gluten is consumed. Hypothyroidism is a commonly observed comorbidity in patients with CD.

Aim: This study aims to determine the prevalence and characteristics of hypothyroidism in pediatric celiac disease patients to understand and improve the screening and management strategies for affected people.

Methods: A retrospective study design was adopted to conduct the study in Kind Abdulaziz Medical City, NGHA, Jeddah, Saudi Arabia. 55 patients diagnosed with celiac disease were included in this study. A data sheet was used for data collection, and it was managed through proper channels. The data is analyzed by SPSS software.

Results: In the study of 55 pediatric celiac disease patients at King Abdulaziz Medical City, the demographic and clinical characteristics reveal key findings. Females constituted 61.8% (34) of the study, and 45.5% were diagnosed at ages 8 and older. Height analysis showed that 30.9% had low height (≤ 110 cm), 41.8% were of normal height (111 cm to 160 cm), and 7.27% were classified as high height (> 160 cm). Weight distribution was similar, with 38.2% each in low (≤ 20 kg) and normal (20 - 40 kg) weight categories, while 10.9% were of high weight (≥ 40 kg). Hypothyroidism was present in 10.9% of patients, with a higher prevalence (27.2%) in those with a family history of autoimmune conditions. The correlation between gender and hypothyroidism was weak (Pearson's r = 0.155), suggesting gender does not strongly influence hypothyroidism risk.

Conclusion: Our study reveals a high prevalence of hypothyroidism in pediatric celiac disease patients, particularly impacting females and those with autoimmune family histories. Early thyroid screening is crucial in pediatric CD management due to shared genetic and immunological factors. Future research should focus on longitudinal studies to better understand this relationship and improve early screening strategies for enhanced patient care.

Keywords: *Hypothyroidism; Pediatric; Celiac Disease; CD; Autoimmune; Clinical Markers*

Abbreviations

CD: Celiac Disease; CTLA4: T Lymphocyte-Associated Antigen 4; GFD: Gluten-Free Diet; HLA: Histocompatibility Leukocyte Antigen; AITD: Autoimmune Thyroid Disease

Introduction

Celiac disease (CD) is an inflammatory condition that affects the upper small intestine and is usually an aberrant immune response to gluten found in wheat [1,2]. The incidence of Celiac disease (CD) has been steadily increasing 7.5% per year over the past few decades [3]. The prevalence varies across age, gender disparities, ethnic variances, and at-risk groups [4]. In Saudi Arabia, the prevalence of biopsy-proven CD is 1.4%, but the seroprevalence is 2.7%. The frequency of both the seroprevalence and biopsy-proven CD in SA is greater than the prevalence of CD aggregated globally. The exact prevalence of CD among Saudi children is not known. However, serological and biopsy data indicate 0.33 -1.06% prevalence in Sahrawi children [5].

Various symptoms and indicators suggest the degree of intestinal involvement in CD [6]. Therefore, the disease can be subclinical, with Extra-intestinal symptoms like anemia, aphthous ulcer, bone pain, etc., especially at a later age, or overt, with the classic features of diarrhea, abdominal distension, generalized malnutrition, and failure to thrive [7]. The definitive diagnostic for CD is a small intestinal biopsy, and the course of therapy is a lifelong gluten-free diet.

People with type 1 diabetes mellitus [8], autoimmune thyroiditis (and other autoimmune illnesses), and first- and second-degree CD history relatives are among the groups at high risk of developing CD as environmental stimulation and hereditary components trigger autoimmune diseases, mostly [9]. Apart from the aforementioned high-risk cohort, individuals with IgA deficiency and first- and second-degree relatives are also at heightened risk for CD [9]. Currently, 5% to 10% of at-risk populations worldwide have CD [10].

Moreover, CD has also been responsible for other illnesses, including autoimmune disorders, and is thus recognized as a multi-organ ailment. Numerous investigations have demonstrated a robust correlation between celiac disease and a higher incidence of autoimmune thyroid antibodies. Thyroiditis (HR = 3.6; 95% CI = 1.9 - 6.7; P < 0.001), hyperthyroidism (HR = 2.9; 95% CI = 2.0 - 4.2; P < 0.001), and hypothyroidism (HR = 4.4; 95% CI = 3.4 - 5.6; P < 0.001) are all linked to celiac disease. Hypothyroidism HR = 6.0 and 95% CI = 3.4 - 10.6 risk estimations are greatest in children. Also, men were more likely than women to get hypothyroidism when they had celiac disease (HR = 11.2 vs. 3.5) [11].

The existence of similar hereditary characteristics might clarify this correlation between hypothyroidism and celiac disease [12]. Human histocompatibility leukocyte antigen (HLA) DQ2 and DQ8 are observed in people with overlapping hypothyroidism and CD. The elevated T lymphocyte-associated antigen 4 (CTLA4) offers another possible explanation for CD-induced hypothyroidism. Studies on hypothyroidism have all shown elevated expression of CTLA4. In celiac disease, CTLA4 is also elevated than normal. This existence of similar genetic risk factors thus explains the positive correlation between thyroid illness and celiac disease. Patients with CD have also been found to have a higher incidence of antithyroid antibodies. 16.4% of patients in research showed antithyroid antibodies [13].

Children had the highest estimations of thyroid disease risk among those with celiac disease. In CD children, the hypothyroidism incidence was reported as 2% and 7.8%, three times higher than in the general Saudi population [14]. A study on CD of children living in Sardinia demonstrated a prevalence of autoimmune incidence of hypothyroidism of 10.5%, which is 4 times higher than in the general population. There are two plausible hypotheses for this correlation: First, there is a genetic overlap between CD and AITD (Autoimmune Thyroid Disease). Secondly, celiac patients who are not following a gluten-free diet (GFD) may lose intestinal barrier integrity, which could alter the systemic immune response and promote the onset of other autoimmune diseases. Also, the non-autoimmune causes of thyroid illness are more frequent in adults, whereas autoimmune thyroid disease is more common in children [15].

Despite the higher incidence and complex association of CD and hypothyroidism association reported, specifically among children, there is not enough research available on the topic. Hence, the current study aims to determine the prevalence of hypothyroidism

among pediatric patients with celiac disease in King Abdulaziz Medical City, Saudi Arabia. The study will determine the onset age of hypothyroidism among CD patients, compare the prevalence of hypothyroidism among CD patients and healthy population, and among typical and atypical clinical manifestations of CD. The obtained results will fill gaps in CD research by determining not only its prevalence but also by identifying it as a risk factor for hypothyroidism. It will help medical professionals in early diagnosis and prevention of hypothyroidism among CD patients. Also, it will help bring required alterations in health policy and systems to avoid the subsequent occurrence of hypothyroidism.

Materials and Methods

Study design

A retrospective, cross-sectional study design is adopted.

Study area/setting

This study is conducted in King Abdulaziz Medical City, NGHA, Jeddah, Saudi Arabia.

Eligibility criteria

Inclusion criteria

Children less than eighteen years of age at the time of diagnosis with Celiac disease, confirmed by histopathology, who were diagnosed with hypothyroidism confirmed by labs and confirmed by an endocrinologist, are included in this study.

Exclusion criteria

Children with congenital hypothyroidism are excluded.

Sample size

We aimed to include all pediatric celiac disease patients at King Abdulaziz Medical City during the data collection duration; however, we found complete data for only fifty-five patients that met our inclusion criteria.

Sampling technique

Non-probability consecutive sampling technique is used to target the population.

Data collection methods

The data is collected through a proper system. The data sheet is pre-piloted and designed after an intensive literature review and expert consultation to draw the data of patients. This data sheet collected data from eligible patients fitting the inclusion and exclusion criteria through the BestCare system (electronic system for patient care). The data sheet comprises demographic information, age of diagnosis of hypothyroidism, associated conditions, and family history.

Data management

Data management involved secure storage of completed questionnaires, with immediate coding for anonymity. A double-entry verification process minimizes errors and is backed up regularly to prevent data loss. The dataset is organized into variables for demographic information, medical history, laboratory results, clinical evaluation, and family history. Missing data is addressed ethically, either through imputation or exclusion. Access is restricted to authorized personnel, with confidentiality agreements and security measures in place to protect data integrity. At the end of the study, the dataset is archived securely for future use. This systematic approach ensured data accuracy, confidentiality, and accessibility throughout the research process.

Statistical analysis

Then, SPSS is used for statistical analysis. The data is presented as follows: 1. Qualitative variables are reported as frequencies and percentages. 2. Quantitative variables are reported as mean and standard deviation. For inferential statistics, the Student T-test compares two quantitative normally distributed variables, and the ANOVA test compares more than two quantitative customarily distributed variables with the significant level set at P-value < 0.05.

Results

Table 1 summarizes the demographic information of the patients. The study aimed to investigate the prevalence and characteristics of hypothyroidism in pediatric patients with celiac disease and analyzed the 55 participants' data. The gender distribution revealed a higher prevalence of females 34 (61.82%) than males 21 (38.18%). The age of patients varied at the time of diagnosis as 45.5% of patients were diagnosed with it at the age of 8+ years, 32.7% were diagnosed between the ages of 4-8 years, and only 21.8% of patients diagnosed between the ages of 1 - 4 years. At the time of diagnosis with celiac disease, 30.9% of pediatric patients were classified as having low height (≤ 110 cm). In contrast, 41.8% were within the normal height range (111 cm to 160 cm), and only 7.27% of patients had a high height (> 160 cm). Additionally, 20.3% of patients had missing height data, which could impact the overall assessment. In terms of weight, 21 (38.2%) were categorized as having low weight (≤ 20 kg), suggesting a significant proportion of children with celiac disease are experiencing substantial weight loss or malnutrition. Another 21 patients (38.2%) were within the normal weight range (20 - 40 kg). In contrast, 6 patients (10.9%) were classified as having high weight (≥ 40 kg). Additionally, 7 patients (12.7%) had unreported weights, which limits the completeness of the data. The Modified Marsh-Oberhuber classification data for patients with celiac disease shows the following distribution: Type 1 (3.6%), Type 2 (11%), and Type 3, which includes subtypes 3a (31%), 3b (25.6%), and 3c (23.3%) totaling 79.9%. An additional 3(5.45%) patients did not report it.

This demographic distribution highlights the prevalence of females more than males, the majority of diagnoses after 8 years of age, and predominant weight between 16 - 27 kg (Table 1).

Demographic variable	Frequency (N)	Percentage (%)
Gender		
Male	21	38.18
Female	34	61.82
Age (At time of diagnosis)		
1-4 years	12	21.8
4-8 years	18	32.7
8+ years	25	45.5
Height (At time of diagnosis)		
Low Height (≤ 110 cm)	17	30.9
Normal Height (111 cm to 160 cm)	23	41.8
High Height (> 160 cm)	04	7.27
Not reported	11	20.3
Weight (At time of diagnosis)		
Low weight (≤20 kg)	21	38.2
Normal weight (20 - 40 kg)	21	38.2
High weight (≥40 kg)	6	10.9

Not reported	7	12.7
Modified Marsh-Oberhuber classification		
Type 1	2	3.6
Type 2	6	11
Type 3	Type 3a: 17 Type 3b: 14 Type 3c: 13	31 25.6 23.3
N\A	3	5.45

Table 1: *Demographic statistics table of participants.*

Table 2 summarizes the clinical variables of pediatric celiac disease patients. Results showed that among the 55 patients, the majority, 39 (70.6%) of the patients had a duration of disease less or equal to 3 years, and significant patients, 38 (69.1%), adhered to a gluten-free diet. Hypothyroidism was reported in only 6 (10.9%) patients. In terms of signs and symptoms, 22 (40.0%) patients had gastrointestinal symptoms (abdominal pain, bloating, diarrhea, constipation or lethargy) at the time of diagnosis, 33 (60%) had general nonspecific symptoms. Family history revealed celiac disease in 31 (56.3%) patients and hypothyroidism in 2 (3.6%) patients. Laboratory tests showed that 44 (80.0%) patients have normal TSH level between 0.4 - 4.0 mIU/L, while 43 (78.18%) patients have normal FT4 level from 9.0 - 19.0 pmol/L. Normal IgA level 0.70 - 4.0 g/L was reported in 20 (36.36%) of the total cases. Normal Vitamin D level from 30-100 ng/mL was observed in 30(54.55%) of the cases. Additionally, tTG IgA level was high in 80% of the patients. The values of standard deviation, p-value, and chi-square test showed significant differences in all levels and highlighted the critical need for targeted clinical management in this patient population (Table 2).

Variable	Frequency N (%)		Standard deviation	p-value	Chi-square value
Duration of disease	<=3y >3y	39 (70.6) 16 (29.1)	±3.089	0.0015	10.07
Adherence to gluten-free diet	Yes No	38 (69.1) 17 (30.9)	±0.462	0.004	8.02
Does the patient have hypothyroidism?	Yes No Not reported	6 (10.9) 48 (87.3) 1 (1.8)	±1.22	0.002	0.25
Signs and symptoms	Gastrointestinal General	22 (40.0) 33 (60)	±2.79	0.005	8.44
Family history	Hypothyroidism Celiac Disease Others Not reported	2 (3.6) 31 (56.3) 17 (30.9) 5 (9.2)	±3.40	0.041	6.54
TSH level	Normal (0.4 - 4.0 mIU/L) Borderline (4.0 mIU/L and <= 10.0 mIU/L) High (> 10.0 mIU/L)	44 (80.0) 7 (12.73) 4 (7.27)	±2.71	0.006	5.44
FT4 level	Normal (9.0 - 19.0 pmol/L) Low (<=9.0 pmol/L) High (>19.0 pmol/L)	43 (78.18%) 5 (9.09) 7 (12.73)	±1.94	0.005	3.84

IgA level	Normal (0.70 - 4.00 g/L) Low (below 0.70 g/L) High (Above 4.00 g/L)	20 (36.36) 10 (18.18) 25 (45.45)	±3.55	0.041	2.98
Vitamin D level	Normal (30 - 100 ng/mL) Low (below 30 ng/mL) High (Above 100 ng/mL)	30 (54.55) 10 (18.18) 15 (27.27)	±4.01	0.001	3.57
tTG IgA level	Normal (1-20 U/mL) Low (less than 1 U/mL) High (Above 20 U/mL)	11 (20%) 0 (0) 44 (80%)	±2.88	0.04	4.41

Table 2: *Clinical characteristics of participants.*

Table 3 investigates the correlation between the family history of autoimmune conditions and the prevalence of hypothyroidism. Among the 22 patients with a family history of autoimmune conditions, 6 had hypothyroidism, resulting in a 27.2% prevalence of hypothyroidism. Among the 19 patients without a family history of autoimmune conditions, only 2 still had hypothyroidism, revealing a 10.5% prevalence of hypothyroidism even without a family history of hypothyroidism. These findings reveal a high prevalence of hypothyroidism with a family history of autoimmune conditions, highlighting a potential link between genetics and the development of hypothyroidism among pediatric celiac disease patients (Table 3).

Family History of Autoimmune Conditions Total	Hypothyroidism Present (Yes)	Hypothyroidism Absent (No)	Total patients (N)	Hypothyroidism Prevalence (%)
Yes	6	0	22	27.2%
No	2	17	19	10.5%
Not reported	1	5	6	16.6%

Table 3: *Association between family history of autoimmune conditions and hypothyroidism.*

The correlation between gender (male and female) and tend of hypothyroidism was assessed by using Pearson's correlation coefficient. The analysis showed a Pearson correlation value of 0.155, indicating a weak correlation between these variables of gender and hypothyroidism. Therefore, it is suggested that the development of hypothyroidism is not strongly influenced by gender (Table 4).

Correlations			
		Gender	Does the patient have hypothyroidism?
Gender	Pearson Correlation	1	.155
	Sig. (2-tailed)		.259
	N	55	55
Does the patient have hypothyroidism?	Pearson Correlation	.155	1
	Sig. (2-tailed)	.259	
	N	55	55

Table 4: *Correlation between gender and tend of hypothyroidism.*

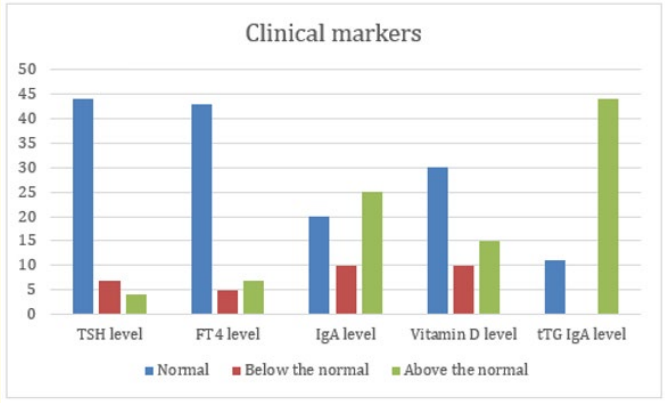

Figure 1: *Summary of clinical markers in pediatric celiac disease patients.*

This graph summarizes the distribution of biochemical variables among the patients. TSH level was normal in 44 patients, below the normal in 7 patients, and above the normal in only 4 patients. Similarly, FT4 level was normal in prominent patients (43), below in 5 patients, and above the normal in 7 patients. IgA showed significant variability as only 20 patients had normal levels, 10 were below the normal, and 25 were above the normal. Vitamin D level was normal in 30 patients, below normal in 10 patients, and above normal in 15 patients. Lastly, tTG IgA was normal in 11 patients, below normal in 0 patients, and above normal in 44 patients. This data indicates the need for close monitoring of these clinical variables in pediatric celiac disease patients.

Discussion

This study investigated the prevalence and characteristics of hypothyroidism in pediatric patients with celiac disease at King Abdulaziz Medical City. Among the 55 participants, females were more prevalent (61.82%) than males (38.18%), with the majority of diagnoses occurring after the age of 8 years (45.5%). Hypothyroidism was present in 10.9% of patients, with a higher prevalence (27.2%) among those with a family history of autoimmune conditions. Most patients (70.6%) had a disease duration of three years or less, and 69.1% adhered to a gluten-free diet. Clinical variables showed that 80.0% had normal TSH levels, 78.18% had normal FT4 levels, and significant variances were noted in IgA and vitamin D levels. Pearson's correlation indicated a weak association between gender and hypothyroidism. These findings emphasize the critical need for targeted clinical management and routine monitoring of thyroid function and other clinical variables in pediatric celiac disease patients.

Several studies have highlighted the association between celiac disease and thyroid disorders. For instance, a survey conducted by Aljulifi., *et al*. (2021) focused on the prevalence of celiac disease among patients with type 1 diabetes mellitus (T1DM) in Saudi Arabia, revealing that 11.5% of the T1DM patients also had positive celiac test results [16]. Although this study primarily investigated the coexistence of celiac disease and T1DM, the prevalence of thyroid disorders was also considered, and it was found that thyroid disorder prevalence did not differ significantly between celiac positive and negative groups, suggesting a common autoimmune background [17].

In another meta-analysis conducted by Safi (2018), the prevalence of celiac disease in at-risk populations in Saudi Arabia, including those with T1DM, short stature, and Down syndrome, was explored. The study found that 15.6% of the at-risk population had seropositive celiac disease, with a biopsy-proven prevalence of 10.6% [18]. The female-to-male ratio was similar to that found in our study, indicating a higher prevalence of autoimmune diseases among females. This supports our findings that females with celiac disease are more prone to developing hypothyroidism [19].

Thyroid disorders are among the most prevalent endocrine issues in pediatric populations. A study by Al-Qahtani., *et al*. in a teaching hospital in Saudi Arabia examined 148 pediatric patients with thyroid disorders over seven years, finding that acquired hypothyroidism was the most common condition, accounting for 34% of cases [20]. This was followed by congenital hypothyroidism and Hashimoto's thyroiditis. The study also noted a female predominance, with females constituting 64% of the patients, reinforcing our findings of a higher prevalence of hypothyroidism among female pediatric celiac patients [21].

Faraj., *et al*. assessed physician awareness regarding celiac disease screening in high-risk pediatric groups in King Abdulaziz Medical City. The study revealed that while there was moderate knowledge about the symptoms and risk factors of celiac disease, knowledge was deficient regarding the management and diagnosis of the disease among physicians [22]. This highlights the need for increased awareness and training for early detection and management of associated conditions such as hypothyroidism in pediatric celiac patients [23].

In a study by Alfawaz., *et al*. (2021) conducted in the Qassim Region of Saudi Arabia, the clinical characteristics of celiac disease patients were evaluated. The study, which included 58 patients, found that the majority of the patients presented with abdominal pain, diarrhea, and weight loss [24]. Moreover, 64% of the patients had positive anti-tTG IgA tests at the time of diagnosis. This study also noted a high prevalence of thyroid disorders among celiac patients, which is consistent with our findings that emphasize the need for regular screening for thyroid dysfunction in celiac patients [25].

El-Metwally., *et al.* (2019) conducted a systematic review of the epidemiology of celiac disease in Arab countries, including Saudi Arabia. The review included 35 studies with a total of 22,340 participants. The prevalence of celiac disease varied widely across different countries, with the highest prevalence observed in Saudi Arabia (3.2%). The review highlighted that those children with T1DM had a higher prevalence of celiac disease (ranging from 5.5% to 20%) [17]. Furthermore, the review noted that thyroid disease was commonly associated with celiac disease, which underscores the importance of monitoring thyroid function in pediatric celiac disease patients [26].

The findings from our study and the research above collectively underscore the significant overlap between celiac disease and thyroid disorders, particularly hypothyroidism [27]. The higher prevalence of hypothyroidism in pediatric celiac disease patients, especially among females, indicates a potential genetic and autoimmune link. This correlation is further supported by the study of Roy., *et al*. which demonstrated a high prevalence of celiac disease among patients with other autoimmune conditions like T1DM [28].

In a study focusing on the nutritional status of celiac disease patients in a tertiary care hospital in Saudi Arabia, Sudersanadas., *et al*. found significant nutritional deficiencies, including iron deficiency anemia and malnutrition, particularly among female patients. This study emphasized the importance of nutritional monitoring and follow-up for celiac patients to prevent growth retardation and other complications [29]. The findings align with our research, as thyroid dysfunction can exacerbate dietary deficiencies and growth issues in pediatric celiac patients.

Moreover, the study by Barker., *et al*. reinforces the need for vigilant screening and monitoring of thyroid function in celiac patients, given the high seroprevalence and biopsy-proven prevalence of celiac disease in at-risk populations. This aligns with our findings that a significant proportion of pediatric celiac disease patients had elevated tTG IgA levels, indicating active disease and the potential for concurrent autoimmune disorders such as hypothyroidism [30].

The limitations of our study are its retrospective design and the relatively small sample size, which may impact the generalizability of the findings. Additionally, the reliance on medical records might have led to incomplete data capture. Future research should focus on larger, longitudinal studies to provide a more comprehensive understanding of the relationship between hypothyroidism and pediatric celiac disease, potentially uncovering more nuanced interactions and risk factors.

Conclusion

In conclusion, our study highlights a significant prevalence of hypothyroidism among pediatric celiac disease patients at King Abdulaziz Medical City, with a notable higher incidence in females and those with a family history of autoimmune conditions. The findings emphasize on the importance of early screening and monitoring for thyroid dysfunction in pediatric CD patients, given the substantial overlap in genetic and immunological markers between these conditions. Despite the small sample size and retrospective nature of our study, the results suggest that comprehensive management of CD should include regular assessment of thyroid function to prevent potential complications. Future research should focus on larger, longitudinal studies to further elucidate the mechanisms linking CD and hypothyroidism and to develop targeted interventions for early diagnosis and treatment, improving overall patient outcomes.

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